SAMARIUM DIIODIDE MEDIATED DECONJUGATION OF α,β-UNSATURATED ESTERS AND THE SYNTHESIS AND BIOLOGICAL STUDY OF BRYOSTATIN ANALOGUES

by

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A dissertation submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

The University of Utah

December 2016

The University of Utah Graduate School

STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

Generally, β,γ-unsaturated carbonyls are thermodynamically less stable than their corresponding α,β-unsaturated isomers. An investigation of SmI_2-mediated deconjugation of α,β-unsaturated esters to provide β,γ-unsaturated esters is described herein. Under almost neutral conditions, α,β-unsaturated esters bearing good leaving groups at the γ-position were reductively deconjugated into β,γ-unsaturated esters in excellent yields at low temperature. The newly formed double bonds slightly favored *E*-geometry, whereas α,β-unsaturated esters bearing poor leaving groups afforded both deconjugated products and saturated products.

Bryostatin 1, a macrocyclic lactone isolated from the bryozoan *Bugula neritina*, has attracted great attention from the scientific community since its structure was identified by Pettit in 1982. Clinical development of bryostatin 1 has been ongoing since 1990. To date, bryostatin 1 has been the subject for various cancers, HIV and Alzheimer's disease in more than 80 human clinical trials. All the unique bioactivities of bryostatin 1 are closely related to its ability to modulate protein kinase C isozymes (PKCs), which are the key players in cell proliferation and death. Clarifying the structure-activity relationship (SAR) of bryostatin 1 promises extraordinary benefits to our understanding of the detailed mechanism of PKC activation and regulation.

The work described herein focuses on the preparation of the *C*-27 des-methyl bryostatin analogue and its biological evaluation. A convergent and efficient route that involved

extension of our pyran-annulation and catalytic asymmetric allylation (CAA) methodologies was developed and successfully delivered the target analogue. Upon addition of a catalytic amount of pyridine, the pyran-annulation reaction was more effective and consistent in terms of its yields. The des-methyl analogue demonstrated that the *C*-27 had no effect on the binding affinity to PKCs and the biological properties of the molecule. This discovery may facilitate future analogue syntheses.

In order to investigate the role of the *C*-*9* hemiketal hydroxyl group in the biological profile of bryostatin 1, a synthetic route was designed to prepare an analogue with the hemiketal alcohol. In this route, SmI_2-mediated reductive cyclization was attempted to construct the hydroxypyran A-ring. Unfortunately, a side reaction occurring on the *C*-ring of the analogue prevented the desired cyclization. Without the cyclized A-ring, an unexpected analogue was finally obtained, which had an expanded macrolactone with a fused C-ring.

Dedicated to my beloved parents and family

For their endless love and support

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STANDARD LIST OF ABBREVIATIONS AND ACRONYMS

$[\alpha]_D^{20}$	specific rotation
Å	angstrom
Ac	acetyl
AcOH	acetic acid
aq	aqueous
BINOL	1,1'-bi-2-naphthol
BITIP	catalyst made by combining 1,1'-bi-2-naphthol and Ti(O*i*-Pr)$_4$
Bn	benzyl
BOM	benzyloxy methyl
BPS	*t*-butyldiphenylsilyl
br	broad (spectral)
Bu	normal butyl
t-Bu	*tert*-butyl
Bz	benzyl
C	carbon
°C	degrees Celsius
CAA	catalytic asymmetric allylation
calcd	calculated
cm^{-1}	wavenumber(s)

COSY	correlation spectroscopy
CSA	10-camphorsulfonic acid
δ	chemical shift in parts per million downfield from tetramethylsilane
d	day(s); doublet (spectral)
DAG	diacylglycerol
DCC	*N,N'*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano- 1,4-benzoquinone
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DIBALH	diisobutylaluminum hydride
DIPEA	*N,N*-diisopropylethylamine
DMA	*N,N*-dimethylacetamide
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DQCOSY	double quantum correlation spectroscopy
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
equiv	equivalent(s)
ESI	electrospray ionization

Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
g	gram(s); prefix to NMR abbreviation denoting gradient-selected (e.g. gCOSY, gHMQC)
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMPA	Hexamethylphosphoramide
HRMS	high-resolution mass spectrum
HMQC	heteronuclear multiple quantum correlation
HSQC	heteronuclear single quantum correlation
Hz	hertz
IBX	*o*-iodoxybenzoic acid
IC_{50}	50% inhibitory concentration
Im	Imidazole
IR	infrared
J	coupling constant (in NMR)
k	kilo
Ki	binding affinity
L	liter(s)
LDA	lithium diisopropyl amide
μ	micro
m	multiplet (spectral); meter(s); milli

M	moles per liter
*m*CPBA	*meta*-Chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
min	minute(s)
mL	milliliter
mol	mole(s)
mp	melting point
MS	mass spectrometry; molecular sieves
Ms	methylsulfonyl (mesyl)
m/z	mass to charge ratio
NCS	*N*-Chlorosuccinimide
nM	nanomolar (nanomoles per liter)
NMO	*N*-methylmorpholie-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	Phenyl
PKC	protein kinase C

PMA	phorbol-12-myristate-13-acetate
PMB	*p*-Methoxybenzyl
ppm	parts per million (in NMR)
PPTS	Pyridinium *p*-toluenesulfonate
Pr	propyl
*i*Pr	isopropyl
Py	pyridine
q	quartet (spectral)
quant	quantitative
quin	quintuplet (spectral)
R_f	retention factor (in chromatography)
ROESY	rotating frame Overhauser effect spectroscopy
rt	Room temperature
s	second(s); singlet (spectral)
SET	single electron transfer
sext	sextet (spectral)
t	triplet (spectral)
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxyl
Tf	trifluoromethanesulfonyl (triflyl)
TfOH	trifluoromethanesulfonic acid

TES	triethylsilyl
Tf	trifluoromethanesulfonoyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl; trtramethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TOCSY	total correlation spectroscopy
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid
UV	ultraviolet
vol	volume
v/v	volume per unit volume (volume-to-volume ratio)
wt	weight
w/w	weight per unit weight (weight-to-weight ratio)

ACKNOWLEDGMENTS

I would like to take this opportunity to express my heartfelt gratitude to all those who helped make this work possible. First and foremost I would like to express my sincere and deepest gratitude to my esteemed mentor **Prof. Gary E. Keck** for his untiring guidance, constant encouragement, and patience throughout the course of research. He has walked with me through all the stages of this project. His patience and support helped me overcome many crisis situations and finish this dissertation. It is my honor to be his student, and I can never thank him for all he has done for me.

I am also deeply indebted to my thesis committee professors, **Dr. Richard D. Ernst**, **Dr. Jon D. Rainier**, **Dr. Janis Louie**, and **Dr. Kuberan Balagurunathan** for their insightful discussions and priceless suggestions in general. They guided me through all these years. I would like to acknowledge **Dr. Charlie Mayne**, **Dr. Dennis Edwards**, **Dr. Peter F. Flynn**, **Dr. James Muller**, and **Dr. Atta M. Arif** for their valuable assistance, technical support, and producing the necessary analytical data. Especially, I appreciate Dr. Dennis Edward for teaching me lots of experimental skills of advanced NMR spectroscopy.

I am grateful to all my lab buddies of the Keck group for their friendship and help in the past years. They all inspired me in research and life through our interactions during the long hours in the lab. Especially, thank you to **Dr. Dennie Shane Welch**, who taught me the "survival" skills of organic chemistry lab, and to **Dr. Arnab Rudra**, who made working long hours enjoyable.

I thank **Jay Ingleby**, **Doug Collins** and **Dave Lykins** for all their help with bringing our needed chemicals and supplies, and **Kevin Teaford** for making and fixing necessary glass apparatus. I also want to thank **Jo Hoovey**, **Leatha Allred**, **Geraldine Ann Collins** (1946 ~ 2008) and other wonderful staff in the Chemistry Department for always being so helpful and friendly.

I would like to thank **Dr. David Baumann** for reviewing and polishing this document. I would like to thank everybody who was important to the realization of this work, as well as expressing my apology that I could not mention everyone personally.

Last but not least, there are no words to express my gratitude and thanks to my beloved parents, family members and friends for always standing by me. Their love has been the major spiritual support in my life.

CHAPTER 1

SAMARIUM DIIODIDE MEDIATED DECONJUGATION OF α,β-UNSATURATED ESTERS

Introduction

The β,γ-unsaturated carbonyl functionalities are widely contained in naturally occurring products, and most of them exhibit unique biological activities.[1-3] Many of them and their synthetic derivatives are currently used as drugs (Figure 1.1). For instance, molfarnate **1.1** is a common antiulcerogenic agent, clavulanic acid **1.2** is an antibiotic drug, and the steroid tibolone **1.3** is utilized worldwide. Ivermectins **1.4** and **1.5** are among the world's most successful antiparasitic drugs in human medicine.[4,5] These are listed on the "World Health Organization's List of Essential Medicines", which is a directory of the most important medication needed in a basic human health system.[6]

The β,γ-unsaturated carbonyl functionalities also serve as intermediates to prepare various homoallylic functional groups, butyrolactones and five-membered rings, thus making them among the important building blocks in organic chemistry. Since the thermodynamically stable α,β-unsaturated carbonyls are readily available, deconjugation is the straightforward method to access their relatively unstable isomers.

Since the seminal report of the usage of samarium diiodide (SmI_2) in organic chemistry by Kagan,[7,8] it has become an important reducing reagent in organic synthesis.[9-18] SmI_2

is a polyvalent single-electron reducing agent and readily available in laboratories.[7,8,19,20] In addition, its reduction ability can be further modified by addition of *Lewis* bases, proton sources, and *Lewis* acids.[21-24] More importantly, SmI_2-mediated reductions demonstrate great chemoselectivity and wide functional group compatibility.[8,25-30] Despite the plethora of synthesis applications in reductive eliminations and fragmentations,[27,31-36] very little precedent exists in the SmI_2-mediated deconjugation of α,β-unsaturated carbonyls. To the best of our knowledge, the successful examples consist of only fluorides and epoxides.[37-40]

Previous *α,β*-Unsaturated Carbonyl Deconjuation Strategies

Generally, α,β-unsaturated carbonyls are more thermodynamically stable than their deconjugated isomers. Thus, in practice, deconjugated carbonyls are frequently isomerized to conjugated carbonyls. Conversely, the application of deconjugation of α,β-unsaturated carbonyls in organic synthesis is limited. In some instances, however, it is necessary to obtain the deconjugated isomers directly from the corresponding α,β-unsaturated carbonyls.

In the vast literature, the most widely used strategy is kinetic protonation or alkylation (Figure 1.2). Using strong bases, such as lithium *N*-isopropylcyclohexylamide (LiICA), the conjugated carbonyl is deprotonated to provide dienolate anion **1.8** at low temperature without self-condensation. This anion predominantly reacts at the alpha carbon.[41-47] That the alpha carbon is more reactive than the gamma carbon is well explained by molecular orbital theory.[41,42] Therefore, when dienolate anions react with electrophiles under kinetic conditions, they provide deconjugated β,γ-unsaturated carbonyls. In the presence of

HMPA, the sterically unfavorable Z-geometrical isomers are predominantly formed.[47] Because the strong base is utilized, the molecules with base sensitive functionalities, especially the advanced intermediate, are excluded from this reaction. This reaction is largely limited to the initial steps of syntheses.

Photochemical deconjugation of α,*β*-unsaturated carbonyls has been studied for a long time. [48-54] For enones, two distinct absorptions are around 210-240 nm and 300-320 nm, corresponding to the π-π^* and n-π^* transition, respectively. Under irradiation, α,*β*-unsaturated carbonyl **1.11** undergoes a rapid *E/Z* isomerization of the double bond to provide geometrical isomer **1.12**, which undergoes a concerted hydrogen migration following the Woodward-Hoffman rules (Figure 1.3). This hydrogen migration provides a photodienol intermediate **1.13** via the single-excited state. The photodienol can finally revert to the starting material, or can furnish β,γ-unsaturated carbonyl **1.14** after tautomerization. This reaction generally suffers a moderate yield, though it has been successfully applied in the synthesis of *Stemona* alkaloids.[55]

α,*β*-Unsaturated acids can be converted to β,γ-unsaturated esters via conjugated ketene imtermediates.[56,57] Treatment of acid **1.18** with DCC provides **1.19**, which undergoes an elimination to afford α,*β*-unsaturated ketene **1.20** (Figure 1.4). Esterification of the unsaturated ketene with alcohol furnishes deconjugated ester **1.21**. Similarly, α,*β*-unsaturated acid chlorides can be converted into β,γ-unsaturated esters via the same ketene intermediates.[58,59] However, α,*β*-unsaturated acids or acid chlorides are not always readily accessible. Thus, this approach is not widely applicable.

Transition metal complexes are good catalysts for olefin migrations, but a mixture of inseparable isomers is generally obtained in deconjugation reactions.[60] Other approaches

are occasionally reported, but they either require very specific reaction conditions, or are restricted to certain precursors. Thus, it remains a great challenge to develop an efficient deconjugation method with wide applicability.

Results and Discussion

In the course of our ongoing bryostatin analogue studies, an interesting observation was made during the total synthesis of a novel analogue. It offered a potential solution to the deconjugation of α,*β*-unsaturated carbonyls problem.

Previously, an annulation strategy was developed in our lab. This protocol allowed us to construct a cyclic ring from allylhalide **1.22** in an intramolecular fashion (Figure 1.5).[61] A model study demonstrated that, upon treatment with SmI_2, the simplified bryostatin AB ring system **1.23** was obtained at 0 ^oC in high yield. However, upon subjection of the real substrate **1.24** to the reductive-cyclization conditions, no desired product was observed. When **1.24** was attempted at -78 ^oC with a limited amount of SmI_2, the eliminated *C*-20 side chain was identified, and the labile allyl iodide functionality was found intact using a crude ^1H NMR analysis. This elimination of the *C*-20 side chain was completed in seconds after an addition of SmI_2 reagent, monitored by TLC. This process presumably occurred via sequential single-electron transfers and an elimination sequence. These observations gave credence to the notion that SmI_2 would be used to selectively deconjugate γ-substituted α,β-unsaturated carbonyls under mild conditions. And we decided to investigate the scopes and limitations of this methodology.

A variety of *γ*-substituted conjugated esters were prepared. They were derived from the *γ*-hydroxycrotonate **1.25g**, which in turn was synthesized from sorbic acid in three

straightforward steps.

Based on the previous observation of the octadienoate elimination (the *C*-20 side chain of **1.24**), *γ*-acetate conjugated ester **1.25a** was probably a good candidate to be used to optimize the reaction conditions for deconjugation at this time. It was then subjected to 5.0 equivalents of SmI_2 in THF at 0 ºC (Table 1.1, entry 1). This was adopted as standard conditions for the model substrates. In this instance, the starting material **1.25a** was consumed completely in seconds after the addition of SmI_2, and the product **1.26** was obtained, however, in a poor yield. Numerous unidentifiable compounds were collected. It was also found that the persistence of characteristic deep-blue color of SmI_2 solution could be used to judge the endpoint of reactions. Unfortunately, lowering the load of SmI_2 did not help increase the yield. Although improved results were obtained at low temperatures, the yields were still moderate.

It was suspected that the low yields were due to the side reactions of the intermediate dienolate anion **1.35**, which was highly reactive and should be quenched immediately. With this in mind, the deconjugation reaction was investigated in the presence of proton sources in an attempt to avoid side reactions. Significantly improved yields were obtained when the reaction was performed in protic sources (Table 1.1, entry 5-7). With 1 equivalent of MeOH at -78ºC, an improved 76% yield was obtained. The optimal result in terms of yield was obtained with more than 10 equivalents of MeOH. The replacement of MeOH by *t*-BuOH afforded essentially the same yield. Under any circumstances, neither simple deacetylation product **1.28** nor olefin-reduced product **1.27a** was observed. It was worth noting that the addition of alcohol would also increase the reducing ability of SmI_2 because of the good coordination ability of alcohols to oxophilic samarium. [21-23]

Substrates with poor leaving groups at the γ-position required elevated temperatures to undergo deconjugations (Table 1.1, entry 10). γ-Methoxy conjugated ester **1.25b** was inert to SmI_2 below -30 ^oC. Even at room temperature, the reaction was sluggish with slightly more SmI_2 and needed 4 hours to consume all the starting material. In addition, the saturated compound **1.27b** was obtained along with the deconjugated product **1.26**, but no **1.28** was observed.

Having identified optimized conditions for deconjugation reaction, a series of primary γ-substituted α,β-unsaturated esters were examined to determine the impact of γ-functionality upon the viability of this approach to deconjugation. These reactions were performed under our optimized conditions, and the results are summarized in Table 1.2. These results clearly demonstrated that the nature of the substituent at the γ-position largely determined the reaction temperature required, and the selectivity as well as the yield of the deconjugation.

In the cases of excellent and moderate leaving groups, the reactions were accomplished almost instantaneously at -78 ^oC under Ar (Table 1.2, entry 1, 3-6, 11-13). Only deconjugated product **1.26** was obtained, and its yield was generally higher than 90%. For instance, γ-iodo conjugated ester **1.25e** furnished the deconjugated product in an almost quantitative yield. The frequently occurred deiodination reaction was not observed, and this phenomenon was consistent with what happened during our bryostatin analogue synthesis.

In contrast, with substituents bearing poor leaving groups, higher temperatures and much longer periods of time were required (Table 1.2, entry 2, 7-10). Along with the deconjugated product **1.26**, the saturated product **1.27** was also obtained. The individual

yields and ratio of these two products varied, depending on the nature of a substituent. Methoxy group, for instance, provided more deconjugated product (**1.26** : **1.27b** = 66% : 18%), whereas silyloxy group favored the saturated product (**1.26** : **1.27i** = 24% : 72%). As for allyloxy group, two products were obtained in equal ratio. Once again, no **1.28** was observed in these reactions.

An interesting case was **1.25g** containing a hydroxy group. It furnished exclusively deconjugated product **1.26** in 94% yield with in a relatively shorter period of time, compared to other substrates bearing poor leaving groups. It assumed that this phenomenon was probably due to the coordination between the free hydroxy group and SmI_2. This coordination made the hydroxy group a good leaving group, thus its elimination was facilitated, leading to the deconjugated product.

As a control reaction, unsubstituted crotonate **1.25n** was subjected to the optimized conditions at room temperature. After 6 hours' treatment with SmI_2, only about 46% of starting material was consumed and reduced to the expected saturated product (Table 1.2, entry 14). It revealed that unsubstituted enoates were quite inert to our conditions. In addition, the reactivity of the substituted (or unsubstituted) enoate was quite consistent with the nature of the leaving group in the molecule.

Introducing an alkyl group at the γ-position of **1.25** could provide two geometric isomers, the *cis* and *trans* forms. In addition, the steric hindrance of the alkyl group would potentially alter the composition of products. To address the impact of the additional substituent on the deconjugation, several secondary γ-substituted conjugated esters of **1.29** were prepared. They were subjected to the optimized conditions. The results are shown in Table 1.3.

The effect of the additional substituent on the chemoselectivity significantly depended on the leaving group involved. The substrates with good leaving groups were not obviously affected (Table 1.3, entry 1-10, 17-19). Either the racemic or chiral substrate furnished only the deconjugated product **1.30** (an inseparable mixture of geometric isomers), whose yield was virtually the same as that of the corresponding primary γ-functionalized enoate. By contrast, substrates with poor leaving groups were significantly influenced to provide more saturated product **1.31** to an extent of 10-20% more (Table 1.3, entry 13-16). For instance, the TBS protected enoate **1.29i** afforded saturated **1.31** as a single product in 93% yield. The free hydroxyl **1.29f** was a unique exception (Table 1.3, entry 11). Its deconjugation pattern closely resembled that of the substrate with a good leaving group, probably because of the previously mentioned coordination of the hydroxyl group.

In all instances, the deconjugated compound **1.30** was obtained as an inseparable mixture of *Z/E* isomers. For the substrates **1.29** with a methyl group at the γ-position, the *E*-isomer was the favored one but the product ratios were largely substituent-dependent. Based on the integration of ^{1}H NMR, substrates with chloride, mesylate and methoxy groups provided relatively good geometric selectivity at 4 : 1 favoring the *E*-isomer. The iodide substituent barely gave any geometric selectivity. Thus, the reductive elimination presumably proceeded via kinetic control, since little equilibration was developed towards the thermodynamically more stable *E*-isomers.

Based on the results, the mechanism of this reductive deconjugation was proposed (Figure 1.6). A single-electron transfer from the SmI_2 to the substrate **1.32** furnished **1.33**. With a good leaving group, a kinetic elimination provided **1.34**, which was rapidly reduced to afford dienolate anion **1.35**. Then, a kinetic protonation gave the deconjugated product.

With a poor leaving group at the γ-position, a protonation reaction competed with the elimination on the intermediate **1.33**, leading to the saturated product.

Conclusion

A new protocol has been developed to prepare deconjugated β,γ-unsaturated esters from γ-functionalized α,*β*-unsaturated esters. Upon treatment with SmI_2 in the presence of alcohol, substrates bearing good leaving groups at the γ-position are exclusively deconjugated rapidly in excellent yields at low temperature. Substrates with a free hydroxyl group at the γ-position are also efficiently converted into deconjugated enoates, but an elevated temperature is required. By contrast, a substrate bearing poor leaving groups generally affords a great amount of saturated product along with the deconjugated one. The geometric selectivity of the newly formed double bond moderately favors the *E*-isomer, with the best ratio as 4:1, obtained from –Cl- and –OMs-substituted substrates.[62]

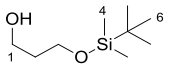
Further work will investigate the scope of this deconjugation reaction with respect to the types of functionalities that can be employed under these conditions. Use of this reaction to prepare branched esters via alkylation will also be studied.

Experimental Section

All solvents were dried and distilled according to the guidelines in *Purification of Laboratory Chemicals, 6th Ed.* (Armarego and Chai, Butterworth-Heinemann: Oxford, U.K., 2009). Diisopropylamine, diisopropylethylamine, triethylamine, pyridine, dichloromethane and ethyl acetate were distilled from CaH_2 under an atmosphere of N_2. Ether solvents (THF and Et_2O) were distilled under N_2 from sodium benzophenone ketyl.

Benzene and toluene were distilled from molten sodium metal under N_2. Solvents and reagents were deoxygenated where necessary by Freeze-Pump-Thaw technique and refilled with nitrogen prior to use. Titanium tetrachloride and titanium isopropoxide were distilled prior to use. Deuterated solvents were purchased from Cambridge Isotope Laboratories (all ≥ atom% D). Reagents were purchased from Acros, Aldrich and Alfa, and used as received unless stated otherwise. Argon, oxygen, and syngas (1:1 mixture of H_2 and CO) were acquired from Airgas and used as received. Glassware for reactions was oven dried at 110 ºC for 4 hours and cooled down under a dry atmosphere prior to use, or flame-dried under an atmosphere of N_2. All air- and moisture-sensitive manipulations were performed by using oven-dried glassware, standard Schlenk techniques, and a glovebox under an atmosphere of N_2. Analytical thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} plates eluting with the solvents indicated, visualized by exposure to UV light (254 nm), and stained with either an ethanolic solution of 12-molybdophosphoric acid or a solution of $KMnO_4/K_2CO_3$/NaOH. Organic solutions were concentrated on a rotovap at aspirator pressure at 20-30 ºC. Flash column chromatography was performed on SiliaFlash® F60 silica gel (230-400 mesh, 60Å), and eluted with solvents indicated. Melting points were recored using open capillary tubes on a Mel-Temp electrochemical melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) spectra were acquired on a Variann Inova 500 spectrometer operating at 500 MHz and 125 MHz for ^1H and ^{13}C separately. All ^1H NMR chemical shifts were quoted in parts per million (ppm) relative to the line of the $CDCl_3$ residual singlet at 7.27 ppm (or the C_6D_6 residual singlet at 7.16 ppm), and ^{13}C NMR chemical shifts were relative to the center line of $CDCl_3$ triplet at 77.23 ppm (or the center line of C_6D_6 triplet at 128.62

ppm). Multiplicities in the ^{1}H NMR spectra were described as follows: s = singlet, d = doublet, t = triplet, q = quartet, ABq = AB quartet, quin = quintet, sext = sextet, m = multiplet, br =broad. Coupling constants were reported in Hz. The structural assignments of ^{1}H and ^{13}C NMR spectra were elucidated with the aid of gCOSY, gDQCOSY, TOCSY, DEPT, HMQC and HMBC experiments. Stereochemical assignments were based on coupling constants where possible, and with the aid of NOSEY1D, ROSEY1D, NOSEY and ROSEY experiments. AA'BB' systems were reported as doublets. Infrared (IR) spectra were recored from a Perkin Elmer FT-IR Paragon 1000 PC spectrometer using a thin film supported between NaCl plates. Optical rotations were acquired on Perkin Elmer Model 343 polarimeter using Na D-line with a 10 cm path length micro cell at 20 ^{o}C from $CHCl_3$ solutions. Ozone was generated by a Welsbach model T-816 generator. Yields refer to purified and spectroscopically pure compounds.



3-(*t*-Butyldimethylsilyloxy)propan-1-ol (1.37): To a round-bottomed flask was charged NaH (60% dispersion in mineral oil, 3.26 g, 81.4 mmol, 1.1 equiv) and anhydrous THF (160 mL, 0.5 M). With an ice-water bath, 1,3-propanediol (6.00 mL, 81.4 mmol, 1.1 equiv) was added dropwise via a syringe over 5 minutes under an atmosphere of N_2. It was allowed to warm to room temperature and stirred for 1 hour. It was then cooled to 0 ^{o}C, and a solution of *t*-butylchlorodimethylsilane (11.4 g, 73.9 mmol, 1.0 equiv) in THF (10 mL) was added into this reaction dropwise via a cannula over 10 minutes. After the addition, it was allowed to warm to room temperature, and stirred at room temperature for 16 hours. It was then quenched with brine (200 mL), and extracted with 3 x 30 mL of EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced

pressure. The remainder was distilled under reduced pressure at 80.0-84.0 °C/2.5 mmHg to provide the titled compound (13.2 g, 69.3 mmol, 99% yield) as a colorless oil.

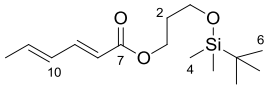
TLC: R_f = 0.26 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$): δ 3.84 (t, *J* = 5.6 Hz, 2H, ***H-3***), 3.81 (t, *J* = 5.6 Hz, 2H, ***H-1***), 2.55 (bs, 1H, ***-OH***), 1.78 (p, *J* = 5.6, 2H, ***H-2***), 0.91 (s, 9H, ***H-6***), 0.083 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 63.2 (***C-3***), 62.7 (***C-1***), 34.4 (***C-2***), 26.1 (***C-6***), 18.4 (***C-5***), -5.3 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 3347 (br), 2931, 2859, 1472, 1389, 1361, 1256, 1096, 964, 837, 777, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_9H_{22}O_2SiNa$ 213.1287; found 213.1293.



(2*E*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl Hexa-2,4-dienoate (1.38): With an ice-water bath, to a mixture of sorbic acid (14.9 g, 131 mmol, 1.2 equiv), **1.37** (20.8 g, 109 mmol, 1.0 equiv) and DMAP (6.76 g, 54.8 mmol, 0.5 equiv) in CH_2Cl_2 (220 mL, 0.5 M) was added a solution of DCC (27.4 g, 131 mmol, 1.2 equiv) in CH_2Cl_2 (65 mL, 2.0 M) via cannula, and the clear solution turned cloudy immediately. This reaction was allowed to warm to room temperature slowly, and stirred for 16 hours under an atmosphere of N_2. The resulting milky reaction was filtered through a pad of celite, and the filtrate was washed with brine containing 1 vol% HCl (300 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (200 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 2-8 vol% of EtOAc in hexanes to provide the titled compound (30.4 g, 107.0

mmol, 98% yield) as a colorless oil.

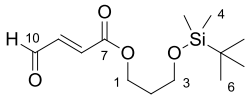
TLC: R_f = 0.68 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.25 (dd, *J* = 15.3, 10.1 Hz, 1H, ***H-9***), 6.26 ~ 6.06 (m, 2H, ***H-11***, ***H-10***), 5.78 (dd, *J* = 15.3, 0.8 Hz, 1H, ***H-8***), 4.24 (t, *J* = 6.5 Hz, 2H, ***H-1***), 3.72 (t, *J* = 6.1 Hz, 2H, ***H-3***), 1.88 (p, *J* = 6.2 Hz, 2H, ***H-2***), 1.86 (d, *J* = 6.0 Hz, 3H, ***H-12***), 0.90 (s, 9H, ***H-6***), 0.055 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 167.5 (***C-7***), 145.2 (***C-9***), 139.5 (***C-11***), 130.0 (***C-10***), 119.2 (***C-8***), 61.4 (***C-1***), 59.7 (***C-3***), 32.1 (***C-2***), 26.1 (***C-6***), 18.9 (***C-5***, ***C-12***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2858, 2120, 1717, 1647, 1619, 1471, 1390, 1360, 1328, 1301, 1244, 1187, 1140, 1104, 1000, 938, 837, 777 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{15}H_{28}O_3SiNa$ 307.1705; found 307.1706.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-oxobut-2-enoate (1.39): To a solution of **1.38** (1.54 g, 5.41 mmol, 1.0 equiv) in 200 proof ethanol (50 mL, 0.1 M) was added Sudan Red 7B (0.6 mg, 2 umol, 0.03% equiv) as an indicator. Then, this solution was cooled down to -78 ºC, and purged with O_3 (3 Psi, 60 Volts) at -78 ºC. When the bright pink-red color faded, the O_3 stream was shut down and O_2 bubbled through the reaction for 5 minutes. Then, DMS (4.0 mL, 54 mmol, 10.0 equiv) was added into this reaction in one portion at this temperature. It was allowed to warm to room temperature, and stirred overnight (*ca.* 16 hours). The solution was concentrated in vacuo. The remainder was purified by a silica gel flash column eluting with 3-9 vol% EtOAc in hexanes to provide the titled compound (1.13g, 4.14 mmol, 77% yield) as a yellow oil.

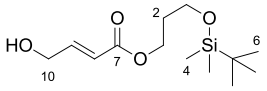
TLC: R_f = 0.33 (Et_2O/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 9.76 (d, *J* = 8.3 Hz, 1H, ***H-10***), 6.96 (dd, *J* = 15.9, 7.6 Hz, 1H, ***H-9***), 6.72 (d, *J* = 16.1 Hz, 1H, ***H-8***), 4.34 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.72 (t, *J* = 5.9 Hz, 2H, ***H-3***), 1.90 (p, *J* = 6.1 Hz, 2H, ***H-2***), 0.88 (s, 9H, ***H-6***), 0.043 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 192.5 (***C-10***), 165.0 (***C-7***), 140.5 (***C-9***), 139.4 (***C-8***), 63.0 (***C-1***), 59.3 (***C-3***), 31.8 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2931, 2858, 1730, 1701, 1643, 1471, 1392, 1361, 1305, 1250, 1176, 1104, 1008, 981, 939, 838, 778, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^{+}] Calcd for $C_{13}H_{24}O_4SiNa$ 295.1342; found 295.1359.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Hydroxybut-2-enoate (1.25g): To a stirred solution of **1.39** (3.17 g, 11.6 mmol, 1.0 equiv) in MeOH (40 mL, 0.3 M) was added $CeCl_3 \cdot 7H_2O$ (8.69 g, 23.3 mmol, 2.0 equiv) in one portion at room temperature. It was stirred for 10 minutes until the entire solid was dissolved, this reaction was cooled down to -15 ^{o}C, and $NaBH_4$ (0.679 g, 17.6 mmol, 1.5 equiv) was added in one portion. After 2 hours, this reaction was diluted with EtOAc (50 mL), and poured into a cold H_2O (100 mL). The aqueous layer was extracted with EtOAc (4 x 15 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by a silica gel flash column eluting with 15-25 vol% EtOAc in hexanes to provide the titled compound (3.07 g, 11.2 mmol, 96% yield) as a colorless oil.

TLC: R_f = 0.25 (EtOA/Hex = 3:7, v/v);

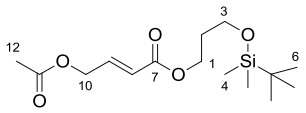
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.02 (dt, *J* = 15.7, 4.2 Hz, 1H, ***H-9***), 6.09 (dt, *J* = 15.7, 2.3 Hz, 1H, ***H-8***), 4.34 (ddd, *J* = 4.0, 2.0, 1.0 Hz, 2H, ***H-10***), 4.24 (t, *J* = 6.4 Hz, 2H, ***H-1***),

3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***), 2.15 (bs, 1H, ***-OH***), 1.86 (p, *J* = 6.2 Hz, 2H, ***H-2***), 0.89 (s, 9H, ***H-6***), 0.043 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.7 (***C-7***), 147.1 (***C-9***), 120.3 (***C-8***), 62.0 (***C-10***), 61.7 (***C-1***), 59.7 (***C-3***), 32.0 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 3431 (br), 2956, 2930, 2858, 1723, 1661, 1471, 1391, 1361, 1278, 1170, 1103, 1009, 837, 778, 717, 664 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{13}H_{26}O_4SiNa$ 297.1498; found 297.1502.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Acetoxybut-2-enoate (1.25a): To a solution of **1.25g** (703 mg, 2.56 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL, 0.1 M) was added DMAP (0.318 g, 2.58 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (4.50 mL, 25.8 mmol, 10.0 equiv) and acetic anhydride (0.73 mL, 7.6 mmol, 3.0 equiv) subsequently, at room temperature. It was stirred for 18 hours, and then quenched with a saturated $NaHCO_3$ solution (30 mL). The aqueous solution was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 3-9 vol% of EtOAc in hexanes to provide the titled compound (738 mg, 2.33 mmol, 91% yield) as a colorless oil.

TLC: R_f = 0.55 (EtOA/Hex = 3:7, v/v);

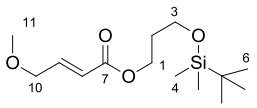
500 MHz ^{1}H NMR ($CDCl_3$) δ 6.92 (ddd, *J* = 15.7, 4.9, 4.4 Hz, 1H, ***H-9***), 6.01 (dt, *J* = 15.7, 2.0 Hz, 1H, ***H-8***), 4.73 (dd, *J* = 4.4, 2.0 Hz, 2H, ***H-10***), 4.24 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***), 2.11 (s, 3H, ***H-12***), 1.86 (p, *J* = 6.2 Hz, 2H, ***H-2***), 0.88 (s, 9H, ***H-***

6), 0.037 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 170.4 (***C-11***), 165.9 (***C-7***), 141.3 (***C-9***), 122.5 (***C-8***), 62.7 (***C-10***), 61.9 (***C-1***), 59.6 (***C-3***), 32.0 (***C-2***), 26.1 (***C-6***), 20.8 (***C-12***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2931, 2858, 1750, 1726, 1667, 1471, 1385, 1363, 1307, 1228, 1177, 1104, 1026, 971, 838, 778, 717, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{15}H_{28}O_5SiNa$ 339.1604; found 339.1614.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Methoxybut-2-enoate (1.25b): To a stirred solution of **1.25g** (134 mg, 0.489 mmol, 1.0 equiv) in DMF (12 mL, 0.1 M) was added NaH (60% dispersion in mineral oil, 40 mg, 1.0 mmol, 2.0 equiv) at 0 ^{o}C. This reaction was stirred for 10 minutes under an atmosphere of N_2 and treated with MeI (125 uL, 1.99 mmol, 4.0 equiv). After 1.5 hours, it was quenched with a saturated solution of NH_4Cl (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 1-6 vol% of ethyl acetate in hexanes to provide the titled compound (45.2 mg, 0.157 mmol, 32% yield) as a colorless oil.

TLC: R_f = 0.52 (EtOA/Hex = 3:7, v/v);

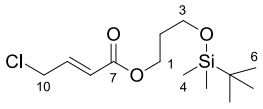
500 MHz ^{1}H NMR ($CDCl_3$) δ 6.94 (dt, *J* = 15.7, 4.4 Hz, 1H, ***H-9***), 6.07 (dt, *J* = 15.7, 2.0 Hz, 1H, ***H-8***), 4.25 (t, *J* = 6.6 Hz, 2H, ***H-1***), 4.09 (dd, *J* = 4.4, 2.0 Hz, 2H, ***H-10***), 3.71 (t, *J* = 6.1 Hz, 2H, ***H-3***), 3.40 (s, 3H, ***H-11***), 1.87 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 0.90 (s, 9H, ***H-***

6), 0.053 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.5 (***C-7***), 144.3 (***C-9***), 121.5 (***C-8***), 71.4 (***C-10***), 61.7 (***C-1***), 59.7 (***C-3***), 58.9 (***C-11***), 32.1 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2858, 1725, 1664, 1471, 1389, 1302, 1258, 1169, 1105, 1039, 838, 777, 664 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{14}H_{28}O_4SiNa$ 311.1655, found 311.1658.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Chlorobut-2-enoate (**1.25c**): To a stirred solution of **1.25g** (250 mg, 0.910 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (9.0 mL, 0.1 M) was added PPh_3 (362 mg, 1.37 mmol, 1.5 equiv). Then a solution of NCS (186 mg, 1.37 mmol, 1.5 equiv) in CH_2Cl_2 (3.4 mL, 0.4 M) was added via cannula at -30 ^{o}C. This reaction was stirred at for 2 hours at 0 ^{o}C under an atmosphere of N_2. Then, it was poured into a mixture of saturated $NaHCO_3$ solution (20 mL) and saturated $Na_2S_2O_3$ solution (20 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was dissolved in 50 mL of Et_2O/hexanes (40:60) mixture, and the precipitate was filtered. The solution was concentrated and purified by flash chromatography on silica gel eluting with 2-10 vol% of Et_2O in hexane to provide the titled compound (186 mg, 0.637 mmol, 70% yield) as a colorless oil.

TLC: R_f = 0.61 (EtOA/Hex = 3:7, v/v);

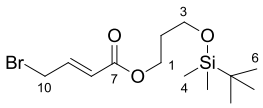
500 MHz ^{1}H NMR ($CDCl_3$) δ 6.97 (dt, *J* = 15.2, 6.1 Hz, 1H, ***H-9***), 6.11 (dt, *J* = 15.2, 1.5 Hz, 1H, ***H-8***), 4.27 (t, *J* = 6.4 Hz, 2H, ***H-1***), 4.17 (dd, *J* = 6.1, 1.7 Hz, 2H, ***H-10***), 3.71 (t,

J = 6.1 Hz, 2H, ***H-3***), 1.88 (p, *J* = 6.2 Hz, 2H, ***H-2***), 0.90 (s, 9H, ***H-6***), 0.054 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 165.8 (***C-7***), 141.9 (***C-9***), 124.3 (***C-8***), 62.0 (***C-1***), 59.6 (***C-3***), 42.7 (***C-10***), 32.0 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2930, 2858, 1726, 1662, 1471, 1391, 1361, 1315, 1271, 1197, 1172, 1151, 1105, 1008, 977, 939, 838, 777, 745, 664 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{13}H_{25}O_3ClSiNa$ 315.1159; found 315.1156.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Bromobut-2-enoate (1.25d): To a stirred solution of **1.25g** (275 mg, 1.00 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (10 mL, 0.1 M) was added CBr_4 (509 mg, 1.52 mmol, 1.5 equiv) and imidazole (103 mg, 1.50 mmol, 1.5 equiv). Then, a solution of PPh_3 (370 mg, 1.40 mmol, 1.4 equiv) in CH_2Cl_2 (3.5 mL, 0.4 M) was added dropwise via addition funnel over a period of 30 minutes at 0 ^{o}C under an atmosphere of N_2. After addition, this reaction was stirred for 1 hour, and poured into a saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL), and the combined organic layers were washed with brine (30 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 2-10 vol% of ethyl ether in hexanes to provide the titled compound (255 mg, 0.755 mmol, 75% yield) as a colorless oil.

TLC: R_f = 0.59 (EtOA/Hex = 3:7, v/v);

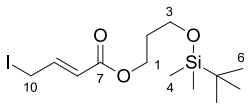
500 MHz ^{1}H NMR ($CDCl_3$) δ 6.99 (dt, *J* = 15.2, 7.3 Hz, 1H, ***H-9***), 6.02 (dt, *J* = 15.2, 1.0 Hz, 1H, ***H-8***), 4.25 (t, *J* = 6.4 Hz, 2H, ***H-1***), 4.00 (dd, *J* = 7.3, 1.0 Hz, 2H, ***H-10***), 3.70 (t,

J = 6.1 Hz, 2H, ***H-3***), 1.87 (p, *J* = 6.3 Hz, 2H, ***H-2***), 0.89 (s, 9H, ***H-6***), 0.043 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 165.6 (***C-7***), 141.9 (***C-9***), 124.8 (***C-8***), 62.0 (***C-1***), 59.6 (***C-3***), 31.9 (***C-2***), 29.2 (***C-10***), 26.1 (***C-6***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2857, 1725, 1657, 1471, 1391, 1360, 1315, 1257, 1191, 1105, 1008, 976, 939, 837, 777, 721, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{13}H_{25}O_3BrSiNa$ 359.0654; found 359.0659.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Iodobut-2-enoate (1.25e): To a stirred mixture of imidazole (296 mg, 4.30 mmol, 5.0 equiv) and PPh_3 (460 mg, 1.74 mmol, 2.0 equiv) in freshly distilled CH_2Cl_2 (9.0 mL) was added I_2 (335 mg, 1.31 mmol, 1.5 equiv) at room temperature. It was stirred for 20 minutes under an atmosphere of N_2. Then the resulting yellowish solution was ready to use.

To another stirred solution of **1.25g** (238 mg, 0.867 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (9.0 mL, 0.1 M) was added the abovementioned solution dropwise via cannula at room temperature under an atmosphere of N_2. After 1 hour, the reaction was diluted with a solution of 15 vol% of Et_2O in hexanes (50 mL). The precipitate was filtered by a pack of Celite®. The solution was concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 1-6 vol% of ethyl acetate in hexanes to provide the titled compound (204 mg, 0.524 mmol, 61% yield) as a yellow oil.

TLC: R_f = 0.61 (EtOA/Hex = 3:7, v/v);

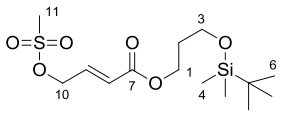
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.04 (dt, *J* = 15.2, 8.3 Hz, 1H, ***H-9***), 5.93 (dt, *J* = 15.3, 1.2 Hz, 1H, ***H-8***), 4.24 (t, *J* = 6.6 Hz, 2H, ***H-1***), 3.93 (dd, *J* = 8.3, 1.0 Hz, 2H, ***H-10***), 3.70 (t,

J = 6.1 Hz, 2H, ***H-3***), 1.87 (p, *J* = 6.2 Hz, 2H, ***H-2***), 0.89 (s, 9H, ***H-6***), 0.048 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 165.7 (***C-7***), 143.7 (***C-9***), 123.4 (***C-8***), 61.9 (***C-1***), 59.6 (***C-3***), 32.0 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), 0.9 (***C-10***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2955, 2929, 2857, 1721, 1648, 1471, 1391, 1360, 1313, 1257, 1194, 1151, 1104, 1008, 973, 837, 777, 718, 663 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{13}H_{25}O_3ISiNa$ 407.0515; found 407.0522.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Methylsulfonyloxybut-2-enoate (1.25f): To a stirred solution of **1.25g** (269 mg, 0.979 mmol, 1.0 equiv) in anhydrous Et_2O (20 mL, 0.05 M) and CH_3CN (10 mL, 0.1 M) was added $AgNO_3$ (333 mg, 1.96 mmol, 2.0 equiv) in one portion at room temperature. Until the salt was completely dissolved, DIPEA (680 uL, 3.90 mmol, 4.0 equiv) was added, followed by addition of MsCl (155 uL, 1.98 mmol, 2.0 equiv) dropwise at 0 ^{o}C. This reaction was allowed to warm to room temperature and stirred for 1 hour under an atmosphere of N_2. Then, it was filtered through a pad of Celite®. The solution was poured into a saturated solution of $NaHCO_3$ (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (40 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 15-25 vol% of ethyl acetate in hexanes to provide the titled compound (324 mg, 0.920 mmol, 94% yield) as a yellowish oil.

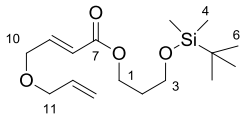
TLC: R_f = 0.58 (EtOA/CH_2Cl_2 = 1:9, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 6.92 (dt, *J* = 15.7, 4.9 Hz, 1H, ***H-9***), 6.15 (dt, *J* = 15.7, 2.0 Hz, 1H, ***H-8***), 4.87 (dd, *J* = 4.7, 1.7 Hz, 2H, ***H-10***), 4.27 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.71 (t, *J* = 5.9 Hz, 2H, ***H-3***), 3.07 (s, 3H, ***H-11***), 1.88 (p, *J* = 6.2 Hz, 2H, ***H-2***), 0.89 (s, 9H, ***H-6***), 0.050 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 165.5 (***C-7***), 138.8 (***C-9***), 124.2 (***C-8***), 67.2 (***C-10***), 62.2 (***C-1***), 59.5 (***C-3***), 38.2 (***C-11***), 31.9 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2858, 1725, 1668, 1471, 1361, 1308, 1256, 1175, 1104, 976, 838, 778, 722, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^{+}] Calcd for $C_{14}H_{28}O_6SSiNa$ 375.1274; found 375.1282.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Allyloxybut-2-enoate (1.25h): With an ice-water bath, to a stirred mixture of **1.25g** (218 mg, 0.794 mmol, 1.0 equiv) and allyl bromide (280 uL, 3.20 mmol, 4.0 equiv) in anhydrous DMF (8.0 mL, 0.1 M) was added NaH (60% dispersion in mineral oil, 42 mg, 1.1 mmol, 1.3 equiv) at 0 ºC. It was stirred under an atmosphere of N_2 for 1 hour, and then poured into a saturated NH_4Cl solution (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 5-10 vol% of ethyl ether in hexanes to provide the titled compound (52.8 mg, 0.168 mmol, 21% yield) as a yellowish oil.

TLC: R_f = 0.58 (EtOA/CH_2Cl_2 = 1:9, v/v);

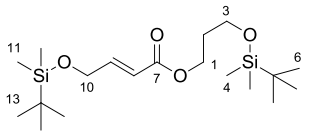
500 MHz ^{1}H NMR ($CDCl_3$) δ 6.95 (dt, *J* = 15.8, 4.2 Hz, 1H, ***H-9***), 6.08 (dt, *J* = 15.7, 2.0 Hz, 1H, ***H-8***), 5.96 ~ 5.86 (m, 1H, ***H-12***), 5.27 (br. d, *J* =17.1 Hz, 1H, ***H-13a***), 5.21 (br. d,

J = 10.6 Hz, 1H, ***H-13b***), 4.24 (t, *J* = 6.4 Hz, 2H, ***H-1***), 4.14 (dd, *J* = 3.9, 2.0 Hz, 2H, ***H-10***), 4.02 (ddd, *J* = 5.4, 2.4, 1.5 Hz, 2H, ***H-11***), 3.71 (t, *J* = 6.1 Hz, 2H, ***H-3***), 1.86 (p, *J* = 6.2 Hz, 2H, ***H-2***), 0.89 (s, 9H, ***H-6***), 0.044 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.5 (***C-7***), 144.5 (***C-9***), 134.4 (***C-12***), 121.5 (***C-8***), 117.5 (***C-13***), 71.9 (***C-11***), 68.8 (***C-10***), 61.6 (***C-1***), 59.7 (***C-3***), 32.0 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2857, 1724, 1664, 1471, 1390, 1360, 1301, 1258, 1172, 1106, 926, 837, 777, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{16}H_{30}O_4SiNa$ 337.1811; found 337.1817.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-(*tert*-Butyldimethylsilyloxy)but-2-enoate (1.25i): To a stirred solution of **1.25g** (279 mg, 1.02 mmol, 1.0 equiv) in DMF (10 mL, 0.1 M) was added imidazole (233 mg, 3.38 mmol, 3.0 equiv) and TBSCl (238 mg, 1.53 mmol, 1.5 equiv) at room temperature, subsequently. This reaction was stirred under an atmosphere of N_2 for 24 hours. Then, it was diluted with Et_2O (10 mL), and the reaction was poured into a saturated solution of $NaHCO_3$ (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (40 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a colorless oil. The crude product was purified by flash chromatography on silica gel eluting with 2-8 vol% of ethyl acetate in hexanes to provide the titled compound (381 mg, 0.981 mmol, 97% yield) as a colorless oil.

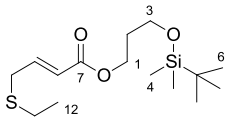
TLC: R_f = 0.61 (EtOA/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 6.98 (dt, *J* = 15.6, 3.4 Hz, 1H, ***H-9***), 6.09 (dt, *J* = 15.6, 2.3 Hz, 1H, ***H-8***), 4.33 (dd, *J* = 3.4, 2.0 Hz, 2H, ***H-10***), 4.24 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.71 (t, *J* = 6.1 Hz, 2H, ***H-3***), 1.87 (p, *J* = 6.2 Hz, 2H, ***H-2***), 0.92 (s, 9H, ***H-13***), 0.89 (s, 9H, ***H-6***), 0.082 (s, 6H, ***H-11***, ***H-11'***), 0.046 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.8 (***C-7***), 147.5 (***C-9***), 119.9 (***C-8***), 62.4 (***C-10***), 61.5 (***C-1***), 59.7 (***C-3***), 32.1 (***C-2***), 26.1 (***C-13***), 26.1 (***C-6***), 18.6 (***C-12***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***, ***C-11***, ***C-11'***);

FTIR (neat): ν_{max} 2956, 2930, 2858, 1725, 1663, 1471, 1390, 1362, 1295, 1256, 1165, 1137, 1021, 965, 837, 777, 722, 664 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^{+}] Calcd for $C_{19}H_{40}O_4Si_2Na$ 411.2363; found 411.2364.



(*E*)-3-((*tert*-Butyldimethylsilyl)oxy)propyl 4-(Ethylthio)but-2-enoate (1.25j): To a stirred solution of **1.25d** (237 mg, 0.702 mmol, 1.0 equiv) in anhydrous acetone (14 mL, 0.05 M) was added ethanethiol (160 uL, 2.10 mmol, 3.0 equiv) and anhydrous K_2CO_3 (196 mg, 1.41 mmol, 2.0 equiv). It was stirred under an atmosphere of N_2 for 3 days and filtrated before being concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 0-10 vol% of ethyl ether in hexanes to provide the titled compound (211 mg, 0.661 mmol, 94% yield) as a colorless oil.

TLC: R_f = 0.58 (EtOA/Hex = 3:7, v/v);

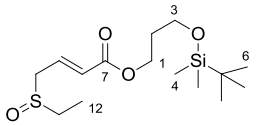
500 MHz ^{1}H NMR ($CDCl_3$) δ 6.88 (dt, *J* = 15.2, 7.4 Hz, 1H, ***H-9***), 5.86 (dt, *J* = 15.2, 1.3 Hz, 1H, ***H-8***), 4.24 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.72 (t, *J* = 5.9 Hz, 2H, ***H-3***), 3.24 (dd, *J* = 7.3, 1.5 Hz, 2H, ***H-10***), 2.48 (q, *J* = 7.3 Hz, 2H, ***H-11***), 1.88 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.24

(t, *J* = 7.3 Hz, 3H, ***H-12***), 0.90 (s, 9H, ***H-6***), 0.052 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.3 (***C-7***), 144.0 (***C-9***), 122.8 (***C-8***), 61.7 (***C-1***), 59.6 (***C-3***), 32.5 (***C-10***), 32.0 (***C-2***), 26.1 (***C-6***), 25.2 (***C-11***), 18.5 (***C-5***), 14.6 (***C-12***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2958, 2930, 2858, 1725, 1662, 1471, 1391, 1360, 1170, 1105, 1016, 978, 838, 777 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{15}H_{30}O_3SSiNa$ 341.1583; found 341.1591.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-(Ethylsulfinyl)but-2-enoate (1.25k): To a stirred mixture of **1.25j** (40 mg, 0.12 mmol, 1.0 equiv) in anhydrous MeOH (6.0 mL, 0.02 M) and D.I. H_2O (4.0 mL, 0.03 M) was added $NaIO_4$ (27 mg, 0.13 mmol, 1.1 equiv) in one portion at 0 ^oC. This reaction was stirred at this temperature for 10 minutes, and slowly warmed up to room temperature over a period of time of 2 hours. Then this reaction was poured into a saturated $NaHCO_3$ solution (30 mL), and the aqueous layer was extracted by EtOAc (4 x 10 mL). The combined organic layers were washed with brine (30 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 15-30 vol% of ethyl acetone in hexanes to provide the titled compound (41 mg, 0.12 mmol, 96% yield) as a colorless oil.

TLC: R_f = 0.17 (Aetone/Hex = 3:7, v/v);

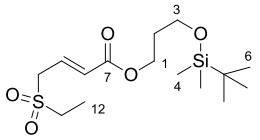
500 MHz ^{1}H NMR ($CDCl_3$) δ 6.93 (dt, *J* = 15.7, 7.8 Hz, 1H, ***H-9***), 6.10 (dt, *J* = 15.7, 1.2 Hz, 1H, ***H-8***), 4.26 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***), 3.60 (ddd, *J* = 13.2, 7.8, 1.5 Hz, 1H, ***H-10a***), 3.53 (ddd, *J* = 12.9, 7.8, 1.5 Hz, 1H, ***H-10b***), 2.77 (dq, *J* =

13.2, 7.5 Hz, 1H, ***H-11a***), 2.74 (dq, *J* = 13.2, 7.5 Hz, 1H, ***H-11b***), 1.87 (pent, *J* = 6.1 Hz, 2H, ***H-2***), 1.35 (t, *J* = 7.6 Hz, 3H, ***H-12***), 0.89 (s, 9H, ***H-6***), 0.043 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 165.3 (***C-7***), 134.9 (***C-9***), 128.6 (***C-8***), 62.1 (***C-1***), 59.5 (***C-3***), 53.6 (***C-10***), 45.2 (***C-11***), 31.9 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), 6.9 (***C-12***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2928, 2858, 1721, 1653, 1461, 1320, 1260, 1197, 1055, 838, 778 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{15}H_{30}O_4SSiNa$ 357.1532; found 357.1538.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-(Ethylsulfonyl)but-2-enoate (1.25l): To a stirred solution of **1.25j** (84 mg, 0.26 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (13 mL, 0.02 M) was added mCPBA (116 mg, 0.672 mmol, 2.5 equiv) in one portion at room temperature. This reaction was stirred overnight and poured into a saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL), and the combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with 15-30 vol% of acetone in hexanes to provide the titled compound (81.2 mg, 0.232 mmol, 81% yield) as a colorless oil.

TLC: R_f = 0.29 (Aetone/Hex = 3:7, v/v);

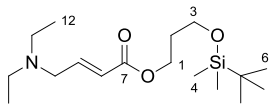
500 MHz ^{1}H NMR ($CDCl_3$) δ 6.91 (dt, *J* = 15.6, 7.8 Hz, 1H, ***H-9***), 5.98 (dt, *J* = 15.7, 1.3 Hz, 1H, ***H-8***), 4.26 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.83 (dd, *J* = 7.8, 1.2 Hz, 2H, ***H-10***), 3.69 (t, *J* = 6.0 Hz, 2H, ***H-3***), 3.00 (q, *J* = 7.5 Hz, 2H, ***H-11***), 1.86 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.39

(t, J = 7.5 Hz, 3H, ***H-12***), 0.87 (s, 9H, ***H-6***), 0.024 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 164.9 (***C-7***), 133.2 (***C-9***), 129.6 (***C-8***), 62.3 (***C-1***), 59.5 (***C-3***), 55.3 (***C-10***), 47.0 (***C-11***), 31.8 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), 6.7 (***C-12***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2930, 2858, 1724, 1657, 1463, 1391, 1361, 1321, 1280, 1200, 1117, 983, 939, 838, 778, 700, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{15}H_{30}O_5SSiNa$ 373.1481; found 373.1485.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-(Diethylamino)but-2-enoate (1.25m): To a stirred solution of **1.25d** (154 mg, 0.456 mmol, 1.0 equiv) in freshly distilled THF (20 mL, 0.02 M) was added diethylamine (2.0 mL, 19 mmol, 40 equiv) and K_2CO_3 (126 mg, 0.903 mmol, 2.0 equiv) at room temperature. It was stirred under an atmosphere of N_2 for 2 days and filtrated before being concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 20-40 vol% of EtOAc in hexanes to provide the titled compound (145 mg, 0.441 mmol, 97% yield) as a colorless oil.

TLC: R_f = 0.17 (EtOAc/Hex = 3:7, v/v);

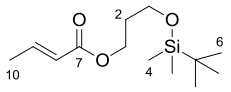
500 MHz ^{1}H NMR ($CDCl_3$) δ 6.98 (dt, J = 15.8, 6.1 Hz, 1H, ***H-9***), 5.98 (dt, J = 15.7, 1.7 Hz, 1H, ***H-8***), 4.23 (t, J = 6.4 Hz, 2H, ***H-1***), 3.71 (t, J = 6.1 Hz, 2H, ***H-3***), 3.24 (dd, J = 6.1, 1.7 Hz, 2H, ***H-10***), 2.54 (q, J = 7.2 Hz, 4H, ***H-11***, ***H-11'***), 1.87 (pent, J = 6.2 Hz, 2H, ***H-2***), 1.04 (t, J = 7.3 Hz, 6H, ***H-12***, ***H-12'***), 0.89 (s, 9H, ***H-6***), 0.046 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.5 (***C-7***), 146.6 (***C-9***), 123.0 (***C-8***), 61.5 (***C-1***), 59.7 (***C-3***), 54.3 (***C-10***), 47.4 (***C-11***, ***C-11'***), 32.0 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), 12.1 (***C-12***, ***C-12'***),

-5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2959, 2931, 2858, 2804, 1724, 1658, 1471, 1387, 1360, 1258, 1162, 1104, 837, 777, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{17}H_{35}NO_3SiNa$ 352.2284; found 352.2287.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl But-2-enoate (1.25n): To a stirred mixture of crotonic acid (80.1 mg, 0.912 mmol, 1.0 equiv), **1.37** (173 mg, 0.908 mmol, 1.0 equiv), and DMAP (113 mg, 0.913 mmol, 1.0 equiv) in toluene (10 mL, 0.1 M) was added freshly distilled NEt_3 (640 uL, 4.59 mmol, 5.0 equiv). This reaction was then cooled down to 0 ^oC, and 2,4,6-trichlorobenzoylchloride (160 uL, 1.00 mmol, 1.1 equiv) was then added in dropwise via syringe. The reaction turned cloudy and precipitated immediately. It was stirred under an atmosphere of N_2, and allowed to warm to room temperature slowly, and stirred for 3 hours. Then, the resulting yellow solution was concentrated and purified by flash chromatography on silica gel eluting with 2-6 vol% of ethyl acetate in hexane to provide the titled compound (202 mg, 0.781 mmol, 86% yield) as a colorless oil.

TLC: R_f = 0.68 (EtOAc/Hex = 3:7, v/v);

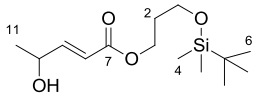
500 MHz ^1H NMR ($CDCl_3$) δ 6.97 (dq, *J* = 15.7, 6.8 Hz, 1H, ***H-9***), 5.84 (dq, *J* = 15.7, 1.8 Hz, 1H, ***H-8***), 4.22 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.71 (t, *J* = 6.1 Hz, 2H, ***H-3***), 1.88 (dd, *J* = 6.8, 2.0 Hz, 3H, ***H-10***), 1.86 (p, *J* = 6.3 Hz, 2H, ***H-2***), 0.89 (s, 9H, ***H-6***), 0.050 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.8 (***C-7***), 144.6 (***C-9***), 123.0 (***C-8***), 61.4 (***C-1***), 59.7 (***C-3***), 32.1 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), 18.1 (***C-10***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2930, 2858, 1724, 1661, 1472, 1445, 1390, 1361, 1311, 1258, 1183,

1102, 1024, 971, 940, 838, 777, 720, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{13}H_{26}O_3SiNa$ 281.1549; found 281.1551.



(*E*)-3-((*tert*-butyldimethylsilyl)oxy)propyl 4-hydroxypent-2-enoate (1.29f): With a -78 °C bath, to a solution of **1.39** (3.33 g, 12.2 mmol, 1.0 equiv) in freshly distilled THF (30 mL, 0.4 M) was added MeMgBr (3.0 M in Et_2O, 4.9 mL, 15 mmol, 1.2 equiv) via syringe pump at the rate of 7 mL/h under an atmosphere of N_2. The reaction mixture was stirred for further 1 hour after addition. Then, it was quenched at this temperature with a saturated NH_4Cl solution (30 mL), and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 10-20 vol% of EtOAc in hexanes to provide the titled compound (2.35 g, 8.14 mmol, 67% yield) as a pale yellow oil.

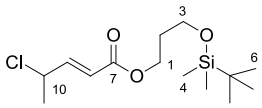
TLC: R_f = 0.26 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 6.96 (dd, *J* = 15.7, 4.4 Hz, 1H, ***H-9***), 6.03 (dd, *J* = 15.7, 1.5 Hz, 1H, ***H-8***), 4.56 ~ 4.44 (m, 1H, ***H-10***), 4.25 (t, *J* = 6.5 Hz, 2H, ***H-1***), 3.72 (t, *J* = 6.1 Hz, 2H, ***H-3***), 1.88 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.74 (br. s, 1H, ***-OH***), 1.35 (d, *J* = 6.4 Hz, 3H, ***H-11***), 0.90 (s, 9H, ***H-6***), 0.053 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.8 (***C-7***), 151.1 (***C-9***), 119.8 (***C-8***), 67.4 (***C-10***), 61.7 (***C-1***), 59.6 (***C-3***), 32.0 (***C-2***), 26.1 (***C-6***), 23.0 (***C-11***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 3438 (br), 2957, 2930, 2858, 1723, 1658, 1471, 1391, 1361, 1257, 1175, 1104, 1008, 979, 940, 837, 777, 719, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{14}H_{28}O_4SiNa$ 311.1655; found 311.1653.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Chloropent-2-enoate (1.29a): To a stirred solution of **1.29f** (130 mg, 0.450 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (9.0 mL, 0.05 M) was added PPh_3 (179 mg, 0.674 mmol, 1.5 equiv). Then a solution of NCS (92 mg, 0.67 mmol, 1.5 equiv) in CH_2Cl_2 (2.5 mL, 0.3 M) was added via cannula at -30 °C. This reaction was stirred at for 2 hours at 0 °C under an atmosphere of N_2. Then, it was poured into a mixture of saturated $NaHCO_3$ solution (15 mL) and saturated $Na_2S_2O_3$ solution (15 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 2-10 vol% of Et_2O in hexanes to provide the titled compound (63.4 mg, 0.203 mmol, 45% yield) as a colorless oil.

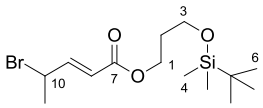
TLC: R_f = 0.69 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 6.94 (dd, *J* = 15.5, 7.1 Hz, 1H, ***H-9***), 6.01 (dd, *J* = 15.7, 1.5 Hz, 1H, ***H-8***), 4.62 (dqd, *J* = 7.1, 6.9, 1.5 Hz, 1H, ***H-10***), 4.26 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.72 (t, *J* = 6.1 Hz, 2H, ***H-3***), 1.88 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.65 (d, *J* = 6.9 Hz, 3H, ***H-11***), 0.90 (s, 9H, ***H-6***), 0.055 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.1 (***C-7***), 147.3 (***C-9***), 121.8 (***C-8***), 62.0 (***C-1***), 59.6 (***C-3***), 55.0 (***C-10***), 31.9 (***C-2***), 26.1 (***C-6***), 24.5 (***C-11***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2930, 2858, 1725, 1661, 1471, 1390, 1360, 1341, 1272, 1178, 1106, 1017, 975, 838, 777, 727, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{14}H_{27}ClO_3SiNa$ 329.1316; found 329.1326.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Bromopent-2-enoate (1.29b): To a stirred solution of **1.29f** (137 mg, 0.475 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (9.0 mL, 0.05 M) was added CBr_4 (239 mg, 0.714 mmol, 1.5 equiv) and imidazole (48 mg, 0.70 mmol, 1.5 equiv). Then, a solution of PPh_3 (176 mg, 0.664 mmol, 1.4 equiv) in CH_2Cl_2 (3.5 mL, 0.2 M) was added dropwise via addition funnel over a period of time of 5 minutes at 0 ^oC under an atmosphere of N_2. After addition, this reaction was stirred for 1 hour and poured into a saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL), and the combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 0-10 vol% of ethyl ether in hexanes to provide the titled compound (133 mg, 0.378 mmol, 80% yield) as a colorless oil.

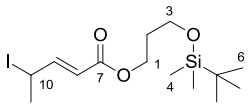
TLC: R_f = 0.65 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.01 (dd, *J* = 15.7, 8.3 Hz, 1H, ***H-9***), 5.93 (dd, *J* = 15.5, 1.0 Hz, 1H, ***H-8***), 4.69 (dqd, *J* = 8.3, 6.6, 1.0 Hz, 1H, ***H-10***), 4.25 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***), 1.87 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.82 (d, *J* = 6.4 Hz, 3H, ***H-11***), 0.88 (s, 9H, ***H-6***), 0.042 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.0 (***C-7***), 147.7 (***C-9***), 121.2 (***C-8***), 62.0 (***C-1***), 59.6 (***C-3***), 45.0 (***C-10***), 31.9 (***C-2***), 26.1 (***C-6***), 24.9 (***C-11***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2858, 1723, 1655, 1471, 1390, 1360, 1341, 1266, 1203, 1170, 1104, 1010, 975, 939, 837, 777, 722, 663 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{14}H_{27}BrO_3SiNa$ 373.0811; found 373.0815.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Iodopent-2-enoate (1.29c): To a stirred mixture of imidazole (152 mg, 2.22 mmol, 5.0 equiv) and PPh_3 (235 mg, 0.886 mmol, 2.0 equiv) in freshly distilled CH_2Cl_2 (9.0 mL) was added I_2 (170 mg, 0.662 mmol, 1.5 equiv) at room temperature. It was stirred for 20 minutes under an atmosphere of N_2. Then the resulting yellowish solution was ready to use.

To other stirred solution of **1.29f** (128 mg, 0.442 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (4.5 mL, 0.1 M) was added the abovementioned solution dropwise via cannula at room temperature under an atmosphere of N_2. After 1 hour, the reaction was diluted with a solution of 15 vol% of Et_2O in hexanes (50 mL). The precipitate was filtered by a pack of Celite®. The solution was concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 1-6 vol% of EtOAc in hexanes to provide the titled compound (85 mg, 0.21 mmol, 48% yield) as a colorless oil.

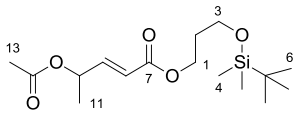
TLC: R_f = 0.65 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.15 (dt, *J* = 15.4, 8.6 Hz, 1H, ***H-9***), 5.84 (dt, *J* = 15.4, 1.2 Hz, 1H, ***H-8***), 4.90 (dqd, *J* = 8.6, 6.8, 1.2 Hz, 1H, ***H-10***), 4.24 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.71 (t, *J* = 6.1 Hz, 2H, ***H-3***), 2.00 (d, *J* = 6.8 Hz, 3H, ***H-11***), 1.87 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 0.89 (s, 9H, ***H-6***), 0.050 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.1 (***C-7***), 150.2 (***C-9***), 119.0 (***C-8***), 62.0 (***C-1***), 59.6 (***C-3***), 31.9 (***C-2***), 26.6 (***C-11***), 26.1 (***C-6***), 21.1 (***C-10***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2857, 1720, 1645, 1471, 1390, 1360, 1340, 1260, 1191, 1106, 1007, 976, 939, 837, 777, 721, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{14}H_{27}IO_3SiNa$ 421.0672; found 421.0681.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Acetoxypent-2-enoate (1.29d): To a solution of **1.29f** (109 mg, 0.378 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL, 0.04 M) was added DMAP (46 mg, 0.38 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (660 uL, 3.79 mmol, 10 equiv) and acetic anhydride (110 uL, 1.15 mmol, 3.0 equiv) subsequently, at room temperature. It was stirred for 18 hours, and then quenched with a saturated $NaHCO_3$ solution (20 mL). The aqueous solution was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 3-9 vol% of EtOAc in hexanes to provide the titled compound (100 mg, 0.304 mmol, 81% yield) as a colorless oil.

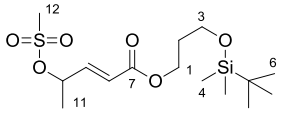
TLC: R_f = 0.55 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 6.86 (dd, *J* = 15.8, 5.1 Hz, 1H, ***H-9***), 5.95 (dd, *J* = 15.7, 2.0 Hz, 1H, ***H-8***), 5.48 (qdd, *J* = 6.8, 4.9, 1.8 Hz, 1H, ***H-10***), 4.24 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.70 (t, *J* = 5.9 Hz, 2H, ***H-3***), 2.08 (s, 3H, ***H-13***), 1.86 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.36 (d, *J* = 6.9 Hz, 3H, ***H-11***), 0.88 (s, 9H, ***H-6***), 0.041 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 170.2 (***C-12***), 166.3 (***C-7***), 146.5 (***C-9***), 121.1 (***C-8***), 69.0 (***C-10***), 61.9 (***C-1***), 59.6 (***C-3***), 31.9 (***C-2***), 26.1 (***C-6***), 21.3 (***C-13***), 19.8 (***C-11***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2931, 2858, 1746, 1725, 1664, 1472, 1373, 1305, 1236, 1176, 1103, 1048, 977, 837, 777, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{16}H_{30}O_5SiNa$ 353.1760; found 353.1756.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Methylsulfonyloxypent-2-enoate (1.29e): To a stirred solution of **1.29f** (106 mg, 0.366 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (7.0 mL, 0.05 M) was added DIPEA (260 uL, 1.49 mmol, 4.0 equiv), followed by addition of MsCl (56 uL, 0.72 mmol, 2.0 equiv) dropwise at 0 ºC. This reaction was stirred for 1 hour under an atmosphere of N_2. Then, it was poured into a saturated solution of $NaHCO_3$ (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 10-20 vol% of ethyl acetate in hexanes to provide the titled compound (72 mg, 0.20 mmol, 53% yield) as a yellowish oil.

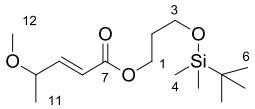
TLC: R_f = 0.58 (EtOAc/CH_2Cl_2 = 1:9, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 6.88 (dd, *J* = 15.7, 5.4 Hz, 1H, ***H-9***), 6.09 (dd, *J* = 15.7, 1.5 Hz, 1H, ***H-8***), 4.87 (qdd, *J* = 6.8, 5.4, 1.5 Hz, 1H, ***H-10***), 4.27 (t, *J* = 6.6 Hz, 2H, ***H-1***), 3.71 (t, *J* = 6.1 Hz, 2H, ***H-3***), 3.03 (s, 3H, ***H-12***), 1.88 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.55 (d, *J* = 6.9 Hz, 3H, ***H-11***), 0.89 (s, 9H, ***H-6***), 0.051 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 165.7 (***C-7***), 144.2 (***C-9***), 123.0 (***C-8***), 76.6 (***C-10***), 62.2 (***C-1***), 59.5 (***C-3***), 39.2 (***C-12***), 31.9 (***C-2***), 26.1 (***C-6***), 21.4 (***C-11***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2932, 2858, 1724, 1665, 1471, 1362, 1306, 1259, 1178, 1102, 1035, 975, 896, 838, 814, 778 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{15}H_{30}O_6SSiNa$ 389.1430; found 389.1433.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Methoxybut-2-enoate (1.29g): To a stirred solution of **1.29f** (169 mg, 0.585 mmol, 1.0 equiv) in DMF (12 mL, 0.05 M) was added NaH (60% dispersion in mineral oil, 48 mg, 1.2 mmol, 2.0 equiv) at 0 ^oC. This reaction was stirred for 10 minutes under an atmosphere of N_2, and treated with MeI (150 uL, 2.39 mmol, 4.0 equiv). After 1.5 hours, it was quenched with a saturated solution of NH_4Cl (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 1-6 vol% of ethyl acetate in hexanes to provide the titled compound (78 mg, 0.26 mmol, 44% yield) as a colorless oil.

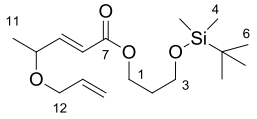
TLC: R_f = 0.56 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 6.81 (dd, *J* = 15.9, 6.1 Hz, 1H, ***H-9***), 5.97 (dd, *J* = 15.9, 1.2 Hz, 1H, ***H-8***), 4.24 (t, *J* = 6.6 Hz, 2H, ***H-1***), 3.90 (qdd, *J* = 6.4, 6.4, 1.2 Hz, 1H, ***H-10***), 3.71 (t, *J* = 5.9 Hz, 2H, ***H-3***), 3.30 (s, 3H, ***H-12***), 1.87 (p, *J* = 6.1 Hz, 2H, ***H-2***), 1.27 (d, *J* = 6.4 Hz, 3H, ***H-11***), 0.88 (s, 9H, ***H-6***), 0.038 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.5 (***C-7***), 149.2 (***C-9***), 121.4 (***C-8***), 76.4 (***C-10***), 61.7 (***C-1***), 59.6 (***C-3***), 56.9 (***C-12***), 31.9 (***C-2***), 26.1 (***C-6***), 20.6 (***C-11***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2931, 2858, 1724, 1660, 1471, 1360, 1298, 1258, 1174, 1112, 1008, 981, 838, 777 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{15}H_{30}O_4SiNa$ 325.1811; found 325.1814.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Allyloxypent-2-enoate (1.29h): With an ice-water bath, to a stirred mixture of **1.29f** (123 mg, 0.427 mmol, 1.0 equiv) in anhydrous DMF (9.0 mL, 0.05 M) was added NaH (60% dispersion in mineral oil, 35 mg, 0.89 mmol, 2.0 equiv) at 0 °C. It was stirred for 10 minutes under an atmosphere of N_2. Then, allyl bromide (150 uL, 1.72 mmol, 4.0 equiv) was added into this mixture in one portion. This reaction was stirred for further one hour and diluted with Et_2O (15 mL). This mixture was poured into a saturated NH_4Cl solution (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 0-5 vol% of ethyl acetate in hexanes to provide the titled compound (60 mg, 0.18 mmol, 43% yield) as a colorless oil.

TLC: R_f = 0.66 (EtOAc/Hex = 3:7, v/v);

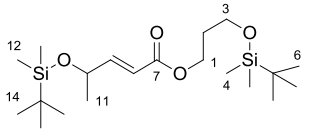
500 MHz ^{1}H NMR ($CDCl_3$) δ 6.84 (dd, *J* = 15.9, 6.1 Hz, 1H, ***H-9***), 5.98 (dd, *J* = 15.7, 1.5 Hz, 1H, ***H-8***), 5.90 (dddd, *J* = 17.1, 10.8, 5.9, 5.4 Hz, 1H, ***H-13***), 5.27 (dq, *J* =17.4, 1.5 Hz, 1H, ***H-14a***), 5.18 (dq, *J* = 10.8, 1.5 Hz, 1H, ***H-14b***), 4.24 (t, *J* = 6.4 Hz, 2H, ***H-1***), 4.07 (qdd, *J* = 6.7, 6.4, 1.5 Hz, 1H, ***H-10***), 4.01 (ddt, *J* = 12.7, 5.4, 1.5 Hz, 1H, ***H-12a***), 3.91 (ddt, *J* = 12.7, 5.9, 1.5 Hz, 1H, ***H-12a***), 3.71 (t, *J* = 6.1 Hz, 2H, ***H-3***), 1.87 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.29 (d, *J* = 6.8 Hz, 3H, ***H-11***), 0.89 (s, 9H, ***H-6***), 0.044 (s, **6H, *H-4, H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.5 (***C-7***), 149.5 (***C-9***), 134.8 (***C-13***), 121.3 (***C-8***), 117.2 (***C-14***), 74.1 (***C-10***), 70.0 (***C-12***), 61.7 (***C-1***), 59.6 (***C-3***), 31.9 (***C-2***), 26.1 (***C-6***), 20.8 (***C-***

11), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2930, 2858, 1723, 1659, 1471, 1361, 1297, 1258, 1175, 1105, 982, 924, 837, 777, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{17}H_{32}O_4SiNa$ 351.1968; found 351.1965.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-(*tert*-Butyldimethylsilyloxy)pent-2-enoate (1.29i): To a stirred solution of **1.29f** (94 mg, 0.33 mmol, 1.0 equiv) in DMF (6.5 mL, 0.05 M) was added imidazole (67 mg, 0.97 mmol, 3.0 equiv) and TBSCl (73 mg, 0.47 mmol, 1.5 equiv) at room temperature, subsequently. This reaction was stirred under an atmosphere of N_2 for 18 hours. Then, it was diluted with Et_2O (10 mL), and the reaction was poured into a saturated solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a colorless oil. The crude product was purified by flash chromatography on silica gel eluting with 2-8 vol% of ethyl acetate in hexanes to provide the titled compound (96 mg, 0.24 mmol, 73% yield) as a colorless oil.

TLC: R_f = 0.68 (EtOAc/Hex = 3:7, v/v);

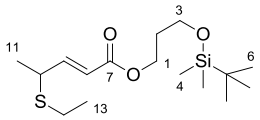
500 MHz ^{1}H NMR ($CDCl_3$) δ 6.92 (dd, *J* = 15.2, 3.9 Hz, 1H, ***H-9***), 6.09 (dd, *J* = 15.3, 1.7 Hz, 1H, ***H-8***), 4.46 (qdd, *J* = 6.4, 3.9, 1.7 Hz, 1H, ***H-10***), 4.25 (dt, *J* = 10.8, 6.4 Hz, 1H, ***H-1a***), 4.22 (dt, *J* = 10.8, 6.4 Hz, 1H, ***H-1b***), 3.72 (t, *J* = 6.1 Hz, 2H, ***H-3***), 1.88 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.26 (d, *J* = 6.8 Hz, 3H, ***H-11***), 0.91 (s, 9H, ***H-14***), 0.89 (s, 9H, ***H-6***), 0.082 (s, 6H, ***H-11***), 0.072 (s, 3H, ***H-12***); 0.064 (s, 3H, ***H-12'***); 0.048 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 167.1 (***C-7***), 152.2 (***C-9***), 119.1 (***C-8***), 67.9 (***C-10***), 61.5 (***C-***

1), 59.7 (***C-3***), 32.0 (***C-2***), 26.1 (***C-14***), 26.0 (***C-6***), 23.7 (***C-11***), 18.5 (***C-13***), 18.4 (***C-5***), -4.7 (***C-12***), -4.7 (***C-12'***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2930, 2858, 1725, 1661, 1472, 1390, 1361, 1294, 1257, 1164, 1099, 1007, 979, 837, 777, 717, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{20}H_{42}O_4Si_2Na$ 425.2519; found 425.2524.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-(Ethylthio)pent-2-enoate (1.29j): To a stirred solution of **1.29b** (106 mg, 0.301 mmol, 1.0 equiv) in anhydrous acetone (15 mL, 0.02 M) was added ethanethiol (70 uL, 0.92 mmol, 3.0 equiv) and anhydrous K_2CO_3 (85 mg, 0.61 mmol, 2.0 equiv). It was stirred under an atmosphere of N_2 for 3 days and filtrated before being concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 0-10 vol% of ethyl ether in hexanes to provide the titled compound (100 mg, 0.301 mmol, 100% yield) as a colorless oil.

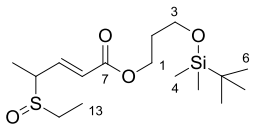
TLC: R_f = 0.58 (EtOA/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 6.75 (dd, *J* = 15.3, 9.1 Hz, 1H, ***H-9***), 5.74 (dd, *J* = 15.5, 0.9 Hz, 1H, ***H-8***), 4.24 (t, *J* = 6.4 Hz, 1H, ***H-1a***), 4.23 (t, *J* = 6.4 Hz, 1H, ***H-1b***), 3.71 (t, *J* = 6.0 Hz, 2H, ***H-3***), 3.43 (dqd, *J* = 9.2, 6.9, 0.8 Hz, 1H, ***H-10***), 2.43 (q, *J* = 7.4 Hz, 2H, ***H-12***), 1.87 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.36 (d, *J* = 6.8 Hz, 3H, ***H-11***), 1.22 (t, *J* = 7.4 Hz, 3H, ***H-13***), 0.89 (s, 9H, ***H-6***), 0.043 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.5 (***C-7***), 149.4 (***C-9***), 120.0 (***C-8***), 61.7 (***C-1***), 59.6 (***C-3***), 40.7 (***C-10***), 31.9 (***C-2***), 26.1 (***C-6***), 24.9 (***C-12***), 19.7 (***C-11***), 18.5 (***C-5***), 14.7 (***C-13***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2958, 2930, 2858, 1721, 1649, 1471, 1390, 1360, 1335, 1260, 1212, 1170, 1105, 1016, 978, 838, 777 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{16}H_{32}O_3SSiNa$ 355.1739; found 355.1747.



(*E*)-3-((*tert*-Butyldimethylsilyl)oxy)propyl 4-(Ethylsulfinyl)pent-2-enoate (1.29k): To a stirred mixture of **1.29j** (49 mg, 0.15 mmol, 1.0 equiv) in anhydrous MeOH (7.5 mL, 0.02 M) and D.I. H_2O (5 mL, 0.03 M) was added $NaIO_4$ (32 mg, 0.15 mmol, 1.0 equiv) in one portion at 0 ºC. This reaction was stirred at this temperature for 10 minutes, and slowly warmed up to room temperature over a period of 2 hours. Then this reaction was poured into a saturated $NaHCO_3$ solution (30 mL), and the aqueous layer was extracted by EtOAc (4 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 15-30 vol% of acetone in hexanes to provide the titled compound (about 1:2 diastereomeric mixture denoted here as compound A and B, 50 mg, 0.14 mmol, 96% yield) as a colorless oil.

TLC: R_f = 0.16 (Aetone/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$):

A: δ 6.91 (dd, *J* = 15.7, 8.6 Hz, 1H, ***H*$_A$-9**), 6.01 (dd, *J* = 15.7, 0.9 Hz, 1H, ***H*$_A$-8**), 4.24 (t, *J* = 6.4 Hz, 2H, ***H*$_A$-1**), 3.69 (t, *J* = 6.0 Hz, 2H, ***H*$_A$-3**), 3.43 (dqd, *J* = 8.6, 6.8, 0.9 Hz, 1H, ***H*$_A$-10**), 2.67 (dq, *J* = 13.2, 7.3 Hz, 1H, ***H*$_A$-12a**), 2.55 (dq, *J* = 13.2, 7.5 Hz, 1H, ***H*$_B$-12b**), 1.86 (pent, *J* = 6.2 Hz, 2H, ***H*$_A$-2**), 1.50 (d, *J* = 6.8 Hz, 3H, ***H*$_A$-11**), 1.32 (t, *J* = 7.6 Hz, 3H, ***H*$_A$-13**), 0.87 (s, 9H, ***H*$_A$-6**), 0.030 (s, 6H, ***H*$_A$-4**, ***H*$_A$-4'**);

B: δ 6.84 (dd, *J* = 15.7, 8.7 Hz, 1H, ***H*$_B$-*9***), 6.03 (dd, *J* = 15.7, 0.9 Hz, 1H, ***H*$_B$-*8***), 4.24 (t, *J* = 6.4 Hz, 2H, ***H*$_B$-*1***), 3.69 (t, *J* = 6.0 Hz, 2H, ***H*$_B$-*3***), 3.51 (dqd, *J* = 8.7, 6.8, 0.9 Hz, 1H, ***H*$_B$-*10***), 2.72 (dq, *J* = 13.2, 7.6 Hz, 1H, ***H*$_B$-*12a***), 2.60 (dq, *J* = 13.2, 7.5 Hz, 1H, ***H*$_B$-*12b***), 1.86 (pent, *J* = 6.2 Hz, 2H, ***H*$_B$-*2***), 1.48 (d, *J* = 6.8 Hz, 3H, ***H*$_B$-*11***), 1.35 (t, *J* = 7.6 Hz, 3H, ***H*$_B$-*13***), 0.87 (s, 9H, ***H*$_A$-*6***), 0.030 (s, 6H, ***H*$_A$-*4***, ***H*$_A$-*4'***);

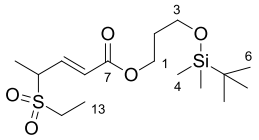
125 MHz ^{13}C NMR ($CDCl_3$):

A: 165.4 (***C*$_A$-*7***), 141.0 (***C*$_A$-*9***), 126.1 (***C*$_A$-*8***), 62.0 (***C*$_A$-*1***), 59.5 (***C*$_A$-*3***), 56.2 (***C*$_A$-*10***), 42.7 (***C*$_B$-*12***), 31.9 (***C*$_A$-*2***), 26.1 (***C*$_A$-*6***), 18.5 (***C*$_A$-*5***), 13.3 (***C*$_A$-*11***), 7.5 (***C*$_A$-*13***), -5.2 (***C*$_A$-*4***, ***C*-*4'***);

B: 165.5 (***C*$_B$-*7***), 141.6 (***C*$_B$-*9***), 125.8 (***C*$_B$-*8***), 62.1 (***C*$_B$-*1***), 59.5 (***C*$_B$-*3***), 58.4 (***C*$_B$-*10***), 42.8 (***C*$_B$-*12***), 31.9 (***C*$_B$-*2***), 26.1 (***C*$_B$-*6***), 18.4 (***C*$_B$-*5***), 13.5 (***C*$_B$-*11***), 7.1 (***C*$_B$-*13***), -5.2 (***C*$_B$-*4***, ***C*-*4'***);

FTIR (neat): ν_{max} 2957, 2930, 2857, 1721, 1650, 1461, 1389, 1360, 1333, 1258, 1178, 1104, 1060, 838, 778, 727, 666 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{16}H_{32}O_4SSiNa$ 371.1688; found 371.1695.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-(Ethylsulfonyl)pent-2-enoate (1.29l): To a stirred solution of **1.29j** (42 mg, 0.13 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (6.5 mL, 0.02 M) was added mCPBA (49 mg, 0.28 mmol, 2.2 equiv) in one portion at -10 °C. After 20 minutes, the cooling bath was removed, and the reaction was stirred at room temperature for 6 hours under an atmosphere of N_2 for 6. Then, it was poured into a saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL) and the combined organic layers were washed with brine (30 mL) and

dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 10-30 vol% of acetone in hexanes to provide the titled compound (45 mg, 0.12 mmol, 96% yield) as a colorless oil.

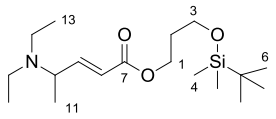
TLC: R_f = 0.16 (Aetone/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$): δ 6.92 (dd, *J* = 15.7, 8.8 Hz, 1H, ***H-9***), 6.10 (dd, *J* = 15.7, 1.0 Hz, 1H, ***H-8***), 4.26 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.81 (dqd, *J* = 9.2, 6.9, 1.0 Hz, 1H, ***H-10***), 3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***), 2.97 (q, *J* = 7.3 Hz, 2H, ***H-12***), 1.87 (pent, *J* = 6.1 Hz, 2H, ***H-2***), 1.57 (d, *J* = 7.3 Hz, 3H, ***H-11***), 1.39 (t, *J* = 7.3 Hz, 3H, ***H-13***), 0.88 (s, 9H, ***H-6***), 0.040 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 165.1 (***C-7***), 140.3 (***C-9***), 127.0 (***C-8***), 62.3 (***C-1***), 59.8 (***C-10***), 59.5 (***C-3***), 44.9 (***C-12***), 31.8 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), 12.4 (***C-11***), 6.2 (***C-13***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2930, 2857, 1723, 1656, 1461, 1390, 1361, 1312, 1183, 1109, 982, 838, 779, 715, 663 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{16}H_{32}O_5SSiNa$ 387.1637; found 387.1642.



(*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-(Ethylthio)pent-2-enoate (1.29m): To a stirred solution of **1.29b** (83 mg, 0.24 mmol, 1.0 equiv) in freshly distilled THF (12 mL, 0.02 M) was added diethylamine (1.3 mL, 12 mmol, 50 equiv) at room temperature. It was stirred under an atmosphere of N_2 for 2 days and filtrated before being concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 20-40 vol% of EtOAc in hexanes to provide the

titled compound (58 mg, 0.17 mmol, 72% yield) as a colorless oil.

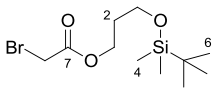
TLC: R_f = 0.16 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 6.96 (dd, *J* = 15.7, 6.8 Hz, 1H, ***H-9***), 5.87 (dd, *J* = 15.7, 1.5 Hz, 1H, ***H-8***), 4.23 (t, *J* = 6.6 Hz, 2H, ***H-1***), 3.71 (t, *J* = 6.1 Hz, 2H, ***H-3***), 3.47 (dqd, *J* = 6.8, 6.7, 1.5 Hz, 1H, ***H-10***), 2.56 (dq, *J* = 13.2, 7.2 Hz, 2H, ***H-12a***, ***H-12a'***), 2.49 (dq, *J* = 13.2, 7.2 Hz, 2H, ***H-12b***, ***H-12b'***), 1.87 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.17 (d, *J* = 6.8 Hz, 3H, ***H-11***), 1.03 (t, *J* = 7.1 Hz, 6H, ***H-13***, ***H-13'***), 0.89 (s, 9H, ***H-6***), 0.047 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.8 (***C-7***), 151.6 (***C-9***), 121.4 (***C-8***), 61.5 (***C-1***), 59.7 (***C-3***), 56.4 (***C-10***), 43.8 (***C-12***, ***C-12'***), 32.0 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), 16.2 (***C-11***), 13.6 (***C-13***, ***C-13'***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2959, 2930, 2858, 1723, 1652, 1471, 1387, 1258, 1170, 1105, 1008, 983, 837, 777 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{18}H_{38}O_3NSi$ 344.2621; found 344.2620.



3-(*tert*-Butyldimethylsilyloxy)propyl 2-Bromoacetate (1.40): To a stirred mixture of bromoacetic acid (7.31 g, 51.5 mmol, 1.2 equiv), **1.37** (7.99 g, 42.0 mmol, 1.0 equiv) and DMAP (2.53 g, 20.5 mmol, 0.5 equiv) in CH_2Cl_2 (100 mL, 0.5 M) was added DCC (10.76 g, 51.65 mmol, 1.2 equiv) in one portion at 0 °C. The clear solution turned cloudy immediately. This reaction was allowed to warm to room temperature slowly, and stirred for 16 hours under an atmosphere of N_2. The resulting milky reaction was filtered through a pad of celite, and the filtrate was washed with brine containing 1 vol% HCl (100 mL). The aqueous layer was extracted CH_2Cl_2 (3 x 30 mL). The combined organic layers were

washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 1-5 vol% of EtOAc in hexanes to provide the titled compound (6.87 g, 22.1 mmol, 53% yield) as a colorless oil.

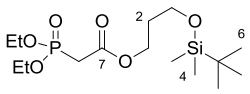
TLC: R_f = 0.64 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 4.29 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.83 (s, 2H, ***H-8***), 3.71 (t, *J* = 6.0 Hz, 2H, ***H-3***), 1.87 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 0.89 (s, 9H, ***H-6***), 0.055 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 167.4 (***C-7***), 63.5 (***C-1***), 59.3 (***C-3***), 31.7 (***C-2***), 26.1 (***C-6***, ***C-8***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2858, 1741, 1471, 1409, 1361, 1281, 1257, 1165, 1106, 1008, 971, 837, 777, 716, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{11}H_{23}O_3BrSiNa$ 333.0498; found 333.0500.



3-(*tert*-Butyldimethylsilyloxy)propyl 2-(Diethoxyphosphoryl)acetate (1.41): To a stirred solution of **1.40** (4.11 g, 13.2 mmol, 1.0 equiv) was added triethyl phosphate (2.8 mL, 16 mmol, 1.2 equiv) in benzene (25 mL, 0.5 M) at room temperature. This reaction was then reluxed for 30 hours under an atmosphere of N_2. It was concentrated in reduced pressure, and the remainder was purified by a flash column on silica gel eluting with 5-20 vol% acetone in hexanes to provide the titled compound (4.78 g, 13.0 mmol, 98% yield) as a colorless oil.

TLC: R_f = 0.35 (Acetone/Hex = 5:5, v/v);

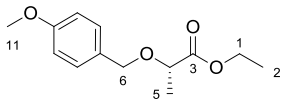
500 MHz ^{1}H NMR ($CDCl_3$) δ 4.22 (t, *J* = 6.4 Hz, 2H, ***H-1***), 4.15 (dq, *J* = 8.2, 7.0 Hz, 4H,

H-9), 3.67 (t, *J* = 6.0 Hz, 2H, ***H-3***), 2.94 (d, *J* = 21.6 Hz, 2H, ***H-8***), 1.83 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.32 (td, *J* = 7.0, 0.5 Hz, 6H, ***H-10***), 0.86 (s, 9H, ***H-6***), 0.021 (s, 6H, ***H-4***, ***H-4'***); 125 MHz ^{13}C NMR ($CDCl_3$) δ 166.0 (d, $J_{c,p}$ = 6.1 Hz, ***C-7***), 62.8 (***C-1***), 62.8 (d, $J_{c,p}$ = 6.1 Hz, ***C-9***), 59.4 (***C-3***), 34.5 (***C-8***), 31.9 (***C-2***), 26.0 (***C-6***), 18.4 (***C-5***), 16.5 (d, $J_{c,p}$ = 6.1 Hz, ***C-10***), -5.3 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2931, 2858, 1740, 1472, 1392, 1273, 1164, 1102, 1027, 971, 838, 778, 663 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{15}H_{33}O_6PSiNa$ 391.1682; found 391.1688.

(*S*)-Ethyl 2-(4-methoxybenzyloxy)propanoate (1.42):



4-Methoxybenzyltrichloroacetimidate (PMBTCA): To a stirred suspension of NaH (60% dispersion in mineral oil, 0.631 g, 15.8 mmol) in Et_2O (80 mL) was added a solution of 4-methoxybenzyl alcohol (10.0 mL, 78.9 mmol) in Et_2O (8 mL) dropwise at 0 ºC. The resulting cloudy orange mixture was stirred for 30 minutes at room temperature then cooled to 0 ºC, and trichloroaetonitrile (8.50 mL, 83.1 mmol) was added dropwise. This reaction was allowed to warm to room temperature and stirred for 5 hours. The reaction mixture was then concentrated under reduced pressure. The resulting residue was diluted with hexane (80 mL, 1.0 M) and filtered with Celite. The filtrate was concentrated under reduced pressure to give the crude product (22.9 g, 80.9 mmol, 100% yield) as a yellow-orange oil. It was used in the next step without any further purification. 500 MHz ^{1}H NMR ($CDCl_3$) δ 8.37 (bs, 1H, ***NH***), 7.38 (d, *J* = 8.7 Hz, 2H, ***Ar-H***), 6.92 (d, *J* = 8.7 Hz, 2H, ***Ar-H***), 5.29 (s, 2H, -***OCH$_2$***Ar), 3.83 (s, 3H, -***OCH$_3$***); 125 MHz ^{13}C NMR ($CDCl_3$) δ 162.84 (-***C***=*NH*), 159.93 (***Ar-C***-OCH_3), 129.92 (2x***Ar-C***), 127.73(***Ar-C***-CH_2O-), 114.13 (2x***Ar-C***), 91.71(-***CCl$_3$***),

70.90(-*OCH₂Ar*), 55.48(-*OCH₃*);

With an ice-water bath, to a stirred solution of (*S*)-(-)-ethyl lactate (6.00 mL, 51.9 mmol, 1.0 equiv) in anhydrous toluene (100 mL, 0.5 M) was added $Sc(OTf)_3$ (261 mg, 0.524 mmol, 0.01 equiv) in one portion. Then, a solution of abovementioned PMBTCA (22.7 g, 80.2 mmol, 1.5 equiv) in toluene (40 mL, 2.0 M) was added via cannula to this mixture. This mixture was allowed to warm to room temperature over 6 hours under an atmosphere of N_2. It was then concentrated in vacuo. The remainder was diluted with a cold mixture of Et_2O/Hex (1:9, v/v) solution (50 mL) and filtered with Celite. The pad of Celite was washed with cold mixute Et_2O/Hex (1:9, v/v) solution (4 x 10 mL). The combined filtrate was concentrated under vacuum. The crude product was purified by flash chromatography on silica gel eluting with 5-12 vol% of EtOAc in hexanes to provide the titled compound (11.9 g, 50.0 mmol, 96% yield) as a colorless oil.

TLC: R_f = 0.51 (EtOAc/Hex = 3:7, v/v);

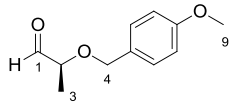
$[\alpha]_D^{20}$ -76.4 (*c* 1.94, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.30 (d, *J* = 8.8 Hz, 2H, ***H-8***, ***H-8'***), 6.88 (d, *J* = 8.6 Hz, 2H, ***H-9***, ***H-9'***), 4.63 (d, *J* = 11.2 Hz, 1H, ***H-6a***), 4.39 (d, *J* = 11.2 Hz, 1H, ***H-6b***), 4.24 (dq, *J* = 10.8, 7.1 Hz, 1H, ***H-1a***), 4.21 (dq, *J* = 10.7, 7.1 Hz, 1H, ***H-1b***), 4.03 (q, *J* = 6.8 Hz, 1H, ***H-4***), 3.88 (s, 3H, ***H-11***), 1.42 (d, *J* = 6.8 Hz, 3H, ***H-5***), 1.30 (t, *J* = 7.1 Hz, 3H, ***H-2***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 173.6 (***C-3***), 159.6 (***C-10***), 129.9 (***C-7***, ***C-8***, ***C-8'***), 114.0 (***C-9***, ***C-9'***), 73.9 (***C-4***), 71.8 (***C-6***), 61.0 (***C-1***), 55.5 (***C-11***), 18.9 (***C-5***), 14.4 (***C-2***);

FTIR (neat): ν_{max} 2985, 2938, 2838, 1745, 1613, 1587, 1514, 1464, 1372, 1302, 1250, 1199, 1143, 1065, 1034, 916, 823, 757, 666 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{13}H_{18}O_4Na$ 261.1103; found 261.1095.



(*S*)-2-(4-Methoxybenzyloxy)propanal (1.43): To a solution of **1.42** (11.9 g, 50.0 mmol, 1.0 equiv) in CH_2Cl_2 (250 mL, 0.2 M) was introduced DIBAL solution (1.0 M in CH_2Cl_2, 60 mL, 60 mmol, 1.0 equiv) by a syringe pump at 15 mL/h at -78 ^oC under an atmosphere of N_2. When the reaction was completed (monitored by TLC), methanol (10 mL) was added into this reaction via a syringe pump at 15 mL/h. The cold bath was then removed. A saturated Rochelle's salt solution (200 mL) was added and vigorously stirred overnight (ca. 8 hours). The separated aqueous layer was extracted by Et_2O (3 x 30 mL). The combined organic layers were washed by brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in a vacuum. The crude colorless oil was purified by flash chromatography on silica gel eluting with 5-15 vol% of ethyl acetate in hexanes to provide the titled compound (9.22 g, 47.5 mmol, 95% yield) as a colorless oil.

TLC: R_f = 0.33 (EtOAc/Hex = 3:7, v/v);

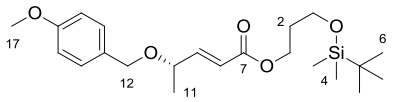
$[\alpha]_D^{20}$ -50.1 (*c* 1.10, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$): δ 9.64 (d, *J* = 1.8 Hz, 1H, ***H-1***), 7.30 (d, *J* = 8.8 Hz, 2H, ***H-6***, ***H-6'***), 6.90 (d, *J* = 8.8 Hz, 2H, ***H-7***, ***H-7'***), 4.57 (ABq, *J* = 11.4 Hz, *Δv* = 12.4 Hz, 2H, ***H-4***), 3.88 (qd, *J* = 6.9, 1.8 Hz, 1H, ***H-2***), 3.82 (s, 3H, ***H-9***), 1.32 (d, *J* =7.0 Hz, 3H, ***H-3***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 203.8 (***C-1***), 159.7 (***C-8***), 129.8 (***C-6***, ***C-6'***), 129.5 (***C-5***), 114.1 (***C-7***, ***C-7***), 79.3 (***C-2***), 71.9 (***C-4***), 55.5 (***C-9***), 15.5 (***C-3***);

FTIR (neat): ν_{max} 2957, 2935, 2857, 1734, 1613, 1586, 1514, 1464, 1374, 1303, 1249, 1175, 1095, 1035, 822, 757 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{11}H_{14}O_3Na$ 217.0841; found 217.0848.



(*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-(4-Methoxybenzyloxy)pent-2-enoate (1.44): With an ice-water bath, to a stirred mixture of NaH (60% dispersion in mineral oil, 1.48 g, 36.9 mmol, 1.05 equiv) and anhydrous THF (90 mL, 0.4 M) was added a solution of **1.41** (12.94 g, 35.11 mmol, 1.0 equiv) in THF (70 mL, 0.5 M) dropwise via cannula over a period of 15 minutes. This reaction was then stirred under an atmosphere of N_2 for 10 minutes, whereupon a solution of **1.43** (6.819 g, 35.11 mmol, 1.0 equiv) in THF (90 mL, 0.4 M) was added via a cannula over a period of 15 minutes. It was kept stirring in this condition for 2 hours. Then, a saturated $NaHCO_3$ solution (200 mL) was added. The separated aqueous layer was extracted by ether (3 x 50 mL). The combined organic layers were washed with brine (300 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 5-15 vol% of ethyl acetate in hexanes to afford the titled compound (13.35 g, 32.67 mmol, 93% yield) as a yellowish oil.

TLC: R_f = 0.62 (Acetone/Hex = 5:5, v/v);

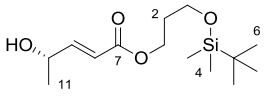
$[\alpha]_D^{20}$ -30.9 (*c* 1.29, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.26 (d, *J* = 8.8 Hz, 2H, ***H-14***, ***H-14'***), 6.89 (dd, *J* = 8.8 Hz, 2H, ***H-15***, ***H-15'***), 6.89 (dd, *J* = 15.7, 6.4 Hz, 1H, ***H-9***), 6.02 (dd, *J* = 15.7, 1.5 Hz, 1H, ***H-8***), 4.51 (d, *J* = 11.3 Hz, 1H, ***H-12a***), 4.37 (d, *J* = 11.3 Hz, 1H, ***H-12b***), 4.26 (t, *J* = 6.6 Hz, 2H, ***H-1***), 4.11 (qdd, *J* = 6.4, 6.4, 1.5 Hz, 1H, ***H-10***), 3.82 (s, 3H, ***H-17***), 3.73 (t, *J* = 6.1 Hz, 2H, ***H-3***), 1.89 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.31 (d, *J* = 6.4 Hz, 3H, ***H-11***), 0.90 (s, 9H, ***H-6***), 0.062 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.6 (***C-7***), 159.4 (***C-16***), 149.6 (***C-9***), 130.4 (***C-13***), 129.5 (***C-14***, ***C-14'***), 121.4 (***C-8***), 114.0 (***C-15***, ***C-15'***), 73.7 (***C-10***), 70.6 (***C-12***), 61.7 (***C-1***), 59.6 (***C-3***), 55.5 (***C-17***), 32.0 (***C-2***), 26.1 (***C-6***), 20.9 (***C-11***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2931, 2858, 1722, 1658, 1614, 1514, 1467, 1390, 1300, 1251, 1174, 1104, 1037, 981, 837, 777 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{22}H_{36}O_5SiNa$ 431.2230; found 431.2209.



(*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Hydroxypent-2-enoate (1.29f-(*S*)): To a stirred solution of **1.44** (13.04 g, 31.91 mmol, 1.0 equiv) in CH_2Cl_2 (160 mL, 0.2 M) was added H_2O (30 mL, 1.0 M) and DDQ (8.223 g, 35.50 mmol, 1.1 equiv) in one portion at room temperature. This reaction was then stirred for 1 hour and quenched by a saturated $NaHCO_3$ solution (200 mL). The aqueous layer was extracted by EtOAc (3 x 50 mL). The combined organic layers were washed with brine (200 mL) and dried over anhydrous Na_2SO_4. The solution was filtrated and concentrated in vacuo to provide brownish oil. The crude product was purified by flash chromatography on silica gel eluting with 10-20 vol% of ethyl acetate in hexanes to provide the titled compound (8.594 g, 29.79 mmol, 93% yield) as a pale yellow oil.

TLC: R_f = 0.26 (EtOAc/Hex = 3:7, v/v);

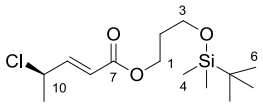
$[\alpha]_D^{20}$ +13.1 (*c* 1.52, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 6.96 (dd, *J* = 15.7, 4.7 Hz, 1H, ***H-9***), 6.03 (dd, *J* = 15.7, 1.7 Hz, 1H, ***H-8***), 4.50 (qdd, *J* = 6.5, 4.6, 1.7 Hz, 1H, ***H-10***), 4.25 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.72 (t, *J* = 6.1 Hz, 2H, ***H-3***), 1.88 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.71 (br. s, 1H, ***-OH***), 1.35 (d, *J* = 6.6 Hz, 3H, ***H-11***), 0.90 (s, 9H, ***H-6***), 0.053 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.8 (***C-7***), 151.1 (***C-9***), 119.8 (***C-8***), 67.4 (***C-10***), 61.7 (***C-1***), 59.6 (***C-3***), 32.0 (***C-2***), 26.1 (***C-6***), 23.0 (***C-11***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 3438 (br), 2957, 2930, 2858, 1723, 1658, 1471, 1391, 1361, 1257, 1175, 1104, 1008, 979, 940, 837, 777, 719, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{14}H_{28}O_4SiNa$ 311.1655; found 311.1631.



(*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Chloropent-2-enoate (1.29a-(*R*)): With an ice-water bath, to a stirred solution of **1.29f-(*S*)** (127 mg, 0.441 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (9.0 mL, 0.05 M) was added PPh_3 (178 mg, 0.672 mmol, 1.5 equiv) and NCS (90 mg, 0.66 mmol, 1.5 equiv) subsequently. This reaction was then stirred at for 1 hour under an atmosphere of N_2. It was then poured into a mixture of saturated $NaHCO_3$ solution (15 mL) and saturated $Na_2S_2O_3$ solution (15 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 2-10 vol% of Et_2O in hexanes to provide the titled compound (96.9 mg, 0.316 mmol, 72% yield) as a colorless oil.

TLC: R_f = 0.69 (EtOAc/Hex = 3:7, v/v);

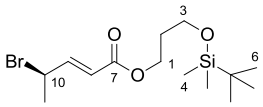
$[\alpha]_D^{20}$ -3.3 (*c* 1.08, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 6.94 (dd, *J* = 15.5, 7.1 Hz, 1H, ***H-9***), 6.01 (dd, *J* = 15.7, 1.5 Hz, 1H, ***H-8***), 4.62 (dqd, *J* = 7.1, 6.9, 1.5 Hz, 1H, ***H-10***), 4.26 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.72 (t, *J* = 6.1 Hz, 2H, ***H-3***), 1.88 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.65 (d, *J* = 6.9 Hz, 3H, ***H-11***), 0.90 (s, 9H, ***H-6***), 0.055 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.1 (***C-7***), 147.3 (***C-9***), 121.8 (***C-8***), 62.0 (***C-1***), 59.6 (***C-3***), 55.0 (***C-10***), 31.9 (***C-2***), 26.1 (***C-6***), 24.5 (***C-11***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2930, 2858, 1725, 1661, 1471, 1390, 1360, 1341, 1272, 1178, 1106, 1017, 975, 838, 777, 727, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{14}H_{27}ClO_3SiNa$ 329.1316; found 329.1319.



(*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Bromopent-2-enoate (1.19b-(*R*)): To a stirred solution of **1.29f-(*S*)** (535 mg, 1.856 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (25 mL, 0.08 M) was added CBr_4 (940 mg, 2.81 mmol, 1.5 equiv) and imidazole (194 mg, 2.82 mmol, 1.5 equiv). Then, PPh_3 (691 mg, 2.61 mmol, 1.4 equiv) was added in one portion at 0 ºC. This reaction was stirred under an atmosphere of N_2 for 1 hour and poured into a saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL), and the combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 0-10 vol% of Et_2O in hexanes to provide the titled compound (475 mg, 1.35 mmol, 73% yield) as a colorless oil.

TLC: R_f = 0.65 (EtOAc/Hex = 3:7, v/v);

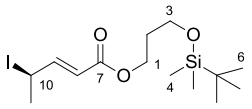
$[\alpha]_D^{20}$ +4.2 (*c* 1.28, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.01 (dd, *J* = 15.7, 8.3 Hz, 1H, ***H-9***), 5.93 (dd, *J* = 15.5, 1.0 Hz, 1H, ***H-8***), 4.69 (dqd, *J* = 8.3, 6.6, 1.0 Hz, 1H, ***H-10***), 4.25 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***), 1.87 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.82 (d, *J* = 6.4 Hz, 3H, ***H-11***), 0.88 (s, 9H, ***H-6***), 0.042 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.0 (***C-7***), 147.7 (***C-9***), 121.2 (***C-8***), 62.0 (***C-1***), 59.6 (***C-3***), 45.0 (***C-10***), 31.9 (***C-2***), 26.1 (***C-6***), 24.9 (***C-11***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2858, 1723, 1655, 1471, 1390, 1360, 1341, 1266, 1203, 1170, 1104, 1010, 975, 939, 837, 777, 722, 663 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{14}H_{27}BrO_3SiNa$ 373.0811; found 373.0817.



(*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Iodopent-2-enoate (1.29c-(*R*)): To a stirred solution of **1.29f-(*S*)** (170 mg, 0.588 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (6.0 mL, 0.1 M) was added imidazole (207 mg, 3.00 mmol, 5.0 equiv), PPh_3 (314 mg, 1.19 mmol, 2.0 equiv) and I_2 (277 mg, 1.08 mmol, 1.8 equiv) at room temperature. This reaction was stirred for 1 hour under an atmosphere of N_2. Then, it was diluted with a solution of 15 vol% of Et_2O in hexanes (50 mL). The precipitate was filtered by a pack of Celite®. The solution was concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 1-6 vol% of EtOAc in hexanes to provide the titled compound (124 mg, 0.310 mmol, 53% yield) as a yellow oil.

TLC: R_f = 0.65 (EtOAc/Hex = 3:7, v/v);

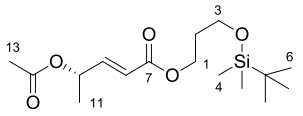
$[\alpha]_D^{20}$ -0.7 (*c* 1.10, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.15 (dt, *J* = 15.4, 8.6 Hz, 1H, ***H-9***), 5.84 (dt, *J* = 15.4, 1.2 Hz, 1H, ***H-8***), 4.90 (dqd, *J* = 8.6, 6.8, 1.2 Hz, 1H, ***H-10***), 4.24 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.71 (t, *J* = 6.1 Hz, 2H, ***H-3***), 2.00 (d, *J* = 6.8 Hz, 3H, ***H-11***), 1.87 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 0.89 (s, 9H, ***H-6***), 0.050 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.0 (***C-7***), 150.2 (***C-9***), 119.0 (***C-8***), 62.0 (***C-1***), 59.6 (***C-3***), 31.9 (***C-2***), 26.6 (***C-11***), 26.1 (***C-6***), 21.1 (***C-10***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2857, 1720, 1645, 1471, 1390, 1360, 1340, 1260, 1191, 1106, 1007, 976, 939, 837, 777, 721, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{14}H_{27}IO_3SiNa$ 421.0672; found 421.0671.



(*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Acetoxypent-2-enoate (1.29d-(*S*)): To a solution of **1.29f-(*S*)** (133 mg, 0.460 mmol, 1.0 equiv) in CH_2Cl_2 (9.0 mL, 0.05 M) was added DMAP (57 mg, 0.46 mmol, 1.0 equiv), *N*,*N*-diisopropylethylamine (800 uL, 4.59 mmol, 10.0 equiv) and acetic anhydride (130 uL, 1.36 mmol, 3.0 equiv) subsequently, at room temperature. It was stirred for 18 hours, and then quenched with a saturated $NaHCO_3$ solution (20 mL). The aqueous solution was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 3-9 vol% of EtOAc in hexanes to provide the titled compound (138 mg, 0.417 mmol, 91% yield) as a colorless oil.

TLC: R_f = 0.55 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ -21.3 (*c* 1.38, $CHCl_3$);

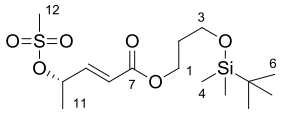
500 MHz ^{1}H NMR ($CDCl_3$) δ 6.86 (dd, *J* = 15.8, 5.1 Hz, 1H, ***H-9***), 5.95 (dd, *J* = 15.7, 2.0 Hz, 1H, ***H-8***), 5.48 (qdd, *J* = 6.8, 4.9, 1.8 Hz, 1H, ***H-10***), 4.24 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.70 (t, *J* = 5.9 Hz, 2H, ***H-3***), 2.08 (s, 3H, ***H-13***), 1.86 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.36 (d, *J* = 6.9 Hz, 3H, ***H-11***), 0.88 (s, 9H, ***H-6***), 0.041 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 170.2 (***C-12***), 166.3 (***C-7***), 146.5 (***C-9***), 121.1 (***C-8***), 69.0 (***C-10***), 61.9 (***C-1***), 59.6 (***C-3***), 31.9 (***C-2***), 26.1 (***C-6***), 21.3 (***C-13***), 19.8 (***C-11***), 18.5 (***C-***

5), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2931, 2858, 1746, 1725, 1664, 1472, 1373, 1305, 1236, 1176, 1103, 1048, 977, 837, 777, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{16}H_{30}O_5SiNa$ 353.1760; found 353.1765.



(*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)propyl 4-Methylsulfonyloxypent-2-enoate (1.29e-(*S*)): To a stirred solution of **1.29f-(*S*)** (147 mg, 0.509 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (10.0 mL, 0.05 M) was added DIPEA (360 uL, 2.07 mmol, 4.0 equiv), followed by addition of MsCl (80 uL, 1.0 mmol, 2.0 equiv) dropwise at 0 °C. This reaction was stirred for 1 hour under an atmosphere of N_2. Then, it was poured into a saturated solution of $NaHCO_3$ (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 10-20 vol% of ethyl acetate in hexane to provide the titled compound (149 mg, 0.406 mmol, 80% yield) as a yellowish oil.

TLC: R_f = 0.58 (EtOAc/CH_2Cl_2 = 1:9, v/v);

$[\alpha]_D^{20}$ -23.2 (*c* 1.33, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 6.88 (dd, *J* = 15.7, 5.4 Hz, 1H, ***H-9***), 6.09 (dd, *J* = 15.7, 1.5 Hz, 1H, ***H-8***), 4.87 (qdd, *J* = 6.8, 5.4, 1.5 Hz, 1H, ***H-10***), 4.27 (t, *J* = 6.6 Hz, 2H, ***H-1***), 3.71 (t, *J* = 6.1 Hz, 2H, ***H-3***), 3.03 (s, 3H, ***H-12***), 1.88 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.55 (d, *J* = 6.9 Hz, 3H, ***H-11***), 0.89 (s, 9H, ***H-6***), 0.051 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 165.7 (***C-7***), 144.2 (***C-9***), 123.0 (***C-8***), 76.6 (***C-10***), 62.2 (***C-***

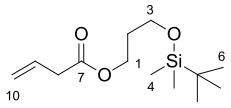
1), 59.5 (***C-3***), 39.2 (***C-12***), 31.9 (***C-2***), 26.1 (***C-6***), 21.4 (***C-11***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2932, 2858, 1724, 1665, 1471, 1362, 1306, 1259, 1178, 1102, 1035, 975, 896, 838, 814, 778 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{15}H_{30}O_6SSiNa$ 389.1430; found 389.1438.

General procedure of preparing 0.1 M SmI_2 solution: To an oven dried flask, equipped with a stirring bar, was added Sm chips (301 mg, 2.0 mmol, 2.0 equiv), and stirred vigorously overnight. Then, freshly distilled THF (10.0 mL, 0.1 M) was added into this flask, followed by CH_2I_2 (81.5 uL, 1.00 mmol, 1.0 equiv) at room temperature under an atmosphere of N_2. After 5 hours, a deep blue/purple SmI_2 solution was ready to use.

General procedure of SmI_2 mediated reductive deconjugation reaction:



3-(tert-Butyldimethylsilyloxy)propyl But-3-enoate (1.26): Under an atmosphere of Ar, to a mixture of **1.25a** (34.7 mg 0.110 mmol, 1.0 equiv), MeOH (90 uL, 2.2 mmol, 20 equiv) and freshly distilled THF (5.5 mL, 0.02 M) was added SmI_2 (0.1M solution, 2.2 mL, 2.2 equiv) via syringe pumb over a period of 5 minutes at -78 ^oC. The reaction completed in seconds judged by the disappearance of characteristic deep blue-purple color of SmI_2 solution. Then, the reaction was diluted with Et_2O (10 mL) and poured into a saturated Rochelle's salt solution (20 mL). The aqueous solution was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 0-6 vol% of Et_2O in hexanes to provide the titled compound (26.7 mg, 0.103 mmol, 94% yield) as a

colorless oil.

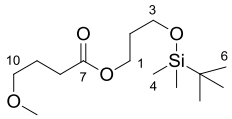
TLC: R_f = 0.20 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 5.93 (ddt, *J* = 17.1, 10.0, 7.3 Hz, 1H, ***H-9***), 5.22 ~ 5.12 (m, 2H, ***H-10***), 4.20 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.70 (t, *J* = 6.3 Hz, 2H, ***H-3***), 3.09 (dt, *J* = 6.9, 1.5 Hz, 2H, ***H-8***), 1.85 (p, *J* = 6.3 Hz, 2H, ***H-2***), 0.90 (s, 9H, ***H-6***), 0.055 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 171.8 (***C-7***), 130.6 (***C-9***), 118.7 (***C-10***), 61.9 (***C-1***), 59.6 (***C-3***), 39.4 (***C-8***), 31.9 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2930, 2858, 1742, 1644, 1471, 1391, 1361, 1328, 1257, 1174, 1104, 1010, 974, 921, 837, 777, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{13}H_{26}O_3SiNa$ 281.1549; found 281.1546.



3-(*tert*-Butyldimethylsilyloxy)propyl 4-Methoxybutanoate (1.27b): The tilted compound (5.6 mg, 0.019 mmol, 18% yield) as a colorless oil and compound **1.26** (18.3 mg, 0.0708 mmol, 66% yield) were obtained from **1.25b** (30.8 mg, 0.107 mmol, 1.0 equiv) with SmI_2 (0.1 M solution, 3.2 mL, 0.32 mmol, 3.0 equiv) as the general procedure described above but at room temperature for 4 hours. The titled compound was purified by flash chromatography on silica gel eluting with 6-10 vol% of Et_2O in hexanes.

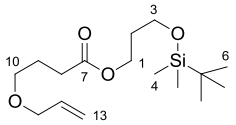
TLC: R_f = 0.15 (Et_2O/Hex = 1:9, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 4.18 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***), 3.41 (t, *J* = 6.1 Hz, 2H, ***H-10***), 3.33 (s, 3H, ***H-11***), 2.39 (t, *J* = 7.6 Hz, 2H, ***H-8***), 1.90 (tt, *J* = 7.6, 6.1 Hz, 2H, ***H-9***), 1.84 (p, *J* = 6.4 Hz, 2H, ***H-2***), 0.90 (s, 9H, ***H-6***), 0.056 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 173.7 (***C-7***), 71.8 (***C-10***), 61.6 (***C-1***), 59.7 (***C-3***), 58.8 (***C-11***), 32.0 (***C-2***), 31.2 (***C-8***), 26.1 (***C-6***), 25.2 (***C-9***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2858, 1738, 1471, 1362, 1256, 1168, 1119, 837, 777, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{14}H_{30}O_4SiNa$ 313.1811; found 313.1811.



3-(*tert*-Butyldimethylsilyloxy)propyl 4-(Allyloxy)butanoate (1.27h): The titled compound (16.5 mg, 0.0521 mmol, 46% yield) as a colorless oil and compound **1.26** (13.1 mg, 0.0507 mmol, 45% yield) were obtained from **1.25h** (35.3 mg, 0.112 mmol, 1.0 equiv) with SmI_2 (0.1 M solution, 3.3 mL, 0.33 mmol, 3.0 equiv) as the general procedure described above but at room temperature for 4 hours. The titled compound was purified by flash chromatography on silica gel eluting with 3-10 vol% of Et_2O in hexanes.

TLC: R_f = 0.16 (Et_2O/Hex = 1:9, v/v);

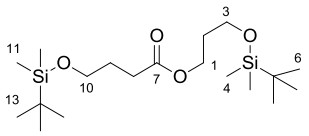
500 MHz ^{1}H NMR ($CDCl_3$) δ 5.90 (ddt, *J* = 17.1, 10.3, 5.9 Hz, 1H, ***H-12***), 5.27 (ddt, *J* =17.1, 2.0, 1.5 Hz, 1H, ***H-13a***), 5.17 (ddt, *J* = 10.5, 2.0, 1.5 Hz, 1H, ***H-13b***), 4.17 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.96 (ddd, *J* = 5.4, 1.5, 1.5 Hz, 2H, ***H-11***), 3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***), 3.47 (t, *J* = 6.1 Hz, 2H, ***H-10***), 2.41 (t, *J* = 7.3 Hz, 2H, ***H-8***), 1.91 (tt, *J* = 7.3, 6.1 Hz, 2H, ***H-9***), 1.84 (p, *J* = 6.2 Hz, 2H, ***H-2***), 0.90 (s, 9H, ***H-6***), 0.053 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 173.7 (***C-7***), 135.1 (***C-12***), 117.0 (***C-13***), 72.0 (***C-11***), 69.4 (***C-10***), 61.6 (***C-1***), 59.7 (***C-3***), 32.0 (***C-2***), 31.3 (***C-8***), 26.1 (***C-6***), 25.3 (***C-9***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2858, 1738, 1472, 1391, 1361, 1256, 1174, 1106, 923, 837,

777, 664 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{16}H_{32}O_4SiNa$ 339.1968; found 339.1971.



3-(*tert*-Butyldimethylsilyloxy)propyl 4-(*tert*-Butyldimethylsilyloxy)butanoate (1.27i): The titled compound (35.7 mg, 0.0914 mmol, 72% yield) as a colorless oil and compound **1.26** (7.8 mg, 0.0302 mmol, 24% yield) were obtained from **1.25i** (49.1 mg, 0.126 mmol, 1.0 equiv) with SmI_2 (0.1 M solution, 3.8 mL, 0.38 mmol, 3.0 equiv) as the general procedure described above but at room temperature for 4 hours. The tiltled compound was purified by flash chromatography on silica gel eluting with 3-10 vol% of Et_2O in hexanes.

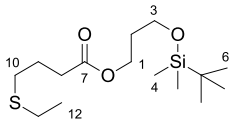
TLC: R_f = 0.29 (Et_2O/Hex = 1:9, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 4.17 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***), 3.64 (t, *J* = 6.1 Hz, 2H, ***H-10***), 2.39 (t, *J* = 7.3 Hz, 2H, ***H-8***), 1.88 ~ 1.80 (m, 4H, ***H-2***, ***H-9***), 0.90 (s, 18H, ***H-6***, ***H-13***), 0.053 (s, 6H, ***H-4***, ***H-4'***), 0.047(s, 6H, ***H-11***, ***H-11'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 173.9 (***C-7***), 62.2 (***C-10***), 61.5 (***C-1***), 59.7 (***C-3***), 32.1 (***C-2***), 30.9 (***C-8***), 28.2 (***C-9***), 26.1 (***C-6***, ***C-13***), 18.5 (***C-5***, ***C-12***), -5.2 (***C-11***, ***C-11'***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2858, 1739, 1472, 1390, 1362, 1256, 1171, 1106, 1007, 967, 837, 777, 720, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{19}H_{42}O_4Si_2Na$ 413.2519; found 413.2525.



3-(*tert*-Butyldimethylsilyloxy)propyl 4-(Allylthio)butanoate (1.27j): The titled compound (18.3 mg, 0.0571 mmol, 43% yield) as a colorless oil and

compound **1.26** (15.2 mg, 0.0588 mmol, 45% yield) were obtained from **1.25j** (42.1 mg, 0.132 mmol, 1.0 equiv) with SmI_2 (0.1 M solution, 4.0 mL, 0.40 mmol, 3.0 equiv) as the general procedure described above but at room temperature for 4 hours. The tilteld compound was purified by flash chromatography on silica gel eluting with 3-10 vol% of Et_2O in hexanes.

TLC: R_f = 0.38 (Et_2O/Hex = 2:8, v/v);

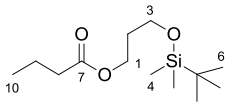
500 MHz ^{1}H NMR ($CDCl_3$) δ 4.18 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***), 2.57 (t, *J* = 7.2 Hz, 2H, ***H-10***), 2.55 (q, *J* = 7.6 Hz, 2H, ***H-11***), 2.44 (t, *J* = 7.3 Hz, 2H, ***H-8***), 1.92 (p, *J* = 7.2 Hz, 2H, ***H-9***), 1.84 (p, *J* = 6.2 Hz, 2H, ***H-2***), 1.26 (t, *J* = 7.3 Hz, 3H, ***H-12***), 0.90 (s, 9H, ***H-6***), 0.057 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 173.4 (***C-7***), 61.7 (***C-1***), 59.7 (***C-3***), 33.3 (***C-8***), 32.0 (***C-2***), 31.1 (***C-10***), 26.1 (***C-6***), 26.0 (***C-11***), 25.0 (***C-9***), 18.5 (***C-5***), 15.0 (***C-12***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2930, 2858, 1738, 1471, 1367, 1260, 1170, 1115, 838, 777 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{15}H_{32}O_3SSiNa$ 343.1739; found 343.1736.

3-(*tert*-Butyldimethylsilyloxy)propyl butyrate (1.27n):



Following the general procedure, **1.25n** (30.9 mg, 0.120 mmol, 1.0 equiv) was treated with SmI_2 (0.1 M solution, 3.6 mL, 0.36 mmol, 3.0 equiv) at room temperature for 6 hours to funish the titled compound (11.5 mg, 0.0442 mmol, 37% yield) as a colorless oil, along with the recovered starting material **1.25n** (16.7 mg, 0.0646 mmol, 54% yield). The tilteld compound was purified by flash chromatography on silica gel eluting with 2-10 vol% of Et_2O in hexanes.

TLC: R_f = 0.48 (Et_2O/Hex = 2:8, v/v);

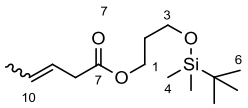
500 MHz ^{1}H NMR ($CDCl_3$) δ 4.17 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***),

2.28 (t, *J* = 7.6 Hz, 2H, ***H-8***), 1.84 (p, *J* = 6.2 Hz, 2H, ***H-2***), 1.66 (sext, *J* = 7.4 Hz, 2H, ***H-9***), 0.96 (t, *J* = 7.3 Hz, 3H, ***H-10***), 0.90 (s, 9H, ***H-6***), 0.054 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 173.9 (***C-7***), 61.4 (***C-1***), 59.7 (***C-3***), 36.5 (***C-8***), 32.1 (***C-2***), 26.1 (***C-6***), 18.7 (***C-9***), 18.5 (***C-5***), 13.9 (***C-10***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2858, 1739, 1470, 1362, 1257, 1112, 835, 777 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{13}H_{28}O_3SiNa$ 283.1705; found 283.1707.



3-((*tert*-Butyldimethylsilyl)oxy)propyl pent-3-enoate (1.30): To a solution of **1.29b** (38.2 mg, 0.109 mmol, 1.0 equiv) in THF was added SmI_2 solution SmI_2 (0.1 M solution, 2.4 mL, 0.24 mmol, 2.2 equiv) as the general procedure described above. The reaction was purified by flash chromatography on silica gel eluting with 0-6 vol% of Et_2O in hexanes to provide the titled compound (29.5 mg, 0.108 mmol, 99% yield) as a colorless oil, which was an inseparable mixture of *Z/E* isomers (*Z*:*E* = 1:3 based on ^{1}HNMR intergration).

TLC: R_f = 0.61 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$):

E*-isomer:** δ 5.63 ~ 5.49 (m, 2H, ***H-9, ***H-10***), 4.17 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.69 (t, *J* = 6.1 Hz, 2H, ***H-3***), 3.07 ~ 2.93 (m, 2H, ***H-8a***, ***H-8b***), 1.84 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.73 ~ 1.66 (m, 3H, ***H-11***), 0.89 (s, 9H, ***H-6***), 0.047 (s, 6H, ***H-4***, ***H-4'***);

Z*-isomer:** δ 5.65 (dqt, *J* = 12.0, 6.6, 1.6 Hz, 1H, ***H-10), 5.57 (dtq, *J* = 12.0, 6.9, 1.5 Hz, 1H, ***H-9***), 4.18 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.69 (t, *J* = 6.1 Hz, 2H, ***H-3***), 3.12 ~ 3.06 (m, 2H, ***H-8a***, ***H-8b***), 1.84 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.67 ~ 1.61 (m, 3H, ***H-11***), 0.89 (s, 9H, ***H-6***), 0.045 (s, 6H, ***H-4***, ***H-4'***);

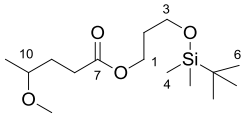
125 MHz ^{13}C NMR ($CDCl_3$):

E*-isomer:** δ 172.4 (C-7***), 129.5 (***C-10***), 123.0 (***C-9***), 61.7 (***C-1***), 59.6 (***C-3***), 38.3 (***C-8***), 31.9 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), 18.1 (***C-11***), -5.2 (***C-4***, ***C-4'***);

Z*-isomer:** δ 172.2 (C-7***), 127.6 (***C-10***), 122.1 (***C-9***), 61.8 (***C-1***), 59.6 (***C-3***), 32.9 (***C-8***), 32.0 (***C-2***), 26.1 (***C-6***), 18.5 (***C-5***), 13.1 (***C-11***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2930, 2858, 1741, 1472, 1390, 1361, 1256, 1164, 1103, 1008, 967, 837, 777, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{14}H_{28}O_3SiNa$ 295.1705; found 295.1713.



3-(*tert*-Butyldimethylsilyloxy)propyl 4-Methoxypentanoate (1.31g): The titled compound (13.8 mg, 0.0453 mmol, 38% yield) as a colorless oil and compound **1.30** (18.2 mg, 0.0668 mmol, 56% yield) were obtained from **1.29g** (35.9 mg, 0.119 mmol, 1.0 equiv) with SmI_2 (0.1 M solution, 3.6 mL, 0.36 mmol, 3.0 equiv) as the general procedure described above but at room temperature for 6 hours. The tilteld compound was purified by flash chromatography on silica gel eluting with 3-10 vol% of Et_2O in hexanes.

TLC: R_f = 0.19 (EtOAc/Hex = 1:9, v/v);

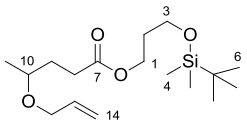
500 MHz ^{1}H NMR ($CDCl_3$) δ 4.17 (t, *J* = 6.6 Hz, 2H, ***H-1***), 3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***), 3.33 (sxet, *J* = 6.0 Hz, 1H, ***H-10***), 3.31 (s, 3H, ***H-12***), 2.41 (ddd, *J* = 16.1, 7.8, 7.3, 1H, ***H-8a***), 2.37 (ddd, *J* = 16.1, 7.8, 7.3, 1H, ***H-8b***), 1.84 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.82 ~ 1.75 (m, 2H, ***H-9a***, ***H-9b***), 1.15 (d, *J* = 6.4 Hz, 3H, ***H-11***), 0.90 (s, 9H, ***H-6***), 0.053 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 174.0 (***C-7***), 76.0 (***C-10***), 61.5 (***C-1***), 59.7 (***C-3***), 56.3 (***C-***

12), 32.0 (***C-2***), 31.6 (***C-9***), 30.5 (***C-8***), 26.1 (***C-6***), 19.1 (***C-11***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2956, 2930, 2858, 1738, 1464, 1257, 1170, 1100, 837, 777 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{15}H_{32}O_4SiNa$ 327.1968; found 327.1969.



3-(*tert*-Butyldimethylsilyloxy)propyl 4-(Allyloxy)pentanoate (1.31h): The titled compound (25.3 mg, 0.765 mmol, 71% yield) as a colorless oil and compound **1.30** (7.7 mg, 0.283 mmol, 26% yield) were obtained from **1.29h** (35.6 mg, 0.108 mmol, 1.0 equiv) with SmI_2 (0.1 M solution, 3.3 mL, 0.33 mmol, 3.0 equiv) as the general procedure described above but at room temperature for 6 hours. The tilteld compound was purified by flash chromatography on silica gel eluting with 3-10 vol% of Et_2O in hexanes.

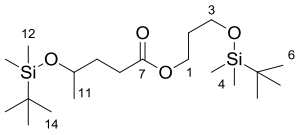
TLC: R_f = 0.29 (EtOAc/Hex = 1:9, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 5.90 (ddt, *J* = 17.1, 10.3, 5.9 Hz, 1H, ***H-13***), 5.26 (ddt, *J* = 17.1, 2.0, 1.5 Hz, 1H, ***H-14a***), 5.15 (ddt, *J* = 10.3, 2.0, 1.5 Hz, 1H, ***H-14b***), 4.16 (t, *J* = 6.4 Hz, 2H, ***H-1***), 4.03 (ddt, *J* = 12.7, 5.9, 1.5 Hz, 1H, ***H-12a***), 3.90 (ddt, *J* = 12.7, 5.9, 1.5 Hz, 1H, ***H-12b***), 3.69 (t, *J* = 6.1 Hz, 2H, ***H-3***), 3.49 (sext, *J* = 6.1 Hz, 1H, ***H-10***), 2.43 (ddd, *J* = 16.1, 7.8, 7.3 Hz, 1H, ***H-8a***), 2.38 (ddd, *J* = 16.1, 7.8, 7.3 Hz, 1H, ***H-8b***), 1.83 (pent, *J* = 6.1 Hz, 1H, ***H-2***), 1.80 (td, *J* = 7.6, 6.0 Hz, 2H, ***H-9a***, ***9b***), 1.16 (d, *J* = 5.9 Hz, 3H, ***H-11***), 0.89 (s, 9H, ***H-6***), 0.049 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 174.0 (***C-7***), 135.5 (***C-13***), 116.7 (***C-14***), 74.0 (***C-10***), 69.7 (***C-12***), 61.5 (***C-1***), 59.7 (***C-3***), 32.0 (***C-2***), 31.8 (***C-9***), 30.5 (***C-8***), 26.1 (***C-6***), 19.7 (***C-11***), 18.5 (***C-5***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2930, 2858, 1738, 1464, 1376, 1339, 1257, 1175, 1101, 1007, 922, 837, 777, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{17}H_{34}O_4SiNa$ 353.2124; found 353.2124.



3-(*tert*-Butyldimethylsilyloxy)propyl 4-((*tert*-Butyldimethyl)-silyloxy)pentanoate (1.31i): The titled compound (39.5 mg, 0.0976 mmol, 93% yield) as a colorless oil was obtained from **1.29i** (42.3 mg, 0.105 mmol, 1.0 equiv) with SmI_2 (0.1 M solution, 3.3 mL, 0.33 mmol, 3.0 equiv) as the general procedure described above but at room temperature for 6 hours. The tilteld compound was purified by flash chromatography on silica gel eluting with 3-5 vol% of Et_2O in hexanes.

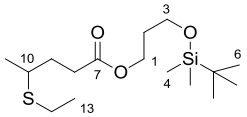
TLC: R_f = 0.31 (Et_2O/Hex = 1:9, v/v);

500 MHz ^1H NMR ($CDCl_3$) δ 4.17 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.85 (sxet, *J* = 6.0 Hz, 1H, ***H-10***), 3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***), 2.40 (ddd, *J* = 16.1, 9.2, 6.4, 1H, ***H-8a***), 2.34 (ddd, *J* = 16.1, 8.8, 6.8, 1H, ***H-8b***), 1.84 (pent, *J* = 6.2 Hz, 2H, ***H-2***), 1.80 ~ 1.70 (m, 2H, ***H-9a***, ***H-9b***), 1.14 (d, *J* = 6.4 Hz, 3H, ***H-11***), 0.90 (s, 9H, ***H-6***), 0.89 (s, 9H, ***H-14***), 0.053 (s, 9H, ***H-4***, ***H-4'***, ***H-12***), 0.043 (s, 3H, ***H-12'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 174.1 (***C-7***), 67.7 (***C-10***), 61.5 (***C-1***), 59.7 (***C-3***), 34.6 (***C-9***), 32.0 (***C-2***), 30.6 (***C-8***), 26.1 (***C-6***), 26.1 (***C-14***), 23.9 (***C-11***), 18.5 (***C-5***), 18.3 (***C-13***), -4.2 (***C-12***), -4.6 (***C-12'***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2957, 2930, 2858, 1740, 1471, 1361, 1256, 1171, 1095, 1006, 837, 776, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{20}H_{44}O_4Si_2Na$ 427.2676; found 427.2682.



3-(*tert*-Butyldimethylsilyloxy)propyl 4-(Ethylthio)pentanoate (1.31j): The titled compound (19.1 mg, 0.0571 mmol, 43% yield) as a colorless oil and compound **1.30** (16.3 mg, 0.0598 mmol, 45% yield) were obtained from **1.29j** (44.3 mg, 0.133 mmol, 1.0 equiv) with SmI_2 (0.1 M solution, 4.0 mL, 0.40 mmol, 3.0 equiv) as the general procedure described above but at room temperature for 6 hours. The tilteld compound was purified by flash chromatography on silica gel eluting with 3-10 vol% of Et_2O in hexanes.

TLC: R_f = 0.35 (Et_2O/Hex = 2:8, v/v);

500 MHz ^{1}H NMR ($CDCl_3$) δ 4.18 (t, *J* = 6.4 Hz, 2H, ***H-1***), 3.70 (t, *J* = 6.1 Hz, 2H, ***H-3***), 2.80 (sxet, *J* = 6.7 Hz, 1H, ***H-10***), 2.55 (q, *J* = 7.5 Hz, 2H, ***H-12***), 2.50 ~ 2.43 (m, 2H, ***H-8a***, ***H-8b***), 1.97 ~ 1.75 (m, 4H, ***H-2***, ***H-9a***, ***H-9b***), 1.29 (d, *J* = 6.8 Hz, 3H, ***H-11***), 1.25 (t, *J* = 7.3 Hz, 3H, ***H-13***), 0.90 (s, 9H, ***H-6***), 0.053 (s, 6H, ***H-4***, ***H-4'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 173.7 (***C-7***), 61.6 (***C-1***), 59.6 (***C-3***), 39.3 (***C-10***), 32.0 (***C-2***), 31.9 (***C-9***), 31.8 (***C-8***), 26.1 (***C-6***), 24.3 (***C-12***), 21.6 (***C-11***), 18.5 (***C-5***), 15.1 (***C-13***), -5.2 (***C-4***, ***C-4'***);

FTIR (neat): ν_{max} 2958, 2929, 2858, 1738, 1462, 1378, 1361, 1257, 1167, 1104, 1008, 969, 837, 777 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{16}H_{34}O_3SSiNa$ 357.1896; found 357.1897.

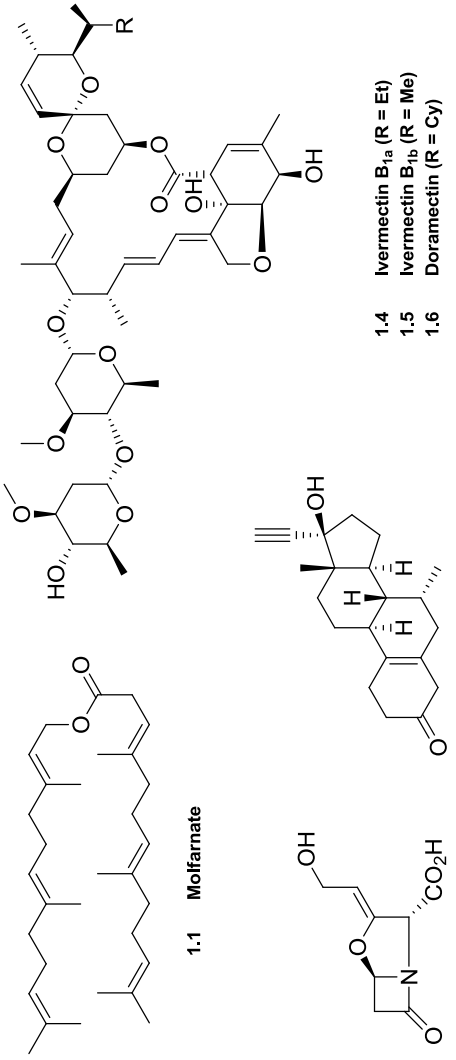


Figure 1.1 Drugs Containing β,γ-Unsaturated Carbonyl Functionality

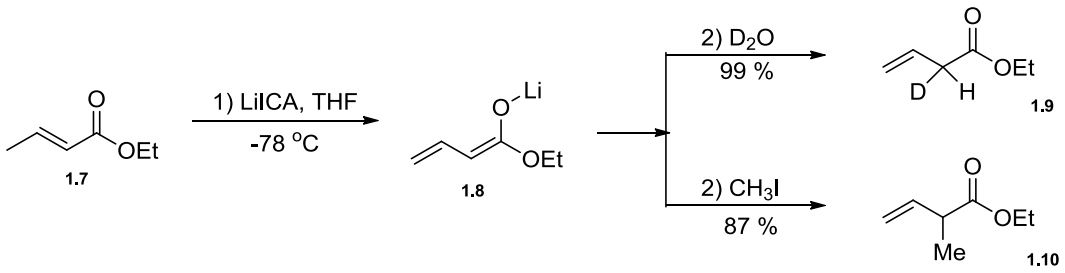


Figure 1.2 Deconjugation by Kinetic Protonation and Alkylation of Dienolate Anion

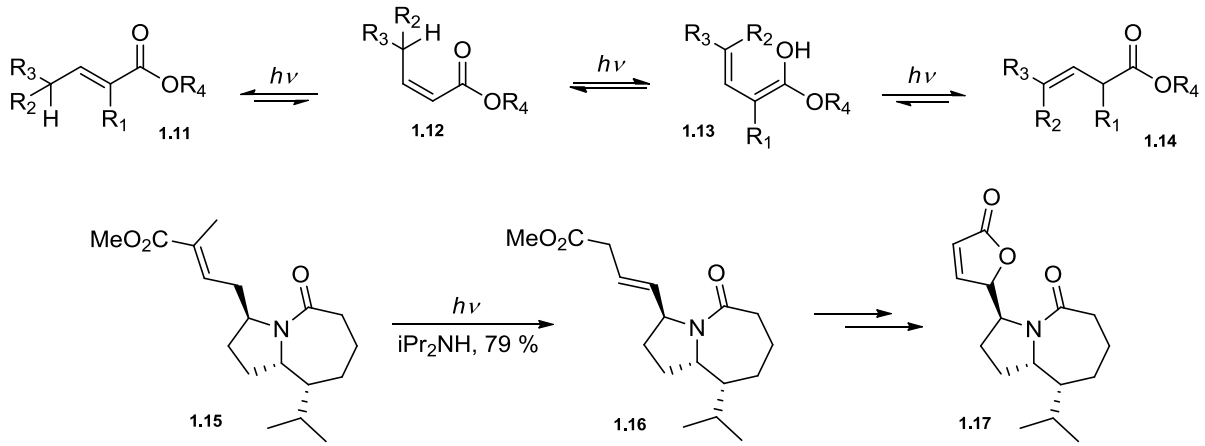


Figure 1.3 Photochemical Deconjugation

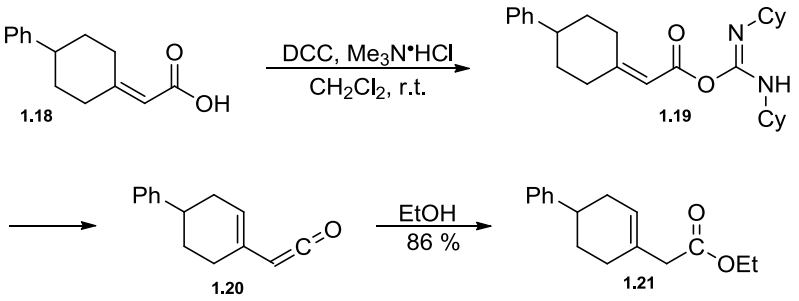


Figure 1.4 Deconjugation via Conjugated Ketene Intermediates

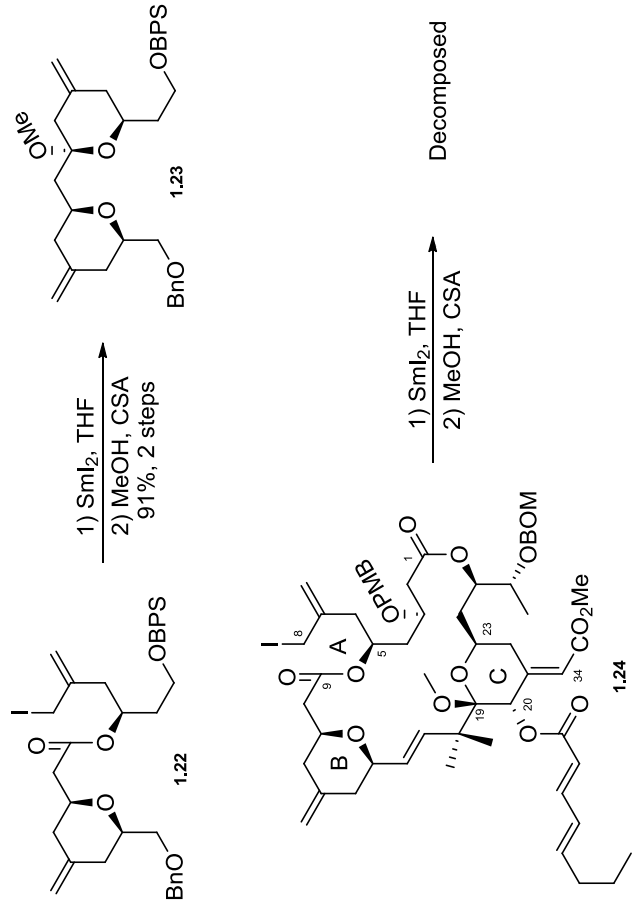
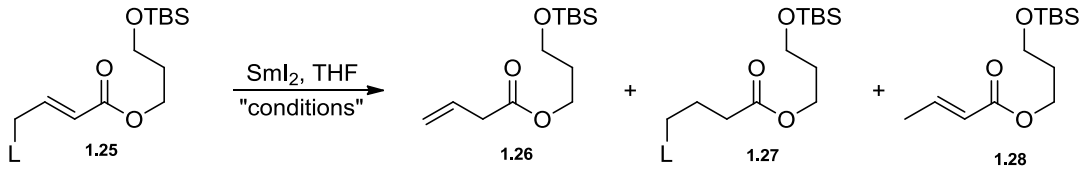


Figure 1.5 SmI_2-Mediated Reductive Cyclization

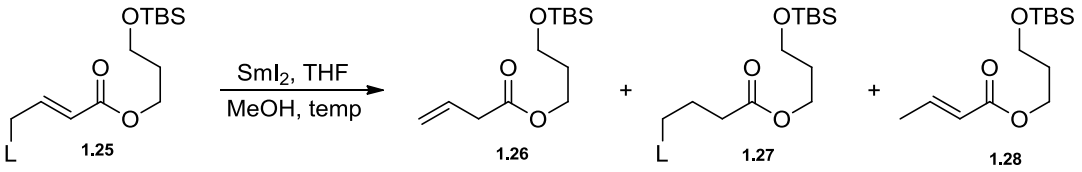
Table 1.1 Reaction Conditions of SmI_2-Mediated Deconjugation



Entry	Compound[a]	SmI_2 (equiv)	Additive (equiv)	Temp (°C)	Time[b]	Yield[c] 1.26(%)	Yield[c] 1.27 (%)	Yield[c] 1.28 (%)
1	**1.25a** (L = -OAc)	5.0	--	0	~ 5 min	23	--	--
2	**1.25a** (L = -OAc)	2.2	--	0	~ 5 min	25	--	--
3	**1.25a** (L = -OAc)	2.2	--	-41	~ 5 min	33	--	--
4	**1.25a** (L = -OAc)	2.2	--	-78	~ 5 min	41	--	--
5	**1.25a** (L = -OAc)	2.2	MeOH 1.0 eq	-78	~ 5 min	76	--	--
6	**1.25a** (L = -OAc)	2.2	MeOH > 10 eq	-78	~ 5 min	94	--	--
7	**1.25a** (L = -OAc)	2.2	*t*-BuOH > 10 eq	-78	~ 5 min	89	--	--
8	**1.25b** (L = -OMe)	3.0	MeOH > 10 eq	-78	4 h		no reaction	
9	**1.25b** (L = -OMe)	3.0	MeOH > 10 eq	-31	4 h		no reaction	
10	**1.25b** (L = -OMe)	3.0	MeOH > 10 eq	rt	4 h	66	18	--

[a] *To a solution of about 0.1 mmol of the starting material in 5 mL of THF was added SmI2 solution under Ar.*
[b] *The time started since SmI2 solution was added into the reaction via syringe pumb over a period of 5 min..*
[c] *Isolated yields*

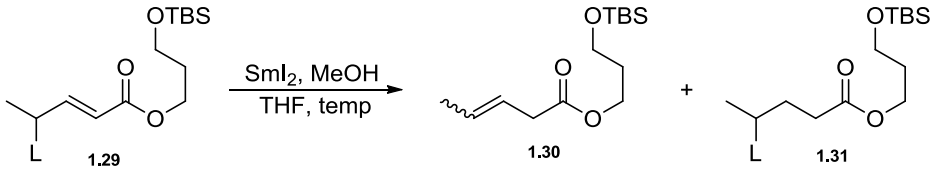
Table 1.2 SmI_2-Mediated Deconjugation of Primary γ-Substituted Esters



Entry	Compound[a]	Temp[b] (°C)	Time[c]	Yield[d] 1.26(%)	Yield[d] 1.27 (%)	Yield[d] 1.28 (%)
1	**1.25a** (L = -OAc)	-78	~ 5 min	94	--	--
2	**1.25b** (L = -OMe)	rt	4 h	66	18	--
3	**1.25c** (L = -Cl)	-78	~ 5 min	97	--	--
4	**1.25d** (L = -Br)	-78	~ 5 min	99	--	--
5	**1.25e** (L = -I)	-78	~ 5 min	99	--	--
6	**1.25f** (L = -OMs)	-78	~ 5 min	96	--	--
7	**1.25g** (L = -OH)	rt	3 h	94	--	--
8	**1.25h** (L = -OAllyl)	rt	4 h	45	46	--
9	**1.25i** (L = -OTBS)	rt	4 h	24	72	--
10	**1.25j** (L = -SEt)	rt	4 h	45	43	--
11	**1.25k** (L = -SOEt)	-78	5 min	73	--	--
12	**1.25l** (L = -SO_2Et)	-78	5 min	93	--	--
13	**1.25m** (L = -NEt_2)	-78	5 min	95	--	--
14	**1.25n** (L = -H)	rt	6 h		37[e]	--

[a] *To a mixture of about 0.1 mmol of the starting material and 20 equiv of MeOH in 5 mL of THF was added SmI2 solution under Ar.*
[b] *Reactions at -78 oC were added 2.2 equiv of SmI2, and reactions at rt were added 3.0 equiv of SmI2.*
[c] *The time started since SmI2 solution was added into the reaction via syringe pumb over a period of 5 minutes.*
[d] *Isolated yields.*
[e] *54% Starting material was recovered..*

Table 1.3 SmI_2-Mediated Deconjugation of Secondary γ-Substituted Esters



Entry	Compound[a]	Stereo-chemistry	Temp (°C); Time[b]	Yield[c] 1.30(%)	1.30[d] Z/E (%)	Yield[c] 1.31 (%)
1	**1.29a** (L = -Cl)	racemic	-78; 5 min	95	18/82	--
2	**1.29a-(*R*)** (L = -Cl)	*R*	-78; 5 min	95	19/81	
3	**1.29b** (L = -Br)	racemic	-78; 5min	99	25/75	--
4	**1.29b-(*R*)** (L = -Br)	*R*	-78; 5 min	98	25/75	
5	**1.29c** (L = -I)	racemic	-78; 5 min	97	43/57	--
6	**1.29c-(*R*)** (L = -I)	*R*	-78; 5 min	96	43/57	
7	**1.29d** (L = -OAc)	racemic	-78; 5 min	97	37/63	--
8	**1.29d-(*S*)** (L = -OAc)	*S*	-78; 5 min	94	36/64	
9	**1.29e** (L = -OMs)	racemic	-78; 5 min	92	23/77	--
10	**1.29e-(*S*)** (L = -OMs)	*S*	-78; 5 min	96	20/80	
11	**1.29f** (L = -OH)	racemic	rt; 4 h	92	30/70	--
12	**1.29f-(*S*)** (L = -OH)	*S*	rt; 4 h	90	33/67	
13	**1.29g** (L = -OMe)	racemic	rt; 6 h	56	19/81	38
14	**1.29h** (L = -OAllyl)	racemic	rt; 6 h	26	26/74	71
15	**1.29i** (L = -OTBS)	racemic	rt; 6 h	0		93
16	**1.29j** (L = -SEt)	racemic	rt; 6 h	45	33/67	43
17	**1.29k** (L = -SOEt)	racemic	-78; 5 min	86	25/75	--
18	**1.29l** (L = -SO_2Et)	racemic	-78; 5 min	85	33/67	--
19	**1.29m** (L = -NEt_2)	racemic	-78; 5 min	85	25/75	--

[a] *To a mixture of about 0.1 mmol of the starting material and 20 equiv of MeOH in 5 mL of THF was added SmI2 solution under Ar.*
[b] *Reactions at -78 oC were added 2.2 equiv of SmI2, and reactions at rt were added 3.0 equiv of SmI2. The time started since SmI2 solution was added into the reaction via syringe pumb over a period of 5 minutes.*
[c] *Isolated yields*
[d] *The ratios were based on the integration of 500 MHz 1HNMR.*

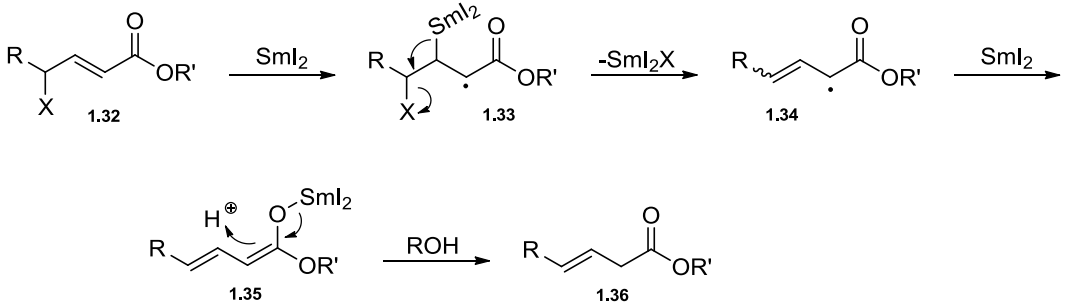


Figure 1.6 Mechanism of SmI_2-Mediated Reductive Deconjugation

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CHAPTER 2

THE DEVELOPMENT, SYNTHESIS AND BIOLOGICAL EVALUATION OF *C*-27 DES-METHYL NORTHERN HEMISPHERE SIMPLIFIED BRYOSTATIN ANALOGUE

Introduction

The planet we share is called Earth, and it is the only planet in our solar system whose name is not derived from Greek or Roman mythology.[1] The name "Earth" originates from the Old English word "eor(th)e" or "ertha", which can be traced back to an Anglo-Saxon word "erda" and its Germanic equivalent 'Erde', meaning ground or soil. Ironically, our planet "Earth" is something of an "ocean planet". The oceans cover about 71% of the surface of our planet and over 90% of the volume of its crust.[2] Actually, all the exposed planetary land has a mean elevation of about 840 meters, and can be completely hidden in the oceans, which have an average depth of 3795 meters. The total volume of the oceans is estimated at about 1.37×10^9 km. Considering that a typical milliliter (cm^3) of seawater contains approximately 10^3 fungi, 10^6 bacteria and 10^7 viruses,[3] gigantic amounts of microorganisms exist in the oceans. To adapt to and survive in diverse marine environments, from the frigidity of the Antarctic Ocean to overheated hydrothermal vents, from photic continental shelves to dark benthic zones, from highly salty areas to extremely toxic and acidic regions, marine life, especially the microorganisms, have enormous

biodiversity, and many of them have no terrestrial equivalents. For example, with more than 30 recognized phyla, all Animalia are represented in the oceans except the phylum Onychophora.[4]

Thanks to a complex system of biochemical reactions, marine organisms produce some organic molecules which are called metabolites. They are further divided into primary metabolites and second metabolites. The primary metabolites are used by cells for their own function and reproduction in favor of a single origin of life, which is a common phenomenon to all living organisms from bacteria to human beings. On the other hand, the secondary metabolites are not necessary to maintain the producers' essential growth, but represent diversity and specificity to help them adapt to the unique environments to get better chances of survival and development. The primary metabolites thus reflect the unity of the living world, while the secondary metabolites represent its diversity.[5] Many of these marine metabolites demonstrate antiviral, anti-inflammatory, antitumor, cytotoxic, neurotoxic and other strong biological activities, which are of considerable biochemical interest. They are still the major source of drug models, drug leads and promising pharmaceutical agents today.

However, intense study of the oceans, especially for the purpose of pharmaceutics, began very late in the history of human beings. In all recorded human history, the earliest documented medicine may date back to a time as early as 3,000-4,000 years ago in ancient Egypt, India, and China.[6] Until the 19th century terrestrial plants and animals were still utilized as the main source of medicinal agents. Historically, humans had the misconception that the massive ocean was only a huge reservoir of terrestrial streams and a place for fishing. This situation was changed when modern chemical and biological

sciences developed. The discoveries of penicillin by Fleming in 1928[7] and sulfonamides by Gerhard Domagk in the 1930s[8] opened the gate to the "Golden Age of Antibiotics". At that time, terrestrial microorganisms became the focal point for one of the most prolific drug discovery methods ever. The intensity of these investigations to discoveries of new microorganisms reached virtually all accessible terrestrial environments, from frigid arctic areas to tropical regions. Although the massive ocean was less probed, pioneering work by Claude Zobell,[9] Giuseppe Brotz[10] and Werner Bergmann[11] revealed a new, incredibly diverse world to us. In the middle of the 1970s, the systematic investigations of marine environments as new sources of novel pharmaceutical agents began intensely. Bacteria, fungi, certain groups of algae, sponges (phylum Porifera), bryozoans, cnidarians (formerly coelenterate), and mollusca were the most studied marine organisms among the phyla found in the oceans.

Discovery of Bryostatins

Bryostatins and Their Origin

In the context of raising interest in marine organisms, George R. Pettit and his collaborators found some extracts exhibiting extraordinary antineoplastic activity, which were from certain marine animals including bryozoans (the name means "moss animals", phylum Bryozoa) and other invertebrates and vertebrates from a broad geographic area.[12] These compounds were further isolated and identified from 500 kg of bryozoan *Bugula neritina* (Figure 2.1) collected from the Gulfs of Mexico, California, and Sagami off Japan. Because of their origin and biological activity, these compounds were named bryostatins. The structure of bryostatin 1 was elucidated by crystallographic and spectroscopic

techniques,[13] and was further confirmed by X-ray diffraction analysis of a heavy atom dispersion of 7-*p*-bromobenzoate derived from bryostatin 2.[14] Currently, a total of 21 bryostatins have been isolated and well documented, mainly as a result of the work of Pettit and colleagues.[13-27.]

Figure 2.2 summarizes the structures of all 21 members of the bryostatin family. All of them are featured with a unique 26-membered macrolactone skeleton, in which a smaller 20-membered ring was embedded, and some constant structures. The larger macrolactone ring contains three highly functionalized pyran rings (referred to as A-, B-, and C-rings anticlockwise from the right northern side to the southern part of the molecule sequentially) that are successively linked by a methylene bridge, an *E*-geometrical olefin, and an ester tether; all the bryostatins have germinal dimethyl at *C*-8; and all the family members have free hydroxyl groups at *C*-3, *C*-9 and *C*-26. Most bryostatins have an exocyclic methyl enoate in both their B-ring (*C*-13) and C-ring (*C*-21), except bryostatin 3, 19, and 20, which have a fused butenolide instead of the aforementioned methyl enoate. Virtually, each bryostatin has a free hydroxyl group at *C*-19 as a part of cyclized hemiketal moiety, but bryostatin 16 and 17 have this hydroxyl eliminated and possess a glycal moiety. In most cases, the vast variation occurs at *C*-7 on the A-ring and *C*-19 on the C-ring. Bryostatin 21, the latest member, is surprisingly different from others, which has only one methyl group at *C*-18 instead of germinal dimethyl, and demonstrates increased cytotoxicity.[27]

Most bryostatins are isolated from bryozoan *Bugula neritina* from diverse geographical origins, but are also found in another bryozoan species, *Amathia convoluta*.[28] Bryozoans mainly living on bacteria and phytoplankton are fouling organisms, and usually colonize on the surface of other substrates, such as algae, shells, rocks and boat hulls. Because they

are specifically preyed upon by sea slugs and fish, as a strategy for their survival, secondary metabolites, which are often toxic, are secreted to defend against external attacks. Thus the bryozoans were recognized as the ultimate origin of bryostatins. However, this notion was challenged by several facts. The low abundance of bryostatin collected from *B. neritina* (Table 2.1); bryostatin ratios varied between different sites and depths where the bryozoans were harvested (average abundance 10^{-6}-10^{-5} wt%[28] except at the Gulf of Aomori in Japan[29]); and all the other marine organisms containing bryostatins were found within the biomass of bryozoans.

By using a small subunit (SSU) of ribosomal RNA gene sequence, Haygood and Davidson discovered a noncultured symbiotic bacterium which was a new species of γ-proteobacteria, and named it "*Candidatus* Endobugula sertula". They also suggested that this symbiont was the actual producer of the bryostatin.[30] Evidence collected by molecular techniques supported this hypothesis. After an antibiotic-treatment of *B. neritina* larvae, the content of bryostatins was reduced concomitant with the reduction of *Candidatus* Endobugula sertula which could not be eliminated, whereas the bryozoan hosts were not affected by this treatment. [31,32] Moreover, the different strains found in the *Candidatus* Endobugula sertula were always coincident with the diversity of bryostatins.[33,34] Additional evidence came from the role of *Candidatus* Endobugula sertula in the biosynthesis of bryostatins. Expression of mRNA from the *bry* gene cluster (a bacterial gene cluster containing a sequence of gene codes from several modular polyketides synthases) was detected by *in situ* hybridization in *Candidatus* Endobugula sertula cells, not in the host *B.neritina* cells. And the biosynthetic compound 'bryostatin 0', which was the precursor of bryostatins, was produced by the symbiont *Candidatus* Endobugula

sertula.[32] Later, the Haygood group tried to express this *bry* cluster in another host to produce the bryostatin or its precursor, and tried to regulate the process of bryostatin biosynthesis.[35]

Attractive Biological Activities of Bryostatins

As the initial aim of Pettit's group was to find antineoplastic agents from marine organisms, bryostatins exhibited extraordinary antitumor activities at the very beginning of their discovery. In the first report, a 168-200% life extension against murine P388 lymphocytic leukemia cell lines (PS system) was observed in several doses.[12] Later, this group documented in detail ED_{50} (effective dose to reduce the cytopathic effect of a given virus by 50% *in vitro* tests) values of most bryostatin members known by that time against the same cell lines. At the same time, an incredible T/C ($\frac{T}{C} = \frac{average\ time\ of\ the\ survial\ of\ the\ tested\ group}{average\ time\ of\ the\ survival\ of\ the\ control\ group}\ x\ 100\%$) value was reported as high as 170-200% of bryostatin 1.[13-24,28] Generally, the ED_{50} reflects the antiviral activity of tested compounds, and it is considered very active when the value is less than 1 g/mL. And a pure product is regarded as interesting when its T/C ratio is larger than 125%. Most bryostatins demonstrate the ED_{50} results at the scale of 10^{-3} ug/mL (Table 2.1)! Therefore, great attention was attracted on these compounds, and they were quickly in clinical investigations. Soon, a wide range of biological activities of bryostatins were discovered, which included growth inhibition, immune stimulation, cell differentiation, nervous system activation, and so forth. These activities were recognized to associate with protein kinase C isozymes (PKCs), according to the initial experiments by Blumberg's group at the US National Cancer Institute (NCI).[36,37]

Biology of Bryostatins - PKC Activators

Protein Kinase C (PKC)

A kinase, in biochemistry, is a type of enzyme that catalyzes the transfer of phosphate groups from phosphate donor molecules to specific substrates in living organisms. A protein kinase, directly from its name, is a kinase enzyme that transfers the phosphate to proteins, specific substrates, to regulate their functions. In the human body, a total 518 protein kinases, constituting about 1.7% of all human genes, regulate an estimated 30% of all human proteins![38]

Classification of PKCs

Protein Kinase C (PKC) is a family of protein kinase enzymes that control the proteins containing serine or threonine amino acids particularly, and play an important role in the cellular signal transduction associated with proliferation, differentiation, apoptosis, transformation, cognition, and so forth. It was discovered by Yasutomi Nishizuka at Kobe University in 1977. The enzyme which was first identified needed a calcium (in PKC, C is for calcium) ion to fully activate itself.[39] Nowadays, the PKC family is composed of 10 isoforms (isozymes) at least (the former PKC-μ and PKC-υ are now classified in PKD[40]), which can be further classified into three groups, namely classical PKC (cPKC), novel PKC (nPKC) and atypical PKC (aPKC), based on their protein structure and the necessity of a secondary messenger (a second activator or cofactor). All the PKCs share the same structure in common, consisting of a regulatory domain and a kinase domain (or catalytic domain). Typically, the regulatory domain contains C1 and C2 (or C2-like), two highly conserved functional modules, except those of aPKCs which do not have the C2 modules.

The kinase domain has C3 and C4 functional modules (Figure 2.3).

Structure of PKCs

The regulatory domain is at the N-terminal of PKCs. The C1 module is a cysteine-rich motif duplicated in most isozymes (except in aPKCs), called C1A and C1B. These two siblings are the binding sites for the endogenous ligand diacylglycerol (DAG) as well as for the exogenous ligands such as phorbol esters, but they do not have equal chances to bind to the ligands.[41] In aPKCs, the C1 module is not duplicated, and its single ligand-binding pocket cannot bind to any activator such as DAG because it is impaired. Towards the NH_2-terminal, the C1 module is attached to a pseudosubstrate (PS) region, which is a small sequence of amino acids without serine or threonine phosphoacceptor residues. For this reason, the PS keeps the enzyme inactive when it is mimicking a substrate binding to the kinase domain, thus preventing the activation of the enzyme by inappropriate stimuli and conditions.

The C2 module contains the recognition site for acidic lipids. The three PKC subtypes have a huge difference in this module. In cPKCs, the C2 module contains a Ca^{2+} binding site, and binds to anionic phospholipids in a Ca^{2+}-dependent manner. In nPKCs, the real C2 module is replaced by a structurally similar C2-like module which does not have any functional group to modulate Ca^{2+} binding. In aPKCs, no C2 residue exists. Instead, a protein-protein interaction module PB1 (Phox and Bem 1) is contained, which regulates interactions with other proteins containing PB1.

The C-terminal kinase domain is responsible for the phosphotransfer activity, and hosts the C3 and C4 modules which bind respectively to ATP and the substrate to be

transphosphorylated. Besides these two modules, the kinase domain also contains some phosphorylation sites, which are essential to activate the enzymes. The cPKCs and nPKCs have three phosphorylation sites, namely activation loop, turn motif (TM), and hydrophobic motif (HM). The aPKCs only have the first two sites for phosphorylation, whereas the subsititution of a glutamic acid for a serine in the third region makes the phosphorylation impossible in this site due to the same electronic charge of the phosphorylation donor and the receiver.

The regulatory domain and kinase domain are connected by a hinge. When the enzyme is bound to a membrane, this hinge is proteolyzed and the two domains are separated, and a proteolytically generated kinase domain (protein kinase M) is then released.

Activation of PKCs

Based on the structural differences, these PKC isozymes exhibit varying co-factor regulation and activity. To active the cPKC (α, βI, βII and γ) isozymes, which are initially identified by Nishizuka, a diacylglycerol (DAG) for the C1 module, a Ca^{2+} ion for the C2 module, and a phosphatidylserine for the phosphorylation sites in the kinase domain are necessary. The activation of nPKCs (δ, ε, η and θ) is similar to that of the cPKCs, expect the former is in a Ca^{2+}-independent manner. The aPKCs (ζ, ι/λ) are significantly different from the other two PKC subtypes with respect to the C1 module, the C2 module, and the phosphorylation sites, and no DAG and Ca^{2+} are required for the activation. Since the aPKCs do not bind to DAG, they do not bind to any DAG-competing ligands, such as tumor-promoting phorbol esters, either.[42]

When PKCs are inactive, the pseudosubstrate motif in the regulatory domain mimics a substrate and is bound to the substrate-binding pocket in the C4 module, thereby suppressing kinase activity.

The first step of activation is a rate-limiting phosphorylation step at the activation loop of the kinase domain by an upstream kinase 3-phosphoinositide-dependent kinase-1 (PDK-1).[43,44] This phosphorylation is mediated by another lipid molecule phosphoinositide 3-kinase (PI3K) and in a PI3K-dependent manner. The PI3K pathway produces an inositol phospholipid containing an additional phosphate at its third position, which subsequently activates the PKD-1 and then the PKC.[45] In the case of cPKCs, the phosphorylation of the activation loop promotes the autophosphorylation of the turn motif (TM), followed by the autophosphorylation of the hydrophobic motif (HM), which is the major determinant of PKC's stability. In the case of nPKCs, additional kinases are required for the third phosphorylation, i.e., the phosphorylation of the hydrophobic motif (HM).[46] After all the three residues are phosphorylated, the cPKCs and nPKC are converted into thermally active conformations and are ready to receive the signals from secondary messengers.[43,44,46-48] In the case of aPKCs, the PDK-1 phosphorylation of the turn motif (TM) is catalyzed by a rapamycin complex 2 (mTORC2),[49] and an acidic phosphomimetic (e.g. aspartic or glutamic acid) in the hydrophobic motif (HM) enhances the binding to PKD-1.

At this stage, PKCs are "mature", but are not activated yet. To become catalytically active, PKCs need to bind to cofactors. These cofactors (secondary messengers) are produced by an enzyme phospholipase C (PLC) that facilitates the hydrolysis of phosphoinositides. Promoted by agonists (external signals), PLCs catalyze the hydrolysis of 4,5-bisphosphate (PIP_2) to generate DAG, whose prominent intracellular targets are the

PKC family and inositol trisphosphate (IP_3) which mobilizes intracellular calcium (Ca^{2+}).[50] The Ca^{2+} binds to the C2 module of cPKCs, and increases the affinity of cPKCs for membranes (negatively charged lipids) by electrostatic interaction in a coordinated manner. However, this affinity is relatively low, and cPKCs still diffuse within the plane of the lipid bilayer. After Ca^{2+} signaling, the binding of the membrane-restricted DAG to the C1 module enhances the affinity for membrane lipids, and changes the conformation of the cPKC. The pseudosubstrate motif is then expelled from the substrate-binding pocket, resulting in the activation of the cPKC (Figure 2.4).[51,52] Due to the lack of Ca^{2+} binding sites, the nPKCs are an order slower than the cPKCs to translocate to membranes. Since the aPKCs do not bind to DAG and Ca^{2+}, they are translocated to membranes by the interaction of the PB1 module with lipid components, such as arachidonic acid, ceramide and phosphatidylinositol-3,4,5-trisphosphate. Generally, the translocation of PKC isozymes from the cytosol to membranes is the sign of activation. However, this is only a simple model that is not sufficient to explain all the complex reality.

Distribution of PKCs and Signal Transduction

Some proteins act as anchoring proteins (intracellular receptors) for PKCs, and they are divided into receptors for inactive C-kinase (RICKs) and receptors for activated C-kinase isozymes (RACKs).[53] The PKCs interact with RACKs through their regulatory domains,[54] while release of PKCs from RICKs is promoted by PKC activators.

These anchoring proteins play an important role in the distribution of PKCs. By changing receptors, inactive PKCs are translocated from cytosols to membrane lipids as activated ones. Moreover, each PKC isozyme has its unique and specific function,[44,54,55]

and the isozyme-specific binding relationship of PKCs to RACKs/RICKs is responsible for the heterogeneity, not only in the unique subcellular localization of different PKC isozymes but also in the different intracellular distribution of the same isoform respective to tissues, cell types, and organisms.[55] For instance, some isozymes, such as PKC-α, PKC-δ and PKC-ζ, are expressed widely and are recognized in all tissues;[55,56] while other isozymes are found only in a specific tissue or several tissues, such as PKC-βIs in the spleen, PKC-βIIs in the spleen and brain, PKC-η in keratinocytes, PKC-θ in skeletal muscle, T cells and epidermis, and PKC-ι/λ in the testis and insulin-secreting cells.[55-57] In addition, the distribution of PKCs in subcellular compartments varies depending on the organism, tissue, and stimulation. Different diets can also affect the expression and localization of PKC isozymes.[55-57] Peptides that mimic either the PKC-binding site on RACKs or the RACK-binding site on PKCs are isozyme-specific translocation inhibitors of PKCs.

After the translocation on various membranes including plasma, nuclear membranes, and cytoskeleton via their anchoring proteins, PKCs initiate signal transduction via phosphorylation of various proteins and enzymes downstream, therefore regulating their properties and activities. For instance, PKCs activate Akt signaling and regulate cell migration-related molecules, including focal adhesion kinase, paxillin, and vinculin. Because of their important role in signal transduction cascades and specific functions, PKCs, as well as their activators and receptors, have gained extensive attention as therapeutic targets for several diseases.

Bryostatins and Disease Therapies

Generally, with few exceptions, the biological activities of all bryostatin family members are essentially the same. The differences are only the extent of potencies in a given system.

Bryostatin and Cancer

In cancer cells, PKC isozymes participate in cell proliferation, apoptosis, migration, angiogenesis, invasion, and anticancer drug resistance as in the same way of the signal transduction in normal cells. Figure 2.5 illustrates the regulation and signal transduction pathways of PKCs in cancer cells. These cascades shown in black arrows indicate that the PKCs play an active role in the process directly or indirectly, while the red arrows indicate they act in an inhibitory role. For example, the PKCs increase the proliferation and survival of cancer cells via their association with the stimulation of the Ras-Raf-MEK-ERK pathway, one of the most important signaling pathways in cancer. Mediated by PKCs, the pathway is initiated by the binding of a signal ligand to a growth factor receptor tyrosine kinase on the cell surface, and this signal is transferred to the cell nucleus subsequently via Ras, Raf, mitogen-activated protein kinase (MEK) and finally extracellular signal-regulated kinase (ERK), which regulates gene expression in cell division, growth, differentiation, and migration. Meanwhile, the expression of apoptotic signals or pathways, such as the caspase cascade or Bax subfamily, which are related to the suppression of cancer, are inhibited. It is worth noting that PKC isozymes may exhibit similar expression patterns and functions in several types of cancer, but in some cases they demonstrate specific patterns and functions largely engaged in the specific type of cancer concerned.

For instance, cPKC-α demonstrates a proliferative effect in several types of cancers, but has an antiproliferative function in colon cancers.[58,59]

As good competitive binding ligands for the C1 module of PKC isozymes, bryostatins are able to bind to various individual PKCs. The abovementioned isozyme-specific binding relationship between PKCs and their receptors distributes the specific PKC-bryostatin complexes to the different compartments of cells, and subsequently modulates PKC's functions and expression patterns within the cells.[53]

Some tumors are caused by that overexpression or up-regulation of some PKC isozymes stimulates the Ras-Raf-MEK-ERK pathway of cancers. For example, elevated nPKC-ε levels in rat NIH3T3 cells and fibroblasts made them both malignant and tumorigenic,[60,61] also high cPKC-α levels were related to human A549 lung cancer.[62] For those overexpressed PKC isozymes, bryostatins were able to selectively down-regulate them through an induced conformational change via binding, thus favoring plasma membrane insertion and degradation. In the high cPKC-α level case, treatment with bryostatin 1, the growth of A549 lung cancer cells was inhibited by down-regulation of bryostatin 1 activated cPKC-α.[62] The detailed mechanism was demonstrated by using the ^{32}P labeled cPKC-α in renal epithelial cells along with cPKC-α and nPKC-ε in human fibroblasts.[63-65] After activation and transfer to the plasma membrane, these activated PKC complexes were dephosphorylated by membrane-bound alkaline phosphatases, resulting in catalytically inactive complexes which were ready for ubiquitination, referred to as the "kiss of death" for proteins. The ubiquitin-attached PKCs were then proteolyzed and degraded.

The development of cancer is also due to the apoptotic pathways of cancer cells being

suppressed. nPKC-δ isozymes are responsible for the proliferation and apoptosis of cells. Overexpression of nPKC-δ in mouse keratinocytes inhibited tumors successfully via the apoptosis of cancer cells.[66] Blumberg and coworkers found that the tumor-promoting phorbol ester PMA translocated nPKC-δ to the plasma membrane primarily, where these isozymes suffered down-regulation seriously.[67,68] Bryostatins could protect some tumor-suppressors including nPKC-δ isozymes from undergoing down-regulation in certain cells.[67,69,70] With the isozyme-specific binding relationship, bryostatin 1 translocated them mainly to the nuclear membrane, and therefore prevented them from being proteolyzed.[68] One additional example was that nPKC-δ isozymes, which were involved in the contact-dependent inhibition of growth in human FH109 and murine NIH3T3 fibroblasts, were prevented from being down-regulated by co-application of bryostatin 1 and PMA.[70]

Bryostatin and Immune System Disorders

Among the key players of the immune system, nPKC-θ isozyme has an unique role in immune responses.[71] This family member of PKCs modulates several important molecules, including nuclear factor kappa-light-chain-enhacecer of activated B cell (NF-κB), activator protein 1 (AP-1), mitogen-activated protein kinase (MAPK), and c-Jun N-terminal kinase (JNK). Those molecules are critical in regulating the immune response to bacterial and viral infections, in directing cell proliferation and apoptosis, and in controlling the transcription of DNA and cytokine production. nPKC-θ also interacts with downstream effectors to regulate the activation, differentiation, and migration of T cells, which are a type of white blood cell that plays a central role in cell-mediated immunity. Disorders of nPKC-θ lead to several diseases, such as inflammation, autoimmunity, muscular dystrophy,

and cancer.

Besides the direct antineoplastic properties, numerous studies have shown bryostatins have strong immunostimulatory activities. Medicated by PKCs, bryostatin 1 was able to activate human resting T and B cells, and then promoted their proliferation.[72,73] Bryostatin 1 also stimulated the tumor antigen-specific cytotoxic T lymphocytes (CTLs) to produce a variety of cytokines, including tumor necrosis factor-α (TNF-α), TNF-γ and certain interleukins (IL),[74-77] which were normally produced after immunostimulation by the body. Synergized by IFN-γ, bryostatin 1 significantly elevated both levels of nitic oxide (NO) measured as accumulated nitrite (NO_2^-) in culture supernatant and inducible nitric oxide synthase (*i*-NOS) gene expression in the murine macrophage cell line ANA-1.[78] The *i*-NOS gene was known to catalyze the production of NO, which also induced apoptosis in tumor cells, from an amino acid L-arginine. Nagarkatti's group demonstrated that bryostatin 1 could activate bone marrow-derived dendritic cells, which were antigen-presenting cells and played a critical role in the regulation of the adaptive immune response as a toll-like receptor 4 (TLR4) ligand.[79] In vivo treatment, the dendritic cells promoted a TLR4-dependent activation of NF-κB, and induced a variety of cytokines, including interleukins (IL-5, IL-6 and IL-10) and chemokines (RANTES and MIP1-α). In vivo administration of bryostatin 1 induced a TLR4-dependent T helper cell 2 (Th2) cytokine response, and increased a subset of myeloid dendritic cells.[79] All the studies suggested that the antitumor activities of bryostatins could be partially ascribed to their immunostimulatory properties.

It is worth noting that the immunostimulatory activities of bryostatins are associated with their *C*-20 side chains. The class of *C*20-deoxy bryostatins such as bryostatin 13 does

not exhibit this activity. In the stimulation experiment of normal human hematopoietic cells, bryostatin 1, 3, 8, and 9, all of which had *C*-20 carboxylic side chains, could directly stimulate bone marrow progenitor cells to form colonies *in vitro* and could functionally activate neutrophils; whereas bryostatin 13 without *C*-20 side chain fail to do so completely.[74] Similarly, bryostatin 1 but not bryostatin 13 was able to induce human polymorphonuclear neutrophil (PMN) and monocyte release of reactive oxygen radicals.[80]

AIDS is still an incurable disease which is caused by the virus HIV. HIV attacks the CD4+ T cells, which are a type of white blood cell helping the immune system fight off infections, thus weakening and destroying the body's immune system. Current HIV/AIDS therapies can only turn this "death sentence" into a chronic illness, since they have no effect on latent HIV-infected cells. When a small fraction of the HIV-infected CD4+ T cells stays in a quiescent state, the HIV genomes inside are latent until the cells are activated. Thus, HIV can hide itself for as long as the drugs are taken. When antiretroviral therapy is interrupted, the HIV-infected cells become active eventually, and trigger the replication and spread of the HIV quickly. Clinical studies of bryostatins as promising agents to eradicate the latent HIV are under way. Bryostatin 1 reactivated the latent HIV-1 through a classical PKC-dependent pathway in Jurkat-LAT-GFP cells, a tractable model of HIV-1 latency.[81] Through MAPKs and NF-κB pathways, bryostatin 1 synergized with several histone deacetylase (HDAC) inhibitors which were used in current medical practice to antagonize HIV-1 latency. Bryostatin 1 also prevented *de novo* HIV-1 infection in susceptible cells by downregulating the expression of the HIV-1 co-receptors CD4 and CXCR4. Bryostatin 5 inhibited chemotaxis induced by a chemokine stromal cell-derived factor 1 (SDF-1) in Jurkat cells, due to induced receptor desensitization and

downregulation of cell surface CXCR4.[82]

Bryostatins and Neurological Disorders

PKC is present in nervous systems in high concentrations. Actually, the brains of many animal species are the most abundant source of PKCs in terms of both quantity and species. Therefore, PKCs are involved in a variety of neuronal functions. By regulating proliferation and apoptosis the same way as in other cells, PKCs influence the process of neurite outgrowth or necrosis. For instance, PKC plays an important role in neuronal differentiation and synaptogenesis via HuD-mediated mRNA stability in the hippocampal neurons.[83,84] nPKC isozymes are associated with plasmalemmal repair (sealing), which is vital for the survival of damaged neurons.[85] For victims of neurotrauma, loss of nerve cells leads to loss of functional behaviors and even paralysis. PKC is also the key player of synaptic plasticity, which is the ability of synapses to change the connection strength between neurons and is the foundation for the models of learning and memory. The most widely studied form of synaptic plasticity in mammals is long-term potentiation (LTP), a mechanism for the establishment of stable memories. Evidence demonstrates that activation of PKCs, particularly cPKC-α, nPKC-ε and PKMζ (the independent catalytic domain of aPKC-ζ), is critical in developing LTP.[86-89] It is believed PKMζ is synthesized *de novo* as an active kinase which is involved in the molecular mechanism of lasting memory.[90,91] Memory task learning is also associated with cPKC-γ immunoreactivity in the principal hippocampal neurons and cholinergic receptors.[92,93]

Intensive studies demonstrated that bryostatins greatly repaired and improved memory and learning by activation of the PKCs which were involved in synaptogenesis, presynaptic

ultrastructural specialization, and protein synthesis.[94] In the Morris spatial water maze task, improved performance of rats was observed upon the intracerebral ventricular administration of bryostatin 1.[95] After 15 days' treatment of bryostatin 1 and training, the densities of mushroom spine synapses and memories of the aged rats that had lower levels were restored to the levels of young rats, thus reversing the decline in aging.[96] Stimulated by bryostatin 1, PKC activation induced the synthesis of proteins necessary and sufficient for subsequent long-term memory consolidation in *Hermissenda*, a sea slug and valuable animal model for studying the mechanisms of learning and memory.[87,94,97] Further study proved that bryostatin could activate cPKC-α and nPKC-ε, and therefore facilitated LTP induction in the Schaffer-collateral fibers of the hippocampus.[87]

Alzheimer's disease (AD) is closely associated with the plaques which are clumps of the protein pieces referred to as β-amyloids. These amyloid plaques are involved in the destruction of brain cells, though the ultimate causes of brain-cell death in AD are not fully understood. When amyloid precursor protein (APP) is cleaved by β-secretase and γ-secretase, the "sticky" β-amyloids are produced and gradually build up to form plaques, resulting in inflammation and cell-to-cell signaling obstruction. α-Secretase enzyme preferentially stimulates APP processing toward the nontoxic soluble α-amyloid precursor protein (sAPP-α) and precludes β-amyloid formation, thereby suppressing inflammation and angiogenic processes.[98,99] Thus, an increase in α-secretase cleavage is considered a therapeutic approach for AD. It is known that PKC isozymes can activate α-secretase. As a nontumor activator of PKCs, bryostatins significantly improved cognitive performance in AD mouse models, and reduced extracellular senile plague formation.[99] In AD double-transgenic mice, bryostatin 1, at the concentration of 0.1 nM or 0.01 nM, dramatically

enhanced the secretion of the α-secretase and produced soluble sAPP-α in fibroblasts from AD patients. Furthermore, the accumulations of both β-amyloid-40 and β-amyloid-42 were reduced efficiently.[100]

Bryostatins and Cancer Multidrug Resistance (MDR)

Many chemotherapy drugs suffer failure in cancer therapies due to multidrug resistance (MDR) developed by cancer cells. Among various mechanisms, the drug efflux pump MDR is predominant. In this mechanism, the ATP-binding cassette transporter membrane proteins, such as P-glycoprotein (P-gp), referred to as the multidrug efflux pump, are responsible for the expulsion of drug out of the cell. After exposure to chemotherapy drugs, cancer cells overexpress the P-gp protein, which is broadly distributed in cancers and is encoded by the multidrug resistance 1 (MDR1) gene. By an ATP-dependent efflux of the drugs and decreasing their intracellular concentration, the cellular functions of cancer cells are not impeded. Since PKCs, particularly cPKC-α and nPKC-ε, promote the P-gp-mediated MDR, inhibition of the corresponding PKCs is a therapeutic approach to remove MDR, therefore enhancing the apoptosis of cancer cells.[101]

In the course of bryostatin antitumor studies, it was found that bryostatin 1 was able to modulate the P-gp-mediated MDR. Bryostatin 1 could reverse the resistance to chemotherapy drugs vinblastine and colchicine in two cell lines overexpressing a mutant MDR1-encoded P-gp, namely KB-C1 and HeLa cells transfected with an MDR1-V185 construct (HeLa-MDR1-V185) in which glycine at position 185 (G185) was substituted for valine (V185).[102] It also was reported that bryostatin 1 decreased MDR1 RNA expression after 24 hours in a diffusing large cell lymphoma (DLCL) model after sequential

administration of anticancer drug vincristine and bryostatin 1.[103]

Bryostatins and Synergistic Interactions

Much attention is also focused on synergistic interactions between bryostatins and other cytotoxic agents. When bryostatin 1 is used in combination with other chemotherapy drugs, the antitumor effect is greater than the sum of its individual effects. Therefore, lower dosages of cytotoxic agents can be used to obtain better therapeutic effects with fewer side effects and less potential MDR. This is achieved by downregulating antiapoptotic protein B-cell lymphoma 2 (Bcl-2), which prevents programmed cell death (PCD), and by upregulating cytotoxic drug-mediated caspases, which control cell apoptosis.[104] For instance, the leukemia patients who had failed in high-dose cytosine arabinoside (Ara-C) therapy exhibited highly positive responses with the administration of a combination of high levels of Ara-C and low levels of bryostatin 1, including 5 complete responses out of 23 patients.[104] Some early cases of synergistic interaction between bryostatin 1 and other drugs, which trigger further evaluations in clinical trials, are summarized in Table 2.2.[105] However, it is worth mentioning that these synergistic effects largely exhibit both schedule- and dose-dependence.

Bryostatins in Clinical Trials

To date, bryostatin 1 has been in more than 80 clinical trials, including more than 20 trials completed at both phase I and phase II levels. Although several other members of this family have been used in animal tests and preclinical trials, only bryostatin 1 has been evaluated in human clinical trials so far. The main reason is that the isolation required to

meet the current good manufacturing practice (cGMP) regulations for clinical trials is prevented by the abundances of bryostatins in natural sources (Table 2.1). Most of the bryostatin 1 used in clinical trials was collected from the Bay of California under the NCI's auspices.

The study undertaken in mice demonstrated that bryostatin 1 was widely distributed in many organs but accumulated in the lung, liver, gastrointestinal tract, and fatty tissue.[106] The major side effect of bryostatin 1 in humans was dose-limiting myalgia whose maximum toxicity was of WHO grade 3.[107] Other minor adverse reactions were photophobia, eye pain, headache, and flu-like symptoms, which were occasionally reported in several clinic trials.

Initially, bryostatin 1 was investigated in a variety of monotherapies of solid or blood tumors, including melanomas, epithelial ovarian, pancreatic carcinoma, breast, esophageal, gastric, renal, myeloid and varied leukemia cancers, as a promising antitumor agent. Unfortunately, phase II trials exhibited minimal activity of bryostatin 1, though the results of phase I trials were encouraging. Moreover, relapses arose in many cases soon after the treatment was interrupted. Therefore, bryostatin 1 was not effective enough to enter phase III trials as a single chemotherapeutic agent.

Soon, the discovery of its synergistic effect with other cytotoxic drugs and the ability to decrease MDR led bryostatin 1 into a new direction of cancer therapy. Recently, bryostatin 1 was investigated in combination with paclitaxel, cisplatin, fludarabine, vincristine and other cytotoxins in several cancer therapy phase I and phase II trials. It was reported that a combination of bryostatin 1 and vincristine or fludarabine succeeded in the treatment of Non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia

(CLL).[108] The efficacy of this combination was achieved in a phase II study too.[109] The overall response rate was 31%, with two complete-response cases.

Currently, bryostatin 1 is involved in a phase I trial against HIV infection (identifier number: NCT02269605), and two phase II trials against Alzheimer's disease (NCT00606164 and NCT02431468). These trials have not been completed yet, and they may broaden the application of bryostatins in PKC-target therapies.

Bryostatin Supply

Due to extensive studies by the medical community, the annual demand of bryostatin 1 is estimated to be in the range of about 100–200 g. To date, almost all of the supply still depends on the collection of natural source material.

Natural Sources (Wild Collection)

The low abundance of bryostatin 1 in its natural source makes its isolation exceptionally difficult and costly. This is exemplified by a typical isolation conducted under the NCI's auspices.[110] After the demonstration of its antitumor activity in the initial preclinical trial, gram quantities of bryostatin 1 of the current Good Manufacturing Practice (cGMP, regulations enforced by FDA for the design, monitoring and control of pharmaceutical manufacturing processes and facilities) grade were required for phase I and phase II studies. Collected off the coast of California, approximately 12.7 tons (12,7000 Kg) of wet bryozoans *B. neritina*, corresponding to a volume of about 40,000 L in isopropanol, shipped to the lab in Colorado. The bryostatins were then concentrated to 78 L via a four-stage extraction-concentration process, which was further divided into 15

aliquots each of 5.2 L. Each aliquot was subjected to chromatography on a column approximately 1 m in length and 50 cm in diameter, containing 53 Kg of silica gel. After 15 purifications of a multistep procedure, a total of 18 g of 99% pure bryostatin 1 was isolated after 10 months of work! Later, technique improvements, especially the substitution of supercritical fluid extraction (technique of the American company Aphios) for conventional liquid-liquid extraction, reduced the processing time to under a month and provided the bryostatin 1 with a similar purity in higher yield. The market price of bryostatin 1, however, is still about 150 US$ for 10 ug.

Besides the cost, ecological considerations also necessitate a new source of bryostatins. In a long term view, it is not possible to harvest bryostatin largely from its natural sources. Therefore, considerable effort has been devoted to the obtention of alternative sources.

Aquaculture and Biosynthesis

The limitations of wild collections were recognized at the very beginning of the isolation "direct from the sea". In the early 1990s, the NCI funded a now-defunct company CalBioMarine via the Small Business Innovation Research program (SBIR) to investigation aquaculture of *B. neritina* for the acquirement of bryostatins. Subsequently, the contract (phase I) was extended to phase II, and the project was successful. It was claimed by the former president of the company that bryozoans were capable of growing under controlled-system conditions both on land and in sea, with the lowest environmental impact when compared with open-sea systems, which were all subject to the unpredictable vagaries of nature. The isolation of bryostatins from aquacultured animals was in adequate quantities and proved cost-effective, though significant optimization of feeding, recovery

and other protocols was needed.[111] However, the aquaculture supply was never implemented in market. Soon after that report was published, CalBioMarine closed its business due to a funding deficit.

During the course of the collaboration with CalBioMarine in aquaculturing bryostatins, the Haygood group found that a bacterial flora was associated with the production of bryostatins. This noncultured symbiont bacterium, referred to as *Candidatus* Endobugula sertula,[32] was suggested to be the actual producer of bryostatins.[30] Later, this group identified and cloned the putative biosynthetic gene cluster of this bacterium successfully. By using this cluster, a macrolidic structure called bryostatin 0 was produced, which might be further elaborated by tailoring enzymes to achieve the real bryostatin molecules. Further identification of different symbionts from other *Bugula* species producing bryostatins led to the discovery of the putative *bryA* gene cluster.[112] Recently, the complete putative genomic sequence of *bryA* was elucidated. Unfortunately, neither the *Candidatus* Endobugula sertula cluster nor *bryA* cluster has been successfully expressed in a heterologous host. Moreover, to date, the tailoring enzymes aforementioned converting bryostatin 0 into real bryostatins have not been elucidated yet.

Chemical Synthesis

Chemical synthesis was another potential option for bryostatin supply. The first total synthesis was that of bryostatin 7 by Masamune and co-workers in 1990.[113] Seven years later, Evans' group reported a remarkable symmetric total synthesis of bryostatin 2 in 1998.[114] In 2000, bryostatin 3, one of the most complex types containing a fused butenolide, was synthesized by Nishiyama and Yamamura.[115] A relatively short and elegant synthesis

of bryostatin 16, involving metal-catalyzed reactions, was reported by Trost's group in 2008.[116] Up to that time, bryostatin 1 was never formally synthesized, though Pettit's group demonstrated bryostatin 1 could be converted from bryostatin 2 or 12.[117] In 2011, the Keck group published an impressive asymmetric de novo total synthesis of bryostatin 1.[118] Almost at the same time, bryostatin 9 was synthesized by Wender et al.,[119] a pioneer in early bryostatin analogue design and synthesis. Further, two additional total syntheses of bryostatin 7 were also reported by Hale et al. in 2006 and Krische in 2011,[120,121] along with the synthetic efforts of several other research groups.

While great achievements have been made in the total synthesis of bryostatin 1 and its analogues, none of them can be used to supply sufficient amounts of bryostatins in practice. All these synthetic approaches are either too long or complex. For instance, the shortest route still requires more than 36 steps.

More importantly, bryostatins are produced by bryozoans for their own sake, but not for human beings as therapeutic drugs. Therefore, bryostatins demonstrate unsatisfactory clinical performances as a monotherapeutic reagent for tumors, and several undesired side effects. Thus, the structural modification of bryostatins is necessary to improve their biological activities and to remove off-target effects. These modified bryostatins (analogues) are also useful probes for us to explore PKC's profile. Consequently, the analogues of bryostatins are a more feasible solution and an active area of current research.

Bryostatin Analogues

A multitude of naturally occurring compounds are PKC activators (Figure 2.6), and therefore modulate various biological events, such as cell proliferation, differentiation,

apoptosis and so on. Many of these compounds, including phorbol esters and teleocidins serving as drug leads, are investigated in clinical trials against some diseases. Actually, most exogenous PKC ligands are associated with a range of tumor-promoting activity. For instance, the indolactam teleocidins exhibit relatively weak tumor-promoting properties, while the phorbol ester PMA is one of the most potent tumor promotors. Bryostatins are unique in that they are little known for their tumor-promoting properties[122] and even suppress the tumor-promoting effects of PMA when co-administrated.[123]

As good competitors with the endogenous ligand DAG in binding to the C1 module of PKC isozymes, bryostatin 1 and PMA share highly similar binding affinity (K_i). On the other hand, they differ from each other in downstream effects. In primary mouse keratinocytes, bryostatin 1 at low concentrations downregulated nPKC-δ to a similar extent to PMA, but at high concentration bryostatin 1 antagonized PMA and protected nPKC-δ from downregulation.[69] Their distinguished biological activities were probably ascribed to their lipophilicity and their distribution via isozyme-specific function.[67,68,70] The more hydrophilic ligand bryostatin 1 translocated nPKC-δ mainly to the nuclear membrane, whereas the more hydrophobic ligand PMA translocated it to the plasma membrane in CHO-K1 cells. In addition, bryostatin 1 but not PMA exhibited a transient response followed by loss of responsiveness in primary mouse epidermal cells.[124] Bryostatin 1 could cause more rapid downregulation of some PKCs as compared to PMA. The mechanisms of the behaviors of different PKC ligands are not fully understood. Analogues of bryostatins are excellent models to clarify the mechanism of cellular signaling pathways involving PKC, thus facilitating the development of PKC-targeted pharmaceuticals.

Wender's Analogue Study

Wender's Initial Analogue Design

The collaboration of the Wender, Blumberg, and Pettit groups resulted in a pharmacophoric model of bryostatin, based upon various structure-activity studies of several PKC activators.[125] By comparing the binding affinities of bryostatins and their semisynthetic derivatives to PKC, it was soon recognized that the *C*-26 hydroxyl group was involved in binding, since either esterification or epimerization of this functional group caused significant loss of binding affinity (Figure 2.7, entries 1-3, 5-6). Because PKC activators bound to the C1 module of PKCs in a competitive manner, it was reasonable to postulate that DAG, PMA, and bryostatins shared a common chemical structure as a pharmacophore which interacted with the proteins. Using the *C*-26 hydroxy group as a reference, computational studying revealed additional binding elements involving the *C*-1 carbonyl and *C*-19 hydroxyl groups. These three oxygen heteroatoms composed a triad, which could be superimposed on the corresponding triads in the structural rigid PMA and endogenous DAG (Figure 2.8). Significantly, these triads were in the lowest energy conformation, which was critical in fitting the lipid domains in spatial array. Later evidence derived from an X-ray crystal structure strongly supported this hypothesis.[126] The complex of phorbol 13-acetate bound to the C1B motif of murine nPKC-δ demonstrated the 3D model of the triads in the reality (Figure 2.8).

In contrast, minor modification of only bryostatin's northern hemisphere did not affect binding affinity considerably. Neither epoxidation of the *C*13-*C*30 exocyclic olefin of bryostatin 4 nor hydrogenation of that of bryostatin 2 changed the binding affinities significantly (Figure 2.7, entry 4, 8).[125,127] However, when the hydrogenation product

aforementioned was further hydrogenated on the *C*21-*C*34 olefin of C-ring, the binding affinity varied dramatically (Figure 2.7, entry 9). It was concluded that the essential property of bryostatin's northern hemisphere was a lipophilic element referred to as spacer domain. It did not interact with or bind to PKCs directly, but served to properly align the conformation of molecules for binding.

It is very clear that this hypothesis focuses on binding affinity. It cannot explain the difference between tumor-promoters and nonpromoters. Nevertheless, it is still a good starting point for the exploration of bryostatins and their analogues.

Wender's Analogues

Under the guidance of this hypothesis, Wender's group synthesized a great number of bryostatin analogues. Their strategy was to divide the molecule into two pieces, northern and southern pieces, for maximum convergent benefit. The southern hemisphere retained the pharmacophoric C-ring for binding to PKCs, and the northern fragment was allowed for modification and simplification. With a few exceptions, the macrolactone scaffold was maintained in order to mimic the conformation of bryostatin 1. The coupling of two fragments was accomplished by Yamaguchi esterification and acetalization cyclization. An alternative macrocyclization approach was the construction of the *C*16-17 double bound, but it was proved to be a formidable obstacle in many contemporaneous total synthesis efforts due to the adjacent *gem*-dimethyl group. The acetalization was achieved in a mild condition, and could be applied to the reactions in the presence of various sensitive functional groups. Therefore, the naturally occurring tetrahydropyran B-ring was largely replaced by 1,3-dioxane in Wender's analogues.

Several representative bryostatin analogues of Wender's are shown in Figure 2.9. Analogue **2.1,** with a simplified spacer domain, exhibited a comparable PKC binding affinity (Ki =3.4 nM) with bryostatin 1 (Ki = 1.35 nM) when treated with mixed rat brain PKCs.[128] Esterification of the *C*-26 hydroxyl group led to compound **2.2**, which lost its binding affinity drastically, over 3 orders of magnitude. Once again, it was confirmed that the *C*-26 alcohol was an important binding site for PKCs.

In the cases of analogues **2.5-2.9**, the A-ring was depleted, but the *C*-5 and *C*-9 were retained as an ether linkage to maintain the preferred macrocyclic conformation. Their binding affinities were essentially the same as that of analogue **2.1**, indicating that the A-ring was not necessary for keeping PKC potency.[129-131] Further removal of the ether linkage (the compound not shown in Figure 2.9) resulted in the lack of 20-membered macrocyclic backbone, and therefore lost the binding affinity entirely.

Analogues **2.10-2.14** varying at *C*-20 ester proved that this position was not crucial in binding, but was more amenable to the adjustment of the lipophilicity and solubility.[132-134] A simple acyl group **2.10** diminished the binding affinity, while hydrophobic phenyl groups **2.12** and **2.14** or saturated long hydrocarbon chains **2.11** and **2.13** maintained high binding affinities. Thus, the *C*-20 ester could be applied to optimize physical properties, including those related to the pharmaceutical criteria ADME (absorption, distribution, metabolism, and excretion), and could be used to attach a fluorescent tag in mechanism studies.

Although the early study demonstrated that the A-ring had little contribution to the binding affinity, substituents at the *C*-7 could be used to modulate molecule's activity. The magnitude of alteration in binding affinity depended on both the type of functionalities

(**2.15 - 2.17**) and the stereochemistry of the carbon center (**2.18**, **2.19**).[135] This hotspot for PKC affinity discovered in these analogues was not observed in natural bryostatins. It was recommended by the author that the *C*-7 functionalities could potentially be used for the selective regulation of PKC isozymes.

According to Wender's binding hypothesis, the *C*-3 hydroxyl group made a nominal contribution to the binding affinity. However, both the inversion **2.3** and the removal **2.4** of the *C*-3 hydroxyl resulted in the loss of 2 orders of magnitude. This result coincided with the early observation of Kamano's group. By using solution NMR techniques, Kamano et al. found a temperature-dependent variation in chemical shift for the *C*-3 hydroxyl and *C*-19 hemiketal hydroxyl groups, and proposed an intramolecular hydrogen-bonding network.[136] In this network, the H-bonding connected the *C*-3 hydroxyl, *C*-19 hemiketal hydroxyl, and the two oxygens in the tetrahydropyran A- and B-rings together. Thus, this H-bonding was critical for the molecule to maintain the lowest energy conformation. The lack of a proper H-bonding network in *epi*-**2.3** and deoxy-**2.4** led to a distorted conformation, therefore decreasing the binding affinity drastically.

Finally, the removal of the *C*-27 terminal methyl group eliminated the adjacent stereocenter, while still retaining high PKC potency, demonstrated by analogues **2.15-2.19**. It can be used to simplify future analogue syntheses.

Keck's Analogues Study

Markó-Keck Annulation Strategy

The Keck group has committed to the development of new synthetic methodology and the total synthesis of natural products for a long time. During the course of bryostatin

analogue program as well as the total synthesis of bryostatin 1, the Markó-Keck annulation and the SmI_2-mediated esterification-reductive cyclization strategies were developed. [137]

Initially, Markó reported a Sakurai-Prins cyclization strategy which he called an "intramolecular silyl-modified Sakurai (ISMS) reaction".[138,139] Envisioning its great convergent value in total synthesis, soon the Keck group further developed this methodology in an asymmetric manner, as well as the reaction condition. Then, they first applied this reaction in a total synthesis, and successfully set up the absolute stereochemistry at the *C*-2 and *C*-6 positions of the resulted tetrahydropyran, with an excellent yield.[140]

Shown in Scheme 2.1, this two-step strategy commences with a CAA (catalytic asymmetric allylation) reaction, establishing the stereocenter of alcohol **2.22**. Promoted by a slight excess of TMSOTf, combination of the *β*-hydroxylallylsilane **2.22** with aldehyde **2.23** provides tetrahydropyran **2.25** at -78 ^{o}C. Anhydrous diethyl ether turns out to be the ideal solvent for this coupling, since it provides the best stereoselectivity and yield.[140] This reaction is via a six-membered chair transition state **2.24**, by which the substituent R_1 at the pre-established stereocenter directs the substituent R_2 in the *syn*-position, and therefore the absolute stereochemistry of the newly formed chiral center. This methodology allows us to quickly install the simplified A- and B-ring scaffolds in our bryostatin analogues.

A- and B-Ring Simplified Analogues

Several A- and B-ring simplified analogues of the Keck group are shown in Figure 2.10.[141-144] These bryostatin analogues are identified via Merle numbers in honor of the

great musician, singer and instrumentalist Merle Haggard. The Keck group collaborates with Dr. Peter Blumberg, who is a leading expert on protein kinases at the National Cancer Institute (NCI), in accomplishing Merle analogue's biological studies. Their aim is to clarify the structure-activity relationships (SARs) of bryostatin 1 and the PKC-mediated mechanism of its antitumor activity, therefore helping develop a highly effective antitumor drug with the fewest necessary structures.

Keck's first bryostatin analogue, **2.26**, which was synthesized by Dr. Truong, was significantly simplified and served as a springboard for their future work. This analogue was designed to validate the application of Markó-Keck annulation in the synthesis of a complex molecule and to probe the roles of *C*-20 ester and *C*-21 exo-enoate. Eventually, the accomplishment of **2.26** provided a synthetically accessible route to a series of analogues.

The synthetic plan is outlined in Figure 2.11. The backbone of the target molecule was achieved from the combination of enal **2.32**, allylsilane **2.33** and **2.34** via sequential ring-annulations as the key reactions, followed by a Yamaguchi macrolactonization. The truncated C-ring enal **2.32** was prepared from an advanced acyclic thioester, which was further derived from the commercially available **2.35** though a serials of carbon-chain elongation reactions, including allylations, prenylation and Horner-Emmons olefination. Both allylsilane **2.33** and **2.34** were obtained from the common source diol **2.36** though the well-established CAA reation,[141] but with different enantioselectivity.

Segment **2.34** was obtained via 6 sequential steps as shown in Scheme 2.2. The synthesis began with the monoprotection of diol **2.36** with a silyl group and then a Swern oxidation to afford aldehyde **2.37**. A Keck's asymmetric allylation installed the

stereocenter in alcohol **2.38**, with both excellent yield and enantioselectivity. The resulting alcohol was strategically protected as the PMB ether **2.38**, which would participate in 1,3-chelation controlled allylation. After an oxidative cleavage, the resulting aldehyde **2.39** was converted into β-hydroxyallylsilane **2.34** as a single diastereomer. The TMS-allylstannane, which was used in the last step, was also used to react with aldehyde **2.37** to produce compound **2.33** by Keck's asymmetric allylation.

The longest linear sequence in this synthesis was the preparation of enal **2.32** (Scheme 2.3). The chiral lactate **2**.**35** was protected as a BOM ether, which would be engaged to achieve 1,3- chelation, and then the resulting intermediate was reduced to aldehyde **2.40**. Chelation-controlled allylation by reaction with allylstannane in the presence of $MgBr_2$ etherate provided a homoallylic alcohol, which was protected by PMB, leading to compound **2.41**. After ozonolysis, the resulting aldehyde **2.42** was subjected to a second chelation-controlled allylation, followed by silyl ether protection to provide olefin **2.43**. Hydroformylation was accomplished under the Buchwald conditions catalyzed by bulky ligand BIPHEPHOS, which enriched the desired terminal aldehyde **2.44**. Indium-mediated prenylation followed by a chromium-based oxidation afforded ketone **2.45**. The alkene unit in this ketone was oxidatively cleaved, and the resulting aldehyde was elongated by Horner-Emmons reaction to provide α,β-unsaturated thiol ester **2.46**. The introduction of thiol ester instead of oxyl ester into the conjugated molecule was due to its ability amenable to half reduction. This acyclic thiol ester **2.46** was deprotected by fluoride reagent, and the resulting intermediate was converted into glycal **2.47** catalyzed by CSA in benzene. Finally, DIBAL half-reduction of the thiol ester provided enal **2.32** in high yield.

The first pyran annulation was the coupling of enal **2.32** and allylsilane **2.33** to

construct the simplified B-ring (Scheme 2.4). The resulting molecule **2.48** was then converted into aldehyde **2.49** after the removal of the TBDPS-protecting group and the exposure to oxidation. Subsequently, a second pyran annulation combined allylsilane **2.34** with **2.49** smoothly, and installed the truncated A-ring in compound **2.50**. At this time, the C-ring was functionalized by several transformations including epoxidation, methanolysis and TPAP oxidation. Then, trivial manipulations of protecting groups afforded a seco-acid ready for Yamaguchi macrolactonization. With macrolactone **2.51** in hand, Keck's first bryostatin analogue **2.26** was achieved after global deprotection by $LiBF_4$.

The analogue containing a fully functionalized C-ring was synthesized by Dr. Sanchez from the highly advanced intermediate **2.51** (Scheme 2.5).[142] The free hydroxyl was protected as silyl ether **2.52**, which in turn was subjected to an aldol reaction to provide a diastereomeric mixture. The exo-enoate **2.53** was obtained by an elimination reaction under Burgess' protocol. Luche reduction and a benzoic anhydride esterification installed the *C*-20 ester side chain. A global deprotection provided the analogue **2.27** referred to as Carina 1, which was later renamed as Merle 21. Using a similar strategy but a different order of construction A- and B-rings, Dr. Li and Dr. Kraft synthesized Merle 22 and 23, varying in the size of *C*-20 side chain.

Analogue **2.26** has a binding affinity at Ki = 546 nM, which is over 2 orders of magnitude smaller than that of bryostatin 1 (Ki = 0.48 nM). Similarly, Merle 24 and 25 as shown in Figure 2.10, both lacking exo-enoate at the *C*-21, suffer drastic losses in binding affinity (37.7 nM and 47.1 nM respectively). In contrast, Merle 21, which has the *C*-21 carbomethoxyenoate group, maintains the binding affinity (Ki = 0.70 nM) almost the same as that of bryostatin 1. Previously, Pettit et al. reported a semisynthesis study on bryostatin

2.[127] Simultaneous hydrogenation of the *C*-13 exo-enoate, *C*-20 octadienoate side chain and the *C*-21enoate led to a 100-fold decrease in binding affinity, whereas only hydrogenation the first two positions introduced little impact on the affinity and the resulting analogue was as potent as the original compound (Figure 2.7). All the evidence strongly indicates that the *C*-21enoate plays a crucial role in maintaining the binding affinity. This functional group probably keeps the C-ring in the optimized conformation for the molecule to bind to PKCs.

Merle 21, 22 and 23, containing the simplified northern hemisphere of bryostatin 1, retain the C-ring's essential skeleton of bryostatin 1, including the *C*-21 enoate. The subtle difference between them is the size of the *C*-20 side chain. Their PKC-α potencies (0.70 nM, 1.05 nM and 0.70 nM, respectively) are quite similar to that of bryostatin 1 (0.40 nM). Our results are in accord with the Wender's findings that a modification only in the *C*-20 side chain will not alter the binding affinity drastically.

As noted earlier, the tumor-promoting PMA and antineoplastic bryostatin 1 as PKC activators obtain comparable potency to PKC isozymes, but demonstrate different biological activities. The U937 human leukemia cell lines and the LNCaP human prostate cell lines are good candidates for their identification, because PMA and bryostatin 1 behave distinctively in both cell line assays.

In the U937 cell lines, phorbol ester PMA inhibited proliferation and induced attachment in a dose-dependent manner, whereas bryostatin 1 had less impact on either. Instead, bryostatin 1 would suppress the effect of PMA when co-administered. Figure 2.12 shows the results of U937 proliferation and attachment experiments with Merle 23,[143] Merle 21 and 22 exhibit almost identical results, and therefore their results and diagrams

are not displayed here. In these experiments, the U937 cells were treated with PMA (0.1-100 nM), bryostatin 1(0.1-1000 nM), and Merle 23 (1-1000 nM) for 72 hours. When PMA was co-administered with other compounds, its concentration was 10 nM. The numbers of attached cells were counted, and the attached cells were graphed as percent of total cells. The bars and error bars represented the average percentage and the standard error, respectively. In the cases of mono-administration, Merle 23, along with Merle 21 and 22, resembled tumor-promoting phorbol ester PMA in a dose-dependent manner, and displayed different behavior from bryostatin 1. When Merle-23 was co-administered with PMA, no antagonistic effect against PMA was observed, which was shown by bryostatin 1. In the K-562 human erythroleukemia cell line assays, Merle 23 also exhibited a behavior pattern similar to PMA for inhibiting cell growth.[144,145] That bryostatin analogue Merle 23 resembled the biological response of PMA and not bryostatin 1 in U937 cells strongly suggested that the A- and B-rings of bryostatin 1 play a key role in discriminating bryostatin itself from tumor-promoting PMA.

In order to gain further insight into the relationship between the structural features of bryostatin analogues and their biology, the LNCaP human prostate cell line assays were utilized for the evaluation.[145] In this second system, phorbol ester PMA inhibited proliferation and induced apoptosis, whereas bryostatin 1 failed to do so. The inhibition effect of an indicated compound on cell growth was represented by the difference in confluency of the cells before treatment and 72 hours later, and the apoptosis effect was detected after 48 h treatment. Merle 23 resembled bryostatin 1 and not PMA, neither inhibiting cell growth nor inducing apoptosis (Figure 2.13). When Merle 23 was co-administered with PMA, the latter agent was antagonized in a pattern similar to that of the

combination of bryostatin 1 and PMA. In addition, Merle 23 also demonstrated bryostatin-like effects on tumor necrosis factor alpha (TNF-α) secretion and cell cycle analysis. The cell cycle is the series of events leading to a cell's division and duplication of its DNA, and TNF-α is a key player in the regulation of immune cells. They are both closely associated with a cell's proliferation and apoptosis.

However, the pattern of behavior of Merle 23 relative to bryostatin 1 and PMA was largely determined by the specific conditions.[145] Proteasome inhibitors, such as the well-characterized lactacystin and MG-132, shifted the response pattern of the LNCaP cells to Merle 23 from bryostatin-like to PMA-like, including inhibition of cell growth, apoptosis, and TNF-α secretion. For example, TNF-α secretion induced by Merle 23 was increased in the presence of proteasome inhibitors and the effects of Merle 23 and PMA became similar, whereas the level of TNF-α induced by bryostatin 1 remained very low.

Merle 23 was further compared with bryostatin 1 and PMA in PKC signaling pathways, namely MAPK pathways, using Nano-Pro technology to detect the phosphorylation of the known PKC substrates MARCKS and PKD1.[145] In a number of these downstream responses in LNCaP cell assays, Merle 23 showed a duration of response intermediate between those of bryostatin and PMA. Distinct patterns of down-regulation of the PKC isoforms were also shown for these three compounds. PMA had equal potency for down-regulation of all PKC isoforms and of PKD1. Bryostatin 1 down-regulated PKC-δ biphasically, as described previously,[69] and it was the most potent and efficient in down-regulating PKC-α. It was the least potent in down-regulating PKC-ε and PKD1. Merle 23 was unique in being the most efficient for down-regulating PKC-δ, but the least efficient for PKC-α. It was PMA-like for down-regulating PKC-ε and PKD1. Furthermore, Merle

23, bryostatin 1 and PMA translocated PKCs from cytoplasm to different membrane structures, including plasma membrane, nuclear membrane and mitochondria in distinct patterns. In the translocation study with endogenous PKC-δ, PMA mainly induced the translocation of PKC-δ to plasma membrane, while bryostatin 1 translocated most of it to cytoplasm and internal membranes. Merle 23 was unique, and demonstrated a different translocation pattern from those of PMA and bryostatin 1. PKC-δ localized to both plasma membrane and cytoplasm after the treatment with Merle 23. These findings clearly proved that Merle 23 could not be simply characterized as bryostatin-like or PMA-like.

Overall, Merle 23 displayed a highly complex pattern of activity, depending on the specific conditions and mechanistic changes. It could be bryostatin-like, PMA-like, intermediate in its behavior, or more effective than either. Byrostatin properties could not be simply understood at the level of binding affinity for PKC isozymes, and there was not a single pharmacophore conferring a bryostatin-like as distinct from a PMA-like pattern of response. Dr. Blumberg also suggested that Merle 23 would be considered a novel bryostatin derivative with its own effects, which provided powerful tools to dissect subsets of bryostatin mechanism and response.

Total Synthesis of Novel Analogue Merle 41

Analogue Design and Retrosynthetic Plan

To further evaluate bryostatin structure and activity relationships, a novel bryostatin analogue, **2.54**, is designed. It is based on Merle 23, since analogue Merle 21, 22, and 23, especially Merle 23, demonstrate a complex pattern of activity. To maintain the high binding affinity to PKCs, the binding triad involved in Wender's hypothesis and the *C*-21

enoate vital for keeping the optimized conformation are retained in the new molecule design. The modification is the removal of the *C*-27 terminal methyl. This functional group does not interact with PKCs directly, and both PMA and DAG contain a terminal alcohol in the same position. It is of interest to know the function of this methyl group in bryostatin biological responses.

The necessity of the *C*-26 stereocenter is another matter of great concern. The removal of the *C*-27 methyl group results in the elimination of the *C*-26 stereocenter. It would benefit future analogue synthesis, but could also alter potency. The epimerization of this chiral center in bryostatin 4 decreased the binding affinity significantly (Figure 2.7, entry 2).[125] In contrast, Wender synthesized his most potent analogue "picolog" with the absence of the *C*-27 methyl group, which was more potent than bryostatin 1.[133] However, his picolog contained a 1,3-dioxane B-ring rather than the naturally occurring tetrahydropyran. This variation would induce a conformational distortion, especially in the presence of hydrogen-bond. In addition, not all the Wender's des-methyl analogues maintained high binding affinity.

The successful syntheses of Keck's first analogue and Carina 1 (Merle 21) provided us a feasible and convergent route for accessing a series of bryostatin analogues. Actually, the major disconnections of Keck's first analogue were found in the majority of the Merle analogues. Again, the proposed analogue **2.54** would follow the same synthetic strategy, which is outlined in Figure 2.14. The late stage macrolactonization was expected to be cyclized by Yamaguchi's protocol. Both truncated A- and B-rings were constructed by our pyran-annulation strategy as the key steps. Thus, the analogue **2.54** was disconnected into three pieces. The C-ring aldehyde **2.55** was prepared from allyl alcohol **2.56** via several

carbon-chain elongation reactions which were utilized in the synthesis of Keck's first analogue. Since there was no chirality in this commercially available compound, an asymmetric allylation reaction was applied to set the first desired chiralcenter. The segment **2.33** and **2.34** were both derived from diol **2.36**.

Results and Discussion

*Synthesis of the C-Ring Aldehyde **2.55***

The synthesis of aldehyde **2.55** began with the protection of the commercially available allyl alcohol **2.56**. The BOMCl was freshly prepared by the combination of paraformaldehyde and benzyl alcohol in TMSCl at room temperature.[146] Long-term storage degraded the quality of BOMCl. The crude product **2.57** was subjected to ozonolysis, providing aldehyde **2.58** in 84.2% yield over 2 steps. Alternatively, aldehyde **2.58** could be obtained from 1,4-butendiol in the same way, but dimerization of BOMCl was up to 30% in the first step. Keck's catalytic asymmetric allylation (CAA) reaction with (*R*)-BITIP afforded homoallylic alcohol **2.60** with the desired stereocenter in 93% yield and 99% ee. It was planned that this chiral center at *C*-25 would later be used to establish another stereocenter at *C*-23 through 1,3-chelation control. For this reason, alcohol **2.60** was strategically protected as PMB ether **2.61**. Oxidative cleavage of the olefin with ozone provided aldehyde **2.62** (Scheme 2.6).

With the aldehyde **2.62** in hand, the next reaction was allylation via 1,3-asymmetric induction. A chelation-controlled allylation with stannane **2.59** was initially applied according to the plan. However, a large variety of common chelating *Lewis* acids, including $MgBr_2 \cdot OEt_2$, $Ti(OPr^i)_2Cl_2$, $AlMe_2Cl$, $TiCl_4$ and $SnCl_4$, resulted in moderate

diastereomeric selectivity or side reactions. The best diastereomeric ratio was 4:1, favoring the desired stereocenter. Generally, for a 1,3-asymmetric induction reaction, either internal-chelated transition state or open-chain nonchelated transition state preferred the same diastereomeric selectivity. Therefore, the reaction was also investigated in nonchelated conditions. Unfortunately, the results were far from satisfactory. Using nonchelating *Lewis* acid, such as BF_3 and TMSOTf, or replacement of PMB protecting group by nonchelating silyl group did not improve the selectivity. Finally, a second CAA reaction with (*S*)-BITIP was applied to install this stereocenter in **2.63** with 89% yield and 99% dr on a 20 g scale.

Alcohol **2.63** was protected with TBS group, and the resulting olefin **2.64** was subjected to the hydroformylation conditions developed by Buchwald et al.[147] The results were not consistent with our early experience. The major side reaction was the double bond migration, which led to an unwanted branched aldehyde. Later, it was found that using degassed THF as a solvent was able to solve this problem. By slightly increasing the pressure of syngas, the desired aldehyde **2.65** was obtained with approximate 90% yield consistently.

In our initial experiments, relatively expensive indium metal was utilized for prenylation. Application of zinc dust in aqueous conditions lowered the cost of this reaction, and made manipulations easier.[148] More importantly, this reaction demonstrated exclusive regioselectivity. Crude product **2.67** was obtained as a single regioisomer with quantitative yield. In addition, no purification was necessary at this time. After normal workup, the purity was larger than 95% based on ^{1}H NMR integration (Scheme 2.7).

Oxidized under Swern-modified Moffatt's conditions, the racemic alcohol **2.67** was

converted into ketone **2.68** smoothly. After ozonolysis and sequential Horner-Wadsworth-Emmons reaction with phosphonate **2.70**, the exclusive *E*-olefin **2.71** was produced in one pot with 86% yield. The TBS protecting group was successfully removed by buffered hydrofluoric acid. Using a Dean-Stark apparatus, the resulting free alcohol **2.72** was cyclized and dehydrated in the refluxing toluene with a catalytic amount of CSA. Half reduction of thio-ester **2.73** with DIBAL at low temperature provided enal **2.55** with the essential skeleton of the natural C-ring.

Pyran-Annulation Modification and Synthesis of the Truncated B-ring

The pyran-annulation between aldehyde **2.55** and *β*-hydroxyallylsilane **2.33** installed the truncated B-ring. However, the yield obtained under the standard conditions was capricious and relatively low.[140] A trace of TfOH acid was suspected to be the perpetrator, which induced the decomposition of the acid sensitive moieties, especially the glycal and allylsilane. Actually, the desired compound **2.74** was observed when the polar byproduct was resubmitted to the previous dehydration condition.

Thus, pyridine and other amines were examined to evacuate the trace amount of acid (Table 2.3). It was found that sterically hindered amines, such as triethyl amine and *N*,*N*-diisopropylethylamine, did not prevent the decomposition. They merely acted as bases, and facilitated the protection of the *β*-hydroxy group of the compound **2.33** by TMSOTf. In contrast, addition of a limited amount of pyridine (less than 0.2 equiv respect to aldehyde) largely suppressed decompositions, and the alcohol protection was negligible. When the amount of pyridine was increased to 0.4 equiv, the protection reaction became noticeable, but the resulting TMS ether of **2.33** was still reactive in the pyran-annulation reaction.

Consequently, a much longer period of time was required to complete the reaction. When the amount of pyridine was more than 0.5 equiv, this reaction turned out to be an alcohol protection reaction. Overall, the best results were achieved when 0.2-0.3 equiv of pyridine was added; more pyridine led to an incomplete reaction. To our delight, with this modification, the reaction yield was improved by 20-30%, and the final yield was up to 90% (Scheme 2.8).

To avoid the interference of the labile glycal in the remaining synthetic steps, we decided to oxidize the glycal moiety and fully functionalize the C-ring at this moment. Thus, compound **2.74** was treated with *m*CPBA in methanol. It was chemoselectively epoxidized and subsequently opened with methanol *in situ*. The resulting ketal was subjected to a catalytic amount of PPTS, which shifted the equilibrium of the epimeric mixture further towards the thermodynamically more stable isomer **2.75**. The methoxy group at *C*-19 occupied the axial position, favored by the anomeric effect. These transformations were conducted after the first pyran-annulation because of the "*gem*-dimethyl" effect or Thorpe-Ingold effect. If the abovementioned transformations were accomplished on enal **2.55** or α,β-unsaturated thioester **2.73**, an undesired Michael addition between the *C*-20 alcohol and α,β-unsaturated carbonyl was inevitable. The additional quaternary center adjacent to the *C*-18 *gem*-dimethyl group further significantly increased the propensity of cyclization, which was called "double Thorpe-Ingold effect" by Hale in his review.[149] Similar instances were documented by the Keck group[144] and several other groups.[149,150]

The relatively unstable **2.75** was immediately oxidized to ketone **2.76** with Dess-Martin periodinane in high yield. The addition of *tert*-butyl alcohol was to accelerate the reaction.

Mediated by K_2CO_3, the exocyclic methyl enoate was efficiently furnished by aldol condensation with freshly distilled methyl glyoxylate. It was obtained as a single isomer, whose geometry was predicted by $A^{1,3}$ strain. The Luche reduction of **2.77** proceeded satisfactorily to afford the relatively unstable alcohol **2.78** as a single diastereomer. A subsequent esterification with **2.79** under standard Yamaguchi conditions provided **2.80**, and completed the functionalization of the C-ring (Scheme 2.8).

The absolute configuration of the *C*-23 stereocenter was assigned by Mosher ester analysis of **2.63**. It was, in turn, used to determine the stereochemical and conformational relationships of the substituents on the C-ring with NOESY1D, ROSEY1D and 2D-NOESY experiments. The strong NOE effects observed among the concerned atoms or groups solidly supported our assignment of the stereochemistry. In a similar way, the stereogenic information of the B-ring was also revealed (Figure 2.15).

The geometry of the C-ring exocyclic enoate was confirmed by both NOESY1D experiment and chemical shift variation. The obvious NOE effect between the *C*-20 proton and *C*-34 proton indicated they were close in space. Another convincing piece of evidence came from the observation that Luche reduction significantly changed the chemical shift of the *C*-34 proton. It moved from 6.57 ppm to 5.91 ppm upfield after the ketone reduction. It was well documented that the reduction of ketone **2.83** had little effect on the chemical shift of the remote enoate proton (Figure 2.15).[151,152] In contrast, the removal of the carbonyl group of **2.81** made the chemical shift of the nearby enoate proton move upfield drastically.[151, 153] This was due to the removal of the strong magnetic anisotropic effect of the vicinal carbonyl group.

The following steps were taken to prepare for the second Markó-Keck annulation. The

TBDPS group removed by NH_4F in methanol at reflux, and the resulting alcohol **2.85** was oxidized with DMP providing aldehyde **2.86** in excellent yield (Scheme 2.9). Since there was no way to distinguish the two PMB ethers at *C*-3 and *C*-25 after the second annulation, the protecting group replacement was taken at this point. Thus, alcohol **2.87** was liberated after DDQ-mediated PMB cleavage. An attempt was made to protect this alcohol as TBS ether by using conventional agent TBSCl. However, only a trace amount of the desired compound was obtained, even when employing a large excess of TBSCl. The failure of this reaction could be attributed to steric hindrance. Therefore, the more reactive TBSOTf was used, and the protection was completed in 1 h. The desired **2.88** was obtained in 90% yield, and ready for the annulations.

*Modified Scaled Synthesis of Allylsilane **2.34***

The synthesis of A-ring allylsilane **2.34** employed the approaches previously described. Since several synthetic steps were largely scaled up, the procedures were modified and optimized to circumvent the tedious purifications and cumbersome manipulations.

The synthesis was initiated with the monoprotection of 1,3-propanediol **2.36** with TBDPSCl. By using NaH instead of high-boiling-point amine, most side products could be washed out. After a normal workup, silyl ether **2.89** was used directly in the next step without any further purification (Scheme 2.10). It was subsequently oxidized to aldehyde **2.37** under Swern conditions. The catalytic asymmetric allylation reaction of aldehyde **2.37** with **2.57** and (*R*)-BIITS furnished chiral alcohol **2.90** in 98% yield and 98% ee. This reaction set the desired stereocenter at *C*-5, which was confirmed by Mosher ester analysis.

As previously described, a PMB ether was preferred at this site because the protected

alcohol could retain the ability to participate in a chelation-controlled reaction later. However, the purification was particularly troublesome when **2.90** was protected with PMB-acetimidate and traditional catalyst CSA. Fortunately, using catalytic scandium triflate instead of CSA in toluene,[154] only one chromatography was needed to achieve satisfactory separation. Inspired by this result, we briefly investigated the application of other *Lewis* acids in PMB ether formation. We found that $Sc(OTf)_3$, $Sn(OTf)_2$, $Cu(OTf)_2$, $Yb(OTf)_3$, $Bi(OTf)_3$, $BF_3 \cdot Et_2O$ were more effective than CSA, or at least similarly effective. Generally, the purifications of *Lewis*-acid-catalyzed reactions were much easier than those of CSA- or TsOH-treated reactions. However, *Lewis* acid $CeCl_3$, $MgBr_2 \cdot OEt_2$, $CuBr_2$ were not as good as CSA in terms of yield. It was worth noting that a significant silyl group (TBDPS) migration was observed in the alcohol **2.90** under basic conditions.

Next, **2.38** was oxidatively cleaved with ozone, followed by a 1,3-chelation controlled allylation with TMS-allylstannane **2.91** to provide *β*-hydroxylallylsilane **2.34** in 85% yield and with excellent diastereomeric selectivity. *β*-Hydroxylallylstannane was also obtained in approximately 10% yield, because the allylsilane moiety and allylstannane moiety of **2.91** competed with each other in the allylation reaction. Again, the desired chiral center **2.34** was proved by Mosher ester analysis.

Completion of the Synthesis of Des-Methyl Analogue

With the aldehyde **2.88** and β-hydroxyallylsilane **2.34** in hand, we were able to install the A-ring to achieve the tricyclic core of analogue **2.54**. Based on our previous experience, under the standard pyran-annulation conditions, the second annulations generally gave a moderate yield which was quite lower than that of the first annulations. To our delight,

2.92 was obtained in excellent yield (90% !) under our modified conditions. It proved our modified conditions of the annulation were effective and reliable.

With the carbon backbone in hand, we were several steps away from the completion of the des-methyl analogue. Using ammonium fluoride in methanol at reflux, the TBDPS silyl ether at *C*-1 was selectively deprotected in the presence of secondary TBS silyl ether. Subsequently, a Dess-Martin oxidation reaction afforded aldehyde **2.93** in 57% yield over 2 steps. The aldehyde was oxidized into its corresponding carboxylic acid **2.94** under mild conditions which were developed by Lindgren[155] and Kraus[156] (also called Pinnick oxidation). Next, the removal of the *C*-25 TBS group furnished a seco-acid which was ready for macrocyclization. Yamaguchi macrolactoniztion with high dilution techniques provided macrolactone **2.95**. Removal of PMB with DDQ and subsequent global deprotection with $LiBF_4$ afforded the *C*-27 des-methyl analogue **2.54** or Merle 41.[157] Finally, ^{1}H NMR, ^{13}C NMR, DEPT, gCOSY, gDQCOSY, gHMQC, gHMBC, NOESY1D, 2D-NOESY, 2D-ROESY and 2D-TOCSY experiments were performed on this analogue to obtain its complete structural and stereochemical information.

Biological Evaluation of Merle 41[158]

Binding Affinity

As we know, the isozyme-specific binding relationship causes different ligands or activators to have different binding affinities to different PKC isozymes. To compare Merle 41 with Merle 23, PKC-α, which was used in Merle 23 evaluation, was bound to Merle 41. The binding affinity of Merle 41 was Ki = 0.73 ± 0.05 nM, and closely matched those of Merle 23 and bryostatin 1 (0.70 ± 0.06 and 0.48 nM, respectively).[143] In contrast

to Wender's "piclog" analogue,[133] removal the *C*-27 methyl did not increase the binding affinity. On the other hand, that it did not interfere in binding supported the binding model.

Growth Inhibition and Attachment Studies

The biological profile of Merle 41 in U937 leukemia cell assays was evaluated. As previously described, U937 cells responded to PMA with growth inhibition, whereas bryostatin 1 caused little growth inhibition. Generally, Merle 23 closely resembled PMA in its effect in U937 cells, but demonstrated a somewhat biphasic dose response. The behavioral pattern of Merle 41 was identical to that of Merle 23 (Figure 2.16). When PMA was co-administered with Merle 23 or Merle 41, U937 response was similar to that of being treated with Merle 23 or Merle 41 alone.

In response to PMA, U937 cells release TNF-α, which contributes to the growth inhibition. Bryostatin 1 induces a negligible secretion of TNF-α. Merle 23 and 41 caused a measurable TNF-α secretion, but the amounts were less than that of PMA (Figure 2.17). The dose response curves of these two analogues for TNF-α secretion were identical, with absolute maximal levels of release of 66.6 ± 2.6% and 65.2 ± 2.6%, respectively. In combination with PMA, Merle 23 and 41 both predominated over PMA, and reduced the level of TNF-α secretion.

Unlike U937 leukemia cell lines, the Toledo cell line is one of the most sensitive cell lines for growth inhibition by both PMA and bryostatin 1 (Figure 2.16). Similarly, Merle 23 and Merle 41 inhibited Toledo cell growth too. All the compounds demonstrated similar inhibition patterns. And again, Merle 41 closely resembled Merle 23 both in potency and in the level of inhibition.

In U937 cell assays, PMA induced attachment while bryostatin 1 almost had no effect. Merle 23 and 41 could motivate the attachment to the same level as PMA did, but they displayed biphasic responses and had fewer attachments compared with PMA at concentration 300 nM or above (Figure 2.17). In the combination of PMA and Merle 23 or Merle 41, both analogues partially suppressed the effect of PMA at high concentration. Once again, the patterns of the two analogues were identical.

Down-Regulation of PKC Isozymes and PKD1

As previously observed, the down-regulation patterns of PKCs for PMA and bryostatin 1 were quite distinct in the LNCaP human prostate cancer cell lines.[145] PKC-α was down-regulated by both PMA and bryostatin 1, while the latter induced more down-regulation. Merle 41 acted as Merle 23, less effective than either PMA or bryostatin 1 (Figure 2.18). At low dose instances, two analogues even moderately increased PKC-α. For PKC-δ, the biphasic curve of bryostatin 1 was observed in a dose-dependent manner. PMA caused more down-regulation than bryostatin 1, but did not exhibit the biphasic pattern. Both Merle 23 and 41 caused more extensive down-regulation than PMA, and closely resembled each other. In the case of PKC-ε, PMA, bryostatin 1, and Merle 23 and 41 demonstrated modest down-regulation patterns, while both analogues resembled PMA and had relatively stronger effects than bryostatin 1. Finally, PKD1 was greatly down-regulated by PMA. Again, Merle 23 and 41 acted similarly to each other, and were bryostatin-like to cause little PKD1 down-regulation.

Translocation of PKC Isozymes

Merle 41, like Merle 23, translocated PKC-δ in a unique pattern quite different from PMA and bryostatin 1. PMA initially translocated PKC-δ mainly on plasma membrane, while bryostatin 1 caused more PKC-δ accumulation on nuclear and internal membranes. Merle 23 and 41 behaved in the intermediate between PMA and bryostatin 1, slightly favoring the bryostatin pattern.

PKC-ε isozyme was translocated to the plasma membrane by PMA. Both analogues were relatively less effective at doing so, and bryostatin 1 had even weaker response to PKC-ε compared with Merle 23 as well as Merle 41. Once again, Merle 41 resembled Merle 23. Because the extents of differences were so small, the comparison of translocations was not able to determine the minor differences in behavior of these compounds.

Dose Dependence of the Induced Gene Expression

To reveal the subtle differences in the response to Merle 23 and 41, the time and dose dependence of the induction of gene expression approach was employed in the evaluations of the responses caused by the analogues in both the U937 cell lines and the LNCaP cell assays. After the treatment for 2 hours, PMA, bryostatin 1, Merle 23 and 43 caused responses similar to each other in LNCaP cells (Figure 2.19). By 6 hours, the responses to bryostatin 1 decreased to variable extents, depending on the type of individual genes, compared with those caused by PMA, and the curves representing the responses to Merle 23 and Merle 41 began to separate from that of PMA. By 24 hours, the curves of Merle 23 and Merle 41 further separated from that of PMA, and were closer to that of bryostatin 1.

In each case, the curve of Merle 41 almost overlapped with that of Merle 23, indicating that the responses to Merle 41 were identical to those to Merle 23 in essence.

The more complex approach, namely the complete dose response curves, was used to examine the response of the individual gene in a dose- and time-dependent manner. Out of the 15 genes examined in the LNCaP cells and the 12 genes examined in the U937 cells, a modest, statistically significant difference in the responses to Merle 23 and Merle 41 was observed in only one case. These results further confirmed that Merle 41 behaved similarly to Merle 23 under virtually all assay conditions.

Conclusion

As part of the extensive synthetic effort to understand the structure and activity relationship of bryostatin 1, a novel bryostatin analogue, Merle 41, was prepared in a convergent manner. The pyran-annulation strategy developed by our group played a vital role in the construction of the simplified A- and B-rings. Using a catalytic amount of pyridine made this reaction more applicable and reliable. This synthesis route was also optimized for scaled synthesis, and the focus was placed on the easiness of manipulation and purification, as well as the efficiency of time and cost.

Merle 41 and Merle 23 are structurally identical except for the *C*-27 methyl group. Although absent the naturally occurring terminal methyl group, Merle 41 retains the binding affinity identical to Merle 23. It indicates that the *C*-27 methyl group does not interfere with the adjacent *C*-26 alcohol in binding, at least in our work. Furthermore, Merle 41 resembles Merle 23 in all the biological responses, including growth inhibition, TNF-α secretion, attachment, PKC isozyme translocation and down-regulation, and

induced gene-expression. All the convincing evidence makes us assume that the effect of *C*-27 methyl group on the biological activities is negligible. The elimination of the *C*-26 stereocenter will facilitate the synthesis of more efficient analogues, therefore having great significance for the future analogue and drug designs.

Merle 23 differs from bryostatin 1 at only four positions in the northern hemisphere. Extensive studies demonstrated Merle 23 and Merle 41 displayed a highly complex pattern of activity, largely depending on the specific biological response and conditions. They could be bryostatin-like, PMA-like, or intermediate between them. Merle 23 and Merle 41 further sustain our understanding that the major pharmacophoric elements are in the southern hemisphere. In addition, several functional groups in the C-ring, including the *C*-19 hemiketal and the *C*-21 exo-enoate, are pivotal in preserving high binding affinity. The northern hemisphere is not a mere spacer domain. The substitution patterns on the A- and B-rings, as well as the cellular pattern involved, determine the behavior of the analogue in biological responses. To better understand the complex relationships behind the structure, the roles of the substituents on the top half of the bryostatin 1 are systematically studied, which will be discussed in the next chapter.

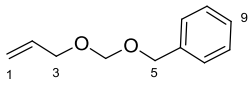
Experimental Section

All solvents were dried and distilled according to the guidelines in *Purification of Laboratory Chemicals, 6th Ed.* (Armarego and Chai, Butterworth-Heinemann: Oxford, U.K., 2009). Diisopropylamine, diisopropylethylamine, triethylamine, pyridine, dichloromethane and ethyl acetate were distilled from CaH_2 under an atmosphere of N_2. Ether solvents (THF and Et_2O) were distilled under N_2 from sodium benzophenone ketyl.

Benzene and toluene were distilled from molten sodium metal under N_2. Solvents and reagents were deoxygenated where necessary by Freeze-Pump-Thaw technique and refilled with nitrogen prior to uses. Titanium tetrachloride and titanium isopropoxide were distilled prior to use. Deuterated solvents were purchased from Cambridge Isotope Laboratories (all ≥ atom% D). Reagents were purchased from Acros, Aldrich and Alfa, and used as received unless stated otherwise. Argon, oxygen, and syngas (1:1 mixture of H_2 and CO) were acquired from Airgas and used as received. Glassware for reactions was oven dried at 110 ºC for 4 hours and cooled down under a dry atmosphere prior to use, or flame-dried under an atmosphere of N_2. All air- and moisture-sensitive manipulations were performed by using oven-dried glassware, standard Schlenk techniques, and a glovebox under an atmosphere of N_2. Analytical thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} plates eluting with the solvents indicated, and visualized by exposure to UV light (254 nm), and stained with either an ethanolic solution of 12-molybdophosphoric acid or a solution of $KMnO_4/K_2CO_3$/NaOH. Organic solutions were concentrated on a rotovap at aspirator pressure at 20-30 ºC. Flash column chromatography was performed on SiliaFlash® F60 silica gel (230-400 mesh, 60Å), and eluted with solvents indicated. Melting points were recored using open capillary tubes on a Mel-Temp electrochemical melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) spectra were acquired on a Variann Inova 500 spectrometer operating at 500 MHz and 125 MHz for ^1H and ^{13}C separately. All ^1H NMR chemical shifts were quoted in parts per million (ppm) relative to the line of the $CDCl_3$ residual singlet at 7.27 ppm (or the C_6D_6 residual singlet at 7.16 ppm), and ^{13}C NMR chemical shifts were relative to the center line of $CDCl_3$ triplet at 77.23 ppm (or the center line of C_6D_6 triplet at 128.62

ppm). Multiplicities in the ^{1}H NMR spectra were described as follows: s = singlet, d = doublet, t = triplet, q = quartet, ABq = AB quartet, quin = quintet, sext = sextet, m = multiplet, br =broad. Coupling constants were reported in Hz. The structural assignments of ^{1}H and ^{13}C NMR spectra were elucidated with the aid of gCOSY, gDQCOSY, TOCSY, DEPT, HMQC, and HMBC experiments. Stereochemical assignments were based on coupling constants where possible, and with the aid of NOSEY1D, ROSEY1D, NOSEY, and ROSEY experiments. AA'BB' systems were reported as doublets. Infrared (IR) spectra were recored from a Perkin Elmer FT-IR Paragon 1000 PC spectrometer using a thin film supported between NaCl plates. Optical rotations were acquired on Perkin Elmer Model 343 polarimeter using Na D-line with a 10 cm path length micro cell at 20 ^{o}C from $CHCl_3$ solutions. Ozone was generated by a Welsbach model T-816 generator. Yields refer to purified and spetroscopically pure compounds.

Allyloxymethyl Benzyl Ether (2.57):



Preparation of BOMCl: To a mixture of paraformaldehyde (3.02 g, 95.7 mmol, 1.0 equiv) and trimethylchlorosilane (50.0 mL, 383 mmol, 4.0 equiv) was added a solution of benzyl alcohol (10.0 mL, 95.7 mmol, 1.0 equiv) dropwise via syringe at room temperature. After 3 hours, solid paraformaldehyde was consumed, and the reaction was concentrated under reduced pressure to provide a colorless oil. The crude product was used directly in the next step without further purification.

With an ice-water bath, to 60% suspension of NaH (7.56 g, 189 mmol, 2.0 equiv) in THF (40 mL) was added allyl alcohol **2.56** (13.0 mL, 189 mmol, 2.0 equiv) dropwise via syringe under an atmosphere of N_2. After 30 minutes, a solution of the aforementioned

crude BOMCl (theoretically 95.67 mmol, 1.0 equiv) in THF (100 mL, 1.0 M) was added dropwise over 1.5 hours via additional funnel. This reaction was allowed to warm to room temperature slowly, and stirred under an atmosphere of N_2 overnight. It was then quenched with an ice cube carefully, followed by the addition of cold 1N HCl solution (100 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with 100 mL of brine and dried over anhydrous K_2CO_3. The solution was filtrated, and concentrated in vacuo. The yellow crude product was used directly in next step without any purification. The analytical sample could be obtained via vacuum distillation collected at 92-94 ^oC/3 mmHg. It was a colorless oil.

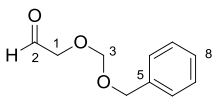
TLC: R_f = 0.57 (Et_2O/Hex = 4:6, v/v);

500 MHz ^1H NMR ($CDCl_3$): δ 7.39-7.33 (m, 8H, ***H-7a***, ***H-7a'***, ***H-7b***, ***H-7b'***, ***H-6a***, ***H-6a'***, ***H-6b***, ***H-6b'***), 7.33-7.28 (m, 2H, ***H-8a***, ***H-8b***), 5.82-5.74 (m, 2H, ***H-1a***, ***H-1b***), 4.78 (s, 4H, ***H-3a***, ***H-3a'***, ***H-3b***, ***H-3b'***), 4.62 (s, 4H, ***H-4a***, ***H-4a'***, ***H-4b***, ***H-4b'***), 4.26-4.19 (m, 4H, ***H-2a***, ***H-2a'***, ***H-2b***, ***H-2b'***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 138.0 (***C-5a***, ***C-5b***), 129.4 (***C-1a***, ***C-1b***), 128.6 (***C-7a***, ***C-7a'***, ***C-7b***, ***C-7b'***), 128.1 (***C-6a***, ***C-6a'***, ***C-6b***, ***C-6b'***), 127.9 (***C-8a***, ***C-8b***), 94.1 (***C-3a***, ***C-3b***), 69.6 (***C-4a***, ***C-4b***), 63.3 (***C-2a***, ***C-2b***);

FTIR (neat): ν_{max} 3032, 2883, 1648, 1497, 1455, 1381, 1172, 1107, 1050, 929, 737, 698, 666 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{11}H_{14}O_2Na$ 201.0891; found 201.0895.



2-(Benzyloxymethoxy)acetaldehyde (2.58): To a solution of crude **2.57** (theoretically 95.67 mmol, 1.0 equiv) in CH_2Cl_2 (350 mL, 0.3 M) was purged with O_3 (3 Psi, 90 Volts) at -78

^{o}C. When the colorless reaction became pinkish, O_3 was turned off, and O_2 flushed through the reaction until it turned colorless again. DMS (30 mL, 400 mmol, 3.0 equiv) was then added into this reaction in one portion. It was allowed to warm to room temperature, then stirred for 6 hours. The solution was concentrated in vacuo. The residue was distilled, and collected at 93-96 ^{o}C /3 mmHg to provide the titled compound (14.52 g, 80.55 mmol, 84.2% yield over 2 steps) as a colorless oil.

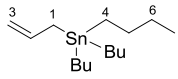
TLC: R_f = 0.24 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$): δ 9.72 (d, *J* = 0.9 Hz, 1H, ***H-2***), 7.40-7.29 (m, 5H, ***H-6***, ***H-6'***, ***H-7***, ***H-7'***, ***H-8***), 4.85 (s, 2H, ***H-3***), 4.67 (s, 2H, ***H-4***), 4.22 (d, *J* = 0.9 Hz, 1H, ***H-1***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 199.9 (***C-2***), 137.4 (***C-5***), 128.7 (***C-7***, ***C-7'***), 128.1 (***C-8***), 128.1 (***C-6***, ***C-6'***), 95.2 (***C-3***), 73.4 (***C-1***), 70.2 (***C-4***);

FTIR (neat): ν_{max} 3423, 3064, 3032, 2889, 1960, 1737, 1497, 1455, 1382, 1209, 1170, 1116, 745, 700 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^{+}] Calcd for $C_{10}H_{12}O_3Na$ 203.0684; found 203.0687.



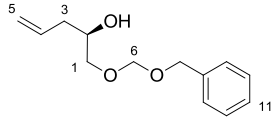
Allyltributylstannane (2.59): A 1000-mL 3-necked round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser, an additional funnel, and a gas inlet was flame dried. Then, magnesium chip (20.7 g, 0.850 mol, 1.5 equiv), anhydrous THF (500 mL) and a small amount of I_2 crystal (half match-head, catalytic amount) was added into this apparatus. This mixture was refluxed with stirring under an atmosphere of N_2. When the red-brown reaction turned yellow, the mixture of Bu_3SnCl (160 mL, 0.566 mol, 1.0 equiv) and allyl bromide (58 mL, 0.65 mol, 1.1 equiv) in THF (70.0 mL) was added dropwise via additional-funnel. It was refluxed for 20 hours, and an ice-water bath was used to precipitate the salt. Then, it was

filtered through a pad of Celit and wash with hexanes. The filtrate was washed with a saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was subjected to vacuum distillation to give a colorless oil (186.4 g, 0.563 mol, 99.5% yield) at 84-86 ^oC/0.2 mmHg.

TLC: R_f = 0.63 (EtOAc/Hex = 1:9, v/v);

500 MHz ^1H NMR ($CDCl_3$): δ 5.94 (ddt, *J* = 16.9, 9.9, 8.7 Hz, 1H, ***H-2***), 4.80 (ddt, *J* = 16.9, 2.1, 1.3 Hz, 1H, ***H-3a***), 4.65 (ddt, *J* = 9.9, 2.1, 0.8 Hz, 1H, ***H-3b***), 1.78 (ddd, *J* = 8.7, 1.3, 0.8 Hz, 2H, ***H-1***), 1.50 (tt, *J* = 8.1, 7.6 Hz, 6H, ***H-5***, ***H-5'***, ***H-5''***), 1.31 (tq, *J* = 7.6, 7.3 Hz, 6H, ***H-6***, ***H-6'***, ***H-6''***), 0.90 (t, *J* = 7.3 Hz, 9H, ***H-7***, ***H-7'***, ***H-7''***), 0.88 (t, *J* = 8.1 Hz, 6H, ***H-4***, ***H-4'***, ***H-4''***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 138.4 (***C-2***), 109.3 (***C-3***), 29.3 (***C-5***, ***C-5'***, ***C-5''***), 27.6 (***C-6***, ***C-6'***, ***C-6''***), 16.4 (***C-1***), 13.9 (***C-7***, ***C-7'***, ***C-7''***), 9.3 (***C-4***, ***C-4'***, ***C-4''***).



(*R*)-1-(Benzyloxymethoxy)pent-4-en-2-ol (2.60): To an oven-dried round-bottomed flask was charged (*R*)-BINOL (1.909 g, 6.601 mmol, 0.2 equiv), 4Å MS (13.24 g, 400 mg/mmol) and freshly distilled CH_2Cl_2 (110 mL, 0.3 M). Under an atmosphere of N_2, Ti(O*i*-Pr)$_4$ (0.980 mL, 3.31 mmol, 0.1 equiv) was introduced into this reaction dropwise via syringe with stirring, followed by addition of TFA (12.5 ul, 0.167 mmol, 0.005 equiv) at room temperature. The resulting dark brown mixture was heated at reflux for a period of 1 h, and then allowed to cool to room temperature. At this point, a solution of aldehyde **2.58** (5.873 g, 32.59 mmol, 1.0 equiv) in dry CH_2Cl_2 (5 mL) was added via cannula, and additional CH_2Cl_2 (2 x 3 mL) rinse was transferred into the reaction flask via cannula. This reaction was stirred for 30 minutes at room temperature, and then cooled to -78 ^oC.

Allyltributylstannane **2.59** (15.5 mL, 46.8 mmol, 1.4 equiv) was then added dropwise via syringe over 10 minutes. This reaction was stirred for further 30 minutes in this condition, and transferred to a -35 ºC freezer. After 7 days, this reaction was diluted with CH_2Cl_2 (100 mL), and filtrated over a pad of Celite. The filtrate was washed with a saturated $NaHCO_3$ solution (100 mL). The aqueous solution was extracted with ethyl ether (3 x 30 mL). The combined organic layers were washed with brine (150 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a brown oil. The remainder was purified by flash chromatography on silica gel eluting with 3-8 vol% of acetone in hexanes, to provide the titled compound (6.736 g, 30.30 mmol, 93.0% yield, 98.9% ee) as a colorless oil.

TLC: R_f = 0.44 (Acetone/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ -0.9 (*c* 1.68, $CHCl_3$);

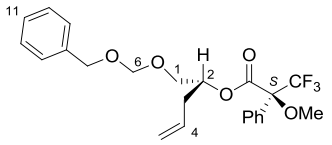
500 MHz ^{1}H NMR ($CDCl_3$): δ 7.40-7.34 (m, 4H, ***H-9***, ***H-9'***, ***H-10***, ***H-10'***), 7.34-7.29 (m, 1H, ***H-11***), 5.86 (dddd, *J* = 17.1, 10.3, 7.3, 6.9 Hz, 1H, ***H-4***), 5.17 (dq, *J* = 17.1, 1.6 Hz, 1H, ***H-5a***), 5.15-5.10 (m, 1H, ***H-5b***), 4.81 (ABq, *J* = 6.9 Hz, *Δv* = 5.5 Hz, 2H, ***H-6***), 4.64 (ABq, *J* = 12.0 Hz, *Δv* = 4.9 Hz, 2H, ***H-7***), 3.87 (qd, *J* = 6.6, 3.0 Hz, 1H, ***H-2***), 3.69 (dd, *J* =10.3, 2.9 Hz, 1H, ***H-1a***), 3.51 (dd, *J* =10.3, 7.1 Hz, 1H, ***H-1b***), 2.52 (br. s, 1H, ***-OH***), 2.29 (ddt, *J* = 7.3, 6.1, 1.5 Hz, 2H, ***H-3***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 137.7 (***C-8***), 134.3 (***C-4***), 128.7 (***C-10***, ***C-10'***), 128.1 (***C-9***, ***C-9'***), 128.0 (***C-11***), 118.0 (***C-5***), 95.3 (***C-6***), 72.6 (***C-1***), 70.0 (***C-2***), 69.9 (***C-7***), 38.1 (***C-3***);

FTIR (neat): ν_{max} 3448(br), 3070, 3032, 2931, 1642, 1497, 1454, 1381, 1209, 1169, 1116, 1044, 963, 917, 741, 699, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{13}H_{18}O_3Na$ 245.1154; found 245.1153.

Determination of Absolute Configuration of the New Stereocenter of Compound (*R*)-1-(Benzyloxymethoxy)pent-4-en-2-ol (2.60) via Mosher Ester Method:



2.60-*S*-MTPA

***(R)-1-(Benzyloxymethoxy)pent-4-en-2-yl (S)-α-Methoxy-α-(trifluoromethyl)phenylacetate (2.60-S-MTPA)*:** To a screw-capped vial equipped with a stirring bar was added **2.60** (36.3 mg, 0.163 mmol, 1.0 equiv), (*S*)-(-)-MTPA-OH acid (42.9 mg, 0.180 mmol, 1.1 equiv), DMAP (19.9 mg, 0.161 mmol, 1.0 equiv) and toluene (3.5 mL, 0.05 M), subsequently, at room temperature. Freshly distilled NEt_3 (115 uL, 0.826 mmol, 5.0 equiv) was then added to this mixture. This reaction was cooled down to 0 ^oC, and 2,4,6-trichlorobenzoylchloride (28.6 uL, 0.179 mmol, 1.1 equiv) was added dropwise via syringe. The reaction turned cloudy and precipitated immediately. The vial was tightly capped. The reaction was allowed to warm to room temperature slowly, and stirred for 6 hours. Then, the resulting yellow mixture was concentrated and purified by flash chromatography on silica gel eluting with 4-8 vol% of ethyl ether in hexanes to provide the titled compound (65.7 mg, 0.150 mmol, 91.8% yield) as a colorless oil.

TLC: R_f = 0.56 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ -36.8 (*c* 2.37, $CHCl_3$);

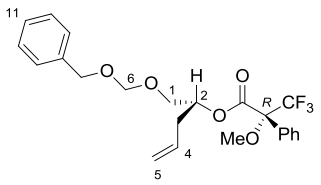
500 MHz ^{1}H NMR ($CDCl_3$): δ 7.62-7.55 (m, 2H, ***Ph-2***, ***Ph-2'***), 7.44-7.28 (m, 8H, ***H-9***, ***H-9'***, ***H-10***, ***H-10'***, ***H-11***, ***Ph-3***, ***Ph-3'***, ***Ph-4***), 5.79 (ddt, *J* = 17.1, 10.3, 7.3 Hz, 1H, ***H-4***), 5.39 (qd, *J* = 6.9, 3.9 Hz, 1H, ***H-2***), 5.20-5.12 (m, 2H, ***H-5***), 4.65 (ABq, *J* = 6.9 Hz, *Δv* = 16.2 Hz, 2H, ***H-6***), 4.50 (s, 2H, ***H-7***), 3.68 (dd, *J* = 11.3, 3.9 Hz, 1H, ***H-1a***), 3.64 (dd, *J* =

10.8, 6.8 Hz, 1H, ***H-1b***), 3.58 (s, 3H, ***-OMe***), 2.55-2.43 (m, 2H, ***H-3***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 166.3 (***C=O***), 137.9 (***C-8***), 132.7 (***C-4***), 132.5 (***Ph-1***), 129.7 (***Ph-4***), 128.6 (***C-10***, ***C-10'***), 128.5 (***Ph-3***, ***Ph-3'***), 128.1 (***C-9***, ***C-9'***), 128.0 (***C-11***), 127.8 (***Ph-2***, ***Ph-2'***), 123.5 (q, $J_{C\text{-}F}$ = 288.6 Hz, ***-CF3***), 119.1 (***C-5***), 94.9 (***C-6***), 84.9 (q, $J_{C\text{-}F}$ = 27.6 Hz, ***-C***C=O), 74.8 (***C-2***), 69.6 (***C-7***), 68.4 (***C-1***), 55.7 (***-OMe***), 35.5 (***C-3***);

FTIR (neat): ν_{max} 3068, 3033, 2949, 1749, 1644, 1497, 1453, 1381, 1265, 1171, 1120, 1025, 924, 836, 719, 699 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{23}H_{25}O_5F_3Na$ 461.1552; found 461.1557.



2.60-*R*-MTPA

(R)-1-(Benzyloxymethoxy)pent-4-en-2-yl (R)-α-Methoxy-α-(trifluoromethyl)phenylacetate (2.60-R-MTPA): To a screw-capped vial equipped with a stirring bar was added compound **2.60** (38.5 mg, 0.173 mmol, 1.0 equiv), (*R*)-(+)-MTPA-OH acid (45.0 mg, 0.190 mmol, 1.1 equiv), DMAP (21.4 mg, 0.173 mmol, 1.0 equiv) and toluene (3.5 mL, 0.05 M), subsequently, at room temperature. Freshly distilled NEt_3 (125 uL, 0.897 mmol, 5.0 equiv) was then added to this mixture. This reaction was cooled down to 0 °C. 2,4,6-Trichlorobenzoylchloride (30.5 uL, 0.191 mmol, 1.1 equiv) was then added dropwise via syringe. The reaction turned cloudy and precipitated immediately. The vial was tightly capped. The reaction was allowed to warm to room temperature slowly, and stirred for 6 hours. Then, the resulting yellow mixture was concentrated and purified by flash chromatography on silica gel eluting with 4-8 vol% of ethyl acetate in hexanes to provide the titled compound (69.7 mg, 0.159 mmol, 91.9% yield) as a colorless oil.

TLC: R_f = 0.57 (EtOAc/Hex = 3:7, v/v);

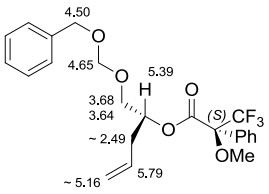
$[\alpha]_D^{20}$ +19.3 (*c* 2.43, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$): δ 7.66-7.57 (m, 2H, ***Ph-2***, ***Ph-2'***), 7.45-7.29 (m, 8H, ***H-9***, ***H-9'***, ***H-10***, ***H-10'***, ***H-11***, ***Ph-3***, ***Ph-3'***, ***Ph-4***), 5.69 (ddt, *J* = 16.6, 10.8, 7.3 Hz, 1H, ***H-4***), 5.38 (qd, *J* = 7.1, 3.7 Hz, 1H, ***H-2***), 5.11-5.04 (m, 2H, ***H-5***), 4.78 (ABq, *J* = 6.6 Hz, *Δv* = 15.5 Hz, 2H, ***H-6***), 4.60 (s, **2**H, ***H-7***), 3.76 (dd, *J* = 11.0, 3.7 Hz, 1H, ***H-1a***), 3.71 (dd, *J* = 11.0, 7.1 Hz, 1H, ***H-1b***), 3.60 (s, 3H, ***-OMe***), 2.48-2.34 (m, 2H, ***H-3***);

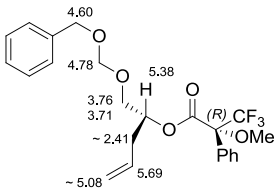
125 MHz ^{13}C NMR ($CDCl_3$): δ 166.4 (***C=O***), 137.8 (***C-8***), 132.7 (***Ph-1***), 132.3 (***C-4***), 129.7 (***Ph-4***), 128.7 (***C-10***, ***C-10'***), 128.5 (***Ph-3***, ***Ph-3'***), 128.1 (***C-9***, ***C-9'***), 128.0 (***C-11***), 127.7 (***Ph-2***, ***Ph-2'***), 123.6 (q, $J_{C\text{-}F}$ = 288.6 Hz, ***-CF$_3$***), 119.026 (***C-5***), 94.9 (***C-6***), 84.9 (q, $J_{C\text{-}F}$ = 27.8 Hz, ***-C***C=O), 74.7 (***C-2***), 69.8 (***C-7***), 68.4 (***C-1***), 55.6 (***-OMe***), 35.4 (***C-3***);

FTIR (neat): ν_{max} 3068, 3033, 2949, 1749, 1645, 1497, 1454, 1381, 1269, 1171, 1121, 1025, 923, 834, 765, 736, 720, 698, 665, 591 cm^{-1};

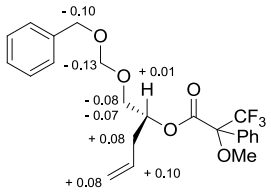
HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{23}H_{25}O_5F_3Na$ 461.1552; found 461.1557.



2.60-*S*-MTPA Mosher Ester

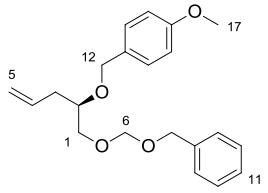


2.60-*R*-MTPA Mosher Ester



***Δδ* (*SR*) =*Δδ* (*S*-MTPA Ester) - *Δδ* (*R*-MTPA Ester)**

The chemical shift differences (in *ppm*) between the (*S*)- and (*R*)-MTPA Mosher esters of the (*R*)-1-(benzyloxymethoxy)pent-4-en-2-ol are consistent for a (*R*)-configuration of the new formed stereocenter.



(*R*)-5-(Benzyloxymethoxy)-4-(4-methoxybenzyloxy)pent-1-ene (2.61): To a 1L rb flask was charged KH (dispersion in mineral oil ~35%, 5.06 g, 44.2 mmol, 1.5 equiv) and freshly distilled THF (90 mL, 0.5 M). With an ice-water bath, a solution of alcohol **2.60** (6.546 g, 29.45 mmol, 1.0 equiv) in dry THF (150 mL, 0.2 M) was added into the reaction flask dropwise via cannula over 30 minutes. After addition, it was then stirred under an atmosphere of N_2 for 10 minutes. A solution of PMB-Br (9.182 g, 45.67 mmol, 1.5 equiv) in anhydrous THF (90 mL, 0.5 M) was added into this reaction via cannula over 30 minutes. This reaction was stirred in this condition for 1 hour, and all the alcohol was consumed. Then diethyl amine (20 mL, 193 mmol) was added, and stirred for a further 1 hour. This reaction was quenched with ice cubes carefully, and poured into a saturated $NaHCO_3$ solution (200 mL). The aqueous layer was extracted by ether (3 x 30 mL). The combined organic layers were washed with brine (200 mL), and dried over anhydrous Na_2SO_4. The solution was filtrated and concentrated by rotary evaporation. The residue was purified by flash chromatography on silica gel eluting with 3-10 vol% of ethyl acetate in hexanes to provide the titled compound (9.710 g, 28.35 mmol, 96.3% yield) as a coloress oil.

TLC: R_f = 0.48 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +3.5 (*c* 2.94, $CHCl_3$);

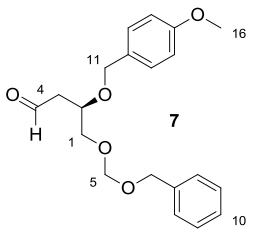
500 MHz ^{1}H NMR ($CDCl_3$): δ 7.39-7.33 (m, 4H, ***H-9***, ***H-9'***, ***H-10***, ***H-10'***), 7.33-7.29 (m, 1H, ***H-11***), 7.27 (d, *J* = 8.7 Hz, 2H, ***H-14***, ***H-14'***), 6.87 (d, *J* = 8.7 Hz, 2H, ***H-15***, ***H-15'***), 5.85 (ddt, *J* = 17.1, 10.2, 7.1 Hz, 1H, ***H-4***), 5.12 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1H, ***H-5a***), 5.08 (ddt, *J* = 10.2, 2.1, 1.1 Hz, 1H, ***H-5b***), 4.79 (ABq, *J* = 6.7 Hz, *Δv* = 3.5 Hz, 2H, ***H-6***), 4.62

(s, 2H, ***H-7***), 4.58 (ABq, J = 11.4 Hz, $\Delta\nu$ = 18.2 Hz, 2H, ***H-12***), 3.81 (s, 3H, ***H-17***), 3.69-3.60 (m, 3H, ***H-1a***, ***H-1b***, ***H-2***), 2.37 (dddd, J = 7.0, 5.8, 1.4, 1.2 Hz, 2H, ***H-3***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 159.3 (***C-16***), 138.1 (***C-8***), 134.8 (***C-4***), 131.0 (***C-13***), 129.5 (***C-14***, ***C-14'***), 128.6 (***C-10***, ***C-10'***), 128.1 (***C-9***, ***C-9'***), 127.9 (***C-11***), 117.4 (***C-5***), 113.9 (***C-15***, ***C-15'***), 95.1 (***C-6***), 77.5 (***C-2***), 71.6 (***C-12***), 69.7 (***C-1***), 69.6 (***C-7***), 55.5 (***C-17***), 36.4 (***C-3***);

FTIR (neat): ν_{max} 3069, 3032, 2934, 1883, 1641, 1613, 1586, 1513, 1458, 1380, 1348, 1301, 1248, 1173, 1043, 917, 822, 741, 699, 666, 589 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{21}H_{26}O_4Na$ 365.1729; found 365.1734.



(*R*)-4-Benzyloxymethoxy-3-(4-methoxybenzyloxy)butanal (2.62): A solution of olefin **2.61** (9.278 g, 27.09 mmol, 1.0 equiv) in CH_2Cl_2 (140 mL, 0.2 M) was purged with O_3 (3 Psi, 60 Volts) at -78 ^{o}C. When the colorless reaction became pinkish, O_3 was turned off, and O_2 flushed through the reaction until it turned colorless again. Triphenylphospine (10.87 g, 41.02 mmol, 1.5 equiv) was then was added into this reaction. It was allowed to warm to room temperature and stirred for 6 hours. The solution was concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with 10-25 vol% of ethyl acetate in hexanes to provide the titled compound (7.702 g, 22.36 mmol, 82.6% yield) as a colorless oil.

TLC: R_f = 0.29 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +13.9 (*c* 1.73, $CHCl_3$);

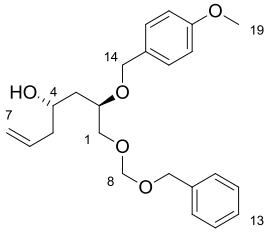
500 MHz ^{1}H NMR ($CDCl_3$) δ 9.77 (t, J = 2.0 Hz, 1H, ***H-4***), 7.40-7.33 (m, 4H, ***H-8***, ***H-8'***,

H-9, ***H-9'***, ***H-10***), 7.33-7.28 (m, 1H, ***H-11***), 7.25 (d, *J* = 8.8 Hz, 2H, ***H-13***, ***H-13'***), 6.88 (d, *J* = 8.8 Hz, 2H, ***H-14***, ***H-14'***), 4.79 (s, 2H, ***H-5***), 4.61 (s, 2H, ***H-6***), 4.57 (ABq, *J* = 11.2 Hz, $\Delta\nu$ = 39.5 Hz, 2H, ***H-11***), 4.11 (dddd, *J* = 7.3, 4.9, 4.9, 4.9 Hz, 1H, ***H-2***), 3.81 (s, 3H, ***H-16***), 3.71 (dd, *J* = 10.6, 4.9 Hz, 1H, ***H-1a***), 3.69 (dd, *J* = 10.5, 5.1 Hz, 1H, ***H-1b***), 2.72 (ddd, *J* = 16.9, 7.3, 2.2 Hz, 1H, ***H-3a***), 2.64 (ddd, *J* = 16.8, 4.9, 2.0 Hz, 1H, ***H-3b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 201.0 (***C-4***), 159.6 (***C-15***), 137.9 (***C-7***), 130.2 (***C-12***), 129.7 (***C-13***, ***C-13'***), 128.7 (***C-9***, ***C-9'***), 128.1 (***C-8***, ***C-8'***), 128.0 (***C-10***), 114.1 (***C-14***, ***C-14'***), 95.1 (***C-5***), 72.9 (***C-2***), 71.9 (***C-11***), 69.9 (***C-6***), 69.1 (***C-1***), 55.5 (***C-16***), 46.5 (***C-3***);

FTIR (neat): ν_{max} 3032, 3003, 2879, 2731, 1886, 1725, 1613, 1586, 1514, 1459, 1382, 1301, 1248, 1173, 1043, 823, 743, 700, 666 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{20}H_{24}O_5Na$ 367.1521; found 367.1529.



(*4S,6R*)-7-(Benzyloxymethoxy)-6-(4-methoxybenzyloxy)hept-1-en-4-ol (2.63): To an oven-dried round-bottomed flask was charged (*S)*-BINOL (5.508 g, 19.04 mmol, 0.2 equiv), 4Å MS (41.47 g, 400 mg/mmol) and freshly distilled CH_2Cl_2 (320 mL, 0.3 M). Under an atmosphere of N_2, Ti(O*i*-Pr)$_4$ (2.80 mL, 9.46 mmol, 0.1 equiv) was introduced into this reaction dropwise via syringe with stirring, followed by addition of TFA (35 ul, 0.47 mmol, 0.005 equiv) at room temperature. The resulting dark brown mixture was heated at reflux for a period of 1 h, and then allowed to cooled to room temperature. Whereupon, a solution of of aldehyde **2.62** (32.63 g, 94.73 mmol, 1.0 equiv) in dry CH_2Cl_2 (9.5 mL, 10 M) was added via cannula, and additional CH_2Cl_2 (2 x 5 mL) rinse was transferred into the reaction flask via cannula. This reaction was stirred for 30 minutes at

room temperature, and then cooled to -78 ºC. Then, allyltributylstannane **2.59** (42 mL, 135 mmol, 1.4 equiv) was added dropwise via syringe over 10 minutes. This reaction was stirred for further 30 minutes in this condition, and transferred to a -35 ºC freezer. After 7 days, this reaction was filtrated over a pad of Celite. The filtrate was washed with a mixture of saturated $NaHCO_3$ solution (200 mL) and saturated KF solution (300 mL). The aqueous solution was extracted with ethyl ether (3 x 100 mL). The combined organic layers were washed with brine (300 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a brown oil. The remainder was purified by flash chromatography on silica gel eluting with 3-10 vol% of acetone in hexanes, to provide the titled compound (32.74 g, 84.70 mmol, 89.4% yield, single diastereomer) as a yellow oil.

TLC: R_f = 0.29 (Et_2O/Hex = 5:5, v/v);

$[\alpha]_D^{20}$ +28.1 (*c* 1.45, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$): δ 7.41-7.35 (m, 4H, ***H-11***, ***H-11'***, ***H-12***, ***H-12'***), 7.35-7.29 (m, 1H, ***H-13***), 7.29 (d, *J* = 8.8 Hz, 2H, ***H-16***, ***H-16'***), 6.89 (d, *J* = 8.8 Hz, 2H, ***H-17***, ***H-17'***), 5.84 (dddd, *J* = 17.3, 9.9, 7.2, 7.2 Hz, 1H, ***H-6***), 5.17-5.12 (m, 1H, ***H-7a***), 5.12-5.08 (m, 1H, ***H-7b***), 4.81 (ABq, *J* = 6.8 Hz, *Δv* = 4.8 Hz, 2H, ***H-8***), 4.64 (s, 2H, ***H-9***), 4.61 (ABq, *J* = 11.3 Hz, *Δv* = 66.0 Hz, 2H, ***H-14***), 3.97-3.84 (m, 1H, ***H-4***), 3.86-3.80 (m, 1H, ***H-2***), 3.81 (s, 3H, ***H-19***), 3.72 (d, *J* = 5.2 Hz, 2H, ***H-1***), 2.39 (br. s, 1H, ***-OH***), 2.30-2.17 (m, 2H, ***H-5***), 1.78 (ddd, *J* = 14.6, 8.2, 2.5 Hz, 1H, ***H-3a***), 1.65 (ddd, *J* = 14.6, 9.6, 3.6 Hz, 1H, ***H-3b***);

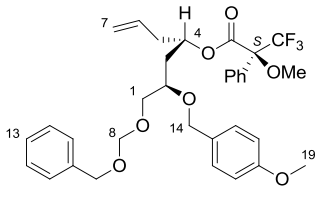
125 MHz ^{13}C NMR ($CDCl_3$): δ 159.5 (***C-18***), 138.0 (***C-10***), 135.0 (***C-6***), 130.6 (***C-15***), 129.8 (***C-16***, ***C-16'***), 128.6 (***C-12***, ***C-12'***), 128.1 (***C-11***, ***C-11'***), 127.9 (***C-13***), 117.9 (***C-7***),

114.0 (***C-17***, ***C-17'***), 95.1 (***C-8***), 75.2 (***C-2***), 72.1 (***C-14***), 70.1 (***C-1***), 69.7 (***C-9***), 67.7 (***C-4***), 55.5 (***C-19***), 42.4 (***C-5***), 38.7 (***C-3***);

FTIR (neat): ν_{max} 3457 (br.), 3069, 2934, 1641, 1613, 1514, 1457, 1380, 1302, 1249, 1172, 1040, 917, 821, 742, 699, 665, 591, 536 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{23}H_{30}O_5Na$ 409.1991; found 409.1992.

Determination of Absolute Configuration of the New Stereocenter of Compound (*4S,6R*)-7-(Benzyloxymethoxy)-6-(4-methoxybenzyloxy)hept-1-en-4-ol (2.63) via Mosher Ester Method:



(4S,6R)-7-(Benzyloxymethoxy)-6-(4-methoxybenzyloxy)hept-1-en-4-yl (S)-α-Methoxy-α-(trifluoromethyl)phenylacetate (2.63-S-MTPA): To a screw-capped vial equipped with a stirring bar was added **2.63** (42.6 mg, 110 umol, 1.0 equiv), (*S*)-(-)-MTPA-OH acid (29.0 mg, 121 umol, 1.1 equiv), DMAP (13.6 mg, 110 umol, 1.0 equiv) and toluene (2.2 mL, 0.05 M), subsequently, at room temperature. Freshly distilled NEt_3 (77.0 uL, 552 umol, 5.0 equiv) was then added to this mixture. This reaction was cooled down to 0 ^oC, 2,4,6-trichlorobenzoylchloride (17.5 uL, 108 umol, 1.1 equiv) was then added dropwise via syringe. The reaction turned cloudy and precipitated immediately. The vial was tightly capped. The reaction was allowed to warm to room temperature slowly and stirred overnight (ca. 10 hours). Then, the resulting white mixture was concentrated and purified by flash chromatography on silica gel eluting with 8-15 vol% of ethyl ether in hexanes to provide the titled compound (61.8 mg, 103 umol, 93.0% yield) as a colorless oil.

TLC: R_f = 0.41 (EtOAc/Hex = 3:7, v/v);

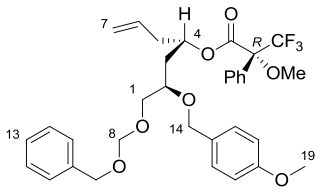
$[\alpha]_D^{20}$ +9.9 (*c* 2.33, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$): δ 7.61-7.52 (m, 2H, ***Ph-2***, ***Ph-2'***), 7.44-7.30 (m, 8H, ***H-11***, ***H-11'***, ***H-12***, ***H-12'***, ***H-13***, ***Ph-3***, ***Ph-3'***, ***Ph-4***), 7.28 (d, *J* = 8.5 Hz, 2H, ***H-16***, ***H-16'***), 6.88 (d, *J* = 8.8 Hz, 2H, ***H-17***, ***H-17'***), 5.66 (dddd, *J* = 15.9, 11.0, 7.1, 7.1 Hz, 1H, ***H-6***), 5.48 (dq, *J* = 7.3, 5.6 Hz, 1H, ***H-4***), 5.08-4.99 (m, 2H, ***H-7***), 4.77 (ABq, *J* = 6.9 Hz, *Δv* = 4.7 Hz, 2H, ***H-8***), 4.61 (s, 2H, ***H-9***), 4.59 (d, *J* = 10.8 Hz, 1H, ***H-14a***), 4.39 (d, *J* = 11.2 Hz, 1H, ***H-14b***), 3.80 (s, 3H, ***H-19***), 3.65 (dd, *J* = 10.5, 4.6 Hz, 1H, ***H-1a***), 3.61 (dd, *J* = 10.1, 4.4 Hz, 1H, ***H-1b***), 3.59-3.53 (m, 1H, ***H-2***), 3.51 (s, 3H, ***-OMe***), 2.51-2.32 (m, 2H, ***H-5***), 1.86 (dd, *J* = 7.3, 5.4 Hz, 2H, ***H-3***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 166.3 (***-C=O***), 159.5 (***C-18***), 138.0 (***C-10***), 132.8 (***C-6***), 132.4 (***Ph-1***), 130.6 (***C-15***), 129.8 (***C-16***, ***C-16'***), 129.8 (***Ph-4***), 128.7 (***C-12***, ***C-12'***), 128.6 (***C-11***, ***C-11'***), 128.0 (***Ph-3***, ***Ph-3'***), 128.0 (***C-13***), 127.8 (***Ph-2***, ***Ph-2'***), 123.6 (q, $J_{C\text{-}F}$ = 288.6 Hz, ***-CF$_3$***), 118.8 (***C-7***), 114.1 (***C-17***, ***C-17'***), 95.1 (***C-8***), 84.9 (q, $J_{C\text{-}F}$ = 27.6 Hz, ***-C***C=O), 74.3 (***C-2***), 73.7 (***C-4***), 72.1 (***C-14***), 69.7 (***C-9***), 69.7 (***C-1***), 55.6 (*Ar*-***OMe***), 55.5 (***C-19***), 39.1 (***C-5***), 37.0 (***C-3***);

FTIR (neat): ν_{max} 3068, 3032, 2934, 1744, 1642, 1612, 1587, 1514, 1454, 1380, 1251, 1171, 1117, 1081, 1041, 962, 924, 820, 737, 720, 699, 644, 591, 536 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{33}H_{37}F_3O_7Na$ 625.2389; found 625.2396.



(4S,6R)-7-(Benzyloxymethoxy)-6-(4-methoxybenzyloxy)hept-1-en-4-yl (R)-α-Methoxy-α-(trifluoromethyl)phenylacetate (2.63-R-MTPA):To a screw-capped vial equipped with a stirring bar was added **2.63** (35.4 mg, 91.6 umol, 1.0 equiv), (*R*)-(+)-MTPA-OH acid (25.1

mg, 106 umol, 1.16 equiv), DMAP (11.9 mg, 96.4 umol, 1.0 equiv) and toluene (2.0 mL, 0.05 M), subsequently, at room temperature. Freshly distilled NEt_3 (65.0 uL, 466 umol, 5.0 equiv) was then added to this mixture. This reaction was cooled down to 0 ^oC, 2,4,6-trichlorobenzoylchloride (17.0 uL, 107 umol, 1.16 equiv) was then added dropwise via syringe. The reaction turned cloudy and precipitated immediately. The vial was tightly capped. The reaction was allowed to warm to room temperature slowly and stirred for 10 hours. Then, the resulting yellow solution was concentrated and purified by flash chromatography on silica gel eluting with 8-15 vol% of ethyl ether in hexanes to provide the titled compound (48.2 mg, 80.0 umol, 87.3% yield) as a colorless oil.

TLC: R_f = 0.49 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +47.1 (*c* 1.81, $CHCl_3$);

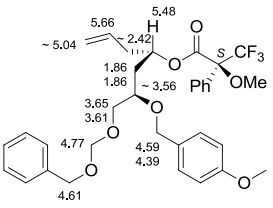
500 MHz ^{1}H NMR ($CDCl_3$): δ 7.65-7.51 (m, 2H, ***Ph-2***, ***Ph-2'***), 7.46-7.28 (m, 8H, ***H-11***, ***H-11'***, ***H-12***, ***H-12'***, ***H-13***, ***Ph-3***, ***Ph-3'***, ***Ph-4***), 7.30 (d, *J* = 8.8 Hz, 2H, ***H-16***, ***H-16'***), 6.90 (d, *J* = 8.8 Hz, 2H, ***H-17***, ***H-17'***), 5.78 (dddd, *J* = 17.1, 9.8, 7.3, 7.3 Hz, 1H, ***H-6***), 5.51 (dddd, *J* = 9.1, 5.9, 5.9, 3.2 Hz, 1H, ***H-4***), 5.20-5.05 (m, 2H, ***H-7***), 4.73 (ABq, *J* = 6.6 Hz, *Δv* = 4.6 Hz, 2H, ***H-8***), 4.59 (s, 2H, ***H-9***), 4.56 (d, *J* = 10.8 Hz, 1H, ***H-14a***), 4.34 (d, *J* = 10.8 Hz, 1H, ***H-14b***), 3.81 (s, 3H, ***H-19***), 3.60 (dd, *J* = 10.7, 4.4 Hz, 1H, ***H-1a***), 3.58 (s, 3H, ***-OMe***), 3.54 (dd, *J* = 10.7, 4.4 Hz, 1H, ***H-1b***), 3.44 (dddd, *J* = 9.5, 4.4, 4.4, 3.2 Hz, 1H, ***H-2***), 2.55-2.44 (m, 2H, ***H-5***), 1.86 (ddd, *J* = 14.7, 9.8, 3.4 Hz, 1H, ***H-3a***), 1.80 (ddd, *J* = 15.1, 9.7, 2.9 Hz, 1H, ***H-3b***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 166.4 (***-C=O***), 159.5 (***C-18***), 138.0 (***C-10***), 133.0 (***C-6***), 132.5 (***Ph-1***), 130.7 (***C-15***), 129.8 (***Ph-4***), 129.7 (***C-16***, ***C-16'***), 128.6 (***C-12***, ***C-12'***), 128.6 (***C-11***, ***C-11'***), 128.0 (***Ph-3***, ***Ph-3'***), 127.9 (***C-13***), 127.6 (***Ph-2***, ***Ph-2'***), 123.7 (q, $J_{C\text{-}F}$ =

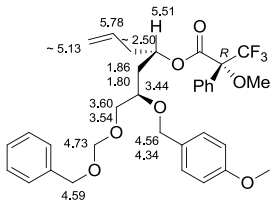
288.8 Hz, -***CF*$_3$**), 118.9 (***C-7***), 114.1 (***C-17***, ***C-17'***), 94.9 (***C-8***), 84.6 (q, $J_{C\text{-}F}$ = 27.4 Hz, -***C***C=O), 74.4 (***C-2***), 73.8 (***C-4***), 72.2 (***C-14***), 69.6 (***C-9***), 69.6 (***C-1***), 55.7 (*Ar*-***OMe***), 55.5 (***C-19***), 39.4 (***C-5***), 37.0 (***C-3***);

FTIR (neat): ν_{max} 3068, 3032, 2946, 1745, 1643, 1612, 1587, 1514, 1454, 1380, 1347, 1251, 1171, 1114, 1082, 1040, 962, 925, 820, 766, 736, 720, 699, 665, 591, 536 cm^{-1};

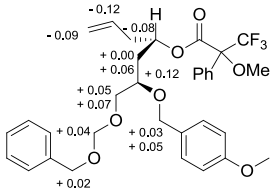
HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{33}H_{37}F_3O_7Na$ 625.2389; found 625.2394.



2.63-*S*-MTPA Mosher Ester

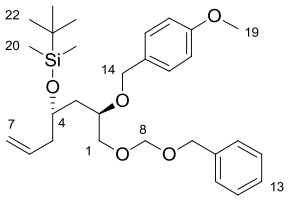


2.63-*R*-MTPA Mosher Ester



***Δδ* (*SR*) =*Δδ* (*S*-MTPA Ester) - *Δδ* (*R*-MTPA Ester)**

The chemical shift differences (in *ppm*) between the (*S*)- and (*R*)-MTPA Mosher esters of the (*4S*,*6R*)-7-(benzyloxymethoxy)-6-(4-methoxybenzyloxy)hept-1-en-4-ol (**2.61**) are consistent for a (*S*)-configuration of the new formed stereocenter.



(*4S*,*6R*)-7-(Benzyloxymethoxy)-4-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxy)hept-1-ene (2.64): To a stirred solution of alcohol **2.63** (9.383 g, 24.28 mmol, 1.0 equiv) in DMF (120 mL, 0.2 M) was added imidazole (6.726 g, 97.80 mmol, 4.0 equiv) and TBSCl (7.549 g, 48.58 mmol, 2.0 equiv) at room temperature, subsequently. This reaction was stirred under an atmosphere of N_2 for 20 hours. Then, it was diluted with Et_2O (100 mL), and the reaction was poured into a saturated solution of $NaHCO_3$ (200 mL). The aqueous layer was extracted by Et_2O (3 x 30 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and

concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 2-6 vol% of ethyl acetate in hexanes to provide the titled compound (12.07 g, 24.11 mmol, 99.3% yield) as a colorless oil.

TLC: R_f = 0.62 (EtOAc/Hex = 3:7, v/v);

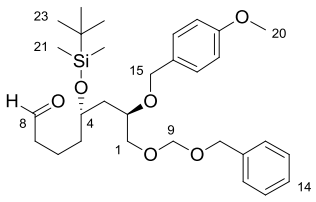
$[\alpha]_D^{20}$ +23.5 (*c* 1.81, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.41-7.35 (m, 4H, ***H-11***, ***H-11'***, ***H-12***, ***H-12'***), 7.35-7.30 (m, 1H, ***H-13***), 7.30 (d, *J* = 8.8 Hz, 2H, ***H-16***, ***H-16'***), 6.90 (d, *J* = 8.8 Hz, 2H, ***H-17***, ***H-17'***), 5.86 (dddd, *J* = 20.0, 9.5, 7.1, 7.1 Hz, 1H, ***H-6***), 5.12-5.04 (m, 2H, ***H-7a***, ***H-7b***), 4.82 (ABq, *J* = 6.6 Hz, *Δv* = 5.5 Hz, 2H, ***H-8***), 4.69 (d, *J* = 11.0 Hz, 1H, ***H-14a***), 4.65 (s, 2H, ***H-9***), 4.51 (d, *J* = 11.0 Hz, 1H, ***H-14b***), 4.03 (dddd, *J* = 8.8, 4.4, 4.4, 3.9 Hz, 1H, ***H-4***), 3.82 (s, 3H, ***H-19***), 3.83-3.78 (m, 1H, ***H-2***), 3.75 (dd, *J* = 10.3, 3.9 Hz, 1H, ***H-2a***), 3.68 (dd, *J* = 10.3, 5.4 Hz, 1H, ***H-2b***), 2.37-2.23 (m, 2H, ***H-5***), 1.81 (ddd, *J* = 14.2, 8.8, 3.4 Hz, 1H, ***H-3a***), 1.63 (ddd, *J* = 14.2, 8.8, 3.4 Hz, 1H, ***H-3b***), 0.94 (s, 9H, ***H-22***), 0.12 (s, 3H, ***H-20a***), 0.11 (s, 3H, ***H-20b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 159.3 (***C-18***), 138.1 (***C-10***), 134.8 (***C-6***), 131.3 (***C-15***), 129.2 (***C-16***, ***C-16'***), 128.6 (***C-12***, ***C-12'***), 128.0 (***C-11***, ***C-11'***), 127.8 (***C-13***), 117.3 (***C-7***), 113.9 (***C-17***, ***C-17'***), 95.0 (***C-8***), 75.4 (***C-2***), 71.4 (***C-14***), 70.5 (***C-1***), 69.6 (***C-9***), 69.0 (***C-4***), 55.4 (***C-19***), 42.9 (***C-5***), 40.1 (***C-3***), 26.1 (***C-22***), 18.3 (***C-21***), -3.8 (***C-20a***), -4.3 (***C-20b***);

FTIR (neat): ν_{max} 3070, 3032, 2931, 2858, 1641, 1613, 1587, 1514, 1464, 1380, 1301, 1250, 1172, 1045, 915, 834, 775, 739, 698, 666, 591 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{29}H_{44}O_5SiNa$ 523.2856; found 523.2858.



(*5S,7R*)-8-(Benzyloxymethoxy)-5-(*tert*-butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)octanal (2.65): To an oven-dried flask equipped with a stirring bar was added dicarbonylacetylacetonatorhodium (I) (17.9 mg, 0.0687 mmol, 0.5 mol%), BIPHEPHOS (217 mg, 0.276 mmol, 2.0 mol%) and freshly distilled degassed THF (70 mL). This flask was evacuated and refilled with N_2 by 3 times. It was then stirred at room temperature under an atmosphere of N_2 for 10 minutes, whereupon the mixture was dissolved. The solution of olefin **2.64** (6.906 g, 13.79 mmol, 1.0 equiv) in degassed THF (7 mL, 2.0 M) was added into this flask via cannula. This flask was unsealed and put into a Parr autoclave quickly. Then the Parr pressure vessel was sealed tightly. The atmosphere of this reaction vessel was exchanged with 100 psi of CO/H_2 (1:1 mixture) three times by being evacuated with an oil pump and refilled with syngas. Then, the reaction vessel was pressurized with CO/H_2 (1:1 mixture) at 100 psi., and stirred at 57 ^oC for 36 hours. After cooling to room temperature, the reaction was depressurized and concentrated by rotary vacuum. The remainder was purified by flash chromatography on silica gel eluting with 7-16 vol% of ethyl acetate in hexanes to provide the titled compound (6.399 g, 12.06 mmol, 87.4% yield) as a yellowish oil.

TLC: R_f = 0.43 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +17.8 (*c* 1.87, $CHCl_3$);

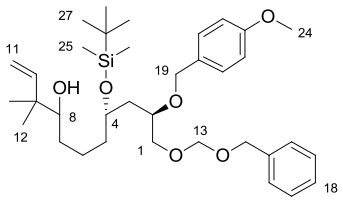
500 MHz ^{1}H NMR ($CDCl_3$) δ 9.75 (t, *J* = 1.5 Hz, 1H, ***H-8***), 7.40-7.33 (m, 4H, ***H-12***, ***H-12'***, ***H-13***, ***H-13'***), 7.33-7.28 (m, 1H, ***H-14***), 7.27 (d, *J* = 8.6 Hz, 2H, ***H-17***, ***H-17'***), 6.88 (d, *J* = 8.8 Hz, 2H, ***H-18***, ***H-18'***), 4.80 (ABq, *J* = 6.6 Hz, $\Delta\nu$ = 5.5 Hz, 2H, ***H-9***), 4.67 (d, *J*

= 11.3 Hz, 1H, ***H-15a***), 4.63 (s, 2H, ***H-10***), 4.47 (d, *J* = 11.3 Hz, 1H, ***H-15b***), 3.94 (dddd, *J* = 8.8, 5.4, 5.4, 4.4 Hz, 1H, ***H-4***), 3.81 (s, 3H, ***H-20***), 3.74 (dddd, *J* = 8.5, 4.9, 4.5, 3.9 Hz, 1H, ***H-2***), 3.72 (dd, *J* = 10.3, 3.9 Hz, 1H, ***H-1a***), 3.65 (dd, *J* = 10.3, 4.9 Hz, 1H, ***H-1b***), 2.34 (td, *J* = 7.3, 1.5 Hz, 2H, ***H-7***), 1.75 (ddd, *J* = 13.5, 8.6, 3.9 Hz, 1H, ***H-3a***), 1.72-1.60 (m, 3H, ***H-3b***, ***H-6a***, ***H-6b***), 1.59-1.44 (m, 2H, ***H-5a***, ***H-5b***), 0.91 (s, 9H, ***H-23***), 0.068 (s, 3H, ***H-21a***), 0.066 (s, 3H, ***H-21b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 202.6 (***C-8***), 159.3 (***C-19***), 138.1 (***C-11***), 131.1 (***C-16***), 129.3 (***C-17***, ***C-17'***), 128.6 (***C-13***, ***C-13'***), 128.0 (***C-12***, ***C-12'***), 127.9 (***C-14***), 114.0 (***C-18***, ***C-18'***), 95.0 (***C-9***), 75.4 (***C-2***), 71.5 (***C-15***), 70.3 (***C-1***), 69.6 (***C-10***), 69.1 (***C-4***), 55.5 (***C-20***), 44.2 (***C-7***), 40.1 (***C-3***), 37.5 (***C-5***), 26.1 (***C-23***), 18.3 (***C-22***), 17.4 (***C-6***), -3.9 (***C-21a***), -4.2 (***C-21b***);

FTIR (neat): ν_{max} 3032, 2932, 2717, 2062, 1726, 1613, 1587, 1514, 1463, 1382, 1301, 1250, 1173, 1047, 835, 776, 740, 699, 665 cm^{-1};

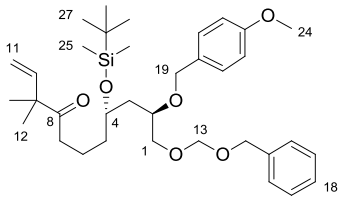
HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{30}H_{46}O_6SiNa$ 553.2961; found 553.2963.



(*8S,10R*)-11-(Benzyloxymethoxy)-8-(*tert*-butyldimethylsilyloxy)-10-(4-methoxybenzyloxy)-3,3-dimethylundec-1-en-4-ol (2.67): To a stirred mixture of aldehyde **2.65** (3.976 g, 7.491 mmol, 1.0 equiv) and 1-bromo-3-methylbut-2-ene **2.66** (1.40 mL, 11.6 mmol, 1.5 equiv) in THF (15 mL, 0.5 M) and saturate aqueous NH_4Cl solution (75 mL, 0.1 M) was added Zn dust (0.776 g, 11.6 mmol, 1.5 equiv) in one portion at room temperature. It was stirred overnight (ca. 12 hours), then Et_2O (50 mL) was poured into this reaction. The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers

were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Filtered, it was then concentrated by rotary vacuum to give a yellow oil (4.591 g, 7.640 mmol, 100% yield), which was used in the next step without further purification.

TLC: R_f = 0.53 (EtOAc/Hex = 3:7, v/v).



(*8S,10R*)-11-(Benzyloxymethoxy)-8-(*tert*-butyldimethylsilyloxy)-10-(4-methoxybenzyloxy)-3,3-dimethylundec-1-en-4-one (2.68): With a –78 °C bath, to a stirred solution of oxalyl chloride (1.00 mL, 11.4 mmol, 1.5 equiv) in dry CH_2Cl_2 (60 mL, 0.2 M) was added a solution of DMSO (1.60 mL, 22.5 mmol, 3.0 equiv) in dry CH_2Cl_2 (40 mL, 0.5 M) dropwise via cannula under an atmosphere of N_2. After 30 minutes, the solution of crude alcohol **2.67** (4.573 g, theoretically 7.607 mmol, 1.0 equiv) in dry CH_2Cl_2 (80 mL, 0.1 M) was added dropwise via cannula. This reaction was stirred for 1 hour in this condition. Then, NEt_3 (5.4 mL, 39 mmol, 5.0 equiv) was introduced dropwise via syringe. After 5 minutes, the cooling bath was removed, and the reaction was stirred at room temperature for 1.5 hours. The solution was poured into a saturated solution of NH_4Cl (150 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (200 mL) and dried over anhydrous Na_2SO_4. Filtered, it was then concentrated by rotary vacuum. The remainder was purified by flash chromatography on silica gel eluting with 5-12 vol% of ethyl acetate in hexanes to provide the titled compound (4.152 g, 6.932 mmol, 91.1% yield in two steps) as a yellow oil.

TLC: R_f = 0.65 (EtOAc/Hex = 3:7, v/v);

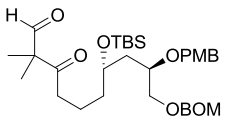
$[\alpha]_D^{20}$ +15.7 (*c* 2.17, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.41-7.33 (m, 4H, ***H-16***, ***H-16'***, ***H-17***, ***H-17'***), 7.33-7.28 (m, 1H, ***H-18***), 7.28 (d, *J* = 8.6 Hz, 2H, ***H-21***, ***H-21'***), 6.87 (d, *J* = 8.3 Hz, 2H, ***H-22***, ***H-22'***), 5.91 (dd, *J* = 17.6, 10.8 Hz, 1H, ***H-10***), 5.14 (d, *J* = 16.6 Hz, 1H, ***H-11a***), 5.14 (d, *J* = 11.2 Hz, 1H, ***H-11b***), 4.79 (ABq, *J* = 6.6 Hz, *Δv* = 4.6 Hz, 2H, ***H-13***), 4.66 (d, *J* = 11.2 Hz, 1H, ***H-19a***), 4.63 (s, 2H, ***H-14***), 4.48 (d, *J* = 11.2 Hz, 1H, ***H-19b***), 3.92 (dddd, *J* = 9.0, 5.4, 5.4, 3.9 Hz, 1H, ***H-4***), 3.80 (s, 3H, ***H-24***), 3.76 (dddd, *J* = 8.6, 5.4, 3.9, 3.9 Hz, 1H, ***H-2***), 3.71 (dd, *J* = 10.3, 3.9 Hz, 1H, ***H-1a***), 3.64 (dd, *J* = 10.3, 5.4 Hz, 1H, ***H-1b***), 2.46 (dt, *J* = 17.1, 7.2 Hz, 1H, ***H-7a***), 2.41 (dt, *J* = 17.1, 7.2 Hz, 1H, ***H-7b***), 1.75 (ddd, *J* = 14.2, 8.8, 3.9 Hz, 1H, ***H-3a***), 1.62 (ddd, *J* = 14.2, 8.3, 3.9 Hz, 1H, ***H-3b***), 1.61-1.53 (m, 2H, ***H-6a***, ***H-6b***), 1.48-1.40 (m, 2H, ***H-5a***, ***H-5b***), 1.23 (s, 6H, ***H-12a***, ***H-12b***), 0.91 (s, 9H, ***H-27***), 0.066 (s, 3H, ***H-25a***), 0.061 (s, 3H, ***H-25b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 212.9 (***C-8***), 159.3 (***C-23***), 142.8 (***C-10***), 138.1 (***C-15***), 131.3 (***C-20***), 129.2 (***C-21***, ***C-21'***), 128.6 (***C-17***, ***C-17'***), 128.1 (***C-16***, ***C-16'***), 127.8 (***C-18***), 114.3 (***C-11***), 114.0 (***C-22***, ***C-22'***), 95.1 (***C-13***), 75.5 (***C-2***), 71.4 (***C-19***), 70.6 (***C-1***), 69.6 (***C-14***), 69.4 (***C-4***), 55.5 (***C-24***), 50.9 (***C-9***), 40.1 (***C-3***), 37.7 (***C-7***), 37.7 (***C-5***), 26.2 (***C-27***), 23.7 (***C-12a***, ***C-12b***), 19.5 (***C-6***), 18.3 (***C-26***), -3.8 (***C-25a***), -4.2 (***C-25b***);

FTIR (neat): ν_{max} 2932, 2858, 1710, 1613, 1514, 1464, 1379, 1302, 1250, 1172, 1107, 1044, 921, 835, 775, 738, 698, 665 cm^{-1};

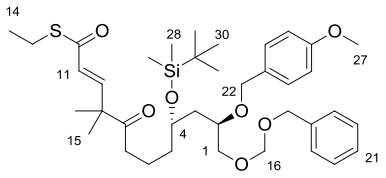
HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{35}H_{54}O_6SiNa$ 621.3587; found 621.3592.



(7*S*,9*R*)-10-(Benzyloxymethoxy)-7-(*tert*-butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-2,2-dimethyl-3-oxodecanal (2.69): With an acetone/dry ice bath

(–78 ºC), a steam of O_3 (3.0 psi, 60 Volts) purged through a solution of olefin **2.68** (5.644 g, 9.423 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL, 0.1 M) until the colorless solution turned pinkish. Whereupon, the O_3 was turned off, and a stream of N_2 flushed the solution until the color faded. Then, triphenylphosphine (3.716 g, 14.02 mmol, 1.5 equiv) was added at one portion. The reaction was stirred at room temperature for 6 hours. The resulting yellow solution was concentrated under reduced pressure. Then, an ice-cold solution of 30% (v/v) Et_2O in pentane (100 mL, 0.1 M) was added into the remainder. It was stirred at 0 ºC for 30 minutes. The white precipitate was filtrated, and washed with an ice-cold solution of 10% (v/v) Et_2O in pentane (3 x 10 mL). The solution was concentrated by rotary evaporation to give a yellow oil which was used directly in the next step without any further purification.

TLC: R_f = 0.50 (EtOAc/Hex = 3:7, v/v).



(9*S*,11*R*,*E*)-*S*-Ethyl 12-(Benzyloxymethoxy)-9-(*tert*-butyldimethylsilyloxy)-11-(4-methoxybenzyloxy)-4,4-dimethyl-5-oxododec-2-enethioate (2.71): To a round-bottomed flask was charged NaH (60% dispersion in mineral oil, 0.574 g, 14.4 mmol, 1.5 equiv) and anhydrous THF (35 mL, 0.4 M). With an ice-water bath, a solution of diethyl ethylthiocarbonylmethylphosphonate **2.70** (3.00 mL, 14.3 mmol, 1.5 equiv) in THF (30 mL, 0.5 M) was added dropwise via cannula. This reaction was then stirred under an atmosphere of N_2 for 10 minutes, whereupon a solution of aldehyde **2.69** (theoretically 9.423 mmol, 1.0 equiv) in THF (25 mL, 0.4 M) was added via a cannula. It was kept stirring in this condition for 2 hours. Then, a saturated $NaHCO_3$ solution (100 mL) was

added. The separated aqueous layer was extracted by ether (3 x 20 mL). The combined organic layers were washed with brine (100 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 4-10 vol% of ethyl acetate in hexanes to afford the titled compound (5.550 g, 8.078 mmol, 85.7% yield over two steps) a yellowish oil.

TLC: R_f = 0.60 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +13.7 (*c* 1.79, $CHCl_3$);

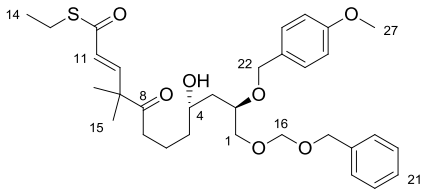
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.39-7.33 (m, 4H, ***H-19***, ***H-19'***, ***H-20***, ***H-20'***), 7.33-7.28 (m, 1H, ***H-21***), 7.27 (d, *J* = 8.8 Hz, 2H, ***H-24***, ***H-24'***), 6.96 (d, *J* = 16.1 Hz, 1H, ***H-10***), 6.87 (d, *J* = 8.8 Hz, 2H, ***H-25***, ***H-25'***), 6.14 (d, *J* = 15.8 Hz, 1H, ***H-11***), 4.79 (ABq, *J* = 6.6 Hz, *Δv* = 4.6 Hz, 2H, ***H-16***), 4.66 (d, *J* = 11.2 Hz, 1H, ***H-22a***), 4.62 (s, **2**H, ***H-17***), 4.47 (d, *J* = 10.8 Hz, 1H, ***H-22b***), 3.91 (dddd, *J* = 9.0, 5.6, 5.4, 3.9 Hz, 1H, ***H-4***), 3.80 (s, 3H, ***H-27***), 3.74 (dddd, *J* = 8.8, 5.0, 3.9, 3.9 Hz, 1H, ***H-2***), 3.70 (dd, *J* = 10.8, 3.9 Hz, 1H, ***H-1a***), 3.64 (dd, *J* = 10.8, 5.1 Hz, 1H, ***H-1b***), 2.97 (q, *J* = 7.3 Hz, 2H, ***H-13***), 2.44 (ddd, *J* = 17.6, 7.3, 7.3 Hz, 1H, ***H-7a***), 2.41 (ddd, *J* = 17.6, 7.3, 6.9 Hz, 1H, ***H-7b***), 1.74 (ddd, *J* = 14.2, 8.6, 3.7 Hz, 1H, ***H-3a***), 1.62 (ddd, *J* = 14.2, 8.3, 3.4 Hz, 1H, ***H-3b***), 1.61-1.53 (m, 2H, ***H-6a***, ***H-6b***), 1.48-1.38 (m, 2H, ***H-5a***, ***H-5b***), 1.30 (t, *J* = 7.3 Hz, 3H, ***H-14***), 1.28 (s, 6H, ***H-15a***, ***H-15b***), 0.90 (s, 9H, ***H-30***), 0.056 (s, 3H, ***H-28a***), 0.053 (s, 3H, ***H-28b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 210.5 (***C-8***), 190.0 (***C-12***), 159.3 (***C-26***), 147.3 (***C-10***), 138.1 (***C-18***), 131.2 (***C-23***), 129.2 (***C-24***, ***C-24'***), 128.6 (***C-20***, ***C-20'***), 128.0 (***C-19***, ***C-19'***), 127.8 (***C-21***), 127.7 (***C-11***), 113.9 (***C-25***, ***C-25'***), 95.0 (***C-16***), 75.5 (***C-2***), 71.4 (***C-22***), 70.5 (***C-1***), 69.6 (***C-17***), 69.3 (***C-4***), 55.4 (***C-27***), 50.6 (***C-9***), 40.1 (***C-3***), 38.5 (***C-7***), 37.6 (***C-5***),

26.1 (***C-30***), 23.7 (***C-15a***, ***C-15b***), 23.5 (***C-13***), 19.2 (***C-6***), 18.3 (***C-29***), 14.9 (***C-14***), -3.8 (***C-28a***), -4.3 (***C-28b***);

FTIR (neat): ν_{max} 2932, 2885, 2859, 1713, 1671, 1622, 1587, 1514, 1463, 1408, 1380, 1299, 1250, 1172, 1109, 1049, 835, 775, 740, 699, 665 cm^{-1};

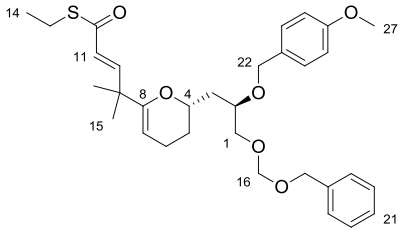
HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{38}H_{58}O_7SiSNa$ 709.3570; found 709.3580.



(9*S*,11*R*,*E*)-*S*-Ethyl 12-(Benzyloxymethoxy)-9-hydroxy-11-(4-methoxybenzyloxy)-4,4-dimethyl-5-oxododec-2-enethioate (2.72): To an ice-cold solution of protected alcohol **2.71** (4.031 g, 5.867 mmol, 1.0 equiv) in MeCN (60 mL, 0.1 M) was added pyridine (60 mL, 0.1 M) and DI H_2O (3.0 mL, 2.0 M). Then, aqueous HF solution (48 wt%, 9.0 mL, 0.25 mol, 40 equiv) was added dropwise. This reaction was allowed to warm to room temperature for 3 hours, and other portion of HF solution (48 wt%, 9.0 mL, 0.25 mol, 40 equiv) was added dropwise. Then, HF solution (48 wt%, 9.0 mL, 0.25 mol, 40 equiv) was added dropwise every 6 hours until 45 mL of HF solution (200 equiv) was added. This reaction was stirred for 36 hours, whereupon solid $NaHCO_3$ (40.8 g, 0.482 mol, 80 equiv) was carefully added into this reaction in several portions over 3 hours. Then, it was carefully poured into a mixture of saturated $NaHCO_3$ solution (200 mL) and 100 mL EtOAc. The aqueous phase was further extracted with EtOAc (3 x 50 mL). The combined organic solutions were washed with brine (200 mL), a saturated solution of Cu_2SO_4 (200 mL), and subsequently brine (200 mL). The organic solution was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide a yellow oil (crude 3.380 g, 5.902 mmol, 100% yield), which was used directly in the next

step without further purification.

TLC: R_f = 0.13 (EtOAc/Hex = 3:7, v/v).



(*E*)-*S*-Ethyl 4-((*S*)-2-((*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)propyl)-3,4-dihydro-*2H*-pyran-6-yl)-4-methylpent-2-enethioate (2.73): To a solution of crude **2.72** (3.380 g, theoretically 5.867 mmol, 1.0 equiv) in toluene (120 mL, 0.05 M) was added CSA (41 mg, 0.17 mmol, 0.03 equiv) in one portion at room temperature. This reaction was refluxed with dean-stark apparatus for an hour under an atmosphere of N_2. Then, freshly distilled pyridine (1.0 mL, 12 mmol) was added into this reaction. It was cooled down to room temperature under an atmosphere of N_2, and poured into a saturated $NaHCO_3$ solution (150 mL). The aqueous layer was extracted by ethyl ether (3 x 30 mL). The combined organic layers were washed with brine (150 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellow oil. The crude product was purified by flash chromatography on silica gel eluting with 10-25 vol% of ethyl ether in hexanes to afford the titled compound (2.555 g, 4.606 mmol, 78.5% yield in 2 steps) a yellowish oil.

TLC: R_f = 0.52 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +45.2 (*c* 1.18, $CHCl_3$);

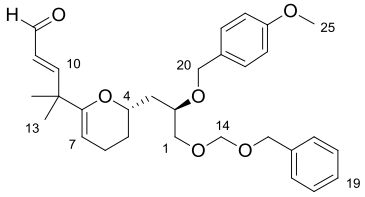
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.41-7.33 (m, 4H, ***H-19***, ***H-19'***, ***H-20***, ***H-20'***), 7.33-7.28 (m, 1H, ***H-21***), 7.26 (d, *J* = 9.0 Hz, 2H, ***H-24***, ***H-24'***), 6.97 (d, *J* = 15.7 Hz, 1H, ***H-10***), 6.86 (d, *J* = 8.8 Hz, 2H, ***H-25***, ***H-25'***), 6.09 (d, *J* = 15.7 Hz, 1H, ***H-11***), 4.80 (ABq, *J* = 6.6 Hz,

$\Delta\nu$ = 4.6 Hz, 2H, ***H-16***), 4.65 (d, *J* = 10.8 Hz, 1H, ***H-22a***), 4.63 (s, 2H, ***H-17***), 4.60 (dd, *J* = 5.2, 2.7 Hz, 1H, ***H-7***), 4.50 (d, *J* = 10.8 Hz, 1H, ***H-22b***), 4.00 (dddd, *J* = 9.8, 9.3, 3.4, 2.5 Hz, 1H, ***H-4***), 3.90 (dddd, *J* = 9.0, 4,4, 4.4, 4.4 Hz, 1H, ***H-2***), 3.80 (s, 3H, ***H-27***), 3.71 (dd, *J* = 10.5, 4.2 Hz, 1H, ***H-1a***), 3.64 (dd, *J* = 10.5, 5.1 Hz, 1H, ***H-1b***), 2.90 (q, *J* = 7.3 Hz, 2H, ***H-13***), 2.09 (dddd, *J* = 16.6, 9.3, 6.4, 2.7 Hz, 1H, ***H-6$_{eq}$***), 1.99 (dddd, *J* = 17.1, 6.1, 4.9, 3.4 Hz, 1H, ***H-6$_{ax}$***), 1.77 (app. ddt, *J* = 13.2, 5.8, 2.9 Hz, 1H, ***H-5$_{eq}$***), 1.75 (ddd, *J* = 14.2, 9.3, 3.9 Hz, 1H, ***H-3a***), 1.71 (ddd, *J* = 14.2, 9.3, 3.4 Hz, 1H, ***H-3b***), 1.50 (dddd, *J* = 13.5, 9.8, 9.8, 6.1 Hz, 1H, ***H-5$_{ax}$***), 1.24 (t, *J* = 7.3 Hz, 3H, ***H-14***), 1.23 (s, 3H, ***H-15a***), 1.22 (s, 3H, ***H-15b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 190.6 (***C-12***), 159.4 (***C-26***), 157.2 (***C-8***), 152.0 (***C-10***), 138.2 (***C-18***), 131.2 (***C-23***), 129.6 (***C-24***, ***C-24'***), 128.6 (***C-20***, ***C-20'***), 128.1 (***C-19***, ***C-19'***), 127.9 (***C-21***), 125.8 (***C-11***), 114.0 (***C-25***, ***C-25'***), 95.1 (***C-16***), 94.6 (***C-7***), 74.9 (***C-2***), 72.8 (***C-22***), 72.0 (***C-4***), 70.6 (***C-1***), 69.6 (***C-17***), 55.5 (***C-27***), 41.4 (***C-9***), 38.5 (***C-3***), 28.1 (***C-5***), 25.3 (***C-15a***), 25.2 (***C-15b***), 23.3 (***C-13***), 20.5 (***C-6***), 14.9 (***C-14***);

FTIR (neat): ν_{max} 3032, 2929, 2877, 1711, 1667, 1625, 1587, 1513, 1456, 1380, 1289, 1248, 1171, 1094, 1044, 940, 824, 782, 740, 698 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{32}H_{42}O_6SNa$ 577.2600; found 577.2607.



(*E*)-4-((*S*)-2-((*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)propyl)-3,4-dihydro-*2H*-pyran-6-yl)-4-methylpent-2-enal (2.55): With a –78 °C bath, to a stirred solution of thio ester **2.73** (2.555 g, 4.606 mmol, 1.0 equiv) in fresh distilled CH_2Cl_2 (50 mL, 0.1 M) was added a DIBAL solution (1.0 M solution in CH_2Cl_2, 6.90 mL, 6.90 mmol, 1.5 equiv) at the rate of

10 mL/h via syringe pump under an atmosphere of N_2. After addition, it was stirred for 30 minutes, and EtOAc (5 mL) was then added into the reaction at the same rate above. Then, a saturated Rochelle's salt solution (100 mL) was added, and the mixture was stirred vigorously for 3 hours, whereupon two clear phases appeared. The aqueous layer was extracted by Et_2O (3 x 20 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with 5-15 vol% of ethyl acetate in hexanes to provide the titled compound (1.825 g, 3.690 mmol, 80.1% yield) as a colorless oil.

TLC: R_f = 0.40 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +35.2 (*c* 1.90, $CHCl_3$);

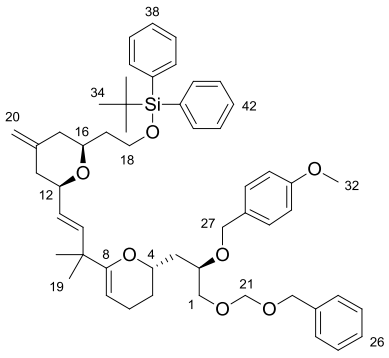
500 MHz ^{1}H NMR ($CDCl_3$) δ 9.49 (d, *J* = 7.8 Hz, 1H, ***H-12***), 7.41-7.33 (m, 4H, ***H-17***, ***H-17'***, ***H-18***, ***H-18'***), 7.33-7.28 (m, 1H, ***H-19***), 7.25 (d, *J* = 8.8 Hz, 2H, ***H-22***, ***H-22'***), 6.87 (d, *J* = 9.2 Hz, 2H, ***H-23***, ***H-23'***), 6.86 (d, *J* = 15.7 Hz, 1H, ***H-10***), 6.11 (dd, *J* = 15.9, 7.6 Hz, 1H, ***H-11***), 4.80 (ABq, *J* = 6.4 Hz, *Δv* = 6.1 Hz, 2H, ***H-14***), 4.66 (d, *J* = 11.2 Hz, 1H, ***H-20a***), 4.63 (s, 2H, ***H-15***), 4.63 (dd, *J* = 5.8, 2.8 Hz, 1H, ***H-7***), 4.47 (d, *J* = 10.8 Hz, 1H, ***H-20b***), 4.06 (dddd, *J* = 9.8, 9.3, 3.7, 2.4 Hz, 1H, ***H-4***), 3.87 (dddd, *J* = 8.8, 4.9, 4.4, 3.9 Hz, 1H, ***H-2***), 3.80 (s, 3H, ***H-25***), 3.70 (dd, *J* = 10.3, 4.4 Hz, 1H, ***H-1a***), 3.64 (dd, *J* = 10.3, 5.1 Hz, 1H, ***H-1b***), 2.11 (dddd, *J*= 16.9, 9.8, 6.3, 2.9 Hz, 1H, ***H-6$_{eq}$***), 2.00 (dddd, *J* = 17.1, 5.9, 4.9, 3.4 Hz, 1H, ***H-6$_{ax}$***), 1.79 (dddd, *J* = 13.2, 6.4, 3.4, 2.9 Hz, 1H, ***H-5$_{eq}$***), 1.77 (ddd, *J* = 14.2, 9.3, 3.9 Hz, 1H, ***H-3a***), 1.72 (ddd, *J* = 14.2, 9.3, 3.4 Hz, 1H, ***H-3b***), 1.51 (dddd, *J* = 13.2, 9.8, 9.8, 5.9 Hz, 1H, ***H-5$_{ax}$***), 1.26 (s, 3H, ***H-13a***), 1.25 (s, 3H, ***H-13b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 194.7 (***C-12***), 165.6 (***C-10***), 159.4 (***C-24***), 156.9 (***C-8***),

138.1 (***C-16***), 131.0 (***C-21***), 129.8 (***C-11***), 129.5 (***C-22***, ***C-22'***), 128.6 (***C-18***, ***C-18'***), 128.0 (***C-17***, ***C-17'***), 127.9 (***C-19***), 114.0 (***C-23***, ***C-23'***), 95.2 (***C-14***), 94.9 (***C-7***), 74.8 (***C-2***), 72.6 (***C-20***), 72.1 (***C-4***), 70.6 (***C-1***), 69.7 (***C-15***), 55.5 (***C-25***), 42.1 (***C-9***), 38.5 (***C-3***), 28.1 (***C-5***), 25.3 (***C-13a***), 25.2 (***C-13b***), 20.5 (***C-6***);

FTIR (neat): ν_{max} 2928, 2879, 1690, 1613, 1587, 1513, 1459, 1381, 1349, 1298, 1248, 1171, 1096, 1043, 940, 822, 741, 699, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{30}H_{38}O_6Na$ 517.2566; found 517.2563.



(2-((2*S*,6*R*)-6-((*E*)-3-((*S*)-2-(*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)propyl)-3,4-dihydro-2*H*-pyran-6-yl)-3-methylbut-1-en-1-yl)-4-methylenetetrahydro-2*H*-pyran-2-yl)ethoxy)(*tert*-butyl)diphenylsilane (2.74):

With a –78 ºC bath, to a stirred mixtue of aldehyde **2.55** (608 mg, 1.23 mmol, 1.0 equiv) and compound *β*-hydroxyallylsilane **2.33** (812 mg, 1.84 mmol, 1.5 equiv) in fresh distilled Et_2O (25 mL, 0.05 M) was added pyridine (30.0 uL, 0.371 mmol, 0.3 equiv) via syringe under an atmosphere of N_2. Then, a solution of 1.0 M TMSOTf in Et_2O (1.5 mL, 1.5 mmol, 1.2 equiv) was introduced into this reaction dropwise via syringe. It was stirred for 30 minutes, and quenched with DIPEA (2.2 mL, 13 mmol, 10 equiv) at this temperature. After another 30 minutes, it was poured into a saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a colorless oil. The crude product was

purified by flash chromatography on silica gel eluting with 5-20 vol% of Et_2O in hexanes to provide the titled compound (967 mg, 1.14 mmol, 93.2% yield) as a colorless oil.

TLC: R_f = 0.38 (Et_2O:Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +21.3 (*c* 1.07, $CHCl_3$);

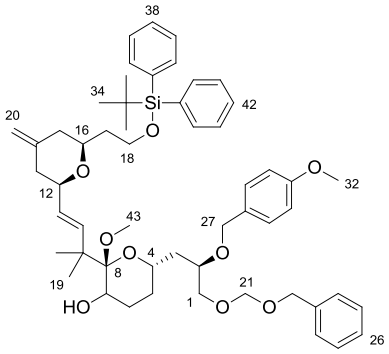
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.74-7.64 (m, 4H, ***H-36***, ***H-36'***, ***H-40***, ***H-40'***), 7.48-7.33 (m, 10H, ***H-24***, ***H-24'***, ***H-25***, ***H-25'***, ***H-37***, ***H-37'***, ***H-38***, ***H-41***, ***H-41'***, ***H-42***), 7.33-7.28 (m, 1H, ***H-26***), 7.28 (d, *J* = 8.8 Hz, 2H, ***H-29***, ***H-29'***), 6.86 (d, *J* = 8.8 Hz, 2H, ***H-30***, ***H-30'***), 5.79 (dd, *J* = 16.1, 1.0 Hz, 1H, ***H-10***), 5.52 (dd, *J* = 16.1, 6.1 Hz, 1H, ***H-11***), 4.81 (ABq, *J* = 6.8 Hz, $\Delta\nu$ = 4.7 Hz, 2H, ***H-21***), 4.73 (d, *J* = 2.0 Hz, 1H, ***H-20a***), 4.72 (d, *J* = 2.0 Hz, 1H, ***H-20b***), 4.68 (d, *J* = 10.8 Hz, 1H, ***H-27a***), 4.64 (s, 2H, ***H-22***), 4.55 (t, *J* = 3.9 Hz, 1H, ***H-7***), 4.54 (d, *J* = 10.8 Hz, 1H, ***H-27b***), 4.06 (dddd, *J* = 9.8, 9.3, 2.9, 2.4 Hz, 1H, ***H-4***), 3.96 (dddd, *J* = 9.3, 9.3, 5.1, 4.1 Hz, 1H, ***H-2***), 3.87 (ddd, *J* = 10.3, 7.8, 5.4 Hz, 1H, ***H-18a***), 3.79 (s, 3H, ***H-32***), 3.82-3.74 (m, 2H, ***H-12***, ***H-18b***), 3.72 (dd, *J* = 10.5, 4.1 Hz, 1H, ***H-1a***), 3.75 (dd, *J* = 10.5, 5.1 Hz, 1H, ***H-1b***), 3.55 (dddd, *J* = 12.5, 7.6, 5.1, 2.4 Hz, 1H, ***H-16***), 2.30-2.23 (m, 1H, ***H-13$_{eq}$***), 2.26-2.20 (m, 1H, ***H-15$_{eq}$***), 2.15-2.02 (m, 2H, ***H-6$_{eq}$***, ***H-13$_{ax}$***), 2.02-1.82 (m, 3H, ***H-6$_{ax}$***, ***H-15$_{ax}$***, ***H-17a***), 1.82-1.66 (m, 4H, ***H-17b***, ***H-5$_{eq}$***, ***H-3a***, ***H-3b***), 1.50 (dddd, *J* = 13.4, 9.8, 9.8, 6.1 Hz, 1H, ***H-5$_{ax}$***), 1.19 (s, 6H, ***H-19a***, ***H-19b***), 1.06 (s, 9H, ***H-34***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 159.4 (***C-31***), 159.2 (***C-8***), 145.0 (***C-14***), 139.1 (***C-10***), 138.1 (***C-23***), 135.8 (***C-36***, ***C-36'***, ***C-40***, ***C-40'***), 134.3 (***C-35***), 134.2 (***C-39***), 131.2 (***C-28***), 129.7 (***C-38***), 129.7 (***C-42***), 129.6 (***C-29***, ***C-29'***), 128.6 (***C-25***, ***C-25'***), 128.1 (***C-24***), (***C-24'***), 127.8 (***C-26***, ***C-37***, ***C-37'***, ***C-41***, ***C-41'***), 127.6 (***C-11***), 114.0 (***C-30***, ***C-30'***), 108.6 (***C-20***), 95.1 (***C-21***), 93.4 (***C-7***), 79.2 (***C-12***), 75.4 (***C-16***), 75.1 (***C-2***), 72.8 (***C-27***), 71.7 (***C-4***),

70.8 (***C-1***), 69.6 (***C-22***), 60.6 (***C-18***), 55.5 (***C-32***), 41.4 (***C-13***), 40.9 (***C-15***), 40.7 (***C-9***), 39.3 (***C-17***), 38.6 (***C-3***), 28.2 (***C-5***), 27.1 (***C-34***), 26.1 (***C-19a***), 25.9 (***C-19b***), 20.5 (***C-6***), 19.5 (***C-33***);

FTIR (neat): ν_{max} 3070, 2931, 2856, 1660, 1613, 1513, 1471, 1428, 1380, 1358, 1292, 1247, 1172, 1088, 1039, 972, 939, 891, 822, 737, 700 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{53}H_{68}O_7SiNa$ 867.4632; found 867.4637.

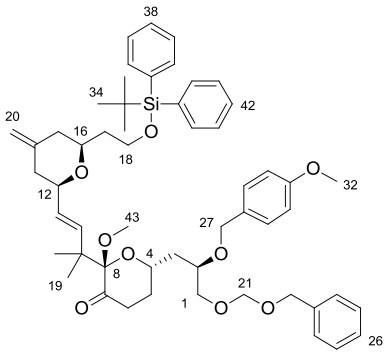


(2*S*,6*S*)-6-((*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)propyl)-2-((*E*)-4-((2*R*,6*S*)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxytetrahydro-2*H*-pyran-3-ol (2.75): With a –10 ºC bath, to a stirred solution of glycol **2.74** (391 mg, 0.463 mmol, 1.0 equiv) in fresh distilled CH_2Cl_2 (23 mL, 0.02 M) and MeOH (12 mL, 0.04 M) was added a solution of *m*CPBA(120 mg, 0.695 mmmol, 1.5 equiv) in CH_2Cl_2 (7.0 mL, 0.1 M) via cannula. This reaction was stirred at this temperature under an atmosphere of N_2 for 2 hours. Then, a saturated solution $Na_2S_2O_3$ (20 mL) was added. It was stirred at room temperature for 30 minutes. It was then poured into H_2O (20 mL). The aqueous layer was extracted by EtOAc (3 x 10 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a colorless oil.

To the solution of the crude product above in MeOH (46 mL, 0.01 M) was added PPTS (11.6 mg, 0.0462 mmol, 0.1 equiv) in one portion at room temperature. It was stirred

under an atmosphere of N_2 for 2 hours. It was then poured into a saturated solution of $NaHCO_3$ (100 mL). The aqueous layer was extracted with 1:1 (v/v) mixture of EtOAc/Hex (3 x 20 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated by rotary evaporation. The remainder (397 mg, 0.445 mmol, 96.2% yield, crude) was used directly in next step without any further purification.

TLC: R_f = 0.39 and 0.42 (EtOAc/Hex = 3:7, v/v).



(2*S*,6*S*)-6-((*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)propyl)-2-((*E*)-4-((2*R*,6*S*)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxydihydro-2*H*-pyran-3(4*H*)-one (2.76): To a stirred solution of alcohol **2.75** (397 mg, theoretically 0.445 mmol, 1.0 equiv) in dry CH_2Cl_2 (45 mL, 0.01 M) was added *t*-BuOH (56 uL, 0.59 mmol, 1.3 equiv) and freshly distilled pyridine (110 uL, 1.36 mmol, 3.0 equiv). Then, this reaction was cooled down to 0 ^oC, and Dess-Martin periodinane (291 mg, 0.664 mmol, 1.5 equiv) was added in one portion. The cooling bath was removed, and the reaction was stirred at room temperature for 1 hour under an atmosphere of N_2. At this point, the reaction was diluted with Et_2O (20 mL), and a saturated $NaHCO_3$ solution (30 mL) was added, followed by a saturated $Na_2S_2O_3$ solution (30 mL). This mixture was stirred for 10 minutes at room temperature. The aqueous layer was extracted by Et_2O (3 x 15 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution

was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 10-20 vol% of EtOAc in hexanes to provide the titled compound (368 mg, 0.413 mmol, 89.3% yield in 2 steps) as a yellow oil.

TLC: R_f = 0.48 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +8.1 (*c* 3.54, $CHCl_3$);

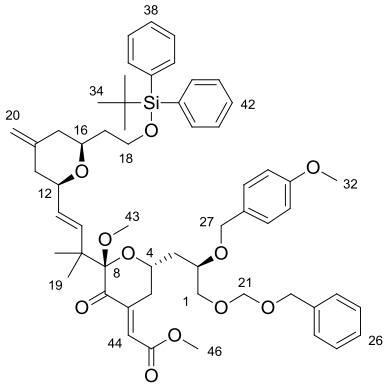
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.73-7.64 (m, 4H, ***H-36***, ***H-36'***, ***H-40***, ***H-40'***), 7.48-7.34 (m, 10H, ***H-24***, ***H-24'***, ***H-25***, ***H-25'***, ***H-37***, ***H-37'***, ***H-38***, ***H-41***, ***H-41'***, ***H-42***), δ 7.34-7.28 (m, 1H, ***H-26***), 7.25 (d, *J* = 8.6 Hz, 2H, ***H-29***, ***H-29'***), 6.87 (d, *J* = 8.6 Hz, 2H, ***H-30***, ***H-30'***), 6.02 (d, *J* = 16.1 Hz, 1H, ***H-10***), 5.51 (dd, *J* = 16.1, 6.0 Hz, 1H, ***H-11***), 4.82 (ABq, *J* = 6.6 Hz, $\Delta\nu$ = 6.4 Hz, 2H, ***H-21***), 4.76 (br. s, 2H, ***H-20a***, ***H-20b***), 4.72 (d, *J* = 10.9 Hz, 1H, ***H-27a***), 4.65 (s, 2H, ***H-22***), 4.48 (d, *J* = 10.9 Hz, 1H, ***H-27b***), 4.18 (dddd, *J* = 9.1, 8.8, 3.4, 3.1 Hz, 1H, ***H-4***), 3.97 (dq, *J* = 8.3, 4.4 Hz, 1H, ***H-2***), 3.85 (ddd, *J* = 10.1, 7.8, 5.3 Hz, 1H, ***H-18a***), 3.79 (s, 3H, ***H-32***), 3.82-3.74 (m, 3H, ***H-18b***, ***H-12***, ***H-1a***), 3.69 (dd, *J* = 10.6, 4.8 Hz, 1H, ***H-1b***), 3.56 (dddd, *J* = 11.9, 7.3, 4.9, 2.1 Hz, 1H, ***H-16***), 3.26 (s, 3H, ***H-43***), 2.45 (ddd, *J* = 17.7, 9.9, 7.8 Hz, 1H, ***H-6$_{eq}$***), 2.39 (ddd, *J* = 17.7, 7.5, 3.9 Hz, 1H, ***H-6$_{ax}$***), 2.29-2.20 (m, 2H, ***H-13$_{eq}$***, ***H-15$_{eq}$***), 2.03 (dd, *J* = 12.9, 11.4 Hz, 1H, ***H-13$_{ax}$***), 1.98-1.66 (m, 7H, ***H-15$_{ax}$***, ***H-3a***, ***H-5$_{eq}$***, ***H-17a***, ***H-3b***, ***H-5$_{ax}$***, ***H-17b***), 1.18 (s, 3H, ***H-19a***), 1.12 (s, 3H, ***H-19b***), 1.06 (s, 9H, ***H-34***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 207.2 (***C-7***), 159.4 (***C-31***), 144.7 (***C-14***), 138.1 (***C-23***), 136.8 (***C-10***), 135.7 (***C-36***, ***C-36'***, ***C-40***, ***C-40'***), 134.2 (***C-35***), 134.1 (***C-39***), 130.9 (***C-28***), 129.7 (***C-25***, ***C-25'***), 129.4 (***C-11***), 129.4 (***C-29***, ***C-29'***), 128.6 (***C-38***, ***C-42***), 128.0 (***C-24***, ***C-24'***), 127.9 (***C-26***), 127.8 (***C-37***, ***C-37'***, ***C-41***, ***C-41'***), 114.0 (***C-30***, ***C-30'***), 108.8 (***C-20***), 104.1 (***C-8***), 95.2 (***C-21***), 79.0 (***C-12***), 75.5 (***C-16***), 74.9 (***C-2***), 71.7 (***C-27***), 70.2 (***C-1***),

69.7 (***C-22***), 69.6 (***C-4***), 60.6 (***C-18***), 55.4 (***C-32***), 52.3 (***C-43***), 44.3 (***C-9***), 41.3 (***C-13***), 40.9 (***C-15***), 39.4 (***C-17***), 39.4 (***C-3***), 37.6 (***C-6***), 30.3 (***C-5***), 27.1 (***C-34***), 22.9 (***C-19a***), 22.3 (***C-19b***), 19.4 (***C-33***);

FTIR (neat): ν_{max} 2933, 1737, 1613, 1514, 1463, 1428, 1372, 1302, 1244, 1172, 1109, 1041, 892, 821, 735, 700 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{54}H_{70}O_9SiNa$ 913.4687; found 913.4682.



(*E*)-Methyl 2-((2*S*,6*S*)-6-((*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)propyl)-2-((*E*)-4-((2*R*,6*S*)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-3-oxodihydro-*2H*-pyran-4(*3H*)-ylidene)acetate (2.77):

Preparation of Methyl Glyoxylate: With an acetone/dry ice bath (–78 ºC), a steam of O_3 (3.0 psi, 90 Volts) purged through a solution of dimethyl maleate (5.00 mL, 38.3 mmol, 1.0 equiv) in CH_2Cl_2 (75 mL, 0.5 M) for 1.5 hours. At this point, the O_3 was turned off, and a stream of O_2 flushed the dark purple solution until the color faded. Then, DMS (3.4 mL, 46 mmol, 1.2 equiv) was added dropwise at this temperature. This reaction was then stirred at room temperature for 6 hours. The solvent was removed by rotary evaporation. The remainder was distilled under a vacuum to provide a pale yellow oil (aobut 5 mL) at 45-55 ºC/aspirator.

To a stirred solution of keone **2.76** (748 mg, 0.840 mmol, 1.0 equiv) in dry MeOH (8.5 mL,

0.1 M) was added K_2CO_3 solid (333 mg, 2.39 mmol, 5.0 equiv). Then a solution of above freshly distilled methyl glyoxylate (about 4 mL, 45 mmol, 50 equiv) in dry THF (5.0 M, 8.0 mL) was added into this reaction via syringe in one portion at room temperature. It was stirred under an atmosphere of N_2 for 2.5 hours, whereupon, the reaction was diluted with Et_2O (20 mL). It was poured into a saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 20-30 vol% of Et_2O in hexanes to provide the titled compound (617 mg, 0.642 mmol, 76.4% yield, E:Z > 95:5) as a yellow oil.

TLC: R_f = 0.36 (Et_2O/Hex = 5:5, v/v);

$[\alpha]_D^{20}$ -43.9 (*c* 1.56, $CHCl_3$);

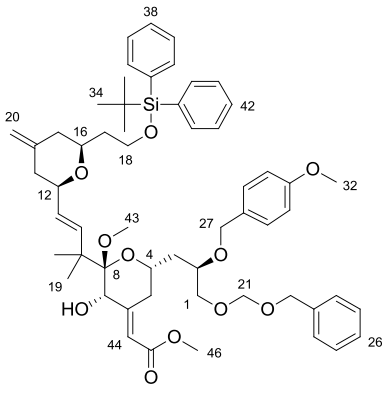
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.68 (ddd, *J* = 7.9, 3.4, 1.5 Hz, 4H, ***H-36***, ***H-36'***, ***H-40***, ***H-40'***), 7.47-7.34 (m, 10H, ***H-24***, ***H-24'***, ***H-25***, ***H-25'***, ***H-37***, ***H-37'***, ***H-38***, ***H-41***, ***H-41'***, ***H-42***), 7.31 (tt, *J* = 8.3, 3.9 Hz, 1H, ***H-26***), 7.22 (d, *J* = 8.8 Hz, 2H, ***H-29***, ***H-29'***), 6.84 (d, *J* = 8.8 Hz, 2H, ***H-30***, ***H-30'***), 6.57 (dd, *J* = 3.4, 2.0 Hz, 1H, ***H-44***), 5.82 (dd, *J* = 15.9, 1.2 Hz, 1H, ***H-10***), 5.41 (dd, *J* = 16.1, 5.9 Hz, 1H, ***H-11***), 4.82 (ABq, *J* = 6.8 Hz, $\Delta\nu$ = 7.0 Hz, 2H, ***H-21***), 4.73 (d, *J* = 1.5 Hz, 1H, ***H-20a***), 4.71 (d, *J* = 1.5 Hz, 1H, ***H-20b***), 4.71 (d, *J* = 11.3 Hz, 1H, ***H-27a***), 4.65 (s, 2H, ***H-22***), 4.46 (d, *J* = 10.8 Hz, 1H, ***H-27b***), 4.21 (dddd, *J* = 12.2, 9.3, 2.4, 1.9 Hz, 1H, ***H-4***), 3.99 (dtd, *J* = 7.8, 4.5, 3.4 Hz, 1H, ***H-2***), 3.84 (ddd, *J* = 10.3, 7.6, 5.6 Hz, 1H, ***H-18a***), 3.79 (s, 3H, ***H-32***), 3.81-3.74 (m, 2H, ***H-18b***, ***H-1a***), 3.74 (s, 3H, ***H-46***), 3.75-3.67 (m, 2H, ***H-1a***, ***H-12***), 3.55-3..47 (m, 1H, ***H-16***), 3.29 (dt, *J* = 18.6, 2.0, 1H, $\boldsymbol{H\text{-}5_{eq}}$), 3.25 (s, 3H, ***H-43***), 2.85 (ddd, *J* = 18.8, 12.5, 3.4, 1H, $\boldsymbol{H\text{-}5_{ax}}$), 2.23 (br. d,

J = 12.7 Hz, 1H, ***H-15$_{eq}$***), 2.11 (br. d, *J* = 13.2 Hz, 1H, ***H-13$_{eq}$***), 1.99-1.89 (m, 3H, ***H-13$_{ax}$***, ***H-3a***, ***H-15$_{ax}$***), 1.89-1.80 (m, 2H, ***H-3b***, ***H-17a***), 1.74 (dddd, *J* = 13.4, 7.6, 5.9, 5.9 1H, ***H-17b***), 1.15 (s, 3H, ***H-19a***), 1.07 (s, 9H, ***H-34***), 1.06 (s, 3H, ***H-19b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 197.6 (***C-7***), 166.2 (***C-45***), 159.4 (***C-31***), 148.2 (***C-6***), 144.6 (***C-14***), 138.0 (***C-23***), 135.7 (***C-10***, ***C-36***, ***C-36'***, ***C-40***, ***C-40'***), 134.2 (***C-35***), 134.1 (***C-39***), 130.7 (***C-28***), 130.3 (***C-11***), 129.7 (***C-38***), 129.7 (***C-42***), 129.2 (***C-29***, ***C-29'***), 128.6 (***C-25***, ***C-25'***), 128.0 (***C-24***, ***C-24'***), 127.9 (***C-26***), 127.8 (***C-37***, ***C-37'***, ***C-41***, ***C-41'***), 123.1 (***C-44***), 114.0 (***C-30***, ***C-30'***), 108.8 (***C-20***), 104.7 (***C-8***), 95.2 (***C-21***), 79.0 (***C-12***), 75.5 (***C-16***), 74.5 (***C-2***), 71.4 (***C-27***), 70.0 (***C-1***), 69.8 (***C-22***), 69.3 (***C-4***), 60.6 (***C-18***), 55.4 (***C-32***), 52.3 (***C-43***), 51.9 (***C-46***), 44.9 (***C-9***), 40.8 (***C-15***), 40.7 (***C-13***), 39.3 (***C-3***), 39.2 (***C-17***), 36.2 (***C-5***), 27.1 (***C-34***), 22.6 (***C-19a***), 21.7 (***C-19b***), 19.4 (***C-33***);

FTIR (neat): ν_{max} 3071, 2937, 1706, 1651, 1613, 1588, 1514, 1463, 1429, 1383, 1361, 1303, 1249, 1207, 1178, 1113, 894, 823 cm^{-1};

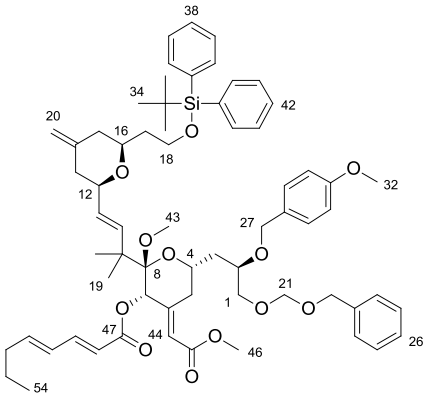
HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{57}H_{72}O_{11}SiNa$ 983.4742; found 983.4756.



(*E*)-Methyl 2-((2*S*,3*S*,6*S*)-6-((*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)propyl)-2-((*E*)-4-((2*R*,6*S*)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)-2-methylbut-3-en-2-yl)-3-hydro-2-methoxydihydro-2*H*-pyran-4(*3H*)-ylidene)acetate (2.78): To a stirred solution of keone **2.77** (564 mg, 0.587 mmol, 1.0 equiv) in the mixture of toluene (0.6 mL, 1.0 M) and MeOH

(60 mL, 0.01 M) was added $CeCl_3 \cdot 7H_2O$ (2.19 g, 5.88 mmol, 10.0 equiv) in one portion at room temperature. It was stirred for 10 minutes until the entire solid was dissolved, this reaction was cooled down to -78 °C, and $NaBH_4$ (160 mg, 4.14 mmol, 7.0 equiv) was added in one portion. It was stirred for 2 hours at -78 °C, and then stirred further 15 minutes at 0 °C. The reaction was diluted with EtOAc (30 mL), and poured into a cold H_2O (100 mL). The aqueous layer was extracted with EtOAc (4 x 15 mL). The combined organic layers were washed with brine (50 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was used in the next step without any further purification.

TLC: R_f = 0.33 (EtOAc/Hex = 3:7, v/v).



(2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)propyl)-2-((*E*)-4-((2*R*,6*S*)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-4-methylenetetrahydro-*2H*-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-*2H*-pyran-3-yl Octa-2,4-dienoate (2.80): To a stirred solution of (2*E*,4*E*)-octa-2,4-dienoic acid **2.79** (246 mg, 1.76 mmol, 3.0 equiv) in dry toluene (35 mL, 0.05 M) was added freshly distilled NEt_3 (820 uL, 5.88 mmol, 10.0 equiv), followed by 2,4,6-trichlorobenzoylchloride (280 uL, 1.76 mmol, 3.0 eq) at 0 °C. After 10 minutes, the cooling bath was removed, and the reaction was stirred at room temperature under an atmosphere of N_2 for 2 hours. Then this reaction was transferred to

a solution of crude alcohol **2.78** (crude 564 mg, theoretically 0.587 mmol, 1.0 equiv) in toluene (6.0 mL, 0.1 M) via cannula at 0 ^{o}C. Then, a solution of DMAP (108 mg, 0.873 mmol, 1.5 equiv) in toluene (9.0 mL, 0.1 M) was added into this mixture via cannula. After 10 minutes, the cooling bath was removed, and this reaction was stirred at room temperature for 3 hours. Then, methanol (1.0 mL, 25 mmol) was added at room temperature. This reaction was stirred further 2 hours. It was diluted with ether (10 mL) and poured into a saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The reminder was purified by flash chromatography on silica gel eluting with 10-15 vol% of EtOAc in hexanes to provide a single diastereomer (592 mg, 0.546 mmol, 93.0% yield, dr > 95:5) as a yellow oil.

TLC: R_f = 0.50 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ -10.8 (*c* 0.93, $CHCl_3$);

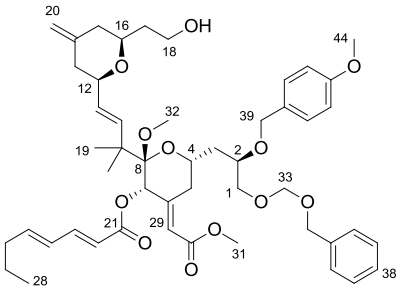
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.71-7.63 (m, 4H, ***H-36***, ***H-36'***, ***H-40***, ***H-40'***), 7.47-7.32 (m, 10H, ***H-37***, ***H-37'***, ***H-38***, ***H-41***, ***H-41'***, ***H-42***, ***H-24***, ***H-24'***, ***H-25***, ***H-25'***), 7.32-7.25 (m, 2H, ***H-26***, ***H-49***), 7.23 (d, *J* = 8.6 Hz, 2H, ***H-29***, ***H-29'***), 6.84 (d, *J* = 8.8 Hz, 2H, ***H-30***, ***H-30'***), 6.20-6.10 (m, 2H, ***H-50***, ***H-51***), 6.02 (dd, *J* = 16.1, 1.3 Hz, 1H, ***H-10***), 5.91 (dd, *J* = 1.0, 0.8 Hz, 1H, ***H-44***), 5.78 (d, *J* = 15.3 Hz, 1H, ***H-48***), 5.57 (s, 1H, ***H-7***), 5.40 (dd, *J* = 16.1, 5.7 Hz, 1H, ***H-11***), 4.80 (ABq, *J* = 6.6 Hz, *Δv* = 5.6 Hz, 2H, ***H-21***), 4.72 (d, *J* = 1.8 Hz, 1H, ***H-20a***), 4.69 (d, *J* = 11.1 Hz, 1H, ***H-27a***), 4.69 (d, *J* = 1.6 Hz, 1H, ***H-20b***), 4.63 (s, 2H, ***H-22***), 4.46 (d, *J* = 10.9 Hz, 1H, ***H-27b***), 4.13 (dddd, *J* = 11.9, 9.4, 2.9, 2.8 Hz, 1H, ***H-4***), 3.98 (dddd, *J* = 9.3, 4.5, 4.2, 3.9 Hz, 1H, ***H-2***), 3.85 (ddd, *J* = 10.1, 7.5, 5.5 Hz, 1H,

H-18a), 3.78 (s, 3H, ***H-32***), 3.78-3.72 (m, 2H, ***H-1a***, ***H-18b***), 3.72-3.66 (m, 2H, ***H-12***, ***H-1b***), 3.68 (s, 3H, ***H-46***), 3.56-3.48 (m, 1H, ***H-16***), 3.51-3.43 (m, 1H, $\boldsymbol{H\text{-}5_{eq}}$), 3.24 (s, 3H, ***H-43***), 2.35 (ddd, J = 16.0, 11.5, 2.1 Hz, 1H, $\boldsymbol{H\text{-}5_{ax}}$), 2.32 (ddd, J = 14.0, 1.8, 1.7 Hz, 1H, $\boldsymbol{H\text{-}15_{eq}}$), 2.20 (ddd, J = 13.4, 1.8, 1.6 Hz, 1H, $\boldsymbol{H\text{-}13_{eq}}$), 2.14 (td, J = 7.1, 5.3 Hz, 2H, ***H-52***), 2.00 (dd, J = 13.0, 11.7 Hz, 1H, $\boldsymbol{H\text{-}13_{ax}}$), 1.95-1.68 (m, 5H, $\boldsymbol{H\text{-}15_{ax}}$, ***H-3a***, ***H-17a***, ***H-3b***, ***H-17b***), 1.45 (sext, J = 7.4 Hz, 2H, ***H-53***), 1.15 (s, 6H, ***H-19a***, ***H-19b***), 1.05 (s, 9H, ***H-34***), 0.92 (t, J = 7.4 Hz, 3H, ***H-54***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.6 (***C-45***), 165.5 (***C-47***), 159.3 (***C-31***), 152.8 (***C-6***), 146.6 (***C-49***), 145.7 (***C-51***), 144.8 (***C-14***), 138.5 (***C-10***), 138.0 (***C-23***), 135.7 (***C-36***, ***C-36'***, ***C-40***, ***C-40'***), 134.2 (***C-35***), 134.1 (***C-39***), 130.8 (***C-28***), 129.7 (***C-38***, ***C-42***), 129.4 (***C-29***, ***C-29'***), 128.6 (***C-25***, ***C-25'***, ***C-50***), 128.0 (***C-24***, ***C-24'***), 127.8 (***C-27***), 127.8 (***C-37***, ***C-37'***, ***C-41***, ***C-41'***), 126.8 (***C-11***), 118.7 (***C-48***), 117.2 (***C-44***), 114.0 (***C-30***, ***C-30'***), 108.6 (***C-20***), 102.9 (***C-8***), 95.1 (***C-21***), 79.0 (***C-12***), 75.5 (***C-16***), 74.7 (***C-2***), 71.9 (***C-7***), 71.7 (***C-27***), 70.2 (***C-1***), 69.7 (***C-22***), 68.2 (***C-4***), 60.6 (***C-18***), 55.4 (***C-32***), 51.5 (***C-43***), 51.2 (***C-46***), 46.1 (***C-9***), 40.9 (***C-15***), 40.9 (***C-13***), 39.5 (***C-17***), 39.3 (***C-3***), 35.2 (***C-52***), 33.0 (***C-5***), 27.1 (***C-34***), 24.2 (***C-19a***), 24.1 (***C-19b***), 22.0 (***C-53***), 19.4 (***C-33***), 13.8 (***C-54***);

FTIR (neat): ν_{max} 2932, 1738, 1717, 1641, 1613, 1514, 1463, 1372, 1359, 1302, 1241, 1157, 1132, 1104, 1042, 1000, 859, 734, 701, 634 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{65}H_{84}O_{12}SiNa$ 1107.5630; found 1107.5640.



(2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)propyl)-2-((*E*)-4-((2*R*,6*S*)-6-(2-hydroxyethyl)-4-methylenetetrahydro-*2H*-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-*2H*-pyran-3-yl Octa-2,4-dienoate (2.85): To a stirred solution of protected alcohol **2.80** (516 mg, 0.476 mmol, 1.0 equiv) in MeOH (25 mL, 0.02 M) was added NH_4F solid (352 mg, 9.42 mmol, 20 equiv) in one portion at room temperature. This reaction was stirred at 60 ^oC for 20 hours, whereupon it was diluted with EtOAc (20 ml) and poured into H_2O (30 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 20-30 vol% of EtOAc in hexanes to provide the titled compound (369 mg, 0.435 mmol, 91.6% yield) as a yellow oil.

TLC: R_f = 0.21 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ -21.1 (*c* 0.81, $CHCl_3$);

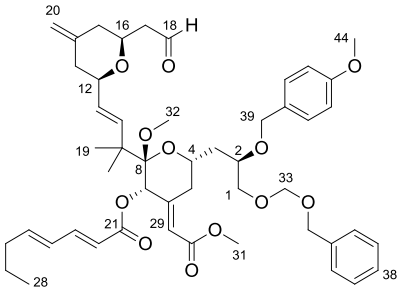
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.39-7.33 (m, 4H, ***H-36***, ***H-36'***, ***H-37***, ***H-37'***), 7.33-7.26 (m, 2H, ***H-38***, ***H-23***), 7.23 (d, *J* = 8.6 Hz, 2H, ***H-41***, ***H-41'***), 6.84 (d, *J* = 8.8 Hz, 2H, ***H-42***, ***H-42'***), 6.22-6.14 (m, 2H, ***H-24***, ***H-25***), 6.02 (dd, *J* = 15.8, 1.0 Hz, 1H, ***H-10***), 5.89 (br. s, 1H, ***H-29***), 5.79 (d, *J* = 15.3 Hz, 1H, ***H-22***), 5.61 (br. s, 1H, ***H-7***), 5.35 (dd, *J* = 16.1, 6.0 Hz, 1H, ***H-11***), 4.83 (ABq, *J* = 6.6 Hz, *Δv* = 5.6 Hz, 2H, ***H-33***), 4.73 (d, *J* = 1.8 Hz, 1H, ***H-***

20a), 4.71 (d, *J* = 10.9 Hz, 1H, ***H-39a***), 4.71 (d, *J* = 2.1 Hz, 1H, ***H-20b***), 4.65 (s, 2H, ***H-34***), 4.46 (d, *J* = 10.9 Hz, 1H, ***H-39b***), 4.15 (dddd, *J* = 12.1, 9.4, 3.1, 2.9 Hz, 1H, ***H-4***), 4.00 (dq, *J* = 8.7, 4.0 Hz, 1H, ***H-2***), 3.81 (dd, *J* = 10.5, 4.0 Hz, 1H, ***H-1a***), 3.78 (s, 3H, ***H-44***), 3.79-3.74 (m, 2H, ***H-18a***, ***H-18b***), 3.73 (dd, *J* = 10.6, 4.9 Hz, 1H, ***H-1b***), 3.72-3.66 (m, 1H, ***H-12***), 3.67 (s, 3H, ***H-31***), 3.52 (dddd, *J* = 11.3, 8.7, 3.5, 2.5 Hz, 1H, ***H-16***), 3.43 (dd, *J* = 16.1, 2.6 Hz, 1H, ***H-5$_{eq}$***), 3.25 (s, 3H, ***H-32***), 2.97 (br. s, 1H, ***-OH***), 2.42 (ddd, *J* = 15.9, 11.7, 1.7 Hz, 1H, ***H-5$_{ax}$***), 2.24-2.10 (m, 4H, ***H-26***, ***H-13$_{eq}$***, ***H-15$_{eq}$***), 2.07-1.98 (m, 1H, ***H-15$_{ax}$***), 2.03-1.94 (m, 1H, ***H-13$_{ax}$***), 1.91 (ddd, *J* = 14.4, 9.3, 2.9 Hz, 1H, ***H-3a***), 1.84 (ddd, *J* = 14.4, 9.3, 3.2 Hz, 1H, ***H-3b***), 1.83-1.64 (m, 2H, ***H-18a***, ***H-18b***), 1.47 (sext, *J* = 7.4 Hz, 2H, ***H-27***), 1.14 (s, 3H, ***H-19a***), 1.12 (s, 3H, ***H-19b***), 0.93 (t, *J* = 7.4 Hz, 3H, ***H-28***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.7 (***C-30***), 165.5 (***C-21***), 159.3 (***C-43***), 153.3 (***C-6***), 146.6 (***C-23***), 145.8 (***C-25***), 144.1 (***C-14***), 139.0 (***C-10***), 138.0 (***C-35***), 130.8 (***C-40***), 129.4 (***C-41***, ***C-41'***), 128.6 (***C-24***, ***C-37***, ***C-37'***), 128.0 (***C-36***, ***C-36'***), 127.9 (***C-38***), 126.4 (***C-11***), 118.6 (***C-22***), 116.6 (***C-29***), 114.0 (***C-42***, ***C-42'***), 109.0 (***C-20***), 102.8 (***C-8***), 95.1 (***C-33***), 79.4 (***C-12***), 78.1 (***C-16***), 74.6 (***C-2***), 71.6 (***C-39***, ***C-7***), 70.3 (***C-1***), 69.7 (***C-34***), 68.2 (***C-4***), 60.9 (***C-18***), 55.4 (***C-44***), 51.2 (***C-31***, ***C-32***), 46.2 (***C-9***), 41.0 (***C-13***), 40.8 (***C-15***), 39.4 (***C-3***), 38.4 (***C-17***), 35.2 (***C-26***), 33.2 (***C-5***), 24.2 (***C-19a***), 23.9 (***C-19b***), 22.0 (***C-27***), 13.8 (***C-28***);

FTIR (neat): ν_{max} 3527 (br.) 2931, 1717, 1642, 1614, 1514, 1456, 1435, 1381, 1348, 1248, 1157, 1134, 1102, 1043, 1002, 889, 820, 737, 699 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{49}H_{66}O_{12}Na$ 869.4452; found 869.4448.



(2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)propyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-((*E*)-2-methyl-4-((2*R*,6*S*)-4-methylene-6-(2-oxoethyl)tetrahydro-*2H*-pyran-2-yl)but-3-en-2-yl)tetrahydro-*2H*-pyran-3-yl Octa-2,4-dienoate (2.86): To a stirred solution of alcohol **2.85** (492 mg, 0.580 mmol, 1.0 equiv) in dry CH_2Cl_2 (60 mL, 0.01 M) was added *t*-BuOH (72 uL, 0.75 mmol, 1.3 equiv) and freshly distilled pyridine (140 uL, 1.73 mmol, 3.0 equiv). Then this reaction was cooled down to 0 ^oC, and Dess-Martin periodinane (381 mg, 0.871 mmol, 1.5 equiv) was added in one portion. After 10 minutes, the cooling bath was removed and the reaction was stirred at room temperature for 1 hour under an atmosphere of N_2. Then, a saturated $NaHCO_3$ solution (30 mL) was added into this reaction, followed by addition of a saturated $Na_2S_2O_3$ solution (30 mL). This mixture was stirred for 10 minutes at ambient temperature. The aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 12-20 vol% of EtOAc in hexanes to provide the titled compound (474 mg, 0.561 mmol, 96.6% yield) as a yellowish oil.

TLC: R_f = 0.39 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ -24.3 (*c* 0.745, $CHCl_3$);

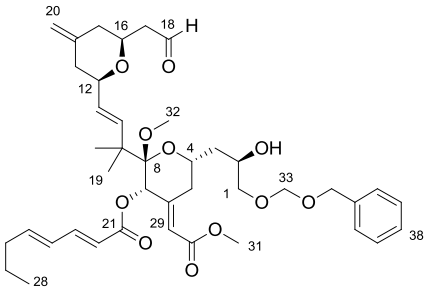
500 MHz ^{1}H NMR ($CDCl_3$) δ 9.79 (dd, *J* = 2.3, 2.1, 1H, ***H-18***), 7.41-7.33 (m, 4H, ***H-36***, ***H-36'***, ***H-37***, ***H-37'***), 7.33-7.25 (m, 2H, ***H-38***, ***H-23***), 7.23 (d, *J* = 8.8 Hz, 2H, ***H-41***, ***H-***

41'), 6.84 (d, *J* = 8.8 Hz, 2H, ***H-42***, ***H-42'***), 6.27-6.11 (m, 2H, ***H-24***, ***H-25***), 6.03 (dd, *J* = 15.8, 1.3 Hz, 1H, ***H-10***), 5.89 (br. s, 1H, ***H-29***), 5.78 (d, *J* = 15.1 Hz, 1H, ***H-22***), 5.57 (br. s, 1H, ***H-7***), 5.35 (dd, *J* = 16.1, 5.7 Hz, 1H, ***H-11***), 4.83 (ABq, *J* = 6.7 Hz, $\Delta\nu$ = 5.3 Hz, 2H, ***H-33***), 4.76 (q, *J* = 1.8 Hz, 1H, ***H-20a***), 4.74 (q, *J* = 1.8 Hz, 1H, ***H-20b***), 4.71 (d, *J* = 11.1 Hz, 1H, ***H-39a***), 4.66 (s, 2H, ***H-34***), 4.46 (d, *J* = 10.9 Hz, 1H, ***H-39b***), 4.14 (dddd, *J* = 11.7, 9.4, 3.1, 2.9 Hz, 1H, ***H-4***), 3.99 (dq, *J* = 8.1, 4.4 Hz, 1H, ***H-2***), 3.86 -3.76 (m, 1H, ***H-16***), 3.80 (dd, *J* = 10.4, 4.2 Hz, 1H, ***H-1a***), 3.78 (s, 3H, ***H-44***), 3.76-3.70 (m, 1H, ***H-12***), 3.73 (dd, *J* = 10.5, 5.1 Hz, 1H, ***H-1b***), 3.67 (s, 3H, ***H-31***), 3.46 (dd, *J* = 16.2, 2.9 Hz, 1H, ***H-5$_{eq}$***), 3.25 (s, 3H, ***H-32***), 2.66 (ddd, *J* = 16.4, 7.5, 2.6 Hz, 1H, ***H-17a***), 2.51 (ddd, *J* = 16.4, 4.9, 1.8 Hz, 1H, ***H-17b***), 2.37 (ddd, *J* = 15.8, 11.7, 2.3 Hz, 1H, ***H-5$_{ax}$***), 2.30-2.09 (m, 4H, ***H-15$_{eq}$***, ***H-13$_{eq}$***, ***H-26***), 2.05-1.94 (m, 2H, ***H-13$_{ax}$***, ***H-15$_{ax}$***), 1.91 (ddd, *J* = 14.5, 9.6, 2.8 Hz, 1H, ***H-3a***), 1.82 (ddd, *J* = 14.5, 9.6, 3.3 Hz, 1H, ***H-3b***), 1.47 (sex, *J* = 7.4 Hz, 2H, ***H-27***), 1.14 (s, 3H, ***H-19***), 1.13 (s, 3H, ***H-19'***), 0.93 (t, *J* = 7.4 Hz, 3H, ***H-28***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 201.1 (***C-18***), 166.6 (***C-30***), 165.5 (***C-21***), 159.3 (***C-43***), 152.9 (***C-6***), 146.6 (***C-23***), 145.9 (***C-25***), 143.5 (***C-14***), 139.1 (***C-10***), 138.1 (***C-35***), 130.8 (***C-40***), 129.4 (***C-41***, ***C-41'***), 128.6 (***C-37***, ***C-37'***), 128.6 (***C-24***), 128.0 (***C-36***, ***C-36'***), 127.9 (***C-38***), 126.1 (***C-11***), 118.6 (***C-22***), 117.0 (***C-29***), 114.0 (***C-42***, ***C-42'***), 109.6 (***C-20***), 102.8 (***C-8***), 95.2 (***C-33***), 79.4 (***C-12***), 74.7 (***C-2***), 73.6 (***C-16***), 71.8 (***C-7***), 71.7 (***C-39***), 70.3 (***C-1***), 69.7 (***C-34***), 68.2 (***C-4***), 55.4 (***C-44***), 51.4 (***C-32***), 51.2 (***C-31***), 49.9 (***C-17***), 46.1 (***C-9***), 40.6 (***C-13***), 40.5 (***C-15***), 39.5 (***C-3***), 35.2 (***C-26***), 33.1 (***C-5***), 24.1 (***C-19***, ***C-19'***), 22.0 (***C-27***), 13.8 (***C-28***);

FTIR (neat): ν_{max} 2933, 1717, 1641, 1613, 1513, 1455, 1435, 1380, 1302, 1244, 1132, 1100, 1039, 1001, 889, 860, 819, 735, 698 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{49}H_{64}O_{12}Na$ 867.4295; found 867.4302.



(2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((*R*)-3-(Benzyloxymethoxy)-2-hydroxypropyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-((*E*)-2-methyl-4-((2*R*,6*S*)-4-methylene-6-(2-oxoethyl)tetrahydro-*2H*-pyran-2-yl)but-3-en-2-yl)tetrahydro-*2H*-pyran-3-yl Octa-2,4-dienoate (2.87): To a stirred solution of compound **2.86** (435 mg, 0.515 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL, 0.05M) was added a 0.1 M phosphate *p*H = 6 buffer solution (5 mL, 0.1 M). Then, this reaction was cooled down to 0 ^oC, and DDQ (239 mg, 1.03 mmol, 2.0 equiv) was added in one portion. It was stirred for 4 hours at this temperature. Then, this reaction was diluted with EtOAc (10 mL), and poured into a saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 28-38% of EtOAc in hexanes to provide the titled compound (368 mg, 0.507 mol, 98.5% yield) as a pale yellow oil.

TLC: R_f = 0.20 (EtOAc/Hex = 4:6, v/v);

$[\alpha]_D^{20}$ -18.5 (*c* 1.31, $CHCl_3$);

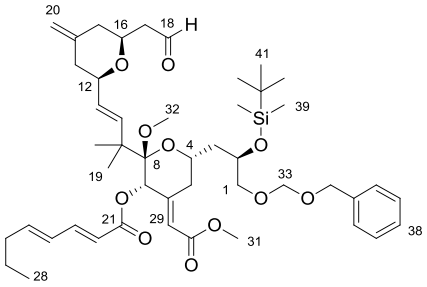
500 MHz ^{1}H NMR ($CDCl_3$) δ 9.81 (dd, *J* = 2.5, 2.2, 1H, ***H-18***), 7.40-7.33 (m, 4H, ***H-36***, ***H-36'***, ***H-37***, ***H-37'***), 7.33-7.23 (m, 2H, ***H-38***, ***H-23***), 6.23-6.12 (m, 2H, ***H-24***, ***H-25***), 6.00 (dd, *J* = 15.9, 1.2 Hz, 1H, ***H-10***), 5.89 (br. s, 1H, ***H-29***), 5.77 (d, *J* = 15.2 Hz, 1H, ***H-22***),

5.59 (br. s, 1H, ***H-7***), 5.34 (dd, *J* = 15.9, 5.9 Hz, 1H, ***H-11***), 4.83 (ABq, *J* = 6.6 Hz, $\Delta\nu$ = 6.2 Hz, 2H, ***H-33***), 4.76 (dt, *J* = 2.0, 1.8 Hz, 1H, ***H-20a***), 4.74 (dt, *J* = 2.0, 1.8 Hz, 1H, ***H-20b***), 4.65 (ABq, *J* = 11.9 Hz, $\Delta\nu$ = 4.9 Hz, 2H, ***H-34***), 4.26-4.13 (m, 2H, ***H-2***, ***H-4***), 3.82 (dddd, *J* = 11.4, 7.6, 5.1, 2.4 Hz, 1H, ***H-16***), 3.73 (dd, *J* = 10.3, 3.4 Hz, 1H, ***H-1a***), 3.74-3.70 (m, 1H, ***H-12***), 3.67 (s, 3H, ***H-31***), 3.53 (dd, *J* = 10.2, 7.2 Hz, 1H, ***H-1b***), 3.45 (dd, *J* = 15.0, 2.8 Hz, 1H, ***H-5$_{eq}$***), 3.34 (s, 3H, ***H-32***), 2.79 (d, *J* = 4.2 Hz, 1H, ***-OH***), 2.68 (ddd, *J* = 16.3, 7.6, 2.6 Hz, 1H, ***H-17a***), 2.52 (ddd, *J* = 16.3, 5.0, 2.0 Hz, 1H, ***H-17b***), 2.42 (ddd, *J* = 15.8, 12.0, 2.0 Hz, 1H, ***H-5$_{ax}$***), 2.32-2.18 (m, 2H, ***H-15$_{eq}$***, ***H-13$_{eq}$***), 2.15 (q, *J* = 6.7 Hz, 2H, ***H-26***), 2.06-1.93 (m, 2H, ***H-13$_{ax}$***, ***H-15$_{ax}$***), 1.81-1.66 (m, 2H, ***H-3a***, ***H-3b***), 1.47 (sex, *J* = 7.3 Hz, 2H, ***H-27***), 1.13 (s, 3H, ***H-19***), 1.12 (s, 3H, ***H-19'***), 0.93 (t, *J* = 7.3 Hz, 3H, ***H-28***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 201.4 (***C-18***), 166.7 (***C-30***), 165.5 (***C-21***), 153.0 (***C-6***), 146.7 (***C-23***), 146.0 (***C-25***), 143.6 (***C-14***), 139.2 (***C-10***), 137.8 (***C-35***), 128.7 (***C-37***, ***C-37'***), 128.6 (***C-24***), 128.1 (***C-36***, ***C-36'***), 128.0 (***C-38***), 126.2 (***C-11***), 118.6 (***C-22***), 116.9 (***C-29***), 109.7 (***C-20***), 103.0 (***C-8***), 95.5 (***C-33***), 79.4 (***C-12***), 73.7 (***C-1***), 73.6 (***C-16***), 71.8 (***C-7***), 70.0 (***C-34***), 68.4 (***C-4***), 67.1 (***C-2***), 51.5 (***C-32***), 51.3 (***C-31***), 49.9 (***C-17***), 46.2 (***C-9***), 40.7 (***C-13***), 40.5 (***C-15***), 39.4 (***C-3***), 35.3 (***C-26***), 32.9 (***C-5***), 24.2 (***C-19***), 24.0 (***C-19'***), 22.1 (***C-27***), 13.9 (***C-28***);

FTIR (neat): ν_{max} 3447 (br), 2950, 1719, 1642, 1615, 1497, 1456, 1435, 1382, 1359, 1312, 1245, 1165, 1133, 1105, 1046, 1004, 892, 861 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{41}H_{56}O_{11}Na$ 747.3720; found 747.3732.



(2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((*R*)-3-(Benzyloxymethoxy)-2-(*tert*-butyldimethylsilyloxy)propyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-((*E*)-2-methyl-4-((2*R*,6*S*)-4-methylene-6-(2-oxoethyl)tetrahydro-*2H*-pyran-2-yl)but-3-en-2-yl)tetrahydro-*2H*-pyran-3-yl Octa-2,4-dienoate (2.88): With a -78 °C bath, to a stirred solution of alcohol **2.87** (603 mg, 0.832 mmol, 1.0 equiv) in freshly distilled CH_2Cl_2 (17 mL, 0.05 M) was added 2,6-lutidine (300 uL, 2.55 mmol, 3.0 equiv) via syringe. Then, TBSOTf (295 uL, 1.26 mmol, 1.5 eq) was added dropwise via syringe. This reaction was stirred under an atmosphere of N_2 for 1 hour and poured into a saturated $NaHCO_3$ solution (30 mL) . The aqueous layer was then extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 5-15 vol% of ethyl acetate in hexanes to provide the titled compound (625 mg, 0.745 mmol, 89.6% yield) as pale yellow oil.

TLC: R_f = 0.64 (EtOAc/Hex = 4:6, v/v);

$[\alpha]_D^{20}$ -22.9 (*c* 0.52, $CHCl_3$);

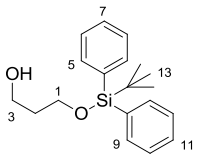
500 MHz ^{1}H NMR ($CDCl_3$) δ 9.80 (dd, *J* = 2.3, 2.1, 1H, ***H-18***), 7.41-7.32 (m, 4H, ***H-36***, ***H-36'***, ***H-37***, ***H-37'***), 7.32-7.23 (m, 2H, ***H-38***, ***H-23***), 6.23-6.14 (m, 2H, ***H-24***, ***H-25***), 5.99 (dd, *J* = 16.0, 1.2 Hz, 1H, ***H-10***), 5.90 (br. s, 1H, ***H-29***), 5.78 (d, *J* = 15.3 Hz, 1H, ***H-22***), 5.62 (br. s, 1H, ***H-7***), 5.36 (dd, *J* = 16.1, 6.0 Hz, 1H, ***H-11***), 4.79 (ABq, *J* = 6.6 Hz, *Δv* = 5.6 Hz, 2H, ***H-33***), 4.76 (dt, *J* = 2.1, 1.8 Hz, 1H, ***H-20a***), 4.74 (dt, *J* = 2.0, 1.8 Hz, 1H, ***H-***

20b), 4.63 (s, 2H, ***H-34***), 4.18-4.02 (m, 2H, ***H-2***, ***H-4***), 3.80 (dddd, *J* = 12.0, 7.5, 5.2, 2.3 Hz, 1H, ***H-16***), 3.73 (dddd, *J* = 11.4, 6.0, 2.6, 1.1 Hz, 1H, ***H-12***), 3.68 (s, 3H, ***H-31***), 3.65 (dd, *J* = 10.0, 4.5 Hz, 1H, ***H-1a***), 3.58 (dd, *J* = 10.1, 6.0 Hz, 1H, ***H-1b***), 3.46 (ddd, *J* = 15.0, 2.9, 1.0 Hz, 1H, ***H-5$_{eq}$***), 3.32 (s, 3H, ***H-32***), 2.67 (ddd, *J* = 16.3, 7.5, 2.3 Hz, 1H, ***H-17a***), 2.51 (ddd, *J* = 16.3, 5.2, 2.1 Hz, 1H, ***H-17b***), 2.38 (ddd, *J* = 16.1, 11.4, 2.1 Hz, 1H, ***H-5$_{ax}$***), 2.29-2.20 (m, 2H, ***H-15$_{eq}$***, ***H-13$_{eq}$***), 2.15 (q, *J* = 6.7 Hz, 2H, ***H-26***), 2.05-1.94 (m, 2H, ***H-13$_{ax}$***, ***H-15$_{ax}$***), 1.94 (ddd, *J* = 14.3, 8.6, 4.8 Hz, 1H, ***H-3a***), 1.73 (ddd, *J* = 14.3, 7.0, 3.4 Hz, 1H, ***H-3b***), 1.47 (sext, *J* = 7.4 Hz, 2H, ***H-27***), 1.13 (s, 3H, ***H-19***), 1.12 (s, 3H, ***H-19'***), 0.93 (t, *J* = 7.3 Hz, 3H, ***H-28***), 0.89 (s, 9H, ***H-41***), 0.11 (s, 3H, ***H-39***), 0.09 (s, 3H, ***H-39'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 201.2 (***C-18***), 166.7 (***C-30***), 165.6 (***C-21***), 153.1 (***C-6***), 146.7 (***C-23***), 145.9 (***C-25***), 143.5 (***C-14***), 139.0 (***C-10***), 138.1 (***C-35***), 128.6 (***C-24***, ***C-37***, ***C-37'***), 128.1 (***C-36***, ***C-36'***), 127.9 (***C-38***), 126.5 (***C-11***), 118.6 (***C-22***), 116.9 (***C-29***), 109.7 (***C-20***), 102.9 (***C-8***), 95.1 (***C-33***), 79.5 (***C-12***), 73.6 (***C-16***), 72.9 (***C-1***), 71.5 (***C-7***), 69.6 (***C-34***), 69.4 (***C-2***), 68.7 (***C-4***), 51.6 (***C-32***), 51.3 (***C-31***), 49.9 (***C-17***), 46.1 (***C-9***), 42.2 (***C-3***), 40.7 (***C-13***), 40.5 (***C-15***), 35.3 (***C-26***), 33.4 (***C-5***), 26.1 (***C-41***), 24.1 (***C-19***, ***C-19'***), 22.0 (***C-27***), 18.4 (***C-40***), 13.9 (***C-28***), -3.7 (***C-39***), -4.4 (***C-39'***);

FTIR (neat): ν_{max} 3070, 2930, 1719, 1643, 1616, 1497, 1463, 1436, 1383, 1360, 1250, 1105, 893, 836, 811, 777 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{47}H_{70}O_{11}SiNa$ 861.4585; found 861.4596.



3-(*tert*-Butyldiphenylsilyloxy)propan-1-ol (2.89): To a round-bottomed flask was charged NaH (60% dispersion in mineral oil, 1.63 g, 40.8 mmol, 1.1 equiv) and anhydrous THF (80 mL). With an ice-water bath, freshly distilled 1,3-

propanediol **2.36** (3.00 mL, 40.7 mmol, 1.1 equiv) was added dropwise via a syringe over 5 minutes under an atmosphere of N_2. It was allowed to warm to room temperature for 30 minutes, and refluxed for 1 hour. It was then cooled to 0 °C, and *t*-butylchlorodiphenylsilane (9.80 mL, 36.9 mmol, 1.0 equiv) was added into this reaction dropwise via a syringe over 10 minutes. After the addition, it was allowed to warm to room temperature, and refluxed with stirring for 24 hours. It was then quenched with brine (100 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The pale yellow crude product was used in next step without further purification.

The analytic smalple could be obtained by flash column chromatography on silica gel with 5-10 vol% ethyl acetate in hexanes to provide the titled compound (12.26 g, 38.97 mmol, 95.8% yield) as a colorless oil. It was crytalized as a white crystalline solid (m.p.: 38.2-39.9 °C) after couple days on bench.

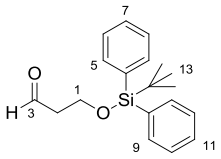
TLC: R_f = 0.33 (EtOAc/Hex = 3:7, v/v);

500 MHz ^{1}H NMR ($CDCl_3$): δ 7.74-7.66 (m, 4H, ***H-5***, ***H-5'***, ***H-9***, ***H-9'***), 7.49-7.37 (m, 6H, ***H-6***, ***H-6'***, ***H-7***, ***H-10***, ***H-10'***, ***H-11***), 3.86 (d, *J* = 5.7 Hz, 2H, ***H-1***), 3.86 (td, *J* = 5.6, 5.3 Hz, 2H, ***H-3***), 2.37 (t, *J* = 5.3 Hz, 1H, ***-OH***), 1.83 (tt, *J* = 5.7, 5.6 Hz, 2H, ***H-2***), 1.07 (s, 9H, ***H-13***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 135.7 (***C-5***, ***C-5'***, ***C-9***, ***C-9'***), 133.5 (***C-4***, ***C-8***), 129.9 (***C-7***, ***C-11***), 127.9 (***C-6***, ***C-6'***, ***C-10***, ***C-10'***), 63.2, (***C-3***), 61.8 (***C-1***), 34.6(***C-2***), 27.0 (***C-13***), 19.3 (***C-12***);

FTIR (neat): ν_{max} 3282 (br), 3070, 2933, 2859, 1962, 1896, 1826, 1469, 1427, 1110, 821, 737, 704 cm^{-1};

LRMS(ESI-TOF) *m/z*: [M+H$^+$] Calcd for $C_{19}H_{27}O_2Si$ 315.2; found 314.9.



3-*tert*-Butyldiphenylsilyloxypropanal (2.37): To a solution of oxalyl chloride (0.68 mL, 7.8 mmol, 1.5 equiv) in CH_2Cl_2 (40 mL, 0.2 M) at –78 ^oC was added a solution of DMSO (1.2 mL, 17 mmol, 3.0 equiv) in CH_2Cl_2 (35 mL, 0.5 M) dropwise via cannula under an atmosphere of N_2. After stirring for 30 minutes, the solution of alcohol **2.89** (1.631 g, 5.185 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL, 0.1 M) was added dropwise via cannula. After stirring further 30 minutes in this condition, triethylamine (3.6 mL, 26 mmol, 5.0 equiv) was added dropwise via syringe. After 5 minutes, the cooling bath was removed, and the reaction was allowed to warm to room temperature over one hour. The solution was poured into a saturated NH_4Cl solution (100 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a pale yellow oil. The crude product was purified by flash chromatography on silica gel eluting with 3-5 vol% of ethyl acetate in hexanes to provide the titled compound (1.577 g, 5.048 mmol, 97.4% yield) as a colorless oil. It was crystallized as white crystalline solid (m.p.: 45.5-47.5 ^oC) after couple days on bench.

TLC: R_f = 0.58 (EtOAc/Hex = 3:7, v/v);

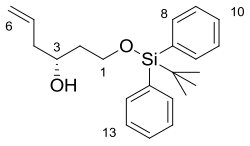
500 MHz ^{1}H NMR ($CDCl_3$): δ 9.83 (t, *J* = 2.2 Hz, 1H, ***H-3***), 7.70-7.64 (m, 4H, ***H-5***, ***H-5'***, ***H-9***, ***H-9'***), 7.48-7.37 (m, 6H, ***H-6***, ***H-6'***, ***H-7***, ***H-10***, ***H-10'***, ***H-11***), 4.04 (t, *J* = 6.0 Hz, 2H, ***H-1***), 2.62 (td, *J* = 6.0, 2.2 Hz, 2H, ***H-2***), 1.05 (s, 9H, ***H-13***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 202.1 (***C-3***), 135.8 (***C-5***, ***C-5'***, ***C-9***, ***C-9'***), 133.5 (***C-4***, ***C-***

8), 130.0 (***C-7***, ***C-11***), 128.0 (***C-6***, ***C-6'***, ***C-10***, ***C-10'***), 58.5 (***C-1***), 46.6 (***C-2***), 27.0 (***C-13***), 19.4 (***C-12***);

FTIR (neat): ν_{max} = 3072, 2933, 2890, 2859, 2730, 1729, 1471, 1428, 1390, 1111, 823, 741, 704, 613 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{19}H_{24}O_2SiNa$ 335.1443; found 335.1446.



(*R*)-1-(*tert*-Butyldiphenylsilyloxy)hex-5-en-3-ol (2.90): To an oven-dried round-bottomed flask was charged (*R*)-BINOL (1.618 g, 5.594 mmol, 0.2 equiv), 4Å MS (11.19 g, 0.4 g/mmol) and freshly distilled CH_2Cl_2 (100 mL, 0.3 M). Under an atmosphere of N_2, Ti(O*i*-Pr)$_4$ (0.83 mL, 2.8 mmol, 0.1 equiv) was introduced into this reaction dropwise via syringe with stirring, followed by addition of TFA (10.5 ul, 0.140 mmol, 0.005 equiv) at room temperature. The resulting dark brown mixture was heated at reflux for a period of 1 h, and then allowed to cooled to room temperature, whereupon a solution of aldehyde **2.37** (8.742 g, 27.98 mmol, 1.0 equiv) in dry CH_2Cl_2 (5 mL) was added via cannula, and additional CH_2Cl_2 (2 x 3 mL) rinse was transferred into the reaction flask via cannula. This reaction was stirred for 30 minutes at room temperature, and then cooled to -78 ^oC. Allyltributylstannane **2.57** (13 mL, 42 mmol, 1.5 equiv) was added dropwise via syringe over 10 minutes. This reaction was stirred for further 30 minutes in this condition, and transferred to a -35 ^oC freezer. After 7 days, this reaction was diluted with CH_2Cl_2 (100 mL), and filtrated over a pad of Celite. The filtrate was washed with a saturated $NaHCO_3$ solution (100 mL). The aqueous solution was extracted with ethyl ether (3 x 30 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a

brown oil. The crude product was then diluted with acetonitrile (300 mL) and washed with hexanes (100 mL). The acetonitrile portion was concentrated. The remainder was purified by flash chromatography on silica gel eluting with 1-5 vol% of acetate in hexanes, to provide the titled compound (9.708 g, 27.38 mmol, 97.9% yield, 97.8% ee) as a colorless oil.

TLC: R_f = 0.49 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +4.1 (*c* 1.16, $CHCl_3$);

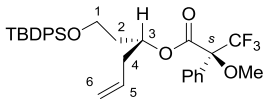
500 MHz ^{1}H NMR ($CDCl_3$): δ 7.65-7.81 (m, 4H, ***H-8***, ***H-8'***, ***H-12***, ***H-12'***), 7.35-7.56 (m, 6H, ***H-9***, ***H-9'***, ***H-10***, ***H-13***, ***H-13'***, ***H-14***), 5.88 (dddd, *J* = 7.2, 7.2, 10.1, 17.2 Hz, 1H, ***H-5***), 5.06-5.23 (m, 2H, ***H-6***), 3.96-4.08 (m, 1H, ***H-3***), 3.80-3.95 (m, 2H, ***H-1***), 3.26 (s, 1H, -***OH***), 2.23-2.37 (m, 2H, ***H-4***), 1.63-1.83 (m, 2H, ***H-2***), 1.08 (s, 9H, ***H-16***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 135.8 (***C-8***, ***C-8'***), 135.8 (***C-13***, ***C-13'***), 135.2 (***C-5***), 133.3 (***C-7***), 133.2 (***C-11***), 130.0 (***C-10***), 130.0 (***C-14***), 128.0 (***C-9***, ***C-9'***, ***C-13***, ***C-13'***), 117.6 (***C-6***), 71.0 (***C-1***), 63.5 (***C-3***), 42.2 (***C-2***), 38.1 (***C-4***), 27.0 (***C-16***), 19.3 (***C-15***);

FTIR (neat): ν_{max} 3439(br), 3072, 2933, 2859, 2361, 1641, 1471, 1428, 1390, 1110, 1083, 823, 739, 704, 613 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{22}H_{30}O_2SiNa$ 377.1913; found 377.1912.

Determination of Absolute Configuration of the New Stereocenter of Compound (*R*)-1-(*tert*-Butyldiphenylsilyloxy)hex-5-en-3-ol (2.90) via Mosher Ester Method:



(R)-1-(tert-Butyldiphenylsilyloxy)hex-5-en-3-yl (S)-α-Methoxy-α-(trifluoromethyl)phenylacetate (2.90-S-MTPA): To a screw-capped vial equipped with a stirring bar was added **2.90** (10.0 ul, 10.4 mg, 0.0292 mmol, 1.0 equiv), (*S*)-(-)-MTPA-OH acid

(20.9 mg, 0.0875 mmol, 3..0 equiv), DMAP (10.8 mg, 0.0875 mmol, 3.0 equiv) and DCC (18.3 mg, 0.0878 mmol, 3.0 equiv) subsequently. Freshly distilled CH_2Cl_2 (0.50 mL, 0.05 M) was then added to this vial. This vial was tightly capped. This reaction was stirred at room temperature for 36 hours. It was diluted with Et_2O (5 mL) and poured into brine (20 mL). The aqueous layer was extracted by ether (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 2 vol% of ethyl acetate in hexanes. The titled compound (16.3 mg, 0.0286 mmol, 97.7% yield) was obtained as a colorless oil.

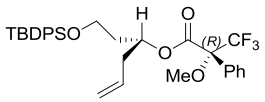
TLC: R_f = 0.62 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ -38.8 (*c* 0.82, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$): δ 7.57-7.73 (m, 4H, ***Ar-H***), 7.48-7.56 (m, 2H, ***Ar-H***), 7.28-7.48 (m, 9H, ***Ar-H***), 5.77 (dddd, *J* = 7.2, 8.4, 8.5, 17.0 Hz, 1H, ***H-5***), 5.45 (dddd, *J* = 6.2, 6.2, 6.3, 6.3 Hz, 1H, ***H-3***), 5.06-5.18 (m, 2H, ***H-6***), 3.55-3.65 (m, 2H, ***H-1***), 3.52 (s, 3H, -***OCH$_3$***), 2.37-2.55 (m, 2H, ***H-4***), 1.73-1.89 (m, 2H, ***H-2***), 1.06 (s, 9H, -*SiPh$_2$**t-Bu***);

FTIR (neat): ν_{max} 3072, 2933, 2858, 1747, 1471, 1390, 1266, 1171, 1110, 1019, 825, 737, 704, 613 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{32}H_{37}O_4F_3SiNa$ 593.2311; found 593.2307.



(R)-1-(tert-Butyldiphenylsilyloxy)hex-5-en-3-yl (R)-α-Methoxy-α-(trifluoromethyl)phenylacetate (2.90-R-MTPA): To a screw-capped vial equipped with a stirring bar was added **2.90** (10.0 ul, 10.4 mg, 0.0292 mmol, 1.0 equiv), (*R*)-(+)-MTPA-OH acid (20.9 mg, 0.0875 mmol, 3.0 equiv), DMAP (10.8 mg, 0.0875 mmol, 3.0 equiv) and DCC

(18.3 mg, 0.0878 mmol, 3.0 equiv) subsequently. Freshly distilled CH_2Cl_2 (0.50 mL, 0.05 M) was then added to this vial. This vial was tightly capped. This reaction was stirred at room temperature for 36 hours. It was diluted with Et_2O (5 mL) and poured into brine (20 mL). The aqueous layer was extracted by ether (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 2 vol% of ethyl acetate in hexanes. The titled compound (16.7 mg, 0.0292 mmol, 100% yield) was obtained as a colorless oil.

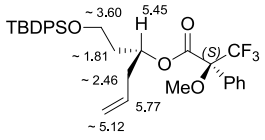
TLC: R_f = 0.63 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +0.2 (*c* 0.57, $CHCl_3$);

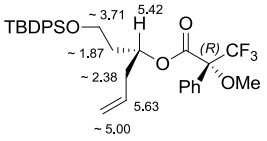
500 MHz ^{1}H NMR ($CDCl_3$): δ 7.58-7.73 (m, 4H, ***Ar-H***), 7.47-7.56 (m, 2H, ***Ar-H***), 7.30-7.47 (m, 9H, ***Ar-H***), 5.63 (dddd, *J* = 7.2, 7.2, 10.1, 17.1 Hz, 1H, ***H-5***), 5.42 (dddd, *J* = 6.2, 6.3, 6.3, 6.3 Hz, 1H, ***H-3***), 4.92-5.09 (m, 2H, ***H-6***), 3.65-3.76 (m, 2H, ***H-1***), 3.45 (s, 3H, -***OCH₃***), 2.29-2.47 (m, 2H, ***H-4***), 1.80-1.93 (m, 2H, ***H-2***), 1.06 (s, 9H, -*SiPh₂**t-Bu***);

FTIR (neat): ν_{max} 3072, 2933, 2858, 1747, 1471, 1390, 1266, 1171, 1110, 1019, 825, 737, 704, 613 cm^{-1};

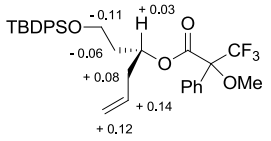
HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{32}H_{37}O_4F_3SiNa$ 593.2311; found 593.2307.



2.90-*S*-MTPA Mosher Ester

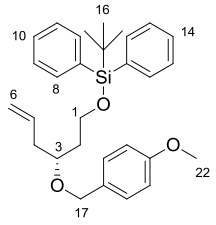


2.90-*R*-MTPA Mosher Ester



***Δδ* (*SR*) =*Δδ* (*S*-MTPA Ester) - *Δδ* (*R*-MTPA Ester)**

The chemical shift differences (in *ppm*) between the (*S*)- and (*R*)-MTPA Mosher esters of the (*R*)-1-(*tert*-butyldiphenylsilyloxy)hex-5-en-3-ol (**2.81**) are consistent for a (*R*)-configuration of the new formed stereocenter.



(*R*)-*tert*-Butyl(3-(4-methoxybenzyloxy)hex-5-enyloxy)diphenylsilane (2.38): Prepariton of 4-Methoxybenzyltrichloroacetimidate: To a stirred suspension of NaH (60% dispersion in mineral oil, 0.631 g, 15.8 mmol, 0.2 equiv) in Et_2O (80 mL, 1.0 M) was added a solution of 4-methoxybenzyl alcohol (10.0 mL, 78.9 mmol, 1.0 equiv) in Et_2O (8 mL) dropwise at 0 ^oC. The resulting cloudy orange mixture was stirred for 30 minutes at room temperature then cooled to 0 ^oC, and trichloroaetonitrile (8.5 mL, 83 mmol, 1.05 equiv) was added dropwise. This reaction was allowed to warm to room temperature and stirred for 5 hours. The reaction mixture was then concentrated under reduced pressure. The resulting residue was diluted with hexanes (80 mL, 1.0 M), and filtered with Celite. The filtrate was concentrated under reduced pressure to give the crude product (22.87 g, 80.94 mmol, 100% yield) as a yellow-orange oil. This crude prouct was used diretly without any further purification.

To a stirred solution of alcohol **2.90** (3.450 g, 9.732 mmol, 1.0 equiv) in anhydrous toluene (100 mL, 0.1 M) was added $Sc(OTf)_3$ (48 mg, 0.097 mmol, 0.01 equiv) at one portion. A solution of above 4-methoxybenzyltrichloroacetimidate (PMBTCA) (5.524 g, 19.55 mmol, 2.0 equiv) in toluene (10 mL, 2.0 M) was then added via cannula at 0 ^oC. This mixture was stirred under an atmosphere of N_2, and allowed to warm to room temperature over 6 hours. It was then concentrated in vacuo. The remainder was diluted with a cold mixture of Et_2O/Hex (1:9) solution (50 mL), and filtered with Celite. The pad of Celite was washed with cold Et_2O/Hex (1:9) solution (4 x 10 mL). The combined filtrate was concentrated under a vacuum. The crude product was purified by flash chromatography on silica gel eluting with 2-5 vol% of ether in hexanes to provide the titled compound

(3.530 g, 7.437 mmol, 76.4% yield) as a colorless oil.

TLC: R_f = 0.51 (Et_2O/Hex = 3:7, v/v);

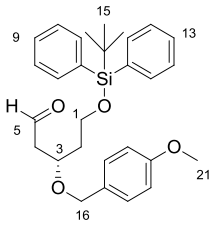
$[\alpha]_D^{20}$ -11.7 (*c* 2.00, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.65-7.70 (m, 4H, ***H-8***, ***H-8'***, ***H-12***, ***H-12'***), 7.41-7.46 (m, 2H, ***H-10***, ***H-14***), 7.36-7.41 (m, 4H, ***H-9***, ***H-9'***, ***H-13***, ***H-13'***), 7.21 (d, *J* = 8.5 Hz, 2H, ***H-19***, ***H-19'***), 6.84 (d, *J* = 8.5 Hz, 2H, ***H-20***, ***H-20'***), 5.85 (ddt, *J* = 17.1, 10.2, 7.1 Hz, 1H, ***H-5***), 5.04-5.13 (m, 2H, ***H-6***), 4.45 (ABq, *J* = 11.1 Hz, *Δv* = 55.7 Hz, 2H, ***H-17***), 3.81-3.87 (m, 1H, ***H-3***), 3.80 (s, 3H, ***H-22***), 3.75 (ddd, *J* = 5.7, 5.7, 10.3 Hz, 1H, ***H-1a***), 3.72 (ddd, *J* = 5.7, 5.7, 7.1 Hz, 1H, ***H-1b***), 2.33 (ddt, *J* = 7.1, 5.8, 1.3 Hz, 2H, ***H-4***), 1.72-1.83 (m, 2H, ***H-2***), 1.06 (s, 9H, ***H-16***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 159.2 (***C-21***), 135.8 (***C-8***, ***C-8'***, ***C-12***, ***C-12'***), 135.1 (***C-5***), 134.1 (***C-7***), 134.1 (***C-11***), 131.1 (***C-18***), 129.8 (***C-10***, ***C-14***), 129.5 (***C-19***, ***C-19'***), 127.8 (***C-9***, ***C-9'***), 127.8 (***C-13***, ***C-13'***), 117.2 (***C-6***), 113.9 (***C-20***, ***C-20'***), 75.3 (***C-3***), 71.0 (***C-17***), 60.7 (***C-1***), 55.5 (***C-22***), 38.7 (***C-4***), 37.2 (***C-2***), 27.1 (***C-16***), 19.4 (***C-15***);

FTIR (neat): ν_{max} 3071, 2933, 2858, 2361, 1613, 1588, 1513, 1467, 1428, 1390, 1359, 1302, 1248, 1175, 1110, 1038, 915, 822, 739, 704, 613 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{30}H_{38}O_3SiNa$ 497.2488; found 497.2493.



(*S*)-5-(*tert*-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)pentananl (2.39): With an acetone/dry ice bath (–78 ºC), a steam of O_3 (3.0 psi, 60 Volts) purged through a solution of oliefin **2.38** (1.679 g, 3.537 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL, 0.1 M), until the colorless solution turned pinkish. At this point, the O_3 was turned off, and a stream of N_2 flushed the solution until the color faded. Then,

triphenylphosphine (1.41 g, 5.30 mmol, 1.5 equiv) was added at one portion. The reaction was stirred at room temperature for 6 hours. The resulting yellow solution was concentrated under reduced pressure. The reminder was purified by flash chromatography on silica gel eluting with 15-20 vol% of Et_2O in hexanes to provide the titled compound (1.558 g, 3.269 mmol, 92.4% yield) as a colorless oil.

TLC: R_f = 0.21 (Et_2O/Hex = 3:7, v/v);

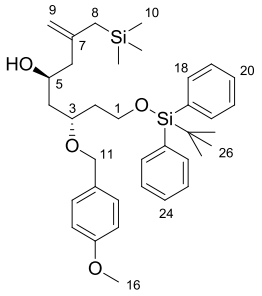
$[\alpha]_D^{20}$ +3.7 (*c* 2.00, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 9.76 (dd, *J* = 1.8, 2.7 Hz, 1H, ***H-5***), 7.64-7.70 (m, 4H, ***H-7***, ***H-7'***, ***H-11***, ***H-11'***), 7.42-7.48 (m, 2H, ***H-9***, ***H-13***), 7.36-7.42 (m, 4H, ***H-8***, ***H-8'***, ***H-12***, ***H-12'***), 7.19 (d, *J* = 8.5 Hz, 2H, ***H-18***, ***H-18'***), 6.85 (d, *J* = 8.5 Hz, 2H, ***H-19***, ***H-19'***), 4.46 (s, 2H, ***H-16***), 4.15-4.23 (m, 1H, ***H-3***), 3.79-3.88 (m, 1H, ***H-1a***), 3.80 (s, 3H, ***H-21***), 3.72-3.78 (m, 1H, ***H-1b***), 2.66 (ddd, *J* = 2.7, 7.2, 16.3 Hz, 2H, ***H-4a***), 2.59 (ddd, *J* = 1.8, 4.9, 16.3 Hz, 2H, ***H-4b***), 1.85-1.98 (m, 1H, ***H-2a***), 1.69-1.84 (m, 1H, ***H-2b***), 1.07 (s, 9H, ***H-15***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 201.8 (***C-5***), 159.5 (***C-20***), 135.8 (***C-7***, ***C-7'***, ***C-11***, ***C-11'***), 133.8 (***C-6***), 133.8 (***C-10***), 130.4 (***C-17***), 129.9 (***C-9***, ***C-13***), 129.6 (***C-18***, ***C-18'***), 127.9 (***C-8***, ***C-8'***, ***C-12***, ***C-12'***), 114.0 (***C-19***, ***C-19'***), 71.5 (***C-3***), 71.3 (***C-16***), 60.3 (***C-1***), 55.5 (***C-21***), 48.8 (***C-4***), 37.3 (***C-2***), 27.1 (***C-15***), 19.4 (***C-14***);

FTIR (neat): ν_{max} 3133, 3070, 3049, 3000, 2955, 2934, 2859, 2728, 1890, 1828, 1725, 1613, 1514, 1467, 1428, 1391, 1360, 1302, 1249, 1176, 1109, 1037, 937, 823, 740, 705 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M-H$^+$] Calcd for $C_{29}H_{35}O_4Si$ 475.2299; found 475.2290.



(4*S*,6*S*)-8-(*tert*-Butyldiphenylsilyloxy)-6-(4-methoxybenzyloxy)-2-((trimethylsilyl)methyl)oct-1-en-4-ol (2.34): To a stirred solution of aldehyde **2.39** (110 mg, 0.213 mmol, 1.0 equiv) in freshly distilled CH_2Cl_2 (10.0 mL, 0.02 M) was added $MgBr_2 \cdot Et_2O$ (111 mg, 0.428 mmol, 2.0 equiv) in one portion at –15 °C under an atmosphere of N_2. After 15 minutes, the mixture was then cooled down to –78 °C, and stirred for further 30 minutes. Whereupon, a solution of 2-(trimethylsilylmethyl)allyltributylstannane **2.91** (134 uL, 0.321 mmol, 1.5 eq) in CH_2Cl_2 (6.0 mL, 0.05 M) was introduced via cannula over 5 minutes. It was kept in this condition for 4 hours, and allowed to warm to 5 °C slowly over 7 hours. The reaction was diluted with Et_2O (10 mL) and poured into a saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (50 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a colorless oil. The crude product was purified by flash chromatography on silica gel eluting with 8-15 vol% of Et_2O in hexanes to provide the titled compound (119 mg, 0.197 mmol, 85.1% yield, single diastereomer) as single diastereomer as a colorless oil.

TLC: R_f = 0.33 (Et_2O/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +13.9 (*c* 1.02, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.59-7.78 (m, 4H, ***H-18***, ***H-18'***, ***H-22***, ***H-22'***), 7.42-7.49 (m, 2H, ***H-20***, ***H-24***), 7.34-7.49 (m, 4H, ***H-19***, ***H-19'***, ***H-23***, ***H-23'***), 7.21 (d, *J* = 8.6 Hz, 2H, ***H-13***, ***H-13'***), 6.85 (d, *J* = 8.6 Hz, 2H, ***H-14***, ***H-14'***), 4.67 (s, 1H, ***H-9a***), 4.65 (s, 1H, ***H-9b***), 4.48 (s, 2H, ***H-11***), 3.93-4.06 (m, 2H, ***H-3***, ***H-5***), 3.78-3.86 (m, 1H, ***H-1a***), 3.80 (s,

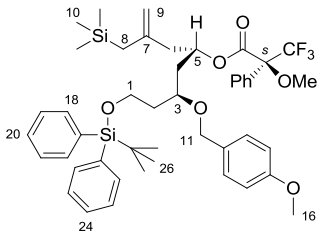
3H, ***H-16***); 3.70-3.78 (m, 1H, ***H-1b***), 2.68 (bs, 1H, ***-OH***), 2.12 (dd, *J* = 8.1, 13.7 Hz, 1H, ***H-6a***), 2.06 (dd, *J* = 5.1, 13.7 Hz, 1H, ***H-6b***), 1.93 (app. ddt, *J* = 5.4, 14.0, 4.9 Hz, 1H, ***H-2a***), 1.79 (app. ddt, *J* = 3.8, 14.0, 6.3 Hz, 1H, ***H-2b***), 1.68 (ddd, *J* = 3.6, 9.1, 14.5 Hz, 1H, ***H-4a***), 1.62 (ddd, *J* = 2.9, 7.3, 14.5 Hz, 1H, ***H-4b***), 1.54 (ABq, *J* = 11.3 Hz, $\Delta\nu$ = 14.8 Hz, 2H, ***H-8***), 1.07 (s, 9H, ***H-26***), 0.04 (s, 9H, ***H-10***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 159.4 (***C-15***), 144.8 (***C-7***), 135.8 (***C-18***, ***C-22***), 134.0 (***C-17***), 134.0 (***C-21***), 130.8 (***C-12***), 129.8 (***C-20***, ***C-24***), 129.7 (***C-13***), 127.9 (***C-19***), 127.8 (***C-23***), 114.0 (***C-14***), 110.2 (***C-9***), 74.0 (***C-3***), 71.6 (***C-11***), 66.2 (***C-5***), 60.7 (***C-1***), 55.5 (***C-16***), 46.9 (***C-6***), 40.8 (***C-4***), 37.2 (***C-2***), 27.1 (***C-26***), 26.9 (***C-8***), 19.4 (***C-25***), -1.2 (***C-10***);

FTIR (neat): ν_{max} 3479 (br), 3071, 2952, 2859, 1888, 1614, 1588, 1514, 1467, 1427, 1392, 1360, 1302, 1249, 1174, 1109, 1038, 934, 850, 739, 704, 665, 613, 536 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{36}H_{52}O_4Si_2Na$ 627.3302; found 627.3306.

Determination of Absolute Configuration of the New Stereocenter of Compound (4*S*, 6*S*)-8-(*tert*-Butyldiphenylsilyloxy)-6-(4-methoxybenzyloxy)-2-((trimethylsilyl)methyl)oct-1-en-4-ol (2.34) via Mosher Ester Method:



((4S,6S)-8-(tert-Butyldiphenylsilyloxy)-6-(4-methoxybenzyloxy)-2-((trimethylsilyl)methyl)oct-1-en-4-yl (S)-α-Methoxy-α-trifluoromethylphenylacetate (2.34-S-MTPA): To a small via, equipped with a stirring bar, was added **33** (26.5 mg, 0.0438 mmol, 1.0 equiv), (*S*)-MTPA-OH (11.8 mg, 0.494 mmol, 1.1 equiv), DMAP (5.4 mg, 0.0438 mmol, 1.0 equiv) and toluene (2.0 mL, 0.02 M). Then freshly distilled NEt_3 (31 uL, 0.22 mmol, 5.0 equiv) was added into this mixture. This reaction was cooled down to 0 °C, 2,4,6-

trichlorobenzoylchloride (7.8 uL, 0.049 mmol, 1.1 equiv) was then added dropwise via syringe. The reaction turned cloudy and white precipitate appeared during the addition. It was allowed to warm to room temperature slowly, and stirred for 6 hours. Then, it was concentrated and purified by flash chromatography on silica gel eluting with 3 vol% of ethyl acetate in hexanes to provide the titled compound (31.2 mg, 0.0380 mmol, 86.8% yield) as a colorless oil.

TLC: R_f = 0.57 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +1.9 (*c* 1.39, $CHCl_3$);

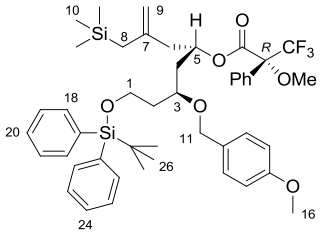
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.68 (app. dt, *J* = 1.5, 8.3 Hz, 4H, -*Si(t-Bu)***Ph₂**), 7.52-7.61 (m, 2H, -***Ph***), 7.42-7.50 (m, 2H, -*Si(t-Bu)***Ph₂**), 7.30-7.50 (m, 7H, -*Si(t-Bu)***Ph₂**, -***Ph***), 7.23 (d, *J* = 8.6 Hz, 2H, ***H-13***, ***H-13'***), 6.86 (d, *J* = 8.6 Hz, 2H, - ***H-14***, ***H-14'***), 5.57 (dddd, *J* =2.8, 6.7, 6.7, 9.5 Hz, 1H, ***H-5***), 4.58 (s, 1H, ***H-9a***), 4.53 (s, 1H, ***H-9b***), 4.36 (ABq, *J* = 10.6 Hz, *Δv* = 52.4 Hz, 2H, ***H-11***), 3.81 (s, 3H, ***H-16***); 3.68-3.79 (m, 2H, ***H-1***), 3.58-3.68 (m, 1H, ***H-3***), 3.49 (s, 3H, -***OCH₃***), 2.34 (dd, *J* = 6.7, 13.9 Hz, 1H, ***H-6a***), 2.09 (dd, *J* = 6.7, 13.9 Hz, 1H, ***H-6b***), 1.67-1.97 (m, 4H, ***H-2***, ***H-4***), 1.52 (ABq, *J* = 13.9 Hz, *Δv* = 13.0 Hz, 2H, ***H-8***), 1.06 (s, 9H, ***H-26***), 0.01 (s, 9H, ***H-10***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.3 (***C=O***), 159.3 (***C-15***), 142.4 (***C-7***), 135.8 (***C-18***, ***C-22***), 133.9 (***C-17***, ***C-21***), 132.3 (***Ph-1'***), 130.8 (***C-12***), 129.8 (***C-20***, ***C-24***), 129.8 (***C-13***), 129.7 (***Ph-4'***), 128.5 (***Ph-2'***), 127.9 (***C-19***, ***C-23***), 127.7 (***Ph-3'***), 123.6 (q, $J_{C\text{-}F}$ = 288.9 Hz, -***CF₃***), 114.0 (***C-14***), 111.4 (***C-9***), 84.8 (q, $J_{C\text{-}F}$ = 27.5 Hz, -***C****C=O*), 73.0 (***C-3***), 72.9 (***C-5***), 71.6 (***C-11***), 60.5 (***C-1***), 55.6 (-***OMe***), 55.5 (***C-16***), 43.6 (***C-6***), 40.0 (***C-4***), 37.5 (***C-2***), 27.1 (***C-26***), 26.5 (***C-8***), 19.3 (***C-25***), -1.2 (***C-10***);

FTIR (neat): ν_{max} 3072, 2953, 2859, 2361, 1743, 1613, 1514, 1467, 1428, 1390, 1360, 1251,

1171, 1110, 1035, 850, 737, 704, 613, 536 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{46}H_{59}O_6F_3Si_2Na$ 843.3700; found 843.3700.



((4S,6S)-8-(tert-Butyldiphenylsilyloxy)-6-(4-methoxybenzyloxy)-2-((trimethylsilyl)methyl)oct-1-en-4-yl (R)-α-Methoxy-α-trifluoromethylphenylacetate (2.34-R-MTPA): To a small via, equipped with a stirring bar, was added **33** (45.0 mg, 0.0744 mmol, 1.0 equiv), (*R*)-MTPA-OH (19.5 mg, 0.0824 mmol, 1.1 equiv), DMAP (10.2 mg, 0.827 mmol, 1.0 equiv) and toluene (2.0 mL, 0.04 M). Then, freshly distilled NEt_3 (50.0 uL, 0.359 mmol, 5.0 equiv) was added into this mixture. This reaction was cooled down to 0 ^oC, and 2,4,6-trichlorobenzoylchloride (13.0 uL, 0.0815 mmol, 1.1 equiv) was then added dropwise via syringe. The reaction turned cloudy and white precipitate appeared during the addition. It was allowed to warm to room temperature slowly, and stirred for 8 hours. Then, it was concentrated and purified by flash chromatography on silica gel eluting with 3% of ethyl acetate in hexanes to provide the titled compound (54.7 mg, 0.0666 mmol, 89.5% yield) as a colorless oil.

TLC: R_f = 0.58 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +29.7 (*c* 1.94, $CHCl_3$);

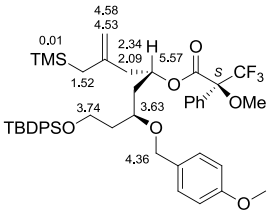
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.63-7.74 (m, 4H, -*Si(t-Bu)***Ph₂**), 7.52-7.61 (m, 2H, -***Ph***), 7.43-7.50 (m, 2H, -*Si(t-Bu)***Ph₂**), 7.37-7.42 (m, 4H, -*Si(t-Bu)***Ph₂**), 7.29-7.37 (m, 2H, -***Ph***), 7.23 (d, *J* = 8.7 Hz, 2H, ***H-13***, ***H-13'***), 6.87 (d, *J* = 8.7 Hz, 2H, ***H-14***, ***H-14'***), 5.59 (dddd, *J* =2.7, 6.7, 6.9, 9.6 Hz, 1H, ***H-5***), 4.67 (s, 1H, ***H-9a***), 4.62 (s, 1H, ***H-9b***), 4.32 (ABq, *J* = 10.5 Hz, *Δv* = 54.1 Hz, 2H, ***H-11***), 3.81 (s, 3H, ***H-16***); 3.69 (app. t, *J* = 6.5 Hz, 2H, ***H-1***),

3.55 (s, 3H, -O***CH₃***), 3.46-3.53 (m, 1H, ***H-3***), 2.44 (dd, *J* = 6.7, 13.9 Hz, 1H, ***H-6a***), 2.20 (dd, *J* = 6.9, 13.9 Hz, 1H, ***H-6b***), 1.85 (ddd *J* = 2.8, 9.9, 15.0 Hz, 1H, ***H-2a***), 1.67-1.81 (m, 3H, ***H-2b***, ***H-4***), 1.58 (ABq, *J* = 14.0 Hz, *Δv* = 7.8 Hz, 2H, ***H-8***), 1.06 (s, 9H, ***H-26***), 0.03 (s, 9H, ***H-10***);

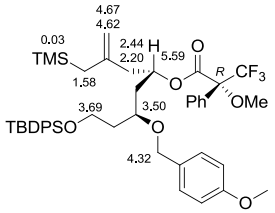
125 MHz ^{13}C NMR ($CDCl_3$) δ 166.3 (***C=O***), 159.3 (***C-15***), 142.6 (***C-7***), 135.8 (***C-18***, ***C-22***), 133.9 (***C-17***, ***C-21***), 132.5 (***Ph-1'***), 130.8 (***C-12***), 129.8 (***C-20***, ***C-24***), 129.7 (***C-13***, ***Ph-4'***), 128.5 (***Ph-2'***), 127.9 (***C-19***, ***C-23***), 127.7 (***Ph-3'***), 123.6 (q, $J_{C\text{-}F}$ = 288.5 Hz, ***-CF₃***), 114.0 (***C-14***), 111.4 (***C-9***), 84.6 (q, $J_{C\text{-}F}$ = 27.5 Hz, ***-C****C=O*), 73.2 (***C-3***), 73.0 (***C-5***), 71.7 (***C-11***), 60.5 (***C-1***), 55.6 (***-OMe***), 55.5 (***C-16***), 43.8 (***C-6***), 40.1 (***C-4***), 37.5 (***C-2***), 27.0 (***C-26***), 26.6 (***C-8***), 19.3 (***C-25***), -1.2 (***C-10***);

FTIR (neat): ν_{max} 3072, 2953, 2859, 1745, 1614, 1514, 1467, 1428, 1391, 1360, 1250, 1171, 1110, 1034, 851, 737, 704, 614, 537 cm^{-1};

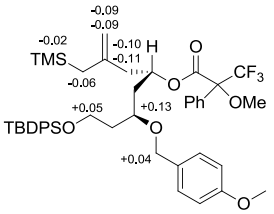
HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{46}H_{59}O_6F_3Si_2Na$ 843.3700; found 843.3694.



2.34-*S*-MTPA Mosher Ester

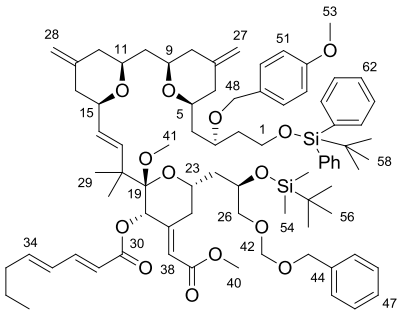


2.34-*R*-MTPA Mosher Ester



***Δδ* (*SR*) =*Δδ* (*S*-MTPA Ester) - *Δδ* (*R*-MTPA Ester)**

The chemical shift differences (in *ppm*) between the (*S*)- and (*R*)-MTPA Mosher esters of the (4*S*, 6*S*)-8-(*tert*-butyldiphenylsilyloxy)-6-(4-methoxybenzyloxy)-2-((trimethylsilyl)methyl)oct-1-en-4-ol (**33**) are consistent for a (*S*)-configuration of the new formed stereocenter.



(2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((*R*)-3-((Benzyloxy)methoxy)-2-(*tert*-butyldimethylsilyloxy)propyl)-2-((*E*)-4-((2*R*,6*S*)-6-(((2*R*,6*S*)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-((4-methoxybenzyl)oxy)butyl)-4-methylenetetrahydro-*2H*-pyran-2-yl)methyl)-4-methylenetetrahydro-*2H*-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-*2H*-pyran-3-yl Octa-2,4-dienoate (2.92): With a –78 °C bath, to a stirred mixture of aldehyde **2.88** (96.2 mg, 0.115 mmol, 1.0 equiv) and *β*-hydroxylallylsilane **2.34** (105.2 mg, 0.1739 mmol, 1.5 equiv) in fresh distilled Et_2O (11 mL, 0.01 M) was added pyridine (1.0 uL, 0.012 mmol, 0.1 equiv) via syringe under an atmosphere of N_2. Then, a solution of 1.0 M TMSOTf in Et_2O (140 uL, 0.140 mmol, 1.2 equiv) was introduced into this reaction dropwise via syringe. It was stirred for 1 hour, and quenched with DIPEA (1.0 mL, 5.7 mmol, 50 equiv) at the same temperature. It was stirred further 30 minutes, and poured into a saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a colorless oil. The crude product was purified by flash chromatography on silica gel eluting with 5-12 vol% of EtOAc in hexanes to provide a pale yellow oil (141 mg, 0.104 mmol, 90.3% yield).

TLC: R_f = 0.63 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ -5.4 (*c* 1.15, $CHCl_3$);

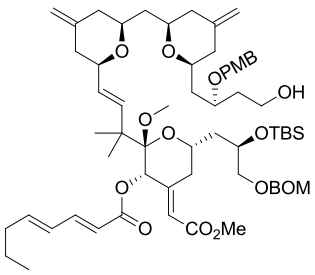
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.75-7.64 (m, 4H, ***H-60a***, ***H-60a'***, ***H-60b***, ***H-60b'***), 7.49-7.40 (m, 2H, ***H-62a***, ***H-62b***), 7.43-7.33 (m, 8H, ***H-61a***, ***H-61a'***, ***H-61***, ***H-61b'***, ***H-45***, ***H-45'***, ***H-46***, ***H-46'***), 7.33-7.26 (m, 2H, ***H-47***, ***H-32***), 7.20 (d, *J* = 8.6 Hz, 2H, ***H-50***, ***H-50'***), 6.86 (d, *J* = 8.8 Hz, 2H, ***H-51***, ***H-51'***), 6.27-6.10 (m, 2H, ***H-33***, ***H-34***), 5.98 (dd, *J* = 16.0, 1.2 Hz, 1H, ***H-17***), 5.92 (br. s, 1H, ***H-38***), 5.80 (d, *J* = 15.3 Hz, 1H, ***H-31***), 5.59 (br. s, 1H, ***H-20***), 5.42 (dd, *J* = 15.8, 6.0 Hz, 1H, ***H-16***), 4.79 (ABq, *J* = 6.5 Hz, *Δν* = 6.0 Hz, 2H, ***H-42***), 4.72 (td, *J* = 2.1, 1.8 Hz, 1H, ***H-28a***), 4.70 (td, *J* = 2.1, 1.8 Hz, 1H, ***H-28b***), 4.63 (s, 2H, ***H-43***), 4.56 (td, *J* = 2.1, 1.6 Hz, 1H, ***H-27a***), 4.47 (br. s, 1H, ***H-27b***), 4.40 (ABq, *J* = 10.8 Hz, *Δν* = 28.8 Hz, 2H, ***H-48***), 4.14 (dddd, *J* = 6.6, 6.1, 4.9, 4.7 Hz, 1H, ***H-25***), 4.09 (ddt, *J* = 11.7, 8.6, 3.2 Hz, 1H, ***H-23***), 3.96-3.89 (m, 1H, ***H-3***), 3.88-3.79 (m, 1H, ***H-1a***), 3.81 (s, 3H, ***H-53***), 3.82-3.75 (m, 1H, ***H-1b***), 3.77-3.70 (m, 1H, ***H-15***), 3.69 (s, 3H, ***H-40***), 3.66 (dd, *J* = 10.2, 4.5 Hz, 1H, ***H-26a***), 3.59 (dd, *J* = 10.1, 6.0 Hz, 1H, ***H-26b***), 3.61-3.54 (m, 1H, ***H-11***), 3.58-3.51 (m, 1H, ***H-5***), 3.52 (dd, *J* = 15.8, 2.6 Hz, 1H, ***H-22$_{eq}$***), 3.52-3.45 (m, 1H, ***H-9***), 3.33 (s, 3H, ***H-41***), 2.38 (ddd, *J* = 15.9, 11.6, 2.1 Hz, 1H, ***H-22$_{ax}$***), 2.32-2.25 (m, 1H, ***H-8$_{eq}$***), 2.29-2.23 (m, 1H, ***H-12$_{eq}$***), 2.23-2.10 (m, 4H, ***H-6$_{eq}$***, ***H-14$_{eq}$***, ***H-35***), 2.06-1.97 (m, 2H, ***H-8$_{ax}$***, ***H-14$_{ax}$***), 1.97 (ddd, *J* = 14.2, 8.7, 5.1 Hz, 1H, ***H-24a***), 1.98-1.88 (m, 2H, ***H-6$_{ax}$***, ***H-12$_{ax}$***), 1.85-1.73 (m, 2H, ***H-2a***, ***H-2b***), 1.75 (ddd, *J* = 14.3, 7.1, 3.4 Hz, 1H, ***H-24b***), 1.72-1.57 (m, 4H, ***H-4a***, ***H-4b***, ***H-10a***, ***H-10b***), 1.48 (sext, *J* = 7.4 Hz, 2H, ***H-36***), 1.16 (s, 3H, ***H-29***), 1.15 (s, 3H, ***H-29'***), 1.09 (s, 9H, ***H-58***), 0.94 (t, *J* = 7.4 Hz, 3H, ***H-37***), 0.92 (s, 9H, ***H-56***), 0.13 (s, 3H, ***H-54***), 0.12 (s, 3H, ***H-54'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.7 (***C-39***), 165.6 (***C-30***), 159.3 (***C-52***), 152.9 (***C-21***), 146.7 (***C-32***), 145.8 (***C-34***), 145.0 (***C-13***), 144.5 (***C-7***), 138.6 (***C-17***), 138.1 (***C-44***), 135.8 (***C-60a***, ***C-60a'***, ***C-60b***, ***C-60b'***), 134.1 (***C-59a***), 134.0 (***C-59b***), 131.2 (***C-49***), 129.8 (***C-***

62a, ***C-62b***), 129.5 (***C-50***, ***C-50'***), 128.6 (***C-33***, ***C-46***, ***C-46'***), 128.0 (***C-45***, ***C-45'***), 127.8 (***C-47***, ***C-61a***, ***C-61a'***, ***C-61b***, ***C-61b***), 127.1 (***C-16***), 118.7 (***C-31***), 117.3 (***C-38***), 114.0 (***C-51***, ***C-51'***), 108.9 (***C-27***), 108.6 (***C-28***), 102.9 (***C-19***), 95.1 (***C-42***), 79.2 (***C-15***), 75.1 (***C-5***), 75.0 (***C-11***), 74.9 (***C-9***), 72.9 (***C-26***), 72.8 (***C-3***), 72.1 (***C-48***), 71.7 (***C-20***), 69.6 (***C-43***), 69.4 (***C-25***), 68.7 (***C-23***), 60.6 (***C-1***), 55.4 (***C-53***), 51.7 (***C-41***), 51.2 (***C-40***), 46.0 (***C-18***), 42.9 (***C-10***), 42.5 (***C-4***), 42.2 (***C-24***), 41.4 (***C-6***), 41.1 (***C-8***), 40.9 (***C-14***), 40.5 (***C-12***), 38.0 (***C-2***), 35.2 (***C-35***), 33.2 (***C-22***), 27.2 (***C-58***), 26.1 (***C-56***), 24.2 (***C-29***), 24.1 (***C-29'***), 22.0 (***C-36***), 19.4 (***C-57***), 18.4 (***C-55***), 13.9 (***C-37***), -3.8 (***C-54***), -4.4 (***C-54'***);

FTIR (neat): ν_{max} 3071, 2934, 2889, 2858, 1720, 1643, 1614, 1588, 1514, 146, 1429, 1383, 1360, 1303, 1248, 1173, 1158, 1133, 1108, 1045, 1003, 890, 835, 824, 777 cm^{-1};

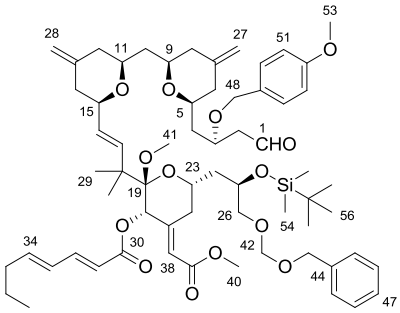
HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{80}H_{112}O_{14}Si_2Na$ 1275.7488; found 1375.7490.



(2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((*R*)-3-(Benzyloxymethoxy)-2-(*tert*-butyldimethylsilyloxy)propyl)-2-((*E*)-4-((2*R*,6*S*)-6-(((2*R*,6*S*)-6-((*S*)-4-hydroxy-2-((4-methoxybenzyl)oxy)butyl)-4-methylenetetrahydro-*2H*-pyran-2-yl)methyl)-4-methylenetetrahydro-*2H*-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-*2H*-pyran-3-yl Octa-2,4-dienoate (2.92a): To a solution of protected alcohol **2.92** (150 mg, 0.110 mmol, 1.0 equiv) in MeOH (11 mL, 0.01 M) was added NH_4F solid (82 mg, 2.1 mmol, 20 equiv) in one portion at room temperature. This reaction was stirred at 60 °C for 26 hours, and quenched with a saturated solution of $NaHCO_3$ (30 mL). It was diluted with EtOAc (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were

washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The yellow crude product was used directly in next step without any purification.

TLC: R_f = 0.16 (EtOAc/Hex = 3:7, v/v).



(2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((*R*)-3-(Benzyloxymethoxy)-2-(*tert*-butyldimethylsilyloxy)propyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-((*E*)-4-((2*R*,6*S*)-6-(((2*R*,6*S*)-6-((*R*)-2-((4-methoxybenzyl)oxy)-4-oxobutyl)-4-methylenetetrahydro-*2H*-pyran-2-yl)methyl)-4-methylenetetrahydro-*2H*-pyran-2-yl)-2-methylbut-3-en-2-yl)tetrahydro-*2H*-pyran-3-yl Octa-2,4-dienoate (2.93): To a stirred solution of crude alcohol **2.92a** (132.6 mg, 0.1104 mmol, 1.0 equiv) in dry CH_2Cl_2 (11.0 mL, 0.01 M) was added *t*-BuOH (14.0 uL, 0.146 mmol, 1.3 equiv) and freshly distilled pyridine (27.0 uL, 0.334 mmol, 3.0 equiv). Then this reaction was cooled down to 0 ^oC, and Dess-Martin periodinane (72.7 mg, 0.166 mmol, 1.5 equiv) was added in one portion. After 10 minutes, the cooling bath was removed and the reaction was stirred at room temperature for 1 hour under an atmosphere of N_2. A saturated $NaHCO_3$ solution (20 mL) was then added into this reaction, followed by addition of a saturated $Na_2S_2O_3$ solution (10 mL). This mixture was stirred for 10 minutes at ambient temperature. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 10-20% of EtOAc in hexanes to provide the

titled compound (69.4 mg, 0.623 mmol, 56.5% yield over two steps) as a colorless oil.

TLC: R_f = 0.57 (EtOAc/Hex = 4:6, v/v);

$[\alpha]_D^{20}$ +0.9 (*c* 1.09, $CHCl_3$);

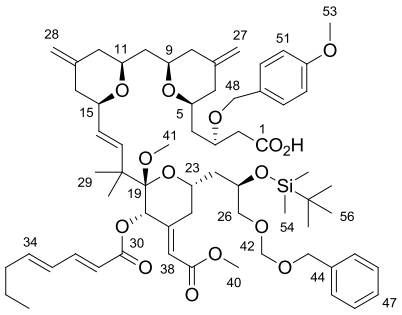
500 MHz ^{1}H NMR ($CDCl_3$) δ 9.79 (t, *J* = 2.3, 1H, ***H-1***), 7.40-7.32 (m, 4H, ***H-45***, ***H-45'***, ***H-46***, ***H-46'***), 7.32-7.25 (m, 2H, ***H-47***, ***H-32***), 7.23 (d, *J* = 8.6 Hz, 2H, ***H-50***, ***H-50'***), 6.88 (d, *J* = 8.8 Hz, 2H, ***H-51***, ***H-51'***), 6.27-6.09 (m, 2H, ***H-33***, ***H-34***), 5.99 (dd, *J* = 16.0, 0.9 Hz, 1H, ***H-17***), 5.92 (br. s, 1H, ***H-38***), 5.80 (d, *J* = 15.3 Hz, 1H, ***H-31***), 5.59 (br. s, 1H, ***H-20***), 5.40 (dd, *J* = 16.0, 6.1 Hz, 1H, ***H-16***), 4.79 (ABq, *J* = 6.7 Hz, $\Delta\nu$ = 5.7 Hz, 2H, ***H-42***), 4.76-4.69 (m, 2H, ***H-27a***, ***H-27b***), 4.66 (td, *J* = 1.9, 1.6 Hz, 1H, ***H-28a***), 4.63 (s, 2H, ***H-43***), 4.60 (td, *J* = 1.8, 1.6 Hz, 1H, ***H-28b***), 4.48 (ABq, *J* = 10.8 Hz, $\Delta\nu$ = 20.9 Hz, 2H, ***H-48***), 4.18 (dddd, *J* = 8.0, 6.0, 6.0, 4.6 Hz, 1H, ***H-3***), 4.12 (dddd, *J* = 6.9, 6.3, 5.9, 4.8 Hz, 1H, ***H-25***), 4.07 (dddd, *J* = 11.5, 8.5, 3.1, 2.8 Hz, 1H, ***H-23***), 3.80 (s, 3H, ***H-53***), 3.72 (dddd, *J* = 11.4, 5.8, 2.4, 1.0 Hz, 1H, ***H-15***), 3.68 (s, 3H, ***H-40***), 3.64 (dd, *J* = 10.3, 4.7 Hz, 1H, ***H-26a***), 3.57 (dd, *J* = 10.4, 6.0 Hz, 1H, ***H-26b***), 3.55-3.46 (m, 3H, ***H-5***, ***H-11***, ***H-22$_{eq}$***), 3.48-3.42 (m, 1H, ***H-9***), 3.32 (s, 3H, ***H-41***), 2.74-2.53 (m, 2H, ***H-2a***, ***H-2b***), 2.35 (ddd, *J* = 15.8, 11.5, 2.0 Hz, 1H, ***H-22$_{ax}$***), 2.28-2.21 (m, 2H, ***H-8$_{eq}$***, ***H-12$_{eq}$***), 2.21-2.11 (m, 4H, ***H-14$_{eq}$***, ***H-6$_{eq}$***, ***H-35***), 2.04-1.87 (m, 5H, ***H-14$_{ax}$***, ***H-8$_{ax}$***, ***H-24a***, ***H-6$_{ax}$***, ***H-12$_{ax}$***), 1.80 (ddd, *J* = 14.3, 8.6, 2.6 Hz, 1H, ***H-4a***), 1.73 (ddd, *J* = 14.3, 7.0, 3.4 Hz, 1H, ***H-24b***), 1.67 (ddd, *J* = 14.3, 9.9, 4.4 Hz, 1H, ***H-4b***), 1.69-1.63 (m, 1H, ***H-10a***), 1.60 (ddd, *J* = 14.0, 7.0, 5.2 Hz, 1H, ***H-10b***), 1.47 (sext, *J* = 7.3 Hz, 2H, ***H-36***), 1.13 (s, 3H, ***H-29***), 1.13 (s, 3H, ***H-29'***), 0.93 (t, *J* = 7.3 Hz, 3H, ***H-37***), 0.90 (s, 9H, ***H-56***), 0.11 (s, 3H, ***H-54***), 0.10 (s, 3H, ***H-54'***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 201.6 (***C-1***), 166.7 (***C-39***), 165.7 (***C-30***), 159.6 (***C-52***), 152.9 (***C-21***), 146.7 (***C-32***), 145.9 (***C-34***), 144.6 (***C-13***), 144.5 (***C-7***), 138.8 (***C-17***), 138.1

(***C-44***), 130.5 (***C-49***), 129.6 (***C-50***, ***C-50'***), 128.6 (***C-33***, ***C-46***, ***C-46'***), 128.1 (***C-45***, ***C-45'***), 127.9 (***C-47***), 127.1 (***C-16***), 118.7 (***C-31***), 117.3 (***C-38***), 114.2 (***C-51***, ***C-51'***), 109.0 (***C-27***, ***C-28***), 102.9 (***C-19***), 95.1 (***C-42***), 79.4 (***C-15***), 75.1 (***C-11***), 75.1 (***C-9***), 75.0 (***C-5***), 72.9 (***C-26***), 72.2 (***C-48***), 71.8 (***C-20***), 71.7 (***C-3***), 69.6 (***C-43***), 69.4 (***C-25***), 68.7 (***C-23***), 55.5 (***C-53***), 51.8 (***C-41***), 51.3 (***C-40***), 49.5 (***C-2***), 46.1 (***C-18***), 42.8 (***C-10***), 42.4 (***C-4***), 42.2 (***C-24***), 41.4 (***C-6***), 40.9 (***C-8***, ***C-14***), 40.6 (***C-12***), 35.3 (***C-35***), 33.2 (***C-22***), 26.2 (***C-56***), 24.2 (***C-29***), 24.2 (***C-29'***), 22.1 (***C-36***), 18.4 (***C-55***), 13.9 (***C-37***), -3.7 (***C-54***), -4.4 (***C-54'***);

FTIR (neat): ν_{max} 2930, 2856, 1721, 1643, 1614, 1514, 1463, 1436, 1382, 1361, 1303, 1249, 1166, 1106, 1043, 892, 836, 777 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{64}H_{92}O_{14}SiNa$ 1135.6154; found 1135.6168.

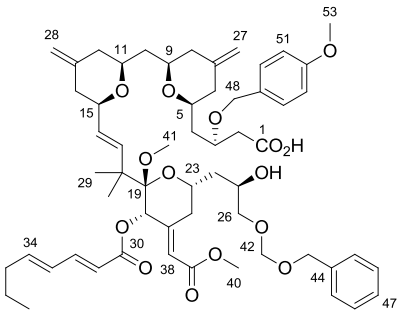


(*R*)-4-((2*S*,6*R*)-6-(((2*S*,6*R*)-6-((*E*)-3-((2*S*,3*S*,6*S*,*E*)-6-((*R*)-3-((Benzyloxy)methoxy)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-3-((2*E*,4*E*)-octa-2,4-dienoyloxy)tetrahydro-*2H*-pyran-2-yl)-3-methylbut-1-en-1-yl)-4-methylenetetrahydro-*2H*-pyran-2-yl)methyl)-4-methylenetetrahydro-*2H*-pyran-2-yl)-3-((4-methoxybenzyl)oxy)butanoic Acid (2.94):

To a stirred solution of aldehyde **2.93** (69.4 mg, 62.3 umol, 1.0 equiv) in CH_3CN (3.1 mL, 0.02 M) was added *t*-BuOH (3.1 mL, 0.02M) and isoamylene (3.1 mL, 0.02 M). With an ice-water bath, a solution of $NaH_2PO_4 \cdot H_2O$ (87 mg, 0.63 mmol, 10.0 equiv) and $NaClO_2$ (70 mg, 0.62 mmol, 10.0 equiv) in D.I. H_2O (1.6 mL, 0.4 M) was added into this reaction. It was stirred for 2 hours at this temperature, and then quenched by addition of a saturated

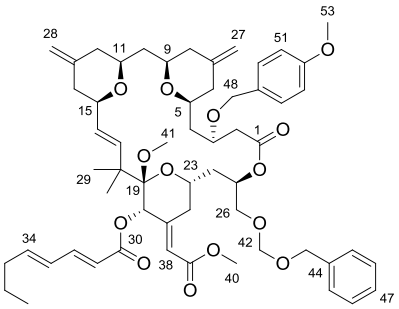
$Na_2S_2O_3$ solution (10 mL). This mixture was stirred for 10 minutes at ambient temperature, and then EtOAc (10 mL) was added before being poured into a saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with EtOAc (4 x 5 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a pale yellow oil (78.3 mg). The crude product was used in next step without any further purification.

TLC: R_f = 0.23 (MeOH/EtOAc/Hex = 1:3:6, v/v/v).



(*R*)-4-((2*S*,6*R*)-6-(((2*S*,6*R*)-6-((*E*)-3-((2*S*,3*S*,6*S*,*E*)-6-((*R*)-3-((benzyloxy)methoxy)-2-((*tert*-butyldimethylsilyl)oxy)propyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-3-((2*E*,4*E*)-octa-2,4-dienoyloxy)tetrahydro-*2H*-pyran-2-yl)-3-methylbut-1-en-1-yl)-4-methylenetetrahydro-*2H*-pyran-2-yl)methyl)-4-methylenetetrahydro-*2H*-pyran-2-yl)-3-((4-methoxybenzyl)oxy)butanoic Acid (2.94a): To a stirred solution of crude acid **2.94** (crude 78.3 mg, theoretically 62.3 umol, 1.0 equiv) in THF (6.2 mL, 0.01 M) was added 30% HF•Py (1.2 mL, 18 mmol, 300 equiv) at room temperature. It was stirred for 32 hours, then diluted with EtOAc (10 mL) before being poured into a saturated NH_4Cl solution (15 mL). The aqueous layer was extracted with EtOAc (4 x 5 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellow oil (110 mg). The crude product was used directly in next step without any further purification.

TLC: R_f = 0.19 (MeOH/EtOAc/Hex = 1:4:5, v/v/v).



(2*E*,4*E*)-(1*R*,3*S*,7*R*,8*E*,11*S*,12*S*,13*E*,15*S*,17*R*,21*R*,23*S*)-17-((Benzyloxymethoxy)methyl)-11-methoxy-13-(2-methoxy-2-oxoethylidene)-21-(4-methoxybenzyloxy)-10,10-dimethyl-5,25-dimethylene-19-oxo-18,27,28,29-tetraoxatetracyclo[21.3.1.1^{3,7}.1^{11,15}]nonacos-8-en-12-yl Octa-2,4-dienoate (2.95): To a stirred solution of crude seco-acid **2.94a** (crude 110 mg, theoretically 62.3 umol, 1.0 equiv) in THF (12.5 mL, 0.005 M) was added *N*,*N*-diisopropylethylamine (DIEPA) (110 uL, 632 umol, 10.0 equiv) and 2,4,6-trichlorobenzoyl chloride (30.0 uL, 188 umol, 3.0 equiv) at room temperature, subsequently. It was stirred for 3 hours under an atmosphere of N_2. Then, this reaction was added into a stirred solution of DMAP (77 mg, 62 umol, 10.0 equiv) in anhydrous toluene (62 mL, 0.001 M) via a syringe pump at the rate of 1 mL/h at 40 ºC, under an atmosphere of N_2. The flask of mixed anhydride was rinse 3 times with anhydrous toluene (3 x 1 mL), which was added into flask containing DMAP solution. After addition, the reaction was stirred further 3 hours before being poured into a saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with EtOAc (4 x 10 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 10-20 vol% of EtOAc in hexanes to provide the titled compound (59.3 mg, 59.5 umol, 95.5% yield) as a yellow oil.

TLC: R_f = 0.81 (MeOH/EtOAc/Hex = 1: 4:5, v/v/v);

$[\alpha]_D^{20}$ +22.1 (*c* 0.36, $CHCl_3$);

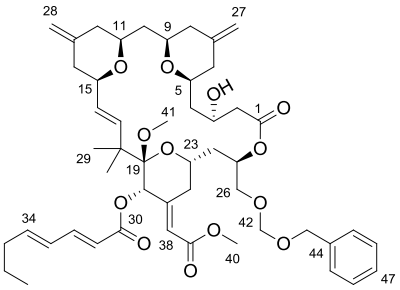
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.37-7.31 (m, 4H, ***H-45***, ***H-45'***, ***H-46***, ***H-46'***), 7.31-7.25 (m, 2H, ***H-47***, ***H-32***), 7.22 (d, *J* = 8.8 Hz, 2H, ***H-50***, ***H-50'***), 6.83 (d, *J* = 8.6 Hz, 2H, ***H-51***, ***H-51'***), 6.22 (d, *J* = 15.8 Hz, 1H, ***H-17***), 6.20-6.14 (m, 2H, ***H-33***, ***H-34***), 5.98 (d, *J* = 1.8 Hz, 1H, ***H-38***), 5.77 (d, *J* = 15.1 Hz, 1H, ***H-31***), 5.59 (dddd, *J* = 11.9, 4.7, 4.7, 2.9 Hz, 1H, ***H-25***), 5.34 (dd, *J* = 15.8, 8.6 Hz, 1H, ***H-16***), 5.26 (s, 1H, ***H-20***), 4.75 (d, *J* = 1.8 Hz, 1H, ***H-28a***), 4.74 (d, *J* = 1.8 Hz, 1H, ***H-28b***), 4.72-4.70 (m, 2H, ***H-27a***, ***H-27b***), 4.69 (d, *J* = 6.7 Hz, 1H, ***H-42a***), 4.62 (d, *J* = 6.7 Hz, 1H, ***H-42b***), 4.57 (ABq, *J* = 11.9 Hz, $\Delta\nu$ = 24.8 Hz, 2H, ***H-43***), 4.48 (ABq, *J* = 10.8 Hz, $\Delta\nu$ = 14.8 Hz, 2H, ***H-48***), 4.15 (dddd, *J* = 10.0, 6.6, 6.6, 3.5 Hz, 1H, ***H-3***), 3.90 (ddd, *J* = 11.1, 8.7, 2.3 Hz, 1H, ***H-15***), 3.81-3.73 (m, 1H, ***H-23***), 3.75 (s, 3H, ***H-53***), 3.71 (dd, *J* = 10.5, 4.3 Hz, 1H, ***H-26a***), 3.69 (s, 3H, ***H-40***), 3.71-3.67 (m, 1H, ***H-22$_{eq}$***), 3.62 (dd, *J* = 10.4, 4.9 Hz, 1H, ***H-26b***), 3.48 (dddd, *J* = 11.5, 7.4, 2.3, 2.1 Hz,, 1H, ***H-11***), 3.36 (tt, *J* = 10.8, 2.6 Hz, 1H, ***H-5***), 3.12 (s, 3H, ***H-41***), 3.15-3.06 (m, 1H, ***H-9***), 2.63 (dd, *J* = 15.3, 2.6 Hz, 1H, ***H-2a***), 2.48 (dd, *J* = 15.3, 10.1 Hz, 1H, ***H-2b***), 2.31 (ddd, *J* = 12.7, 1.8, 1.4 Hz, 1H, ***H-12$_{eq}$***), 2.23-2.00 (m, 8H, ***H-14$_{eq}$***, ***H-6$_{eq}$***, ***H-35***, ***H-22$_{ax}$***, ***H-8$_{eq}$***, ***H-24a***, ***H-14$_{ax}$***), 2.00-1.80 (m, 5H, ***H-8$_{ax}$***, ***H-12$_{ax}$***, ***H-6$_{ax}$***, ***H-24b***, ***H-4a***), 1.75 (ddd, *J* = 14.3, 10.6, 2.1 Hz, 1H, ***H-10a***), 1.55 (ddd, *J* = 14.3, 7.3, 1.6 Hz, 1H, ***H-10b***), 1.48 (ddd, *J* = 17.1, 10.6, 6.6 Hz, 1H, ***H-4b***), 1.46 (sext, *J* = 7.4 Hz, 2H, ***H-36***), 1.11 (s, 3H, ***H-29***), 1.10 (s, 3H, ***H-29'***), 0.93 (t, *J* = 7.3 Hz, 3H, ***H-37***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 172.5 (***C-1***), 167.0 (***C-39***), 165.6 (***C-30***), 159.3 (***C-52***), 151.6 (***C-21***), 146.7 (***C-32***), 145.9 (***C-34***), 144.5 (***C-13***), 144.4 (***C-7***), 142.0 (***C-17***), 138.1 (***C-44***), 131.0 (***C-49***), 129.5 (***C-50***, ***C-50'***), 128.6 (***C-46***, ***C-46'***), 128.6 (***C-33***), 128.0 (***C-***

45, ***C-45'***), 127.9 (***C-47***), 125.5 (***C-16***), 119.5 (***C-38***), 118.7 (***C-31***), 113.9 (***C-51***, ***C-51'***), 109.1 (***C-27***), 109.0 (***C-28***), 103.4 (***C-19***), 95.1 (***C-42***), 81.7 (***C-15***), 76.5 (***C-5***), 76.5 (***C-11***), 76.4 (***C-9***), 75.6 (***C-3***), 73.5 (***C-20***), 71.9 (***C-48***), 69.8 (***C-43***), 69.4 (***C-26***), 68.6 (***C-25***), 67.2 (***C-23***), 55.5 (***C-53***), 52.8 (***C-41***), 51.4 (***C-40***), 45.3 (***C-18***), 44.3 (***C-10***), 43.1 (***C-2***), 41.9 (***C-12***), 41.5 (***C-4***), 41.1 (***C-6***), 41.1 (***C-8***), 41.0 (***C-14***), 37.2 (***C-24***), 35.3 (***C-35***), 31.0 (***C-22***), 26.5 (***C-29***), 22.1 (***C-36***), 20.4 (***C-29'***), 13.9 (***C-37***);

FTIR (neat): ν_{max} 2928, 2856, 1725, 1643, 1614, 1581, 1550, 1514, 1463, 1437, 1379, 1249, 1161, 1108, 1049, 891, 859, 820 cm^{-1};

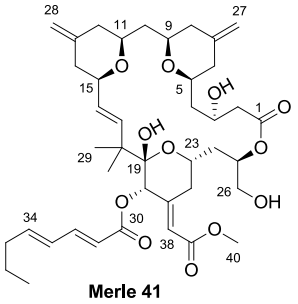
HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{58}H_{76}O_{14}Na$ 1019.5133; found 1019.5138.



(2*E*,4*E*)-(1*R*,3*S*,7*R*,8*E*,11*S*,12*S*,13*E*,15*S*,17*R*,21*R*,23*S*)-17-((Benzyloxymethoxy)methyl)-21-hydroxy-11-methoxy-13-(2-methoxy-2-oxoethylidene)-10,10-dimethyl-5,25-dimethylene-19-oxo-18,27,28,29-tetraoxatetracyclo[21.3.1.1^{3,7}.1^{11,15}]nonacos-8-en-12-yl Octa-2,4-dienoate (2.95a): To a stirred solution of compound **2.95** (59.3 mg, 59.5 umol, 1.0 equiv) in CH_2Cl_2 (12 mL, 0.005M) was added a 0.1 M phosphate pH = 6 buffer solution (1.2 mL, 0.05 M). Then, this reaction was cooled down to 0 °C, and DDQ (41.5 mg, 179 umol, 3.0 equiv) was added in one portion. It was stirred for 3 hours at this temperature. Then, this reaction was diluted with EtOAc (10 mL), and poured into a saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and

concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 15-25 vol% of EtOAc in hexanes to provide the titled compound (38.6 mg, 44.0 umol, 74.0% yield) as a pale yellow oil.

TLC: R_f = 0.32 (EtOAc/Hex = 4:6, v/v).



Merle 41

(2*E*,4*E*)-(1*R*,3*S*,7*R*,8*E*,11*S*,12*S*,13*E*,15*S*,17*R*,21*R*,23*S*)-11,21-dihydroxy-17-(hydroxymethyl)-13-(2-methoxy-2-oxoethylidene)-10,10-dimethyl-5,25-dimethylene-19-oxo-18,27,28,29-tetraoxatetracyclo[21.3.1.1^{3,7}.1^{11,15}]nonacos-8-en-12-yl octa-2,4-dienoate (2.54): To a stirred solution of compound **2.95a** (10.1 mg, 11.5 umol, 1.0 equiv) in CH_3CN (1.2 mL, 0.01 M) was added deionized water (60 uL, 0.2M) and $LiBF_4$ solid (55 mg, 579 umol, 50 equiv). This reaction was stirred at 80 ^oC overnight (ca. 8 hours) and then cooled to room temperature before being concentrated. The remainder was purified by flash chromatography on silica gel eluting with 25-35 vol% of EtOAc in hexanes to provide the titled compound (5.9 mg, 7.9 umol, 69.1% yield) as a colorless oil.

TLC: R_f = 0.36 (EtOAc/Hex = 5:5, v/v);

$[\alpha]_D^{20}$ -7.0 (*c* 0.16, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.32-7.21 (m, 1H, ***H-32***), 6.27-6.08 (m, 2H, ***H-33***, ***H-34***), 6.03 (d, *J* = 2.0 Hz, 1H, ***H-38***), 5.79 (d, *J* = 15.2 Hz, 1H, ***H-31***), 5.76 (d, *J* = 16.2 Hz, 1H, ***H-17***), 5.42-5.33 (m, 1H, ***H-25***), 5.33 (dd, *J* = 15.6, 8.3 Hz, 1H, ***H-16***), 5.23 (br. s, 1H, ***H-20***), 5.20 (br. s, 1H, ***19-OH***), 4.82-4.65 (m, 4H, ***H-28a***, ***H-27a***, ***H-28b***, ***H-27b***), 4.47 (d, *J*

= 12.2 Hz, 1H, ***3-OH***), 4.31-4.17 (m, 1H, ***H-3***), 4.10 (tt, *J* = 11.5, 2.5 Hz, 1H, ***H-23***), 3.94 (ddd, *J* = 11.3, 8.3, 2.4 Hz, 1H, ***H-15***), 3.85 (dd, *J* = 12.0, 3.2 Hz, 1H, ***H-26a***), 3.75-3.69 (m, 1H, ***H-22$_{eq}$***), 3.68 (s, 3H, ***H-40***), 3.69-3.60 (m, 1H, ***H-26b***), 3.55 (app. ddd, *J* = 11.7, 7.3, 2.4 Hz, 1H, ***H-11***), 3.52-3.45 (m, 2H, ***H-5***, ***26-OH***), 3.42 (tt, *J* = 11.3, 2.2 Hz, 1H, ***H-9***), 2.50 (dd, *J* = 12.7, 2.9 Hz, 1H, ***H-2a***), 2.45 (dd, *J* = 12.7, 10.8 Hz, 1H, ***H-2b***), 2.26-1.92 (m, 13H, ***H-35***, ***H-8$_{eq}$***, ***H-6$_{eq}$***, ***H-12$_{eq}$***, ***H-22$_{ax}$***, ***H-14$_{eq}$***, ***H-4a***, ***H-12$_{ax}$***, ***H-24a***, ***H-6$_{ax}$***, ***H-14$_{ax}$***, ***H-8$_{ax}$***), 1.87 (ddd, *J* = 15.4, 11.3, 7.3 Hz, 1H, ***H-10a***), 1.81 (ddd, *J* = 11.7, 11.3, 2.7 Hz, 1H, ***H-24b***), 1.61 (ddd, *J* = 15.2, 3.4, 3.4 Hz, 1H, ***H-4b***), 1.52 (app. dd, *J* = 15.6, 2.4 Hz, 1H, ***H-10b***), 1.47 (sext, *J* = 7.4 Hz, 2H, ***H-36***), 1.14 (s, 3H, ***H-29***), 1.02 (s, 3H, ***H-29'***), 0.93 (t, *J* = 7.3 Hz, 3H, ***H-37***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 172.6 (***C-1***), 167.3 (***C-39***), 165.8 (***C-30***), 152.2 (***C-21***), 146.5 (***C-32***), 145.6 (***C-34***), 144.0 (***C-13***), 143.5 (***C-7***), 138.8 (***C-17***), 129.9 (***C-6***), 128.6 (***C-33***), 119.9 (***C-38***), 118.9 (***C-31***), 109.3 (***C-27***), 108.8 (***C-28***), 99.3 (***C-19***), 80.3 (***C-15***), 79.6 (***C-9***), 77.7 (***C-11***), 76.6 (***C-5***), 74.3 (***C-20***), 71.9 (***C-25***), 68.7 (***C-3***), 66.0 (***C-26***), 64.6 (***C-23***), 51.3 (***C-40***), 45.2 (***C-18***), 43.3 (***C-10***), 42.8 (***C-2***), 42.4 (***C-12***), 41.6 (***C-14***), 41.0 (***C-6***), 40.9 (***C-8***), 40.1 (***C-4***), 36.2 (***C-24***), 35.3 (***C-35***), 31.4 (***C-22***), 25.0 (***C-19***), 22.1 (***C-36***), 19.9 (***C-19'***), 13.9 (***C-37***);

FTIR (neat): ν_{max} 3449 (br), 2931, 2857, 1725, 1614, 1514, 1462, 1382, 1249, 1108, 1046, 890 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{41}H_{58}O_{12}Na$ 765.3826; found 765.3826.

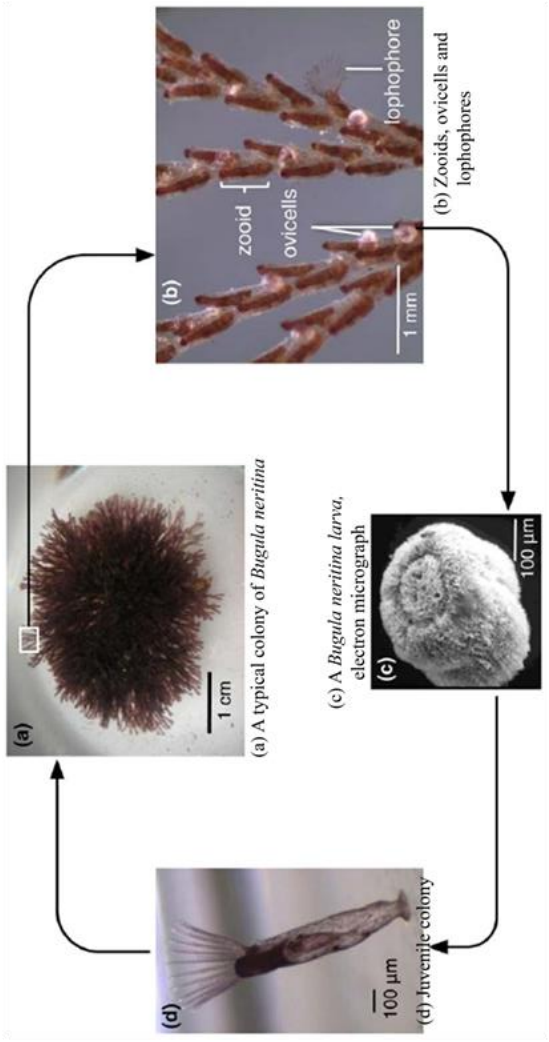
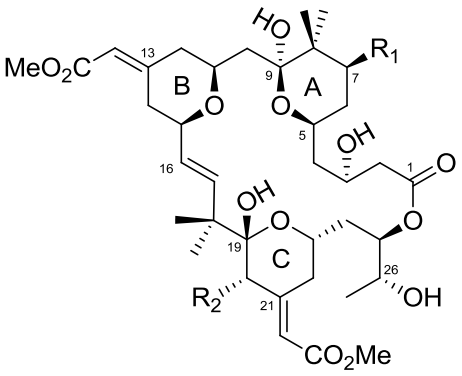
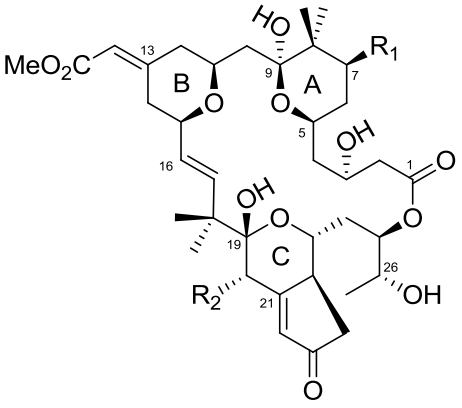


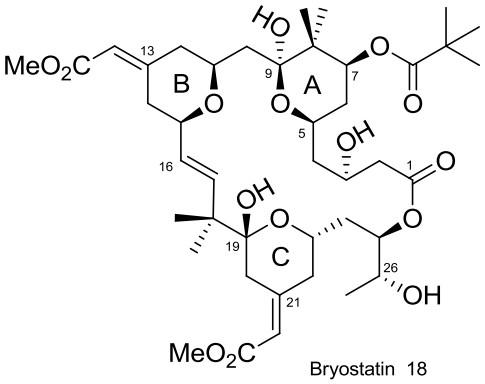
Figure 2.1 The Life Cycle of Bryozoa (*Bugula neritina*)



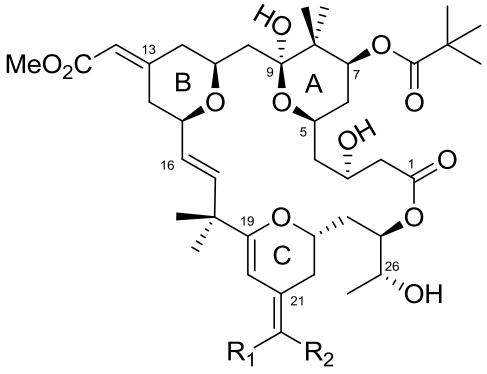
	R_1	R_2
Bryostatin 1	OAc	$OCO(CH)_4Pr$
Bryostatin 2	OH	$OCO(CH)_4Pr$
Bryostatin 4	$OCOBu^i$	OCOPr
Bryostatin 5	$OCOBu^i$	OAc
Bryostatin 6	OCOPr	OAc
Bryostatin 7	OAc	OAc
Bryostatin 8	OCOPr	OCOPr
Bryostatin 9	OCOPr	OAc
Bryostatin 10	$OCOBu^t$	H
Bryostatin 11	OAc	H
Bryostatin 12	OCOPr	$OCO(CH)_4Pr$
Bryostatin 13	OCOPr	H
Bryostatin 14	$OCOBu^t$	OH
Bryostatin 15	OAc	$OCO(CH)_4Pr$



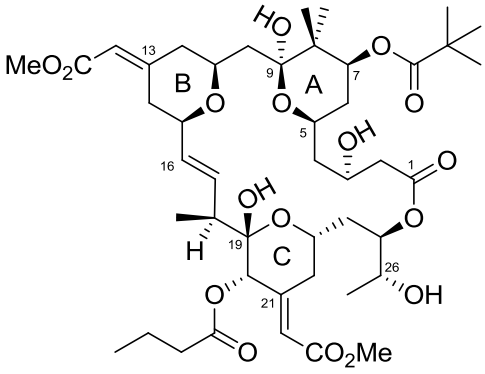
	R_1	R_2
Bryostatin 3	OAc	$OCO(CH)_4Pr$
Bryostatin 19	$OCOBu^t$	OCOPr
Bryostatin 20	$OCOBu^t$	H



Bryostatin 18



	R_1	R_2
Bryostatin 16	H	CO_2M_3
Bryostatin 17	CO_2Me	H



Bryostatin 21

Figure 2.2 Chemical Structures of Bryostatins

Table 2.1 Abundance and Antiviral Activity Values Regarding Bryostatins

Bryostatin	Abundance (wt%)	Ed_{50} (ug/mL) (P388 Leukemia Lines)	Life-span Extension	Injected Dose (ug/Kg)	Ref.
1	2.4×10^{-5}	0.89	52-96%	10-70	13
2	6.2×10^{-7}		60%	30	15
3	1.6×10^{-7}		63%	30	16
4	8.9×10^{-5}	6.7×10^{-4}	62%	46	17
5	2.8×10^{-5}	1.3×10^{-3}-2.6×10^{-4}	88%	185	18
6	1.2×10^{-4}	3.0×10^{-3}	82%	185	18
7	6.2×10^{-5}	2.6×10^{-5}	77%	92	18
8	4.2×10^{-6}	1.3×10^{-3}	74%	110	19
9	2.7×10^{-5}	1.2×10^{-3}	40%	80	20
10	6.7×10^{-7}	7.6×10^{-4}	34%	10	21
11	1.7×10^{-5}	1.8×10^{-5}	64%	92.5	21
12	3.7×10^{-7}	1.4×10^{-2}	47-68%	30-50	22
13	7.0×10^{-8}	5.4×10^{-3}			22
14	1.02×10^{-5}	0.33			23
15	8.6×10^{-7}	1.4			23
16	4.3×10^{-6}	9.3×10^{-3}			24
17	3.4×10^{-6}	1.9×10^{-2}			24
18	6.7×10^{-6}	3.3×10^{-3}			24
19	1.4×10^{-5}	2.8×10^{-3} (U937)			25
20					26
21	3.5×10^{-5}	2.8×10^{-3} (U937)			27

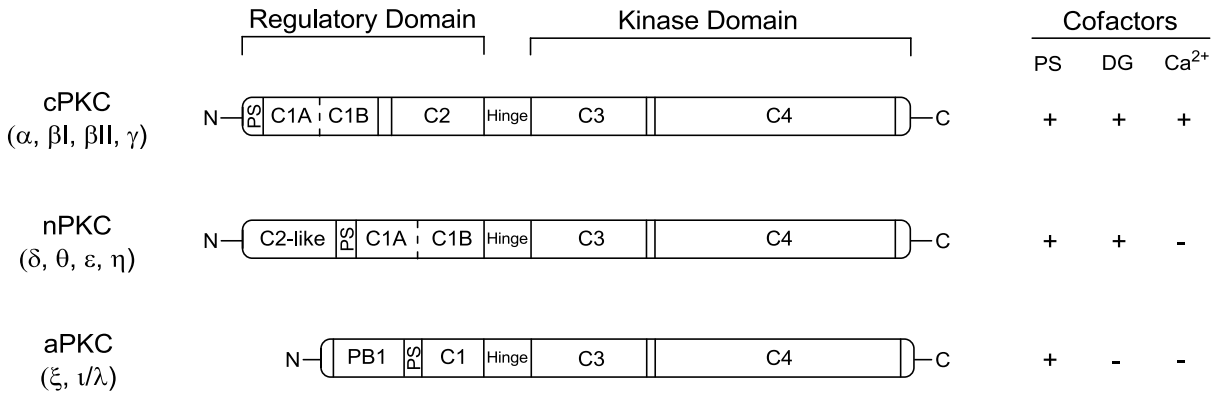


Figure 2.3 Simplified Domain Structures of PKC Isozymes

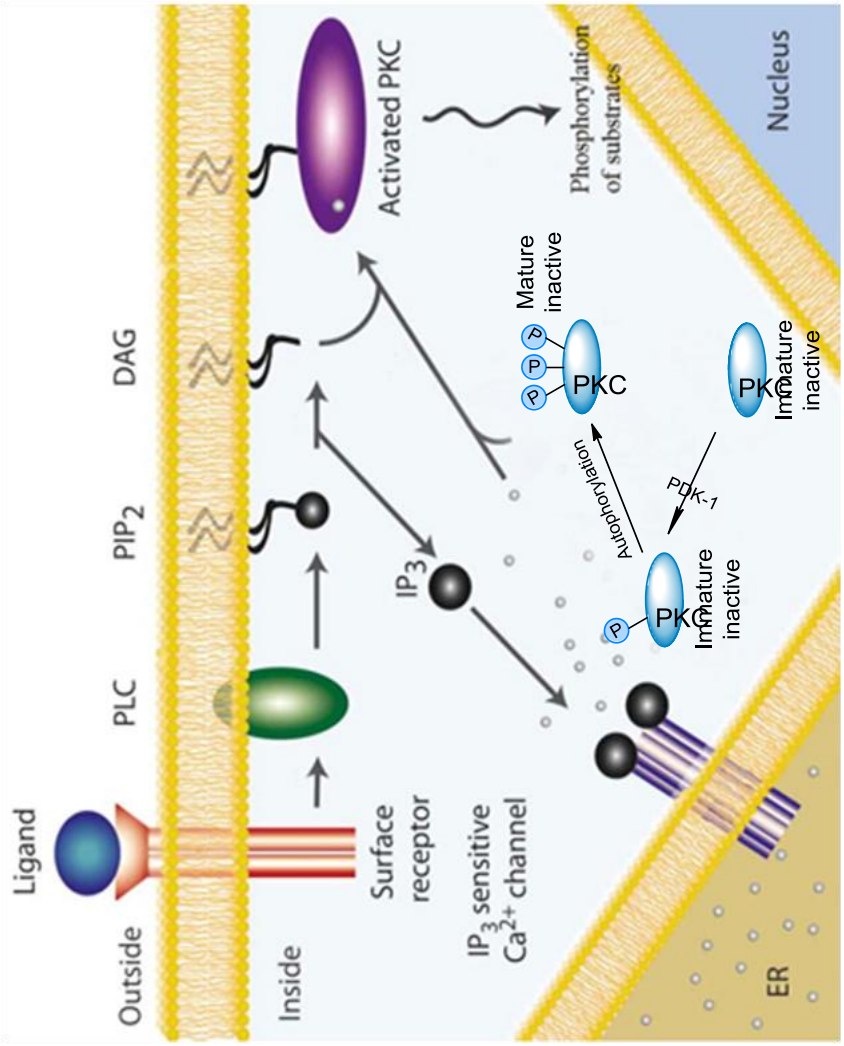


Figure 2.4 Activation Pathway of nPKCs

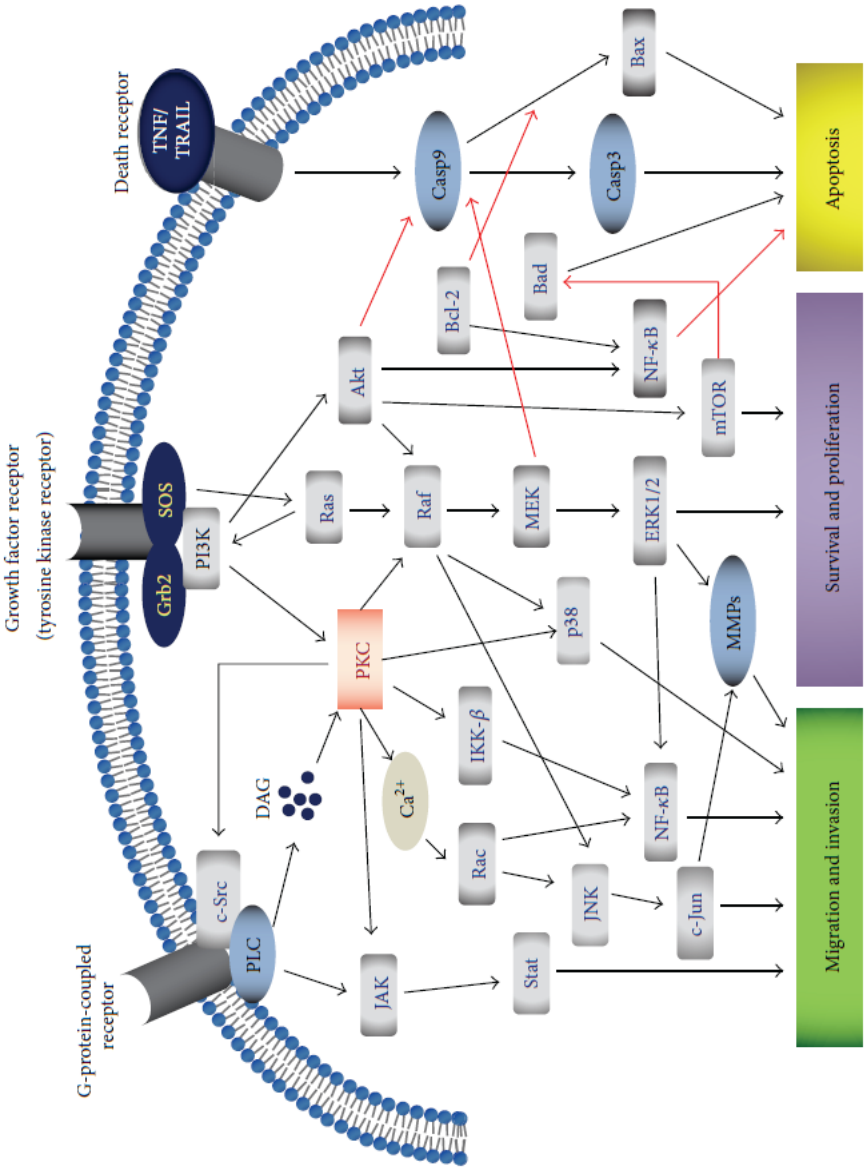


Figure 2.5 PKC Involved Signaling Pathways in Cancer Cell Lines

Table 2.2 Synergistic Effects of Bryostatin 1[105]

Cell line	Synergized Drug	Result
HL-60	Ara-C[65]	Doubled the amount of apoptotic cells
U937	Taxol	Doubled the amount of apoptotic cells
P388	Tamoxifen	Increased growth inhibition 200 times
Reh	Auristatin PE	Enhanced the amount of apoptotic cells
	Vincristine	Enhanced the amount of apoptotic cells
WSU-CLL	2-CdA	Tumor growth delay from 37 days to 76 days
WSU-DLCL2	Vincristine	Tumor growth delay from 16 days to 38 days

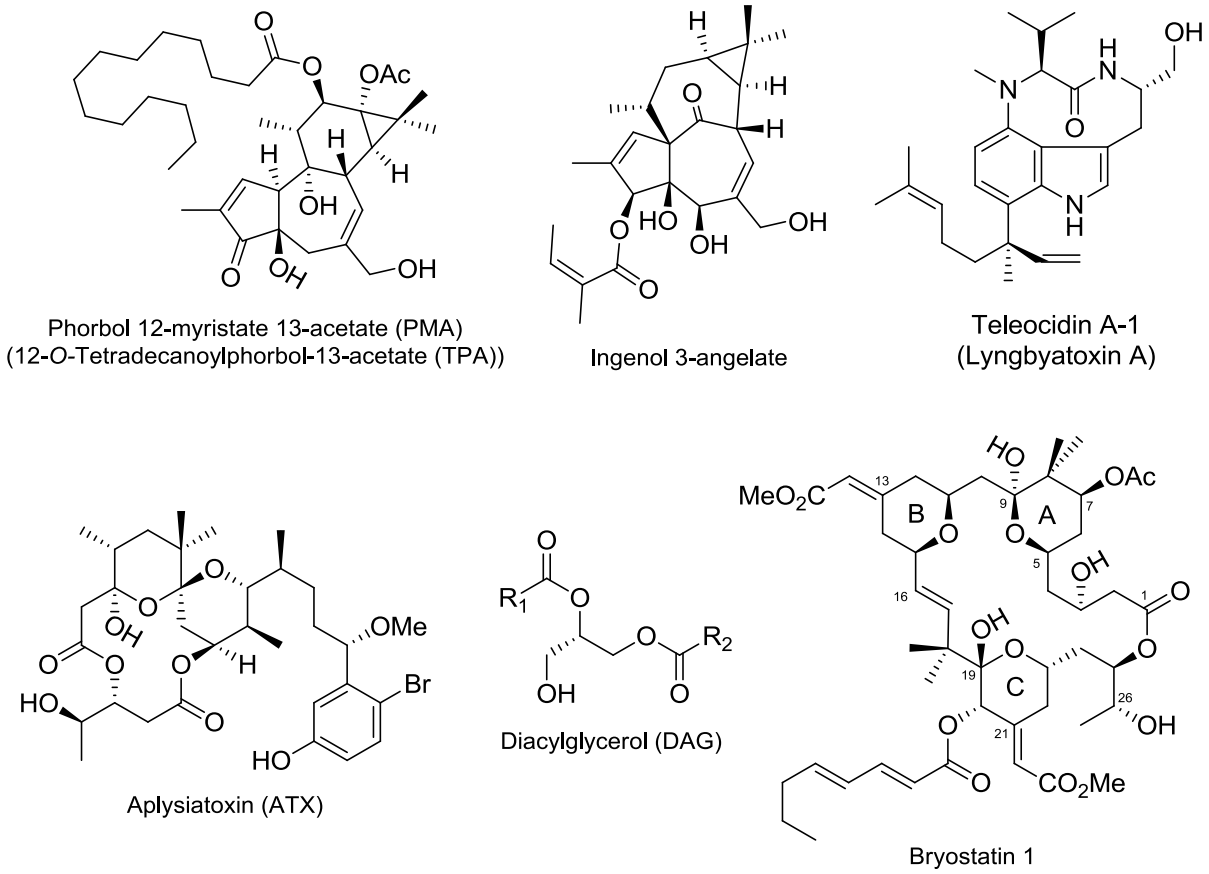
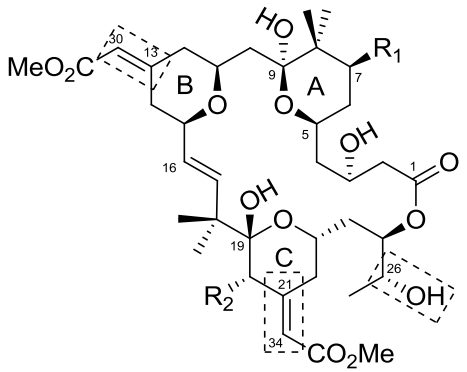


Figure 2.6 Structures of Some PKC Activators



	R_1	R_2
Bryostatin 1	OAc	$OCO(CH)_4Pr$
Bryostatin 2	OH	$OCO(CH)_4Pr$
Bryostatin 4	$OCOBu^t$	OCOPr

Entry	Bryostatin	Ki (nM)
1	4	1.30 ± 0.19
2	4 (*epi*-*C*26)	> 23
3	4 (*C*26-OAc)	>> 100
4	4 (epoxy-*C*13)	0.54 ± 0.07
5	1	1.35 ± 0.17
6	1 (*epi*-*C*26)	32.6 ± 6.6
7	2	5.86 ± 1.13
8	2 (hydro-*C*13)	9.61 ± 0.94
9	2 (hydro-*C*13,21)	473 ± 96

Figure 2.7 Binding Affinities of Some Bryostatins and Derivatives

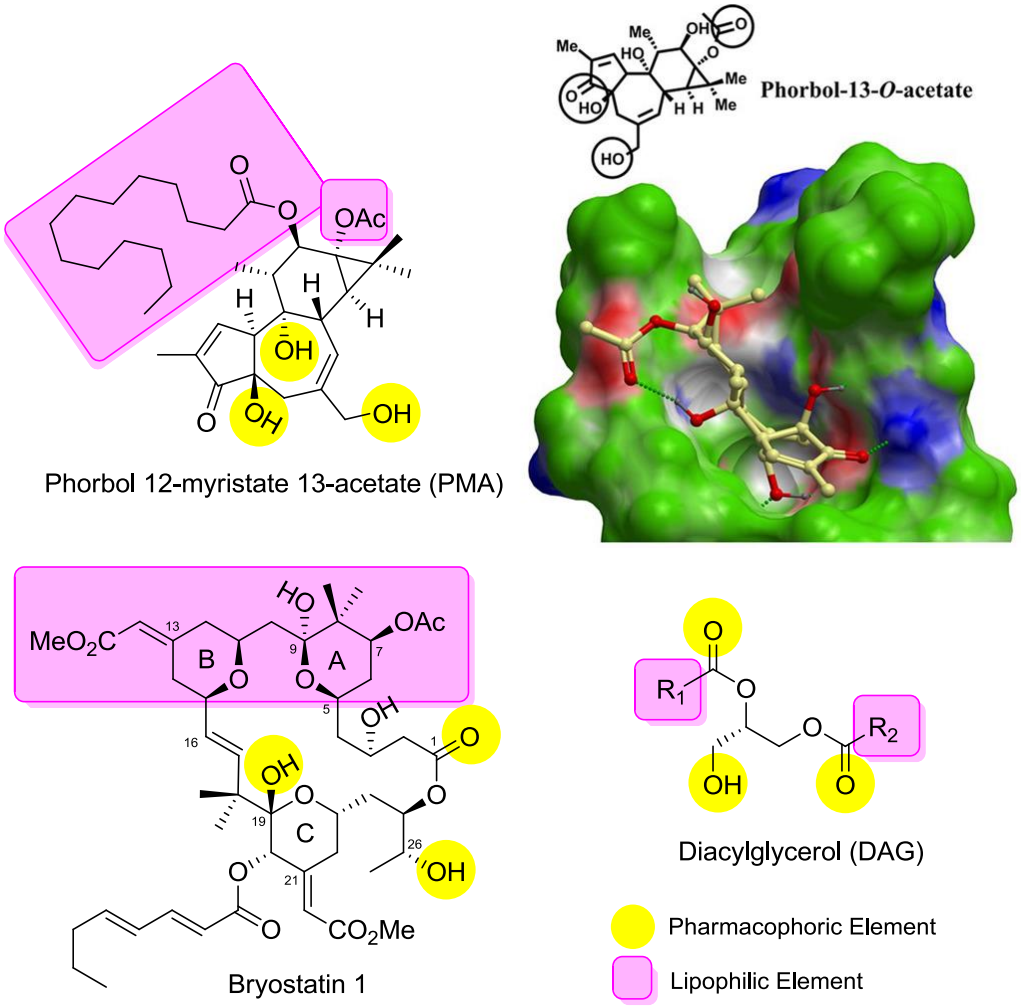
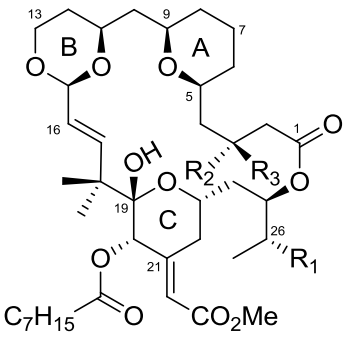
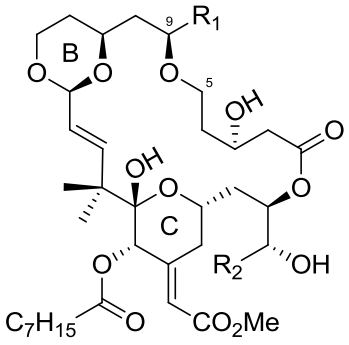


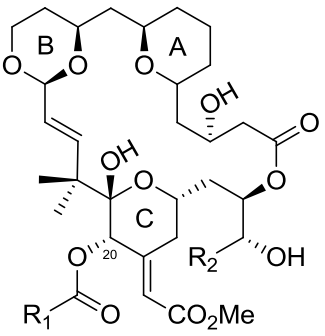
Figure 2.8 Wender's Binding Hypothesis and Crystal Structure of Binding Complex of Phorbol 13-Acetate to C1B Module of nPKC-δ[126]



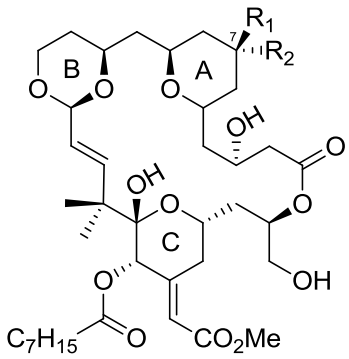
	R_1	R_2	R_3	*Ki (nM)*
2.1	OH	OH	H	*3.4*
2.2	OAc	OH	H	*> 10000*
2.3	OH	H	OH	*297*
2.4	OH	H	H	*285*



	R_1	R_2	*Ki (nM)*
2.5	H	Me	*47*
2.6	H	H	*8.0*
2.7	*t*-Bu	Me	*8.3*
2.8	*t*-Bu	H	*6.5*
2.9	Ph	H	*2.3*

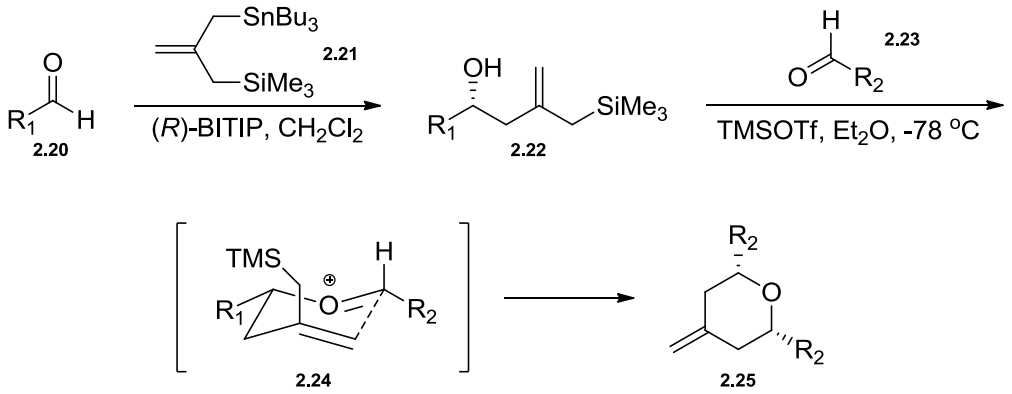


	R_1	R_2	*Ki (nM)*
2.10	Me	Me	*232*
2.11	$C_{13}H_{27}$	Me	*1.5*
2.12	Ph	Me	*7.0*
2.13	C_7H_{15}	H	*0.35*
2.14	3'-NO_2-Ph	H	*10*

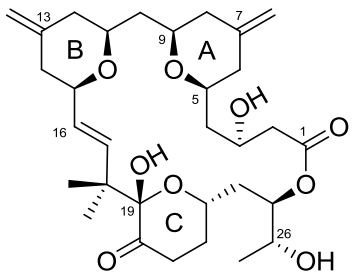


	R_1	R_2	*Ki (nM)*
2.15	OAc	H	*13*
2.16	OMe	H	*26*
2.17	CH_2OH	H	*330*
2.18	OH	H	*1000*
2.19	H	OH	*100*

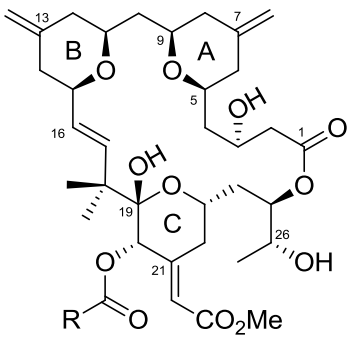
Figure 2.9 Wender's Bryostatin Analogues



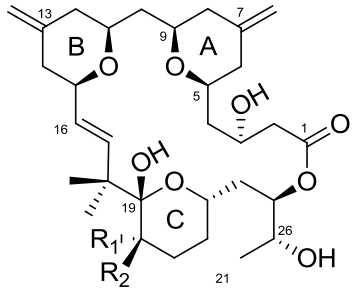
Scheme 2.1 Markó-Keck Annulation Strategy



2.26 *Ki = 546 nM*



	R	*Ki (nM)*
2.27 (Merle 21)	Ph	*0.70*
2.28 (Merle 22)	C_7H_{15}	*1.05*
2.29 (Merle 23)	C_7H_{11}	*0.70*



	R_1	R_2	*Ki (nM)*
2.30 (Merle 24)	H	C_7H_{15}	*37.7*
2.31 (Merle 25)	C_7H_{15}	H	*47.1*

Figure 2.10 Keck's A- and B-Ring Simpilfied Anologues

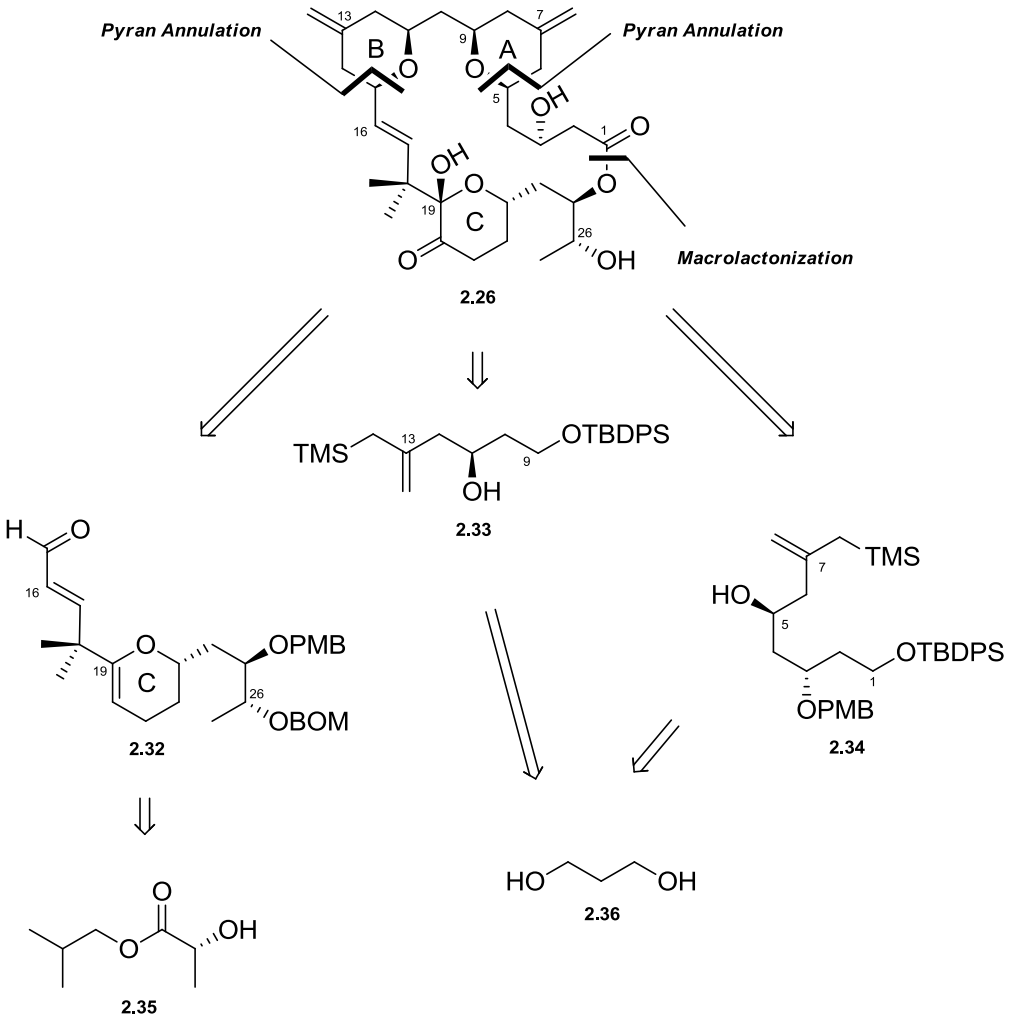
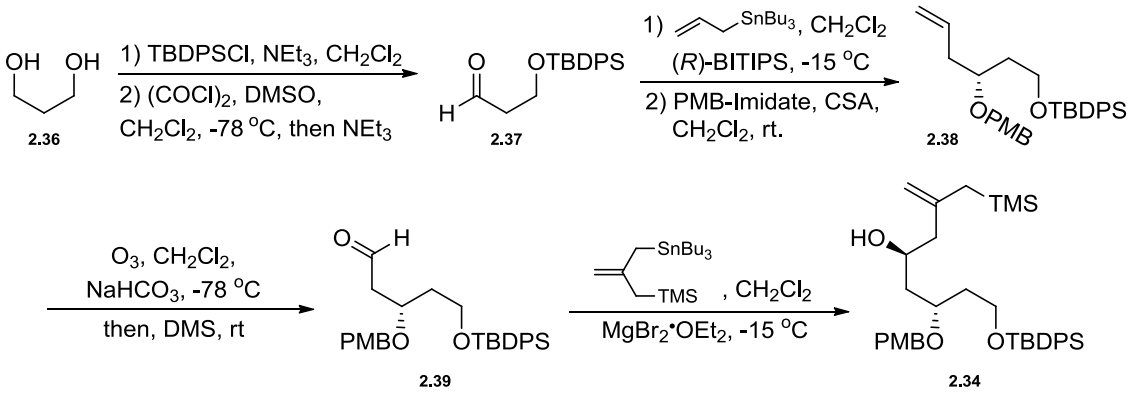
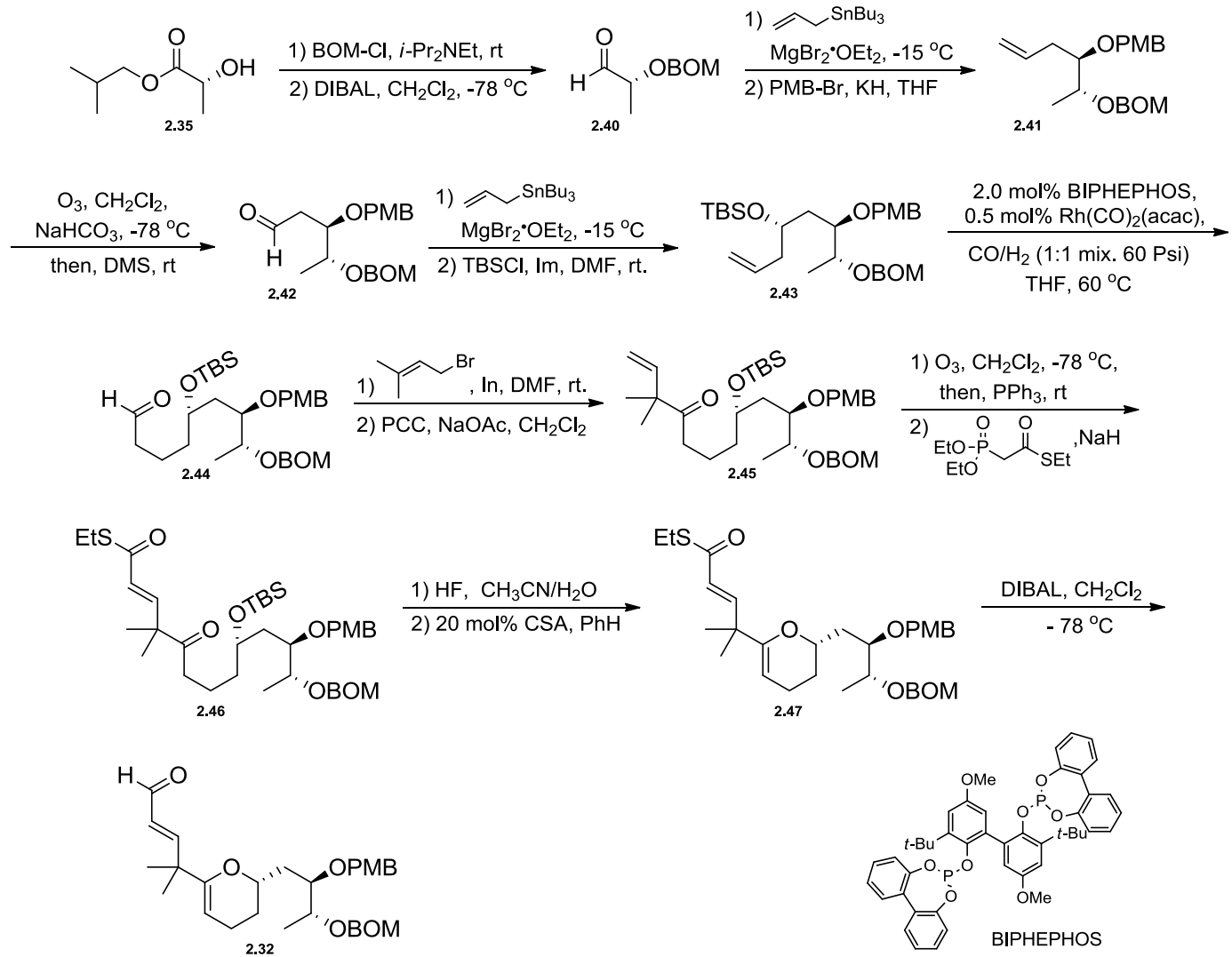


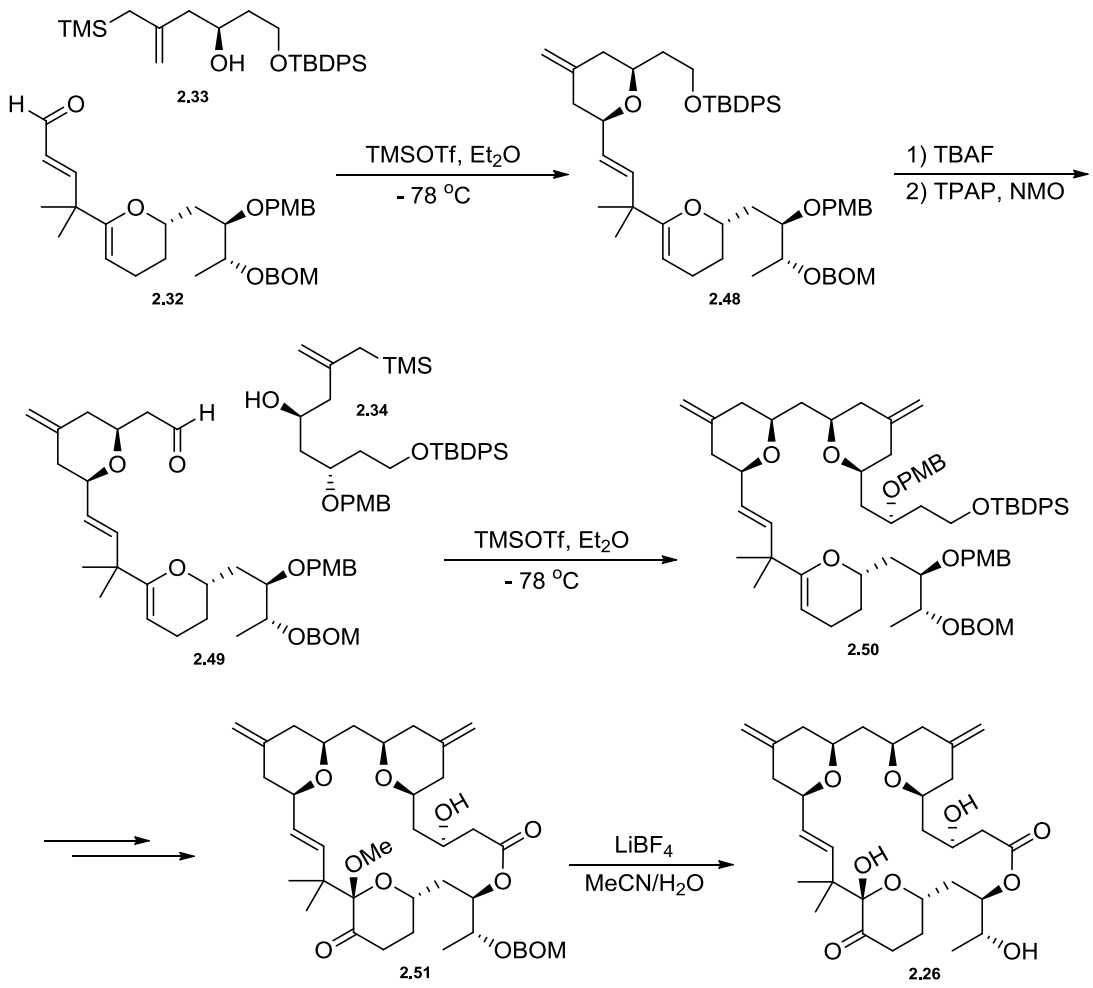
Figure 2.11 Retrosynthetic Plan of Keck's First Analogue



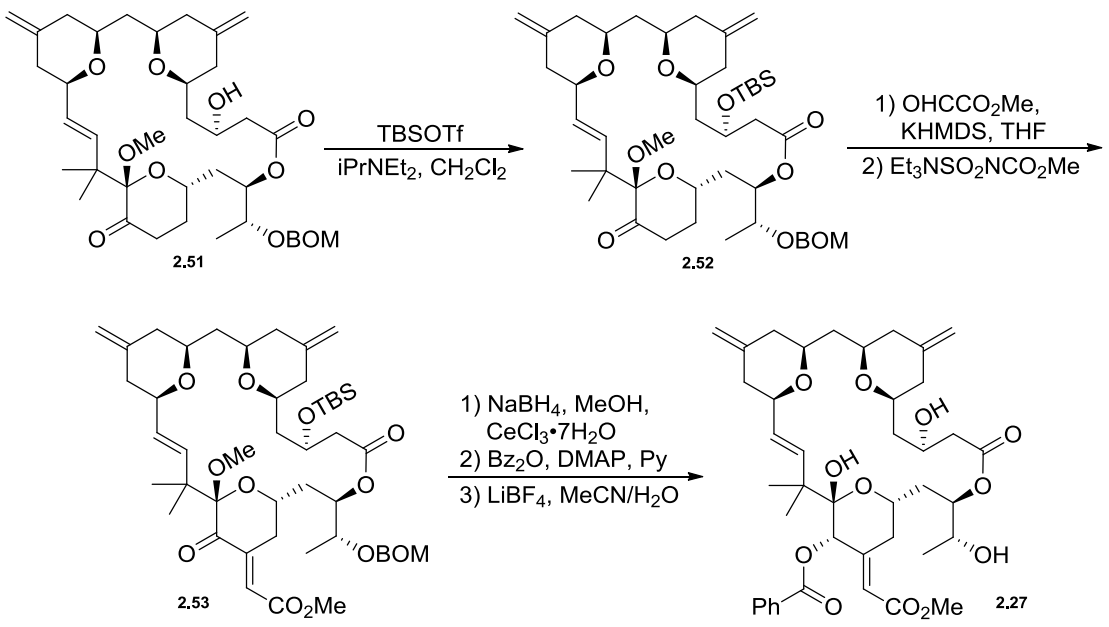
Scheme 2.2 Synthesis of the Northern Segment of Keck's First Analogue



Scheme 2.3 Synthesis of the C-ring of Keck's First Analogue



Scheme 2.4 Accomplishment of Keck's First Analogue



Scheme 2.5 Accomplishment of Merle 21

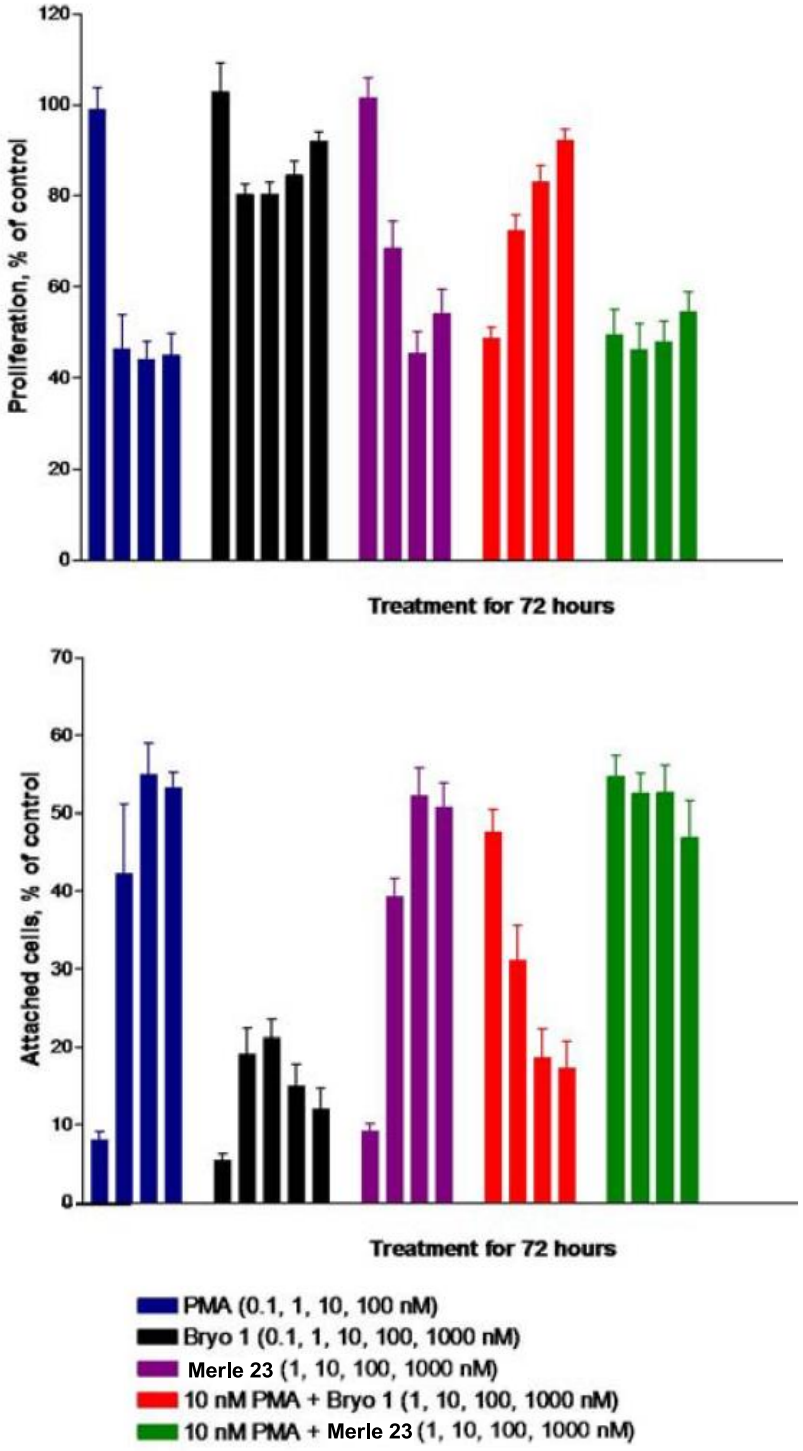
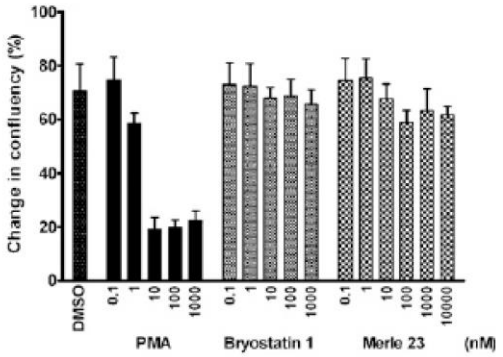
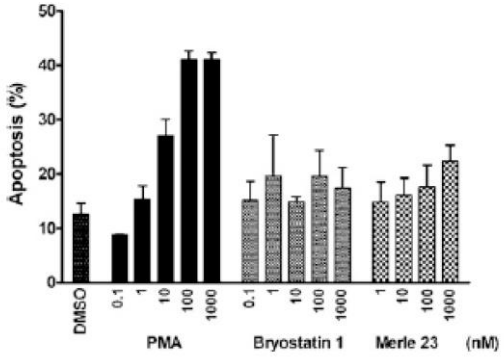


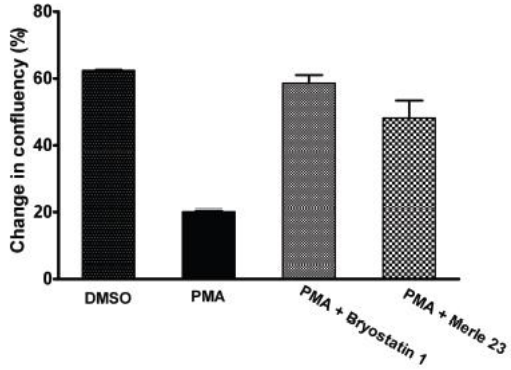
Figure 2.12 U937 Proliferation and Attachment Assays With Merle 23



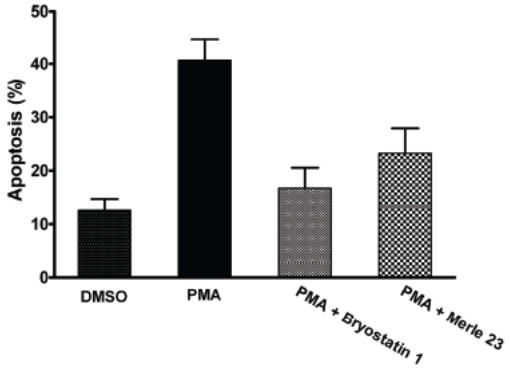
a) Growth of LNCaP cells after 72 hours treatment



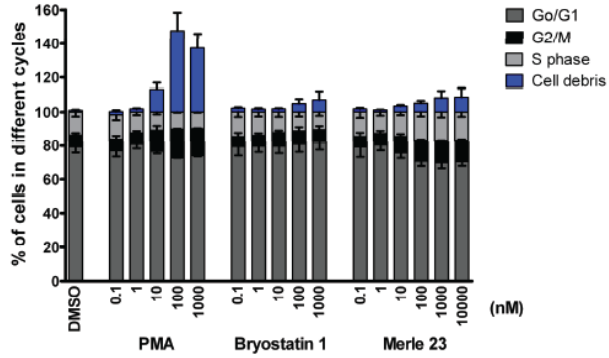
b) Apoptosis of LNCaP cells after 48 hours treatment



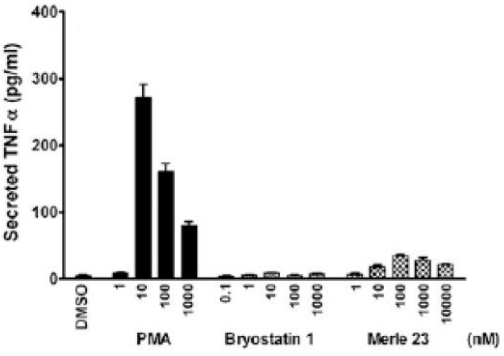
c) Growth of LNCaP cells after 72 hours treatment



d) Apoptosis of LNCaP cells after 48 hours treatment



e) Cell cycle analysis of LNCaP cells after 48 hours treatment



f) TNF-α secreted into the supernatant of LNCaP cells after 24 hours treatment

Figure 2.13 Bioglogical Responses Induced by PMA, Bryostatin 1, Merle 23 in LNCaP Cells

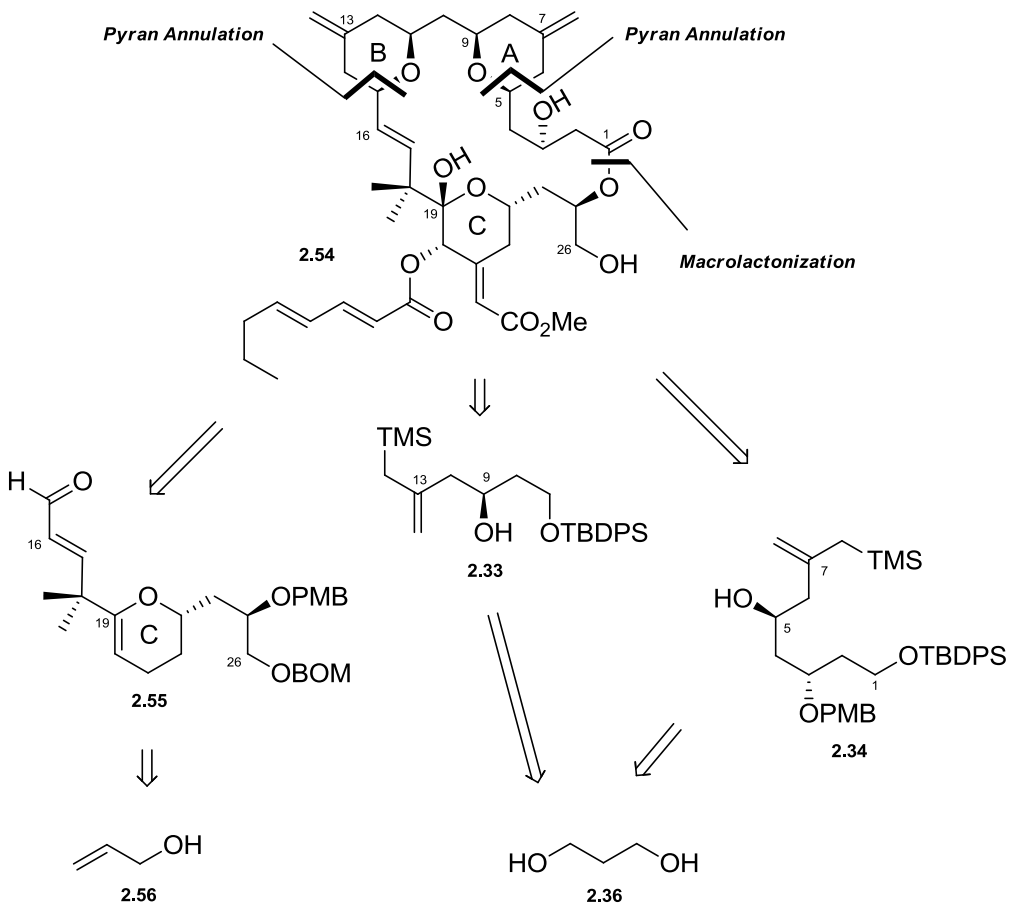
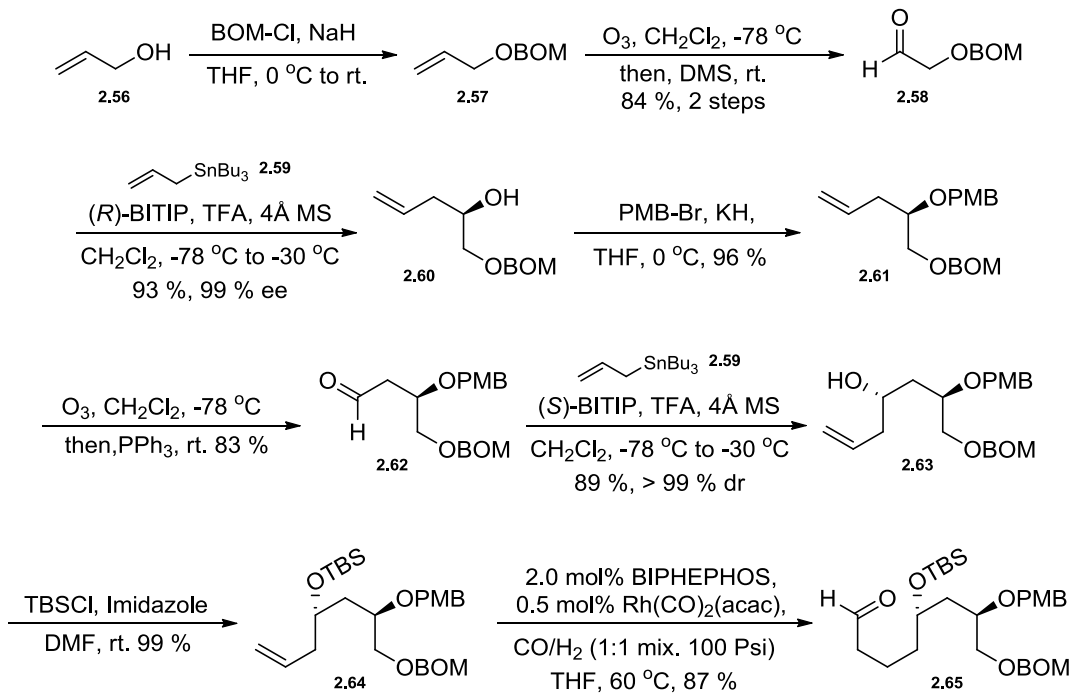
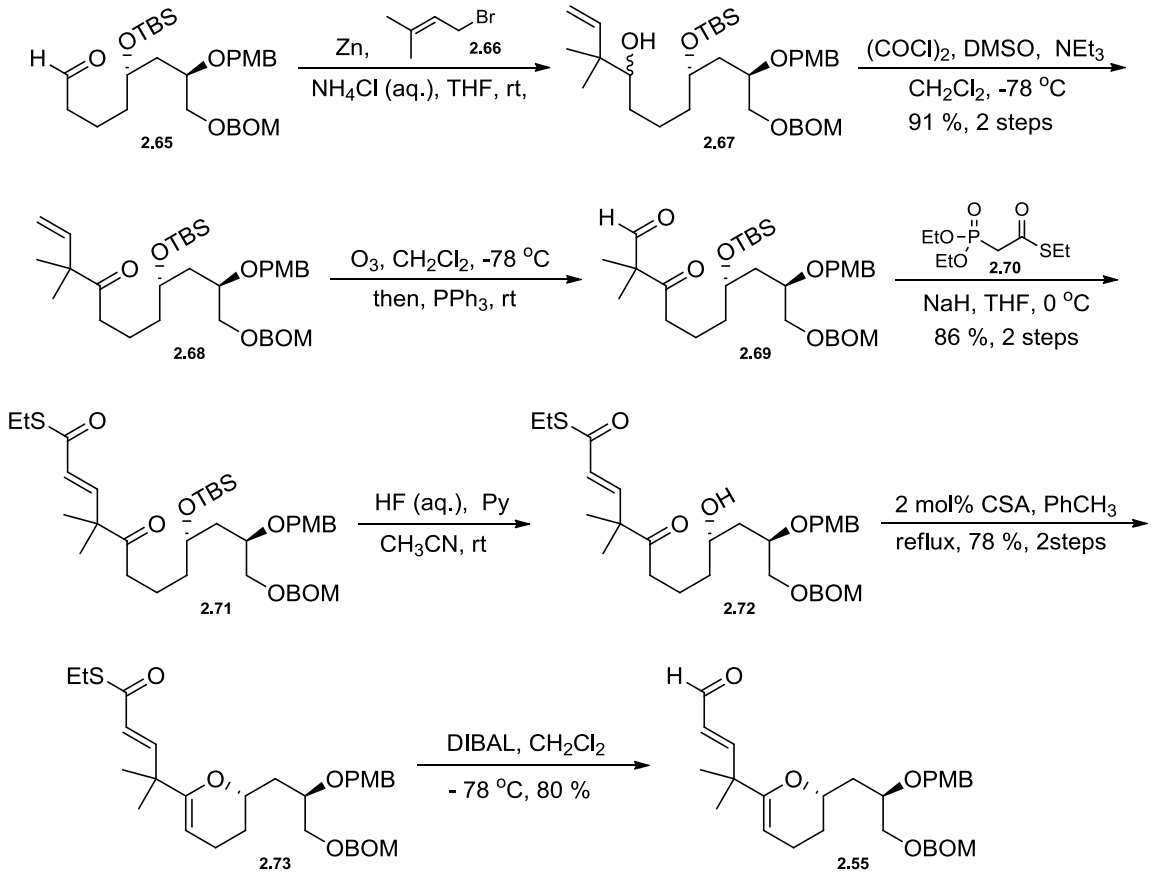


Figure 2.14 Retrosynthetic Plan of Des-Methyl Analogue

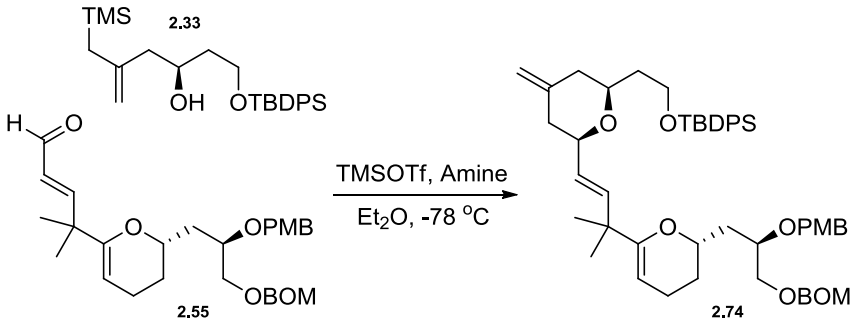


Scheme 2.6 Synthesis of Aldehyde **2.65**

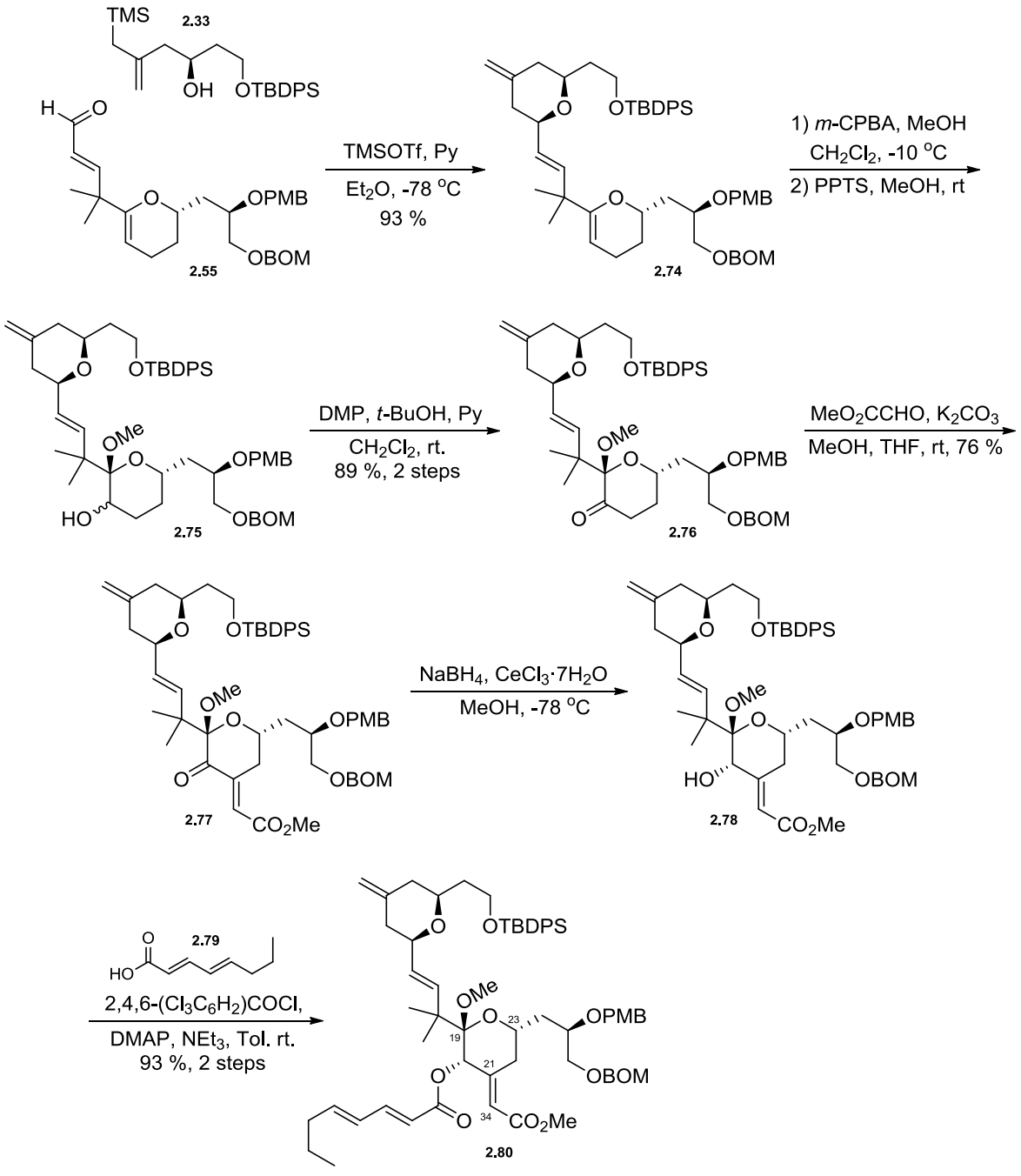


Scheme 2.7 Completion of C-Ring Aldehyde **2.55**

Table 2.3 Optimization of Pyran-Annulation Conditions



Entry	Amines	Amount (respect to aldehyde)	Time	Product(Yield)
1	-	-.	30 min	**2.74** (57%)
2	NEt_3	0.2 equiv	1 h	**2.74** (43%)
3	$^{i}Pr_2NEt$	0.2 equiv	1 h	**2.74** (39%)
4	Py	0.1 equiv	30 min.	**2.74** (79%)
5	Py	0.2 equiv	30 min.	**2.74** (93%)
6	Py	0.3 equiv	30 min.	**2.74** (89%)
7	Py	0.4 equiv	30 min.	**2.74** (59%)
8	Py	0.4 equiv	3 h	**2.74** (87%)
9	Py	0.5 equiv	3 h	**2.74** (26%)



Scheme 2.8 Installation of the B-Ring and Functionalization of the C-Ring

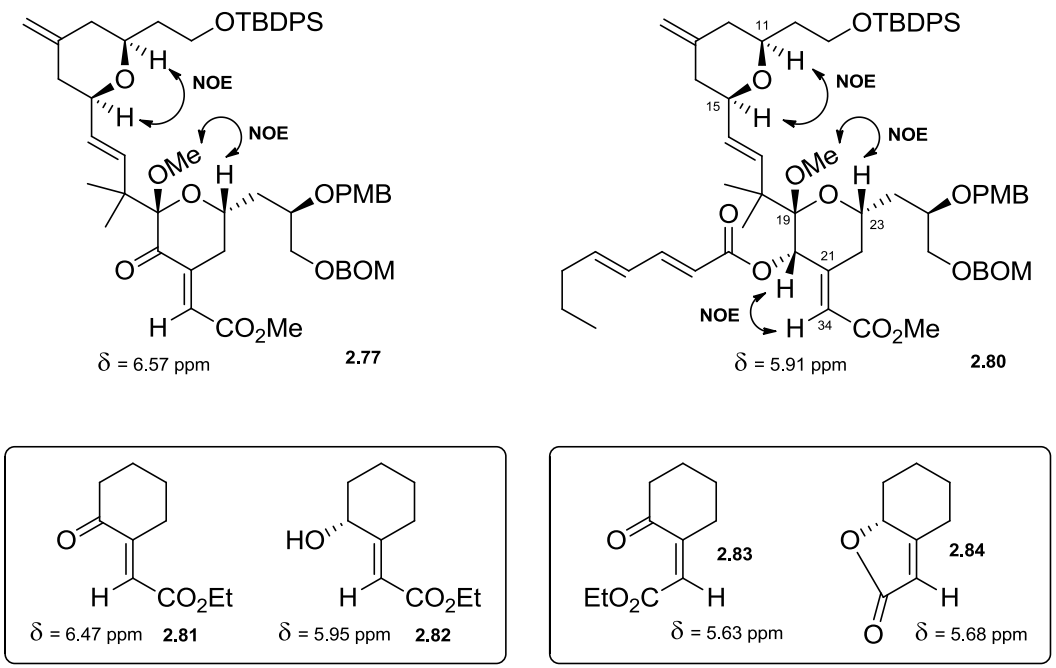
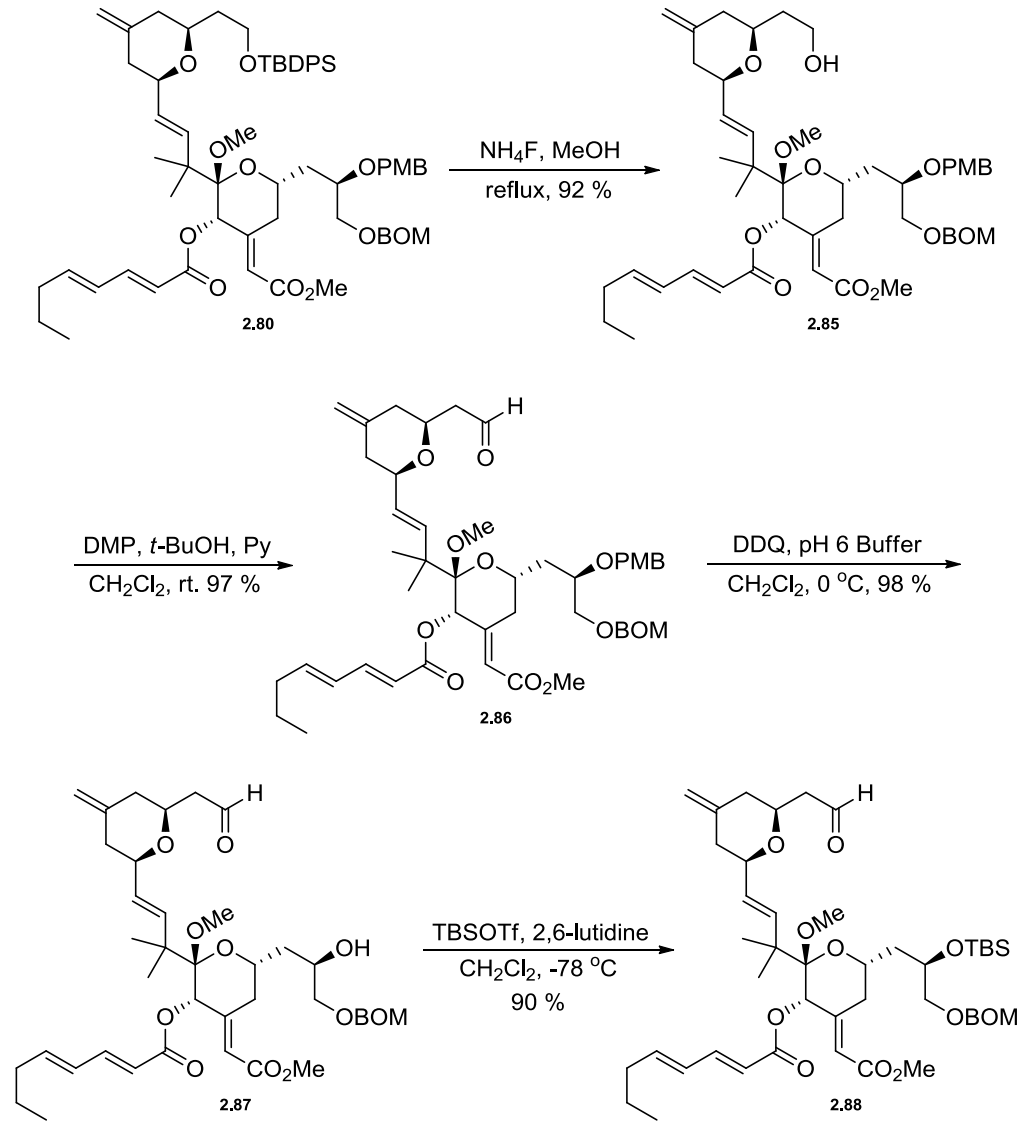
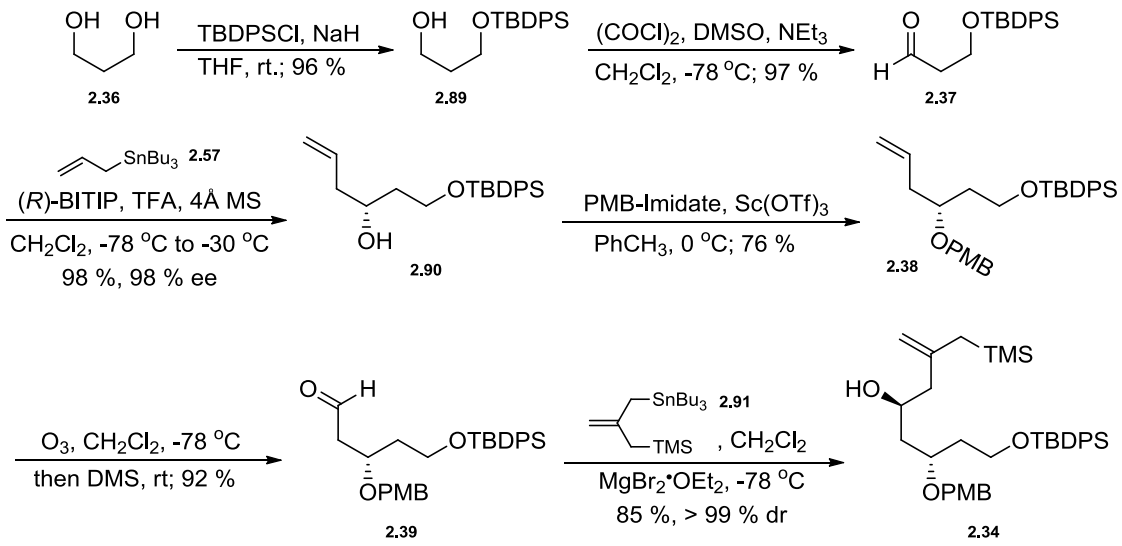


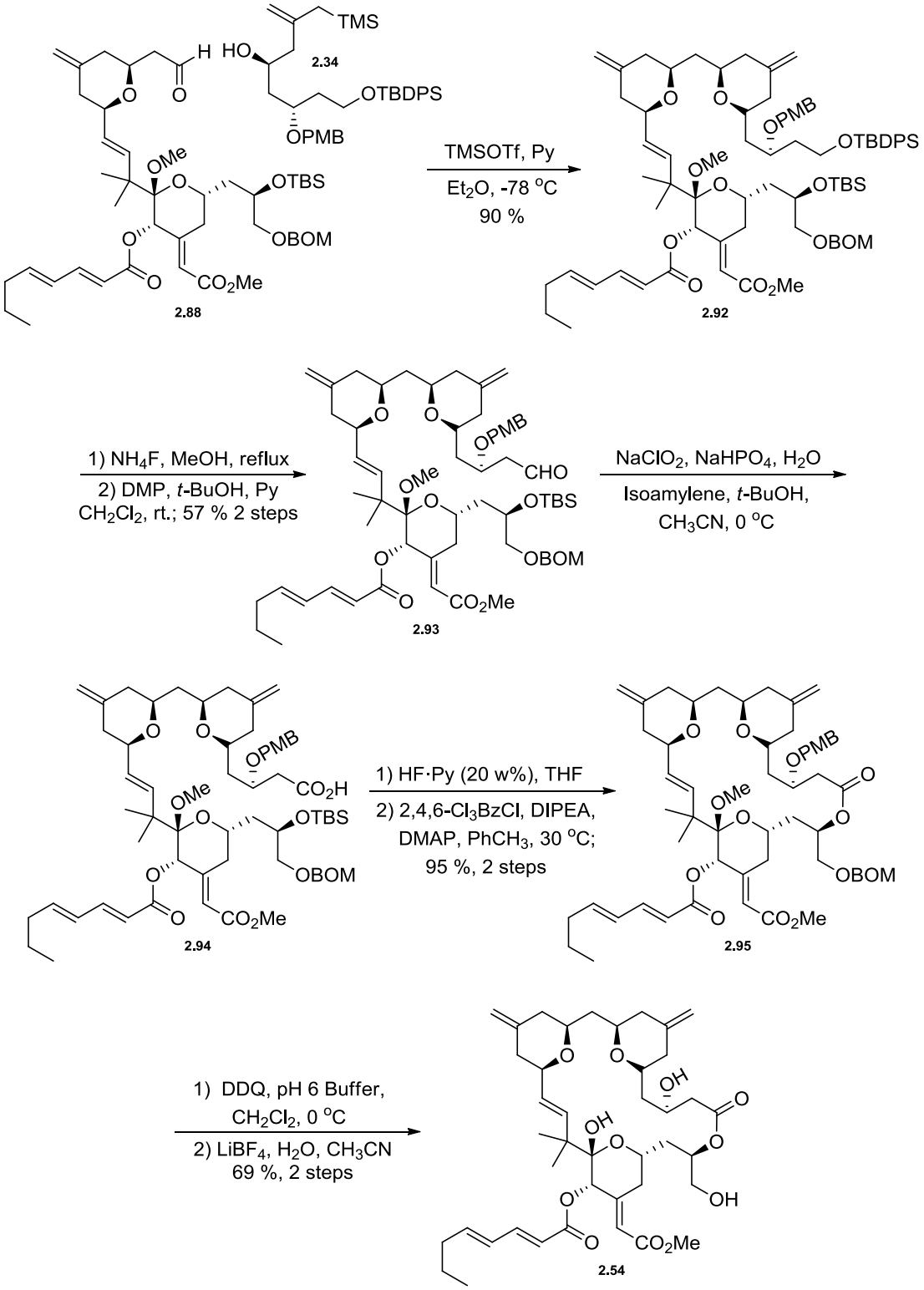
Figure 2.15 Stereochemical and Conformational Relationships



Scheme 2.9 Functional Group Transformation for the Second Annulation



Scheme 2.10 Modified Synthesis of Allylsilane **2.34**



Scheme 2.11 Completion of Des-Methyl Analogue **2.54**

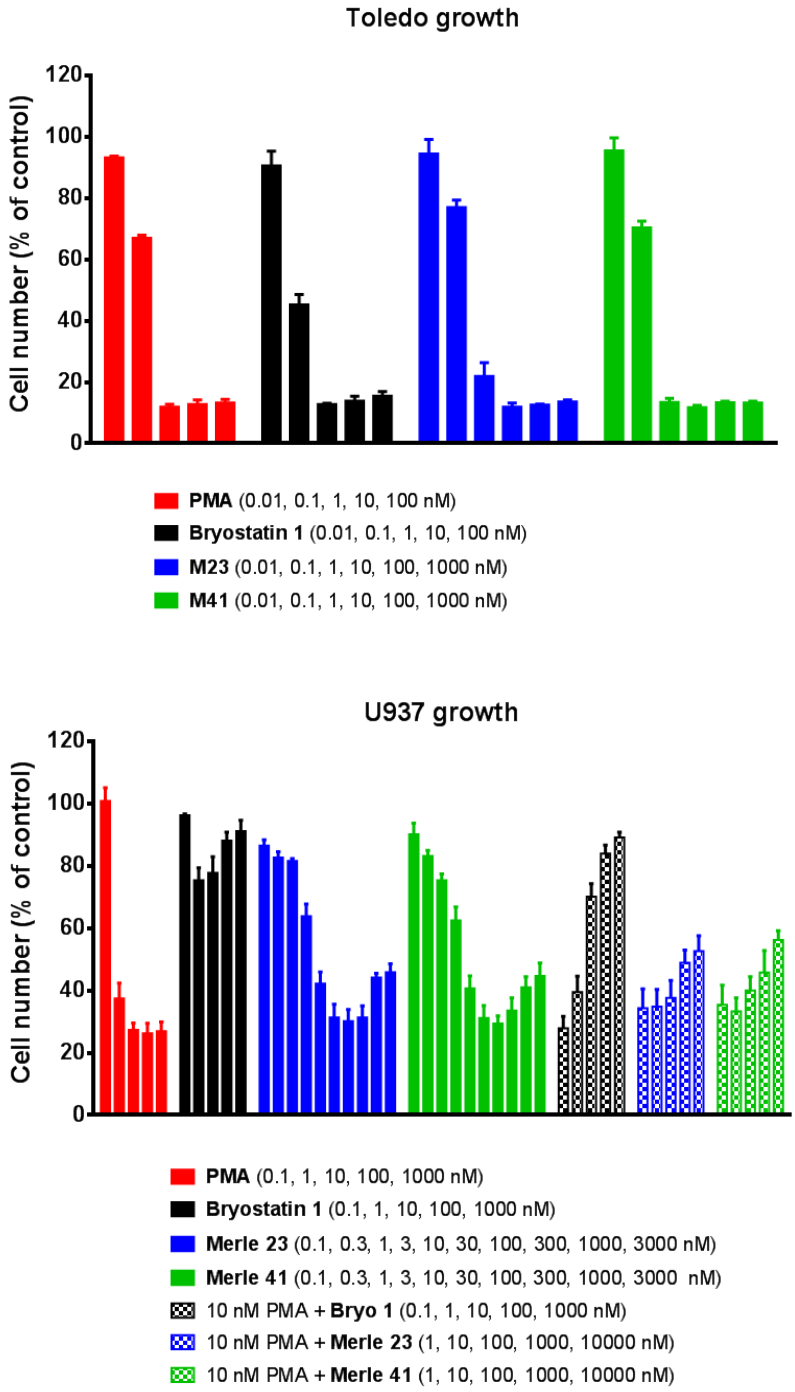


Figure 2.16 Growth Inhibition Assays
on Toledo and U937 Cells with Merle 41 and Merle 23

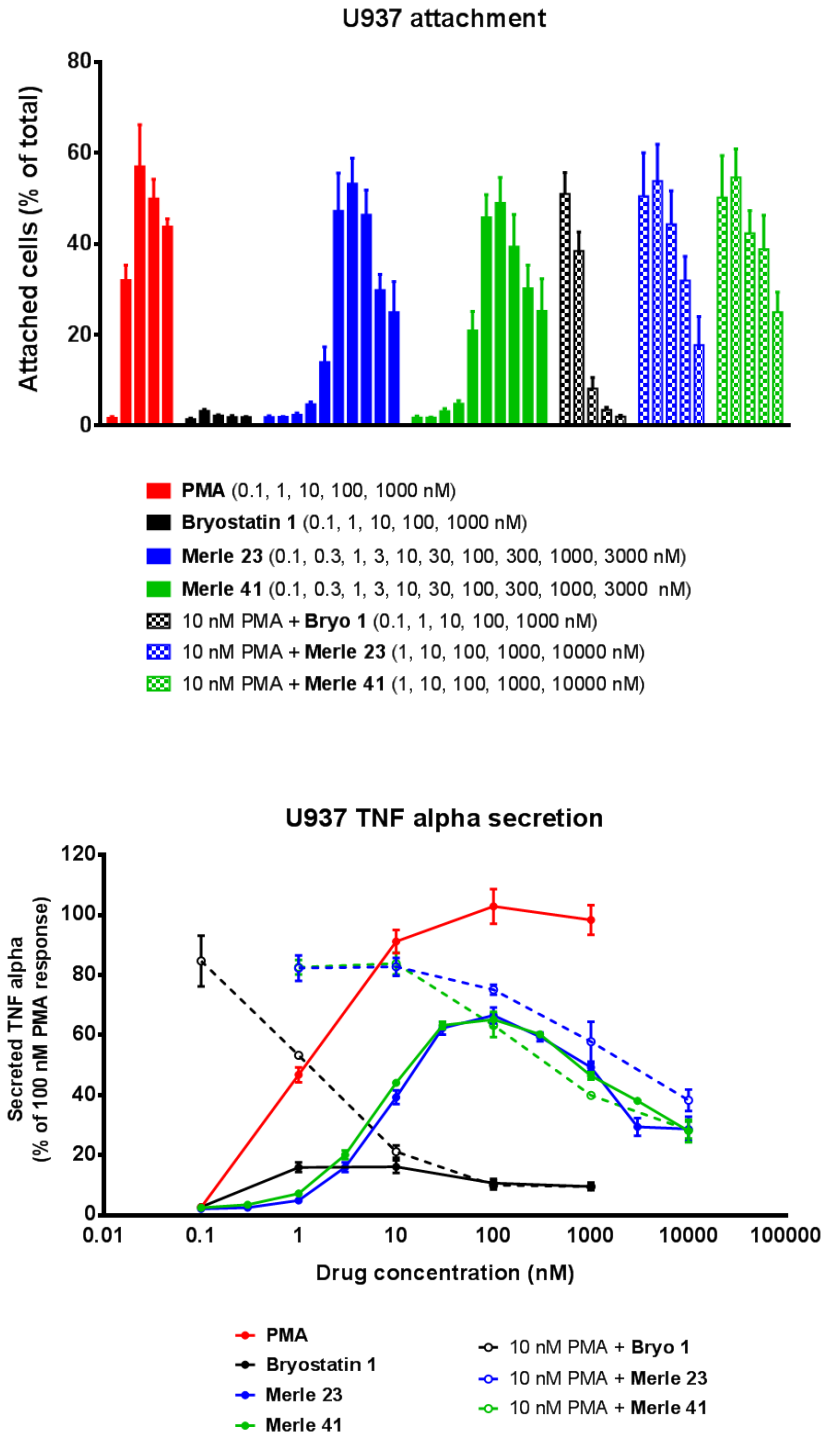


Figure 2.17 U937 Cell Line Attachment and TNF-α Secretion With Merle 41 and Merle 23

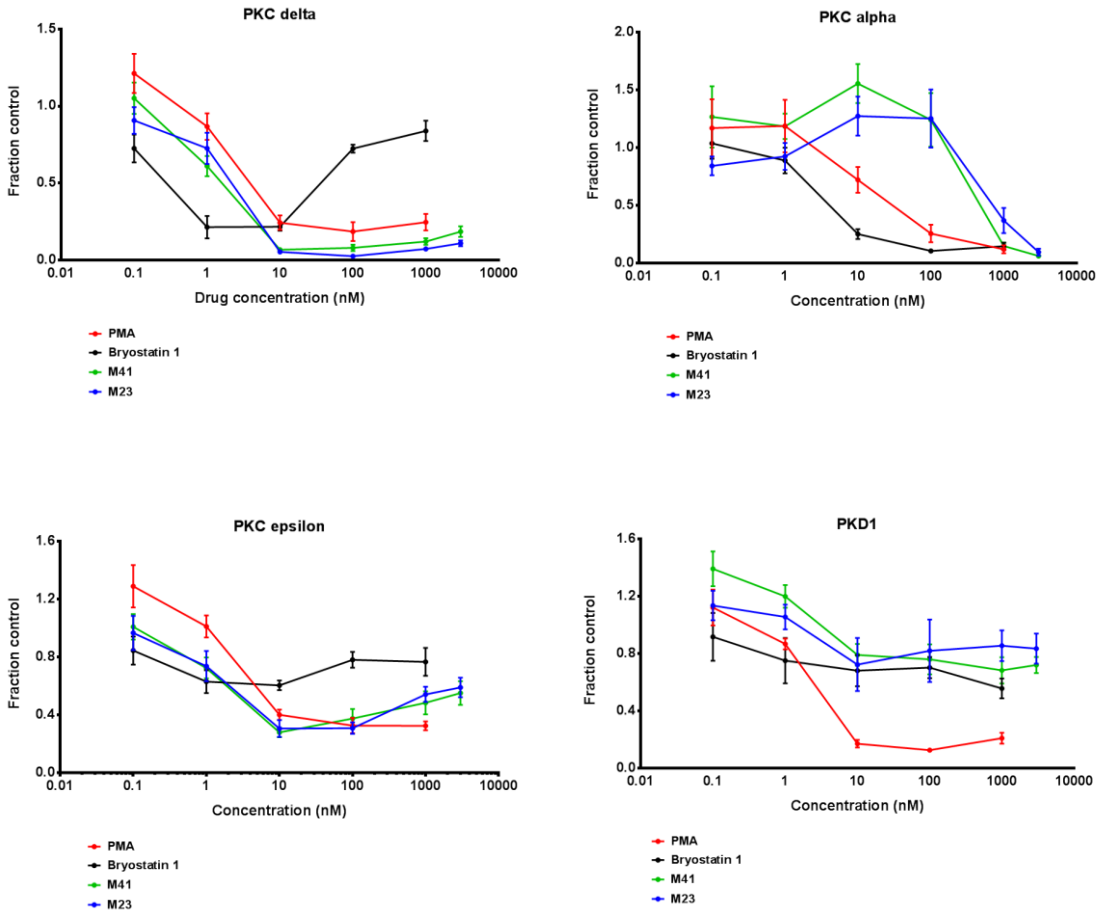


Figure 2.18 Regulation of Protein Kinase Isozymes by Merle 41 and Merle 23

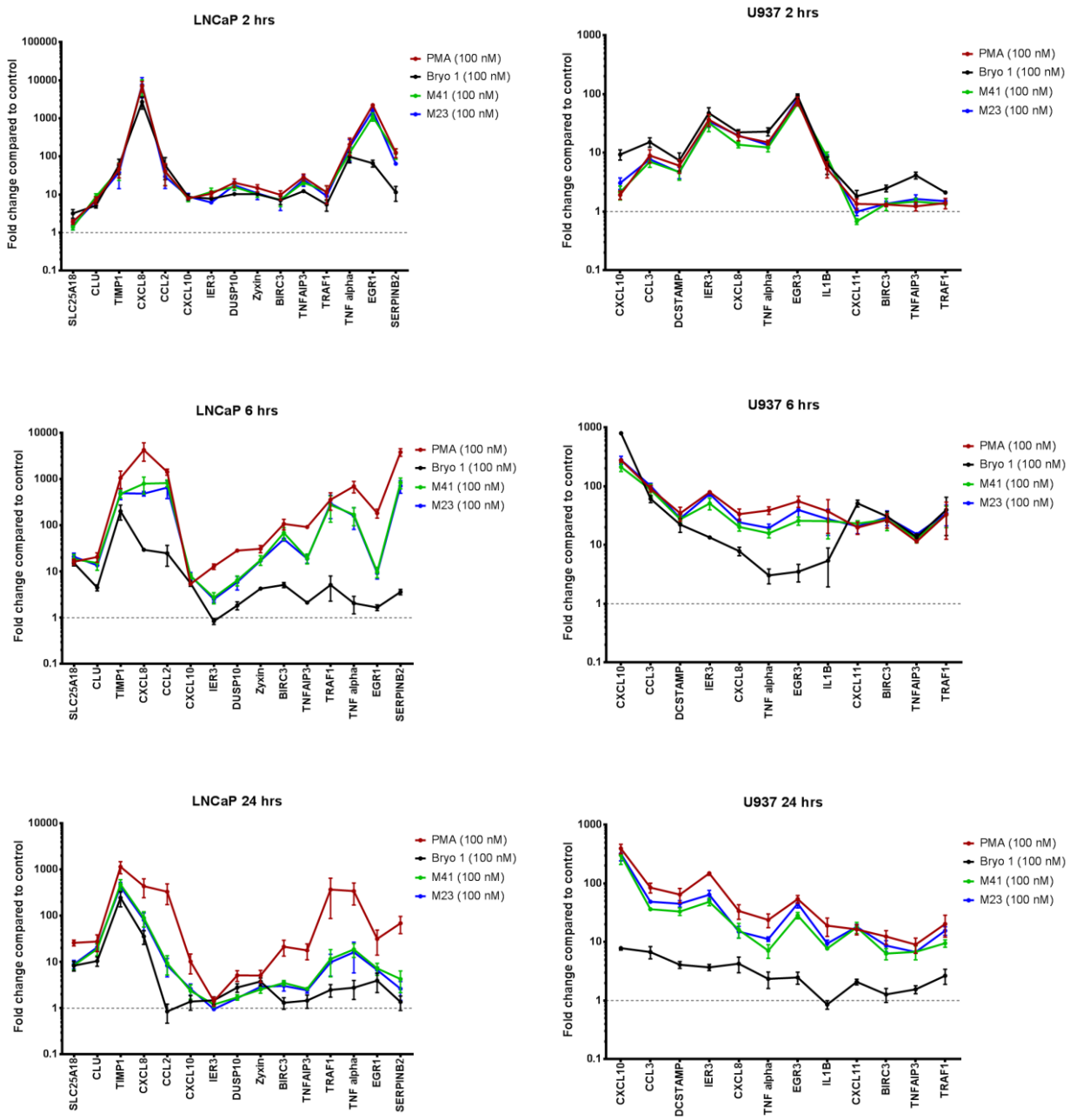


Figure 2.19 Dose Dependence of the Induction of Gene Expression with LNCaP and U937 Cells by Merle 41 and Merle 23

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158. Manuscript is under preparation.

CHAPTER 3

THE DESIGN AND SYNTHESIS STUDY OF THE BRYOSTATIN ANALOGUE WITH C-9 HEMIKETAL

Introduction

Bryostatin 1 is a naturally occurring macrolide lactone isolated from marine organisms. It displays significant and unique antineoplastic activity, and has been a focus of the biological and chemical research community. Bryostatin 1 is a potent modulator of protein kinase Cs (PKCs). PKCs are a group of enzymes that control phosphorylation of proteins. They play fundamental roles in signal transduction pathways that regulate cellular proliferation, differentiation, and apoptosis. Consequently, PKCs are attractive targets for several ailments, such as cancer, Alzheimer's disease, and HIV. As a PKC activator, bryostatin 1 is a promising therapeutic candidate in this area. However, most other PKC ligands demonstrate opposing biological responses. For instance, PMA competes against bryostatin 1 in binding to the cysteine-rich C1 modules of PKCs, but promotes cancers. The detailed mechanism is uncertain.

To identify the mechanism, early research was focused on the binding affinity. Based on a computer model, Wender proposed that the northern hemisphere of bryostatin 1 was a mere "spacer domain" to retain appropriate spatial orientation, and all the pharmacophoric sites were in the southern hemisphere. This hypothesis successfully

helped find out three critical binding sites, which he called a triad. Later, the Keck group and others demonstrated that the *C*-19 hemiketal and *C*-21 exo-enoate were as important as the triad in retaining the potency to PKC. Keeping the southern hemisphere almost intact, the Keck group prepared several bryostatin analogues with a simplified upper half. Their biological properties were evaluated in U937 cell lines and LNCaP cell lines. Rather than displaying bryostatin-like properties, these molecules displayed PMA-like properties. The results revealed that substituents on the A- and B-rings of bryostation 1 are critical elements for bryostatin-like activity.

Biological Properties of Keck's Analogues

As a continual project in our group, the roles of the substituents on the A- and B-rings of bryostatin 1 were investigated. Merle 23 demonstrated a PMA-like pattern in growth inhibition and attachment in U937 cells, and differed from bryostatin 1 only at four positions, namely the *C*-7 acetate, *C*-8 *gem*-dimethyl, *C*-9 hydroxyl and *C*-13 exo-enoate (Figure 3.1).[1] Therefore, a series of bryostatin derivatives was designed, in which the substituents were progressively reintroduced.

Merle analogues used in structural-feature identification are shown in Figure 3.2. Merle 32 differs from Merle 23 in the *C*-8 *gem*-dimethyl group and the *C*-20 side chain.[2] Previously, Merle 22 and 23 already demonstrated that the effect of difference on the side chain was trifling on both binding affinity and biological response.[1] Merle 27 reintroduces the *C*-7 acetate on Merle 23,[3] and Merle 33 further introduces the *C*-13 exo-enoate.[4] In the absence of the *C*-30 carbomethoxy group, Merle 28 is almost a natural bryostatin. The other "almost bryostatin" is Merle 30, which is *C*-9 de-oxy bryostatin.[5]

The binding experiments were performed *in vitro* with mouse PKC-α, and almost all the analogues maintained their binding affinities at the nanomolar level. These binding results are consistent with our understanding of the relationships between the structure and binding affinity, namely that binding largely depends on interactions at the lower half of the molecule and is independent of the A- and B-rings at the upper part.

The relationships between the substitution pattern and biological behavior were investigated using U937 leukemia cell assays, because U937 cells respond to PMA and bryostatin 1 quite differently. PMA inhibited cell growth and increased attachment, whereas bryostatin 1 caused little growth inhibition and attachment (Figure 3.3). Merle 21-23 resembled PMA in both proliferation and attachement.[1] Merle 32, which had an additional nonpolar *gem*-dimethyl group, behaved more as PMA in proliferation, but showed more biphasic properties in attachment.[2] Merle 27 demonstrated that the *C*-7 acetate group alone had little change to the bryostatin-like activity (not shown on Figure 3.3).[3] But with two polar groups, Merle 33 displayed more biphasic nature in both responses and began to resemble bryostatin 1.[4] The two "almost bryostatin" analogues (Merle 28 and 30) and bryostatin 2 closely resembled bryostatin 1.[5,6] The results of the treatments at 72 h are shown in Figure 3.4.[7] Obviously, the substituents on the A- and B-rings altered the biological properties of the molecule. Substitution patterns determined whether the activity was bryostatin-like or PMB-like. The bryostatin-like or PMB-like activity was not all-or-none, and intermediate patterns of activity were also observed. The different extents of bryostatin-like activity indicated that the biological activity could not be ascribed to a single substituent or substituents. It would be the complex integral result of all the substituents.

The effects of these analogues on the induced gene expression of six of the phorbol ester regulated genes were investigated in U937 cells. The genes were treated with the analogues at the concentration of 1000 nM (100 nM in the instance of bryostatin 2). The results were detected by qPCR analysis after 24 hours' treatment. The U937 cells responded to the various analogues to the extents between that of PMA and that of bryostatin 1, or a little below for certain instances (Figure 3.5A).[7] The averaged gene expression data for all of the genes are shown in Figure 3.5B. Similar behavior was observed in the LNCaP cells after 8 hours' treatment with the same concentration (Figure 3.6). Both systems showed a strong correlation between the bryostatin-like patterns of gene expression and the bryostatin-like patterns of biological response, especially in the LNCaP cell lines.[7]

TNF-α secretion is an important contributor to the inhibition of LNCaP cell growth in response to PMA. The same series of analogues were evaluated in the induced secretion of TNF-α in the LNCaP cell lines. PMA induced the most TNF-α secretion, while bryostatin 1 induced the least secretion. All the other compounds induced the secretion at the levels intermediate between that of Merle 23 and bryostatin 1 at 8 h. Similar general behavior was observed in U937 cells. The compounds' effectiveness was shown to be similar in each experiment. This further supported our theory that the substitution patterns on the A- and B-rings had significant effect on the biological activities of the molecule.

Polarity-Lipophilic Hypothesis

Previous study of Blumberg et al. revealed that a phorbol ester binding to PKC did not produce a significant conformational chage within the activator-binding domain.[8] The *C*-

3, *C*-4 and *C*-20 phorbol ester oxygens form hydrogen bonds with the main-chain groups of PKC-δ in the groove of binding. Phorbol binding capped the groove and forms a contiguous hydrophobic surface covering one third of the domain. The long-chain lipid tail of PMA did not interact with PKC in binding, but instead retained itself with the membrane. Thus, the favorable free energy of protein-phorbol binding could be used to drive the insertion of the protein into the membrane. A 2.2 Å resolution X-ray crystal structure demonstrated the clear image of the complex of a murine PKC-δ and PMA. It unambiguously exhibited that PMA sits in the binding groove with the long continuous hydrophobic surface extending over one third of the complex protein (Figure 2.8).

Modeling studies have revealed a different mechanism of bryostatin 1 binding to PKC. Although bryostatin 1 bound to the same strands of PKC with northern hemisphere capping the top of the groove, it bound to both the C1A and C1B modules of the C1 domain. In contrast, PMA selectively bound to the C1B module. Additionally, PMA caused initial translocation of PKC-δ to the plasma membrane, while the highly oxygenated bryostatin 1 made the translocation of PKC-δ directly to the internal membrane.[9,10] The detailed mechanism is still uncertain; the polarity of the upper part of bryostatin 1 is probably partially responsible for the difference.

Computational modeling suggested that the surface generated by bryostatin 1 at the top of the C1 domain was different from that generated by PMA. This surface drove novel interactions, whether intramolecular interactions with another portion of the PKC molecule or intermolecular interactions with other enzymes, adapters or PKC substrate. Further computational study of Merle analogues found that the A- and B-ring regions of bryostatin-like analogues were more hydrophilic than the same regions in PMA-like analogues. Based

on the evidence, it is reasonable to assume that the appropriate amount of hydrophilicity in the A and B-rings makes the special surface at the top of C1 domain, which in turn determines the translocalization and protein-protein interactions of the activated PKCs, rendering them unique biological functions.

New-generation analogues are needed to verify this hypothesis. Beyond that, there are several questions. What is the appropriate amount of hydrophilicity? What is the specific role of the substituents on the upper half of the molecule? Or, are there conformation requirements for the northern hemisphere? Actually, the des-A ring analogue Merle 29u acted as PMA, but it retained high binding affinity and comparable hydrophilicity to Merle 33 (Figure 3.2).[11] In addition, Merle 34 and Merle 38, which were expected to behave more towards bryostatin 1, turned out to be PMA-like analogues.[12] In these instances, the absence of the rigid B-ring was suspected to be the reason.

Sythetic Efforts towards the *C*-9 Hemiketal Analogue

The hemiketal hydroxyl group is the most polar group in the upper half of the natural molecule. As a free hydroxyl group, it is also a hydrogen bond donor. Therefore, it not only increases the hydrophilicity of the molecule but also might alter the conformation via H-bonding. To validate the polarity-lipophilic hypothesis, the analogue with the *C*-9 hemiketal hydroxyl group was designed. Besides investigating the role of this functional group, we also wish to provide a convergent and efficient synthetic route to access analogues containing hemiketal moiety, in particular the SmI_2-mediated cyclization strategy.

SmI_2-Medicated Cyclization Strategy

Previously, our lab developed a strategy to achieve a 2-alkoxytetrahydropyran ring via an acylation-reductive cyclization sequence (Scheme 3.1).[13] The initial reaction in this sequence is to access chiral homoallylic alcohol **3.3**. Taking advantage of the well-established Keck's catalytic asymmetric allylation reaction, either enantiomeric **3.3** is obtainable in high yield with excellent enantioselectivity. After an esterification reaction, the resulting allyl chloride **3.4** is converted to the more reactive allyl iodide **3.5** by halogen exchanging with Finkelstein's protocol.[14] The allyl halide serves as a "stored" allyl carbanion, which is available with SmI_2 under almost neutral conditions. Then, the diastereomeric mixture hemiketal **3.6** is protected as a relatively stable ketal **3.8** in alcohol via an oxocarbenium intermediate **3.7**. Both the anomeric effect and stereoelectronic effect favor the most thermodynamically stable isomer **3.8**.

Retrosynthetic Plan of Analogue **3.9**

The retrosynthetic analysis of analogue **3.9** is outlined in Figure 3.7. To fulfill the goal of using the SmI_2-mediated cyclization strategy, one disconnection was made at the A-ring next to the hemiketal. Once again, the B-ring was planned to be constructed by pyran-annulation. Yamaguchi esterification was designed to link the upper and lower halves together at the other site. Therefore, the analogue **3.9** was disconnected into three equally important segments, namely **3.10**, **3.11**, and **3.12**. Based on experience learned from model studies, the SmI_2-mediated cyclization was planned to be applied at a late stage, since the reaction conditions were almost neutral. To the best of our knowledge by that time, ketals, esters, and a wide variety of protecting groups were inert to SmI_2 reductant in the absence

of any additive at room temperaute.[15] We wished to take advantage of its chemoselectivity to avoid protecting group replacements. Another reason for this disconnection was to obtain the maximum benefits from the previous synthetic work.

Enal aldehyde **3.10** was prepared with the previous route described in Chapter 2, but using modified and scaled approaches with easier manipulations. Allylchloride **3.12** was prepared from the advanced intermediate **2.39**. The route to *β*-hydroxyallylsilane **3.11** was revised, and started with the commercially available compound (*S*)-(+)-aspartic acid **3.14**. In the previous route, at least 2 equivalents of *β*-TMSmethyl-allylstannane **2.21** were required to force the CAA reaction into completion, or the product **3.11** could not be isolated from the starting materials. In addition, **2.21** was in turn prepared from *β*-hydroxyallylsilane over four steps. Last, the revised route was more environmentally friendly.

Results and Discussion

The synthesis of aldehyde **3.21** began with protection of the commercial chiral compound **3.13** with BOMCl under solvent-free conditions (Scheme 3.2). The BOMCl was prepared freshly as previously described, and the sterically hindered Hünig's base was utilized to prevent epimerization. Ester **3.14** was reduced into aldehyde **3.15** in an almost quantitative yield. A chelation-controlled allylation reaction provided the anti-Felkin product **3.16** as a single diastereomer.[16] It was protected by PMB-Br and oxidatively cleaved with ozone to furnish aldehyde **3.18**, which was in turn subjected to a second allylation reaction. Though both chelation-controlled and nonchelation-controlled 1,3-induction allylation favored the same stereoselectivity,[17,18] for some reason only a

moderate diastereomeric selectivity was obtained with a variety of chelating and nonchelating *Lewis* acids. The best result was achieved with $MgBr_2 \cdot OEt_2$ to afford 6-7:1 selectivity, favoring the desired isomer **3.19**. After a TBS protection, the olefin **3.20** was elongated into terminal aldehyde **3.21** by hydroformylation.[19]

Using zinc dust instead of indium metal, prenylation afforded alcohol **3.22** as a diasteromeric mixture (Scheme 3.3).[20,21] In addition, the usage of relatively expensive prenyl bromide was also cut in half. After a normal workup, no chromatography was further needed. This racemic mixture of alcohol was then converted to ketone **3.23** by Swern oxidation in 95% yield over two steps.[22] The olefin was oxidatively cleaved by ozonolysis. Since the intermediate **3.24** was partially decomposed on silica gel, by-product triphenylphosphine oxide was largely removed from the reaction as precipitate using 1: 4 Et_2O/Hexanes solvent system. Next was a Horner-Emmons reaction.[23] Thiophosphonoacetate was used at this point, because an α,β-unsaturated thioester, in contrast to an α,β-unsaturated alkoxyl ester, could be reduced to *α,β*-unsaturated aldehyde with DIBAL. Subsequently, the crude product **3.24** was subjected to a Horner-Emmons reaction, and the desired α,β-unsaturated thioester **3.25** was obtained as a single geometrical isomer in 93% yield over two steps. Then, the TBS protecting group was removed with aqueous HF buffered by pyridine, and a dehydrative cyclization reaction was performed with CSA in toluene at reflux to afford **3.27** with 86.3% yield over two steps. The major by-product in this step was spiral ketal, which came from the hemiketal intermediate. Finally, enal **3.10** was furnished by DIBAL half-reduction.

An attempt of olefin metathesis was also made to install the *C*16-17 internal olefin directly from olefin **3.23**.[24,25] Unfortunately, using Grubbs' II catalyst, this reaction failed

with acrylic ester under various conditions, including with *L*ewis acids at elevated temperature. A wide variety of reagents, such as crotonic esters, protected allylic alcohol and protected crotyl alcohol, were also under investigation but with no success. Fortunately, **3.23** was able to be recovered in most situations. This also implied that **3.23** was inert to the catalyst because of the sterically hindered *gem*-dimethyl group. A similar obstacle was reported by Thomas et al.[26] In their bryostatin analogue synthesis, ring-closure metathesis was designed to complete macrocyclization at a late stage. Compound **3.28** did not undergo ring-closure metathesis with Grubbs' II, Hoveyda, or Schrock catalysts, but destroyed the olefin connecting to the tetrahydropyran B-ring (Figure 3.8). Later, compound **3.30** without *gem*-dimethyl group at *C*-18 was prepared, and it was successfully macrocyclized with Grubbs' II catalyst.

In the revised route, β-hydroxylallylsilane **3.11** was prepared from the commercially available (*S*)-aspartic acid **3.14**. It was converted to bromosuccinate **3.32** by HNO_2-mediated deamination in the presence of potassium bromide (Scheme 3.4).[27] Its configuration was completely retained under the aid of neighboring group participation of the α-carboxyl group.[28] Diacid **3.32** was subsequently reduced to the corresponding diol **3.33** with borane-DMS complex in almost quantitative yield. Using the modified Rapoport's protocol, the oxirane **3.34** was obtained by one-pot reaction of epoxidation and silyl ether protection in sequence.[27] The freshly prepared Grignard reagent derived from **3.35**[29] attacked the less hindered site of the oxirane to afford the allylsilane compound **3.11**. All the physical data matched those of the compound prepared from the previous route.

With both enal **3.10** and β-hydroxyallylsilane **3.11** in hand, the simplified B-ring was furnished by pyran annulations in presence of a catalytic amount of pyridine (Scheme

3.5).[30] The excess of allylsilane **3.11** was recovered by chromatography. The *syn*-relationship between the *C*-11 proton and the *C*-15 proton was proved by NOESY1D experiment. Epoxidation with *m*-CPBA in methanol followed by epimerization with PPTS provided alcohol **3.37** in 90% yield over two steps. This alcohol was then oxidized to ketone **3.38** by DMP in quantitative yield.[31]

Prior to Dess-Martin perodinane (DMP), several other oxidants were attempted to oxidize **3.37** into **3.38**. TPAP-NMO,[32] which achieved success in almost all our analogue syntheses, but surpringly failed to do so at room temperature, as did TEMPO-BAIB oxidation.[33] A variety of activated DMSO oxidations suffered from either incomplete reactions, such as Parikh-Doering,[34] Swern[35] and Corey-Kim,[36] or being accompanied with significant side products, such as Albright-Goldman oxidation.[37] Both PCC[38] and PDC[39] could complete the transformation with approximately 80% yield after 10 hours. The best result was obtained with DMP, which provided the desired product in quantitative yield after 1 hour. The IBX, the precursor of DMP, had no success in this transformation.[40]

Next, aldol condensation with freshly distilled methyl glyoxylate afforded the exclusive *E*-geometrical isomer **3.39** in presence of K_2CO_3. At this point, the *syn*-relationship between the *C*-19 methoxy group and the *C*-23 proton was confirmed by NOESY1D experiment. A Luche reduction reaction followed by an esterification reaction provided the compound **3.41**.[41] The *E*-geometry of the *C*-21 exocyclic enoate was confirmed by NOE experiment. In addition, the chemical shift variation of the enoate proton was consistent with its own geometry.

Synthesis of allylchloride **3.12** was from the intermediate **2.39** (Scheme 3.6). A chelation-controlled allylation reaction of aldehyde **2.39** provided chiral *β*-hydroxyl

allylchloride **3.42** in 79% yield and 97% diastereomeric selectivity. This reaction set the desired stereochemistry at the newly formed chiral center, which was proved by Mosher ester analysis later. Next, the hydroxyl group of **3.42** was protected as a TBS ether, and the primary TBDPS ether was selectively cleaved with NH_4F in MeOH at 60 ^oC.[42] The newly liberated alcohol **3.44** was converted to carboxylic acid **3.12** in two sequential oxidations.[43]

Before the combination of **3.12** and **3.41**, some minor modifications were made on the latter segment (Scheme 3.7). The deprotection of the TBDPS ether followed by a DMP oxidation reaction converted the silyl ether **3.41** to a corresponding aldehyde. Then, DDQ-mediated deprotection of PMB-ether liberated the alcohol at C-25 to afford **3.48** in 93% yield.

Next, the alcohol **3.48** was esterified with **3.12** under Yamaguchi esterification conditions to afford compound **3.49** in 92% yield (Scheme 3.8). According to the SmI_2-mediated cyclization strategy, an esterification between *C*-5 and *C*-9 was needed. Therefore, the *C*-9 aldehyde of **3.48** was converted to corresponding acid under Lindgren oxidation conditions,[43] and the *C*-5 TBS-protected alcohol was liberated with pyridine-buffered HF. Using the high-dilution technique, macrolactonization under Yamaguchi esterification conditions was achieved to furnish compound **3.51** in 75% over two steps. Subsequently, the relatively inert allylchloride moiety was converted into more reactive allyliodide **3.52** with Finkelstein's protocol in a straightforward fashion.[44]

Unfortunately, SmI_2-mediated cyclization failed in installing the A-ring on **3.52** under the standard conditions previously developed. The reaction was completed in seconds at room temperature, but only decomposed by-products were obtained. The reaction was then

attempted at -78 ^{o}C, but no desired product was observed. However, using a limited amount of SmI_2, the decomposed *C*-20 side chain was identified. To our great surprise, a crude ^{1}H NMR experiment demonstrated that the allyliodide moiety, which was generally considered more labile, was intact. Further investigations revealed that an elimination reaction occurred in γ-functionalized α,β-unsaturated carbonyl moiety, which was in the C-ring. This elimination reaction was faster than the planned reductive-cyclization reaction. The detailed discussion is in Chapter 1.

Thus, an attempt was made to construct the A-ring via a 1,5-hydroxyketone intermediate. The plan was to furnish a ketone at *C*-11 by an allylation reaction followed by an oxidization reaction. Then the *C*-11 ketone could react with the *C*-7 alcohol to form the desired hemiketal. Several metals, including Mg, Zn, In, Pd, Cr and B, were used in an attempt to accomplish allylation under a variety of conditions. Unfortunately, in the presence of sensitive functional groups on the C-ring, all the attempts failed because of either the decomposition of the C-ring or the dehalogenation of allyl iodide. Additionally, the microscale of this reaction at the late stage of synthesis greatly increased the difficulty of manipulations.

At this point, an attempt was made to make an analogue without an A-ring, which would be used to investigate the effect of the absence of an A-ring on the biological property of bryostatin 1. Then, the PMB group was removed from **3.51** with DDQ, and the resulting compound was treated with $LiBF_4$ in aqueous acetonitrile at reflux. The final product, **3.56**, was unexpected and more complex. After $LiBF_4$ treatment, the BOM group was removed. Instead of staying as free hydroxyl, the newly liberated alcohol at *C*-26 expanded the macrolactone via transesterification. It released the *C*-25 hydroxyl, which in

turn underwent a Michael addition reaction with exocyclic enoate at *C*-21 to form a fused 6-membered ring. Meanwhile, the *C*-19 methoxy group was eliminated to furnish a glycal moiety.

Because the *C*-26 hydroxyl, which is part of an ester, does not exist as a free alcohol, it cannot bind to PKCs. In addition, the elimination of the *C*-19 hemiketal results in the loss of H-bond, which is critical in retaining the optimized conformation of the molecule for binding. Thus, **3.56** is not potent to PKCs. It is proved by the binding affinity, and no further biological evaluation is needed.

Conclusion

Previous bryostatin analogues demonstrated that the substation patterns on the A- and B-rings determined the biological profiles of the molecules. To investigate the role of the *C*-9 hemiketal and to verify the polarity-lipophilic hypothesis, analogue **3.9** with the *C*-9 hemiketal group was designed. In the designed route, the SmI_2-mediated cyclization developed in our lab was the key step to install the A-ring at the late stage. Unfortunately, it failed in the attempts because of the elimination of the *C*-20 side chain. The failure also led us to a discovery of an unreported reaction, which could be applied to deconjugation. Its scope of application was further investigated.

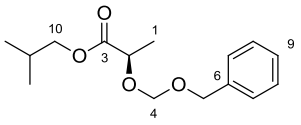
An absent A-ring analogue was finally produced. In the absence of A-ring, the normal size macrolactone was expanded under the deprotection conditions. This was probably due to the favorable conformation for the transesterification. Since the *C*-26 alcohol was part of an ester, the whole molecule lost PKC potency. This negative result also proved the C-26 alcohol was a critical binding site to PKC.

The role of C-9 hemiketal in the biological activity of bryostatin 1 is still of interest. It will help us understand the mechanism of how bryostatin 1 regulates PKCs. Thus analogue **3.9** is still an important analogue to synthesize. A revised convergent route accessing to **3.9** is needed for future synthesis.

Experimental Section

All solvents were dried and distilled according to the guidelines in *Purification of Laboratory Chemicals, 6th Ed.* (Armarego and Chai, Butterworth-Heinemann: Oxford, U.K., 2009). Diisopropylamine, diisopropylethylamine, triethylamine, pyridine, dichloromethane and ethyl acetate were distilled from CaH_2 under an atmosphere of N_2. Ether solvents (THF and Et_2O) were distilled under N_2 from sodium benzophenone ketyl. Benzene and toluene were distilled from molten sodium metal under N_2. Solvents and reagents were deoxygenated where necessary by Freeze-Pump-Thaw technique and refilled with nitrogen prior to use. Titanium tetrachloride and titanium isopropoxide were distilled prior to use. Deuterated solvents were purchased from Cambridge Isotope Laboratories (all ≥ atom% D). Reagents were purchased from Acros, Aldrich and Alfa, and used as received unless stated otherwise. Argon, oxygen, and syngas (1:1 mixture of H_2 and CO) were acquired from Airgas and used as received. Glassware for reactions was oven dried at 110 ^oC for 4 hours and cooled down under a dry atmosphere prior to use, or flame-dried under an atmosphere of N_2. All air- and moisture-sensitive manipulations were performed by using oven-dried glassware, standard Schlenk techniques and glovebox under an atmosphere of N_2. Analytical thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} plates eluting with the solvents indicated, visualized by exposure

to UV light (254 nm), and stained with either an ethanolic solution of 12-molybdophosphoric acid or a solution of $KMnO_4/K_2CO_3/NaOH$. Organic solutions were concentrated on a rotovap at aspirator pressure at 20-30 ^oC. Flash column chromatography was performed on SiliaFlash® F60 silica gel (230-400 mesh, 60Å), and eluted with solvents indicated. Melting points were recored using open capillary tubes on a Mel-Temp electrochemical melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) spectra were acquired on a Variann Inova 500 spectrometer operating at 500 MHz and 125 MHz for ^1H and ^{13}C separately. All ^1H NMR chemical shifts were quoted in parts per million (ppm) relative to the line of the $CDCl_3$ residual singlet at 7.27 ppm (or the C_6D_6 residual singlet at 7.16 ppm), and ^{13}C NMR chemical shifts were relative to the center line of $CDCl_3$ triplet at 77.23 ppm (or the center line of C_6D_6 triplet at 128.62 ppm). Multiplicities in the ^1H NMR spectra were described as follows: s = singlet, d = doublet, t = triplet, q = quartet, ABq = AB quartet, quin = quintet, sext = sextet, m = multiplet, br =broad. Coupling constants were reported in Hz. The structural assignments of ^1H and ^{13}C NMR spectra were elucidated with the aid of gCOSY, gDQCOSY, TOCSY, DEPT, HMQC and HMBC experiments. Stereochemical assignments were based on coupling constants where possible, and with the aid of NOSEY1D, ROSEY1D, NOSEY and ROSEY experiments. AA'BB' systems were reported as doublets. Infrared (IR) spectra were recored from a Perkin Elmer FT-IR Paragon 1000 PC spectrometer using a thin film supported between NaCl plates. Optical rotations were acquired on a Perkin Elmer Model 343 polarimeter using Na D-line with a 10 cm path length micro cell at 20 ^oC from $CHCl_3$ solutions. Ozone was generated by a Welsbach model T-816 generator. Yields refer to purified and spectroscopically pure compounds.



Isobutyl (*R*)-2-(Benzyloxy)methoxypropionate (3.14): To a solution of commercial available isobutyl (*R*)-(+)-lactate **3.13** (25.0 mL, 0.161 mol, 1.0 equiv) in freshly distilled *N, N*-diisopropylethylamine (84.2 mL, 0.483 mol, 3.0 equiv) was added benzyl chloromethyl ether (33.2 mL, 0.242 mol, 1.5 equiv) dropwise via syringe at 0 ^{o}C. This reaction was allowed to warm to room temperature and stirred under an atmosphere of N_2 for 24 hours. It was then quenched with 1N HCl solution (150 mL). The aqueous layer was extracted with ethyl ether (3 x 30 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solution was filtrated, and concentrated in vacuo. The yellow crude product was purified by flash chromatography on silica gel eluting with 1-3 vol% of ethyl acetate in hexanes to provide the tilted compound (40.2 g, 0.151 mol, 93.8% yield) as a yellowish oil.

TLC: R_f = 0.54 (EtOAc/Hex = 3:7, v/v);

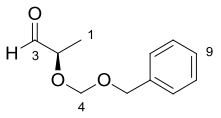
$[\alpha]_D^{20}$ +67.3 (*c* 1.946, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$): δ 7.41-7.27 (m, 5H, ***H-7***, ***H-7'***, ***H-8***, ***H-8'***, ***H-9***), 4.85 (s, 2H, ***H-4***), 4.66 (s, 2H, ***H-5***), 4.33 (t, *J* = 6.8 Hz, 1H, ***H-2***), 3.98-3.83 (m, 2H, ***H-10***), 2.02-1.86 (m, 1H, ***H-11***), 1.45 (d, *J* = 6.8 Hz, 3H, ***H-1***), 0.93 (d, *J* = 6.7 Hz, 6H, ***H-12a***, ***H-12b***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 173.3 (***C-3***), 137.9 (***C-6***), 128.6 (***C-8***, ***C-8'***), 128.1 (***C-7***, ***C-7'***), 127.9 (***C-9***), 94.1 (***C-4***), 71.8 (***C-2***), 71.1 (***C-10***), 70.1 (***C-5***), 27.9 (***C-11***), 19.2 (***C-12a***), 19.2 (***C-12b***), 18.8 (***C-1***);

FTIR (neat): ν_{max} 2963, 2893, 1750, 1456, 1379, 1275, 1176, 1121, 1081, 1050, 989, 740, 699 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{15}H_{22}O_4Na$ 289.1416; found 289.1412.



(*R*)-2-(Benzyloxymethoxy)propanal (3.15): To a solution of ester **3.14** (4.44 g, 16.7 mmol, 1.0 equiv) in CH_2Cl_2 (170 mL, 0.1 M) was introduced DIBAL solution (1.0 M in CH_2Cl_2, 20.0 mL, 20.0 mmol, 1.2 equiv) by a syringe pump at 15 mL/h at -78 ^oC under an atmosphere of N_2. When the reaction was completed (monitored by TLC), methanol (10 mL) was added to quench this reaction by a syringe pump at 15 mL/h at -78 ^oC. The cold bath was then removed. A saturated Rochelle's salt solution (50 mL) was added, and the mixture was stirred vigorously overnight (ca. 8 hours). The separated aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude colorless oil was purified by flash chromatography on silica gel eluting with 8-10 vol% of ethyl acetate in hexanes to provide the titled compound (3.215 g, 16.55 mmol, 99.3% yield) as a colorless oil.

TLC: R_f = 0.36 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +12.7 (*c* 1.99, $CHCl_3$);

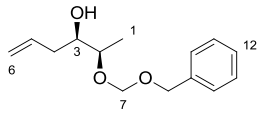
500 MHz ^{1}H NMR ($CDCl_3$): δ 9.66 (d, *J* = 1.5 Hz, 1H, ***H-3***), 7.42-7.28 (m, 5H, ***H-7***, ***H-7'***, ***H-8***, ***H-8'***, ***H-9***), 4.88 (s, 2H, ***H-4***), 4.69 (ABq, *J* = 12.0 Hz, $\Delta\nu$ = 22.7 Hz, 2H, ***H-5***), 4.12 (qd, *J* = 7.0, 1.5 Hz, 1H, ***H-2***), 1.34 (d, *J* =7.0 Hz, 3H, ***H-1***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 202.7 (***C-3***), 137.5 (***C-6***), 128.7 (***C-8***, ***C-8'***), 128.1 (***C-9***), 128.0 (***C-7***, ***C-7'***), 94.4 (***C-4***), 78.4 (***C-2***), 70.3 (***C-5***), 15.5 (***C-1***);

FTIR (neat): ν_{max} 3065, 3033, 2938, 2892, 2813, 2718, 1737, 1498, 1454, 1380, 1176, 1108, 1042, 909, 741 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{11}H_{14}O_3Na$ 217.0841; found 217.0847.

(2*R*,3*R*)-2-(Benzyloxymethoxy)hex-5-en-3-ol (3.16):



To a solution of aldehyde **3.15** (3.616 g, 18.62 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL, 0.2 M) was added $MgBr_2 \cdot OEt_2$ (9.62 g, 37.3 mmol, 2.0 equiv) in one portion. This reaction was then stirred at room temperature for 20 minutes under an atmosphere of N_2. It was cooled down to -15 ^oC, and allyltributyltin **2.59** (6.9 ml, 22 mmol, 1.2 equiv) was introduced dropwise via syringe. It was stirred for a further 6 hours, then quenched with saturated $NaHCO_3$ solution (100 mL) at -15 ^oC. This reaction was allowed to warm to room temperature. The aqueous layer was extracted with ethyl ether (3 x 30 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solution was filtrated and concentrated by rotary evaporation. The residue was dissolved in acetonitrile (150 ml), and washed with hexanes (50 mL). The solution of acetonitrile was concentrated to provide a colorless oil. The crude product was purified by flash chromatography on silica gel eluting with 0-6 vol% of acetone in hexanes to provide titled compound (3.982 g, 16.85 mmol, 90.5% yield, single diastereomer) as a coloress oil.

TLC: R_f = 0.32 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ -31.9 (*c* 0.765, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$): δ 7.39-7.29 (m, 5H, ***H-10***, ***H-10'***, ***H-11***, ***H-11'***, ***H-12***), 5.91 (dddd, *J* = 6.5, 7.6, 10.3, 17.1 Hz, 1H, ***H-5***), 5.15 (dddd, *J* = 1.2, 1.5, 1.5, 17.1 Hz, 1H, ***H-6a***), 5.12 (dddd, *J* = 1.2, 1.2, 1.5, 10.3 Hz, 1H, ***H-6b***), 4.86 (ABq, *J* = 7.3 Hz, $\Delta\nu$ = 20.7 Hz, 2H, ***H-7***), 4.66 (ABq, *J* = 12.0 Hz, $\Delta\nu$ = 17.0 Hz, 2H, ***H-8***), 3.68 (dq, *J* = 5.9, 6.4 Hz, 1H, ***H-2***), 3.56 (dddd, *J* = 4.1, 4.4, 5.9, 8.1 Hz, 1H, ***H-3***), 2.60 (d, *J* = 4.4 Hz, 1H, ***-OH***), 2.38 (ddddd, *J* = 1.2, 1.5, 4.1, 6.5, 14.4 Hz, 1H, ***H-4a***), 2.23 (ddddd, *J* = 1.2, 1.2, 7.6, 8.1,

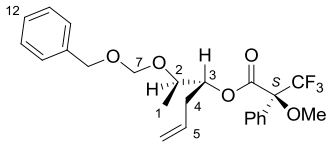
14.4 Hz, 1H, ***H-4b***), 1.24 (d, *J* = 6.4 Hz, 3H, ***H-1***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 137.8 (***C-9***), 134.9 (***C-5***), 128.7 (***C-11***, ***C-11'***,), 128.1 (***C-10***, ***C-10'***), 128.0 (***C-12***), 117.6 (***C-6***), 94.1 (***C-7***), 77.5 (***C-2***), 74.4 (***C-3***), 70.0 (***C-8***), 37.8 (***C-4***), 16.9 (***C-1***);

FTIR (neat): ν_{max} 3461 (br), 3070, 3032, 2977, 2891, 1642, 1497, 1381, 1285, 1208, 1104, 1042, 915, 739, 699 cm^{-1};

HRMS(ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{14}H_{20}O_3Na$ 259.1310; found 259.1311.

Determination of Absolute Configuration of the New Stereocenter of (*2R,3R*)-2-(Benzyloxymethoxy)hex-5-en-3-ol (3.16) via Mosher Ester Method:



(2*R*,3*R*)-2-(Benzyloxymethoxy)hex-5-en-3-yl (*S*)-*α*-Methoxy-*α*-(trifluoromethyl)phenylacetate (3.16-*S*-MTPA): To a screw-capped vial equipped with a stirring bar was added alcohol **3.16** (30.5 mg, 0.129 mmol, 1.0 equiv), (*S*)-(-)-MTPA-OH acid (34.1 mg, 0.143 mmol, 1.1 equiv), DMAP (15.9 mg, 0.129 mmol, 1.0 equiv) and subsequently toluene (2.5 mL, 0.05 M), at room temperature. Freshly distilled NEt_3 (90 uL, 0.65 mmol, 5.0 equiv) was then added to this mixture. This reaction was cooled down to 0 ^oC, 2,4,6-trichlorobenzoylchloride (22.6 uL, 0.142 mmol, 1.1 equiv) was then added dropwise via syringe. The reaction turned cloudy and precipitated immediately. The vial was tightly capped. The reaction was allowed to warm to room temperature slowly, and stirred for 6 hours. Then, the resulting yellow mixture was concentrated and purified by flash chromatography on silica gel eluting with 5-7 vol% of ethyl ether in hexanes to provide the titled compound (56.0 mg, 0.124 mmol, 95.9% yield) as a colorless oil.

TLC: R_f = 0.55 (EtOAc/Hex = 3:7, v/v);

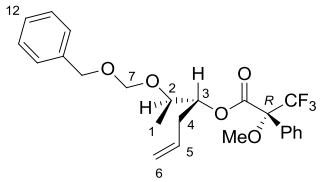
$[\alpha]_D^{20}$ -22.5 (*c* 2.47, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$): δ 7.61-7.53 (m, 2H, ***Ph-2***, ***Ph-2'***), 7.42-7.29 (m, 8H, ***H-10***, ***H-10'***, ***H-11***, ***H-11'***, ***H-12***, ***Ph-3***, ***Ph-3'***, ***Ph-4***), 5.79 (dddd, *J* = 5.9, 7.8, 10.2, 17.1 Hz, 1H, ***H-5***), 5.21 (ddd, *J* = 4.1, 5.9, 8.3 Hz, 1H, ***H-3***), 5.14 (dddd, *J* = 1.5, 1.5, 2.0, 17.1 Hz, 1H, ***H-6a***), 5.12 (dddd, *J* = 1.2, 1.5, 1.5, 10.2 Hz, 1H, ***H-6b***), 4.63 (s, 2H, ***H-7***), 4.53 (ABq, *J* = 11.7 Hz, *Δv* = 18.0 Hz, 2H, ***H-8***), 3.87 (dq, *J* = 5.9, 6.3 Hz, 1H, ***H-2***), 3.58 (s, 3H, ***-OMe***), 2.58 (ddddd, *J* = 1.5, 2.0, 4.1, 5.9, 14.9 Hz, 1H, ***H-4a***), 2.41 (ddddd, *J* = 1.2, 1.5, 7.8, 8.3, 14.9 Hz, 1H, ***H-4b***), 1.12 (d, *J* = 6.3 Hz, 3H, ***H-1***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 166.4 (***C=O***), 137.9 (***C-9***), 133.3 (***C-5***), 132.4 (***Ph-1***), 129.7 (***Ph-4***), 128.6 (***C-11***, ***C-11'***), 128.5 (***Ph-2***, ***Ph-2'***), 128.0 (***C-10***, ***C-10'***), 127.9 (***C-12***), 127.6 (***Ph-3***, ***Ph-3'***), 123.5 (q, $J_{C\text{-}F}$ = 288.7 Hz, ***-CF$_3$***), 118.8 (***C-6***), 94.1 (***C-7***), 84.7 (q, $J_{C\text{-}F}$ = 27.7 Hz, ***-C***C=O), 78.1 (***C-2***), 73.3 (***C-3***), 69.7 (***C-8***), 55.9 (***-OMe***), 34.2 (***C-4***), 16.1 (***C-1***);

FTIR (neat): ν_{max} 3033, 2950, 2361, 1747, 1453, 1267, 1170, 1113, 1081, 1024, 720, 698 cm^{-1};

HRMS(ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{24}H_{27}O_5F_3Na$ 475.1708; found 475.1700.



(2*R*,3*R*)-2-(Benzyloxymethoxy)hex-5-en-3-yl (*R*)-*α*-Methoxy-*α*-(trifluoromethyl)phenylacetate (3.16-*R*-MTPA): To a screw-capped vial equipped with a stirring bar was added alcohol **3.16** (26.5 mg, 0.112 mmol, 1.0 equiv), (*R*)-(+)-MTPA-OH acid (29.2 mg, 0.126 mmol, 1.1 equiv), DMAP (13.9 mg, 0.113 mmol, 1.0 equiv) and subsequently toluene (2.5 mL, 0.05 M), at room temperature. Freshly distilled NEt_3 (80 uL, 0.57 mmol, 5.0 equiv) was then added to this

mixture. This reaction was cooled down to 0 °C, 2,4,6-trichlorobenzoylchloride (19.7 uL, 0.124 mmol, 1.1 equiv) was then added dropwise via syringe. The reaction turned cloudy and precipitated immediately. The vial was tightly capped. The reaction was allowed to warm to room temperature slowly, and stirred for 6 hours. Then, the resulting yellow mixture was concentrated and purified by flash chromatography on silica gel eluting with 5-7 vol% of ethyl ether in hexanes to provide the titled compound (43.6 mg, 0.0964 mmol, 85.9% yield) as a colorless oil.

TLC: R_f = 0.53 (EtOAc/Hex = 3:7, v/v);

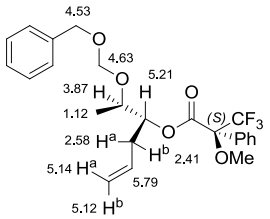
$[\alpha]_D^{20}$ +24.0 (*c* 1.825, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$): δ 7.63-7.54 (m, 2H, ***Ph-2***, ***Ph-2'***), 7.45-7.28 (m, 8H, ***H-10***, ***H-10'***, ***H-11***, ***H-11'***, ***H-12***, ***Ph-3***, ***Ph-3'***, ***Ph-4***), 5.68 (dddd, *J* = 6.1, 8.1, 10.3, 17.1 Hz, 1H, ***H-5***), 5.20 (ddd, *J* = 3.9, 5.9, 7.8 Hz, 1H, ***H-3***), 5.05 (dddd, *J* = 1.2, 1.5, 1.5, 17.1 Hz, 1H, ***H-6a***), 5.03 (dddd, *J* = 1.2, 1.5, 1.5, 10.3 Hz, 1H, ***H-6b***), 4.78 (ABq, *J* = 7.1 Hz, *Δν* = 20.5 Hz, 2H, ***H-7***), 4.61 (ABq, *J* = 11.7 Hz, *Δν* = 24.1 Hz, 2H, ***H-8***), 3.93 (dq, *J* = 5.9, 6.4 Hz, 1H, ***H-2***), 3.55 (s, 3H, ***-OMe***), 2.55 (ddddd, *J* = 1.5, 1.5, 3.9, 6.1, 14.6 Hz, 1H, ***H-4a***), 2.36 (ddddd, *J* = 1.2, 1.2, 7.8, 8.1, 14.6 Hz, 1H, ***H-4b***), 1.25 (d, *J* = 6.4 Hz, 3H, ***H-1***);

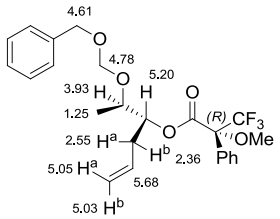
125 MHz ^{13}C NMR ($CDCl_3$): δ 166.4 (***C=O***), 137.8 (***C-9***), 132.8 (***C-5***), 132.3 (***Ph-1***), 129.8 (***Ph-4***), 128.7 (***C-11***, ***C-11'***), 128.5 (***Ph-2***, ***Ph-2'***), 128.1 (***C-10***, ***C-10'***), 128.0 (***C-12***), 127.9 (***Ph-3***, ***Ph-3'***), 123.6 (q, $J_{C\text{-}F}$ = 288.6 Hz, ***-CF$_3$***), 118.8 (***C-6***), 94.1 (***C-7***), 84.9 (q, $J_{C\text{-}F}$ = 27.7 Hz, ***-C***C=O), 78.2 (***C-2***), 73.5 (***C-3***), 69.8 (***C-8***), 55.6 (***-OMe***), 34.4 (***C-4***), 16.5 (***C-1***);

FTIR (neat): ν_{max} 3068, 2949, 1748, 1644, 1497, 1453, 1381, 1255, 1171, 1115, 1044, 921, 851, 699 cm^{-1};

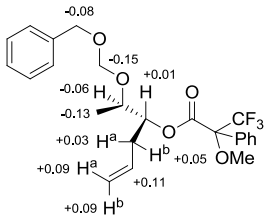
HRMS(ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{24}H_{27}O_5F_3Na$ 475.1708; found 475.1716.



3.16-(*S*)-MTPA-OH Mosher Ester

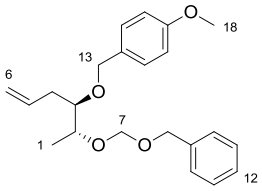


3.16-(*R*)-MTPA-OH Mosher Ester



$\Delta\delta$ (*SR*) =$\Delta\delta$ (*S*-MTPA Ester) - $\Delta\delta$ (*R*-MTPA Ester)

The chemical shift differences (in *ppm*) between the (*S*)- and (*R*)-MTPA Mosher esters of the alcohol **3.16** were consistent for a (*R*)-configuration of the new formed stereocenter.



(4*R*,5*R*)-5-(Benzyloxymethoxy)-4-(4-methoxybenzyloxy)hex-1-ene (3.17): To a 1L rb. flask was charged KH (dispersion in mineral oil ~35%, 7.99g, 69.7 mmol, 1.5 equiv) and freshly distilled THF (140 mL, 0.5 M). With an ice-water bath, a solution of alcohol **3.16** (10.97 g, 46.41 mmol, 1.0 equiv) in dry THF (230 mL, 0.2 M) was added into the reaction flask dropwise via cannula over 30 minutes. After addition, it was then stirred under an atmosphere of N_2 for 10 minutes. A solution of PMB-Br (14.09 g, 70.09 mmol, 1.5 equiv) in dry THF (140 mL, 0.5 M) was added into this reaction via cannula over 30 minutes. This reaction was stirred in this condition for 30 minutes, and quenched with ice cubes carefully. It was poured into a saturated $NaHCO_3$ solution (300 mL). The aqueous layer was extracted by ether (3 x 50 mL). The combined organic layers were washed with brine (200 mL) and dried over anhydrous Na_2SO_4. The solution was filtrated and concentrated by rotary evaporation. The residue was purified by flash chromatography on silica gel eluting with 3-10 vol% of ethyl ether in hexanes to provide a coloress oil (16.54 g, 46.41 mmol, 100% yield).

TLC: R_f = 0.47 (EtOAc/Hex = 3:7, v/v);

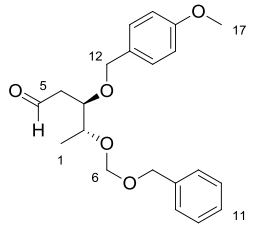
$[\alpha]_D^{20}$ -0.5 (*c* 0.805, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$): δ 7.38-7.32 (m, 4H, ***H-10***, ***H-10'***, ***H-11***, ***H-11'***), 7.32-7.29 (m, 1H, ***H-12***), 7.27 (d, *J* = 8.8 Hz, 2H, ***H-15***, ***H-15'***), 6.87 (d, *J* = 8.8 Hz, 2H, ***H-16***, ***H-16'***), 5.88 (dddd, *J* = 6.8, 7.3, 10.3, 17.1 Hz, 1H, ***H-5***), 5.12 (dddd, *J* = 1.0, 1.5, 2.0, 17.1 Hz, 1H, ***H-6a***), 5.06 (dddd, *J* = 1.0, 1.2, 2.0, 10.3 Hz, 1H, ***H-6b***), 4.84 (ABq, *J* = 7.1 Hz, *Δv* = 12.0 Hz, 2H, ***H-7***), 4.63 (s, 2H, ***H-8***), 4.55 (ABq, *J* = 11.5 Hz, *Δv* = 10.2 Hz, 2H, ***H-13***), 3.90 (dq, *J* = 4.9, 6.3 Hz, 1H, ***H-2***), 3.80 (s, 3H, ***H-18***), 3.44 (ddd, *J* = 4.4, 4.9, 7.3 Hz, 1H, ***H-3***), 2.43 (ddddd, *J* = 1.0, 1.5, 4.4, 6.8, 14.4 Hz, 1H, ***H-4a***), 2.31 (ddddd, *J* = 1.0, 1.2, 7.3, 7.3, 14.4 Hz, 1H, ***H-4b***), 1.21 (d, *J* = 6.3 Hz, 3H, ***H-1***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 159.3 (***C-17***), 138.1 (***C-9***), 135.6 (***C-5***), 130.9 (***C-14***), 129.7 (***C-15***, ***C-15'***), 128.6 (***C-11***, ***C-11'***), 128.0 (***C-10***, ***C-10'***), 127.8 (***C-12***), 117.0 (***C-6***), 113.9 (***C-16***, ***C-16'***), 94.1 (***C-7***), 81.3 (***C-3***), 74.2 (***C-2***), 72.4 (***C-13***), 69.7 (***C-8***), 55.4 (***C-18***), 34.7 (***C-4***), 16.2 (***C-1***);

FTIR (neat): ν_{max} 2953, 2924, 2854, 1614, 1587, 1514, 1463, 1377, 1302, 1248, 1172, 1112, 1043, 911, 820, 776, 734, 666, 590 cm^{-1};

HRMS(ESI-TOF) *m/z*: [M+Na^{+}] Calcd for $C_{22}H_{28}O_4Na$ 379.1885; found 379.1891.



(3*R*,4*R*)-4-Benzyloxymethoxy-3-(4-methoxybenzyloxy)pentalal (3.18): To a solution of olefin **3.17** (6.404 g, 17.97 mmol, 1.0 equiv) in CH_2Cl_2 (180 mL, 0.1 M) was purged with O_3 (3 Psi, 60 Volts) at -78 ºC. When the colorless reaction turned pinkish, the O_3 was turned off, and O_2 flushed through the reaction until it turned colorless again. Triphenylphospine (5.724 g, 21.82 mmol, 1.2 equiv) was then was added into this reaction. It was allowed to warm to room temperature, and stirred for 6 hours. The solution was concentrated in vacuo. The residue

was purified by flash chromatography on silica gel eluting with 8-15 vol% of ethyl acetate in hexanes to provide the titled compound (5.443 g, 15.19 mmol, 84.5% yield) as a yellowish oil.

TLC: R_f = 0.24 (EtOAc/Hex = 3:7, v/v);

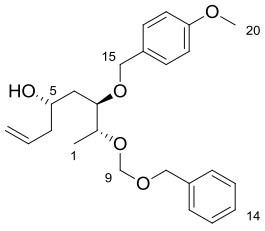
$[\alpha]_D^{20}$ +1.1 (*c* 1.74, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 9.75 (dd, *J* = 1.5, 2.4 Hz, 1H, ***H-5***), 7.41-7.28 (m, 5H, ***H-9***, ***H-9'***, ***H-10***, ***H-10'***, ***H-11***), 7.24 (d, *J* = 8.8 Hz, 2H, ***H-14***, ***H-14'***), 6.87 (d, *J* = 8.8 Hz, 2H, ***H-15***, ***H-15'***), 4.79 (ABq, *J* = 7.1 Hz, *Δv* = 21.6 Hz, 2H, ***H-6***), 4.60 (s, 2H, ***H-7***), 4.53 (ABq, *J* = 11.2 Hz, *Δv* = 11.5 Hz, 2H, ***H-12***), 4.04 (ddd, *J* = 4.4, 4.4, 7.8 Hz, 1H, ***H-3***), 4.00 (dq, *J* = 4.4, 6.3 Hz, 1H, ***H-2***), 3.80 (s, 3H, ***H-17***), 2.68 (ddd, *J* = 1.5, 4.4, 16.6 Hz, 1H, ***H-4a***), 2.62 (ddd, *J* = 2.4, 7.8, 16.6 Hz, 1H, ***H-4b***), 1.21 (d, *J* = 6.3 Hz, 2H, ***H-1***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 201.6 (***C-5***), 159.5 (***C-16***), 137.9 (***C-8***), 130.2 (***C-13***), 129.8 (***C-14***, ***C-14'***), 128.7 (***C-10***, ***C-10***'), 128.0 (***C-9***, ***C-9'***), 128.0 (***C-11***), 114.0 (***C-15***, ***C-15'***), 93.7 (***C-6***), 75.6 (***C-3***), 73.1 (***C-2***), 72.3 (***C-12***), 70.0 (***C-7***), 55.5 (***C-17***), 44.4 (***C-4***), 15.1 (***C-1***);

FTIR (neat): ν_{max} 2891, 1725, 1613, 1514, 1458, 1384, 1302, 1249, 1175, 1039, 822, 741, 699, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{21}H_{26}O_5Na$ 381.1678; found 381.1680.



(4*S*,6*R*,7*R*)-7-(Benzyloxymethoxy)-6-(4-methoxybenzyloxy)oct-1-en-4-ol (3.19): To a stirred solution of aldehyde **3.18** (4.999 g, 13.95 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL, 0.1 M) was added $MgBr_2 \cdot OEt_2$ (7.490 g, 29.01 mmol, 2.0 equiv) in one portion at -15 °C.

It was stirred under an atmosphere of N_2 for 20 minutes, and then cooled down to -78 ^oC and stirred for further 15 minutes. Then, allyltributyltin **2.59** (6.5 ml, 21 mmol, 1.5 equiv) was introduced dropwise via syringe. It was allowed to warm to 0 ^oC slowly over 10 hours. A saturated solution of $NaHCO_3$ (100 mL) was added into this reaction. The aqueous layer was extracted with EtOAc (3 x 30 mL). After being washed with brine (100 mL), the combined organic layers were stirred with salt of $KF{\cdot}2H_2O$ and anhydrous Na_2SO_4 for 30 minutes at room temperature. The solution was filtrated and concentrated by rotary evaporation. The pale yellow residue was purified by flash chromatography on silica gel eluting with 5-15 vol% of acetone in hexanes to provide the titled compound as a yellowish oil (5.262 g, 13.14 mmol, 94.2% yield, dr = 6-7:1 in favor of the desired product).

TLC: R_f = 0.24 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +34.6 (*c* 0.89, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$): δ 7.41-7.35 (m, 4H, ***H-12***, ***H-12'***, ***H-13***, ***H-13'***), 7.35-7.30 (m, 1H, ***H-14***), 7.28 (d, *J* = 8.7 Hz, 2H, ***H-17***, ***H-17'***), 6.88 (d, *J* = 8.7 Hz, 2H, ***H-18***, ***H-18'***), 5.84 (dddd, *J* = 7.3, 7.3, 11.7, 16.8 Hz, 1H, ***H-7***), 5.12 (td, *J* = 1.5, 16.8 Hz, 1H, ***H-8a***), 5.12 (td, *J* = 1.0, 11.7 Hz, 1H, ***H-8b***), 4.86 (ABq, *J* = 6.8 Hz, *Δv* = 11.8 Hz, 2H, ***H-9***), 4.65 (ABq, *J* = 6.8 Hz, *Δv* = 4.9 Hz, 2H, ***H-10***), 4.63 (d, *J* = 11.0 Hz, 1H, ***H-15a***), 4.54 (d, *J* = 11.0 Hz, 1H, ***H-15b***), 4.02 (dq, *J* = 4.1, 6.4 Hz, 1H, ***H-2***), 3.86 (app. quin, *J* = 6.3 Hz, 1H, ***H-5***), 3.80 (s, 3H, ***H-20***), 3.77 (app. dt, *J* = 4.3, 6.3 Hz, 1H, ***H-3***), 2.37 (br. s, 1H, ***-OH***), 2.26 (ddd, *J* = 5.9, 6.8, 14.2 Hz, 1H, ***H-6a***), 2.22 (ddd, *J* = 6.3, 7.3, 14.2 Hz, 1H, ***H-6b***), 1.68 (dd, *J* = 5.4, 6.8 Hz, 1H, ***H-4a***), 1.68 (dd, *J* = 5.4, 6.8 Hz, 1H, ***H-4b***), 1.22 (d, *J* = 6.4 Hz, 3H, ***H-1***);

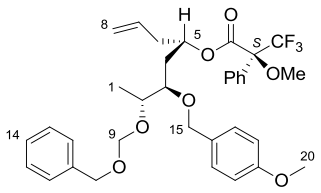
125 MHz ^{13}C NMR ($CDCl_3$): δ 159.4 (***C-19***), 138.0 (***C-11***), 135.0 (***C-7***), 130.6 (***C-16***),

129.7 (***C-17***, ***C-17'***), 128.5 (***C-13***, ***C-13'***), 127.9 (***C-12***, ***C-12'***), 127.8 (***C-14***), 117.9 (***C-8***), 113.9 (***C-18***, ***C-18'***), 93.8 (***C-9***), 78.3 (***C-3***), 73.9 (***C-2***), 72.6 (***C-15***), 69.6 (***C-10***), 67.8 (***C-5***), 55.3 (***C-20***), 42.6 (***C-6***), 36.5 (***C-4***), 15.6 (***C-1***);

FTIR (neat): ν_{max} 3453 (br.), 2974, 2933, 2837, 2060, 1999, 1883, 1613, 1514, 1455, 1382, 1302, 1249, 1175, 1113, 1063, 1040, 820, 748, 699, 666, 586, 535 cm^{-1};

HRMS(ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{24}H_{32}O_5Na$ 423.2147; found 423.2153.

Determination of Absolute Configuration of the New Stereocenter of (*4S,6R,7R*)-7-(Benzyloxymethoxy)-6-(4-methoxybenzyloxy)oct-1-en-4-ol (3.19) via Mosher Ester Method:



(4*S*,6*R*,7*R*)-7-(Benzyloxymethoxy)-6-(4-methoxybenzyloxy)oct-1-en-4-yl (*S*)-*α*-Methoxy-*α*-(trifluoromethyl)phenylacetate (3.19-S-MTPA):To a screw-capped vial equipped with a stirring bar was added alcohol **3.19** (25.9 mg, 64.7 umol, 1.0 equiv), (*S*)-(-)-MTPA-OH acid (17.3 mg, 72.4 umol, 1.1 equiv), DMAP (8.7 mg, 71 umol, 1.0 equiv), and subsequently toluene (1.5 mL, 0.05 M), at room temperature. Freshly distilled NEt_3 (45.0 uL, 323 umol, 5.0 equiv) was then added to this mixture. This reaction was cooled down to 0 ºC, 2,4,6-trichlorobenzoylchloride (11.5 uL, 72.1 umol, 1.1 equiv) was then added dropwise via syringe. The reaction turned cloudy and precipitated immediately. The vial was tightly capped. The reaction was allowed to warm to room temperature slowly, and stirred overnight (ca. 10 hours). Then, the resulting white mixture was concentrated and purified by flash chromatography on silica gel eluting with 10-15 vol% of ethyl ether in hexanes to provide the titled compound (39.9 mg, 64.7 umol, 100% yield) as a colorless

oil.

TLC: R_f = 0.47 (EtOAc/Hex = 3:7, v/v);

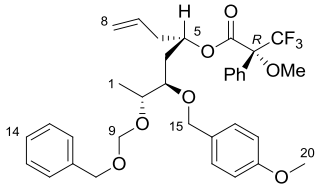
$[\alpha]_D^{20}$ +22.3 (*c* 1.87, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$): δ 7.58 (dd, *J* = 2.4, 8.3 Hz, 2H, ***Ph-2***, ***Ph-2'***), 7.44-7.30 (m, 8H, ***H-12***, ***H-12'***, ***H-13***, ***H-13'***, ***H-14***, ***Ph-3***, ***Ph-3'***, ***Ph-4***), 7.28 (d, *J* = 8.3 Hz, 2H, ***H-17***, ***H-17'***), 6.88 (d, *J* = 8.3 Hz, 2H, ***H-18***, ***H-18'***), 5.67 (dddd, *J* = 6.8, 6.8, 11.0, 15.9 Hz, 1H, ***H-7***), 5.46 (dddd, *J* = 2.9, 5.4, 5.9, 9.5 Hz, 1H, ***H-5***), 5.02 (dt, *J* = 10.7, 1.5 Hz, 1H, ***H-8a***), 5.02 (dt, *J* = 16.1, 1.6 Hz, 1H, ***H-8b***), 4.76 (ABq, *J* = 7.1 Hz, *Δv* = 26.1 Hz, 2H, ***H-9***), 4.60 (ABq, *J* = 12.0 Hz, *Δv* = 23.2 Hz, 2H, ***H-10***), 4.53 (d, *J* = 10.7 Hz, 1H, ***H-15a***), 4.38 (d, *J* = 10.7 Hz, 1H, ***H-15b***), 3.98 (dq, *J* = 4.9, 6.3 Hz, 1H, ***H-2***), 3.80 (s, 3H, ***H-20***), 3.52 (s, 3H, ***-OMe***), 3.47 (ddd, *J* = 2.0, 4.9, 10.7 Hz, 1H, ***H-3***), 2.43 (tddd, *J* = 1.5, 5.4, 6.8, 14.2 Hz, 1H, ***H-6a***), 2.38 (tddd, *J* = 1.6, 5.9, 6.8, 14.2 Hz, 1H, ***H-6b***), 1.92 (ddd, *J* = 2.0, 9.8, 14.9 Hz, 1H, ***H-4a***), 1.73 (ddd, *J* = 2.9, 10.7, 14.9 Hz, 1H, ***H-4b***), 1.17 (d, *J* = 6.3 Hz, 3H, ***H-1***);

125 MHz ^{13}C NMR ($CDCl_3$): δ 166.4 (***-C=O***), 159.5 (***C-19***), 138.0 (***C-11***), 132.9 (***C-7***), 132.2 (***Ph-1***), 130.5 (***C-16***), 129.9 (***C-17***, ***C-17'***), 129.8 (***Ph-4***), 128.7 (***C-13***, ***C-13'***), 128.6 (***C-12***, ***C-12'***), 128.0 (***Ph-2***, ***Ph-2'***), 127.9 (***C-14***), 127.8 (***Ph-3***, ***Ph-3'***), 123.6 (q, $J_{C\text{-}F}$ = 288.4 Hz, ***-CF_3***), 118.8 (***C-8***), 114.1 (***C-18***, ***C-18'***), 93.3 (***C-9***), 84.8 (q, $J_{C\text{-}F}$ = 28.2 Hz, -***C***C=O), 77.1 (***C-3***), 73.9 (***C-5***), 72.8 (***C-2***), 72.6 (***C-15***), 69.6 (***C-10***), 55.6 (***-OMe***), 55.5 (***C-20***), 39.3 (***C-6***), 34.1 (***C-4***), 14.9 (***C-1***);

FTIR (neat): ν_{max} 3066, 2936, 1744, 1613, 1514, 1250, 1169, 1114, 1040, 991, 820, 698, 666, 631, 538 cm^{-1};

HRMS(ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{34}H_{39}O_7F_3Na$ 639.2546; found 639.2554.



(4*S*,6*R*,7*R*)-7-(Benzyloxymethoxy)-6-(4-methoxybenzyloxy)oct-1-en-4-yl (*R*)-*α*-Methoxy-*α*-(trifluoromethyl)phenylacetate (3.19-R-MTPA):

To a screw-capped vial equipped with a stirring bar was added alcohol **3.19** (25.6 mg, 63.9 umol, 1.0 equiv), (*R*)-(+)-MTPA-OH acid (17.6 mg, 74.4 umol, 1.1 equiv), DMAP (9.7 mg, 78.6 umol, 1.0 equiv), and subsequently toluene (1.5 mL, 0.05 M) at room temperature. Freshly distilled NEt_3 (45.0 uL, 323 umol, 5.0 equiv) was then added to this mixture. This reaction was cooled down to 0 ^oC, 2,4,6-trichlorobenzoylchloride (11.5 uL, 72.1 umol, 1.1 equiv) was then added dropwise via syringe. The reaction turned cloudy and precipitated immediately. The vial was tightly capped. The reaction was allowed to warm to room temperature slowly, and stirred for 6 hours. Then, the resulting yellow solution was concentrated and purified by flash chromatography on silica gel eluting with 8-15 vol% of ethyl ether in hexanes to provide the titled compound (39.4 mg, 63.9 umol, 100% yield) as a colorless oil.

TLC: R_f = 0.53 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +56.7 (*c* 1.75, $CHCl_3$);

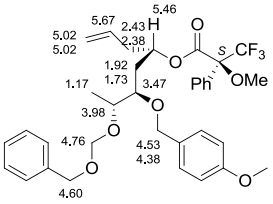
500 MHz ^{1}H NMR ($CDCl_3$): δ 7.59 (dd, *J* = 2.4, 8.3 Hz, 2H, ***Ph-2***, ***Ph-2'***), 7.43-7.31 (m, 8H, ***H-12***, ***H-12'***, ***H-13***, ***H-13'***, ***H-14***, ***Ph-3***, ***Ph-3'***, ***Ph-4***), 7.29 (d, *J* = 8.8 Hz, 2H, ***H-17***, ***H-17'***), 6.90 (d, *J* = 8.8 Hz, 2H, ***H-18***, ***H-18'***), 5.77 (dddd, *J* = 7.1, 7.1, 11.8, 17.8 Hz, 1H, ***H-7***), 5.47 (dddd, *J* = 2.4, 5.9, 5.9, 10.5 Hz, 1H, ***H-5***), 5.11 (dq, *J* = 11.2, 1.5 Hz, 1H, ***H-8a***), 5.10 (dq, *J* = 17.6, 1.5 Hz, 1H, ***H-8b***), 4.67 (ABq, *J* = 7.1 Hz, *Δv* = 34.7 Hz, 2H, ***H-9***), 4.57 (ABq, *J* = 12.2 Hz, *Δv* = 31.4 Hz, 2H, ***H-10***), 4.50 (d, *J* = 10.3 Hz, 1H, ***H-15a***), 4.34 (d, *J* = 10.3 Hz, 1H, ***H-15b***), 3.92 (dq, *J* = 4.9, 6.3 Hz, 1H, ***H-2***), 3.81 (s, 3H, ***H-20***), 3.57

(s, 3H, ***-OMe***), 3.33 (ddd, *J* = 2.0, 4.9, 10.7 Hz, 1H, ***H-3***), 2.48 (app. tt, *J* = 1.5, 7.1 Hz, 2H, ***H-6***), 1.86 (ddd, *J* = 2.0, 10.3, 14.6 Hz, 1H, ***H-4a***), 1.70 (ddd, *J* = 2.4, 10.5, 14.6 Hz, 1H, ***H-4b***), 1.12 (d, *J* = 6.3 Hz, 3H, ***H-1***);

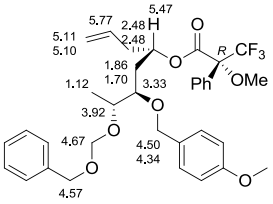
125 MHz ^{13}C NMR ($CDCl_3$): δ 166.5 (***-C=O***), 159.5 (***C-19***), 138.0 (***C-11***), 133.1 (***C-7***), 132.4 (***Ph-1***), 130.6 (***C-16***), 129.8 (***C-17***, ***C-17'***, ***Ph-4***), 128.6 (***C-13***, ***C-13'***), 128.6 (***C-12***, ***C-12'***), 128.0 (***Ph-2***, ***Ph-2'***), 127.9 (***C-14***), 127.6 (***Ph-3***, ***Ph-3'***), 123.6 (q, $J_{C\text{-}F}$ = 288.8 Hz, ***-CF$_3$***), 118.9 (***C-8***), 114.1 (***C-18***, ***C-18'***), 93.2 (***C-9***), 84.5 (q, $J_{C\text{-}F}$ = 27.7 Hz, ***-C***C=O), 77.1 (***C-3***), 73.9 (***C-5***), 73.0 (***C-15***), 72.5 (***C-2***), 69.5 (***C-10***), 55.7 (***-OMe***), 55.5 (***C-20***), 39.5 (***C-6***), 34.1 (***C-4***), 14.9 (***C-1***);

FTIR (neat): ν_{max} 3065, 2935, 1745, 1681, 1613, 1514, 1454, 1251, 1167, 1113, 1064, 1041, 990, 922, 821, 698 cm^{-1};

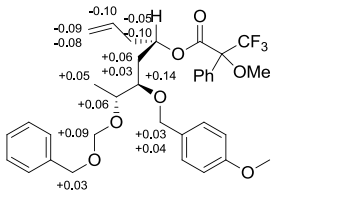
HRMS(ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{34}H_{39}O_7F_3Na$ 639.2546; found 639.2548.



3.16-*S*-MTPA Mosher Ester

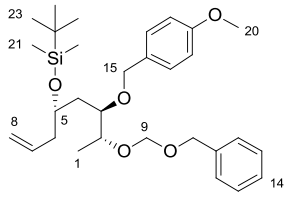


3.16-*R*-MTPA Mosher Ester



Δδ (SR) =Δδ (S-MTPA Ester*) - Δδ (R*-MTPA Ester*)*

The chemical shift differences (in *ppm*) between the (*S*)- and (*R*)-MTPA Mosher esters of the (*4S,6R,7R*)-7-(benzyloxymethoxy)-6-(4-methoxybenzyloxy)oct-1-en-4-ol **3.16** were consistent for a (*S*)-configuration of the new formed stereocenter.



(4*S*,6*R*,7*R*)-7-(Benzyloxymethoxy)-4-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxy)oct-1-ene (3.20): To a stirred solution of alcohol **3.19** (5.135 g, 12.82 mmol, 1.0 equiv) in DMF (70 mL, 0.2 M) was

added imidazole (3.583 g, 52.10 mmol, 4.0 equiv), and subsequently TBSCl (3.989 g, 25.67 mmol, 2.0 equiv) at room temperature. This reaction was stirred under an atmosphere of N_2 for 24 hours. Then, it was diluted with Et_2O (100 mL), and the reaction was poured into a saturated solution of $NaHCO_3$ (200 mL). The aqueous layer was extracted by Et_2O (3 x 30 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 2-6 vol% of ethyl acetate in hexanes to provide the titled compound (6.426 g, 12.48 mmol, 97.4% yield) as a yellowish oil.

TLC: R_f = 0.67 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +26.7 (*c* 1.62, $CHCl_3$);

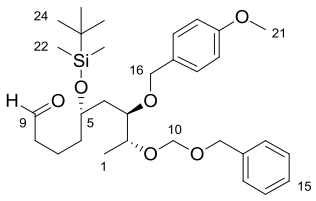
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.41-7.29 (m, 5H, ***H-12***, ***H-12'***, ***H-13***, ***H-13'***, ***H-14***), 7.27 (d, *J* = 8.8 Hz, 2H, ***H-17***, ***H-17'***), 6.89 (d, *J* = 8.8 Hz, 2H, ***H-18***, ***H-18'***), 5.85 (dddd, *J* = 7.1, 7.1, 9.5, 17.8 Hz, 1H, ***H-7***), 5.06 (app. dt, *J* = 9.5, 1.5 Hz, 1H, ***H-8a***), 5.06 (app. dt, *J* = 17.8, 2.0 Hz, 1H, ***H-8b***), 4.83 (ABq, *J* = 6.8 Hz, *Δv* = 10.1 Hz, 2H, ***H-9***), 4.65 (ABq, *J* = 12.9 Hz, *Δv* = 16.9 Hz, 2H, ***H-10***), 4.61 (d, *J* = 11.0 Hz, 1H, ***H-15a***), 4.49 (d, *J* = 11.0 Hz, 1H, ***H-15b***), 4.03 (dq, *J* = 4.9, 6.3 Hz, 1H, ***H-2***), 4.00 (dddd, *J* = 3.4, 4.9, 6.3, 7.7 Hz, 1H, ***H-5***), 3.82 (s, 3H, ***H-20***), 3.68 (ddd, *J* = 3.4, 4.9, 8.8 Hz, 1H, ***H-3***), 2.36-2.25 (m, 2H, ***H-6***), 1.68 (ddd, *J* = 3.4, 7.7, 14.2 Hz, 1H, ***H-4a***), 1.63 (ddd, *J*= 3.4, 8.8, 14.2 Hz, 1H, ***H-4b***), 1.20 (d, *J* = 6.3 Hz, 3H, ***H-1***), 0.92 (s, 9H, ***H-23***), 0.10 (s, 3H, ***H-21a***), 0.08 (s, 3H, ***H-21b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 159.3 (***C-19***), 138.1 (***C-11***), 134.9 (***C-7***), 131.1 (***C-16***), 129.3 (***C-17***, ***C-17'***), 128.6 (***C-13***, ***C-13'***), 128.0 (***C-12***, ***C-12'***), 127.8 (***C-14***), 117.3 (***C-8***), 113.9 (***C-18***, ***C-18'***), 93.3 (***C-9***), 78.1 (***C-3***), 73.0 (***C-2***), 72.1 (***C-15***), 69.5 (***C-10***), 69.2 (***C-***

5), 55.5 (***C-20***), 43.1 (***C-6***), 37.4 (***C-4***), 26.1 (***C-23***), 18.3 (***C-22***), 15.3 (***C-1***), -3.6 (***C-21a***), -4.3 (***C-21b***);

FTIR (neat): ν_{max} 3068, 2954, 2857, 1613, 1514, 1463, 1381, 1302, 1250, 1173, 1100, 1042, 914, 835, 775, 698 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{30}H_{46}O_5SiNa$ 537.3012; found 537.3022.



(5*S*,7*R*,8*R*)-8-(Benzyloxymethoxy)-5-(*tert*-butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)nonanal (3.21): To an oven-dried flask equipped with a stirring bar was added dicarbonylacetylacetonatorhodium (I) (9.3 mg, 0.036 mmol, 0.5 mol%), BIPHEPHOS (113 mg, 0.144 mmol, 2.0 mol%) and freshly distilled degassed THF (70 mL). This flask was evacuated and refilled with N_2 by 3 times. It was then stirred at room temperature under an atmosphere of N_2 for 10 minutes, whereupon the mixture was dissolved. The solution of olefin **3.20** (3.699 g, 7.185 mmol, 1.0 equiv) in degassed THF (7 mL, 1.0 M) was added into this flask via cannula. This flask was unsealed and put into Parr autoclave quickly. Then the Parr pressure vessel was sealed tightly. The atmosphere of this reaction vessel was exchanged with 100 psi of CO/H_2 (1:1 mixture) three times by being evacuated with an oil pump and refilled with syngas. Then, the reaction vessel was pressurized with CO/H_2 (1:1 mixture) at 100 psi, and stirred at 57 ^oC for 36 hours. After cooling to room temperature, the reaction was depressurized and concentrated by rotary vacuum. The remainder was purified by flash chromatography on silica gel eluting with 10-16 vol% of ethyl acetate in hexanes to provide titled compound (3.776 g, 6.932 mmol, 96.5% yield) as a colorless oil.

TLC: R_f = 0.50 (EtOAc/Hex = 3:7, v/v);

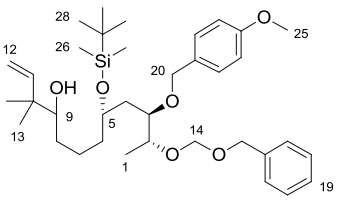
$[\alpha]_D^{20}$ +23.7 (*c* 0.76, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 9.75 (t, *J* = 1.5 Hz, 1H, ***H-9***), 7.39-7.28 (m, 5H, ***H-13***, ***H-13'***, ***H-14***, ***H-14'***, ***H-15***), 7.25 (d, *J* = 8.8 Hz, 2H, ***H-18***, ***H-18'***), 6.87 (d, *J* = 8.8 Hz, 2H, ***H-19***, ***H-19'***), 4.82 (ABq, *J* = 7.1 Hz, *Δv* = 12.0 Hz, 2H, ***H-10***), 4.64 (ABq, *J* = 12.0 Hz, *Δv* = 18.1 Hz, 2H, ***H-11***), 4.60 (d, *J* = 10.7 Hz, 1H, ***H-16a***), 4.45 (d, *J* = 10.7 Hz, 1H, ***H-16b***), 4.03 (dq, *J* = 4.6, 6.8 Hz, 1H, ***H-2***), 3.92 (dddd, *J* = 3.6, 4.9, 5.4, 8.1 Hz, 1H, ***H-5***), 3.81 (s, 3H, ***H-21***), 3.64 (ddd, *J* = 2.4, 4.6, 9.5 Hz, 1H, ***H-3***), 2.40 (app. dt, *J* = 1.5, 7.3 Hz, 2H, ***H-8***), 1.71 (ddd, *J* = 2.4, 8.1, 14.2 Hz, 1H, ***H-4a***), 1.67 (app. ddt, *J* = 6.4, 10.4, 7.3 Hz, 2H, ***H-7***), 1.56 (ddd, *J* = 3.6, 9.5, 14.2 Hz, 1H, ***H-4b***), 1.58-1.39 (m, 2H, ***H-6a***, ***H-6b***), 1.19 (d, *J* = 6.8 Hz, 3H, ***H-1***), 0.90 (s, 9H, ***H-24***), 0.06 (s, 6H, ***H-22***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 202.7 (***C-9***), 159.3 (***C-20***), 138.1 (***C-12***), 131.1 (***C-17***), 129.4 (***C-18***, ***C-18'***), 128.6 (***C-14***, ***C-14'***), 128.0 (***C-13***, ***C-13'***), 127.9 (***C-15***), 114.0 (***C-19***, ***C-19'***), 93.4 (***C-10***), 78.2 (***C-3***), 72.9 (***C-2***), 72.1 (***C-16***), 69.5 (***C-11***), 69.5 (***C-5***), 55.5 (***C-21***), 44.2 (***C-8***), 37.7 (***C-6***), 37.3 (***C-4***), 26.1 (***C-24***), 18.3 (***C-23***), 17.4 (***C-7***), 15.2 (***C-1***), -3.7 (***C-22a***), -4.2 (***C-22b***);

FTIR (neat): ν_{max} 3032, 2952, 2893, 2857, 2718, 1726, 1613, 1556, 1514, 1463, 1383, 1250, 1173, 1112, 1064, 937, 834, 774, 736, 698, 578 cm^{-1};

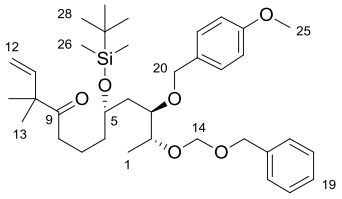
HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{31}H_{48}O_6SiNa$ 567.3118; found 567.3123.



(8*S*,10*R*,11*R*)-11-(Benzyloxymethoxy)-8-(*tert*-butyldimethylsilyloxy)-10-(4-methoxybenzyloxy)-3,3-dimethyldodec-1-en-4-ol (3.22): To a stirred mixture of aldehyde **3.21** (5.048

g, 9.266 mmol, 1.0 equiv), 1-bromo-3-methylbut-2-ene (1.70 mL, 14.0 mmol, 1.5 equiv), THF (18.5 mL, 0.5 M) and saturated NH_4Cl (90 mL, 0.1 M) aqueous solution was added Zn dust (0.932 g, 14.0 mmol, 1.5 equiv) in one portion at room temperature. It was stirred overnight (ca. 12 hours), then Et_2O (50 mL) was poured into this reaction. The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Filtered, it was then concentrated by rotary vacuum to give a yellow oil (5.571 g, 9.271 mmol, 100% yield), which was used in the next step without further purification.

TLC: R_f = 0.53 (EtOAc/Hex = 3:7, v/v).



(8*S*,10*R*,11*R*)-11-(Benzyloxymethoxy)-8-(*tert*-butyldimethylsilyloxy)-10-(4-methoxybenzyloxy)-3,3-dimethyldodec-1-en-4-one (3.23): With a –78 °C bath, to a stirred solution of oxalyl chloride (0.70 mL, 80 mmol, 1.5 equiv) in dry CH_2Cl_2 (40 mL, 0.2 M) was added a solution of DMSO (1.1 mL, 16 mmol, 3.0 equiv) in dry CH_2Cl_2 (30 mL, 0.5 M) dropwise via cannula under an atmosphere of N_2. After 30 minutes, the solution of alcohol **3.22** (3.172 g, 5.158 mmol, 1.0 equiv) in dry CH_2Cl_2 (50 mL, 0.1 M) was added dropwise via cannula. This reaction was stirred for 1 hour in this condition. Then, NEt_3 (3.60 mL, 25.8 mmol, 5.0 equiv) was introduced dropwise via syringe. After 5 minutes, the cooling bath was removed, and the reaction was stirred at room temperature for 1.5 hours. The solution was poured into a saturated solution of NH_4Cl (150 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (200 mL) and dried over anhydrous Na_2SO_4. Filtered, it was then concentrated by rotary vacuum.

The remainder was purified by flash chromatography on silica gel eluting with 5-12 vol% of ethyl acetate in hexanes to provide the titled compound (3.016 g, 4.920 mmol, 95.4% yield over two steps) as a colorless oil.

TLC: R_f = 0.62 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +44.9 (*c* 2.06, $CHCl_3$);

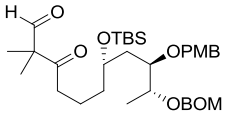
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.29 (m, 5H, ***H-17***, ***H-17'***, ***H-18***, ***H-18'***, ***H-19***), 7.26 (d, *J* = 8.8 Hz, 2H, ***H-22***, ***H-22'***), 6.88 (d, *J* = 8.8 Hz, 2H, ***H-23***, ***H-23'***), 5.91 (dd, *J* = 10.7, 17.3 Hz, 1H, ***H-11***), 5.15 (d, *J* = 10.7 Hz, 1H, ***H-12a***), 5.15 (d, *J* = 17.3 Hz, 1H, ***H-12b***), 4.82 (ABq, *J* = 7.1 Hz, *Δv* = 10.8 Hz, 2H, ***H-14***), 4.65 (ABq, *J* = 11.7 Hz, *Δv* = 19.1 Hz, 2H, ***H-15***), 4.61 (d, *J* = 10.9 Hz, 1H, ***H-20a***), 4.48 (d, *J* = 10.9 Hz, 1H, ***H-20b***), 4.03 (dq, *J* = 4.8, 6.8 Hz, 1H, ***H-2***), 3.91 (dddd, *J* = 3.4, 5.4, 5.4, 8.8 Hz, 1H, ***H-5***), 3.81 (s, 3H, ***H-25***), 3.66 (ddd, *J* = 2.4, 4.8, 9.5 Hz, 1H, ***H-3***), 2.46 (ddd, *J* = 6.8, 7.3, 17.5 Hz, 1H, ***H-8a***), 2.42 (ddd, *J* = 7.3, 7.3, 17.5 Hz, 1H, ***H-8b***), 1.70 (ddd, *J* = 2.4, 8.8, 14.2 Hz, 1H, ***H-4a***), 1.60 (ddd, *J* = 3.4, 9.5, 14.2 Hz, 1H, ***H-4b***), 1.61-1.54 (m, 2H, ***H-7a***, ***H-7b***), 1.51-1.41 (m, 2H, ***H-6a***, ***H-6b***), 1.23 (s, 6H, ***H-13***), 1.20 (d, *J* = 6.8 Hz, 3H, ***H-1***), 0.91 (s, 9H, ***H-28***), 0.072 (s, 3H, ***H-26a***), 0.068 (s, 3H, ***H-26b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 212.9 (***C-9***), 159.3 (***C-24***), 142.8 (***C-11***), 138.2 (***C-16***), 131.2 (***C-21***), 129.3 (***C-22***, ***C-22'***), 128.6 (***C-18***, ***C-18'***), 128.0 (***C-17***, ***C-17'***), 127.8 (***C-19***), 114.3 (***C-12***), 113.9 (***C-23***, ***C-23'***), 93.4 (***C-14***), 78.3 (***C-3***), 73.1 (***C-2***), 72.1 (***C-20***), 69.7 (***C-15***), 69.5 (***C-5***), 55.4 (***C-25***), 50.9 (***C-10***), 37.9 (***C-6***), 37.7 (***C-8***), 37.4 (***C-4***), 26.2 (***C-28***), 23.7 (***C-13a***), 23.7 (***C-13b***), 19.5 (***C-7***), 18.3 (***C-27***), 15.2 (***C-1***), -3.6 (***C-26a***), -4.2 (***C-26b***);

FTIR (neat): ν_{max} 2955, 2932, 2858, 1712, 1613, 1514, 1464, 1380, 1301, 1250, 1174, 1041,

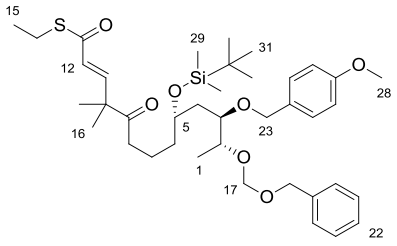
921, 835, 775, 738, 698, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{36}H_{56}O_6SiNa$ 635.3744; found 635.3750.



(7*S*,9*R*,10*R*)-10-(Benzyloxymethoxy)-7-(*tert*-butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-2,2-dimethyl-3-oxoundecanal (3.24): With an acetone/dry ice bath (–78 °C), a steam of O_3 (3.0 psi, 60 Volts) purged through a solution of olefin **3.23** (2.794 g, 4.559 mmol) in CH_2Cl_2 (45 mL, 0.1 M) until the colorless solution turned pinkish, whereupon the O_3 was turned off, and a stream of N_2 flushed the solution until the color faded. Then, triphenylphosphine (1.812 g, 6.839 mmol) was added in one portion. The reaction was stirred at room temperature for 6 hours. The resulting yellow solution was concentrated under reduced pressure. Then, an ice-cold solution of 30 vol% Et_2O in pentane (45 mL, 0.1 M) was added into the remainder. It was stirred at 0 °C for 10 minutes. The white precipitate was filtrated, and washed with an ice-cold solution of 10 vol% Et_2O in pentane (3 x 10 mL). The solution was concentrated by rotary evaporation to give a yellow oil which was used directly in the next step without further purification.

TLC: R_f = 0.48 (EtOAc/Hex = 3:7, v/v).



(9*S*,11*R*,12*R*,*E*)-*S*-Ethyl 12-(Benzyloxymethoxy)-9-(*tert*-butyldimethylsilyloxy)-11-(4-methoxybenzyloxy)-4,4-dimethyl-5-oxotridec-2-enethioate (3.25): To a round-bottomed flask was charged NaH (60% dispersion in mineral oil, 0.274 g, 6.85 mmol, 1.5 equiv) and anhydrous THF (20 mL, 0.4 M). With an ice-water bath, a solution of diethyl

ethylthiocarbonylmethylphosphonate (1.645 g, 6.847 mmol, 1.5 equiv) in THF (20 mL, 0.4 M) was added dropwise via cannula. This reaction was then stirred under an atmosphere of N_2 for 10 minutes, whereupon a solution of abovementioned crude aldehyde **3.24** (theoretically 4.559 mmol, 1.0 equiv) in THF (10 mL, 0.5 M) was added via a cannula. It was kept stirring in this condition for 2 hours. Then, a saturated $NaHCO_3$ solution (100 mL) was added. The separated aqueous layer was extracted with ethyl ether (3 x 20 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 4-10 vol% of ethyl acetate in hexanes to afford the titled compound (2.968 g, 4.233 mmol, 92.9% yield over two steps) as a yellowish oil.

TLC: R_f = 0.57 (EtOAc/Hex = 3:7, v/v);

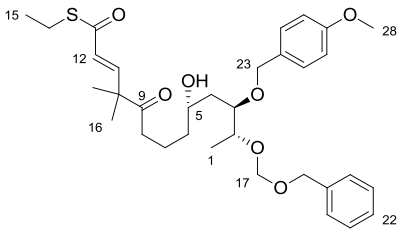
$[\alpha]_D^{20}$ +22.9 (*c* 1.02, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.39-7.28 (m, 5H, ***H-20***, ***H-20'***, ***H-21***, ***H-21'***, ***H-22***), 7.25 (d, *J* = 8.8 Hz, 2H, ***H-25***, ***H-25'***), 6.96 (d, *J* = 15.6 Hz, 1H, ***H-11***), 6.87 (d, *J* = 8.8 Hz, 2H, ***H-26***, ***H-26'***), 6.14 (d, *J* = 15.6 Hz, 1H, ***H-12***), 4.81 (ABq, *J* = 7.1 Hz, $\Delta\nu$ = 11.4 Hz, 2H, ***H-17***), 4.63 (ABq, *J* = 11.7 Hz, $\Delta\nu$ = 19.7 Hz, 2H, ***H-18***), 4.53 (ABq, *J* = 11.0 Hz, $\Delta\nu$ = 67.7 Hz, 2H, ***H-23***), 4.02 (dt, *J* = 4.9, 6.4 Hz, 1H, ***H-2***), 3.89 (dddd, *J* = 3.4, 5.1, 5.1, 8.8 Hz, 1H, ***H-5***), 3.80 (s, 3H, ***H-28***), 3.64 (ddd, *J* = 2.4, 4.9, 9.3 Hz, 1H, ***H-3***), 2.97 (q, *J* = 7.3 Hz, 2H, ***H-14***), 2.42 (dd, *J* = 7.3, 8.8 Hz, 1H, ***H-8a***), 2.42 (dd, *J* = 5.9, 7.3 Hz, 1H, ***H-8b***), 1.69 (ddd, *J* = 2.4, 8.8, 14.1 Hz, 1H, ***H-4a***), 1.64-1.52 (m, 3H, ***H-4b***, ***H-7***), 1.50-1.38 (m, 2H, ***H-6***), 1.30 (t, *J* = 7.3 Hz, 3H, ***H-15***), 1.28 (s, 6H, ***H-16***), 1.18 (d, *J* = 6.4 Hz, 3H, ***H-1***), 0.89 (s, 9H, ***H-31***), 0.06 (s, 3H, ***H-29a***), 0.05 (s, 3H, ***H-29b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 210.6 (***C-9***), 190.0 (***C-13***), 159.2 (***C-27***), 142.3 (***C-11***), 138.1 (***C-19***), 131.1 (***C-24***), 129.3 (***C-25***, ***C-25'***), 128.6 (***C-21***, ***C-21***), 128.0 (***C-20***, ***C-20'***), 127.8 (***C-12***), 127.7 (***C-22***), 113.9 (***C-26***, ***C-26'***), 93.3 (***C-17***), 78.2 (***C-3***), 72.9 (***C-2***), 72.0 (***C-23***), 69.6 (***C-5***), 69.5 (***C-18***), 55.4 (***C-28***), 50.6 (***C-10***), 38.6 (***C-8***), 37.8 (***C-6***), 37.3 (***C-4***), 26.1 (***C-31***), 23.6 (***C-16***), 23.5 (***C-14***), 19.2 (***C-7***), 18.2 (***C-30***), 15.2 (***C-1***), 14.9 (***C-15***), -3.6 (***C-29a***), -4.2 (***C-29b***);

FTIR (neat): ν_{max} 2932, 1713, 1672, 1623, 1514, 1463, 1381, 1250, 1174, 1040, 835, 775, 739, 698, 665 cm^{-1};

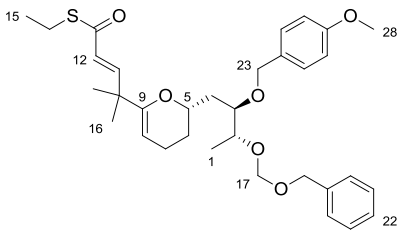
HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{39}H_{60}O_7SiSNa$ 723.3727; found 723.3726.



(9*S*,11*R*,12*R*,*E*)-*S*-Ethyl 12-(Benzyloxymethoxy)-9-hydroxy-11-(4-methoxybenzyloxy)-4,4-dimethyl-5-oxotridec-2-enethioate (3.26): To an ice-cold solution of TBS ether **3.25** (0.9042 g, 1.290 mmol, 1.0 eq) in MeCN (13 mL, 0.1 M) was added pyridine (13 mL, 0.1 M) and DI H_2O (0.8 mL, 2.0 M). Then, a solution of HF (48 wt% in H_2O, 2.0 mL, 55 mmol, 40 equiv) was added dropwise. This reaction was allowed to warm to room temperature for 3 hours, and another portion of HF solution (48 wt%, 2.0 mL, 55 mmol, 40 equiv) was added dropwise. A portion of HF solution (48 wt%, 2.0 mL, 55 mmol, 40 equiv) was added into this reaction every 6 hours until total 200 equiv of HF was added. This reaction was stirred for 36 hours, whereupon it was diluted with ether (50 mL) and slowly poured into a stirred ice-cold suspension of $NaHCO_3$ (32.8 g, 390 mmol, 300 equiv) and H_2O (200 mL) in 5 portions. This reaction was stirred for 1 hour, and the aqueous phase was extracted with EtOAc (3 x

30 mL). The combined organic solutions were washed with brine (200 mL), a saturated solution of Cu_2SO_4 (200 mL), and then brine (200 mL). The organic solution was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide a yellow oil (crude 0.781 g, 1.33 mmol, 100% yield), which was used directly in the next step without further purification.

TLC: R_f = 0.13 (EtOAc/Hex = 3:7, v/v).



(*E*)-*S*-Ethyl 4-((*S*)-6-((2*R*,3*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-5,6-dihydro-*4H*-pyran-2-yl)-4-methylpent-2-enethioate (3.27): To a solution of abovementioned crude alcohol **3.26** (0.781 g, theoretically 1.29 mmol, 1.0 equiv) in toluene (26 mL, 0.05 M) was added CSA (9 mg, 0.04 mmol, 0.03 equiv) in one portion at room temperature. This reaction was refluxed with a dean-stark apparatus for an hour under an atmosphere of N_2. Then, freshly distilled pyridine (0.10 mL, 1.2 mmol) was added into this reaction. It was cooled down to room temperature under an atmosphere of N_2, and poured into a saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted by ethyl ether (3 x 20 mL). The combined organic layers were washed with brine (100 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a yellow oil. The crude product was purified by flash chromatography on silica gel eluting with 10-20 vol% of ethyl ether in hexanes to afford the titled compound (0.633 g, 1.11 mmol, 86.3% yield over two steps) a yellowish oil.

TLC: R_f = 0.59 (EtOAc/Hex = 3:7, v/v);

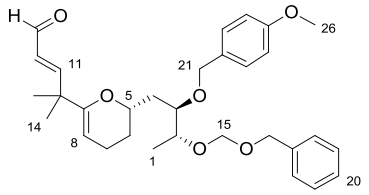
$[\alpha]_D^{20}$ +42.4 (*c* 1.96, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.38-7.33 (m, 4H, ***H-20***, ***H-21***), 7.30 (tt, *J* = 4.4, 7.8 Hz, 1H, ***H-22***), 7.25 (d, *J* = 8.6 Hz, 2H, ***H-25***), 6.97 (d, *J* = 16.1 Hz, 1H, ***H-11***), 6.86 (d, *J* = 8.6 Hz, 2H, ***H-26***), 6.09 (d, *J* = 16.1 Hz, 1H, ***H-12***), 4.83 (ABq, *J* = 7.1 Hz, *Δv* = 7.1 Hz, 2H, ***H-17***), 4.64 (ABq, *J* = 12.2 Hz, *Δv* = 10.4 Hz, 2H, ***H-18***), 4.61 (d, *J* = 10.7 Hz, 1H, ***H-23a***), 4.59 (dd, *J* = 2.9, 5.4 Hz, 1H, ***H-8***), 4.49 (d, *J* = 10.7 Hz, 1H, ***H-23b***), 4.00 (dddd, *J* = 2.0, 2.4, 9.8, 10.3 Hz, 1H, ***H-5***), 3.96 (dq, *J* = 4.9, 6.3 Hz, 1H, ***H-2***), 3.80 (ddd, *J* = 2.4, 4.9, 9.8 Hz, 1H, ***H-3***), 3.80 (s, 3H, ***H-28***), 2.89 (q, *J* = 7.5 Hz, 2H, ***H-14***), 2.09 (dddd, *J* = 2.9, 5.9, 9.8, 16.8 Hz, 1H, ***H-7a***), 1.99 (dddd, *J* = 2.9, 5.4, 6.4, 16.8 Hz, 1H, ***H-7b***), 1.80 (ddd, *J* = 2.0, 9.8, 14.3 Hz, 1H, ***H-4a***), 1.76 (dddd, *J* = 2.4, 2.9, 5.9, 13.4 Hz, 1H, ***H-6a***), 1.61 (ddd, *J* = 2.4, 10.3, 14.3 Hz, 1H, ***H-4b***), 1.50 (dddd, *J* = 6.4, 9.8, 9.8, 13.4 Hz, 1H, ***H-6b***), 1.22 (t, *J* = 7.5 Hz, 3H, ***H-15***), 1.22 (s, 3H, ***H-16a***), 1.21 (s, 3H, ***H-16b***), 1.20 (d, *J* = 6.3 Hz, 3H, ***H-1***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 190.7 (***C-13***), 159.3 (***C-27***), 157.1 (***C-9***), 152.0 (***C-11***), 138.2 (***C-19***), 131.1 (***C-24***), 129.7 (***C-25***), 128.6 (***C-21***), 128.0 (***C-20***), 127.9 (***C-22***), 125.7 (***C-12***), 114.0 (***C-26***), 94.6 (***C-8***), 93.6 (***C-17***), 77.8 (***C-3***), 73.9 (***C-2***), 73.7 (***C-23***), 72.0 (***C-5***), 69.6 (***C-18***), 55.5 (***C-28***), 41.4 (***C-10***), 36.2 (***C-4***), 28.2 (***C-6***), 25.3 (***C-16a***), 25.2 (***C-16b***), 23.3 (***C-14***), 20.5 (***C-7***), 15.6 (***C-1***), 14.9 (***C-15***);

FTIR (neat): ν_{max} 2933, 1711, 1668, 1623, 1513, 1456, 1381, 1249, 1174, 1039, 822, 740, 699 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{33}H_{44}O_6SNa$ 591.2756; found 591.2753.



(*E*)-4-((*S*)-6-((2*R*,3*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-5,6-dihydro-*4H*-pyran-2-yl)-4-methylpent-2-enal (3.10): With a –78 °C bath, to a stirred solution of thioester **3.27** (2.982 g, 5.243 mmol, 1.0 equiv) in fresh distilled CH_2Cl_2 (50 mL, 0.1 M) was added a DIBAL solution (1.0 M solution in CH_2Cl_2, 7.90 mL, 7.90 mmol, 1.5 equiv) at the rate of 15 mL/h via syringe pump under an atmosphere of N_2. After addition, it was stirred for 1 hour, and EtOAc (5 mL) was then added into the reaction at the same rate above. Then, a saturated Rochelle's salt solution (100 mL) was added, and the mixture was stirred vigorously for 3 hours, whereupon two clear phases appeared. The aqueous layer was extracted by Et_2OAc (3 x 20 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with 5-15 vol% of ethyl acetate in hexanes to provide the titled compound (2.245 g, 4.414 mmol, 84.2% yield) as a colorless oil.

TLC: R_f = 0.49 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +44.9 (*c* 2.06, $CHCl_3$);

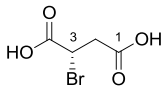
500 MHz ^{1}H NMR ($CDCl_3$) δ 9.48 (d, *J* = 7.8 Hz, 1H, ***H-13***), 7.39-7.28 (m, 5H, ***H-18***, ***H-18'***, ***H-19***, ***H-19'***, ***H-20***), 7.24 (d, *J* = 8.8 Hz, 2H, ***H-23***, ***H-23'***), 6.86 (d, *J* = 8.8 Hz, 2H, ***H-24***, ***H-24'***), 6.86 (d, *J* = 16.1 Hz, 1H, ***H-11***), 6.10 (dd, *J* = 7.8, 16.1 Hz, 1H, ***H-12***), 4.82 (ABq, *J* = 6.8 Hz, *Δν* = 10.7 Hz, 2H, ***H-15***), 4.63 (s, 2H, ***H-16***), 4.63 (dd, *J* = 2.9, 3.4 Hz, 1H, ***H-8***), 4.62 (d, *J* = 10.7 Hz, 1H, ***H-21a***), 4.47 (d, *J* = 10.7 Hz, 1H, ***H-21b***), 4.03 (dddd, *J* = 2.4, 2.9, 9.8, 10.7 Hz, 1H, ***H-5***), 3.98 (dq, *J* = 4.9, 6.3 Hz, 1H, ***H-2***), 3.80 (s, 3H, ***H-***

26), 3.78 (ddd, *J* = 2.4, 4.9, 10.2 Hz, 1H, ***H-3***), 2.10 (dddd, *J*= 2.9, 6.8, 9.8, 17.1 Hz, 1H, ***H-7a***), 2.01 (dddd, *J*= 3.4, 4.9, 5.9, 17.1 Hz, 1H, ***H-7b***), 1.82 (ddd, *J*= 2.9, 10.2, 14.2 Hz, 1H, ***H-4a***), 1.80 (dddd, *J*= 2.4, 4.9, 6.8, 13.2 Hz, 1H, ***H-6a***), 1.62 (ddd, *J* = 2.4, 10.7, 14.2 Hz, 1H, ***H-4b***), 1.52 (dddd, *J*= 5.9, 9.8, 9.8, 13.2 Hz, 1H, ***H-6b***), 1.26 (s, 3H, ***H-14a***), 1.25 (s, 3H, ***H-14b***), 1.20 (d, *J* = 6.3 Hz, 3H, ***H-1***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 194.7 (***C-13***), 165.7 (***C-11***), 159.4 (***C-25***), 156.7 (***C-9***), 138.1 (***C-17***), 130.9 (***C-22***), 129.8 (***C-12***), 129.5 (***C-23***, ***C-23'***), 128.6 (***C-19***, ***C-19'***), 128.0 (***C-18***, ***C-18'***), 127.9 (***C-20***), 114.0 (***C-24***, ***C-24'***), 94.9 (***C-8***), 93.6 (***C-15***), 77.7 (***C-3***), 73.7 (***C-2***), 73.4 (***C-21***), 72.2 (***C-5***), 69.6 (***C-16***), 55.5 (***C-26***), 42.1 (***C-10***), 36.0 (***C-4***), 28.2 (***C-6***), 25.3 (***C-14a***), 25.1 (***C-14b***), 20.5 (***C-7***), 15.5 (***C-1***);

FTIR (neat): ν_{max} 2931, 1691, 1613, 1514, 1458, 1381, 1297, 1248, 1173, 1098, 1040, 822, 739, 699, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{31}H_{40}O_6Na$ 531.2723; found 531.2725.



(*S*)-2-Bromosuccinic Acid (3.32): To the mixture of (*S*)-(+)-aspartic acid **3.14** (10.40 g, 76.57 mmol, 1.0 equiv) and KBr (41.9 g, 345 mmol, 4.5 equiv) was added H_2SO_4 solution (2.5 M, 200 mL, 500 mmol, 6.5 equiv) at -10 °C. A solution of $NaNO_2$ (9.40 g, 135 mmol, 1.8 equiv) in D.I. H_2O (22.5 mL, 6.0 M) was added to this mixture via an additional funnel dropwise over 1 hour, while keeping the temperature below 0 °C. After 4 hours, the resulting brown mixture was extracted with EtOAc (4 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$. The solution was filtered and concentrated under reduced pressure to provide the titled compound (14.02 g, 71.17 mmol, 93.0% yield) as a white solid (mp: 168-170 °C, lit.[27]: 171-172 °C). The compound was directly used in next step without

further purification.

mp: 168-170 °C;

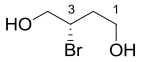
$[\alpha]_D^{20}$ -41.5 (*c* 1.17, H_2O);

500 MHz ^{1}H NMR (CD_3OD) δ 4.93 (br. s, 2H, ***-OHa***, ***-OHb***), 4.56 (dd, *J* = 8.8, 6.2 Hz, 1H, ***H-3***), 3.19 (dd, *J* = 17.2, 8.8 Hz, 1H, ***H-2a***), 2.95 (dd, *J* = 17.2 6.2 Hz, 1H, ***H-2b***);

125 MHz ^{13}C NMR (CD_3OD) δ 173.3 (***C-4***), 172.5 (***C-1***), 40.9 (***C-2***), 40.3 (***C-3***);

FTIR (neat): ν_{max} 3011, 2903, 2530,, 1693, 1420, 1403, 1289, 1245, 1211, 1184, 932, 766, 706, 647, 585 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_4H_5O_6BrNa$ 218.9269; found 218.9274.



(*S*)-2-Bromo-1,4-butanediol (3.33): At -10 °C, under an atmosphere of N_2, to the solution of diacid **3.32** (3.975 g, 20.18 mmol, 1.0 equiv) in dry THF (70 mL, 0.3 M) was added a solution of BH_3•DMS complex (10.0 M, 6.1 mL, 61 mmol, 3.0 equiv) in THF (30 mL, 2.0 M) dropwise via addition funnel over 80 minutes. Then, this reaction was allowed to warm to room temperature slowly over 4 hours. After stirred at room temperature for 1.5 hours, it was cooled down to 0 °C. Then, H_2O (5 mL) was added dropwise into this reaction to quench the excess borane, followed by addition of K_2CO_3 (5.0 g). The mixture was stirred at room temperature for 10 minutes, and filtered through a pad of Celite®. The residue was washed by ether (4 x 20 mL). The combined organic solution was concentrated in reduced pressure. The residue was purified by quick flash chromatography on silica gel eluting with 40-60% v/v EtOAc in hexanes with 3 vol% MeOH to provide the titled compound (3.392 g, 20.07 mmol, 99.4% yield) as a yellowish oil.

TLC: R_f = 0.51 (AcOH/Acetone/Hex = 1:4:5, v/v/v);

$[\alpha]_D^{20}$ -31.0 (*c* 1.705, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 4.35 (dq, *J* = 7.8, 5.2 Hz, 1H, ***H-3***), 3.96-3.76 (m, 4H, ***H-1a***, ***H-1b***, ***H-4a***, ***H-4b***), 2.41 (br. s, 2H, 2 x ***-OH***), 2.23-2.07 (m, 2H, ***H-2a***, ***H-2b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 67.3 (***C-4***), 60.3 (***C-1***), 55.4 (***C-3***), 38.0 (***C-2***);

FTIR (neat): ν_{max} 3317 (br), 2932, 1420, 1234, 1164, 1053, 1026, 930, 820, 642, 568 cm^{-1}.

(*R*)-*tert*-Butyl-(2-(oxiran-2-yl)ethoxy)diphenylsilane (3.34): To a suspension of NaH (60% in mineral oil, 5.84 g, 146 mmol, 3.00 equiv) in freshly distilled THF (300 ml, 0.5 M) was added a solution of diol **3.33** (8.189 g, 48.45 mmol, 1.00 equiv) in THF (100 ml, 0.5 M) via cannula at –15 °C under an atmosphere of N_2. After 20 minutes, a solution of TBDPSCl (13.5 mL, 50.1 mmol, 1.05 equiv) in THF (50.0 ml, 1.0 M) was added at that temperature, and the reaction was allowed to warm to room temperature. It was stirred overnight (ca. 14 hours). Then, the reaction was quenched with ice cubes and poured into a saturated $NaHCO_3$ solution (200 mL). The aqueous layer was extracted with Et_2O (3 x 30 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 2-8 vol% Et_2O in hexanes to provide the titled compound (12.82 g, 39.25 mmol, 81.0% yield) as a yellow oil.

TLC: R_f = 0.61 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +6.2 (*c* 0.97, $CHCl_3$);

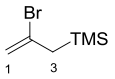
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.72-7.65 (m, 4H, ***H-8***, ***H-8'***, ***H-12***, ***H-12'***), 7.48-7.36 (m, 6H, ***H-9***, ***H-9'***, ***H-13 H-13'***, ***H-10***, ***H-14***), 3.89-3.78 (m, 2H, ***H-1a***, ***H-1b***), 3.12 (dddd, *J* = 5.7, 5.7, 4.0, 2.7 Hz, 1H, ***H-3***), 2.80 (dd, *J* = 5.1, 4.0 Hz, 1H, ***H-4a***), 2.53 (dd, *J* = 5.2, 2.9

Hz, 1H, ***H-4a***), 1.84-1.74 (m, 2H, ***H-2a***, ***H-2b***), 1.07 (s, 9H, ***H-6***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 135.8 (***C-8***, ***C-8'***, ***C-12***, ***C-12'***), 133.9 (***C-7***), 133.8 (***C-11***), 129.9 (***C-10***, ***C-14***), 127.9 (***C-9***, ***C-9'***, ***C-13***, ***C-13'***), 61.1 (***C-1***), 50.3 (***C-3***), 47.5 (***C-4***), 35.9 (***C-2***), 27.0 (***C-6***), 19.4 (***C-5***);

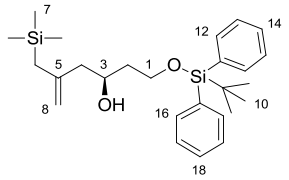
FTIR (neat): ν_{max} 3071, 3049, 2931, 2858, 1590, 1472, 1428, 1390, 1362, 1257, 1112, 910, 866, 824, 740, 703 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{20}H_{26}O_2SiNa$ 349.1600; found 349.1599.



2-Bromoallyltrimethylsilane (3.35): To an oven-dried 300-mL round-bottomed flask equipped with a reflux condenser and a pressure-equalizing additional funnel was added CuCl (0.524 g, 4.92 mmol, 0.05 equiv), anhydrous Et_2O (70 mL, 1.5 M) and freshly distilled NEt_3 (14.5 mL, 104 mmol, 1.0 equiv) subsequently. The mixture of 2,3-dibromopropane (12.0 mL, 104 mmol, 1.0 equiv) and trichlorosilane (12.0 mL, 117 mmol, 1.1 equiv) was added dropwise to the mixture at the rate maintaining a gentle reflux. A voluminous white precipitate formed when the addition started. After addition, this reaction was kept stirring over night (ca. 16 hours) at room temperature. It was then cooled down to 0 ^oC, and MeMgBr (3.0 M solution in Et_2O, 160 mL, 480 mmol, 4.5 equiv) was added slowly. The reaction turned dark black, and it was stirred for a further 18 hours at room temperature. Then, it was carefully quenched with ice cubes at 0 ^oC. A saturated solution of NH_4Cl (300 mL) was added into this reaction, and the mixture was poured into a mixture of Et_2O (100 mL) and H_2O (100 mL). The separated organic layer was washed with H_2O (2 x 50 mL). The combined aqueous layers were extracted with Et_2O (3 x 30 ml). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrated was washed with

CH_2Cl_2 three times. The solvent was removed by normal pressure distillation, and the residue further distilled under reduced pressure of aspirator. The titled compound was obtained as a colorless oil (11.54 g, 59.74 mmol, 57.4% yield) collected at 76.0-82.0 ^oC/aspirator.



(*S*)-1-(*tert*-Butyldiphenylsilyl)oxy-5-((trimethylsilyl)methyl)hex-5-en-3-ol (3.11): To a 100-mL 3-necked flask equipped with a reflux condenser, a pressure-equalizing additional funnel, a rubber septum and a magnetic stirring bar, was added magnesium turnings (2.304 g, 94.80 mmol, 3.0 equiv). This apparatus was flame-dried under a flow of N_2. Then, anhydrous THF (50 mL) was added into this flask at room temperature, followed by addition of a catalytic amount 1,2-dibromoethane (50 uL, 0.57 mmol, 1.3 mol%) to activate the magnesium turnings. It was refluxed for 10 minutes, then a solution of allylsilane **3.35** (8.64 g, 44.7 mmol, 1.4 equiv) in THF (9.0 mL, 5.0 M) was added at the rate maintaining a gentle reflux. This reaction was kept refluxing for further 30 minutes after addition.

To another 250-mL flask, anhydrous CuCl (0.913 g, 4.79 mmol, 0.15 equiv) was mixed with a solution of oxirane **3.34** (10.43 g, 31.95 mmol, 1.0 equiv) in freshly distilled THF (65 mL, 0.5 M) at -78 ^oC. Then, the abovementioned Grignard reagent was quickly transferred into this mixture via cannula. Then, it was allowed to warm to room temperature over 2 hours. It was then quenched with a saturated NH_4Cl solution (100 mL) carefully. The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash

chromatography on silica gel eluting with 2-5 vol% of ethyl ether in hexanes to provide the desired product (4.153 g, 9.422 mmol, 80.1% yield) as a colorless oil.

TLC: R_f = 0.51 (Acetone/cHex = 1:9, v/v);

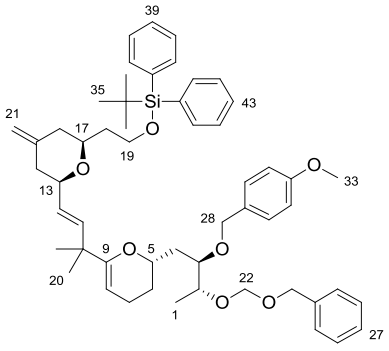
$[\alpha]_D^{20}$ +4.1 (*c* 1.045, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.76-7.62 (m, 4H, ***H-12***, ***H-16***), 7.49-7.34 (m, 6H, ***H-13***, ***H-14***, ***H-17***, ***H-18***), 4.69 (ddd, *J* = 1.0, 1.0, 2.0 Hz, 1H, ***H-8a***), 4.66 (ddd, *J* = 1.0, 1.0, 2.0 Hz, 1H, ***H-8b***), 4.06 (ddddd, *J* = 2.4, 3.9, 5.4, 6.3, 7.8, Hz, 1H, ***H-3***), 3.91 (ddd, *J* = 5.4, 5.4, 10.5 Hz, 1H, ***H-1a***), 3.85 (ddd, *J* = 5.4, 6.8, 10.5 Hz, 1H, ***H-1b***), 2.94 (d, *J* = 2.4 Hz, 1H, ***-OH***), 2.19 (ddd, *J* = 1.0, 7.8, 13.7 Hz, 1H, ***H-4a***), 2.13 (ddd, *J* = 1.0, 5.4, 13.7 Hz, 1H, ***H-4b***), 1.73 (app. q, *J* = 5.7 Hz, 2H, ***H-2***), 1.58 (dABq, *J* = 1.0, 13.2 Hz, *Δv* = 15.7 Hz, 2H, ***H-6***), 1.07 (s, 9H, ***H-10***), 0.05 (s, 9H, ***H-7***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 144.7 (***C-5***), 135.8 (***C-12***, ***C-16***), 133.5 (***C-11***), 133.4 (***C-15***), 130.0 (***C-14***, ***C-18***), 128.0 (***C-13***, ***C-17***), 110.3 (***C-8***), 68.8 (***C-3***), 63.1 (***C-1***), 46.7 (***C-4***), 38.6 (***C-2***), 27.0 (***C-10***), 26.9 (***C-6***), 19.3 (***C-9***), -1.1 (***C-7***);

FTIR (neat): ν_{max} 3516 (br), 3072, 2955, 2859, 1631, 1471, 1427, 1249, 1157, 1110, 851, 738, 703, 613 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{26}H_{40}O_2Si_2Na$ 463.2465; found 463.2471.



(2-((2*S*,6*R*)-6-((*E*)-3-((*S*)-2-((2*R*,3*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-3,4-dihydro-2*H*-pyran-6-yl)-3-methylbut-1-enyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)ethoxy)(*tert*-butyl)diphenylsilane (3.36):

With a –78 °C bath, to a stirred mixture of aldehyde **3.10** (403.1 mg, 0.7925 mmol, 1.0 equiv), and *β*-hydroxyl allylsilane **3.11** (523 mg, 1.19 mmol, 1.5 equiv) in fresh distilled Et_2O (16 mL, 0.05 M) was added pyridine (19.0 uL, 0.235 mmol, 0.3 equiv) via syringe under an atmosphere of N_2. Then, a solution of 1.0 M TMSOTf in Et_2O (0.96 mL, 0.96 mmol, 1.2 equiv) was introduced into this reaction dropwise via syringe. It was stirred for 25 minutes and quenched with DIPEA (1.5 mL, 8.6 mmol, 10 equiv) at this temperature. It was stirred further 30 minutes, and poured into a saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a colorless oil. The crude product was purified by flash chromatography on silica gel eluting with 5-10 vol% of Et_2O in hexanes to provide the titled compound (600 mg, 0.698 mmol, 88.1% yield) as a colorless oil.

TLC: R_f = 0.33 (Et_2O/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +21.9 (*c* 1.56, $CHCl_3$);

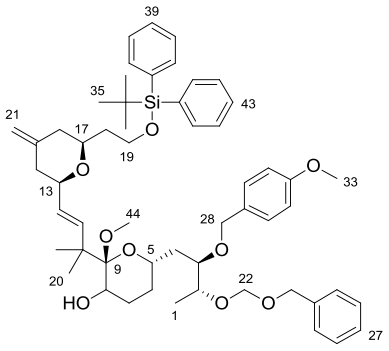
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.74-7.64 (m, 4H, ***H-37***, ***H-37'***, ***H-41***, ***H-41'***), 7.47-7.28 (m, 11H, ***H-25***, ***H-25'***, ***H-26***, ***H-26'***, ***H-27***, ***H-38***, ***H-38'***, ***H-39***, ***H-42***, ***H-42'***, ***H-43***), 7.26 (d, *J* = 8.8 Hz, 2H, ***H-30***, ***H-30'***), 6.86 (d, *J* = 8.8 Hz, 2H, ***H-31***, ***H-31'***), 5.80 (dd, *J* = 1.0, 16.1 Hz, 1H, ***H-11***), 5.53 (dd, *J* = 6.1, 16.1 Hz, 1H, ***H-12***), 4.84 (ABq, *J* = 7.1 Hz, *Δv* = 4.8 Hz, 2H, ***H-22***), 4.72 (d, *J* = 2.0 Hz, 1H, ***H-21a***), 4.71 (d, *J* = 2.0 Hz, 1H, ***H-21b***), 4.65 (ABq, *J* = 12.0 Hz, *Δv* = 9.7 Hz, 2H, ***H-23***), 4.64 (d, *J* = 10.7 Hz, 1H, ***H-28a***), 4.55 (dd, *J* = 3.4, 4.4 Hz, 1H, ***H-8***), 4.54 (d, *J* = 10.7 Hz, 1H, ***H-28b***), 4.03 (dddd, *J* = 2.0, 2.4, 9.8, 10.2 Hz, 1H, ***H-5***), 3.97 (dq, *J* = 5.1, 6.3 Hz, 1H, ***H-2***), 3.90-3.82 (m, 2H, ***H-3***, ***H-19a***), 3.79 (s, 3H, ***H-33***), 3.82-3.72 (m, 2H, ***H-13***, ***H-19b***), 3.54 (dddd, *J* = 2.2, 5.4, 7.6, 11.5 Hz,

1H, ***H-17***), 2.25 (app. t. *J* = 13.4 Hz, 1H, ***H-14a***), 2.25 (app. t. *J* = 13.4 Hz, 1H, ***H-16a***), 2.14-1.97 (m, 2H, ***H-7a***, ***H-16b***), 2.02-1.80 (m, 4H, ***H-4a***, ***H-7b***, ***H-14b***, ***H-18a***), 1.83-1.69 (m, 2H, ***H-6a***, ***H-18b***), 1.62 (ddd, *J* = 2.4, 10.7, 14.1 Hz, 1H, ***H-4b***), 1.50 (dddd, *J* = 6.4, 9.8, 9.8, 13.2 Hz, 1H, ***H-6b***), 1.21 (d, *J* = 6.3 Hz, 3H, ***H-1***), 1.19 (s, 6H, ***H-20***), 1.06 (s, 9H, ***H-35***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 159.4 (***C-32***), 159.0 (***C-9***), 144.9 (***C-15***), 139.1 (***C-11***), 138.1 (***C-24***), 135.7 (***C-37***, ***C-37'***, ***C-41***, ***C-41'***), 134.2 (***C-36***), 134.1 (***C-40***), 131.1 (***C-29***), 129.7 (***C-30***, ***C-30'***, ***C-39***, ***C-43***), 128.6 (***C-26***, ***C-26'***), 128.0 (***C-25***, ***C-25'***), 127.8 (***C-27***, ***C-38***, ***C-38'***, ***C-42***, ***C-42'***), 127.6 (***C-12***), 114.0 (***C-31***, ***C-31'***), 108.7 (***C-21***), 93.6 (***C-22***), 93.4 (***C-8***), 79.2 (***C-13***), 78.0 (***C-3***), 75.4 (***C-17***), 74.1 (***C-2***), 73.7 (***C-28***), 71.7 (***C-5***), 69.6 (***C-23***), 60.5 (***C-19***), 55.5 (***C-33***), 41.3 (***C-16***), 40.9 (***C-14***), 40.7 (***C-10***), 39.2 (***C-18***), 36.4 (***C-4***), 28.3 (***C-6***), 27.1 (***C-35***), 26.1 (***C-20a***), 25.9 (***C-20b***), 20.5 (***C-7***), 19.4 (***C-34***), 15.8 (***C-1***);

FTIR (neat): ν_{max} 3070, 2932, 2887, 2857, 1660, 1613, 1514, 1463, 1428, 1381, 1248, 1111, 1086, 1041, 892, 822, 739, 702 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{54}H_{70}O_7SiNa$ 881.4789; found 881.4797.

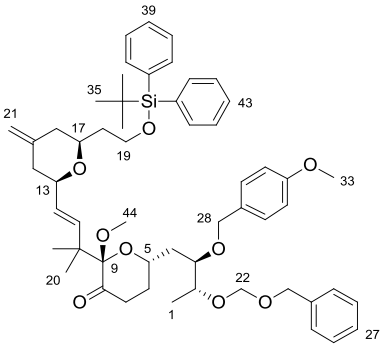


(2*S*,6*S*)-6-((2*R*,3*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxytetrahydro-2*H*-pyran-3-ol (3.37): With a –10 °C bath, to a stirred solution of glycal **3.36** (267 mg,

0.311 mmol, 1.0 equiv) in fresh distilled CH_2Cl_2 (16 mL, 0.02 M) and MeOH (8.0 mL, 0.04 M) was added a solution of *m*CPBA (105 mg, 0.470 mmmol, 1.5 equiv) in CH_2Cl_2 (5.0 mL, 0.1 M) via cannula. This reaction was stirred at this temperature under an atmosphere of N_2 for 3 hours. Then, a saturated solution $Na_2S_2O_3$ (15 mL) was added. It was stirred at room temperature for 30 minutes. It was then poured into a saturated solution of $NaHCO_3$ (15 mL). The aqueous layer was extracted by EtOAc (3 x 10 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a colorless oil.

To the solution of the crude product abovementioned in MeOH (30 mL, 0.01 M) was added a 0.1 M solution of PPTS in MeOH (310 uL, 0.0310 mmol, 0.1 equiv) at room temperature. It was stirred under an atmosphere of N_2 for 1 hour. It was then poured into a saturated solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated by rotary evaporation. The remainder was passed through a pack of sica gel eluting with 15-25 vol% of EtOAc in hexanes to provide a colorless oil.

TLC: R_f = 0.33 (EtOAc/Hex = 3:7, v/v).



(2*S*,6*S*)-6-((2*R*,3*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)-2-

methylbut-3-en-2-yl)-2-methoxydihydro-2*H*-pyran-3(4*H*)-one (3.38): To a stirred solution of alcohol **3.37** (257.3 mg, 0.2836 mmol, 1.0 equiv) in dry CH_2Cl_2 (30 mL, 0.01 M) was added *t*-BuOH (35.0 uL, 0.366 mmol, 1.5 equiv) and freshly distilled pyridine (69.0 uL, 0.853 mmol, 3.0 equiv). Then, this reaction was cooled down to 0 ^oC, and Dess-Martin periodinane (182.4 mg, 0.4171 mmol, 1.5 equiv) was added in one portion. The cooling bath was removed, and the reaction was stirred at room temperature for 1 hour under an atmosphere of N_2, whereupon the reaction was diluted with Et_2O (20 mL), and a saturated $NaHCO_3$ solution (30 mL) was added, followed by a saturated $Na_2S_2O_3$ solution (30 mL). This mixture was stirred for 10 minutes at room temperature. The aqueous layer was extracted by Et_2O (3 x 20 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 10-20% of EtOAc in hexanes to provide the titled compound (256.7 mg, 0.2836 mmol, 96% yield over two steps) as a colorless oil.

TLC: R_f = 0.49 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +14.1 (*c* 0.685, $CHCl_3$);

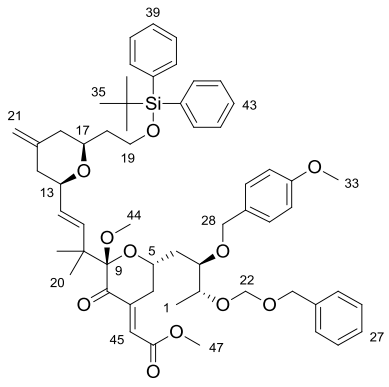
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.68 (ddd, *J* = 1.6, 3.4, 8.1 Hz, 4H, ***H-37***, ***H-37'***, ***H-41***, ***H-41'***), 7.47-7.28 (m, 11H, ***H-25***, ***H-25'***, ***H-26***, ***H-26'***, ***H-27***, ***H-38***, ***H-38'***, ***H-39***, ***H-42***, ***H-42'***, ***H-43***), 7.23 (d, *J* = 8.7 Hz, 2H, ***H-30***, ***H-30'***), 6.86 (d, *J* = 8.7 Hz, 2H, ***H-31***, ***H-31'***), 6.03 (dd, *J* = 1.3, 16.1 Hz, 1H, ***H-11***), 5.50 (dd, *J* = 6.0, 16.1 Hz, 1H, ***H-12***), 4.86 (ABq, *J* = 6.9 Hz, *Δv* = 6.9 Hz, 2H, ***H-22***), 4.75 (br. s, 2H, ***H-21***), 4.67, (s, 2H, ***H-23***), 4.64 (d, *J* = 10.9 Hz, 1H, ***H-28a***), 4.47 (d, *J* = 10.9 Hz, 1H, ***H-28b***), 4.15 (dddd, *J* = 2.6, 2.9, 9.7, 10.1 Hz, 1H, ***H-5***), 4.10 (dq, *J* = 4.8, 6.5 Hz, 1H, ***H-2***), 3.90 (ddd, *J* = 2.1, 4.8, 10.4 Hz, 1H, ***H-***

3), 3.85 (ddd, *J* = 5.2, 7.8, 10.1 Hz, 1H, ***H-19a***), 3.80 (s, 3H, ***H-33***), 3.80-3.73 (m, 2H, ***H-13***, ***H-19b***), 3.55 (dddd, *J* = 2.1, 4.9, 7.3, 11.4 Hz, 1H, ***H-17***), 3.25 (s, 3H, ***H-44***), 2.41 (dd, *J* = 6.8, 9.1 Hz, 1H, ***H-7a***), 2.41 (dd, *J* = 4.7, 8.1 Hz, 1H, ***H-7b***), 2.30-2.19 (m, 2H, ***H-14a***, ***H-16a***), 2.03 (dd, *J* = 11.7, 12.2 Hz, 1H, ***H-14b***), 1,99-1.81 (m, 5H, ***H-4a***, ***H-6a***, ***H-6b***, ***H-16b***, ***H-18a***), 1.76 (dddd, *J* = 2.1, 5.2, 6.9, 14.0 Hz, 1H, ***H-18b***), 1.66 (ddd, *J* = 2.9, 10.4, 14.3 Hz, 1H, ***H-4b***), 1.22 (d, *J* = 6.5 Hz, 3H, ***H-1***), 1.17 (s, 3H, ***H-20a***), 1.12 (s, 3H, ***H-20b***), 1.07 (s, 9H, ***H-35***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 207.5 (***C-8***), 159.4 (***C-32***), 144.7 (***C-15***), 138.0 (***C-24***), 136.7 (***C-11***), 135.7 (***C-37***, ***C-37'***, ***C-41***, ***C-41'***), 134.2 (***C-36***), 134.1 (***C-40***), 130.8 (***C-29***), 129.7 (***C-30***, ***C-30'***), 129.5 (***C-12***), 129.4 (***C-26***, ***C-26'***), 128.6 (***C-39***, ***C-43***), 128.0 (***C-25***, ***C-25'***), 127.9 (***C-27***), 127.8 (***C-38***, ***C-38'***, ***C-42***, ***C-42'***), 114.0 (***C-31***, ***C-31'***), 108.8 (***C-21***), 104.2 (***C-9***), 93.6 (***C-22***), 79.0 (***C-13***), 77.4 (***C-3***), 75.5 (***C-17***), 72.7 (***C-2***), 72.2 (***C-28***), 69.9 (***C-5***), 69.7 (***C-23***), 60.6 (***C-19***), 55.4 (***C-33***), 52.4 (***C-44***), 44.3 (***C-10***), 41.2 (***C-14***), 40.9 (***C-16***), 39.3 (***C-18***), 37.7 (***C-7***), 36.4 (***C-4***), 30.3 (***C-6***), 27.1 (***C-10***), 23.0 (***C-20a***), 22.0 (***C-20b***), 19.4 (***C-34***), 15.0 (***C-1***);

FTIR (neat): ν_{max} 3070, 3031, 2934, 2889, 2858, 1960, 1886, 1822, 1723, 1613, 1514, 1463, 1428, 1382, 1249, 1173, 1111, 1042, 894, 822, 739, 703 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{55}H_{72}O_9SiNa$ 927.4843; found 927.4848.



(*E*)-Methyl 2-((2*S*,6*S*)-6-((2*R*,3*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)-2-

methylbut-3-en-2-yl)-2-methoxy-3-oxodihydro-*2H*-pyran-4(*3H*)-ylidene)acetate (3.39): To a stirred solution of ketone **3.38** (83.8 mg, 0.0926 mmol, 1.0 equiv) in dry MeOH (1.0 mL, 0.1 M) was added K_2CO_3 solid (68 mg, 0.49 mmol, 5.0 equiv). Then a solution of freshly distilled methyl glyoxylate in dry THF (3.0 M, 1.0 mL, 3.0 mmol, 50 equiv) was added into this reaction via syringe in one portion at room temperature. It was stirred under an atmosphere of N_2 for 2.5 hours, whereupon the reaction was diluted with Et_2O (20 mL). It was poured into a saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted by Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 20-30% of Et_2O in hexanes to provide the titled compound (76.1 mg, 0.0780 mmol, 84.3% yield, E:Z > 95:5) as a yellow oil.

TLC: R_f = 0.36 (Et_2O/Hex = 5:5, v/v);

$[\alpha]_D^{20}$ -28.2 (*c* 2.675, $CHCl_3$);

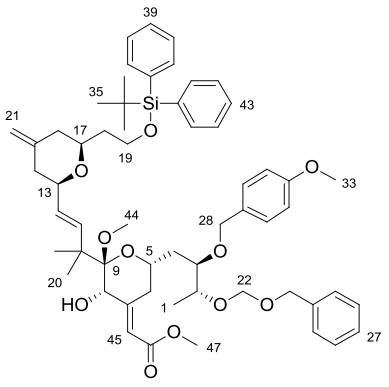
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.68 (ddd, *J* = 1.6, 3.4, 8.1 Hz, 4H, ***H-37***, ***H-37'***, ***H-41***, ***H-41'***), 7.47-7.28 (m, 11H, ***H-25***, ***H-25'***, ***H-26***, ***H-26'***, ***H-27***, ***H-38***, ***H-38'***, ***H-39***, ***H-42***, ***H-42'***, ***H-43***), 7.19 (d, *J* = 8.6 Hz, 2H, ***H-30***, ***H-30'***), 6.83 (d, *J* = 8.6 Hz, 2H, ***H-31***, ***H-31'***), 6.57 (dd, *J* = 1.7, 3.3 Hz, 1H, ***H-45***), 5.83 (dd, *J* = 1.0, 16.0 Hz, 1H, ***H-11***), 5.40 (dd, *J* = 6.1, 16.1 Hz, 1H, ***H-12***), 4.86 (ABq, *J* = 7.0 Hz, *Δv* = 9.7 Hz, 2H, ***H-22***), 4.73 (br. s, 1H, ***H-21a***), 4.71 (br. s, 1H, ***H-21b***), 4.67, (s, 2H, ***H-23***), 4.62 (d, *J* = 11.2 Hz, 1H, ***H-28a***), 4.42 (d, *J* = 11.2 Hz, 1H, ***H-28b***), 4.21-4.08 (m, 1H, ***H-5***), 4.14 (dq, *J* = 4.6, 6.5 Hz, 1H, ***H-2***), 3.91 (ddd, *J* = 2.1, 4.6, 10.1 Hz, 1H, ***H-3***), 3.84 (ddd, *J* = 5.5, 7.8, 10.3 Hz, 1H, ***H-19a***), 3.80-3.73 (m, 1H, ***H-19b***), 3.79 (s, 3H, ***H-33***), 3.74 (s, 3H, ***H-47***), 3.73-3.67 (m, 1H,

H-13), 3.51 (dddd, *J* = 2.0, 5.2, 7.4, 11.4 Hz, 1H, ***H-17***), 3.32 (ddd, *J* = 2.1, 2.1, 18.7, 1H, ***H-6$_{eq}$***), 3.23 (s, 3H, ***H-44***), 2.87 (ddd, *J* = 3.4, 12.5, 18.7, 1H, ***H-6$_{ax}$***), 2.23 (ddd, *J* = 1.6, 2.0, 13.0 Hz, 1H, ***H-16$_{eq}$***), 2.10 (ddd, *J* = 1.6, 1.9, 13.0 Hz, 1H, ***H-14$_{eq}$***), 1.99 (ddd, *J* = 2.1, 9.1, 14.6 Hz, 1H, ***H-4a***), 1,96-1.88 (m, 2H, ***H-14$_{ax}$***, ***H-16$_{ax}$***), 1.86 (dddd, *J* = 5.5, 5.5, 7.4, 13.8 Hz, 1H, ***H-18a***), 1.77 (ddd, *J* = 2.9, 10.1, 14.6 Hz, 1H, ***H-4b***), 1.74 (dddd, *J* = 5.2, 5.7, 7.8, 13.8, 1H, ***H-18b***), 1.23 (d, *J* = 6.5 Hz, 3H, ***H-1***), 1.14 (s, 3H, ***H-20a***), 1.07 (s, 9H, ***H-35***), 1.06 (s, 3H, ***H-20b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 197.7 (***C-8***), 166.2 (***C-46***), 159.4 (***C-32***), 148.2 (***C-7***), 144.6 (***C-15***), 138.0 (***C-24***), 135.8 (***C-11***), 135.7 (***C-37***, ***C-37'***, ***C-41***, ***C-41'***), 134.2 (***C-36***), 134.1 (***C-40***), 130.6 (***C-29***), 130.3 (***C-12***), 129.7 (***C-39***), 129.7 (***C-43***), 129.3 (***C-30***, ***C-30'***), 128.6 (***C-26***, ***C-26'***), 128.0 (***C-25***, ***C-25'***), 127.9 (***C-27***), 127.8 (***C-38***, ***C-38'***, ***C-42***, ***C-42'***), 123.1 (***C-45***), 114.0 (***C-31***, ***C-31'***), 108.8 (***C-21***), 104.7 (***C-9***), 93.6 (***C-22***), 79.0 (***C-13***), 76.9 (***C-3***), 75.5 (***C-17***), 72.3 (***C-2***), 71.7 (***C-28***), 69.7 (***C-23***), 69.6 (***C-5***), 60.5 (***C-19***), 55.4 (***C-33***), 52.3 (***C-44***), 51.9 (***C-47***), 44.9 (***C-10***), 40.8 (***C-16***), 40.5 (***C-14***), 39.2 (***C-18***), 36.3 (***C-4***), 36.1 (***C-6***), 27.1 (***C-35***), 22.6 (***C-20a***), 21.5 (***C-20b***), 19.4 (***C-34***), 14.7 (***C-1***);

FTIR (neat): ν_{max} 3069, 2930, 2856, 1724, 1706, 1514, 1463, 1429, 1249, 1207, 1176, 1111, 1064, 1040, 895, 822, 737, 706, 666, 585 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{58}H_{74}O_{11}SiNa$ 997.4898; found 997.4914.

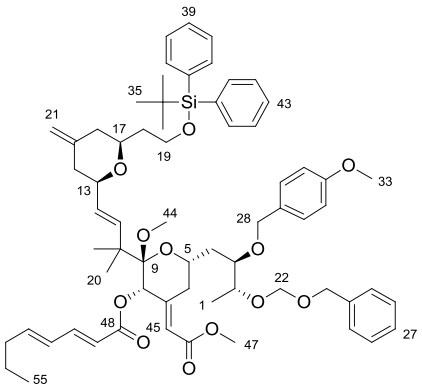


(*E*)-Methyl 2-((2*S*,3*S*,6*S*)-6-((2*R*,3*R*)-3-((Benzyloxy)methoxy)-2-((4-methoxybenzyl)oxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)-2-

methylbut-3-en-2-yl)-3-hydroxy-2-methoxydihydro-2*H*-pyran-4(3*H*)-ylidene)acetate (3.40): To a stirred solution of ketone **3.39** (218 mg, 0.224 mmol, 1.0 equiv) in toluene (1.0 mL, 0.2 M) was added MeOH (25.0 mL, 0.01 M) and then $CeCl_3 \cdot 7H_2O$ (857.8 mg, 2.300 mmol, 10.0 equiv) at room temperature. Until all the solid was dissolved, this reaction was cooled down to -78 °C, and $NaBH_4$ (61 mg, 1.6 mmol, 7.0 equiv) was added in one portion. It was stirred for 2.5 hours at -78 °C, and then stirred for 10 minutes at 0 °C. The reaction was diluted with EtOAc (10 mL), and poured into a cold saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (4 x 10 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a colorless oil (219 mg, 0.224 mmol, 100% yield). The crude product was used in the next step immediately without further purification.

TLC: R_f = 0.36 (EtOAc/Hex = 3:7, v/v);

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{58}H_{76}O_{11}SiNa$ 999.5055; found 999.5051.



(2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-4-methylenetetrahydro-*2H*-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-*2H*-pyran-3-yl Octa-2,4-dienoate (3.41):

To a stirred solution of (2*E*,4*E*), octa-2,4-dienoic acid (94.9 mg, 0.677 mmol, 3.0 equiv) in

dry toluene (13.5 mL, 0.05 M) was added freshly distilled NEt_3 (320 uL, 2.30 mmol, 10.0 equiv), followed by 2,4,6-trichlorobenzoylchloride (108 uL, 0.677 mmol, 3.0 eq) at 0 ^oC. After 10 minutes, the cooling bath was removed, and the reaction was stirred at room temperature under an atmosphere of N_2 for 2 hours.

Then this reaction was transferred to a solution of crude alcohol **3.40** (crude 219 mg, theoretically 0.224 mmol, 1.0 equiv) in toluene (2.5 mL, 0.1 M) via cannula at 0 ^oC. Then, a solution of DMAP (42 mg, 0.34 mmol, 1.5 equiv) in toluene (3.5 mL, 0.1 M) was added into this mixture via cannula. After 10 minutes, the cooling bath was removed, and this reaction was stirred at room temperature for 3 hours. Then, methanol (1 mL, 24.7 mmol) was added at room temperature. This reaction was stirred further 2 hours. It was diluted with ether (10 mL) and poured into a saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The reminder was purified by flash chromatography on silica gel eluting with 10-15 vol% of EtOAc in hexanes to provide a single diastereomer (226 mg, 0.206 mmol, 91.9% yield over two steps, dr > 95:5) as a colorless oil.

TLC: R_f = 0.51 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ -1.8 (*c* 0.47, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.66 (ddd, *J* = 1.6, 2.1, 8.1 Hz, 4H, ***H-37***, ***H-37'***, ***H-41***, ***H-41'***), 7.45-7.23 (m, 11H, ***H-25***, ***H-25'***, ***H-26***, ***H-26'***, ***H-27***, ***H-38***, ***H-38'***, ***H-39***, ***H-42***, ***H-42'***, ***H-43***), 7.27 (dd, *J* = 10.1, 15.1 Hz, 1H, ***H-50***), 7.21 (d, *J* = 8.6 Hz, 2H, ***H-30***, ***H-30'***), 6.83 (d, *J* = 8.6 Hz, 2H, ***H-31***, ***H-31'***), 6.25-6.07 (m, 2H, ***H-51***, ***H-52***), 6.00 (d, *J* = 16.0

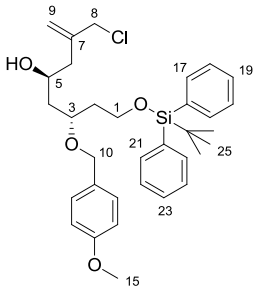
Hz, 1H, ***H-11***), 5.91 (s, 1H, ***H-45***), 5.78 (d, *J* = 15.1 Hz, 1H, ***H-49***), 5.58 (s, 1H, ***H-8***), 5.40 (dd, *J* = 5.5, 16.0 Hz, 1H, ***H-12***), 4.84 (ABq, *J* = 7.0 Hz, $\Delta\nu$ = 5.4 Hz, 2H, ***H-22***), 4.71 (br. s, 1H, ***H-21a***), 4.68 (br. s, 1H, ***H-21b***), 4.66, (s, 2H, ***H-23***), 4.62 (d, *J* = 10.9 Hz, 1H, ***H-28a***), 4.45 (d, *J* = 10.9 Hz, 1H, ***H-28b***), 4.18-4.11 (m, 1H, ***H-5***), 4.10 (dq, *J* = 4.9, 6.5 Hz, 1H, ***H-2***), 3.90 (ddd, *J* = 2.1, 4.7, 10.1 Hz, 1H, ***H-3***), 3.83 (ddd, *J* = 5.7, 7.8, 10.1 Hz, 1H, ***H-19a***), 3.79-3.72 (m, 1H, ***H-19b***), 3.78 (s, 3H, ***H-33***), 3.72-3.66 (m, 1H, ***H-13***), 3.68 (s, 3H, ***H-47***), 3.55-3.45 (m, 1H, ***H-17***), 3.49 (dd, *J* = 2.6, 16.1 Hz, 1H, ***H-6$_{eq}$***), 3.24 (s, 3H, ***H-44***), 2.37 (dd, *J* = 10.7, 16.1 Hz, 1H, ***H-6$_{ax}$***), 2.25-2.20 (m, 1H, ***H-16$_{eq}$***), 2.22-2.17 (m, 1H, ***H-14$_{eq}$***), 2.14 (dt, *J* = 7.2, 7.3 Hz, 2H, ***H-53***), 1,99 (dd, *J* = 12.2, 12.5 Hz, 1H, ***H-14$_{ax}$***), 1.95-1.80 (m, 3H, ***H-4a***, ***H-16$_{ax}$***, ***H-18a***), 1.80-1.67 (m, 2H, ***H-4b***, ***H-18b***), 1.45 (sex, *J* = 7.4 Hz, 2H, ***H-54***), 1.22 (d, *J* = 6.5 Hz, 3H, ***H-1***), 1.14 (s, 6H, ***H-20***), 1.05 (s, 9H, ***H-35***), 0.92 (t, *J* = 7.4 Hz, 3H, ***H-55***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.7 (***C-46***), 165.7 (***C-48***), 159.4 (***C-32***), 153.0 (***C-7***), 146.7 (***C-50***), 145.9 (***C-52***), 144.8 (***C-15***), 138.3 (***C-11***), 138.1 (***C-24***), 135.7 (***C-37***, ***C-37'***, ***C-41***, ***C-41'***), 134.2 (***C-36***), 134.1 (***C-40***), 130.8 (***C-29***), 129.7 (***C-39***, ***C-43***), 129.5 (***C-30***, ***C-30'***), 128.7 (***C-26***, ***C-26'***), 128.6 (***C-51***), 128.0 (***C-25***, ***C-25'***), 127.9 (***C-27***), 127.8 (***C-38***, ***C-38'***, ***C-42***, ***C-42'***), 127.0 (***C-12***), 118.7 (***C-49***), 117.2 (***C-45***), 114.0 (***C-31***, ***C-31'***), 108.7 (***C-21***), 102.9 (***C-9***), 93.6 (***C-22***), 79.0 (***C-13***), 77.1 (***C-3***), 75.6 (***C-17***), 72.7 (***C-2***), 72.2 (***C-28***), 71.8 (***C-8***), 69.7 (***C-23***), 68.3 (***C-5***), 60.7 (***C-19***), 55.5 (***C-33***), 51.5 (***C-44***), 51.3 (***C-47***), 46.2 (***C-10***), 40.9 (***C-16***), 40.8 (***C-14***), 39.3 (***C-18***), 36.6 (***C-4***), 35.3 (***C-53***), 33.2 (***C-6***), 27.1 (***C-35***), 24.3 (***C-20a***), 24.1 (***C-20b***), 22.0 (***C-54***), 19.4 (***C-34***), 15.010 (***C-1***), 13.9 (***C-55***);

FTIR (neat): ν_{max} 2933, 1719, 1643, 1614, 1514, 1431, 1382, 1248, 1107, 891, 822, 739,

704, 613 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{66}H_{86}O_{12}SiNa$ 1121.5786; found 1121.5793.



(4*S*,6*S*)-8-(*tert*-Butyldiphenylsilyloxy)-2-(chloromethyl)-6-(4-methoxybenzyloxy)oct-1-en-4-ol (3.42): To a stirred solution of aldehyde **2.39** (524 mg, 1.10 mmol, 1.0 equiv) in freshly distilled CH_2Cl_2 (22 mL, 0.05 M) was added $MgBr_2{\cdot}Et_2O$ (576 mg, 2.23 mmol, 2.0 equiv) in one portion at –15 °C under an atmosphere of N_2. After 15 minutes, the mixture was then cooled down to –78 °C, and stirred for further 30 minutes, whereupon a solution of 2-(trimethylsilylmethyl)allyltributylstannane (570 uL, 1.67 mmol, 1.5 eq) in CH_2Cl_2 (5.5 mL, 0.3 M) was introduced via cannula over 5 minutes. It was stirred for 4 hours in this condition before being poured into a saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide a colorless oil. The crude product was purified by flash chromatography on silica gel eluting with 2-8 vol% of EtOAc in hexanes to provide the titled compound (494 mg, 0.870 mmol, 79.2% yield, dr = 97:3) as a yellowish oil, and its diastereomer (15.1 mg, 0.0266 mmol, 2.4% yield, dr = 97:3).

TLC: R_f = 0.46 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +8.9 (*c* 1.495, $CHCl_3$);

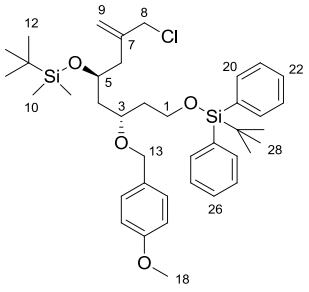
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.74-7.65 (m, 4H, ***H-17***, ***H-17'***, ***H-21***, ***H-21'***), 7.50-7.44 (m, 2H, ***H-19***, ***H-23***), 7.45-7.36 (m, 4H, ***H-18***, ***H-18'***, ***H-22***, ***H-22'***), 7.23 (d, *J* = 8.7 Hz, 2H,

H-12, ***H-12'***), 6.87 (d, *J* = 8.4 Hz, 2H, ***H-13***, ***H-13'***), 5.24 (d, *J* = 1.0 Hz, 1H, ***H-9a***), 5.06 (d, *J* = 1.0 Hz, 1H, ***H-9b***), 4.48 (ABq, *J* = 11.3 Hz, $\Delta\nu$ = 6.9 Hz, 2H, ***H-10***), 4.14-4.07 (m, 2H, ***H-8***), 4.11-4.04 (m, 1H, ***H-5***), 3.99 (dddd, *J* = 6.6, 6.6, 6.6, 3.7 Hz, 1H, ***H-3***), 3.88-3.80 (m, 1H, ***H-1a***), 3.81 (s, 3H, ***H-15***); 3.80-3.73 (m, 1H, ***H-1b***), 2.87 (bs, 1H, ***-OH***), 2.39-2.24 (m, 2H, ***H-6a***, ***H-6b***), 1.99 (dddd, *J* = 13.9, 6.1, 6.1, 6.1 Hz, 1H, ***H-2a***), 1.79 (app. dq, *J* = 14.3, 6.4 Hz, 1H, ***H-2b***), 1.77 (ddd, *J* = 14.7, 9.3, 3.4 Hz, 1H, ***H-4a***), 1.63 (ddd, *J* = 14.6, 6.8, 2.5 Hz, 1H, ***H-4b***), 1.10 (s, 9H, ***H-25***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 159.5 (***C-14***), 142.7 (***C-7***), 135.8 (***C-17***, ***C-17'***, ***C-21***, ***C-21'***), 133.9 (***C-16***), 133.9 (***C-20***), 130.4 (***C-11***), 129.9 (***C-19***, ***C-23***), 129.8 (***C-12***, ***C-12'***), 127.9 (***C-18***, ***C-18'***, ***C-22***, ***C-22'***), 117.2 (***C-9***), 114.0 (***C-13***, ***C-13'***), 74.0 (***C-3***), 71.3 (***C-10***), 66.9 (***C-5***), 60.7 (***C-1***), 55.4 (***C-15***), 48.6 (***C-8***), 41.6 (***C-6***), 40.1 (***C-4***), 36.7 (***C-2***), 27.1 (***C-25a***, ***C-25b***, ***C-25c***), 19.4 (***C-24***);

FTIR (neat): ν_{max} 3480 (br), 3071, 2933, 2859, 1829, 1614, 1588, 1514, 1467, 1428, 1389, 1361, 1301, 1250, 1176, 1108, 912, 831, 739, 704, 666 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{33}H_{43}O_4ClSiNa$ 589.2517; found 589.2526.



(4*S*,6*S*)-4-*(tert*-Butyldimethylsilyloxy)-8-(*tert*-butyldiphenylsilyloxy)-2-(chloromethyl)-6-(4-methoxybenzyloxy)oct-1-ene (3.43): With a -10 ºC bath, to a stirred solution of alcohol **3.42** (1.110 g, 1.957 mmol, 1.0 equiv) in freshly distilled CH_2Cl_2 (40.0 mL, 0.05 M) was added 2,6-lutidine (700 uL, 5.95 mmol, 3.0 equiv) via syringe. Then, TBSOTf (690 uL, 2.94 mmol, 1.5 eq) was added dropwise via syringe. This reaction was stirred under an atmosphere of N_2 for 1 hour, and poured into a saturated $NaHCO_3$

solution (50 mL) . The aqueous layer was then extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (50 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 3 vol% of ethyl acetate in hexanes to provide the desired product (1.276 g, 1.872 mmol, 95.7% yield) as a yellowish oil.

TLC: R_f = 0.63 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +12.0 (*c* 1.635, $CHCl_3$);

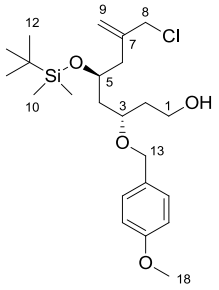
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.69 (app. td, *J* = 6.8, 1.5 Hz, 4H, ***H-20***, ***H-20'***, ***H-24***, ***H-24'***), 7.49-7.34 (m, 6H, ***H-21***, ***H-21'***, ***H-22***, ***H-25***, ***H-25'***, ***H-26***), 7.20 (d, *J* = 8.5 Hz, 2H, ***H-15***, ***H-15'***), 6.86 (d, *J* = 8.5 Hz, 2H, ***H-16***, ***H-16'***), 5.17 (d, *J* = 1.2 Hz, 1H, ***H-9a***), 4.98 (d, *J* = 1.2 Hz, 1H, ***H-9b***), 4.41 (ABq, *J* = 10.9 Hz, $\Delta\nu$ = 29.9 Hz, 2H, ***H-13***), 4.11-4.02 (m, 1H, ***H-5***), 4.06 (br. s, 2H, ***H-8***), 3.85-3.78 (m, 2H, ***H-1***), 3.81 (s, 3H, ***H-18***), 3.83-3.72 (m, 1H, ***H-3***), 2.44 (dd, *J* = 14.2, 5.1 Hz, 1H, ***H-6a***), 2.34 (dd, *J* = 14.2, 7.1 Hz, 1H, ***H-6b***), 1.88-1.75 (m, 2H, ***H-2***), 1.74 (ddd, *J* = 14.2, 8.5, 4.2 Hz, 1H, ***H-4a***), 1.52 (ddd, *J* = 14.3, 7.8, 4.0 Hz, 1H, ***H-4b***), 1.08 (s, 9H, ***H-28***), 0.91 (s, 9H, ***H-12***), 0.10 (s, 3H, ***H-10a***), 0.08 (s, 3H, ***H-10b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 159.3 (***C-17***), 142.4 (***C-7***), 135.8 (***C-20***, ***C-20'***, ***C-24***, ***C-24'***), 134.0 (***C-19***, ***C-23***), 131.2 (***C-14***), 129.8 (***C-22***, ***C-26***), 129.3 (***C-15***, ***C-15'***), 127.9 (***C-21***, ***C-21'***, ***C-25***, ***C-25'***), 117.5 (***C-9***), 114.0 (***C-16***, ***C-16'***), 73.4 (***C-3***), 70.7 (***C-13***), 68.2 (***C-5***), 61.0 (***C-1***), 55.5 (***C-18***), 48.7 (***C-8***), 42.8 (***C-4***), 41.7 (***C-6***), 37.6 (***C-2***), 27.1 (***C-28a***, ***C-28b***, ***C-28c***), 26.2 (***C-12***), 19.4 (***C-27***), 18.2 (***C-11***), -3.8 (***C-10a***), -4.3 (***C-10b***);

FTIR (neat): ν_{max} 3071, 2933, 2858, 1827, 1613, 1588, 1514, 1467, 1429, 1388, 1362, 1301,

1251, 1176, 1108, 1006, 912, 831, 775, 739, 704, 666, 614, 536 cm^{-1}.

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{39}H_{57}O_4ClSi_2Na$ 703.3382; found 703.3384.



(3*S*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(chloromethyl)-3-(4-methoxybenzyloxy)oct-7-en-1-ol (3.44): To a solution of silyl ether **3.43** (379 mg, 0.556 mmol, 1.0 equiv) in MeOH (30 mL, 0.02 M) was added NH_4F solid (409 mg, 11.0 mmol, 20 equiv) in one portion at room temperature. This reaction was heated at 60 °C with stirring for 6 hours, and quenched with a saturated solution of $NaHCO_3$ (100 mL). It was diluted with EtOAc (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The colorless crude product was purified by flash chromatography on silica gel eluting with 18-25 vol% of ethyl acetate in hexanes to provide the desired product (243 mg, 0.548 mmol, 98.6% yield) as a colorless oil.

TLC: R_f = 0.27 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +4.3 (*c* 1.06, $CHCl_3$);

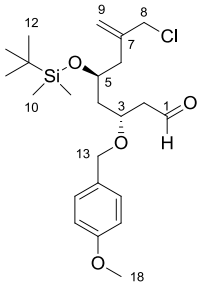
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2H, ***H-15***, ***H-15'***), 6.89 (d, *J* = 8.5 Hz, 2H, ***H-16***, ***H-16'***), 5.21 (d, *J* = 1.0 Hz, 1H, ***H-9a***), 5.01 (d, *J* = 1.2 Hz, 1H, ***H-9b***), 4.48 (ABq, *J* = 10.9 Hz, *Δv* = 23.3 Hz, 2H, ***H-13***), 4.07 (ABq, *J* = 11.7 Hz, *Δv* = 9.5 Hz, 2H, ***H-8***), 4.03 (dddd, *J* = 7.3, 7.2, 5.3, 4.8 Hz, 1H, ***H-5***), 3.86-3.80 (m, 1H, ***H-1a***), 3.81 (s, 3H, ***H-18***), 3.80-3.75 (m, 1H, ***H-3***), 3.76-3.69 (m, 1H, ***H-1b***), 2.42 (dd, *J* = 14.2, 5.5 Hz, 1H, ***H-6a***), 2.34 (dd, *J* = 14.2, 7.1 Hz, 1H, ***H-6b***), 2.24 (br. s, 1H, ***-OH***), 1.95 (dddd, *J* = 14.5, 7.6, 5.1, 4.9 Hz, 1H, ***H-2a***), 1.88 (ddd, *J* = 14.2, 7.4, 4.4 Hz, 1H, ***H-4a***), 1.74 (dddd, *J* =

14.4, 6.4, 6.1, 4.6 Hz, 1H, ***H-2b***), 1.54 (ddd, *J* = 14.3, 7.7, 4.8 Hz, 1H, ***H-4b***), 0.90 (s, 9H, ***H-12***), 0.09 (s, 3H, ***H-10a***), 0.08 (s, 3H, ***H-10b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 159.5 (***C-17***), 142.2 (***C-7***), 130.6 (***C-14***), 129.5 (***C-15***, ***C-15'***), 117.7 (***C-9***), 114.1 (***C-16***, ***C-16'***), 75.6 (***C-3***), 70.8 (***C-13***), 68.4 (***C-5***), 60.5 (***C-1***), 55.5 (***C-18***), 48.8 (***C-8***), 41.9 (***C-4***), 41.624 (***C-6***), 36.207 (***C-2***), 26.1 (***C-12***), 18.2 (***C-11***), -3.9 (***C-10a***), -4.3 (***C-10b***);

FTIR (neat): ν_{max} 3423 (br), 2952, 2858, 1613, 1514, 1466, 1385, 1302, 1251, 1176, 1081, 913, 834, 776, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{23}H_{39}O_4ClSiNa$ 465.2204; found 465.2205.



(3*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(chloromethyl)-3-(4-methoxybenzyloxy)oct-7-enal (3.45): To a stirred solution of alcohol **3.44** (351.4 mg, 0.7931 mmol, 1.0 equiv) in dry CH_2Cl_2 (40 mL, 0.02 M) was added *t*-BuOH (100 uL, 1.04 mmol, 1.3 equiv) and freshly distilled pyridine (193 uL, 2.38 mmol, 3.0 equiv). Then this reaction was cooled down to 0 ºC, and Dess-Martin periodinane (519 mg, 1.19 mmol, 1.5 equiv) was added in one portion. After 10 minutes, the cooling bath was removed and the reaction was stirred at room temperature for 1 hour under an atmosphere of N_2. Then, a saturated $NaHCO_3$ solution (20 mL) was added into this reaction, followed by a saturated $Na_2S_2O_3$ solution (20 mL). This mixture was stirred for 10 minutes at ambient temperature. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel

eluting with 5-12 vol% of EtOAc in hexanes to provide the titled compound (301.4 mg, 0.6833 mmol, 86.2% yield) as a colorless oil.

TLC: R_f = 0.41 (EtOAc/Hex = 3:7, v/v);

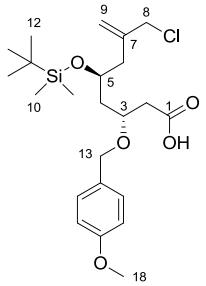
$[\alpha]_D^{20}$ 17.8 (*c* 1.275, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 9.81 (dd, *J* = 2.4, 2.2 Hz, 1H, ***H-1***), 7.24 (d, *J* = 8.7 Hz, 2H, ***H-15***, ***H-15'***), 6.89 (d, *J* = 8.7 Hz, 2H, ***H-16***, ***H-16'***), 5.20 (d, *J* = 1.2 Hz, 1H, ***H-9a***), 5.00 (d, *J* = 1.2 Hz, 1H, ***H-9b***), 4.47 (ABq, *J* = 10.7 Hz, *Δv* = 27.5 Hz, 2H, ***H-13***), 4.14-4.05 (m, 2H, ***H-3***, ***H-5***), 4.06 (dd, *J* = 11.7, 1.0 Hz, 1H, ***H-8a***), 4.03 (dd, *J* = 11.7, 1.0 Hz, 1H, ***H-8b***), 3.81 (s, 3H, ***H-18***), 2.69 (ddd, *J* = 16.1, 5.9, 2.4 Hz, 1H, ***H-2a***), 2.65 (ddd, *J* = 16.2, 5.6, 2.2 Hz, 1H, ***H-2b***), 2.46 (ddd, *J* = 14.2, 4.9, 1.0 Hz, 1H, ***H-6a***), 2.32 (ddd, *J* = 14.2, 7.6, 1.0 Hz, 1H, ***H-6b***), 1.87 (ddd, *J* = 14.3, 8.4, 3.5 Hz, 1H, ***H-4a***), 1.53 (ddd, *J* = 14.3, 8.3, 4.0 Hz, 1H, ***H-4b***), 0.90 (s, 9H, ***H-12***), 0.10 (s, 3H, ***H-10a***), 0.09 (s, 3H, ***H-10b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 201.4 (***C-1***), 159.5 (***C-17***), 142.0 (***C-7***), 130.4 (***C-14***), 129.4 (***C-15***, ***C-15'***), 117.8 (***C-9***), 114.1 (***C-16***, ***C-16'***), 71.8 (***C-3***), 71.1 (***C-13***), 68.0 (***C-5***), 55.5 (***C-18***), 48.9 (***C-2***), 48.7 (***C-8***), 42.8 (***C-4***), 41.8 (***C-6***), 26.1 (***C-12***), 18.2 (***C-11***), -3.8 (***C-10a***), -4.4 (***C-10b***);

FTIR (neat): ν_{max} 2953, 2857, 2725, 1725, 1644, 1613, 1587, 1514, 1466, 1384, 1301, 1251, 1176, 1093, 915, 834, 776, 665, 571 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{23}H_{37}O_4ClSiNa$ 463.2047; found 463.2057.



(3*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(chloromethyl)-3-(4-methoxybenzyloxy)oct-7-enic Acid (3.12): To a stirred solution of aldehyde **3.45** (300 mg, 0.681 mmol, 1.0 equiv) in *t*-BuOH (34 mL, 0.02 M) and isoamylene (17 mL, 0.04 M) was added distilled H_2O (3.5 mL, 0.2 M) and KH_2PO_4 (931 mg, 6.84 mmol, 10 equiv). This mixture was stirred at room temperature for 20 minutes, whereupon it was homogenous. This reaction was then cooled down to 0 ^oC, and $NaClO_2$ (393 mg, 3.48 mmol, 5.0 equiv) was added in one portion. It was stirred at this temperature for 2 hours and quenched with a saturated NaS_2O_3 solution (15 mL). After 30 minutes, it was then poured into a mixture of EtOAc (20 mL) and brine (30 mL). The aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 9-20 vol% of EtOAc in hexanes with 1 vol% methanol to provide the titled compound (311 mg, 0680 mmol, 99.9% yield) as a colorless oil.

TLC: R_f = 0.26 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +16.1 (*c* 1.045, $CHCl_3$);

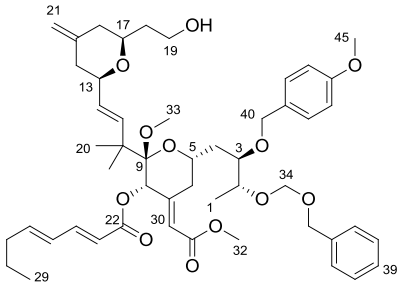
500 MHz ^{1}H NMR ($CDCl_3$) δ 11.01 (br. s, 1H, ***-CO$_2$H***), 7.25 (d, *J* = 8.7 Hz, 2H, ***H-15***, ***H-15'***), 6.88 (d, *J* = 8.7 Hz, 2H, ***H-16***, ***H-16'***), 5.18 (d, *J* =1.0 Hz, 1H, ***H-9a***), 4.99 (d, *J* =1.0 Hz, 1H, ***H-9b***), 4.51 (ABq, *J* = 10.7 Hz, *Δv* = 51.1 Hz, 2H, ***H-13***), 4.11-4.02 (m, 1H, ***H-5***), 4.04 (dd, *J* = 11.8, 0.7 Hz, 1H, ***H-8a***), 4.03 (dd, *J* = 11.7, 1.0 Hz, 1H, ***H-8b***), 4.07-3.99 (m, 1H, ***H-3***), 3.81 (s, 3H, ***H-18***), 2.68 (dd, *J* = 15.4, 5.9 Hz, 1H, ***H-2a***), 2.59 (dd, *J* = 15.4,

6.1 Hz, 1H, ***H-2b***), 2.46 (ddd, *J* = 14.2, 4.9, 1.0 Hz, 1H, ***H-6a***), 2.32 (ddd, *J* = 14.2, 7.6, 0.7 Hz, 1H, ***H-6b***), 1.83 (ddd, *J* = 14.4, 8.5, 3.4 Hz, 1H, ***H-4a***), 1.57 (ddd, *J* = 14.4, 8.3, 3.7 Hz, 1H, ***H-4b***), 0.90 (s, 9H, ***H-12***), 0.10 (s, 3H, ***H-10a***), 0.09 (s, 3H, ***H-10b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 177.3 (***C-1***), 159.5 (***C-17***), 142.0 (***C-7***), 130.4 (***C-14***), 129.5 (***C-15***, ***C-15'***), 117.8 (***C-9***), 114.1 (***C-16***, ***C-16'***), 73.2 (***C-3***), 71.3 (***C-13***), 68.0 (***C-5***), 55.5 (***C-18***), 48.7 (***C-8***), 42.6 (***C-4***), 41.8 (***C-6***), 40.0 (***C-2***), 26.1 (***C-12***), 18.2 (***C-11***), -3.8 (***C-10a***), -4.4 (***C-10b***);

FTIR (neat): ν_{max} 3338 (br), 2954, 2932, 2858, 1711, 1613, 1514, 1465, 1441, 1386, 1363, 1302, 1251, 1174, 1083, 1037, 915, 835, 776, 665 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{23}H_{37}O_5ClSiNa$ 479.1997; found 479.2003.



(2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-(2-hydroxyethyl)-4-methylenetetrahydro-*2H*-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-*2H*-pyran-3-yl Octa-2,4-dienoate (3.46): To a stirred solution of silyl ether **3.41** (331.8 mg, 0.3018 mmol, 1.0 equiv) in MeOH (30.0 mL, 0.01 M) was added NH_4F solid (347 mg, 9.28 mmol, 30.0 equiv) in one portion at room temperature. This reaction was stirred at 60 ^oC for 24 hours, whereupon it was diluted with EtOAc (20 ml) and poured into a saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure.

The remainder was purified by flash chromatography on silica gel eluting with 20-30 vol% of EtOAc in hexanes to provide the titled compound (254.4 mg, 0.2954 mmol, 97.9% yield) as a yellow oil.

TLC: R_f = 0.23 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ -5.5 (*c* 1.985, $CHCl_3$);

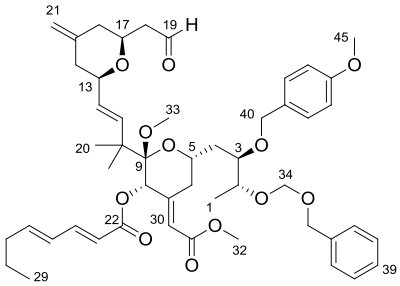
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.33 (m, 4H, ***H-37***, ***H-37'***, ***H-38***, ***H-38'***), 7.32-7.25 (m, 2H, ***H-39***, ***H-24***), 7.22 (d, *J* = 8.8 Hz, 2H, ***H-42***, ***H-42'***), 6.84 (d, *J* = 8.8 Hz, 2H, ***H-43***, ***H-43'***), 6.23-6.14 (m, 2H, ***H-25***, ***H-26***), 6.02 (dd, *J* = 16.0, 1.2 Hz, 1H, ***H-11***), 5.89 (br. s, 1H, ***H-30***), 5.79 (d, *J* = 15.3 Hz, 1H, ***H-23***), 5.61 (br. s, 1H, ***H-8***), 5.36 (dd, *J* = 16.0, 5.9 Hz, 1H, ***H-12***), 4.87 (s, 2H, ***H-34***), 4.73 (d, *J* = 1.8 Hz, 1H, ***H-21a***), 4.70 (dd, *J* = 2.1, 1.8 Hz, 1H, ***H-21b***), 4.68 (s, 2H, ***H-35***), 4.63 (d, *J* = 11.0 Hz, 1H, ***H-40a***), 4.45 (d, *J* = 11.0 Hz, 1H, ***H-40b***), 4.16-4.07 (m, 1H, ***H-5***), 4.13 (qd, *J* = 6.5, 4.7 Hz, 1H, ***H-2***), 3.91 (ddd, *J* = 10.3, 4.7, 2.2 Hz, 1H, ***H-3***), 3.84-3.70 (m, 2H, ***H-19a***, ***H-19b***), 3.79 (s, 3H, ***H-45***), 3.71-3.58 (m, 1H, ***H-13***), 3.67 (s, 3H, ***H-32***), 3.50 (dddd, *J* = 11.4, 8.7, 3.6, 2.7 Hz, 1H, ***H-17***), 3.44 (dd, *J* = 16.1, 2.9 Hz, 1H, ***H-6$_{eq}$***), 3.24 (s, 3H, ***H-33***), 2.94 (br. s, 1H, ***-OH***), 2.43 (ddd, *J* = 15.8, 11.7, 1.6 Hz, 1H, ***H-6$_{ax}$***), 2.24-2.12 (m, 4H, ***H-14$_{eq}$***, ***H-27***, ***H-16$_{eq}$***), 2.07-1.95 (m, 2H, ***H-16$_{ax}$***, ***H-14$_{ax}$***), 1.94 (ddd, *J* = 14.3, 9.6, 2.1 Hz, 1H, ***H-4a***), 1.82-1.69 (m, 3H, ***H-18a***, ***H-18b***, ***H-4b***), 1.47 (sex, *J* = 7.3 Hz, 2H, ***H-28***), 1.24 (d, *J* = 6.2 Hz, 3H, ***H-1***), 1.13 (s, 3H, ***H-20a***), 1.11 (s, 3H, ***H-20b***), 0.93 (t, *J* = 7.4 Hz, 3H, ***H-29***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 166.8 (***C-31***), 165.6 (***C-22***), 159.4 (***C-44***), 153.4 (***C-7***), 146.7 (***C-24***), 145.9 (***C-26***), 144.1 (***C-15***), 138.9 (***C-11***), 138.1 (***C-36***), 130.7 (***C-41***), 129.5 (***C-42***, ***C-42'***), 128.6 (***C-38***, ***C-38'***), 128.6 (***C-25***), 128.0 (***C-37***, ***C-37'***), 127.9 (***C-39***), 126.5 (***C-12***), 118.6 (***C-23***), 116.7 (***C-30***), 114.0 (***C-43***, ***C-43'***), 109.1 (***C-21***), 102.8 (***C-9***), 93.5

(***C-34***), 79.4 (***C-13***), 78.1 (***C-17***), 77.0 (***C-3***), 72.7 (***C-2***), 72.1 (***C-40***), 71.6 (***C-8***), 69.6 (***C-35***), 68.3 (***C-5***), 60.9 (***C-19***), 55.4 (***C-45***), 51.3 (***C-32***, ***C-33***), 46.2 (***C-10***), 40.9 (***C-14***), 40.8 (***C-16***), 38.4 (***C-18***), 36.5 (***C-4***), 35.3 (***C-27***), 33.4 (***C-6***), 24.1 (***C-20a***), 24.0 (***C-20b***), 22.0 (***C-28***), 15.0 (***C-1***), 13.9 (***C-29***);

FTIR (neat): ν_{max} 2936, 1718, 1643, 1614, 1514, 1436, 1248, 1042, 891, 738, 699 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{50}H_{68}O_{12}Na$ 883.4608; found 883.4605.



(2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(Benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-((*E*)-2-methyl-4-((2*R*,6*S*)-4-methylene-6-(2-oxoethyl)tetrahydro-*2H*-pyran-2-yl)but-3-en-2-yl)tetrahydro-*2H*-pyran-3-yl Octa-2,4-dienoate (3.47): To a stirred solution of alcohol **3.46** (243.1 mg, 0.2823 mmol, 1.0 equiv) in dry CH_2Cl_2 (30 mL, 0.01 M) was added *t*-BuOH (35 uL, 0.37 mmol, 1.3 equiv) and freshly distilled pyridine (70 uL, 0.87 mmol, 3.0 equiv). Then this reaction was cooled down to 0 ^oC, and Dess-Martin periodinane (186 mg, 0.425 mmol, 1.5 equiv) was added in one portion. After 10 minutes, the cooling bath was removed and the reaction was stirred at room temperature for 1 hour under an atmosphere of N_2. Then, a saturated $NaHCO_3$ solution (20 mL) was added into this reaction, followed by a saturated $Na_2S_2O_3$ solution (20 mL). This mixture was stirred for 10 minutes at ambient temperature. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash

chromatography on silica gel eluting with 12-20 vol% of EtOAc in hexanes to provide the titled compound (236.8 mg, 0.2757 mmol, 97.6% yield) as a yellowish oil.

TLC: R_f = 0.32 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ -6.1 (*c* 1.03, $CHCl_3$);

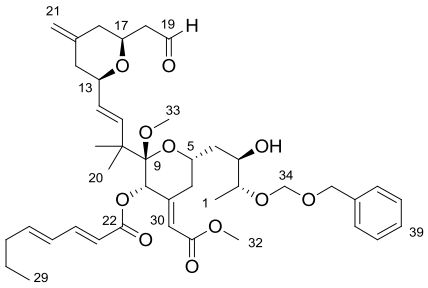
500 MHz ^{1}H NMR ($CDCl_3$) δ 9.77 (t, *J* = 2.2, 1H, ***H-19***), 7.39-7.33 (m, 4H, ***H-37***, ***H-37'***, ***H-38***, ***H-38'***), 7.33-7.24 (m, 2H, ***H-39***, ***H-24***), 7.22 (d, *J* = 8.7 Hz, 2H, ***H-42***, ***H-42'***), 6.84 (d, *J* = 8.7 Hz, 2H, ***H-43***, ***H-43'***), 6.24-6.12 (m, 2H, ***H-25***, ***H-26***), 6.02 (dd, *J* = 16.0, 1.3 Hz, 1H, ***H-11***), 5.90 (br. s, 1H, ***H-30***), 5.78 (d, *J* = 15.1 Hz, 1H, ***H-23***), 5.58 (br. s, 1H, ***H-8***), 5.35 (dd, *J* = 15.9, 5.9 Hz, 1H, ***H-12***), 4.87 (ABq, *J* = 7.1 Hz, $\Delta\nu$ = 3.8 Hz, 2H, ***H-34***), 4.76 (dd, *J* = 3.8, 1.8 Hz, 1H, ***H-21a***), 4.73 (dd, *J* = 3.8, 2.0 Hz, 1H, ***H-21b***), 4.68 (s, 2H, ***H-35***), 4.62 (d, *J* = 10.7 Hz, 1H, ***H-40a***), 4.44 (d, *J* = 10.7 Hz, 1H, ***H-40b***), 4.15-4.08 (m, 1H, ***H-5***), 4.13 (qd, *J* = 6.5, 4.8 Hz, 1H, ***H-2***), 3.91 (ddd, *J* = 10.2, 4.8, 2.2 Hz, 1H, ***H-3***), 3.83-3.75 (m, 1H, ***H-17***), 3.79 (s, 3H, ***H-45***), 3.72 (dddd, *J* = 11.2, 5.9, 2.3, 1.3, 1H, ***H-13***), 3.67 (s, 3H, ***H-32***), 3.47 (dd, *J* = 16.3, 2.7 Hz, 1H, ***H-6$_{eq}$***), 3.24 (s, 3H, ***H-33***), 2.65 (ddd, *J* = 16.3, 7.3, 2.4 Hz, 1H, ***H-18a***), 2.50 (ddd, *J* = 16.3, 5.1, 2.0 Hz, 1H, ***H-18b***), 2.39 (ddd, *J* = 16.1, 11.7, 1.9 Hz, 1H, ***H-6$_{ax}$***), 2.30-2.11 (m, 4H, ***H-16$_{eq}$***, ***H-14$_{eq}$***, ***H-27***), 2.04-1.93 (m, 2H, ***H-14$_{ax}$***, ***H-16$_{ax}$***), 1.92 (ddd, *J* = 14.4, 9.8, 2.2 Hz, 1H, ***H-4a***), 1.74 (ddd, *J* = 14.4, 10.2, 2.7 Hz, 1H, ***H-4b***), 1.47 (sex, *J* = 7.4 Hz, 2H, ***H-28***), 1.23 (d, *J* = 6.4 Hz, 3H, ***H-1***), 1.13 (s, 3H, ***H-20a***), 1.12 (s, 3H, ***H-20b***), 0.93 (t, *J* = 7.3 Hz, 3H, ***H-29***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 201.2 (***C-19***), 166.7 (***C-31***), 165.6 (***C-22***), 159.4 (***C-44***), 153.0 (***C-7***), 146.7 (***C-24***), 146.0 (***C-26***), 143.5 (***C-15***), 139.0 (***C-11***), 138.1 (***C-36***), 130.7 (***C-41***), 129.5 (***C-42***, ***C-42'***), 128.7 (***C-38***, ***C-38'***), 128.6 (***C-25***), 128.0 (***C-37***, ***C-37'***), 127.9 (***C-39***), 126.2 (***C-12***), 118.6 (***C-23***), 117.0 (***C-30***), 114.0 (***C-43***, ***C-43'***), 109.7 (***C-21***), 102.8

(***C-9***), 93.6 (***C-34***), 79.4 (***C-13***), 77.0 (***C-3***), 73.6 (***C-17***), 72.6 (***C-2***), 72.1 (***C-40***), 71.7 (***C-8***), 69.7 (***C-35***), 68.4 (***C-5***), 55.5 (***C-45***), 51.5 (***C-33***), 51.3 (***C-32***), 49.9 (***C-18***), 46.2 (***C-10***), 40.6 (***C-16***), 40.5 (***C-14***), 36.5 (***C-4***), 35.3 (***C-27***), 33.2 (***C-6***), 24.2 (***C-20a***), 24.1 (***C-20b***), 22.1 (***C-28***), 14.9 (***C-1***), 13.9 (***C-29***);

FTIR (neat): ν_{max} 2936, 1719, 1643, 1614, 1514, 1459, 1382, 1304, 1248, 1042, 892, 858, 821, 739, 699, 536 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{50}H_{66}O_{12}Na$ 881.4452; found 881.4451.



(2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(Benzyloxymethoxy)-2-hydroxybutyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-((*E*)-2-methyl-4-((2*R*,6*S*)-4-methylene-6-(2-oxoethyl)tetrahydro-*2H*-pyran-2-yl)but-3-en-2-yl)tetrahydro-*2H*-pyran-3-yl Octa-2,4-dienoate (3.48): To a stirred solution of PMB ether **3.47** (69.5 mg, 80.9 umol, 1.0 equiv) in CH_2Cl_2 (1.6 mL, 0.05M) was added a 0.1 M phosphate *p*H = 6 buffer solution (0.80 mL, 0.1 M). Then, this reaction was cooled down to 0 ºC, and DDQ (38 mg, 160 umol, 2.0 equiv) was added in one portion. It was stirred for 5 hours at this temperature. Then, this reaction was diluted with EtOAc (10 mL), and poured into a saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 28-38 vol% of EtOAc in hexanes to provide the titled compound (55.6 mg, 75.2 umol, 93.0% yield) as a pale colorless oil.

TLC: R_f = 0.20 (EtOAc/Hex = 4:6, v/v);

$[\alpha]_D^{20}$ -14.3 (*c* 2.06, $CHCl_3$);

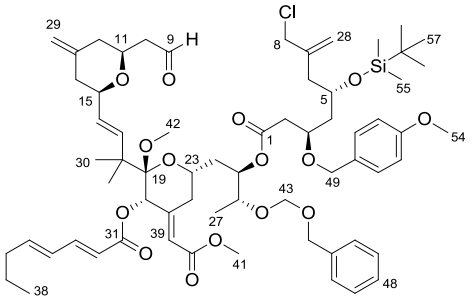
500 MHz ^{1}H NMR ($CDCl_3$) δ 9.81 (t, *J* = 2.2, 1H, ***H-19***), 7.39-7.32 (m, 4H, ***H-37***, ***H-37'***, ***H-38***, ***H-38'***), 7.32-7.24 (m, 2H, ***H-39***, ***H-24***), 6.23-6.11 (m, 2H, ***H-25***, ***H-26***), 6.02 (dd, *J* = 16.1, 1.2 Hz, 1H, ***H-11***), 5.89 (dd, *J* = 1.2, 1.0 Hz, 1H, ***H-30***), 5.78 (d, *J* = 15.4 Hz, 1H, ***H-23***), 5.60 (br. s, 1H, ***H-8***), 5.35 (dd, *J* = 16.0, 6.0 Hz, 1H, ***H-12***), 4.87 (ABq, *J* = 7.0 Hz, *Δv* = 22.2 Hz, 2H, ***H-34***), 4.76 (dd, *J* = 3.7, 2.0 Hz, 1H, ***H-21a***), 4.74 (dd, *J* = 3.8, 1.8 Hz, 1H, ***H-21b***), 4.66 (ABq, *J* = 11.7 Hz, *Δv* = 15.3 Hz, 2H, ***H-35***), 4.22 (dddd, *J* = 11.7, 7.8, 3.2, 3.1 Hz, 1H, ***H-5***), 3.93-3.85 (m, 1H, ***H-3***), 3.82 (dddd, *J* = 11.4, 7.7, 5.1, 2.4 Hz, 1H, ***H-17***), 3.72 (dddd, *J* = 11.3, 5.9, 2.4, 1.2 Hz, 1H, ***H-13***), 3.67 (s, 3H, ***H-32***), 3.69-3.64 (m, 1H, ***H-2***), 3.44 (ddd, *J* = 16.1, 2.4, 0.8 Hz, 1H, ***H-6$_{eq}$***), 3.35 (s, 3H, ***H-33***), 2.77 (d, *J* = 4.4 Hz, 1H, ***-OH***), 2.67 (ddd, *J* = 16.3, 7.6, 2.6 Hz, 1H, ***H-18a***), 2.52 (ddd, *J* = 16.3, 5.1, 2.0 Hz, 1H, ***H-18b***), 2.42 (ddd, *J* = 16.1, 11.7, 2.0 Hz, 1H, ***H-6$_{ax}$***), 2.25 (ddd, *J* = 13.2, 2.1, 1.6 Hz, 1H, ***H-16$_{eq}$***), 2.21 (ddd, *J* = 13.2, 2.1, 1.7 Hz, 1H, ***H-14$_{eq}$***), 2.16 (q, *J* = 6.6 Hz, 2H, ***H-27***), 2.04-1.94 (m, 2H, ***H-14$_{ax}$***, ***H-16$_{ax}$***), 1.78-1.67 (m, 2H, ***H-4a***, ***H-4b***), 1.46 (sext, *J* = 7.3 Hz, 2H, ***H-28***), 1.27 (d, *J* = 6.3 Hz, 3H, ***H-1***), 1.124 (s, 3H, ***H-20a***), 1.117 (s, 3H, ***H-20b***), 0.92 (t, *J* = 7.3 Hz, 3H, ***H-29***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 201.4 (***C-19***), 166.7 (***C-31***), 165.5 (***C-22***), 153.2 (***C-7***), 146.7 (***C-24***), 145.9 (***C-26***), 143.5 (***C-15***), 139.3 (***C-11***), 137.7 (***C-36***), 128.7 (***C-38***, ***C-38'***), 128.5 (***C-25***), 128.1 (***C-37***, ***C-37'***), 128.0 (***C-39***), 126.0 (***C-12***), 118.6 (***C-23***), 116.7 (***C-30***), 109.6 (***C-21***), 102.8 (***C-9***), 93.9 (***C-34***), 79.4 (***C-13***), 78.0 (***C-2***), 73.5 (***C-17***), 71.8 (***C-8***), 71.1 (***C-3***), 70.0 (***C-35***), 68.2 (***C-5***), 51.4 (***C-33***), 51.2 (***C-32***), 49.9 (***C-18***), 46.1 (***C-10***), 40.6 (***C-14***), 40.5 (***C-16***), 39.6 (***C-4***), 35.2 (***C-27***), 33.1 (***C-6***), 24.2 (***C-20a***), 23.9 (***C-20b***),

22.0 (***C-28***), 16.9 (***C-1***), 13.9 (***C-29***);

FTIR (neat): ν_{max} 3513 (br), 2933, 1952, 1771, 1718, 1643, 1617, 1496, 1457, 1436, 1382, 1356, 1313, 1243, 1134, 1105, 1056, 893, 861, 752, 700, 668, 633, 605, 536 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{42}H_{58}O_{11}Na$ 761.3877; found 761.3876.



(2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(Benzyloxymethoxy)-2-(((3*R*,5*S*)-5-(*tert*-butyldimethylsilyloxy)-7-chloromethyl-3-(4-methoxybenzyloxy)oct-7-enoyl)oxy)butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-((*E*)-2-methyl-4-((2*R*,6*S*)-4-methylene-6-(2-oxoethyl)tetrahydro-*2H*-pyran-2-yl)but-3-en-2-yl)tetrahydro-*2H*-pyran-3-yl Octa-2,4-dienoate (3.49): Under an atmosphere of N_2, to a stirred mixture of alcohol **3.48** (181.0 mg, 0.2450 mmol, 1.0 equiv), acid **3.12** (153.5 mg, 0.3358 mmol, 1.3 equiv) and DMAP (33.6 mg, 0.272 mmol, 1.0 equiv) in toluene (12.0 mL, 0.02 M) was added DIPEA (220 uL, 1.26 mmol, 5.0 equiv) at 0 °C. Then, 2,4,6-trichlorobenzoylchloride (51.0 uL, 0.339 mmol, 1.3 equiv) was added dropwise via syringe. The reaction turned cloudy and white precipitate appeared during the addition. It was allowed to warm to room temperature slowly, and stirred overnight (ca. 16 hours). Then, it was diluted with ethyl ether (10 mL), and poured into a saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The reminder was purified by flash chromatography on silica gel eluting with

18-25 vol% of ethyl acetate in hexanes to provide the tiltled compound (264.3 mg, 0.2244 mmol, 91.6% yield) as a colorless oil.

TLC: R_f = 0.48 (EtOAc/Hex = 4:6, v/v);

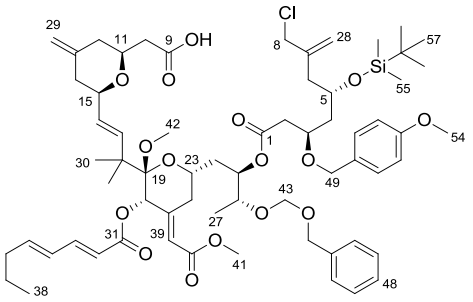
$[\alpha]_D^{20}$ -2.2 (*c* 2.405, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 9.80 (t, *J* = 2.2 Hz, 1H, ***H-9***), 7.43-7.31 (m, 4H, ***H-46***, ***H-46'***, ***H-47***, ***H-47'***), 7.31-7.25 (m, 2H, ***H-48***, ***H-33***), 7.22 (d, *J* = 8.5 Hz, 2H, ***H-51***, ***H-51'***), 6.84 (d, *J* = 8.5 Hz, 2H, ***H-52***, ***H-52'***), 6.25-6.10 (m, 2H, ***H-34***, ***H-35***), 5.99 (d, *J* = 16.1 Hz, 1H, ***H-17***), 5.89 (br. s, 1H, ***H-39***), 5.77 (d, *J* = 15.4 Hz, 1H, ***H-32***), 5.50 (br. s, 1H, ***H-20***), 5.41 (ddd, *J* = 9.8, 4.2, 2.4 Hz, 1H, ***H-25***), 5.33 (dd, *J* = 16.0, 5.7 Hz, 1H, ***H-16***), 5.18 (d, *J* = 0.8 Hz, 1H, ***H-28a***), 4,99 (d, *J* = 1.0 Hz, 1H, ***H-28b***), 4.83 (ABq, *J* = 7.0 Hz, $\Delta\nu$ = 6.7 Hz, 2H, ***H-43***), 4.76 (d, *J* = 2.0 Hz, 1H, ***H-29a***), 4.75 (d, *J* = 2.0 Hz, 1H, ***H-29b***), 4.65 (s, 2H, ***H-44***), 4.55 (d, *J* = 10.9 Hz, 1H, ***H-49a***), 4.41 (d, *J* = 10.9 Hz, 1H, ***H-49b***), 4.13-3.99 (m, 2H, ***H-5***, ***H-3***), 4.03 (br. s, 2H, ***H-8a***, ***H-8b***), 3.94 (qd, *J* = 6.5, 4.0 Hz, 1H, ***H-26***), 3.88-3.75 (m, 2H, ***H-23***, ***H-11***), 3.77 (s, 3H, ***H-54***), 3.75-3.69 (m, 1H, ***H-15***), 3.66 (s, 3H, ***H-41***), 3.39 (dd, *J* = 15.8, 2.1 Hz, 1H, ***H-22$_{eq}$***), 3.21 (s, 3H, ***H-42***), 2.66 (ddd, *J* = 16.4, 7.7, 2.6 Hz, 1H, ***H-10a***), 2.64 (dd, *J* = 15.4, 6.1 Hz, 1H, ***H-2a***), 2.54 (dd, *J* = 15.2, 5.6 Hz, 1H, ***H-2b***), 2.50 (ddd, *J* = 16.4, 5.0, 2.1 Hz, 1H, ***H-10b***), 2.45 (dd, *J* = 14.2, 4.6 Hz, 1H, ***H-6a***), 2.40-2.33 (m, 1H, ***H-22$_{ax}$***), 2.30 (dd, *J* = 14.4, 7.6 Hz, 1H, ***H-6b***), 2.27-2.20 (m, 2H, ***H-14$_{eq}$***, ***H-12$_{eq}$***), 2.16 (dtd, *J* = 7.4, 5.1, 2.7 Hz, 2H, ***H-36***), 2.02-1.82 (m, 4H, ***H-12$_{ax}$***, ***H-14$_{ax}$***, ***H-24a***, ***H-24b***), 1.79 (ddd, *J* = 14.3, 8.7, 3.4 Hz, 1H, ***H-4a***), 1.51 (ddd, *J* = 14.3, 8.5, 3.9 Hz, 1H, ***H-4b***), 1.47 (sext, *J* = 7.3 Hz, 2H, ***H-37***), 1.18 (d, *J* = 6.3 Hz, 3H, ***H-27***), 1.11 (s, 6H, ***H-30a***, ***H-30b***), 0.93 (t, *J* = 7.4 Hz, 3H, ***H-38***), 0.89 (s, 9H, ***H-57***), 0.092 (s, 3H, ***H-55a***), 0.075 (s, 3H, ***H-55b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 201.4 (***C-9***), 170.9 (***C-1***), 166.7 (***C-40***), 165.5 (***C-31***), 159.3 (***C-53***), 152.9 (***C-21***), 146.7 (***C-33***), 146.0 (***C-35***), 143.6 (***C-13***), 142.1 (***C-7***), 139.0 (***C-17***), 138.0 (***C-45***), 130.7 (***C-50***), 129.1 (***C-51***, ***C-51'***), 128.6 (***C-47***, ***C-47'***), 128.6 (***C-34***), 128.1 (***C-46***, ***C-46'***), 127.9 (***C-48***), 126.2 (***C-16***), 118.6 (***C-32***), 117.7 (***C-28***), 117.0 (***C-39***), 114.0 (***C-52***, ***C-52'***), 109.7 (***C-29***), 102.9 (***C-19***), 93.6 (***C-43***), 79.4 (***C-15***), 73.6 (***C-11***), 73.3 (***C-26***), 73.1 (***C-3***), 71.9 (***C-20***, ***C-25***), 71.1 (***C-49***), 69.8 (***C-44***), 68.1 (***C-23***), 67.8 (***C-5***), 55.4 (***C-54***), 51.5 (***C-42***), 51.3(***C-41***), 49.9 (***C-10***), 48.7 (***C-8***), 46.1 (***C-18***), 42.6 (***C-4***), 41.8 (***C-6***), 40.5 (***C-12***, ***C-14***), 40.3 (***C-2***), 36.3 (***C-24***), 35.3 (***C-36***), 32.9 (***C-22***), 26.1 (***C-57***), 24.2 (***C-30a***), 24.0 (***C-30b***), 22.1 (***C-37***), 18.2 (***C-56***), 15.8 (***C-27***), 13.9 (***C-38***), -3.8 (***C-55a***), -4.4 (***C-55b***);

FTIR (neat): ν_{max} 2933, 2858, 1723, 1643, 1615, 1514, 1463, 1382, 1303, 1250, 1102, 1041, 911, 835, 776, 745, 700, 665, 536 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{65}H_{93}O_{15}ClSiNa$ 1199.5870; found 1199.5877.



2-((2*S*,6*R*)-6-((*E*)-3-((2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(Benzyloxymethoxy)-2-(((3*R*,5*S*)-5-(*tert*-butyldimethylsilyloxy)-7-chloromethyl-3-(4-methoxybenzyloxy)oct-7-enoyl)oxy)butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-3-((2*E*,4*E*)-octa-2,4-dienoyloxy)tetrahydro-*2H*-pyran-2-yl)-3-methylbut-1-en-1-yl)-4-methylenetetrahydro-*2H*-pyran-2-yl)acetic Acid (3.50): To a stirred solution of aldehyde **3.49** (80.1 mg, 0.0680 mmol, 1.0 equiv) in CH_3CN (3.5 mL, 0.02 M) was added *t*-BuOH (3.5 mL, 0.02M) and isomylene (1.7 mL, 0.04 M). With an

ice-water bath, a solution of $NaH_2PO_4 \cdot H_2O$ (97 mg, 0.70 mmol, 10.0 equiv) and $NaClO_2$ (80 mg, 0.71 mmol, 10.0 equiv) in D.I. H_2O (1.7 mL, 0.04 M) was added into this reaction. It was stirred for 3 hours, and then quenched by addition of a saturated $Na_2S_2O_3$ solution (10 mL). This mixture was stirred for 10 minutes at ambient temperature. The reaction was diluted by EtOAc (10 mL) and poured into a mixture of a saturated NH_4Cl solution (10 mL) and brine (10 mL). The aqueous layer was extracted with EtOAc (4 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 15-35 vol% of EtOAc in hexanes to provide the titled compound (76.3 mg, 0.0639 mmol, 94.0% yield) as a colorless oil.

TLC: R_f = 0.53 (MeOH/EtOAc/Hex = 1:4:5, v/v/v);

$[\alpha]_D^{20}$ -10.1 (*c* 1.475, $CHCl_3$);

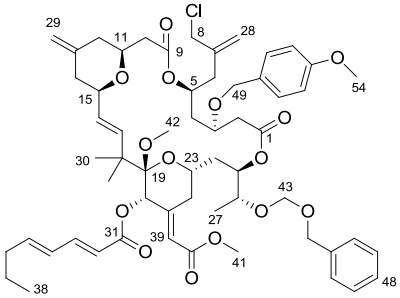
500 MHz ^{1}H NMR ($CDCl_3$) δ ***-CO$_2$H*** not observed, 7.41-7.31 (m, 4H, ***H-46***, ***H-46'***, ***H-47***, ***H-47'***), 7.31-7.24 (m, 2H, ***H-48***, ***H-33***), 7.22 (d, *J* = 8.8 Hz, 2H, ***H-51***, ***H-51'***), 6.84 (d, *J* = 8.8 Hz, 2H, ***H-52***, ***H-52'***), 6.23-6.13 (m, 2H, ***H-34***, ***H-35***), 6.08 (dd, *J* = 16.1, 1.2 Hz, 1H, ***H-17***), 5.90 (br. s, 1H, ***H-39***), 5.76 (d, *J* = 15.4 Hz, 1H, ***H-32***), 5.43 (br. s, 1H, ***H-20***), 5.41 (ddd, *J* = 9.9, 4.1, 2.3 Hz, 1H, ***H-25***), 5.30 (dd, *J* = 16.0, 5.7 Hz, 1H, ***H-16***), 5.17 (d, *J* = 1.0 Hz, 1H, ***H-28a***), 4.98 (d, *J* = 1.2 Hz, 1H, ***H-28b***), 4.84 (ABq, *J* = 7.1 Hz, *Δv* = 5.6 Hz, 2H, ***H-43***), 4.75 (ABq, *J* = 6.8 Hz, *Δv* = 11.8 Hz, 2H, ***H-29***), 4.67 (ABq, *J* = 11.8 Hz, *Δv* = 9.2 Hz, 2H, ***H-44***), 4.54 (d, *J* = 10.9 Hz, 1H, ***H-49a***), 4.41 (d, *J* = 10.9 Hz, 1H, ***H-49b***), 4.11-3.99 (m, 4H, ***H-5***, ***H-3***, ***H-8***), 3.95 (qd, *J* = 6.4, 4.1 Hz, 1H, ***H-26***), 3.85-3.75 (m, 1H, ***H-23***), 3.77 (s, 3H, ***H-54***), 3.79-3.69 (m, 2H, ***H-11***, ***H-15***), 3.66 (s, 3H, ***H-41***), 3.46 (dd, *J* = 15.6, 2.7 Hz, 1H, ***H-22$_{eq}$***), 3.21 (s, 3H, ***H-42***), 2.65 (dd, *J* = 15.1, 6.1 Hz, 1H,

H-2a), 2.61 (dd, *J* = 15.0, 7.7 Hz, 1H, ***H-10a***), 2.56 (dd, *J* = 15.0, 5.5 Hz, 1H, ***H-2b***), 2.52 (dd, *J* = 15.2, 4.8 Hz, 1H, ***H-10b***), 2.44 (dd, *J* = 14.0, 4.5 Hz, 1H, ***H-6a***), 2.36-2.26 (m, 2H, $\boldsymbol{H\text{-}22_{ax}}$, ***H-6b***), 2.28-2.19 (m, 2H, $\boldsymbol{H\text{-}12_{eq}}$, $\boldsymbol{H\text{-}14_{eq}}$), 2.16 (td, *J* = 7.3, 5.7 Hz, 2H, ***H-36***), 2.04-1.95 (m, 3H, $\boldsymbol{H\text{-}12_{ax}}$, $\boldsymbol{H\text{-}14_{ax}}$, ***H-24a***), 1.91 (ddd, *J* = 14.6, 9.9, 2.6 Hz, 1H, ***H-24b***), 1.79 (ddd, *J* = 14.3, 8.7, 3.4 Hz, 1H, ***H-4a***), 1.51 (ddd, *J* = 14.2, 8.4, 3.9 Hz, 1H, ***H-4b***), 1.46 (sex, *J* = 7.3 Hz, 2H, ***H-37***), 1.18 (d, *J* = 6.4 Hz, 3H, ***H-27***), 1.11 (s, 3H, ***H-30a***), 1.10 (s, 3H, ***H-30b***), 0.92 (t, *J* = 7.4 Hz, 3H, ***H-38***), 0.89 (s, 9H, ***H-57***), 0.088 (s, 3H, ***H-55a***), 0.071 (s, 3H, ***H-55b***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 173.2 (***C-9***), 171.3 (***C-1***), 166.8 (***C-40***), 165.5 (***C-31***), 159.3 (***C-53***), 152.5 (***C-21***), 146.7 (***C-33***), 146.0 (***C-35***), 143.2 (***C-13***), 142.1 (***C-7***), 140.0 (***C-17***), 137.8 (***C-45***), 130.6 (***C-50***), 129.2 (***C-51***, ***C-51'***), 128.7 (***C-47***, ***C-47'***), 128.6 (***C-34***), 128.1 (***C-46***, ***C-46'***), 127.9 (***C-48***), 125.2 (***C-16***), 118.6 (***C-32***), 117.7 (***C-28***), 117.5 (***C-39***), 114.0 (***C-52***, ***C-52'***), 109.9 (***C-29***), 102.9 (***C-19***), 93.5 (***C-43***), 79.3 (***C-15***), 74.6 (***C-11***), 73.5 (***C-26***), 73.1 (***C-3***), 72.1 (***C-20***), 72.1 (***C-25***), 71.1 (***C-49***), 69.8 (***C-44***), 68.2 (***C-23***), 67.8 (***C-5***), 55.4 (***C-54***), 51.8 (***C-42***), 51.3 (***C-41***), 48.7 (***C-8***), 46.0 (***C-18***), 42.5 (***C-4***), 41.8 (***C-6***), 41.1 (***C-10***), 40.5 (***C-14***), 40.2 (***C-2***), 40.1 (***C-12***), 36.5 (***C-24***), 35.3 (***C-36***), 32.4 (***C-22***), 26.1 (***C-57***), 24.0 (***C-30a***), 23.9 (***C-30b***), 22.0 (***C-37***), 18.2 (***C-56***), 15.8 (***C-27***), 13.9 (***C-38***), -3.9 (***C-55a***), -4.4 (***C-55b***);

FTIR (neat): ν_{max} 3353 (br), 2933, 1718, 1643, 1615, 1514, 1437, 1382, 1303, 1249, 1159, 1103, 911, 835, 776, 737, 699, 665, 591, 536 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{65}H_{93}O_{16}ClSiNa$ 1215.5819; found 1215.5823.



(2*E*,4*E*)-(1*R*,2*E*,5*S*,6*S*,7*E*,9*S*,11*R*,15*R*,17*S*,21*S*)-11-((*R*)-1-(Benzyloxymethoxy)ethyl)-17-(2-chloromethylallyl)-5-methoxy-7-(2-methoxy-2-oxoethylidene)-15-(4-methoxybenzyloxy)-4,4-dimethyl-23-methylene-13,19-dioxo-12,18,25,26-tetraoxatricyclo[19.3.1.1^{5,9}]hexacos-2-en-6-yl Octa-2,4-dienoate (3.51):

To a stirred solution of acid **3.50** (143.9 mg, 120.5 umol, 1.0 equiv) in THF (6.0 mL, 0.02 M) and MeOH (2.0 mL, 0.06 M) was added HF•Py solution (50 vol%, 0.60 mL, 0.20 M) at 0 ^{o}C. It was allowed to warm to room temperature and stirred for 1 day. Then, it was poured into a solution of brine (20 mL). The separated aqueous layer was extracted with EtOAc (5 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 10-25 vol% of EtOAc in hexanes with 2 vol% MeOH to provide a colorless oil (117.3 mg, 108.6 umol, 90.2% yield).

With an ice-water bath, to a stirred solution of abovementioned seco acid (117.3 mg, 108.6 umol, 1.0 equiv) in toluene (11.0 mL, 0.01 M) was added 2,4,6-trichlorobenzoylchloride (23.0 uL, 144 umol, 1.3 equiv) followed by DIPEA (95.0 uL, 545 umol, 5.0 equiv) under an atmosphere of N_2. After 3 hours, this reaction was transferred to another flask containing 10 mL of toluene and DMAP (13.3 mg, 109 umol, 1.0 equiv) via syring pump at the rate 1mL/1h. It was stiired for 2 hours after addition. Then, it was poured into a saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with

ether (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The reminder was purified by flash chromatography on silica gel eluting with 18-30 vol% of ethyl acetate in hexanes to provide the desired product (95.5 mg, 90.0 umol, 74.7% yield over two steps) as a colorless oil.

TLC: R_f = 0.55 (MeOH/EtOAc/Hex = 1:3:6, v/v/v);

$[\alpha]_D^{20}$ +20.3 (*c* 0.34, $CHCl_3$);

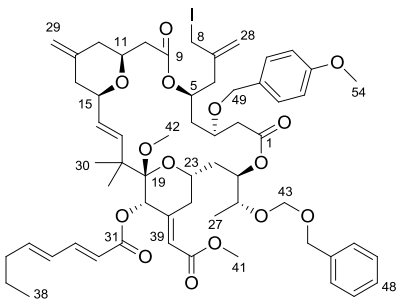
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.48-7.33 (m, 4H, ***H-46***, ***H-46'***, ***H-47***, ***H-47'***), 7.33-7.27 (m, 2H, ***H-48***, ***H-33***), 7.26 (d, *J* = 8.3 Hz, 2H, ***H-51***, ***H-51'***), 6.86 (d, *J* = 8.5 Hz, 2H, ***H-52***, ***H-52'***), 6.34 (d, *J* = 15.9 Hz, 1H, ***H-17***), 6.27-6.11 (m, 2H, ***H-34***, ***H-35***), 5.98 (br. s, 1H, ***H-39***), 5.77 (d, *J* = 15.1 Hz, 1H, ***H-32***), 5.60 (ddd, *J* = 10.1, 4.3, 0.7 Hz, 1H, ***H-25***), 5.35 (dd, *J* = 15.7, 8.2 Hz, 1H, ***H-16***), 5.31 (s, 1H, ***H-20***), 5.25-5.16 (m, 1H, ***H-5***), 5.16 (s, 1H, ***H-28a***), 4.96 (s, 1H, ***H-28b***), 4.85 (ABq, *J* = 7.1 Hz, *Δv* = 9.9 Hz, 2H, ***H-43***), 4.76 (br. s, 1H, ***H-29a***), 4.72 (br. s, 1H, ***H-29b***), 4.67 (s, 2H, ***H-44***), 4.51 (d, *J* = 10.7 Hz, 1H, ***H-49a***), 4.39 (d, *J* = 10.7 Hz, 1H, ***H-49b***), 4.03 (ABq, *J* = 12.0 Hz, *Δv* = 36.6 Hz, 2H, ***H-8***), 4.04-3.95 (m, 2H, ***H-15***, ***H-3***), 3.90 (dq, *J* = 6.6, 6.3 Hz, 1H, ***H-26***), 3.80 (s, 3H, ***H-54***), 3.69 (s, 3H, ***H-41***), 3.76-3.64 (m, 2H, ***H-23***, ***H-22$_{eq}$***), 3.58 (app. t, *J* = 10.1 Hz, 1H, ***H-11***), 3.12 (s, 3H, ***H-42***), 2.79 (dd, *J* = 17.6, 4.6 Hz, 1H, ***H-2a***), 2.55 (dd, *J* = 15.0, 9.1 Hz, 1H, ***H-10a***), 2.46-2.36 (m, 2H, ***H-6***), 2.33 (dd, *J* = 17.7, 7.7 Hz, 1H, ***H-2b***), 2.28 (app. d, *J* = 14.6 Hz, 1H, ***H-10b***), 2.23-2.08 (m, 5H, ***H-22$_{ax}$***, ***H-12$_{eq}$***, ***H-36***, ***H-14$_{eq}$***), 2.07-1.98 (m, 1H, ***H-24a***), 1.99 (t, *J* = 13.4 Hz, 1H, ***H-14$_{ax}$***), 1.97 (t, *J* = 13.1 Hz, 1H, ***H-12$_{ax}$***), 1.90 (td, *J* = 14.1, 9.7 Hz, 1H, ***H-24b***), 1.58 (ddd, *J* = 13.5, 11.8, 2.0 Hz, 1H, ***H-4a***), 1.45 (sext, *J* = 7.3 Hz, 2H, ***H-37***), 1.46-1.38 (m, 1H, ***H-4b***), 1.23 (d, *J* = 6.3 Hz, 3H, ***H-27***), 1.13 (s, 3H, ***H-30a***), 1.09 (s,

3H, ***H-30b***), 0.92 (t, *J* = 7.2 Hz, 3H, ***H-38***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 171.8 (***C-9***), 171.1 (***C-1***), 167.0 (***C-40***), 165.5 (***C-31***), 159.4 (***C-53***), 151.7 (***C-21***), 146.9 (***C-33***), 146.1 (***C-35***), 143.7 (***C-13***), 141.4 (***C-7***), 141.2 (***C-17***), 137.9 (***C-45***), 130.5 (***C-50***), 130.1 (***C-51***, ***C-51'***), 128.7 (***C-47***, ***C-47'***), 128.6 (***C-34***), 128.1 (***C-46***, ***C-46'***), 128.0 (***C-48***), 125.7 (***C-16***), 119.4 (***C-39***), 118.6 (***C-32***), 117.9 (***C-28***), 114.1 (***C-52***, ***C-52'***), 109.4 (***C-29***), 103.3 (***C-19***), 93.5 (***C-43***), 80.5 (***C-15***), 75.1 (***C-11***), 73.9 (***C-26***), 73.0 (***C-20***), 71.9 (***C-49***), 71.5 (***C-3***), 71.1 (***C-25***), 69.9 (***C-44***), 69.7 (***C-5***), 67.4 (***C-23***), 55.5 (***C-54***), 52.7 (***C-42***), 51.4 (***C-41***), 48.1 (***C-8***), 45.1 (***C-18***), 42.7 (***C-10***), 41.5 (***C-12***), 41.2 (***C-14***), 40.9 (***C-4***), 39.8 (***C-2***), 38.7 (***C-6***), 36.0 (***C-24***), 35.3 (***C-36***), 30.8 (***C-22***), 26.8 (***C-30a***), 22.0 (***C-37***), 21.0 (***C-30b***), 16.1 (***C-27***), 13.9 (***C-38***);

FTIR (neat): ν_{max} 2926, 2855, 1722, 1641, 1613, 1513, 1459, 1381, 1249, 1160, 1090, 1044, 739, 700, 666, 590 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na^+] Calcd for $C_{59}H_{77}O_{15}ClNa$ 1083.4849; found 1083.4863.



(2*E*,4*E*)-(1*R*,2*E*,5*S*,6*S*,7*E*,9*S*,11*R*,15*R*,17*S*,21*S*)-11-((*R*)-1-(Benzyloxymethoxy)ethyl)-17-(2-iodomethylallyl)-5-methoxy-7-(2-methoxy-2-oxoethylidene)-15-(4-methoxybenzyloxy)-4,4-dimethyl-23-methylene-13,19-dioxo-12,18,25,26-tetraoxatricyclo[19.3.1.1^{5,9}]hexacos-2-en-6-yl Octa-2,4-dienoate (3.52): To a stirred solution of allylchloride **3.51** (26.5 mg, 25.0 umol, 1.0 equiv) in dry acetone (5.0 mL, 0.005 M) was added NaI solid (32.4 mg, 385 umol, 15 equiv) in one portion at room temperature. It was stirred under an atmosphere of N_2 for 24 hours. This reaction

was added Et_2O (10 mL) and poured into brine (15 mL). The aqueous layer was extracted by Et_2O (4 x 5 mL). The combined organic layers were dried over Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 18-27 vol% of EtOAc in hexanes to provide the titled compound (26.4 mg, 0.229 umol, 91.7% yield) as a pale yellow oil.

TLC: R_f = 0.38 (Et_2O/CH_2Cl_2/Hex = 1:1:2, v/v/v);

$[\alpha]_D^{20}$ +16.0 (*c* 1.31, $CHCl_3$);

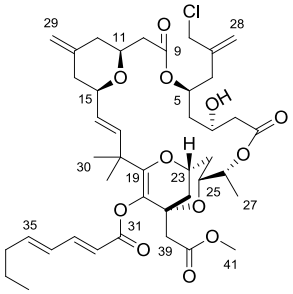
500 MHz ^{1}H NMR ($CDCl_3$) δ 7.45-7.33 (m, 4H, ***H-46***, ***H-46'***, ***H-47***, ***H-47'***), 7.33-7.27 (m, 2H, ***H-48***, ***H-33***), 7.27 (d, *J* = 8.7 Hz, 2H, ***H-51***, ***H-51'***), 6.86 (d, *J* = 8.7 Hz, 2H, ***H-52***, ***H-52'***), 6.33 (d, *J* = 15.9 Hz, 1H, ***H-17***), 6.26-6.11 (m, 2H, ***H-34***, ***H-35***), 5.98 (d, *J* = 2.0 Hz, 1H, ***H-39***), 5.77 (d, *J* = 15.4 Hz, 1H, ***H-32***), 5.59 (ddd, *J* = 10.9, 4.8, 1.8 Hz, 1H, ***H-25***), 5.35 (dd, *J* = 15.8, 8.3 Hz, 1H, ***H-16***), 5.31 (s, 1H, ***H-20***), 5.26 (br. s, 1H, ***H-28a***), 5.19 (dddd, *J* = 8.6, 6.5, 6.5, 2.2 Hz, 1H, ***H-5***), 4.91 (app. d, *J* = 1.0 Hz, 1H, ***H-28b***), 4.85 (ABq, *J* = 7.0 Hz, *Δv* = 9.1 Hz, 2H, ***H-43***), 4.76 (app. q, *J* = 1.8 Hz, 1H, ***H-29a***), 4.72 (app. td, *J* = 1.8, 1.7 Hz, 1H, ***H-29b***), 4.67 (s, 2H, ***H-44***), 4.52 (d, *J* = 10.6 Hz, 1H, ***H-49a***), 4.40 (d, *J* = 10.8 Hz, 1H, ***H-49b***), 4.05-3.96 (m, 2H, ***H-3***, ***H-15***), 3.92 (ABq, *J* = 9.7 Hz, *Δv* = 35.6 Hz, 2H, ***H-8***), 3.89 (qd, *J* = 6.4, 4.8 Hz, 1H, ***H-26***), 3.80 (s, 3H, ***H-54***), 3.69 (s, 3H, ***H-41***), 3.75-3.65 (m, 2H, ***H-23***, ***H-22$_{eq}$***), 3.59 (dddd, *J* = 10.8, 9.4, 2.1, 1.7 Hz, 1H, ***H-11***), 3.13 (s, 3H, ***H-42***), 2.78 (dd, *J* = 17.4, 4.6 Hz, 1H, ***H-2a***), 2.56 (dd, *J* = 14.9, 9.1 Hz, 1H, ***H-10a***), 2.48 (dd, *J* = 14.9, 7.2 Hz, 1H, ***H-6a***), 2.44 (dd, *J* = 14.6, 5.4 Hz, 1H, ***H-6b***), 2.33 (dd, *J* = 17.5, 7.6 Hz, 1H, ***H-2b***), 2.29 (dd, *J* = 14.9, 3.6 Hz, 1H, ***H-10b***), 2.23-2.07 (m, 5H, ***H-22$_{ax}$***, ***H-12$_{eq}$***, ***H-36***, ***H-14$_{eq}$***), 2.07-1.93 (m, 3H, ***H-24a***, ***H-14$_{ax}$***, ***H-12$_{ax}$***), 1.89 (ddd, *J* = 14.5, 9.8, 1.8 Hz, 1H, ***H-24b***), 1.58 (ddd, *J* = 14.6, 10.6, 2.3 Hz, 1H, ***H-4a***), 1.45 (sext, *J* =

7.3 Hz, 2H, ***H-37***), 1.47-1.39 (m, 1H, ***H-4b***), 1.23 (d, *J* = 6.5 Hz, 3H, ***H-27***), 1.13 (s, 3H, ***H-30a***), 1.10 (s, 3H, ***H-30b***), 0.92 (t, *J* = 7.4 Hz, 3H, ***H-38***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 171.8 (***C-9***), 171.1 (***C-1***), 167.0 (***C-40***), 165.5 (***C-31***), 159.4 (***C-53***), 151.7 (***C-21***), 146.9 (***C-33***), 146.1 (***C-35***), 143.7 (***C-13***), 142.8 (***C-7***), 141.2 (***C-17***), 137.9 (***C-45***), 130.5 (***C-50***), 130.1 (***C-51***, ***C-51'***), 128.7 (***C-47***, ***C-47'***), 128.6 (***C-34***), 128.1 (***C-46***, ***C-46'***), 128.0 (***C-48***), 125.7 (***C-16***), 119.3 (***C-39***), 118.6 (***C-32***), 117.1 (***C-28***), 114.1 (***C-52***, ***C-52'***), 109.4 (***C-29***), 103.2 (***C-19***), 93.5 (***C-43***), 80.4 (***C-15***), 75.2 (***C-11***), 73.9 (***C-26***), 72.9 (***C-20***), 71.9 (***C-49***), 71.5 (***C-3***), 71.1 (***C-25***), 69.9 (***C-44***), 69.7 (***C-5***), 67.4 (***C-23***), 55.5 (***C-54***), 52.7 (***C-42***), 51.4 (***C-41***), 45.1 ***C-18***), 42.8 (***C-10***), 41.5 (***C-12***), 41.2 (***C-14***), 40.9 (***C-4***), 39.8 (***C-2***), 39.6 (***C-6***), 36.0 (***C-24***), 35.3 (***C-36***), 30.8 (***C-22***), 30.5 (***C-30a***), 29.9 (***C-30b***), 22.0 (***C-37***), 16.1 (***C-27***), 13.9 (***C-38***), 10.5 (***C-8***);

FTIR (neat): ν_{max} 2929, 2856, 1721, 1628, 1461, 1378, 1259, 1134, 1090, 1062, 913, 838, 734, 667, 618 cm^{-1};

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{59}H_{77}O_{15}INa$ 1175.4205; found 1175.4220.



(2*E*,4*E*)-(1*R*,7*R*,11*S*,15*S*,17*R*,21*R*,22*R*,24*S*,*E*)-15-(2-(Chloromethyl)allyl)-17-hydroxy-24-(2-methoxy-2-oxoethyl)-4,4,21-trimethyl-9-methylene-13,19-dioxo-2,14,20,23,28-pentaoxatetracyclo[20.3.1.13,24.17,11]octacosa-3(27),5-dien-27-yl octa-2,4-dienoate (3.56):

To a stirred solution of compound **3.51** (5.3 mg, 5.3 umol, 1.0 equiv) in CH_2Cl_2 (5 mL, 0.001M) was added a 0.1 M phosphate pH = 6 buffer solution (0.5 mL, 0.01 M). Then, this reaction was cooled down to 0 ºC, and DDQ (4.1 mg, 18 umol, 3.0 equiv) was added

in one portion. It was stirred for 3 hours at this temperature. Then, this reaction was diluted with EtOAc (10 mL), and poured into a saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (20 mL), and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The remainder was purified by flash chromatography on silica gel eluting with 15-25 vol% of EtOAc in hexanes.

To a stirred solution of abovementioned alcohol CH_3CN (6 mL) was added deionized water (60 uL) and $LiBF_4$ solid (24.4 mg, 260 umol). This reaction was stirred at 80 ^oC overnight (ca. 8 hours), and then cooled to room temperature before being concentrated. The remainder was purified by flash chromatography on silica gel eluting with 25-35 vol% of EtOAc in hexanes to provide the titled compound (2.5 mg, 3.2 umol, 61% yield over two steps) as a colorless oil.

TLC: R_f = 0.48 (EtOAc/Hex = 3:7, v/v);

$[\alpha]_D^{20}$ +26.0 (*c* 0.065, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) δ 7.03 (dd, *J* = 15.2, 11.2 Hz, 1H, ***H-33***), 6.42 (dd, *J* = 15.1, 11.1 Hz, 1H, ***H-34***), 6.11 (dt, *J* = 14.9, 7.3 Hz, 1H, ***H-35***), 5.93 (dd, *J* = 15.9, 1.7 Hz, 1H, ***H-17***), 5.79 (d, *J* = 15.2 Hz, 1H, ***H-32***), 5.49 (dddd, *J* = 12.7, 6.8, 4.9, 1.7 Hz, 1H, ***H-5***), 5.79 (dd, *J* = 16.1, 3.9 Hz, 1H, ***H-16***), 5.19 (br. s, 1H, ***H-28a***), 5.02 (br. s, 1H, ***H-28b***), 4.84 (app. ddd, *J* = 13.2, 7.8, 3.4 Hz, 1H, ***H-25***), 4.69 (br. s, 2H, ***H-29a***, ***H-29b***), 4.54 (dq, *J* = 12.2, 6.3 Hz, 1H, ***H-26***), 4.41 (app. t, *J* = 6.4 Hz, 1H, ***H-23***), 4..22 (dd, *J* = 11.7, 1.0 Hz, 1H, ***H-8a***), 4.08 (d, *J* = 11.6 Hz, 1H, ***H-8b***), 4.14-4.00 (m, 1H, ***H-3***), 3.76 (ddd, *J* = 9.5, 8.8, 2.0 Hz, 1H, ***H-11***), 3.65 (s, 3H, ***H-41***), 3.60 (dddd, *J* = 11.7, 3.4, 2.4, 2.0 Hz, 1H, ***H-15***), 3.05 (d, *J* = 15.7 Hz, 1H, ***H-2a***), 2.85 (d, *J* = 16.1 Hz, 1H, ***H-2b***), 2.85 (dd, *J* = 16.9,

13.4 Hz, 1H, ***H-22$_{eq}$***), 2.64 (dd, *J* = 17.6, 10.3 Hz, 1H, ***H-10a***), 2.54 (dd, *J* = 14.2, 4.9 Hz, 1H, ***H-6a***), 2.48-2.38 (m, 2H, ***H-2a***, ***H-2b***), 2.34 (dd, *J* = 14.2, 7.3 Hz, 1H, ***H-6b***), 2.27 (d, *J* = 17.1 Hz, 1H, ***H-10b***), 2.20 (d, *J* = 17.1 Hz, 1H, ***H-22$_{ax}$***), 2.24-2.13 (m, 3H, ***H-36***, ***H-14$_{eq}$***), 2.09 (ddd, *J* = 13.2, 2.0, 1.5 Hz, 1H, ***H-12$_{eq}$***), 2.00 (dd, *J* = 13.2, 12.2 Hz, 1H, ***H-12$_{ax}$***), 1.83-1.73 (m, 2H, ***H-14$_{ax}$***, ***H-24a***), 1.66 (ddd, *J* = 14.2, 10.5, 1.7 Hz, 1H, ***H-4a***), 1.56 (ddd, *J* = 14.2, 1.7, 1.5 Hz, 1H, ***H-4b***), 1.48 (sext, *J* = 7.3 Hz, 2H, ***H-37***), 1.46-1.41 (m, 1H, ***H-24b***), 1.24 (d, *J* = 6.5 Hz, 3H, ***H-27***), 1.13 (s, 3H, ***H-30a***), 1.10 (s, 3H, ***H-30b***), 0.93 (t, *J* = 7.3 Hz, 3H, ***H-38***);

125 MHz ^{13}C NMR ($CDCl_3$) δ 171.5 (***C-1***), 170.7 (***C-9***), 170.5 (***C-40***), 166.1 (***C-31***), 147.4 (***C-33***), 145.1 (***C-35***), 144.5 (***C-13***), 141.7 (***C-7***), 141.4 (***C-20***), 133.8 (***C-17***), 129.9 (***C-34***), 126.5 (***C-16***), 122.8 (***C-21***), 118.8 (***C-32***), 118.1 (***C-28***), 108.6 (***C-29***), 97.9 (***C-19***), 78.0 (***C-15***), 74.2 (***C-11***), 68.2 (***C-5***), 68.1 (***C-26***), 67.1 (***C-25***), 65.7 (***C-23***), 63.5 (***C-3***), 52.3 (***C-41***), 48.1 (***C-8***), 45.0 (***C-2***), 43.4 (***C-18***), 42.0 (***C-4***, ***C-14***), 40.5 (***C-10***), 40.3 (***C-12***), 39.1 (***C-6***), 35.3 (***C-35***), 35.1 (***C-39***), 33.8 (***C-22***), 32.1 (***C-24***), 25.6 (***C-30a***), 22.4 (***C-37***), 21.3 (***C-30b***), 14.2 (***C-27***), 14.1 (***C-38***).

HRMS (ESI-TOF) *m/z*: [M+Na$^+$] Calcd for $C_{42}H_{57}O_{12}ClNa$ 811.3436, found 811.3439.

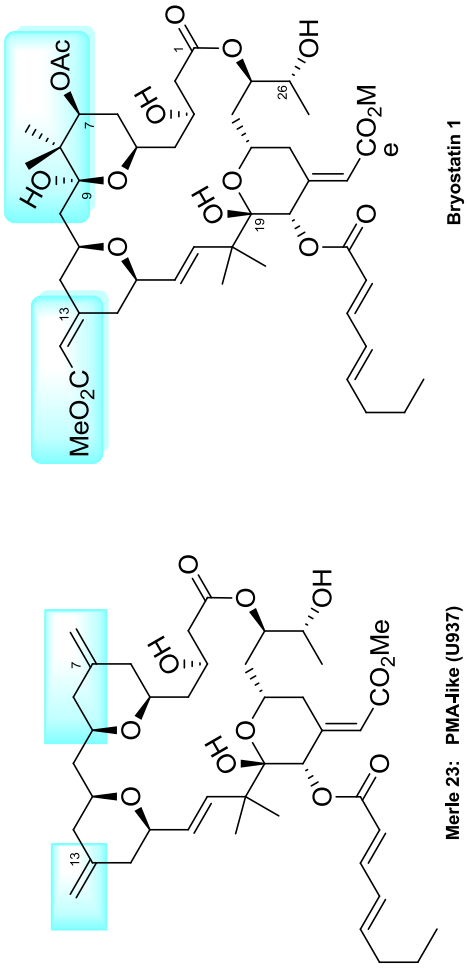
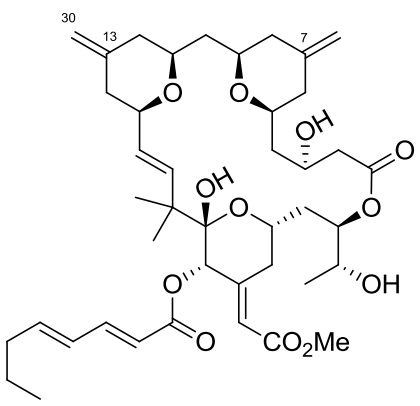
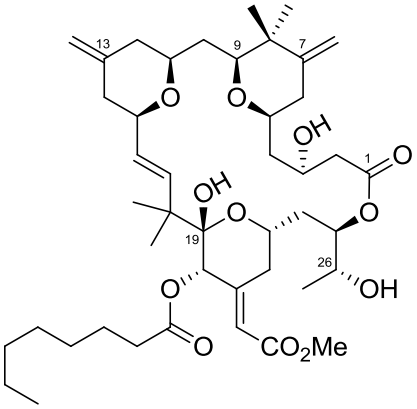


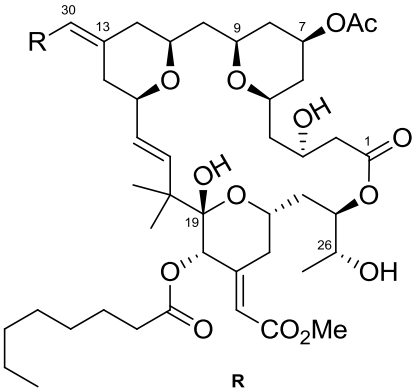
Figure 3.1 Structural Comparision of Merle 23 and Bryostatin 1



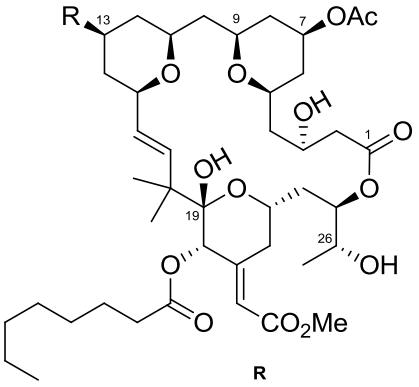
Merle 23 (Ki = 0.70 nM) PMA-like



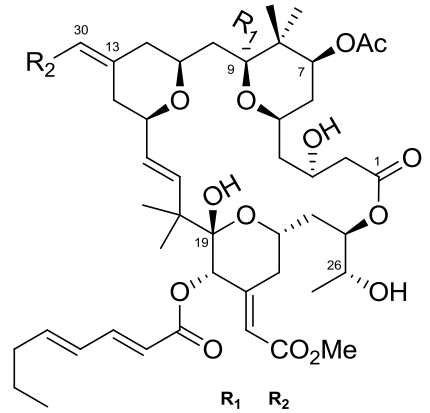
Merle 32 (Ki = 1.08 nM) PMA-like



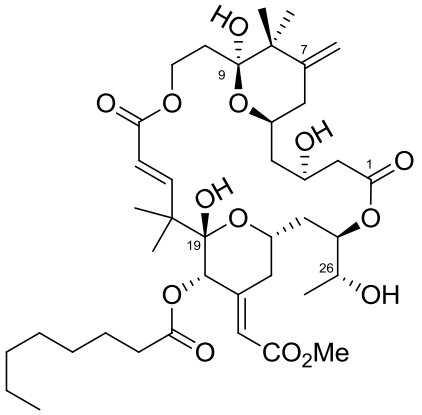
	R	
Merle 27 (Ki = 3.00 nM)	H	PMA-like
Merle 33 (Ki = 0.68 nM)	CO_2Me	Bryo-like



	R	
Merle 34 (Ki = 16.3 nM)	OH	PMA-like
Merle 38 (Ki = 13.2 nM)	OCOEt	PMA-like



	R_1	R_2	
Merle 28 (Ki = 0.52 nM)	OH	H	Bryo-like
Merle 30 (Ki = 0.38 nM)	H	CO_2Me	Bryo-like



Merle 29u PMA-like

Figure 3.2 Merle Analogues with High Binding Affinity

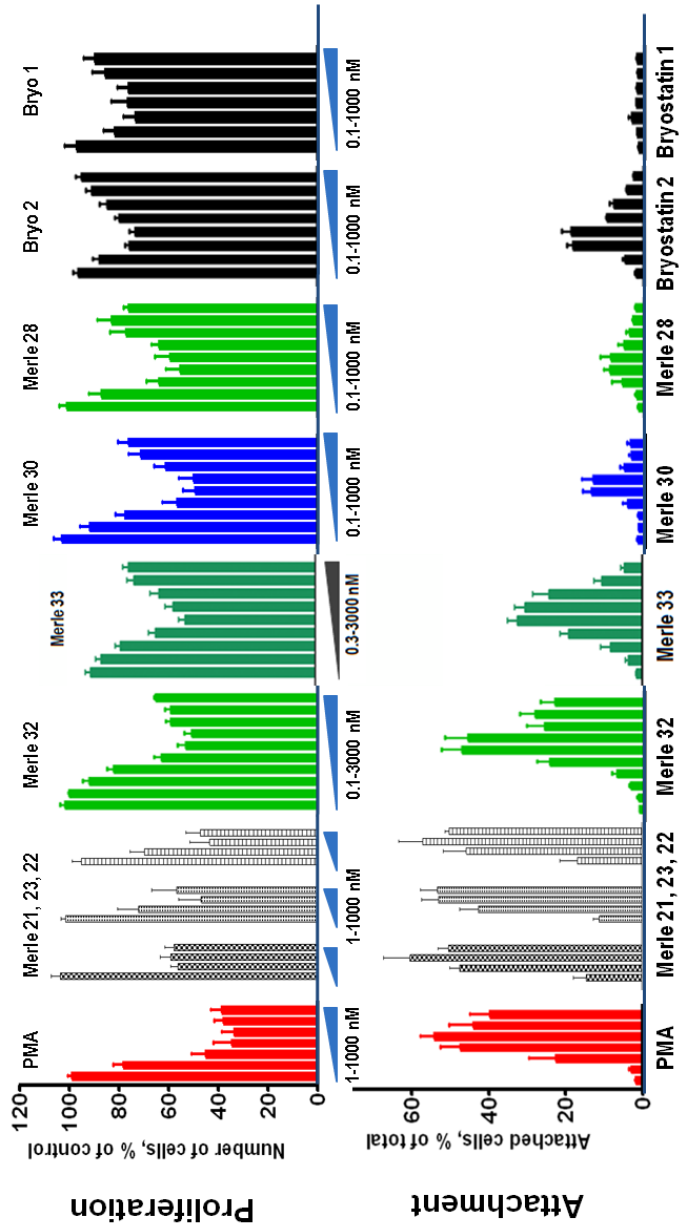


Figure 3.3 U937 Proliferation and Attachment of Merle Analogues and Bryostatin 1 and 2

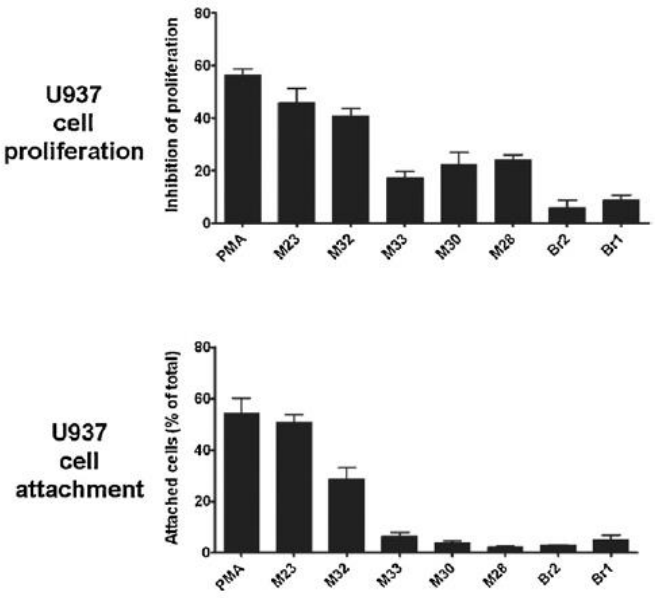


Figure 3.4 U937 Proliferation and Attachment (1000 nM, 72 h)

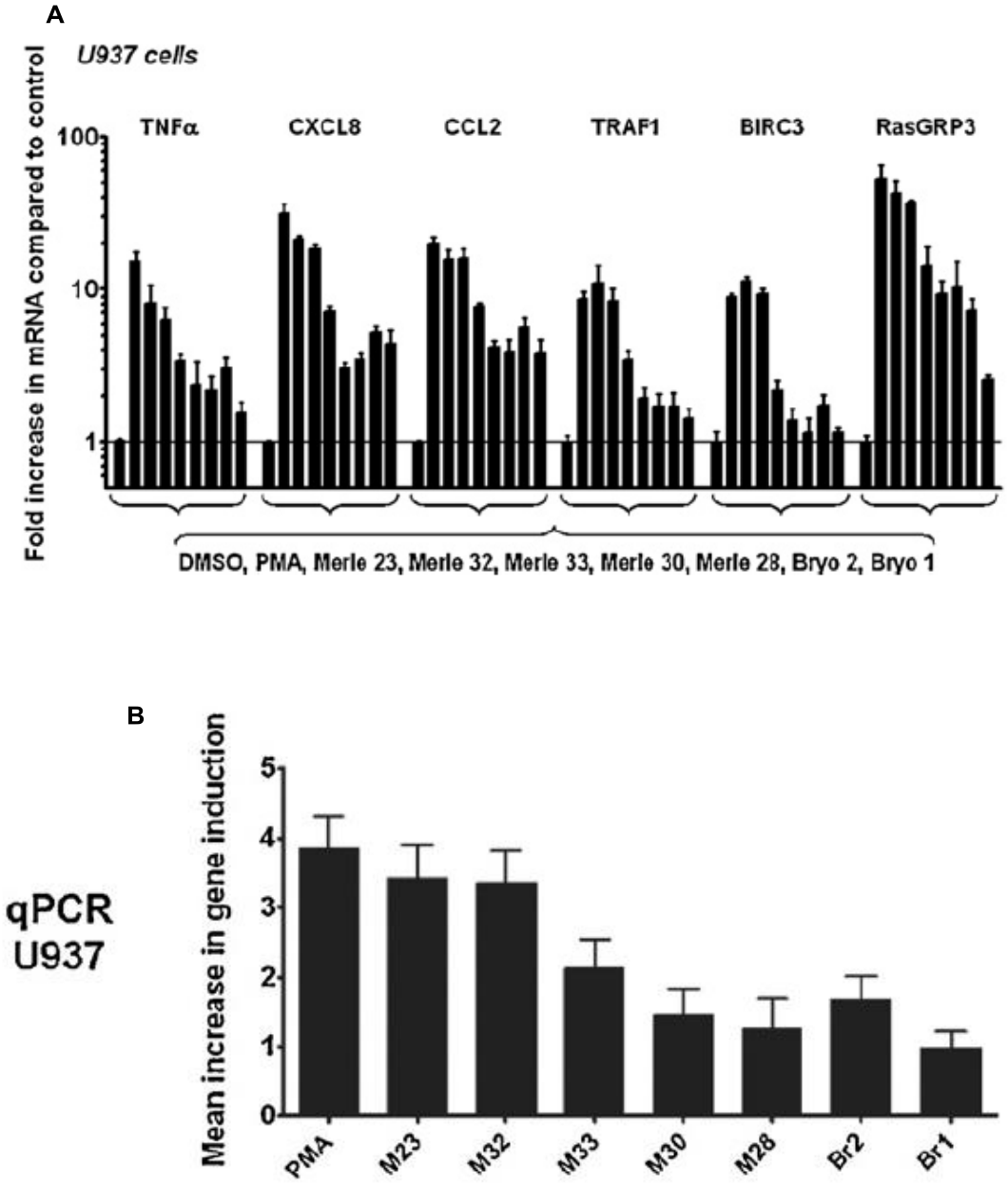


Figure 3.5 Transcriptional Activities of Analogues in U937 Cells

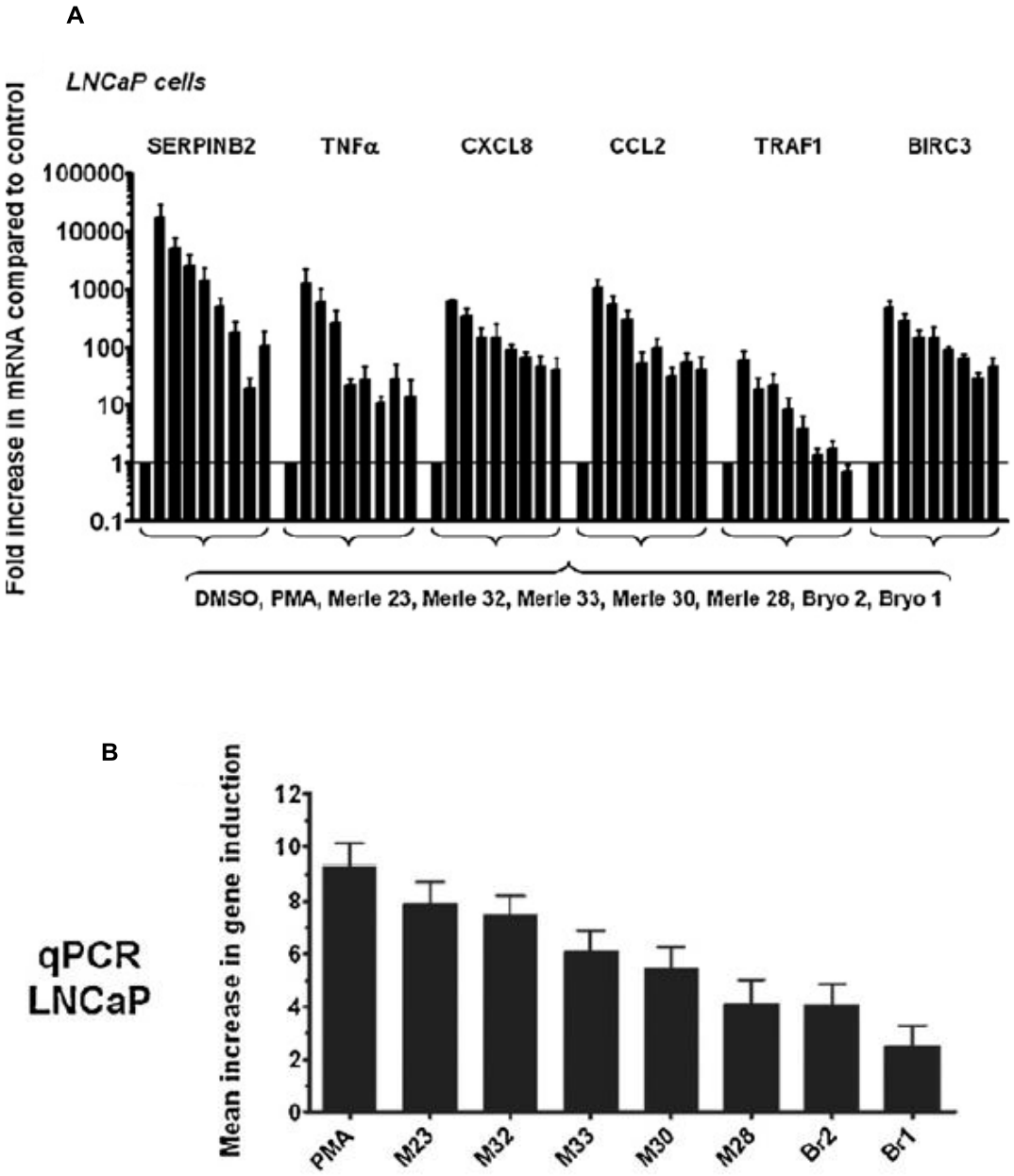
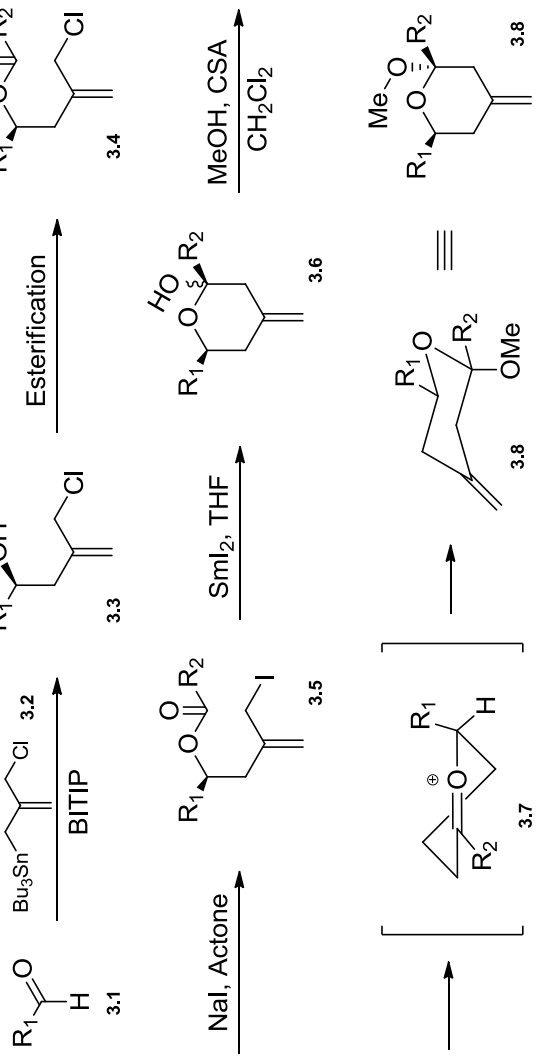


Figure 3.6 Transcriptional Activities of Analogues in LNCaP Cells



Scheme 3.1 Esterification-Reductive Cyclization Strategy

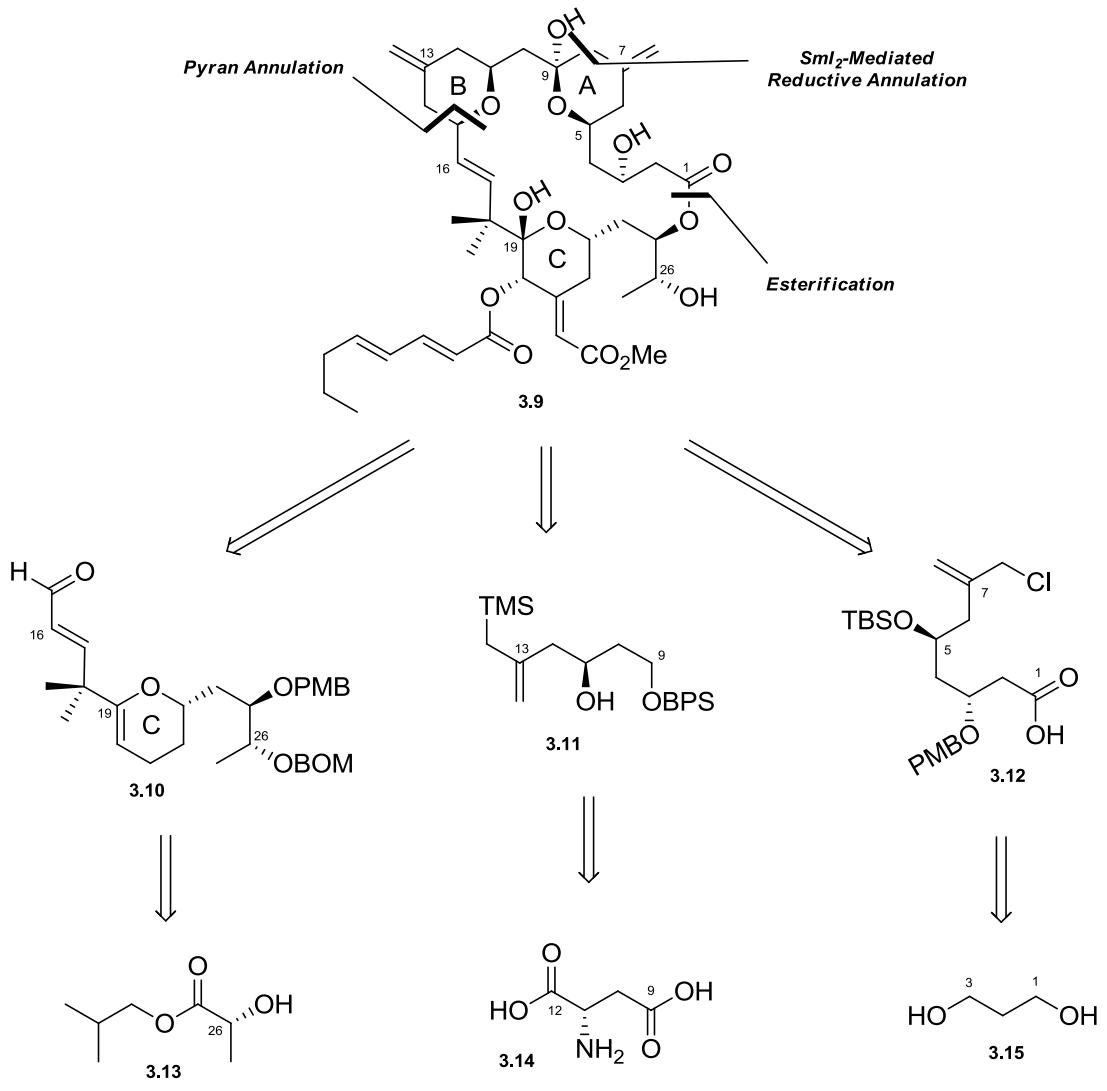
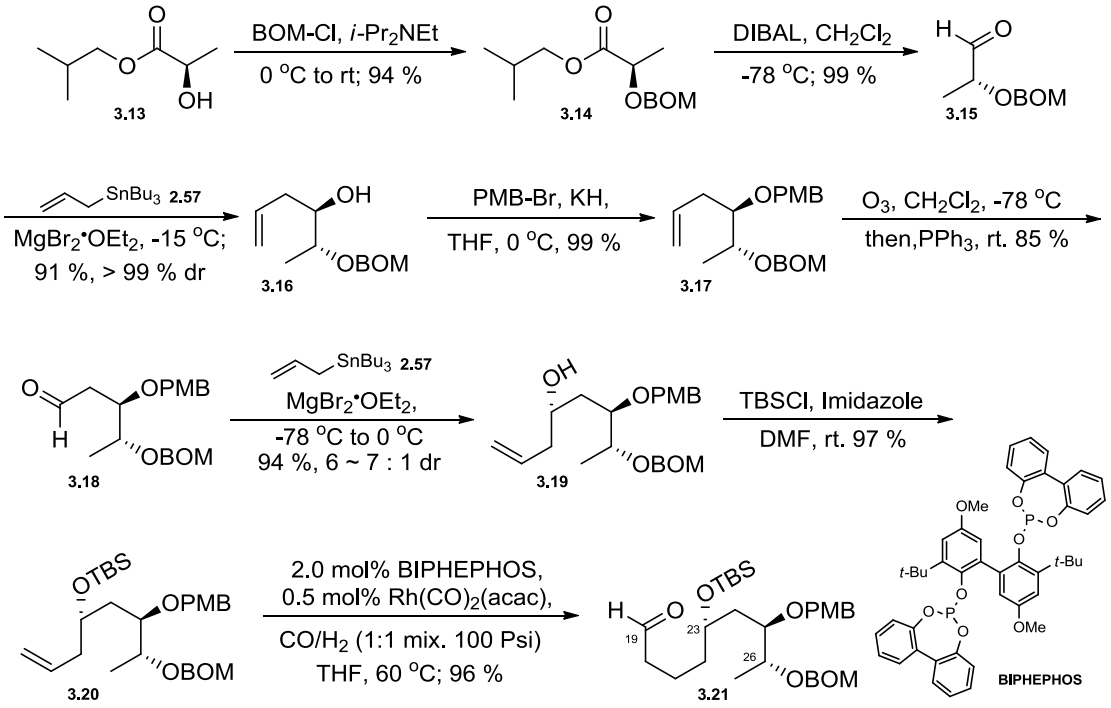
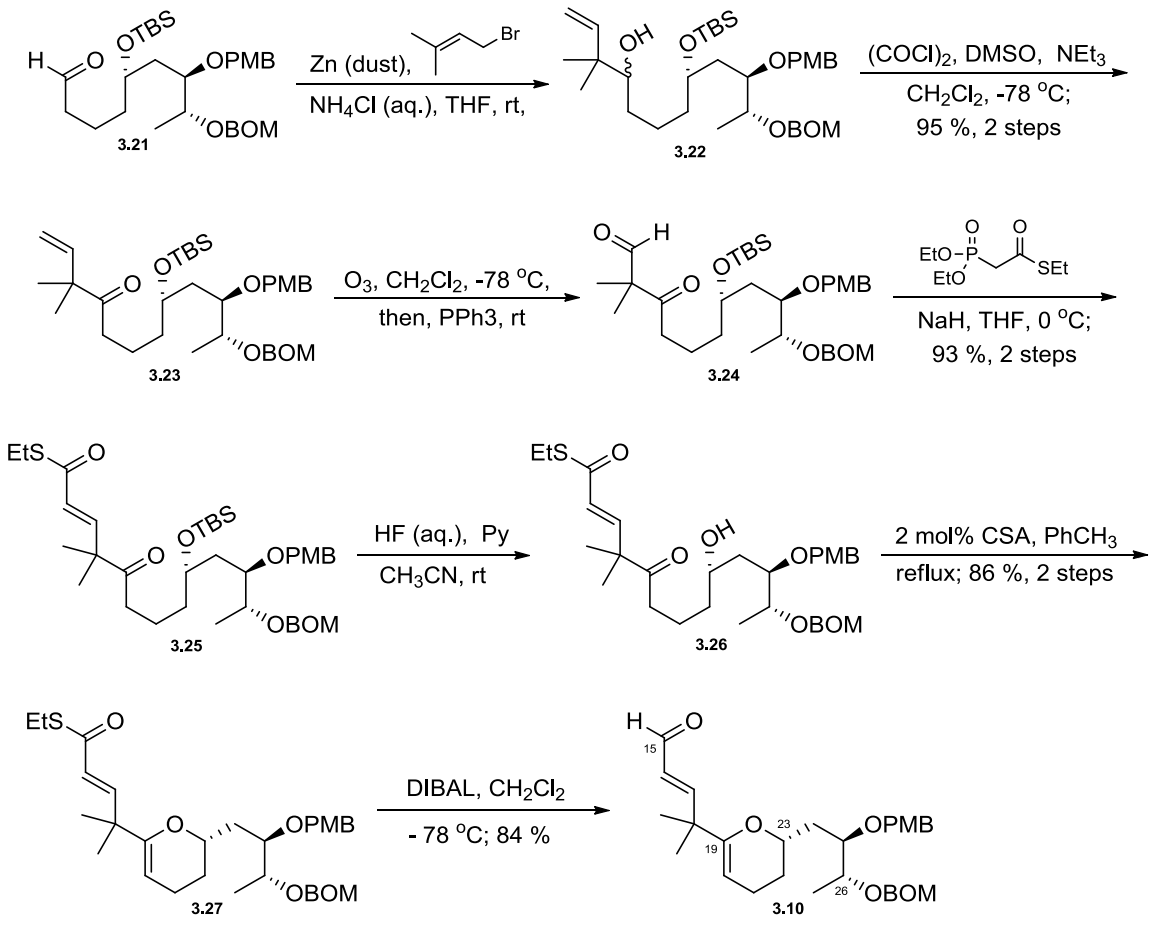


Figure 3.7 Retrosynthetic Plan of Analogue **3.9**



Scheme 3.2 Synthesis of the Aldhehye **3.21**



Scheme 3.3 Synthesis of Enal **3.10**

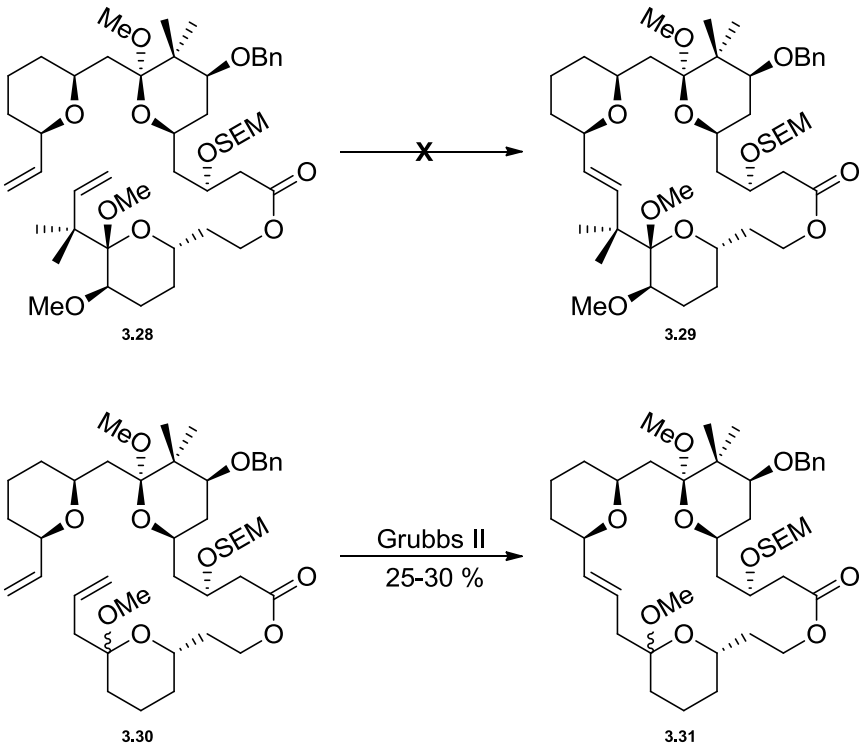
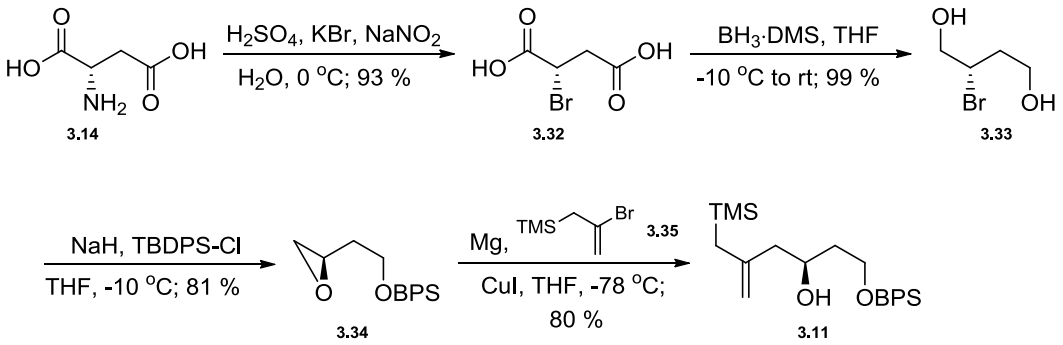
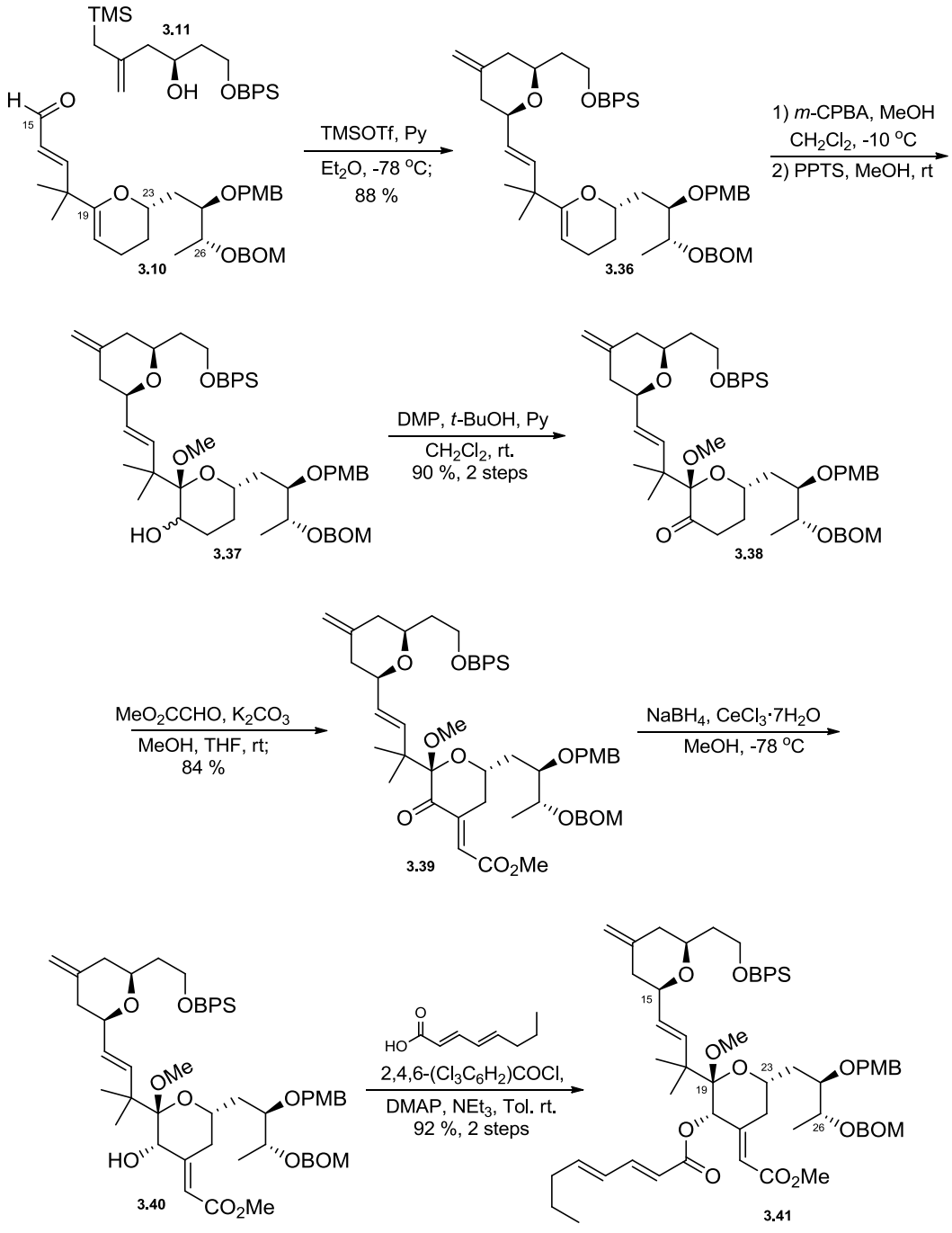


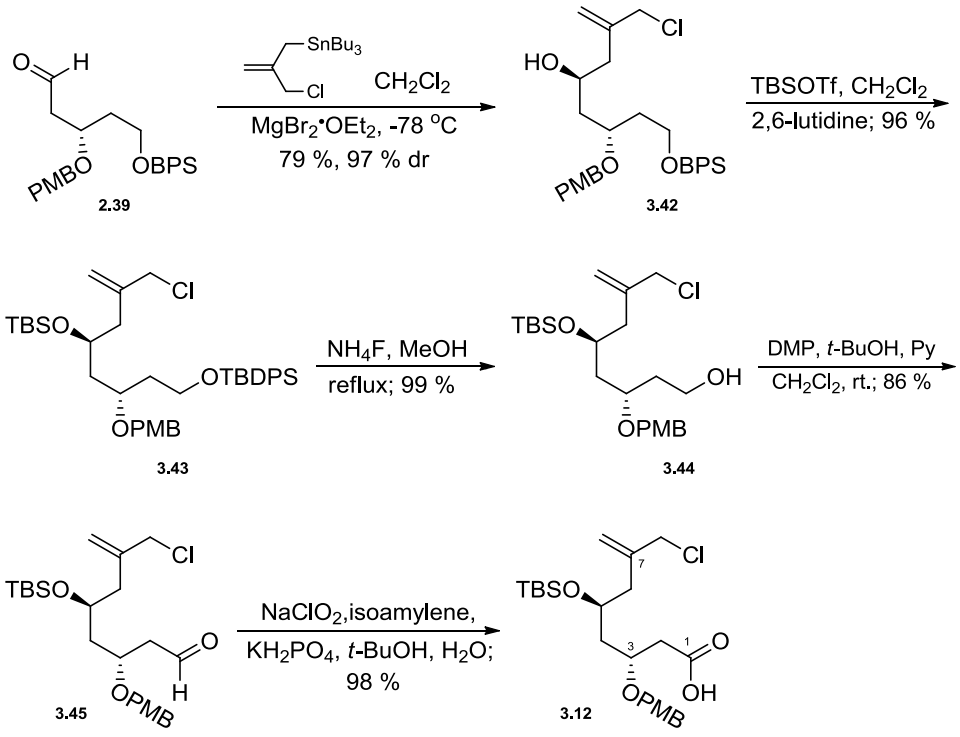
Figure 3.8 Cross Metathesis in Thomas's Synthesis



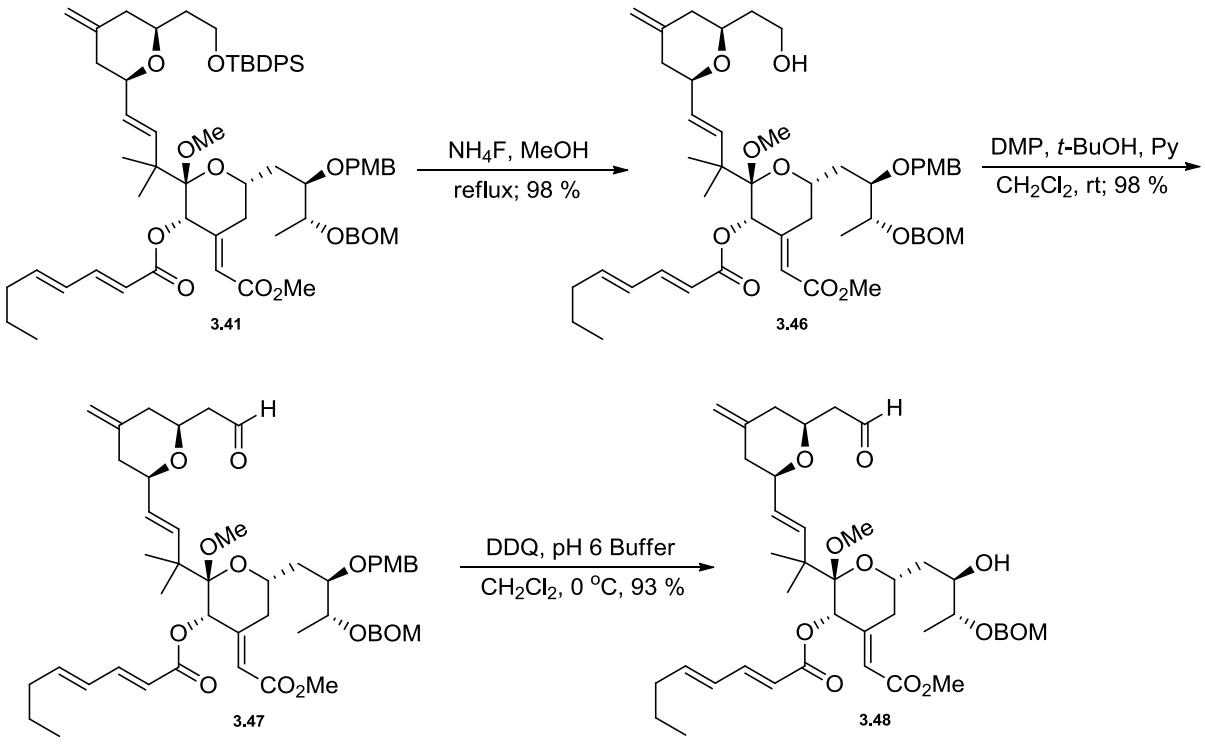
Scheme 3.4 Synthesis of Allylsilane **3.11**



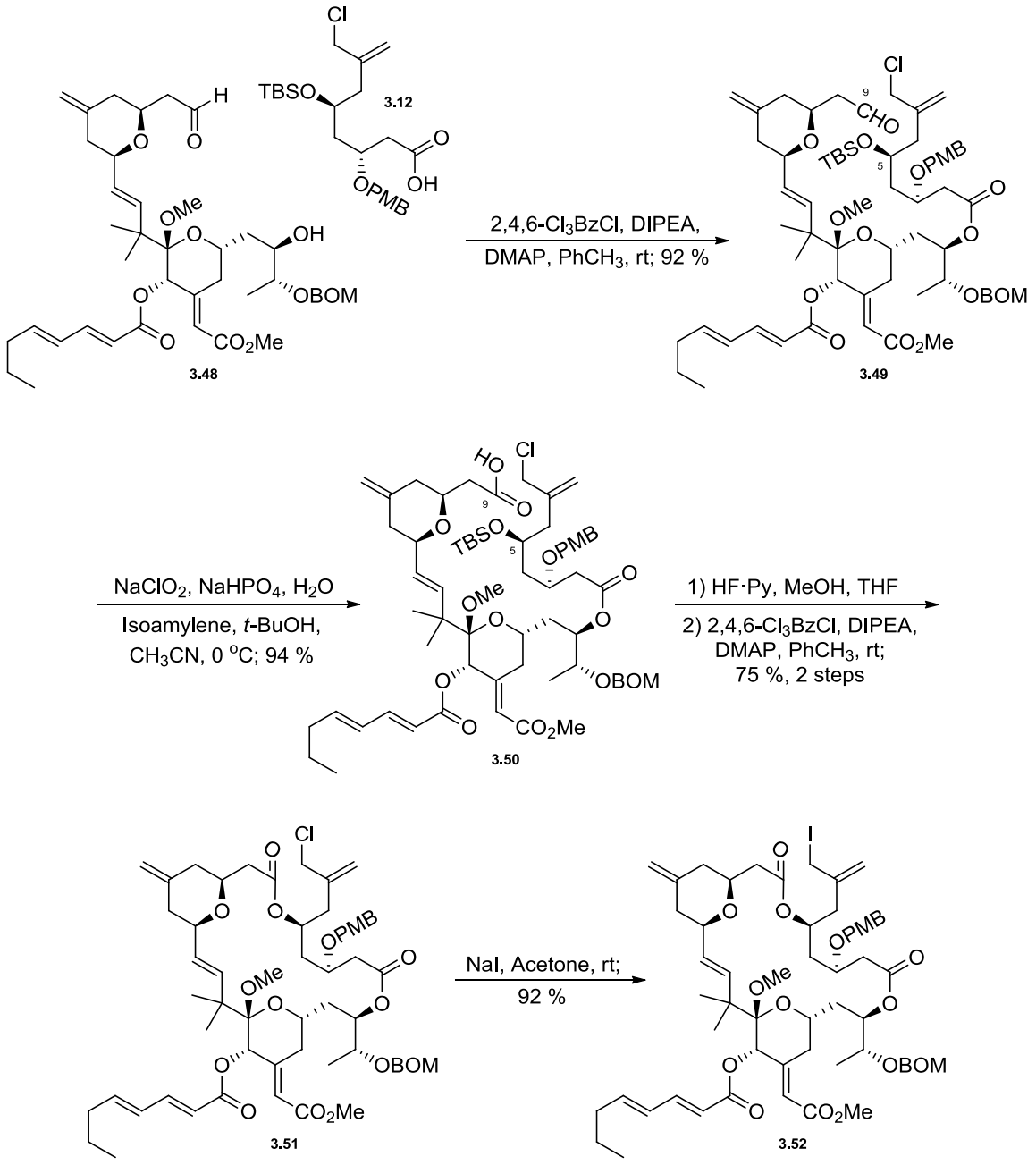
Scheme 3.5 Synthesis of the Segment 3.41



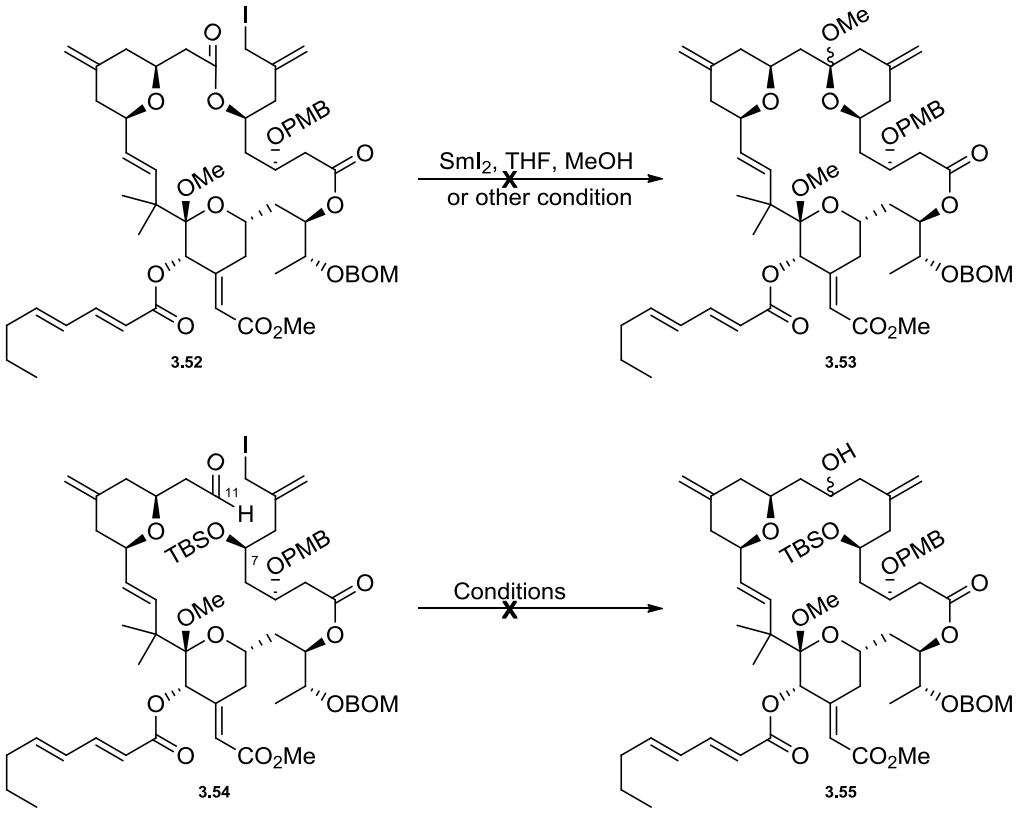
Scheme 3.6 Synthesis of Allylchloride 3.12



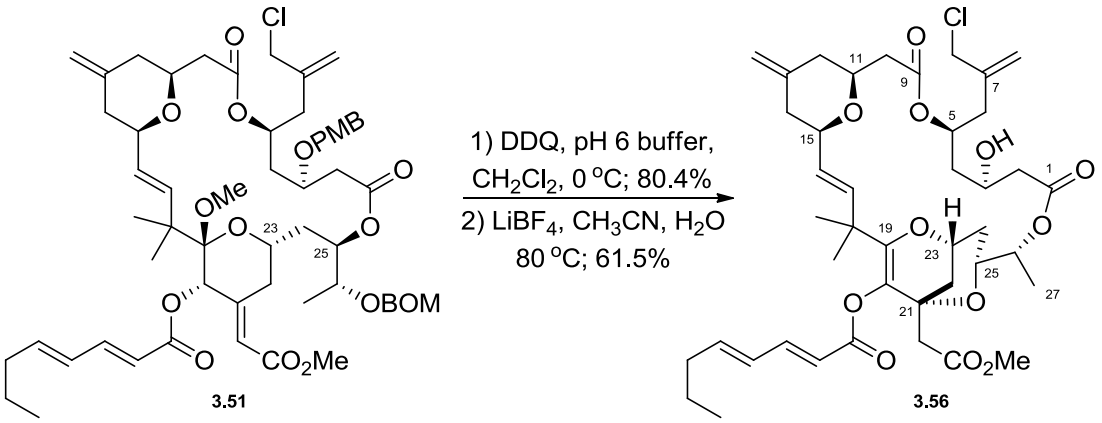
Scheme 3.7 Removal of Protecting Groups for Coupling



Scheme 3.8 Completion of Analogue Backbone



Scheme 3.9 Attempts at A-Ring Cyclization



Scheme 3.10 Completion of an Unexpected Analogue

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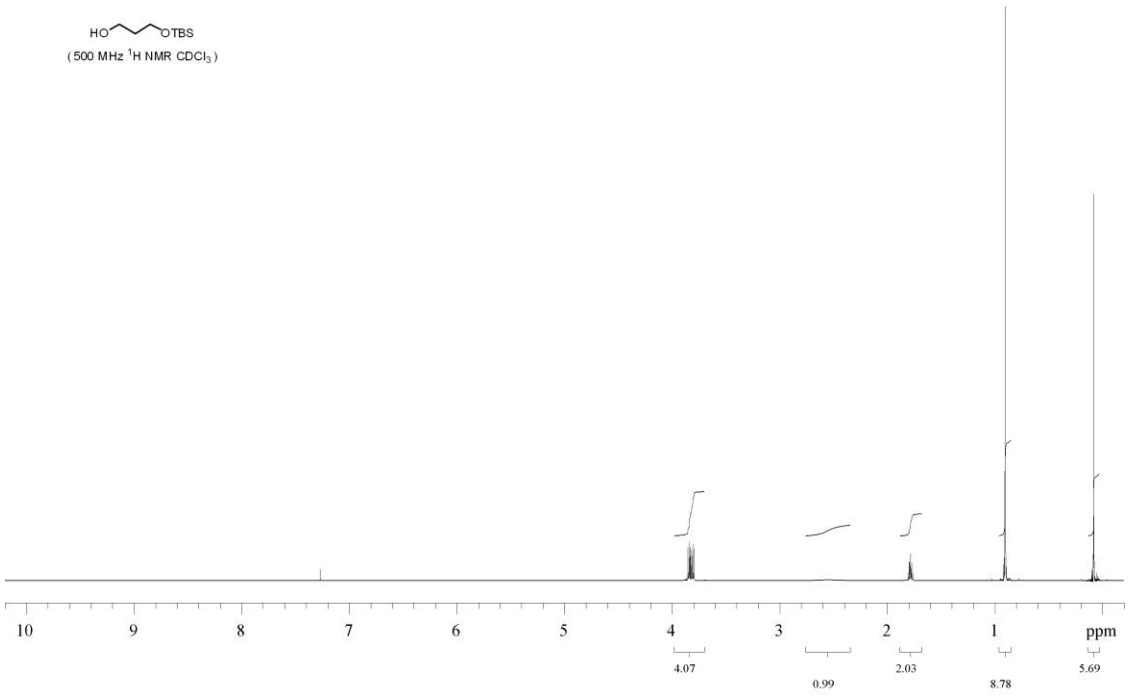
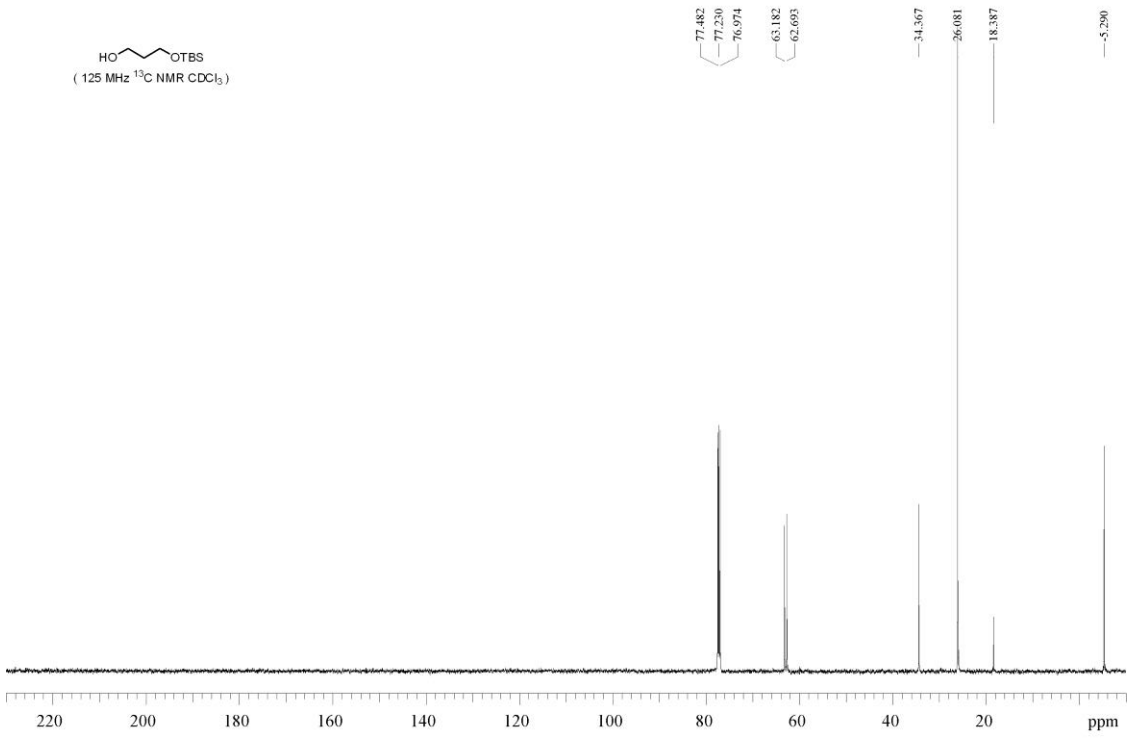
APPENDIX A

NMR SPECTRUM OF CHAPTER 1


HO
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
4.07
0.99
2.03
8.78
5.69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76.974
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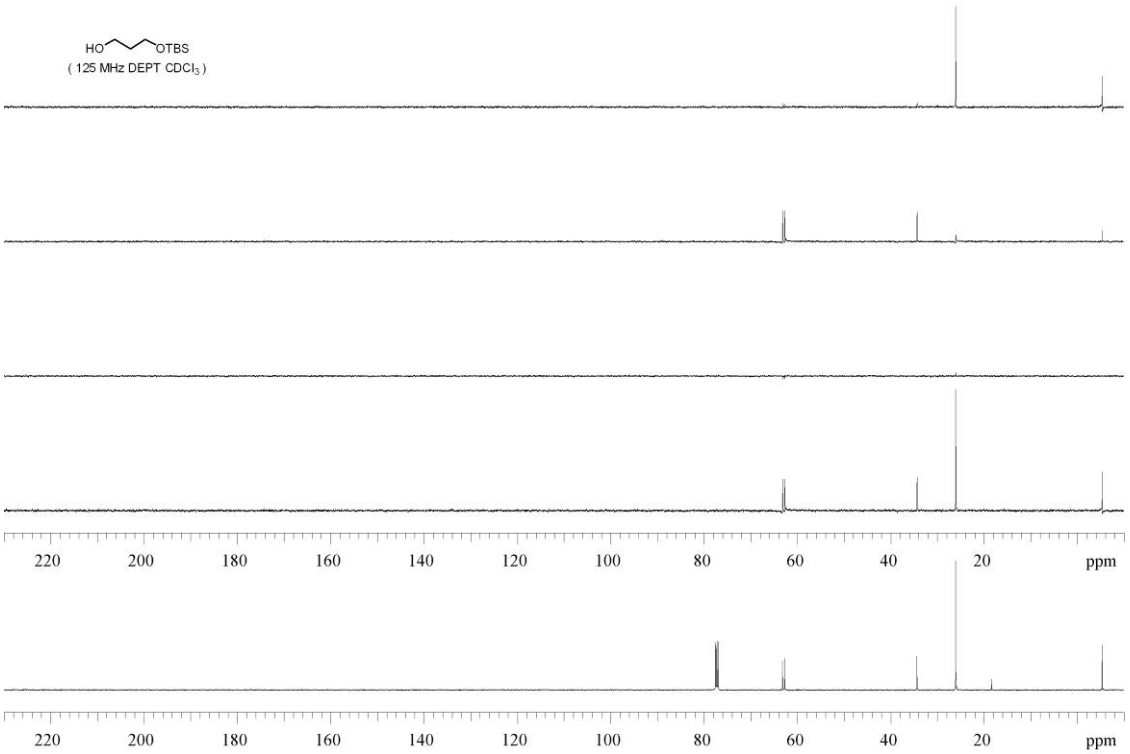
18.387
-5.290
220
200
180
160
140
120
100
80
60
40
20
ppm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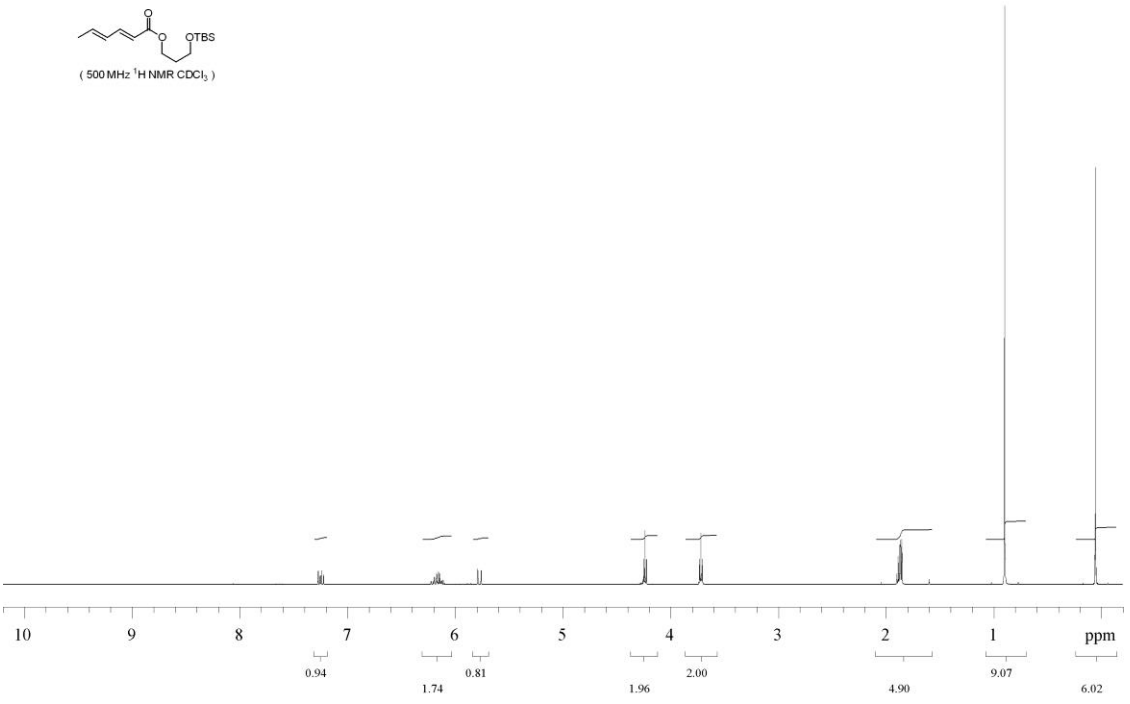
OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm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(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
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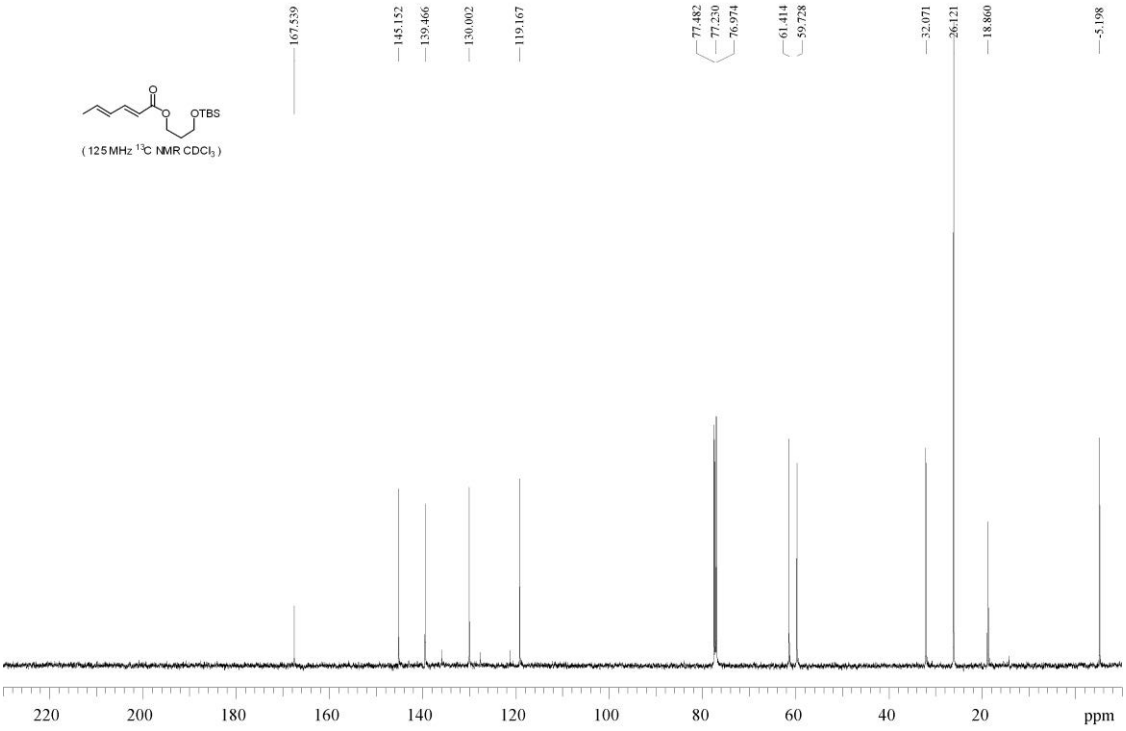
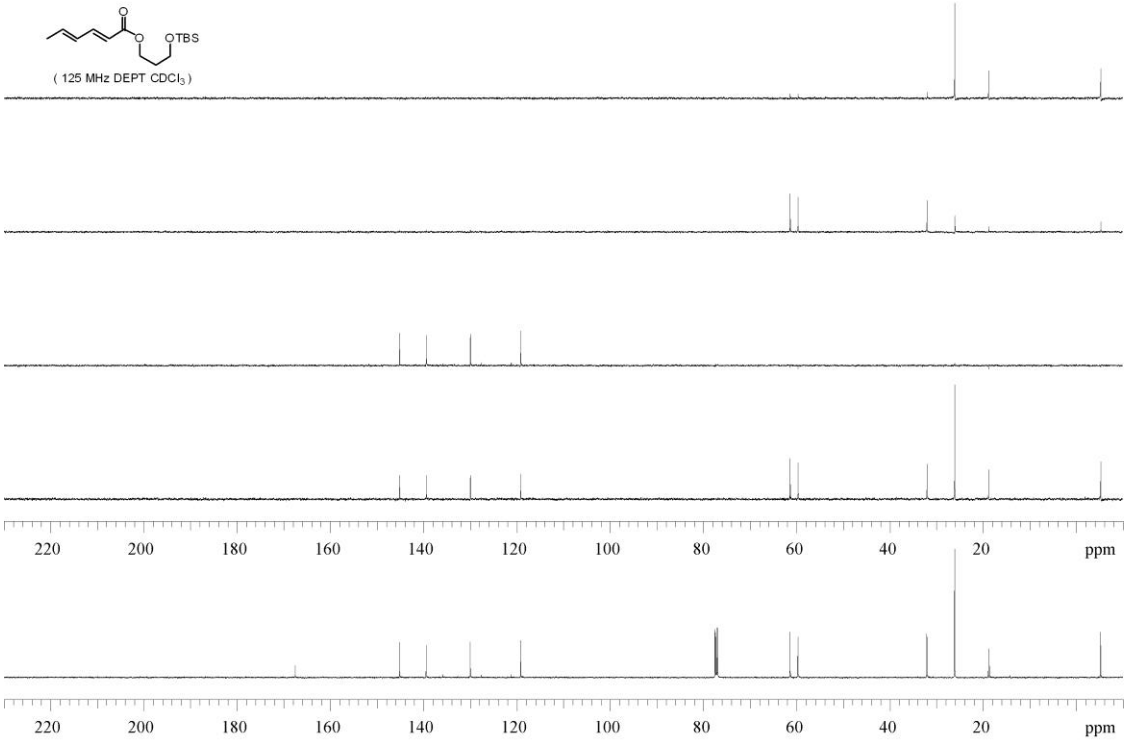
0.81
1.96
2.00
4.90
9.07
6.02


167.539
145.152
139.466
130.002
119.167
77.482
77.230
76.974
61.414
59.728
32.071
26.121
18.860
-5.198
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm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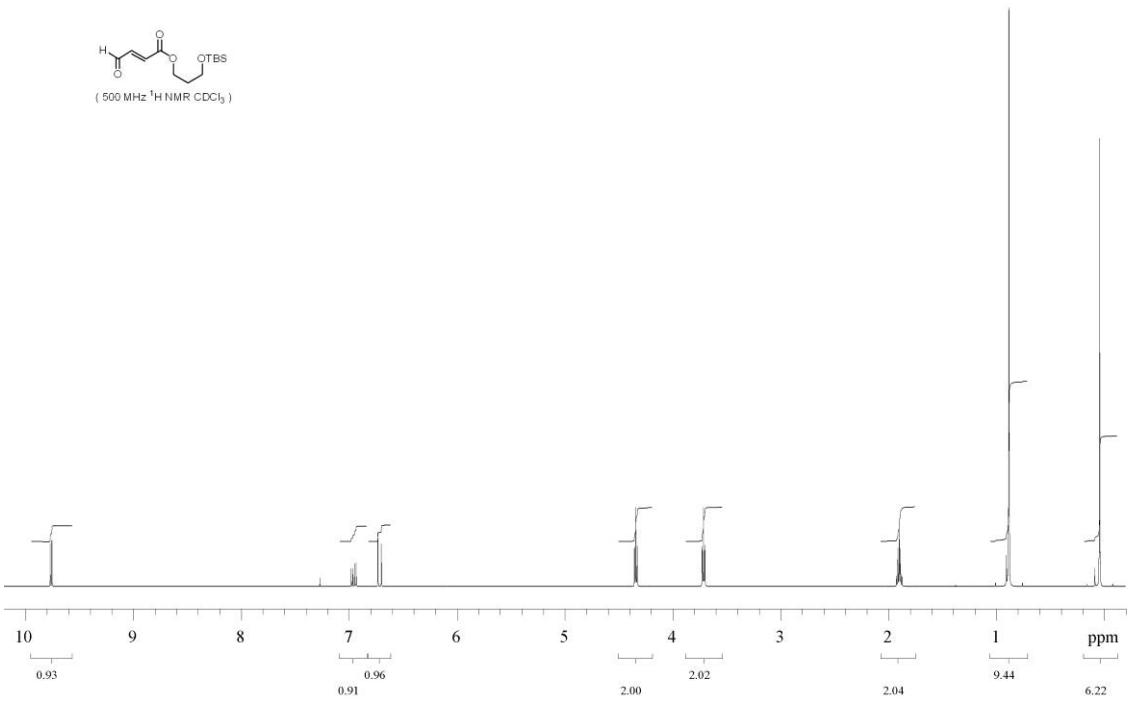
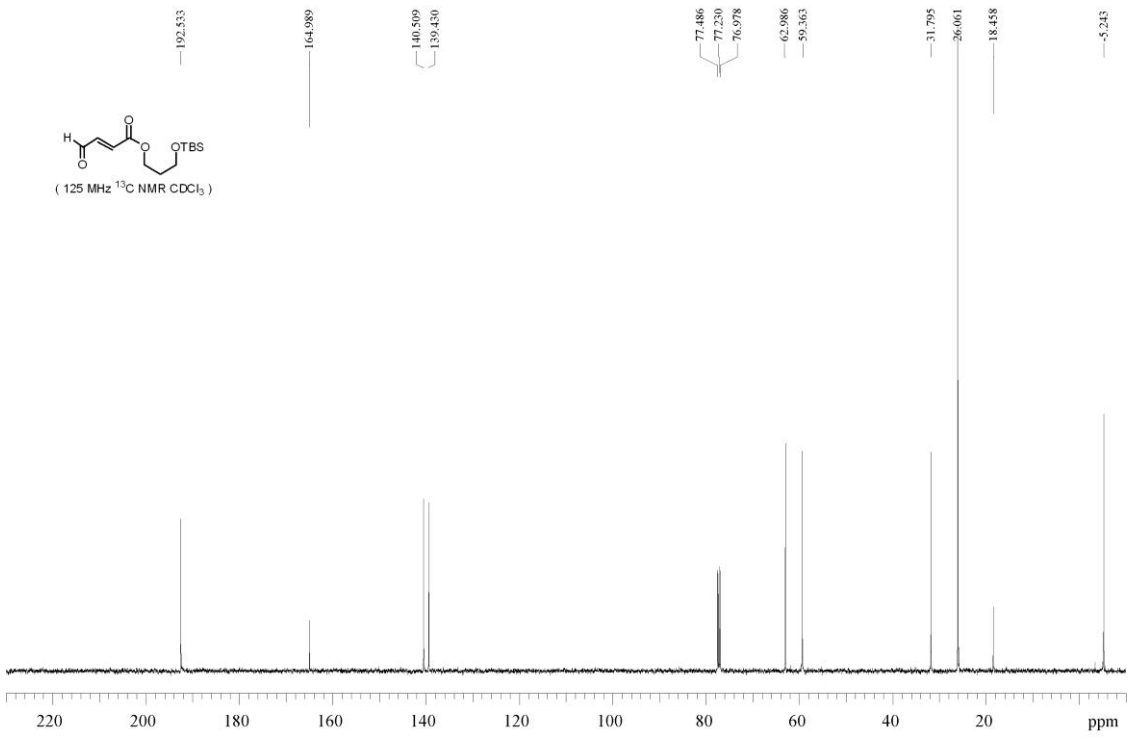
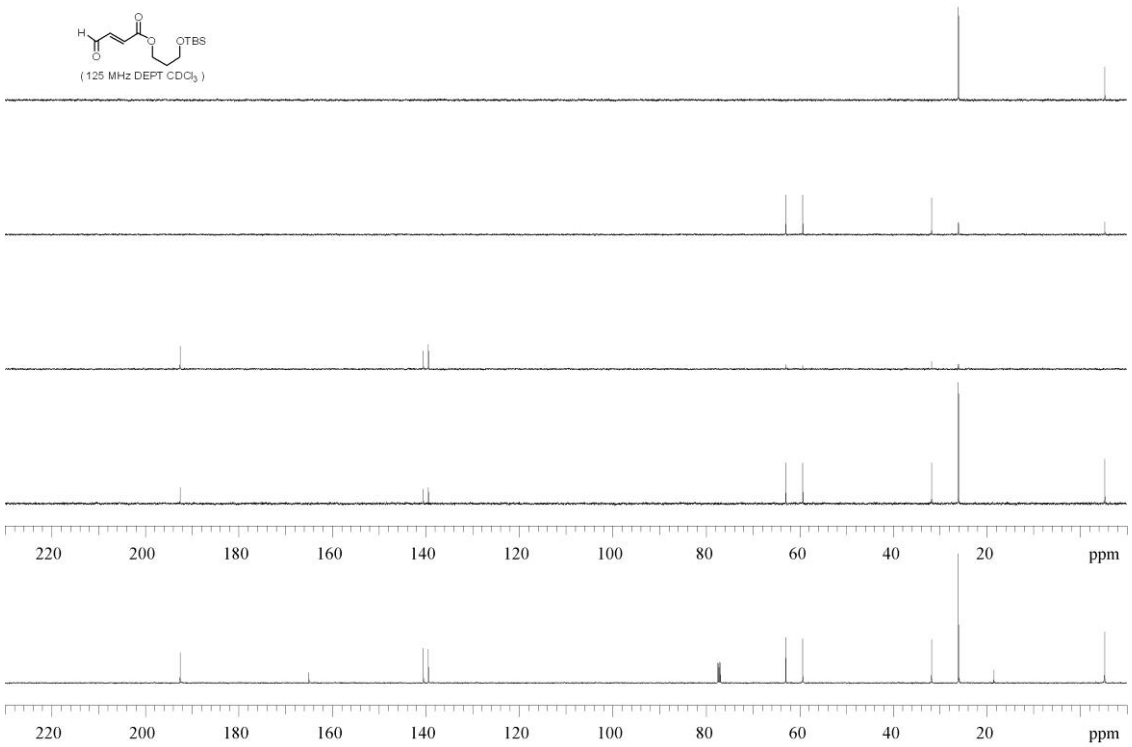
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.93
0.96
0.91
2.00
2.02
2.04
9.44
6.22


192.533
164.989
140.509
139.430
77.486
77.230
76.978
62.986
59.363
31.795
26.061
18.458
-5.243
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm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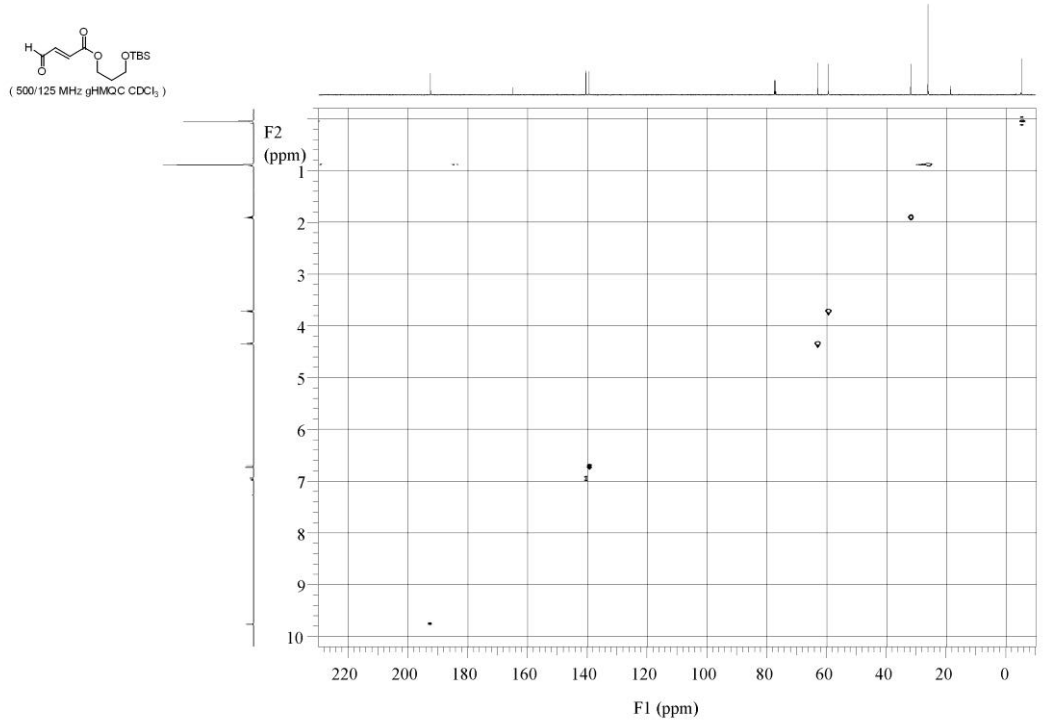
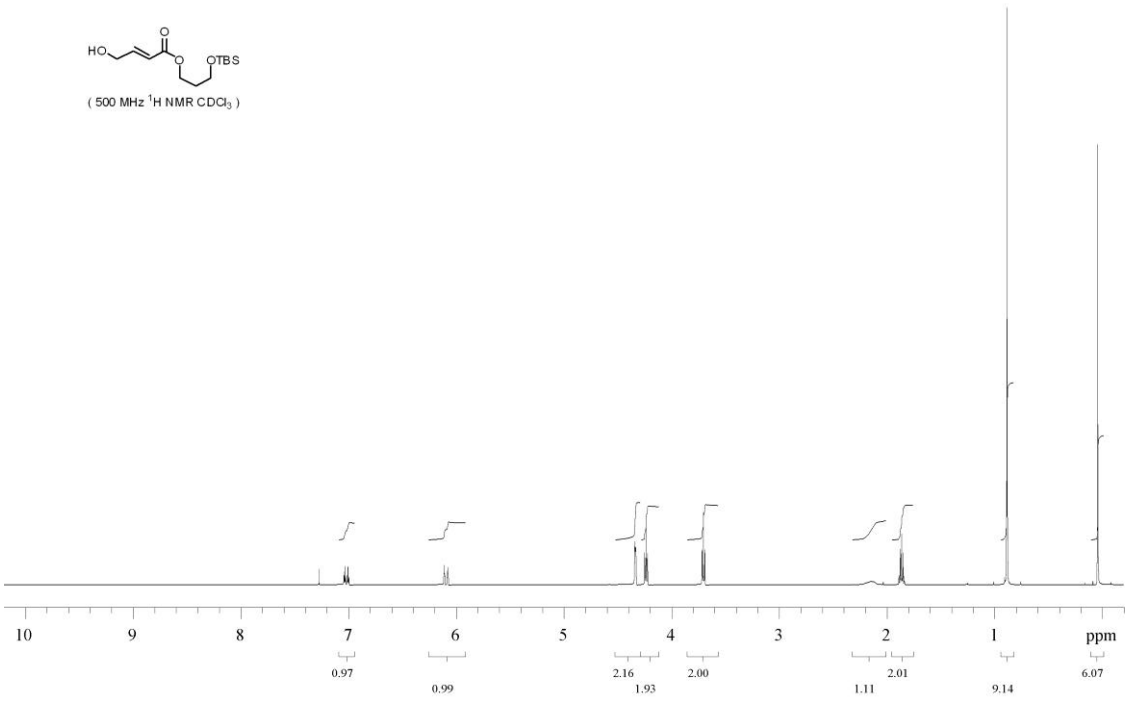
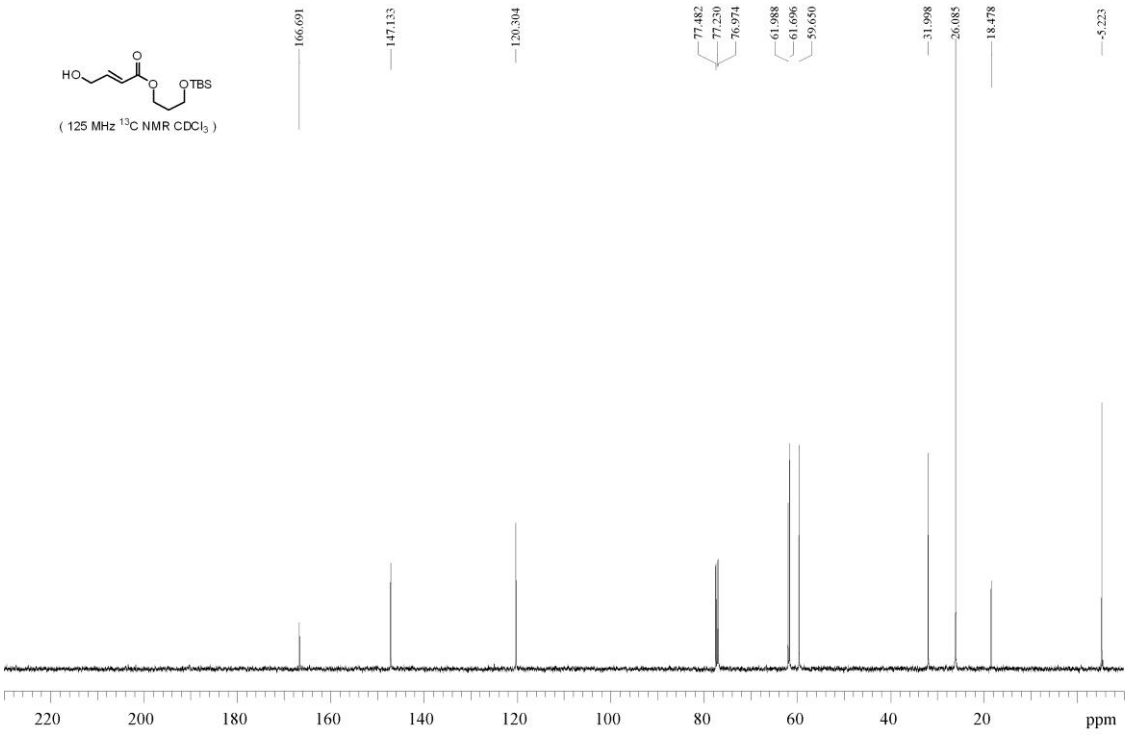
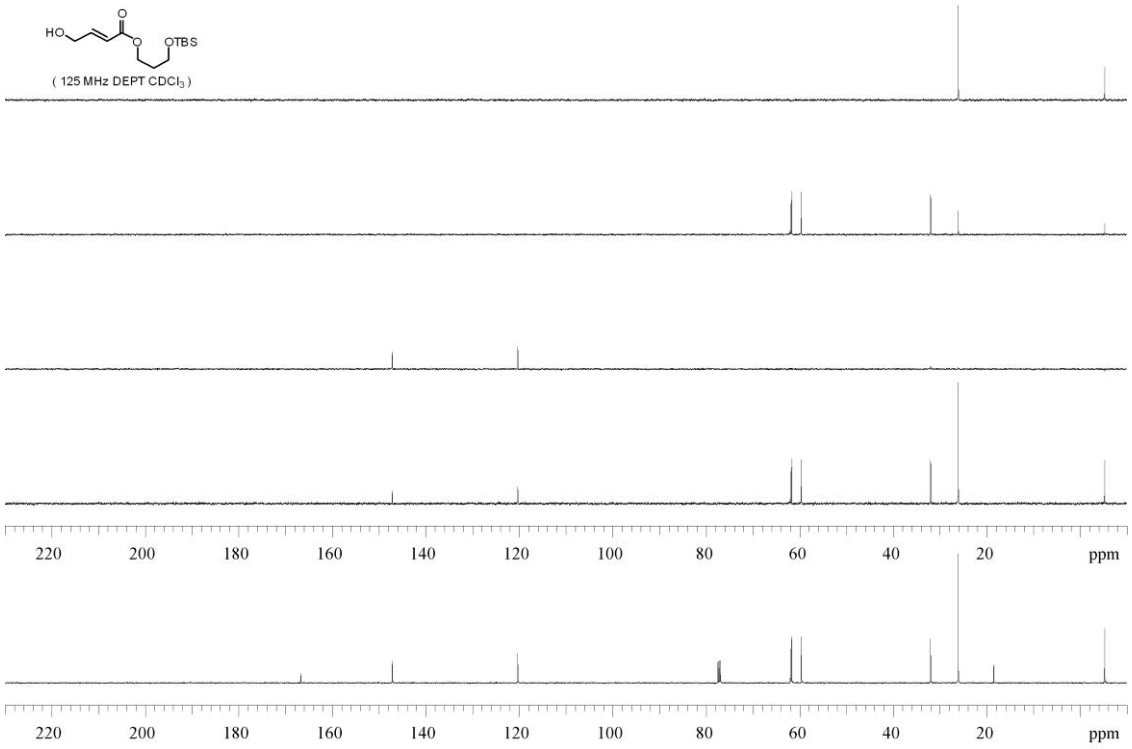
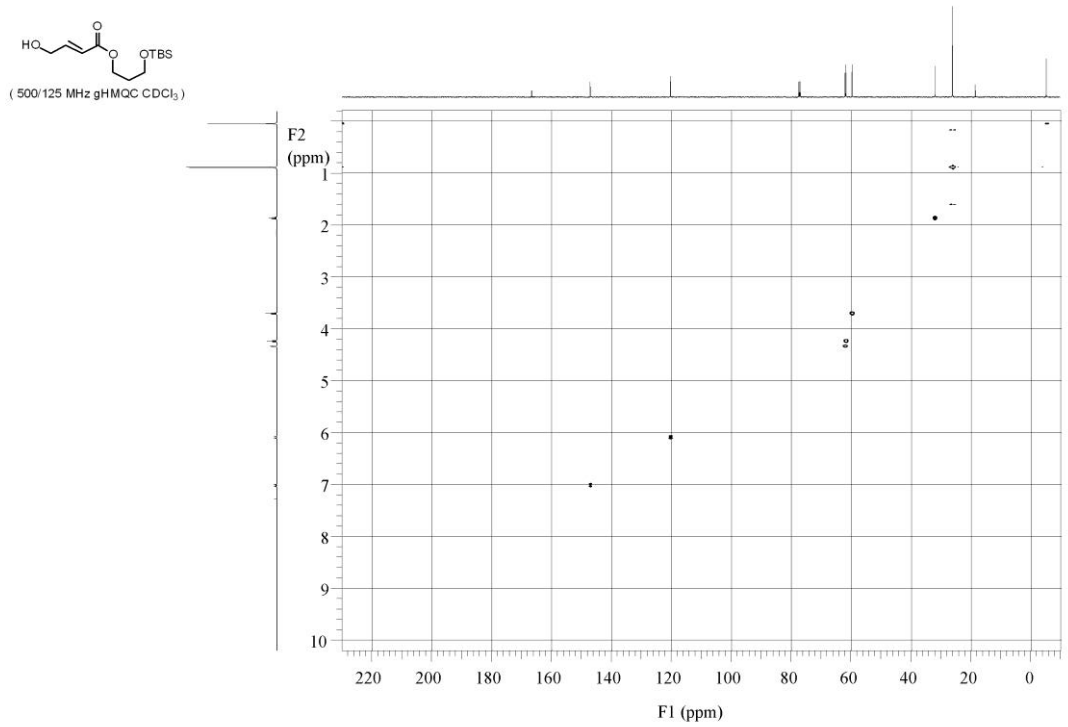
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

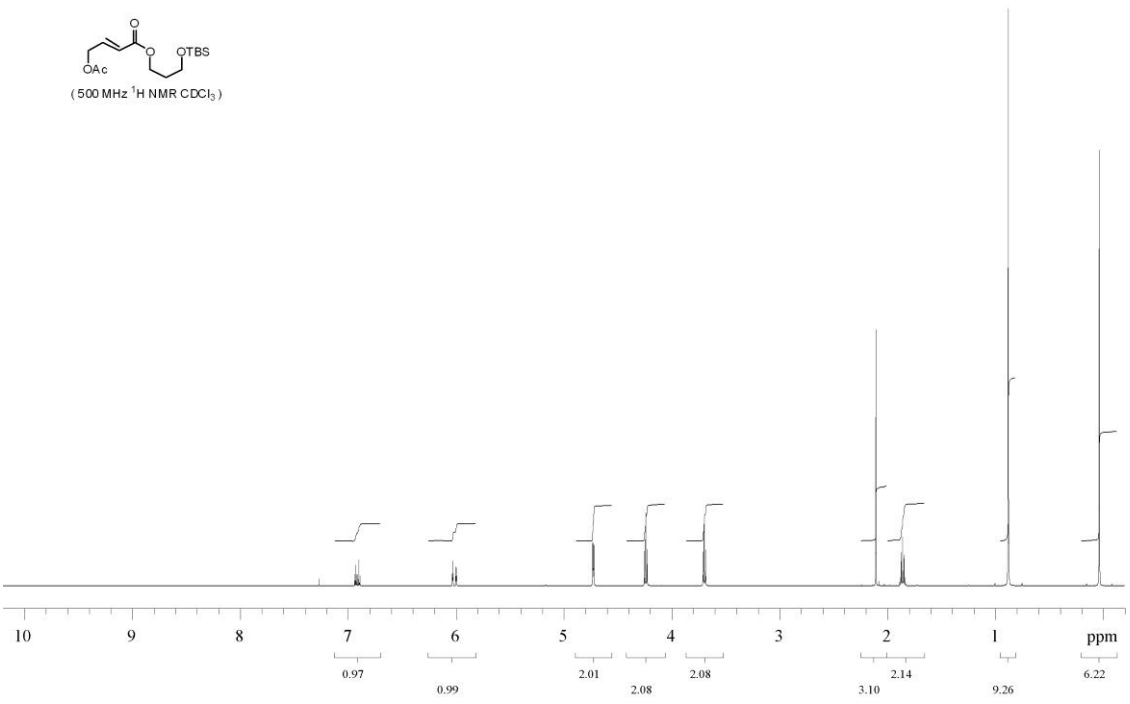

OTBS
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

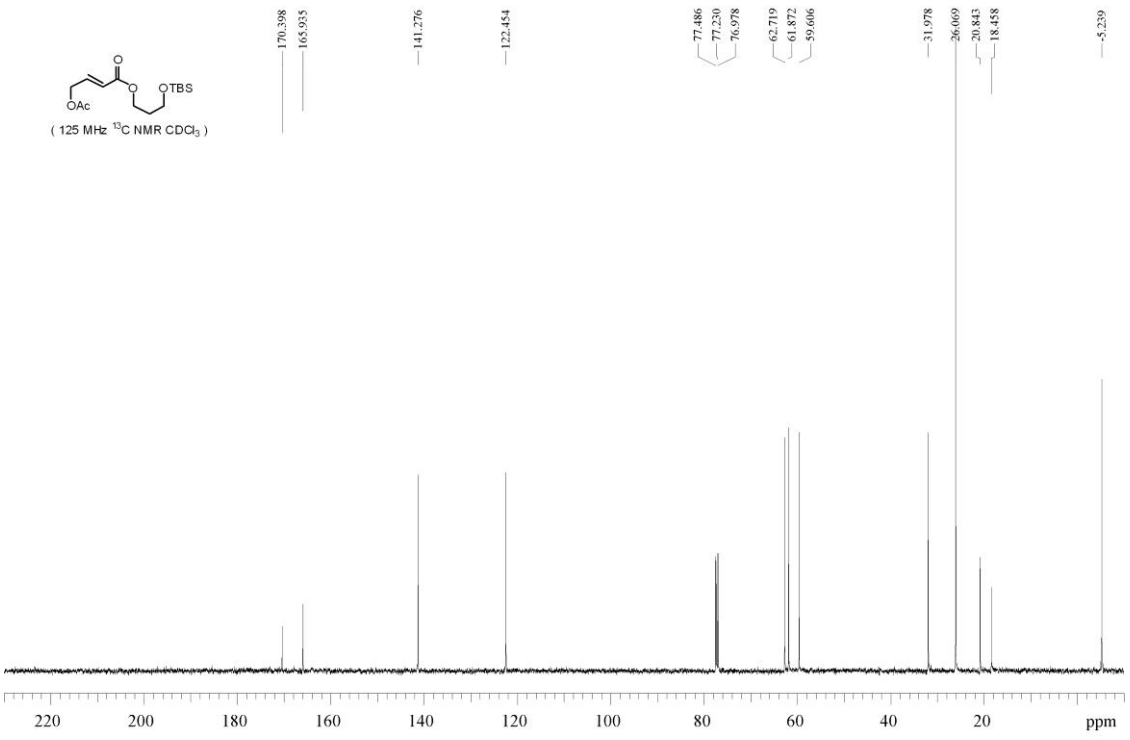

HO
O
O
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.97
0.99
2.16
1.93
2.00
1.11
2.01
9.14
6.07

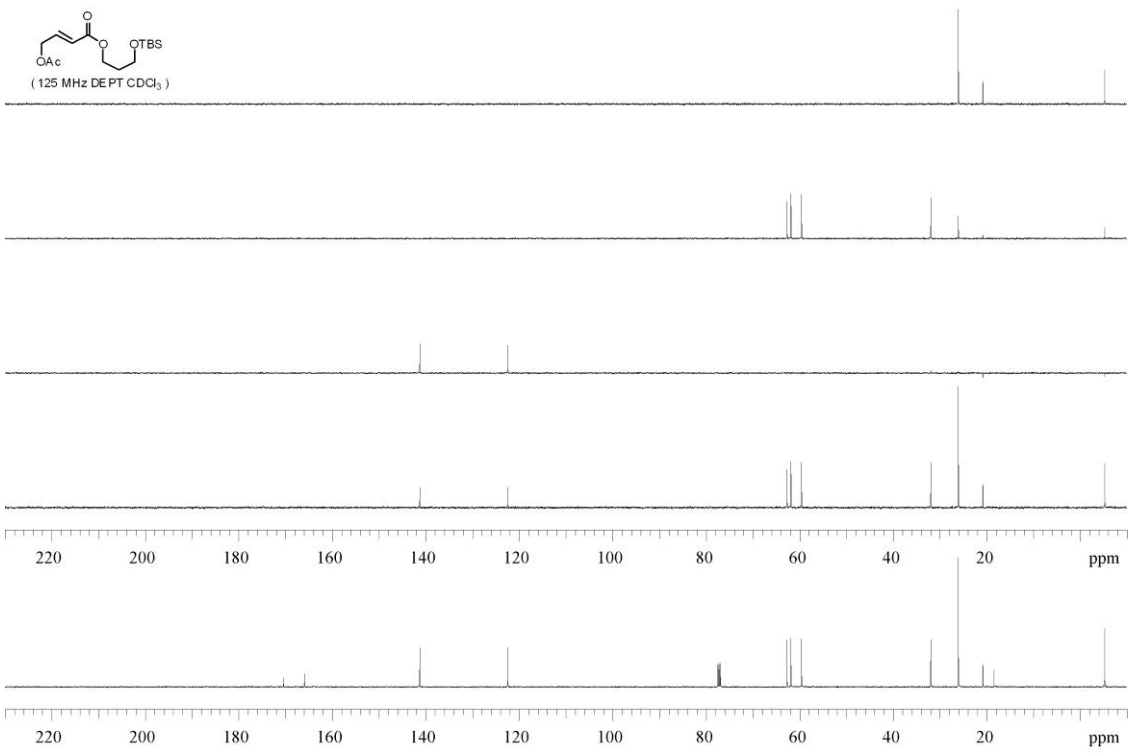

HO
O
O
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.691
147.133
120.304
77.482
77.230
76.974
61.988
61.696
59.650
31.998
26.085
18.478
-5.223
220
200
180
160
140
120
100
80
60
40
20
ppm

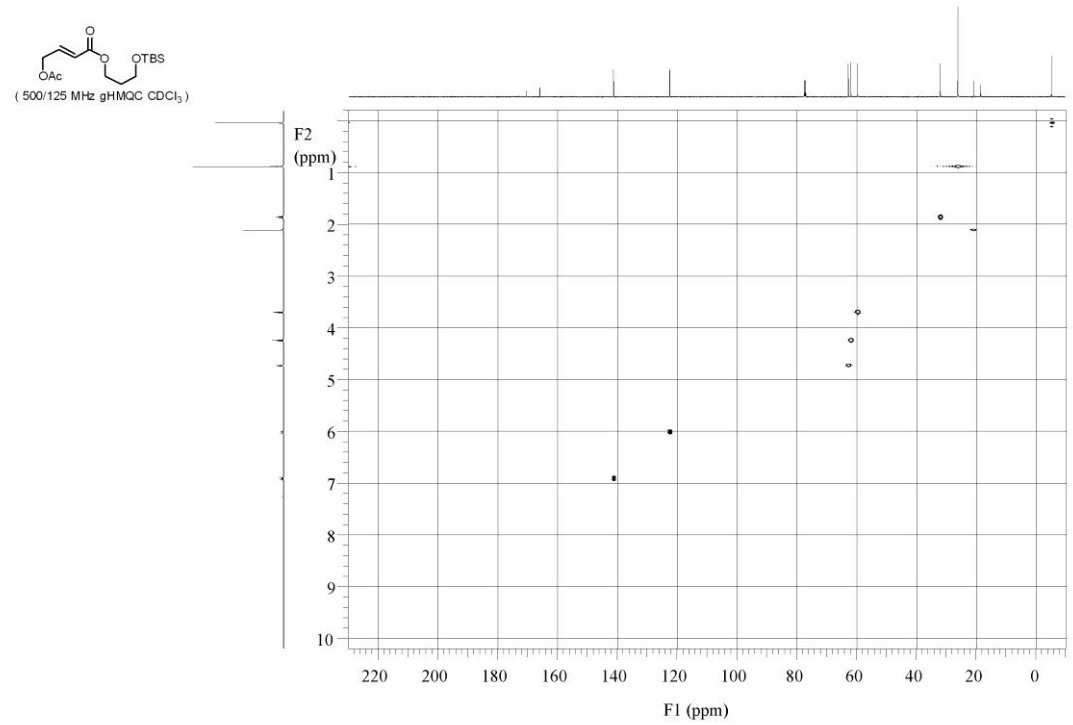

HO
O
O
OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

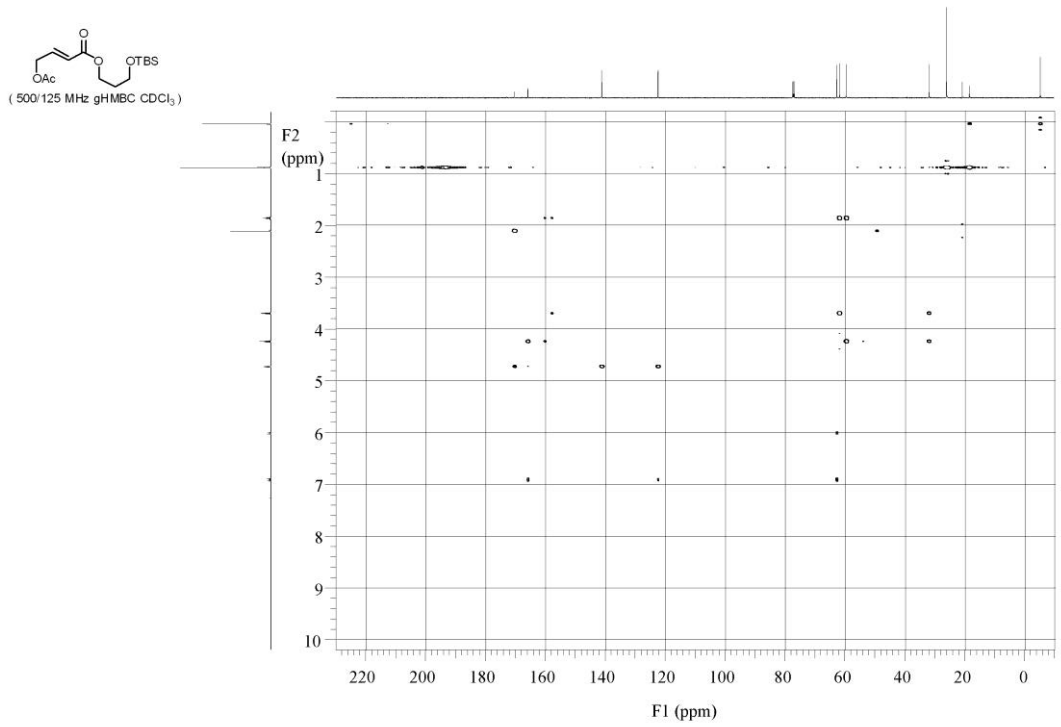

HO
O
O
OTBS
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

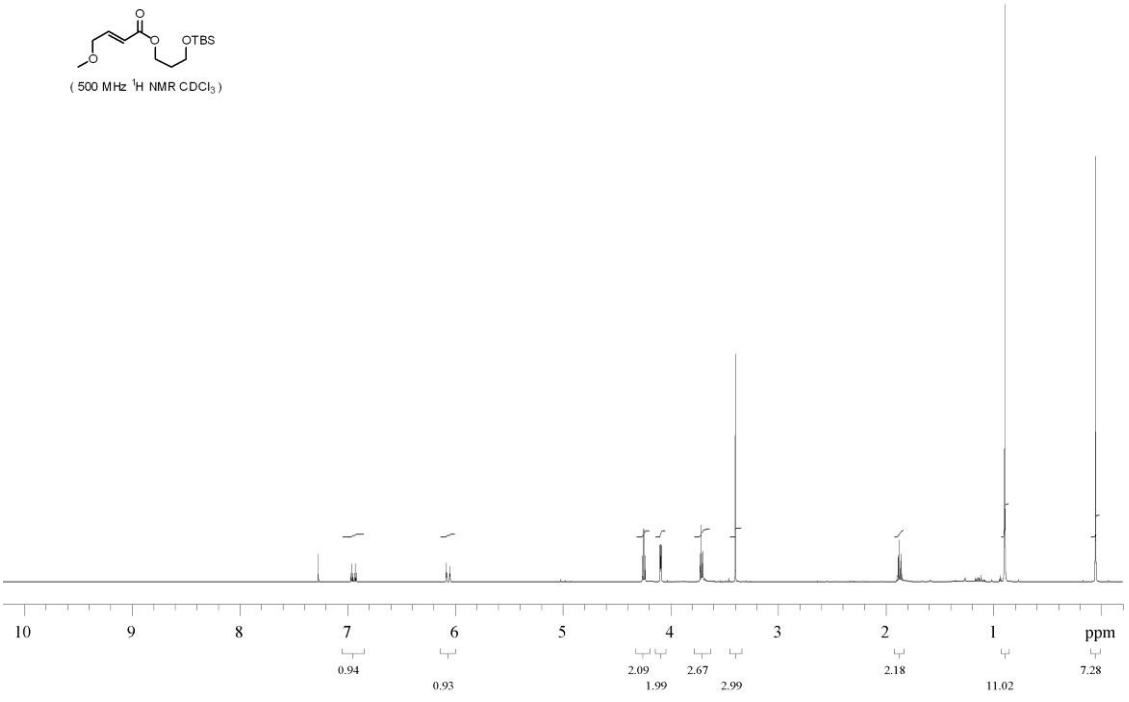

OAc
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.97
0.99
2.01
2.08
2.08
3.10
2.14
9.26
6.22

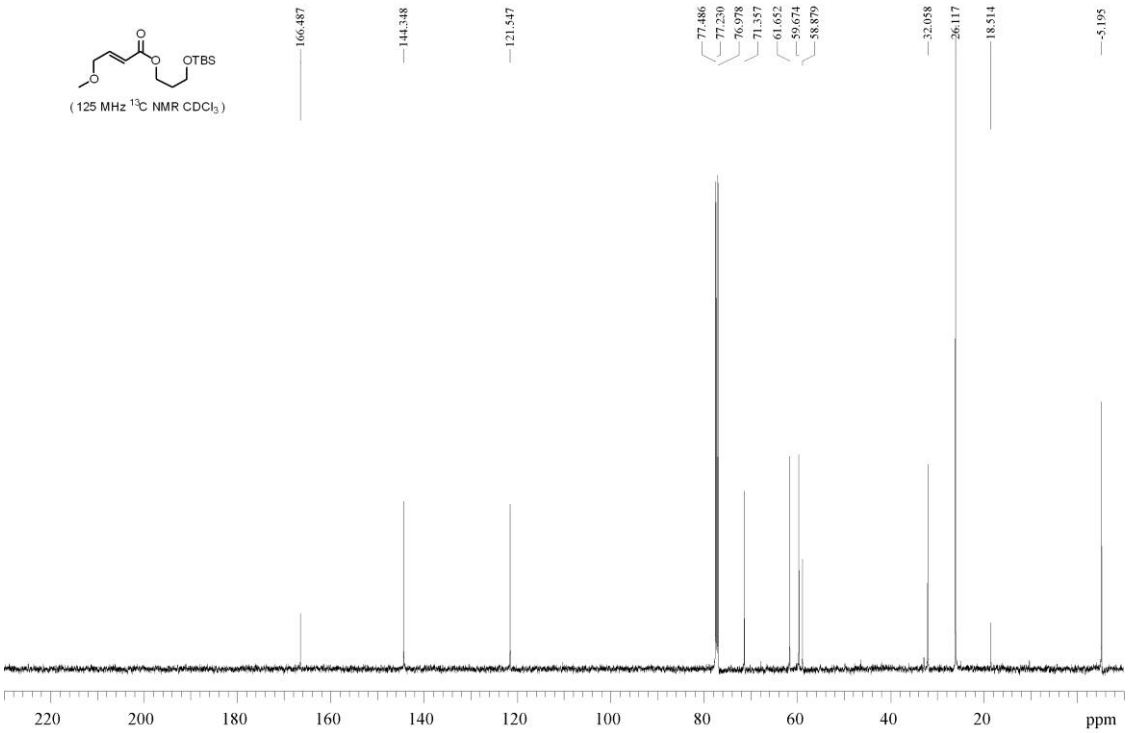

OAc
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
170.398
165.935
141.276
122.454
77.486
77.230
76.978
62.719
61.872
59.606
31.978
26.069
20.843
18.458
-5.239
220
200
180
160
140
120
100
80
60
40
20
ppm

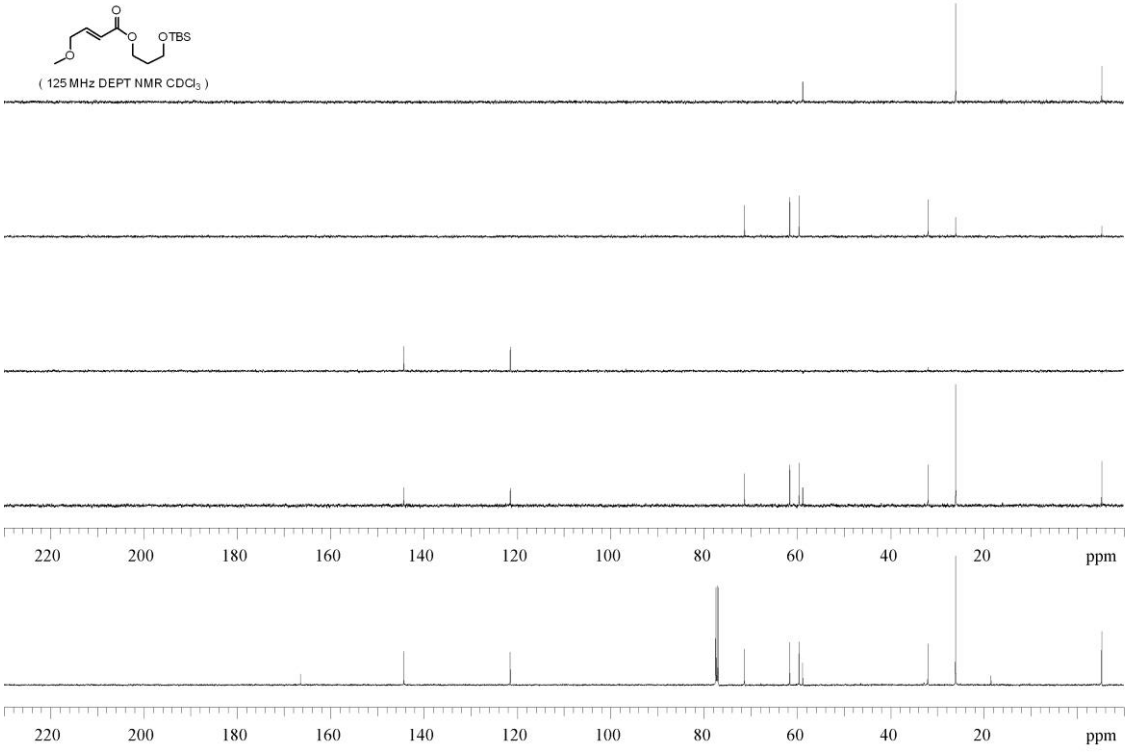

OAc
OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

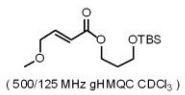

OAc
OTBS
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)


OTBS
OAc
(500/125 MHz gHMBC $CDCl_3$)
F2
(ppm)
F1 (ppm)

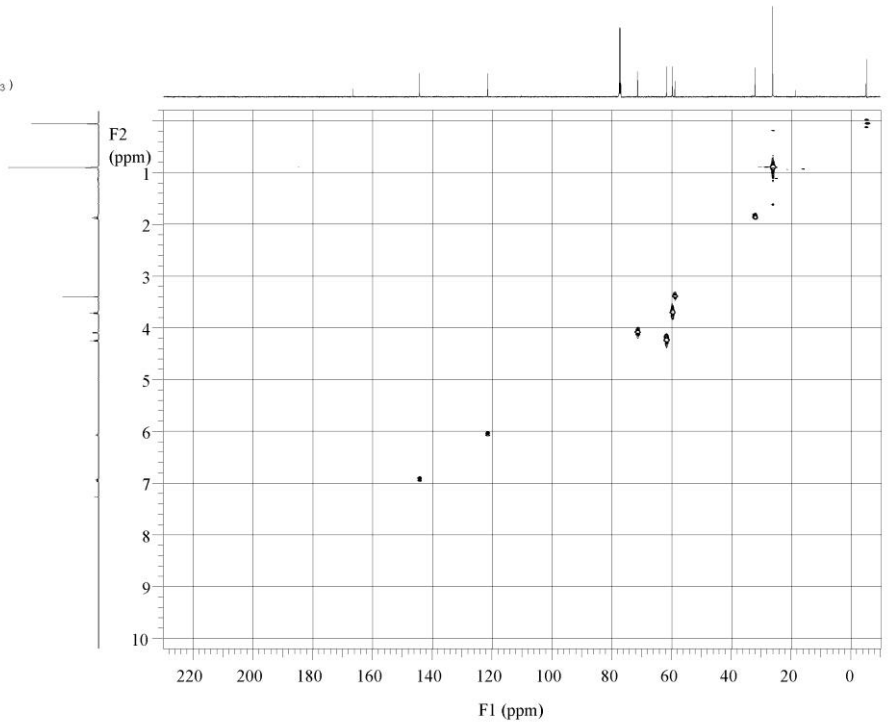

OTBS
(500 MHz ^1H NMR $CDCl_3$)
ppm
0.94
0.93
2.09
1.99
2.67
2.99
2.18
11.02
7.28

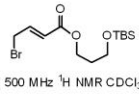

OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.487
144.348
121.547
77.486
77.230
76.978
71.357
61.652
59.674
58.879
32.058
26.117
18.514
-5.195
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
(125 MHz DEPT NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

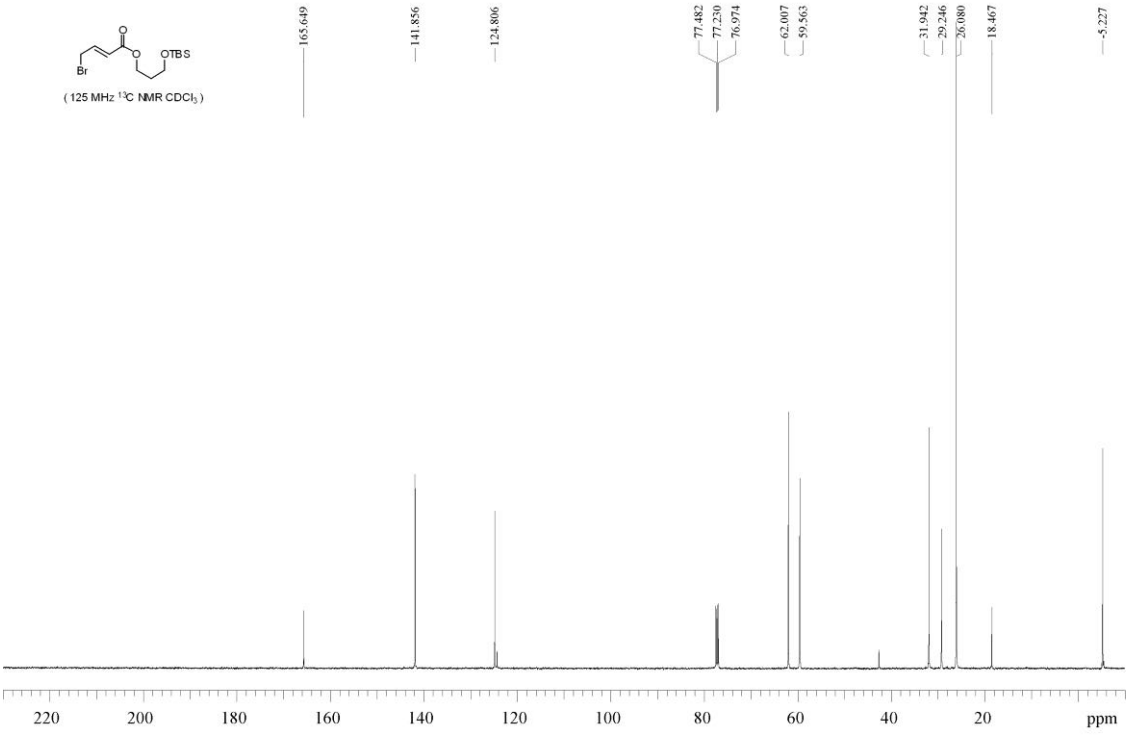


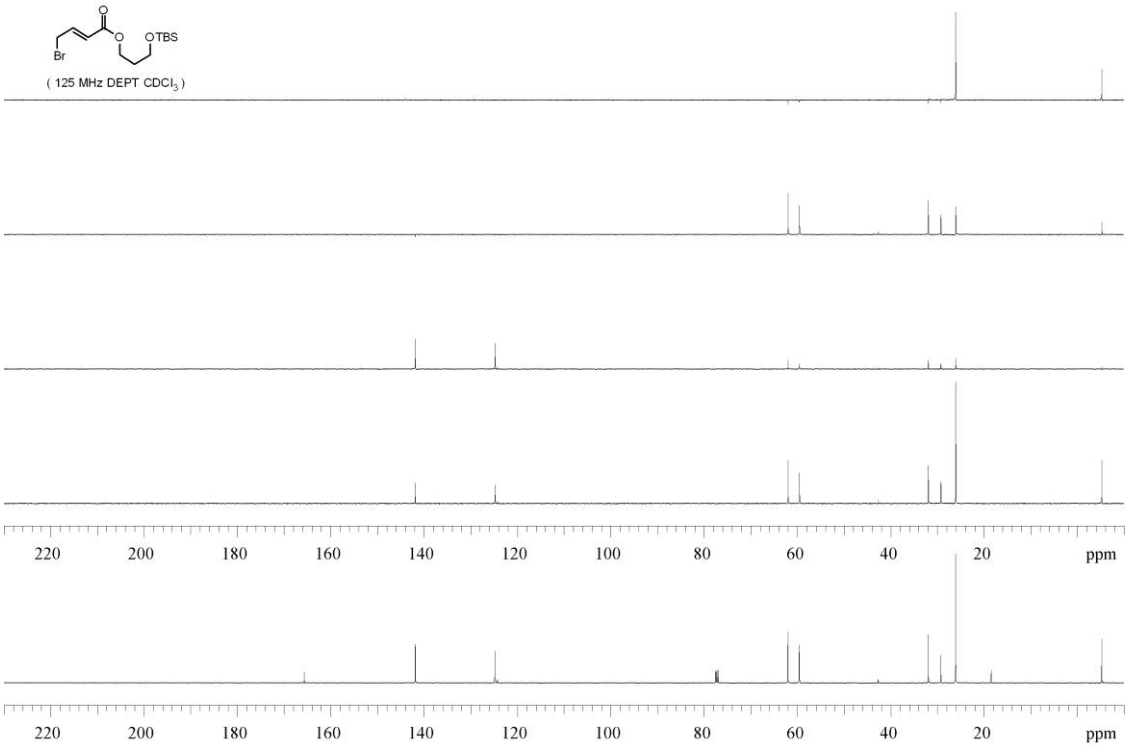
(500/125 MHz gHMQC $CDCl_3$)

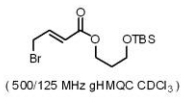




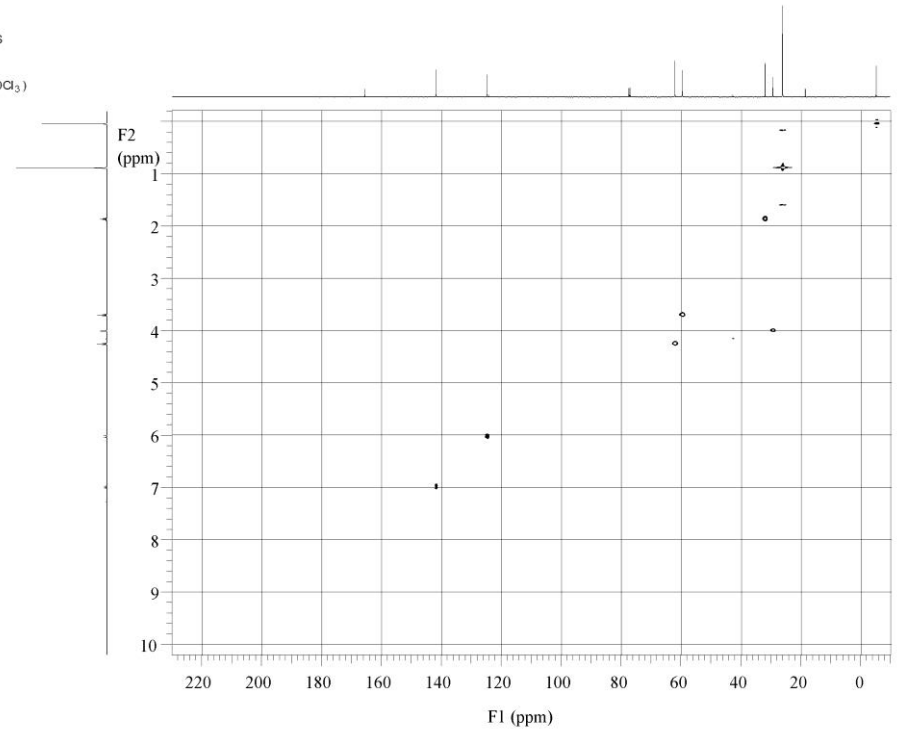
(500 MHz ^1H NMR $CDCl_3$)

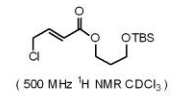

OTBS
Br
(125 MHz ^{13}C NMR $CDCl_3$)
165.649
141.856
124.806
77.482
77.230
76.974
62.007
59.563
31.942
29.246
26.080
18.467
-5.227
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
Br
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

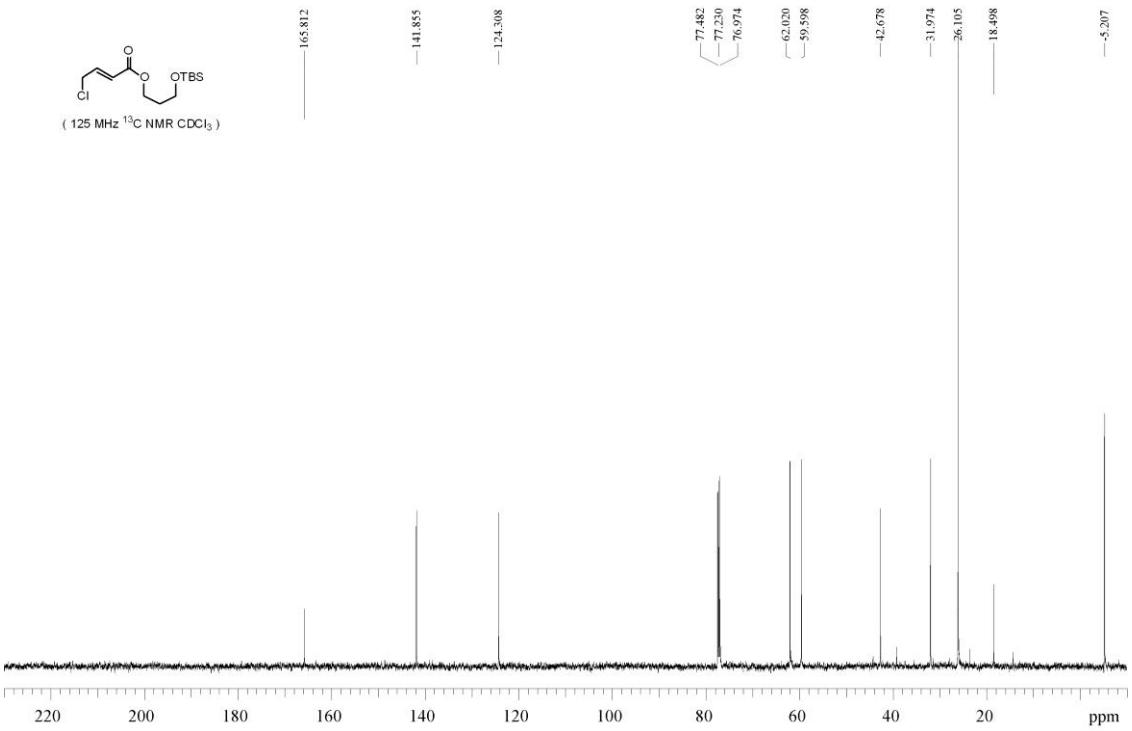


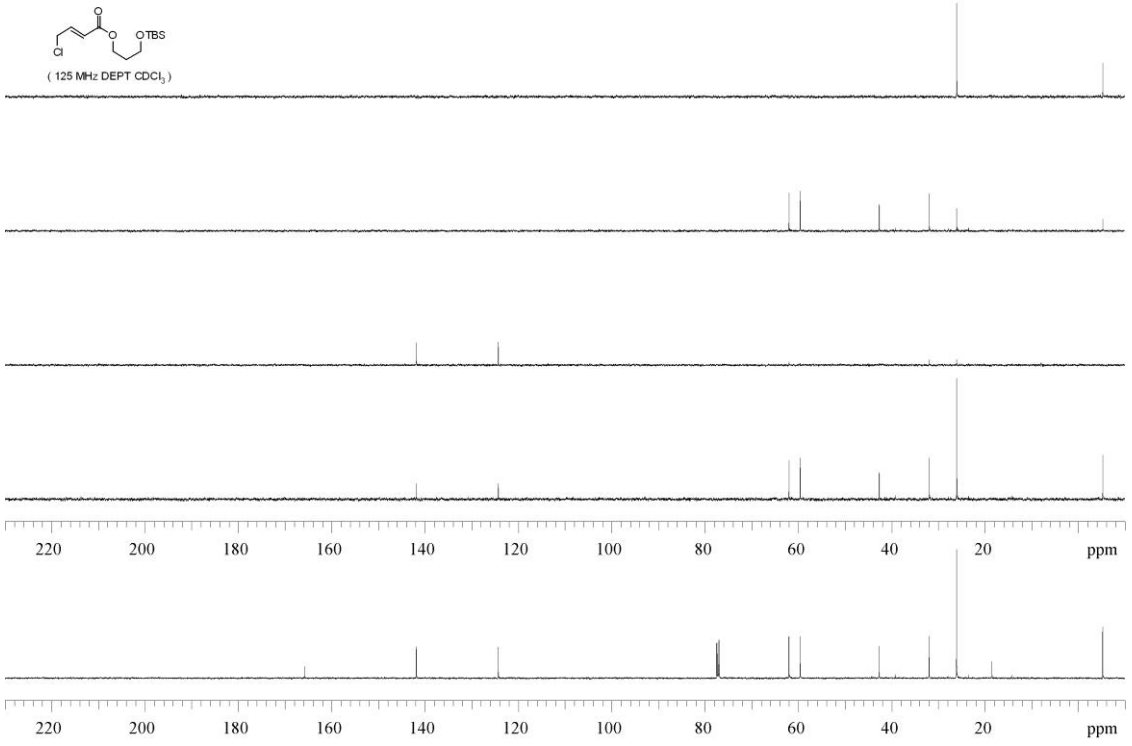
(500/125 MHz gHMQC $CDCl_3$)

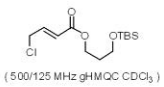




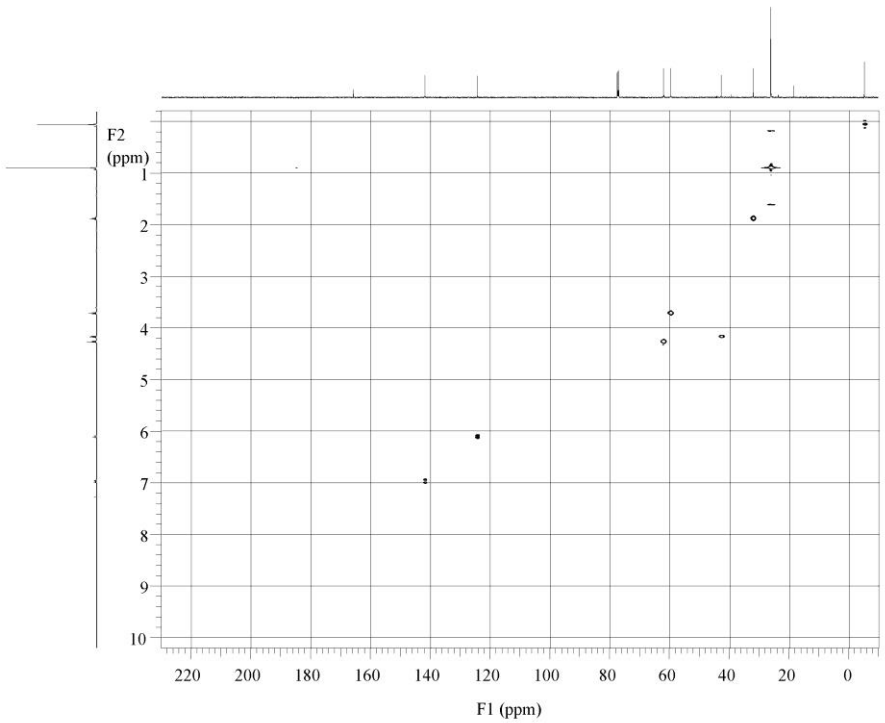
(500 MHz ^1H NMR $CDCl_3$)

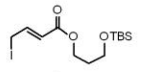

OTBS
Cl
(125 MHz ^{13}C NMR $CDCl_3$)
165.812
141.855
124.308
77.482
77.230
76.974
62.020
59.598
42.678
31.974
26.105
18.498
-5.207
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
Cl
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

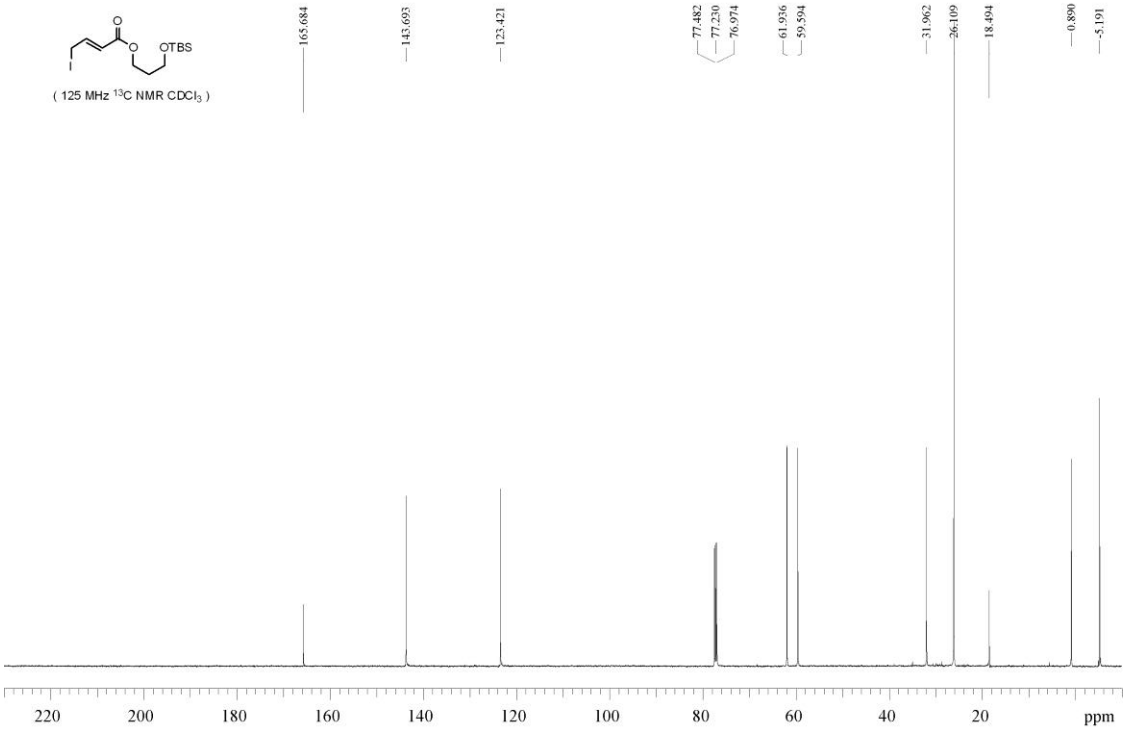


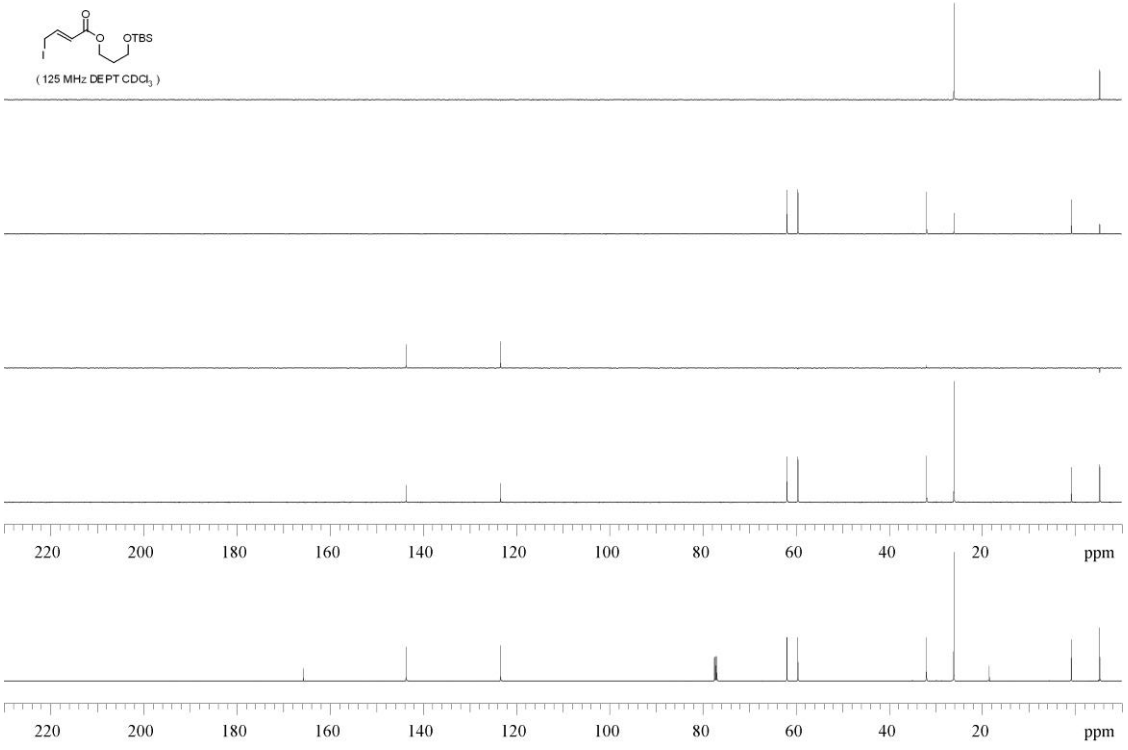
(500/125 MHz gHMQC $CDCl_3$)

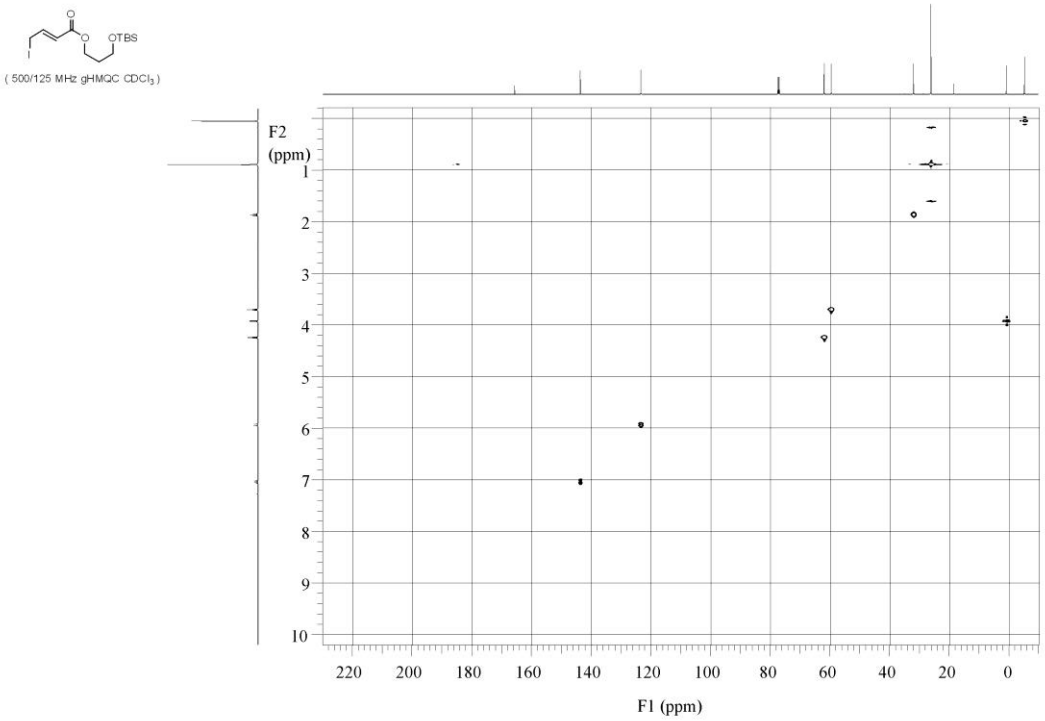


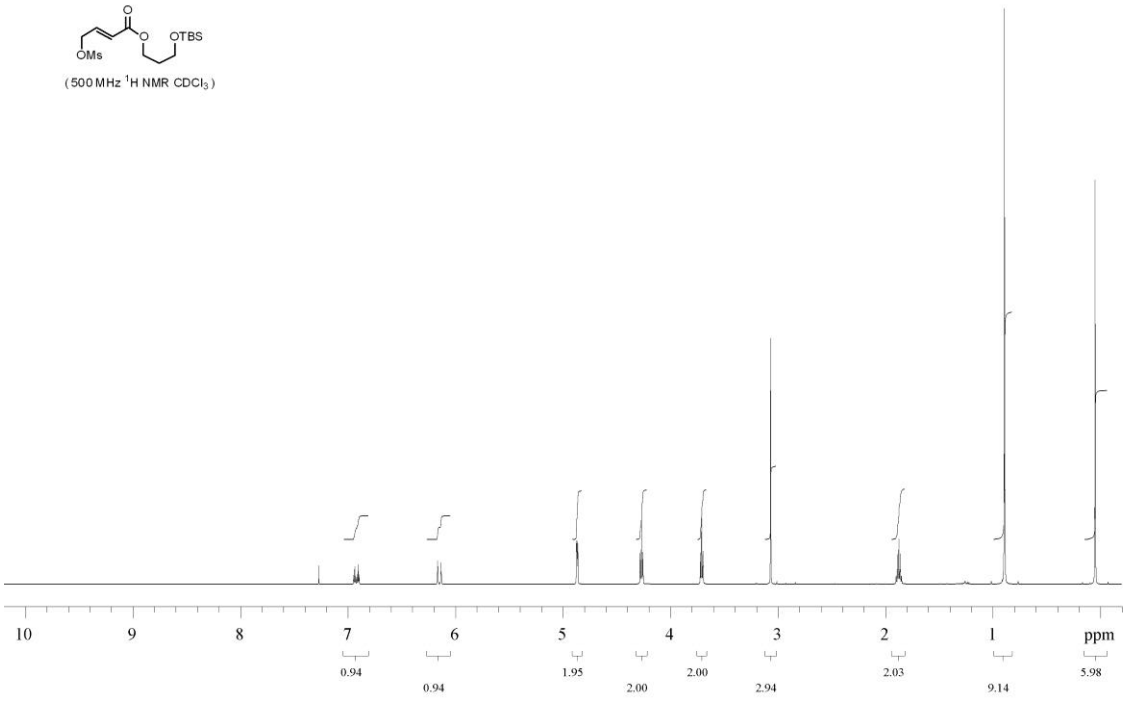


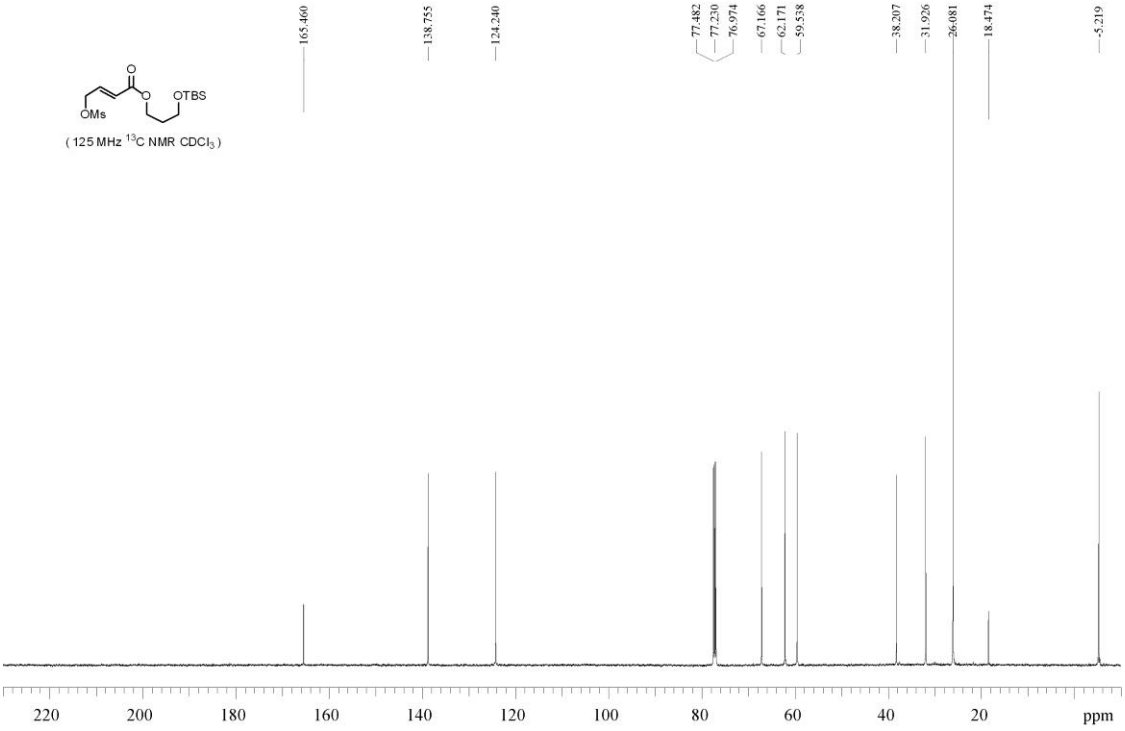
(500 MHz ^1H NMR $CDCl_3$)

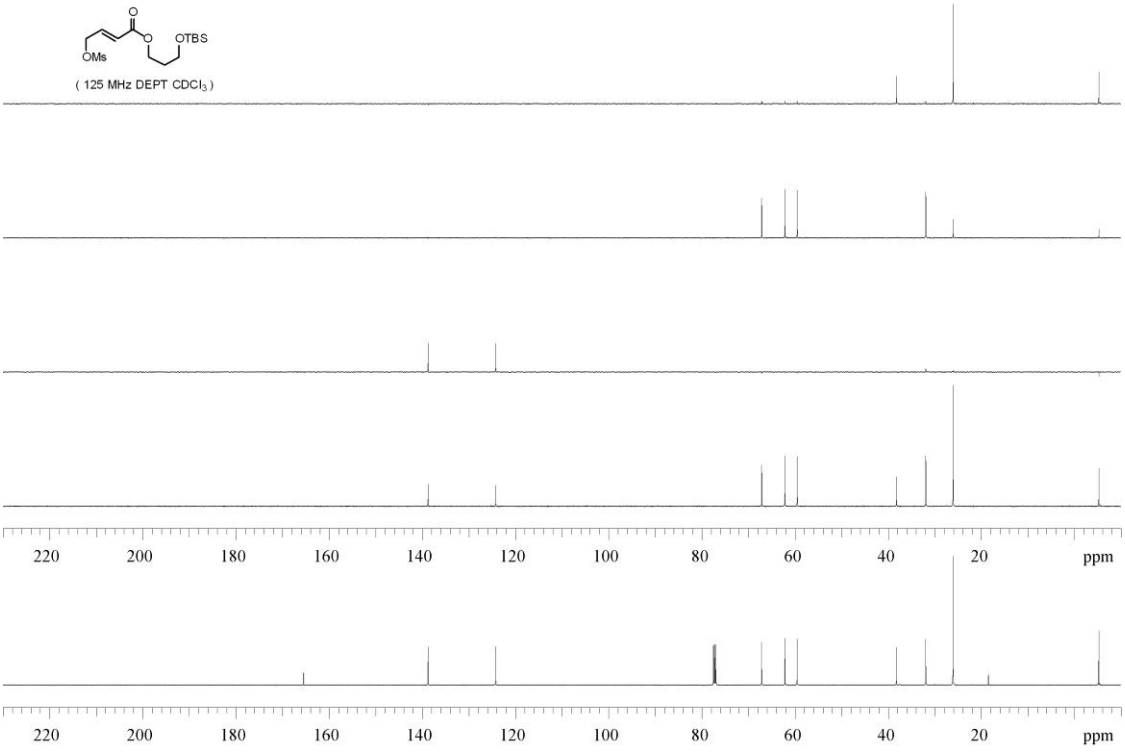

OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
165.684
143.693
123.421
77.482
77.230
76.974
61.936
59.594
31.962
26.109
18.494
-0.890
-5.191
220
200
180
160
140
120
100
80
60
40
20
ppm

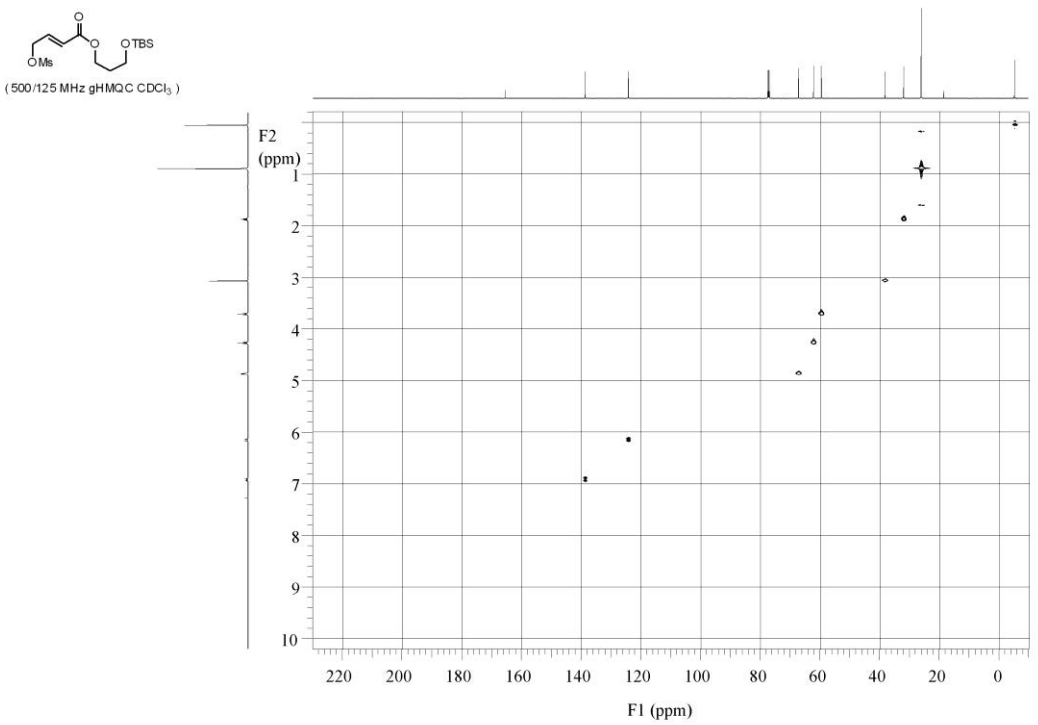

OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

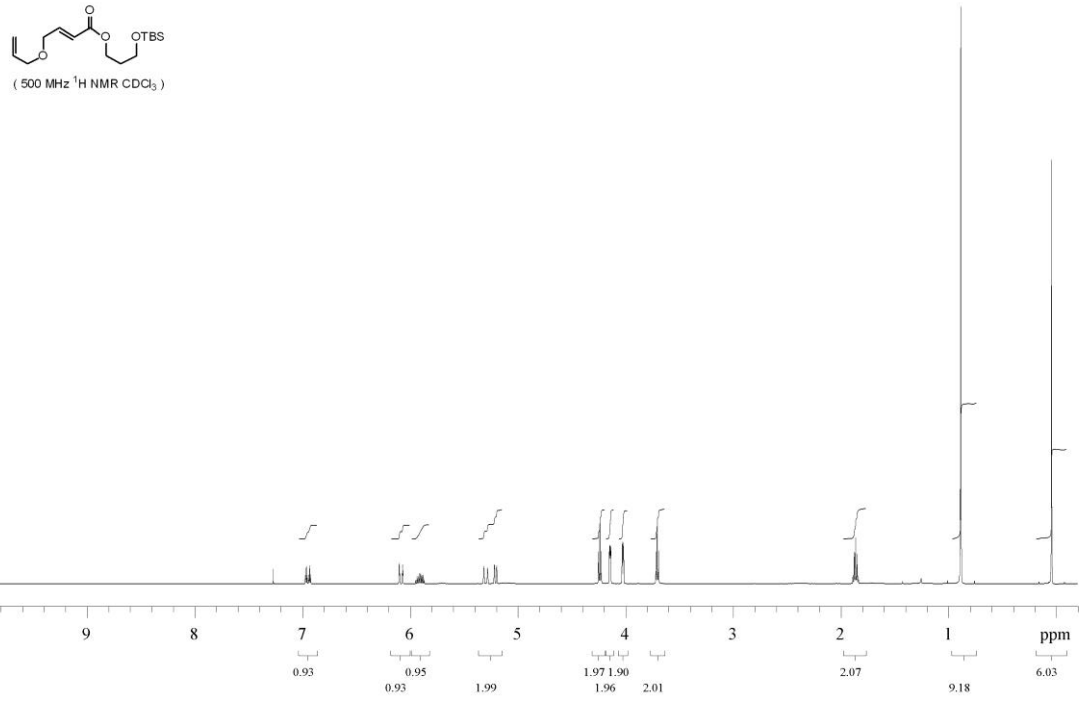

OTBS
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

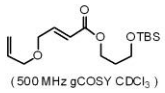

OMs
OTBS
(500 MHz 1H NMR CDCl3)
ppm
0.94
0.94
1.95
2.00
2.00
2.94
2.03
9.14
5.98


165.460
138.755
124.240
77.482
77.230
76.974
67.166
62.171
59.538
38.207
31.926
26.081
18.474
-5.219
OMs
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

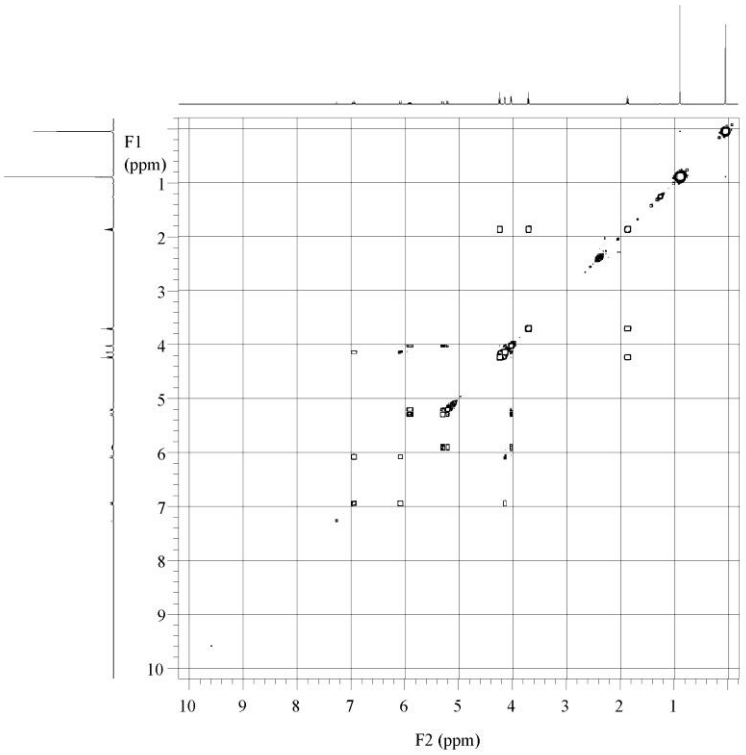

OMs
OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

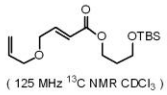

OMs
OTBS
(500/125 MHz gHMQC $CDCl_3$)
F2
(ppm)
F1 (ppm)


OTBS
(500 MHz ^1H NMR $CDCl_3$)
ppm
0.93
0.95
0.93
1.99
1.97
1.90
1.96
2.01
2.07
9.18
6.03

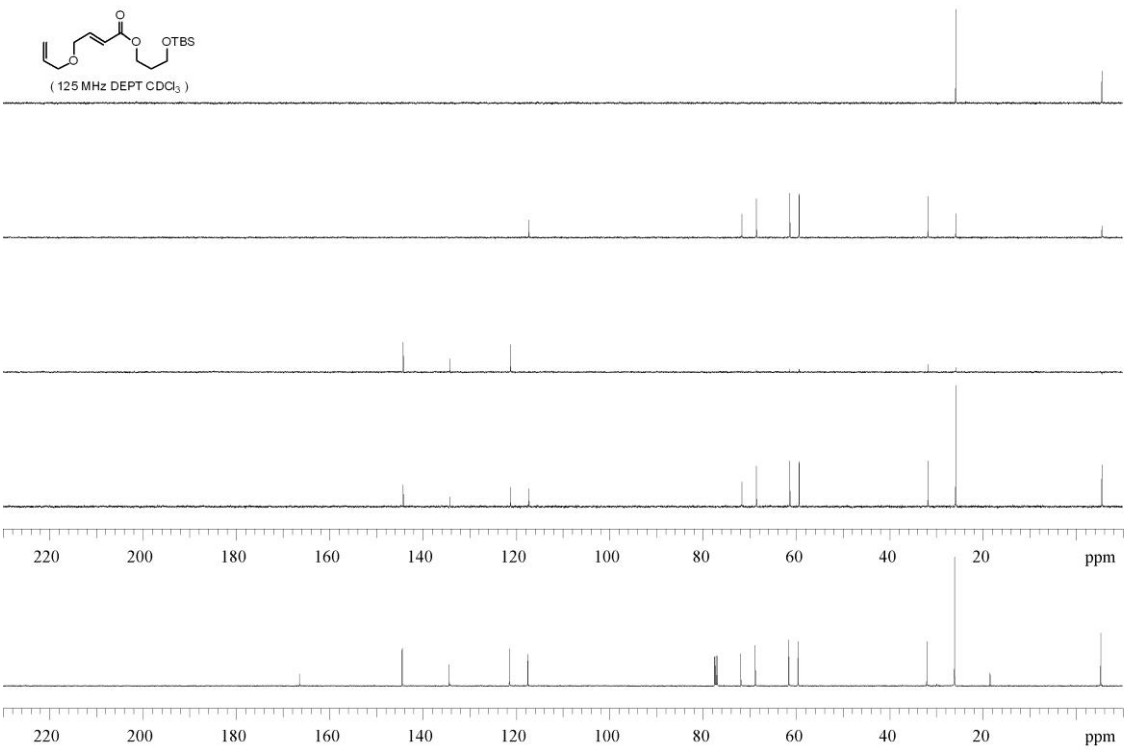


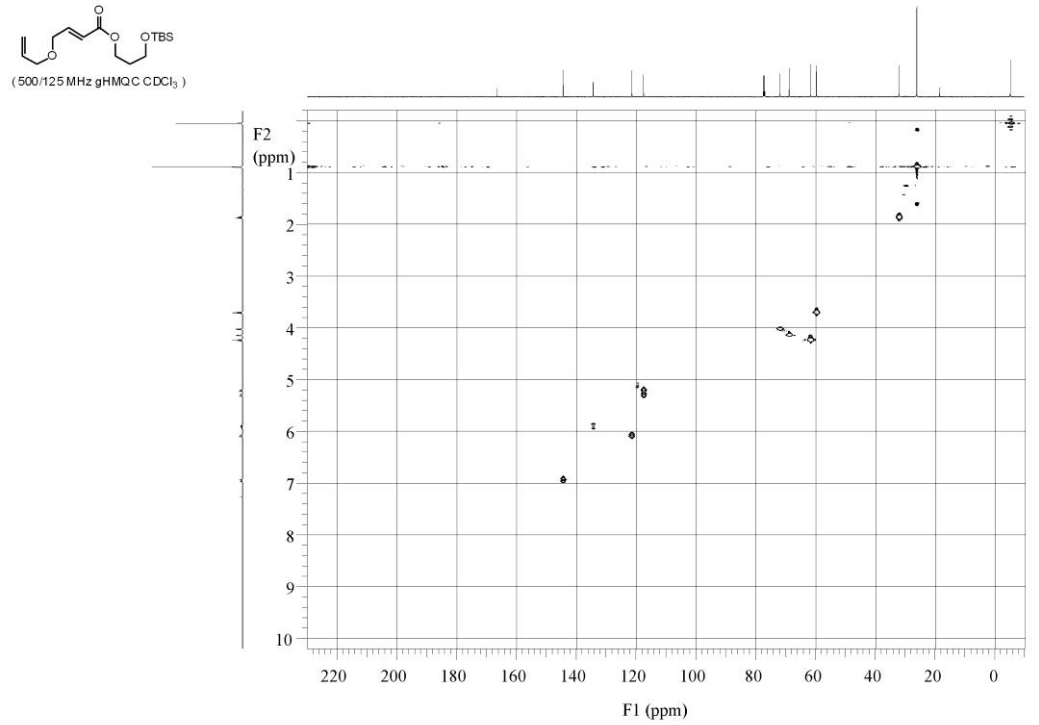
(500 MHz gCOSY $CDCl_3$)

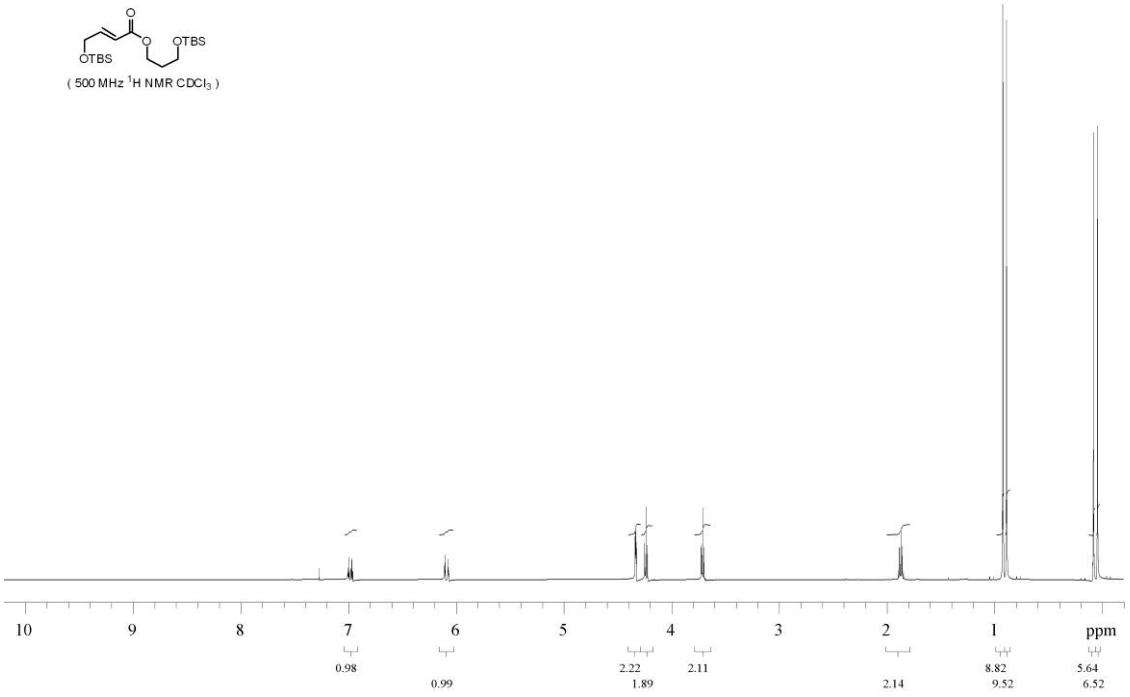


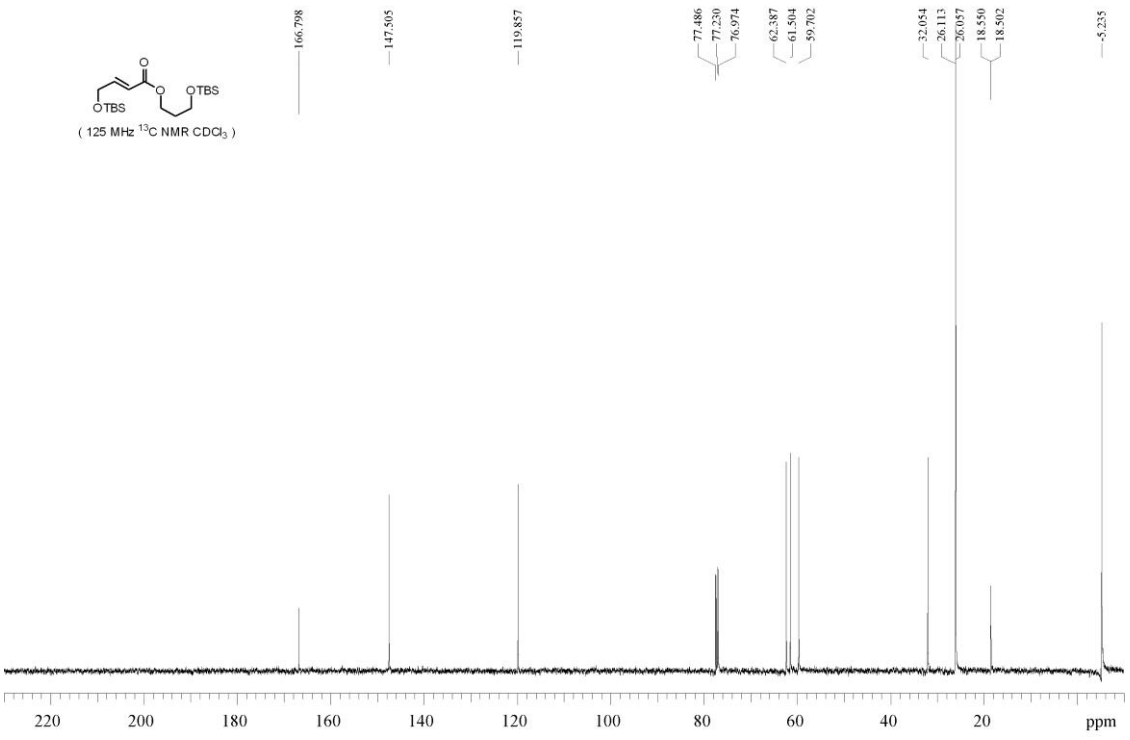


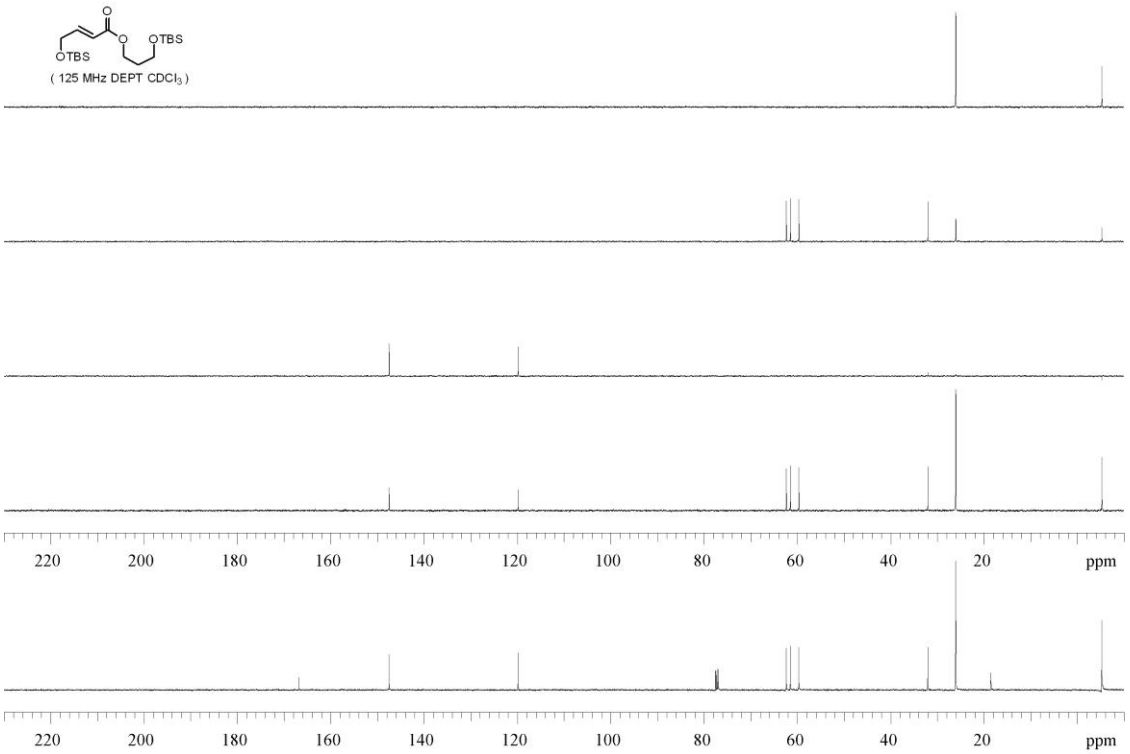
(125 MHz ^{13}C NMR $CDCl_3$)

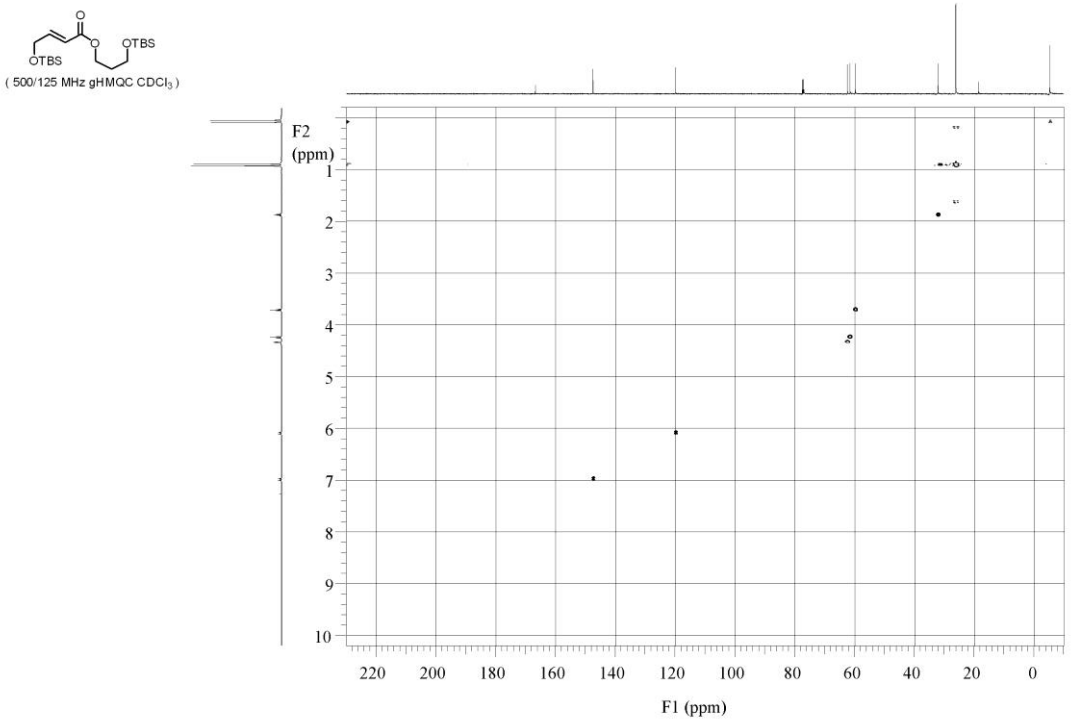

OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

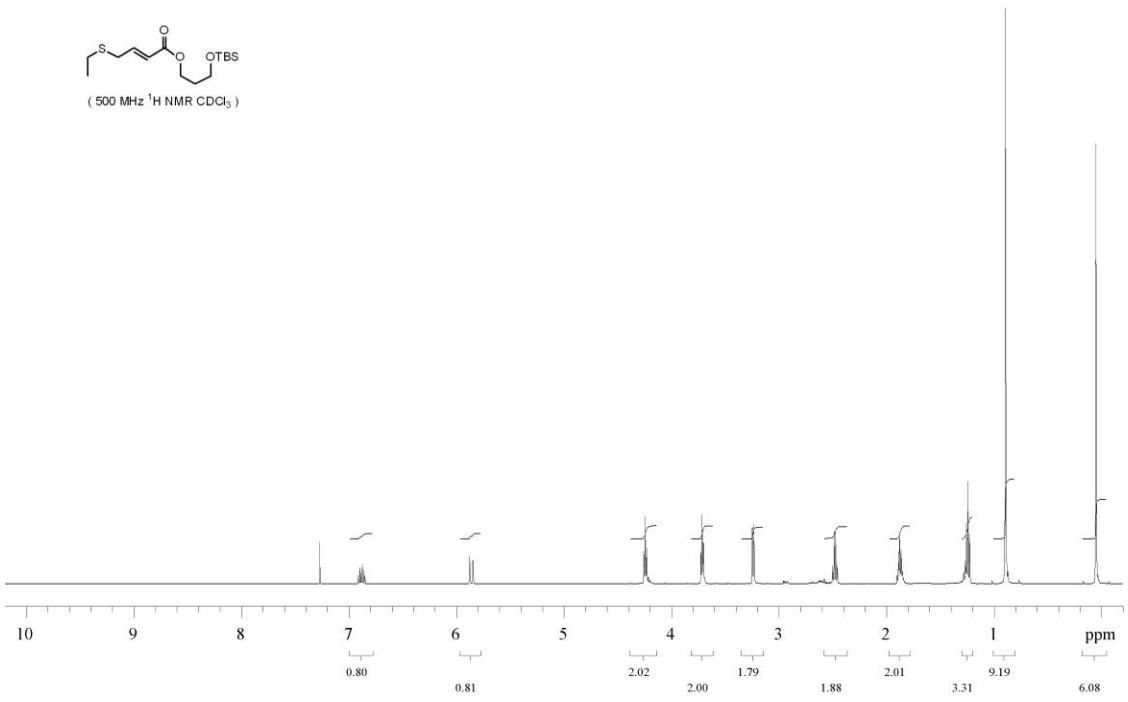

OTBS
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

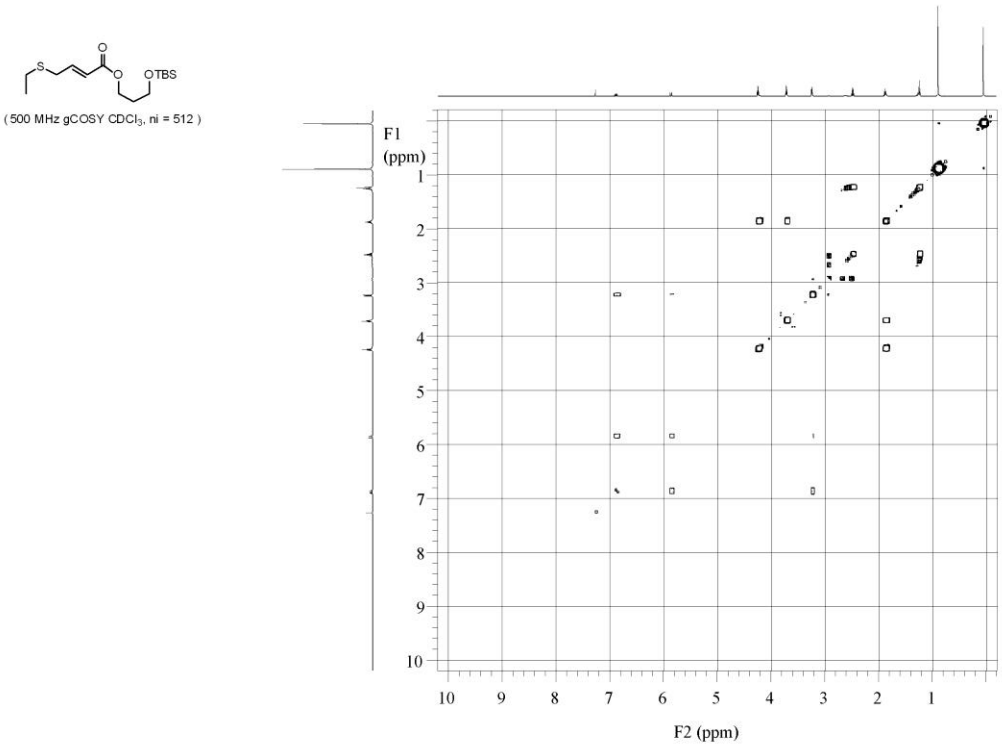

OTBS
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.98
0.99
2.22
1.89
2.11
2.14
8.82
9.52
5.64
6.52

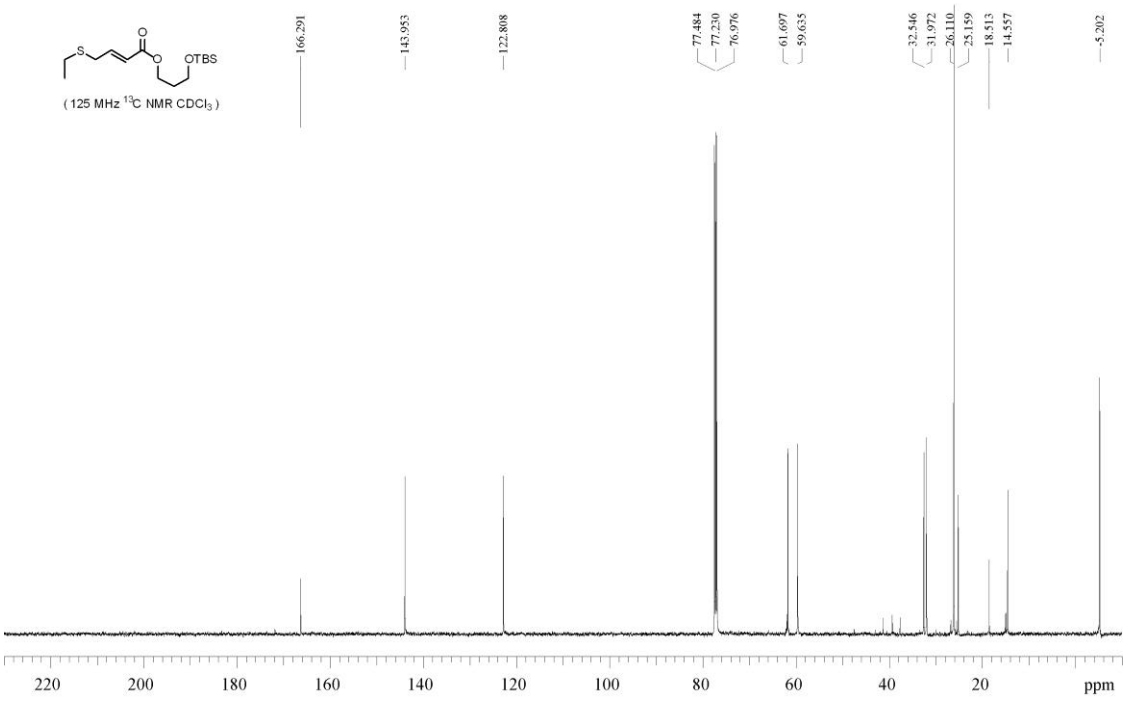

OTBS
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.798
147.505
119.857
77.486
77.230
76.974
62.387
61.504
59.702
32.054
26.113
26.057
18.550
18.502
-5.235
220
200
180
160
140
120
100
80
60
40
20
ppm

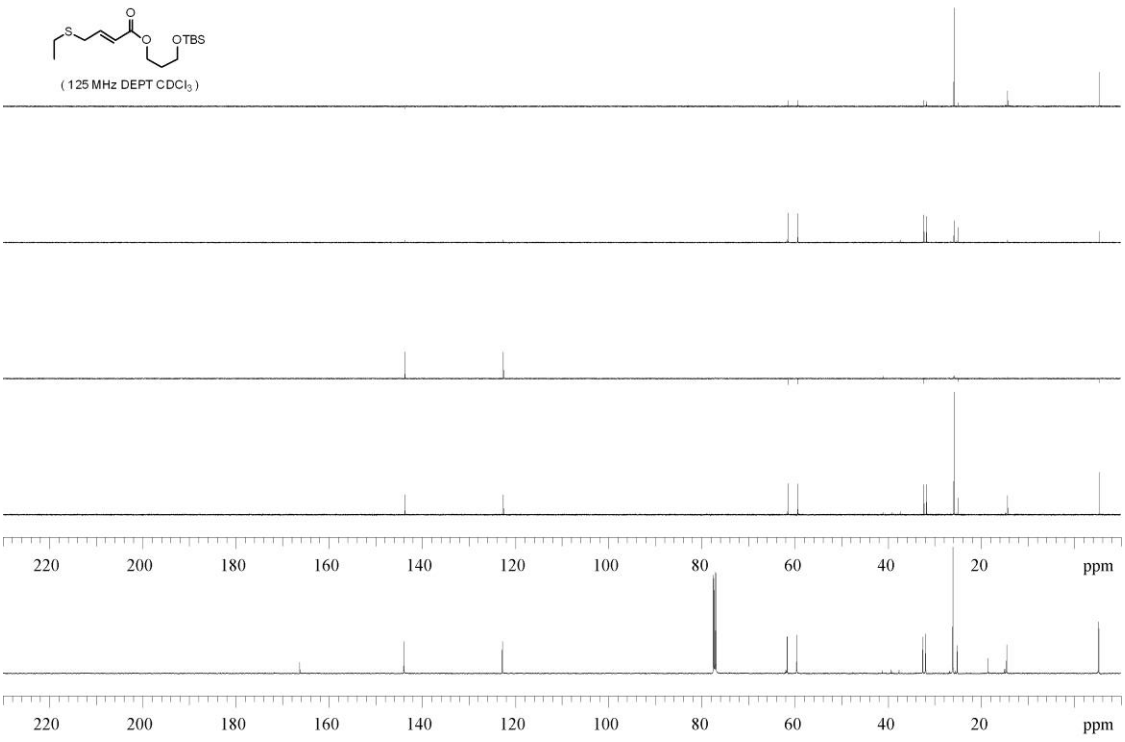

OTBS
OTBS
OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

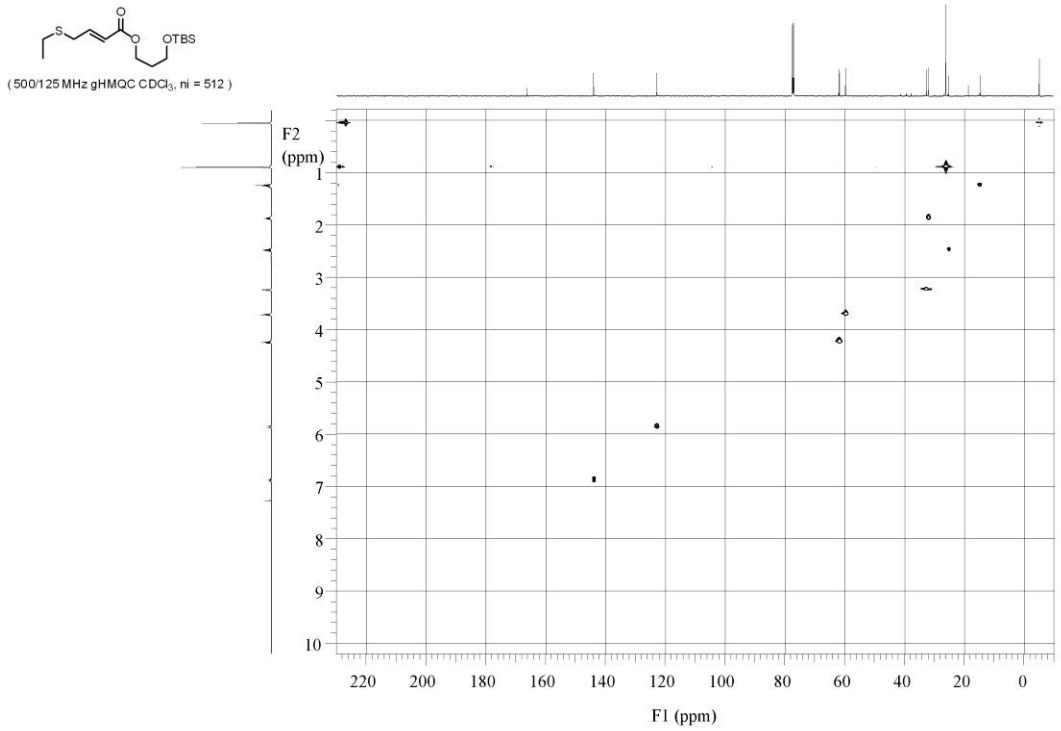

OTBS
OTBS
OTBS
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

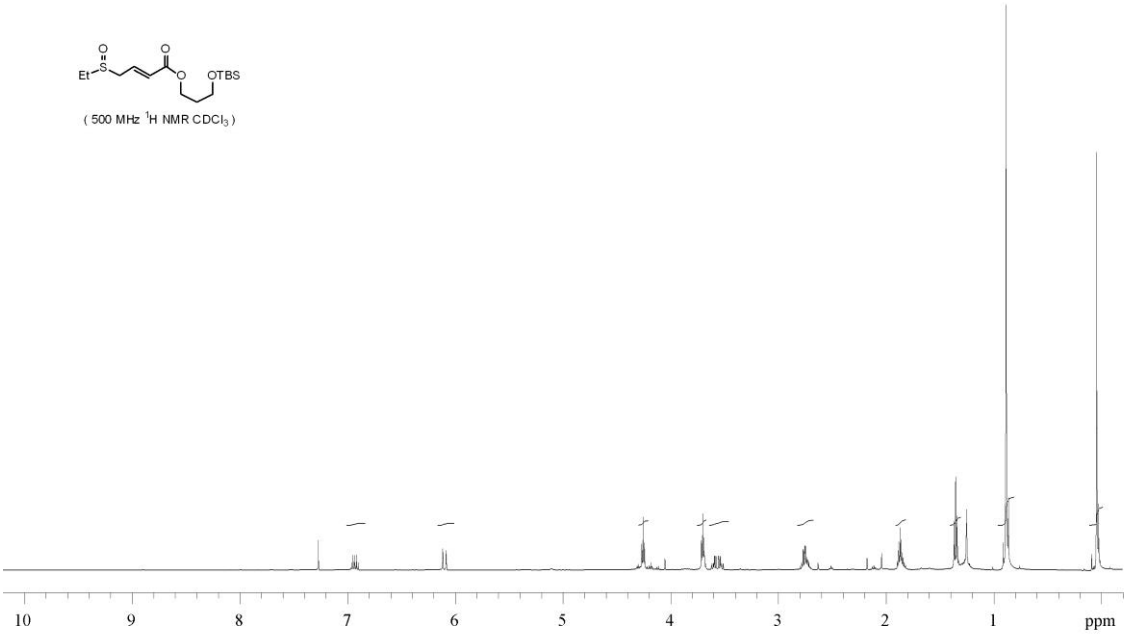

OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.80
0.81
2.02
2.00
1.79
1.88
2.01
3.31
9.19
6.08

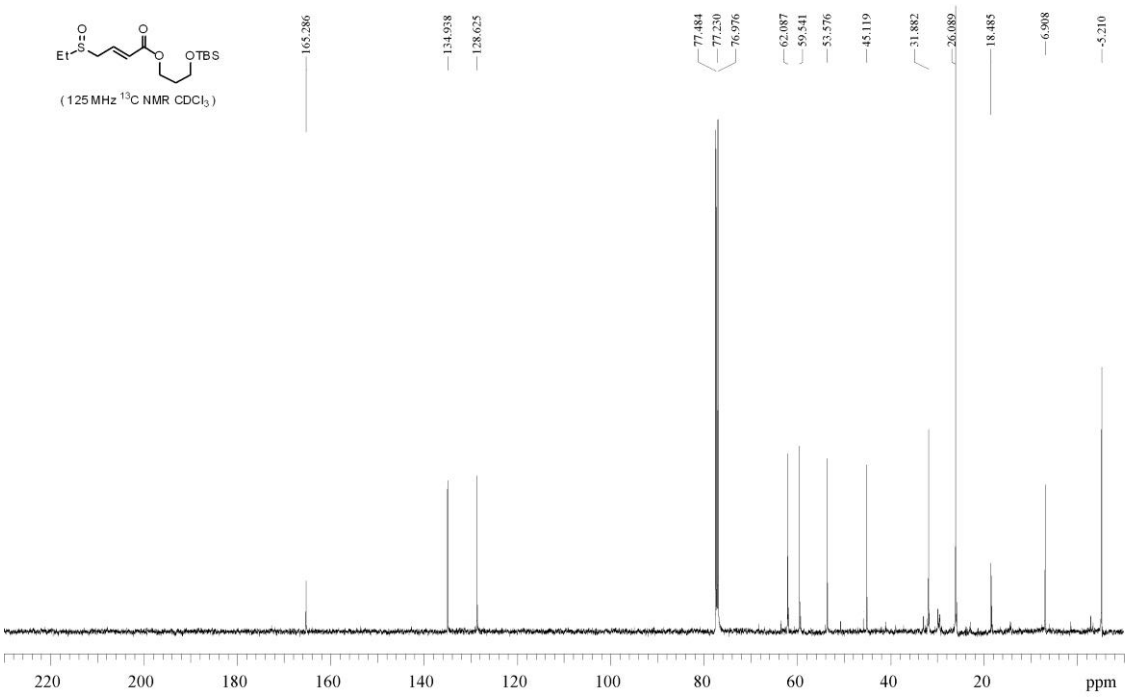

OTBS
(500 MHz gCOSY $CDCl_3$, ni = 512)
F1
(ppm)
F2 (ppm)

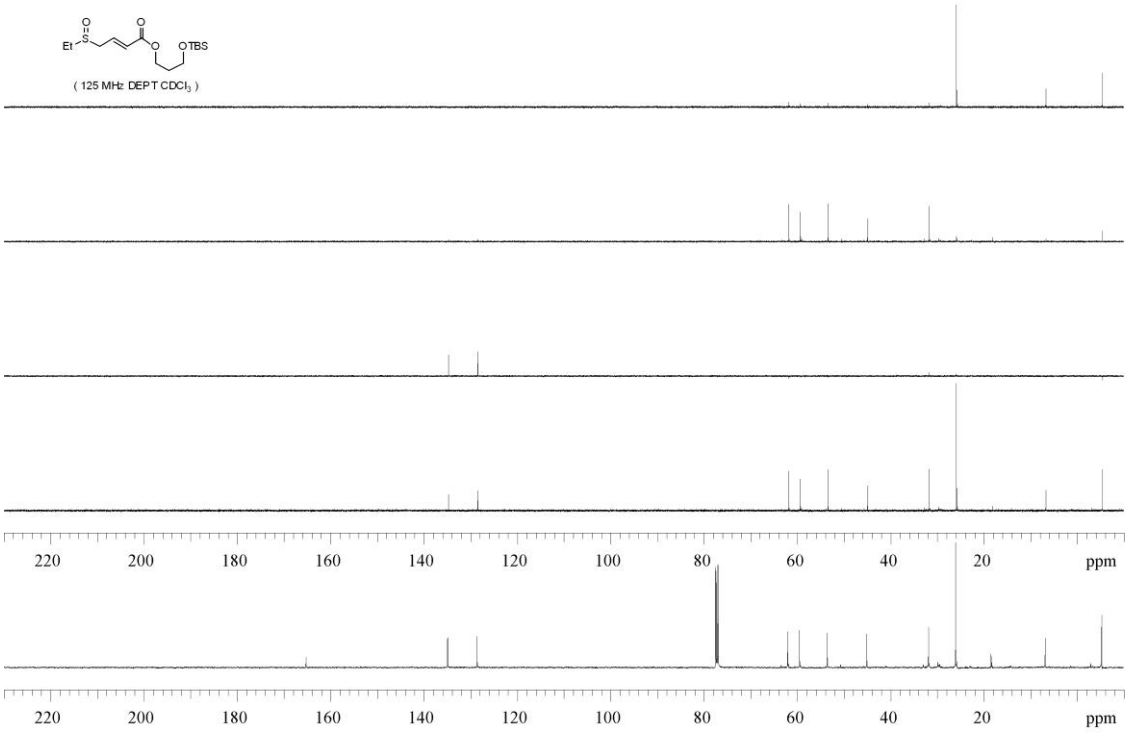

OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.291
143.953
122.808
77.484
77.230
76.976
61.697
59.635
32.546
31.972
26.110
25.159
18.513
14.557
-5.202
220
200
180
160
140
120
100
80
60
40
20
ppm

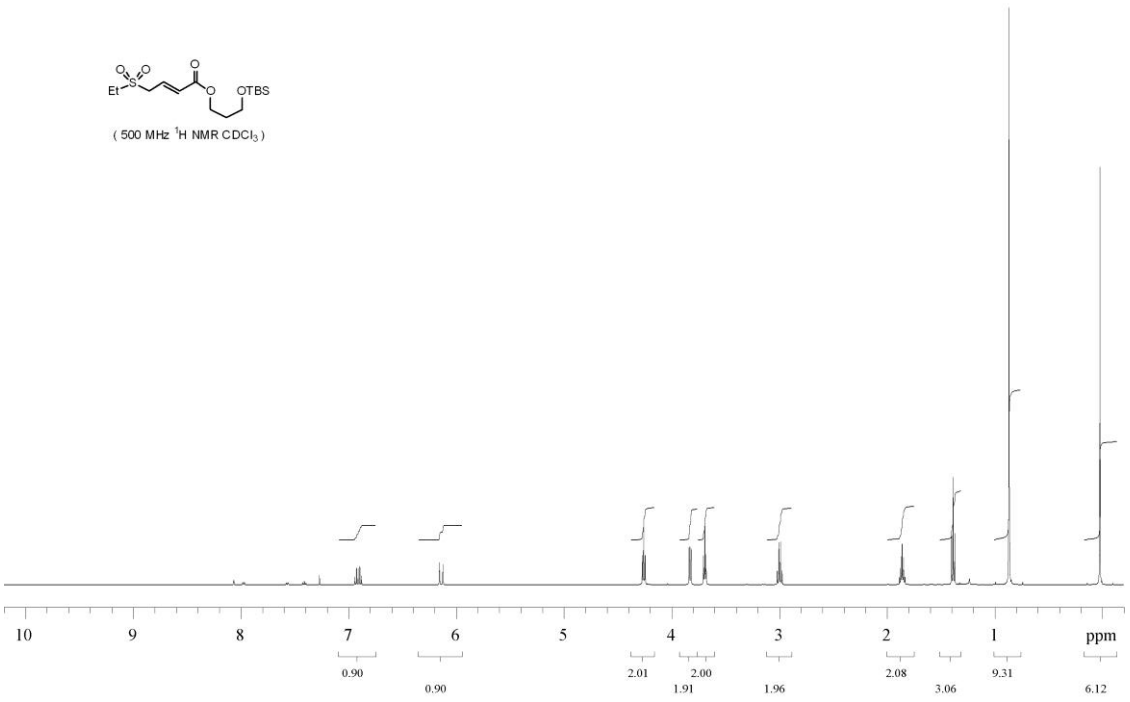

OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

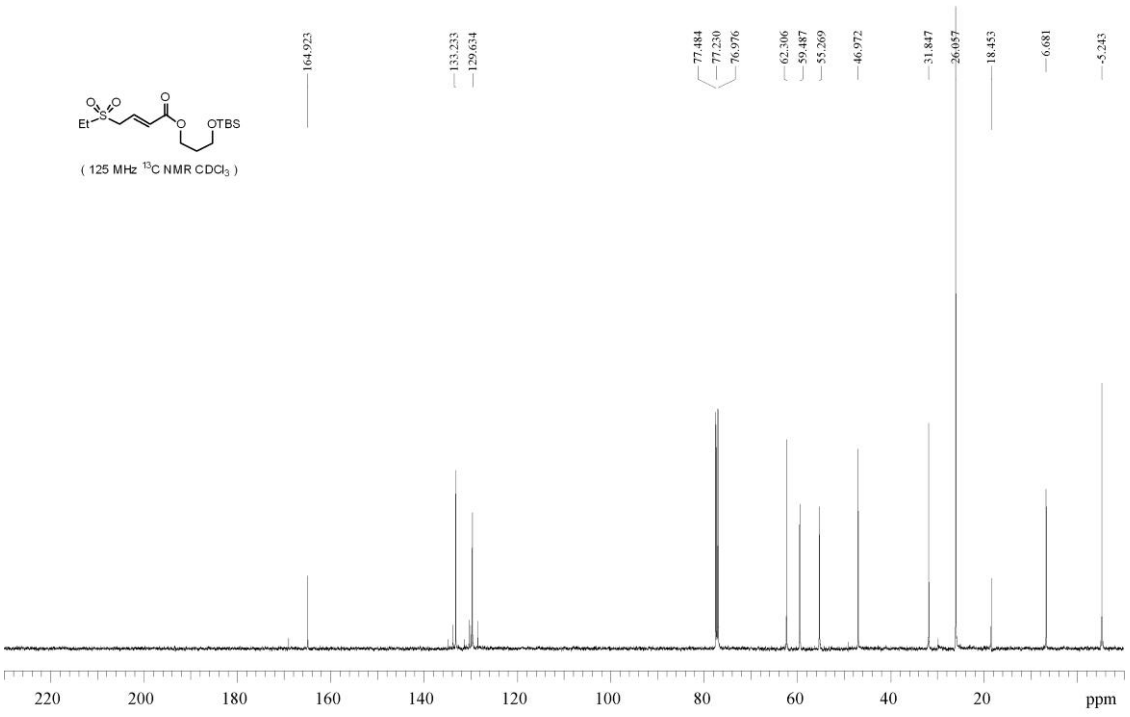

OTBS
(500/125 MHz gHMQC CDCl3, ni = 512)
F2
(ppm)
F1 (ppm)

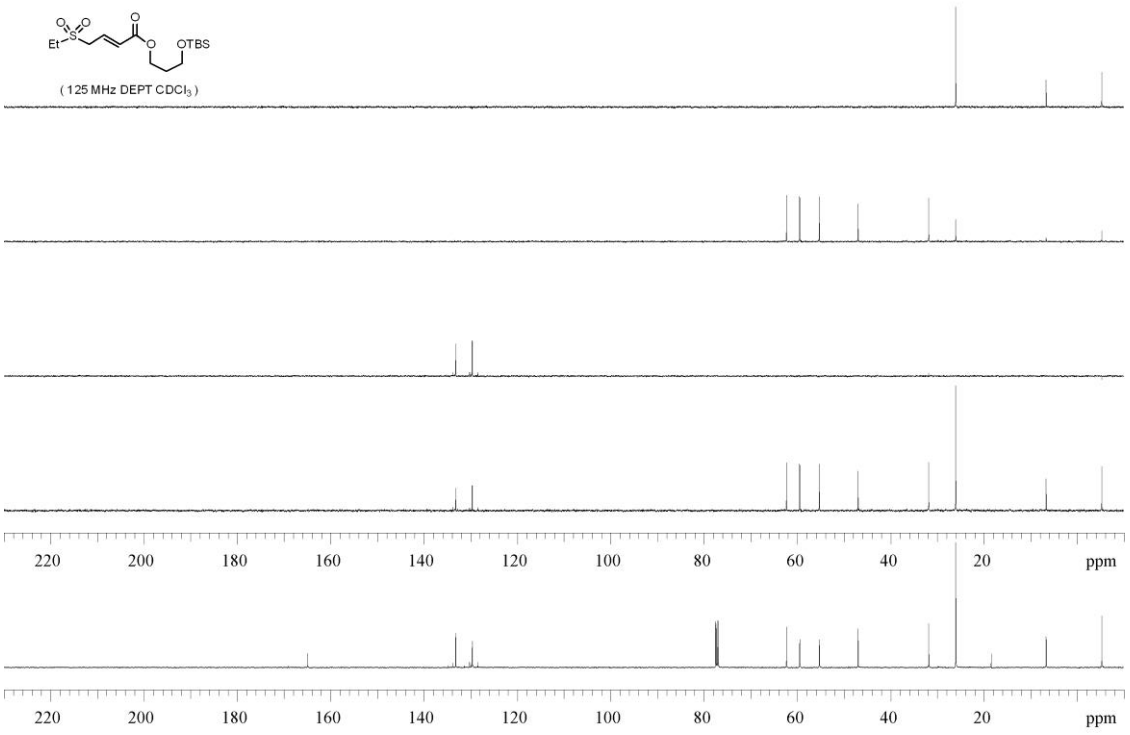

Et
OTBS
(500 MHz 1H NMR CDCl3)
ppm

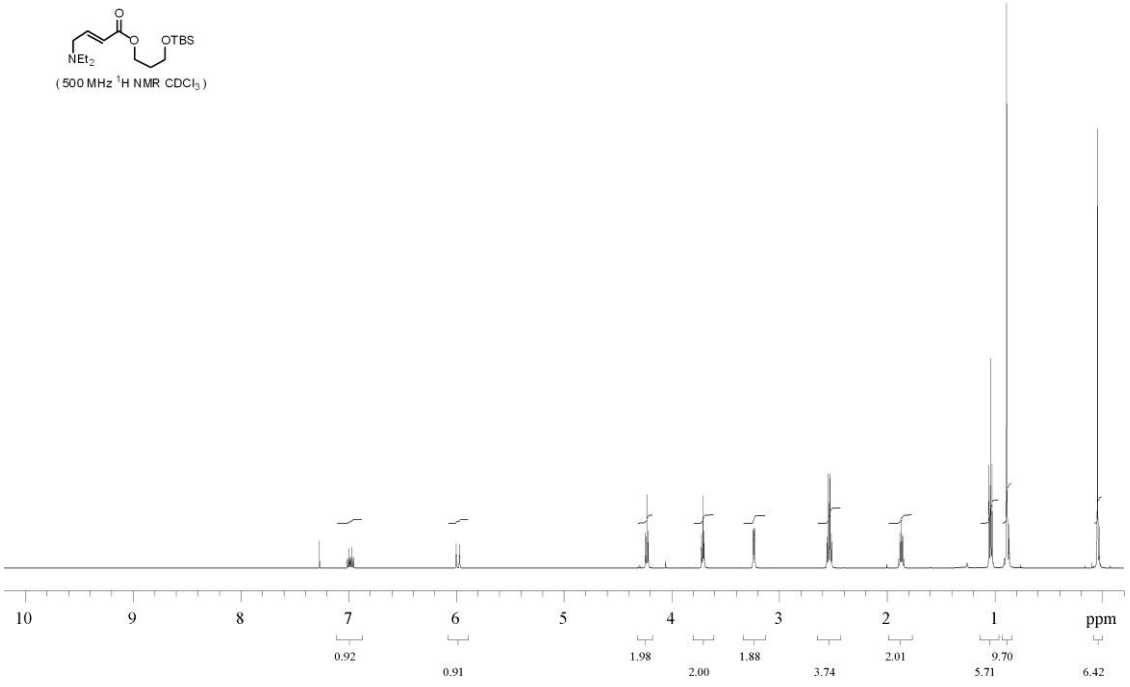

Et
O
S
O
O
O
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
165.286
134.938
128.625
77.484
77.230
76.976
62.087
59.541
53.576
45.119
31.882
26.089
18.485
6.908
5.210
220
200
180
160
140
120
100
80
60
40
20
ppm

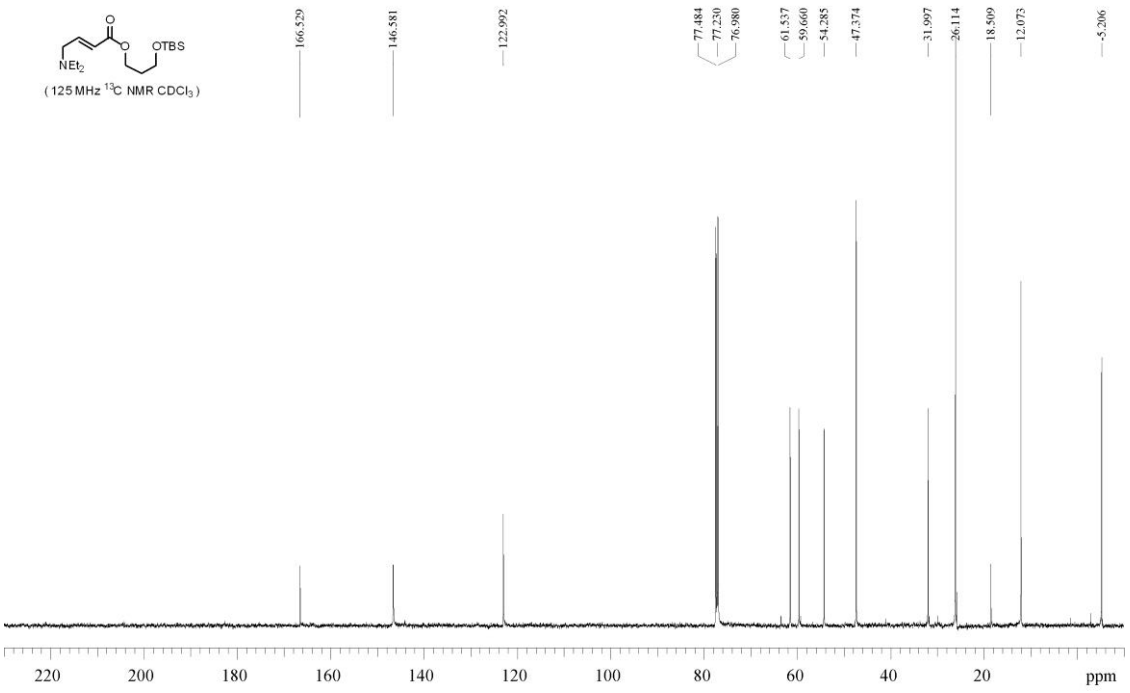

Et
O
S
O
O
O
OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

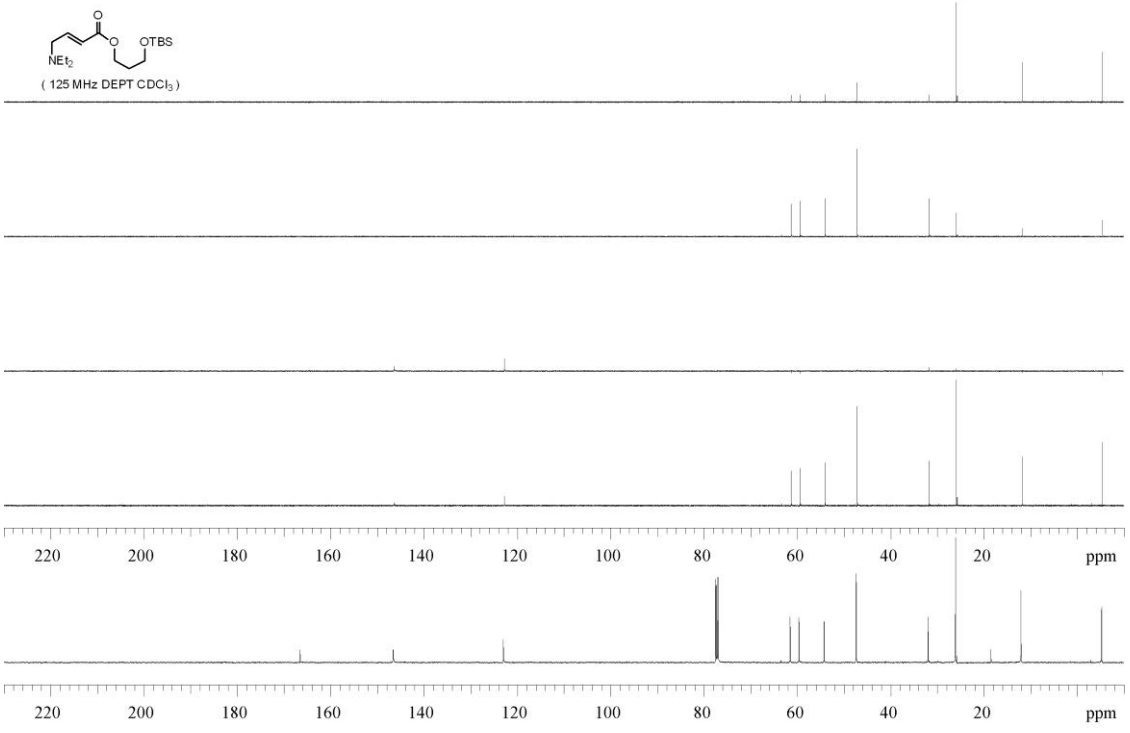

Et
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.90
0.90
2.01
2.00
1.91
1.96
2.08
3.06
9.31
6.12

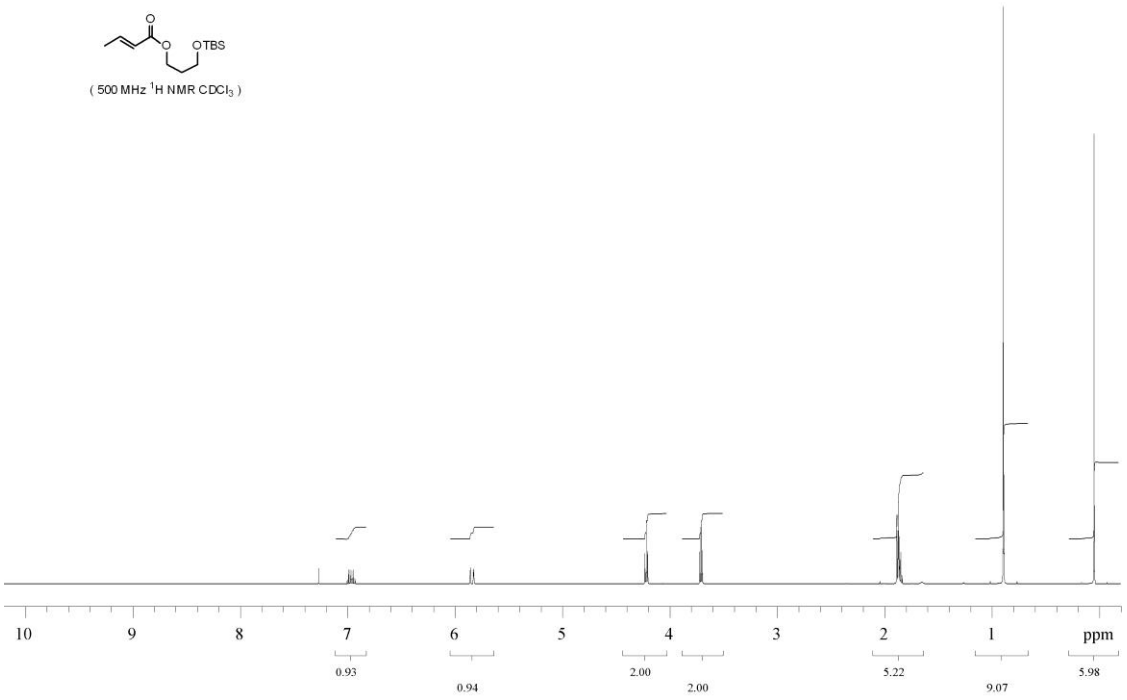

Et
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
164.923
133.233
129.634
77.484
77.230
76.976
62.306
59.487
55.269
46.972
31.847
26.057
18.453
6.681
-5.243
220
200
180
160
140
120
100
80
60
40
20
ppm

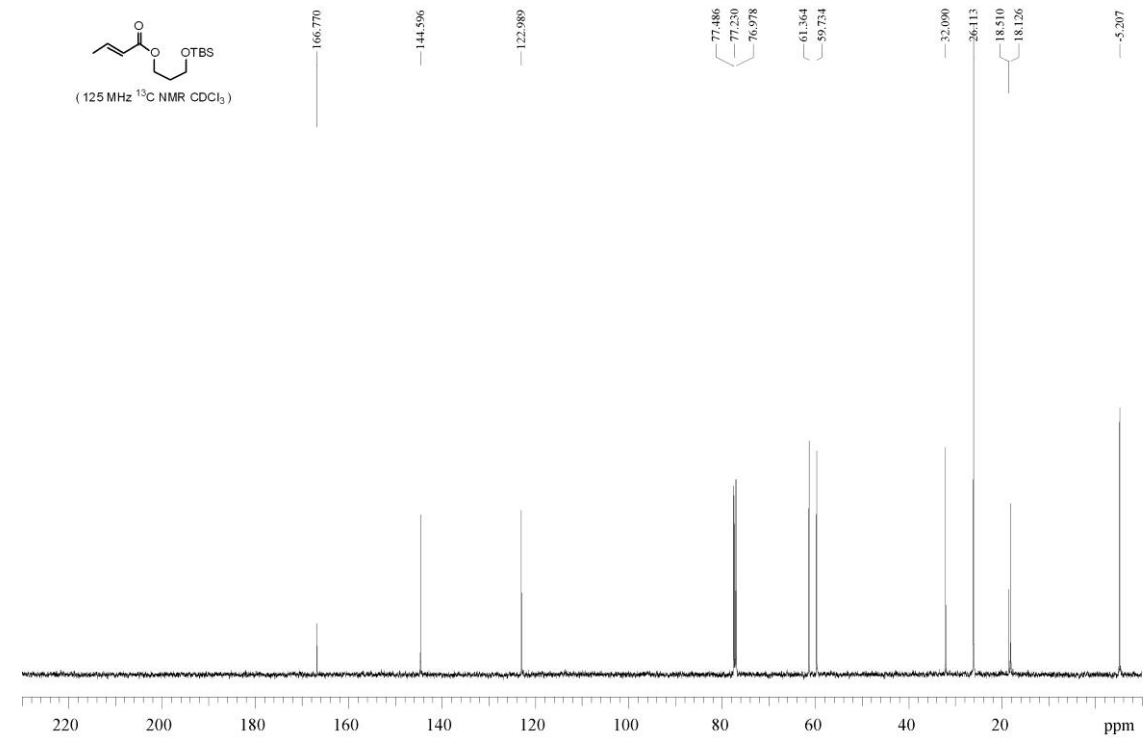

Et
S
O
O
O
O
OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

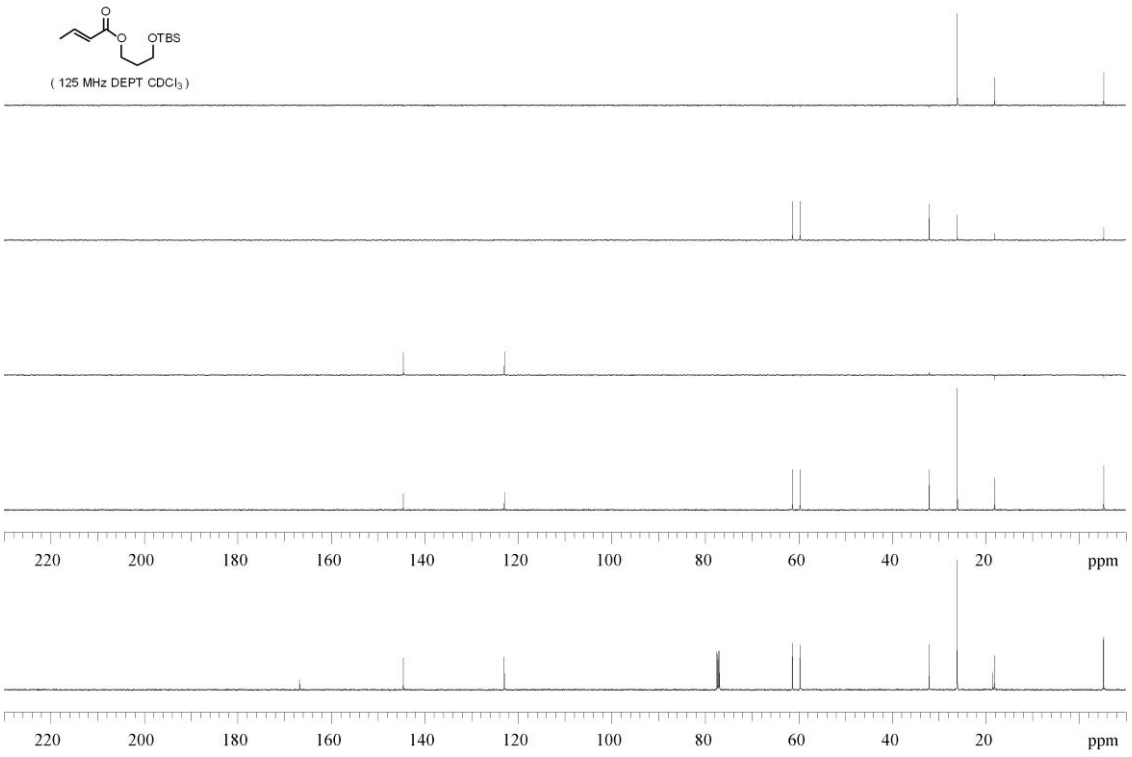

NEt2
O
O
OTBS
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
0.92
0.91
1.98
2.00
1.88
3.74
2.01
5.71
9.70
6.42

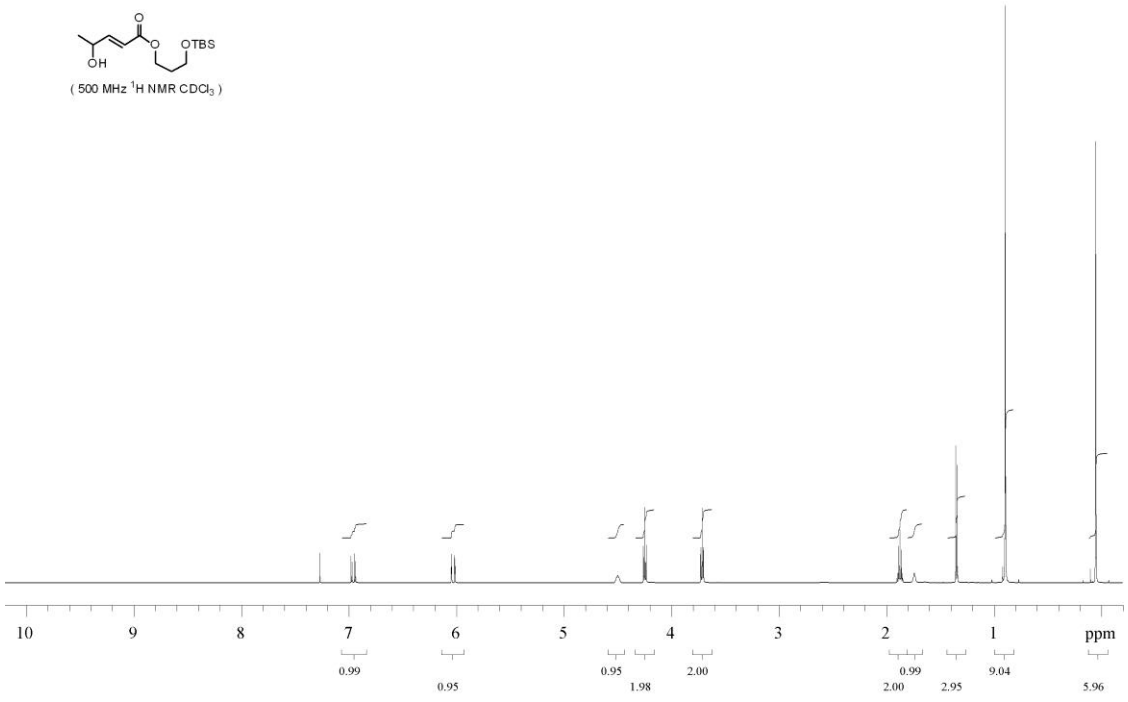

NEt2
OTBS
(125 MHz 13C NMR CDCl3)
166.529
146.581
122.992
77.484
77.230
76.980
61.537
59.660
54.285
47.374
31.997
26.114
18.509
12.073
-5.206
220
200
180
160
140
120
100
80
60
40
20
ppm

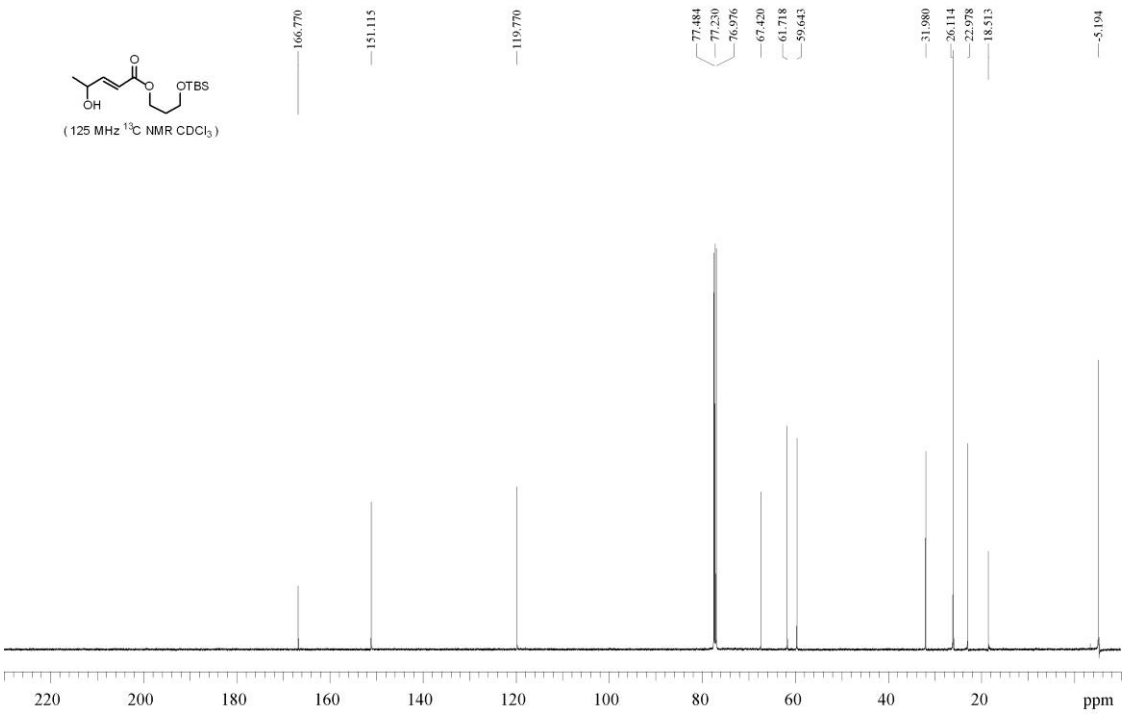

NEt2
OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

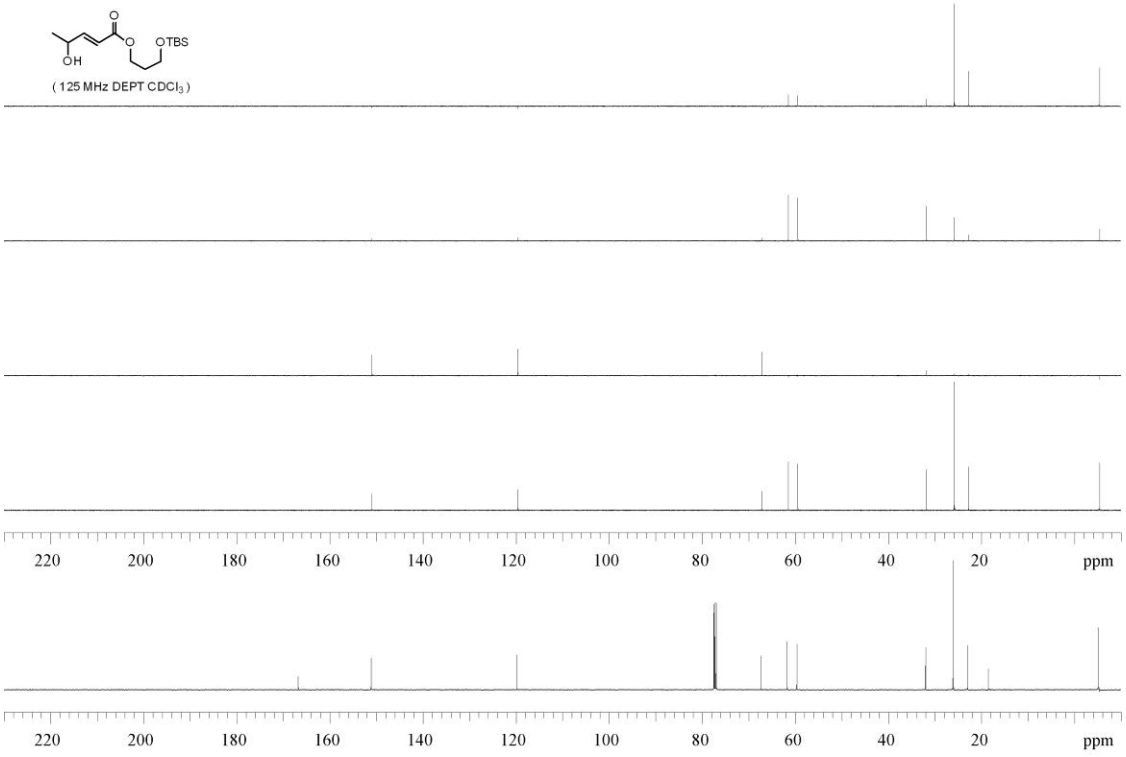

OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.93
0.94
2.00
2.00
5.22
9.07
5.98

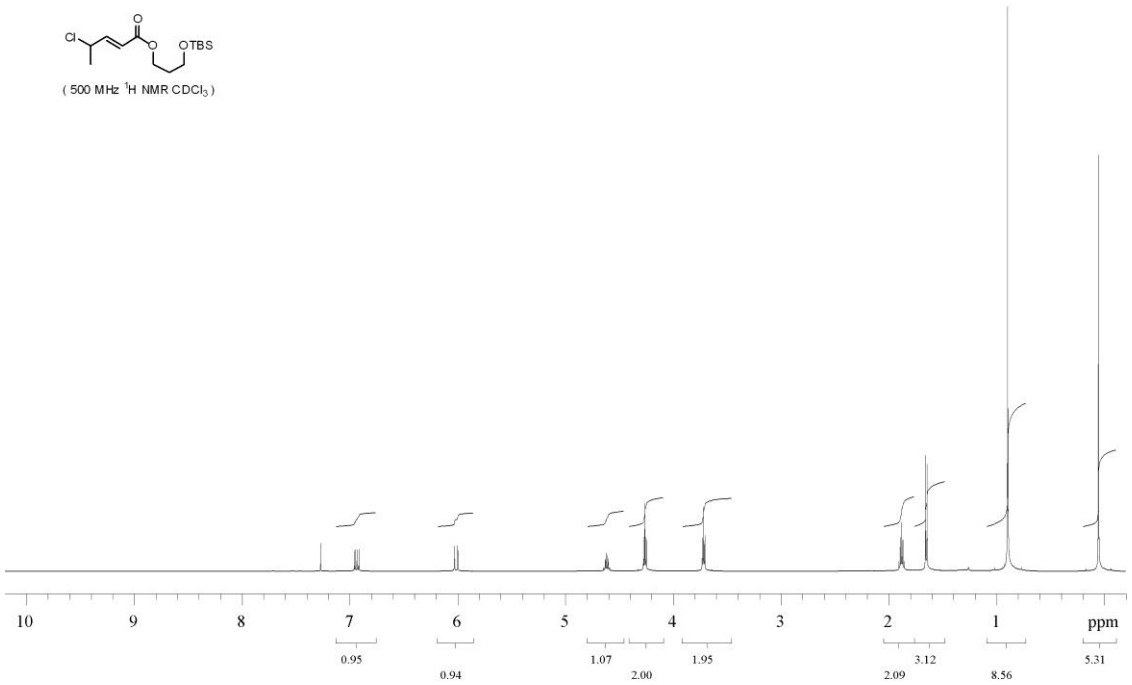

OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.770
144.596
122.989
77.486
77.230
76.978
61.364
59.734
32.090
26.113
18.510
18.126
-5.207
220
200
180
160
140
120
100
80
60
40
20
ppm

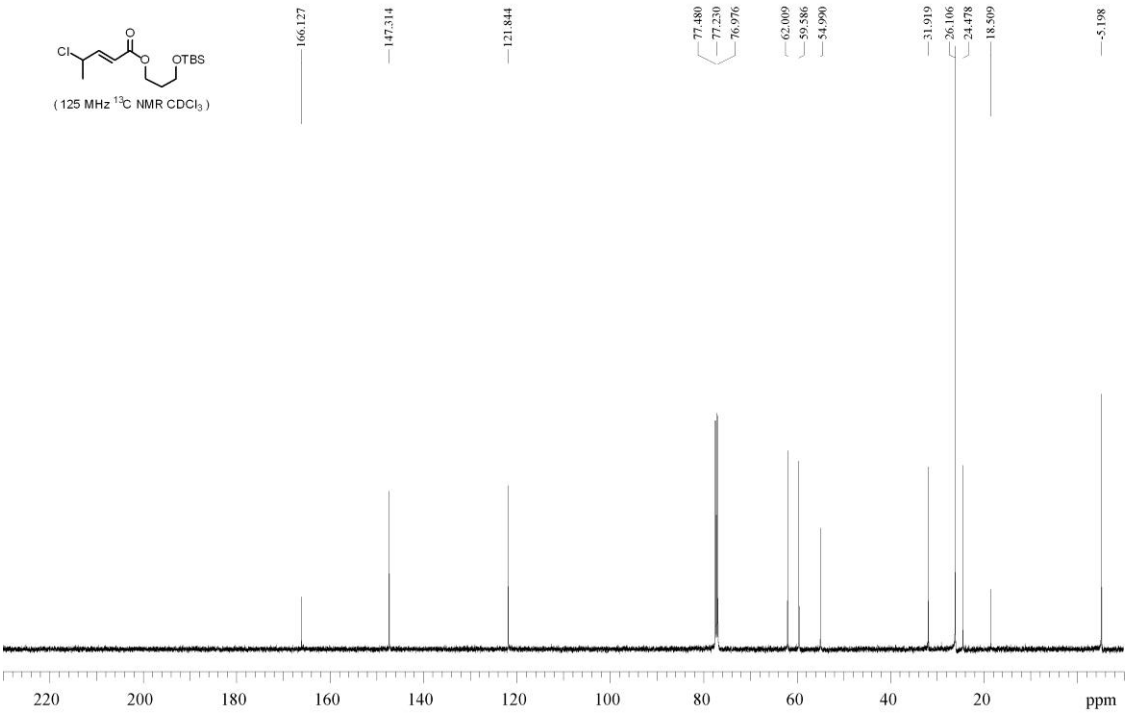

OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

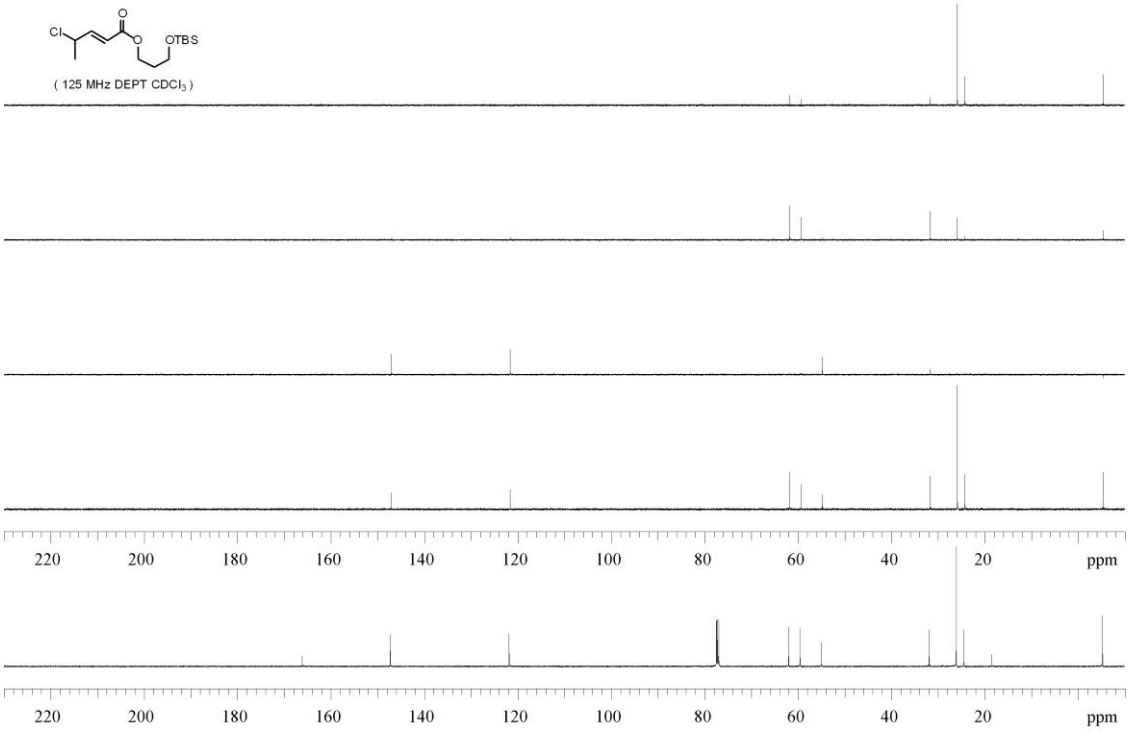

OTBS
OH
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
0.99
0.95
0.95
1.98
2.00
2.00
0.99
2.95
9.04
5.96

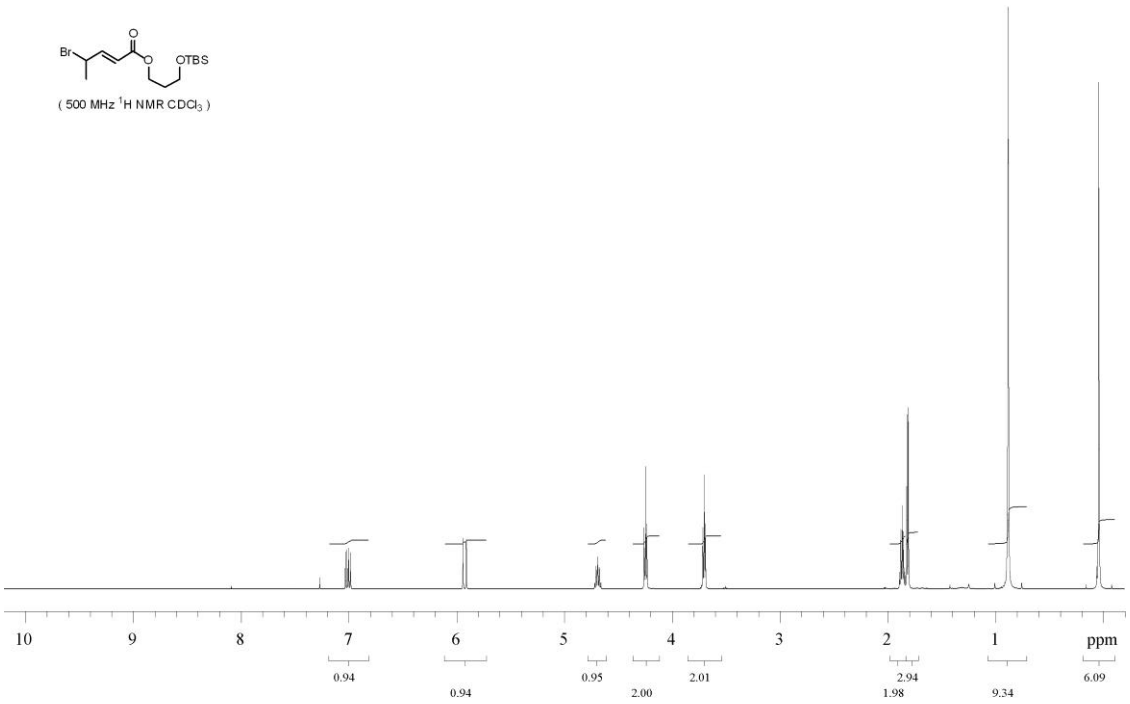

166.770
151.115
119.770
77.484
77.230
76.976
67.420
61.718
59.643
31.980
26.114
22.978
18.513
-5.194
OTBS
OH
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

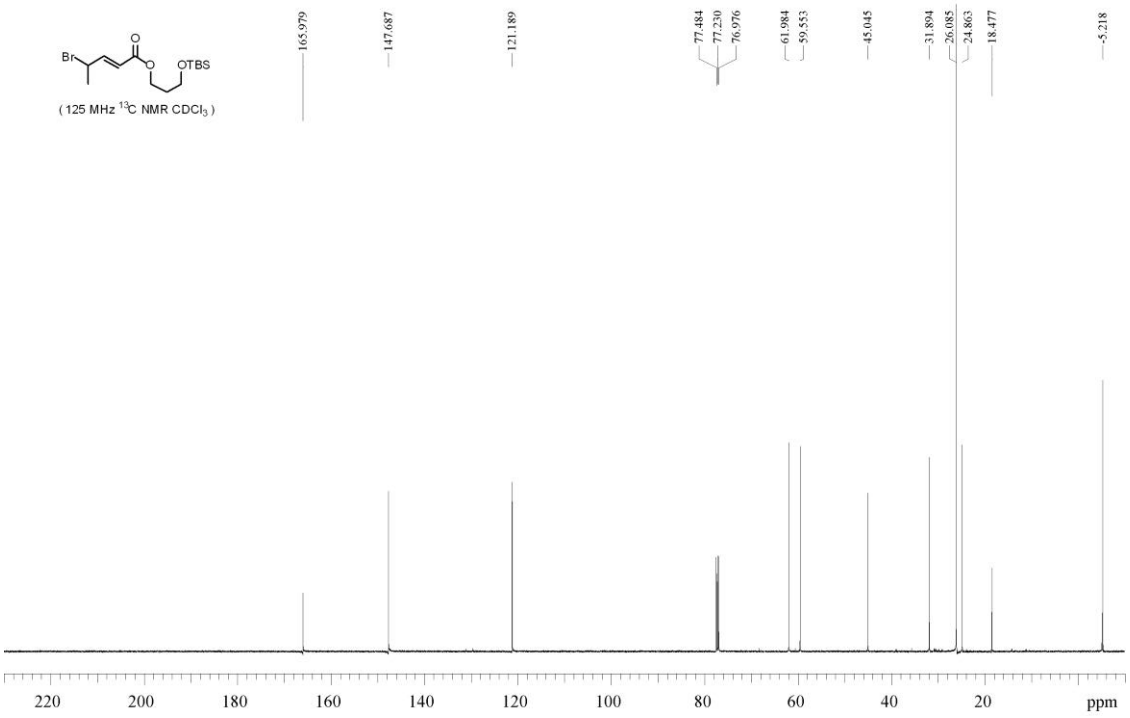

OTBS
OH
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

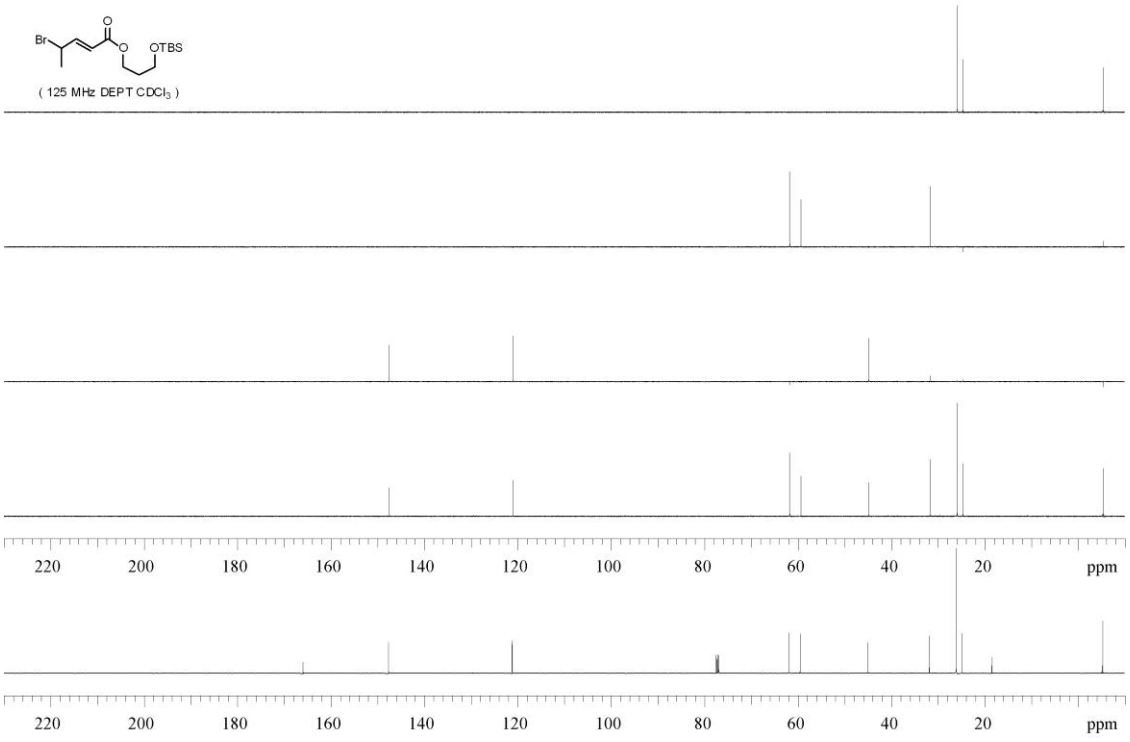

Cl
O
O
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.95
0.94
1.07
2.00
1.95
2.09
3.12
8.56
5.31

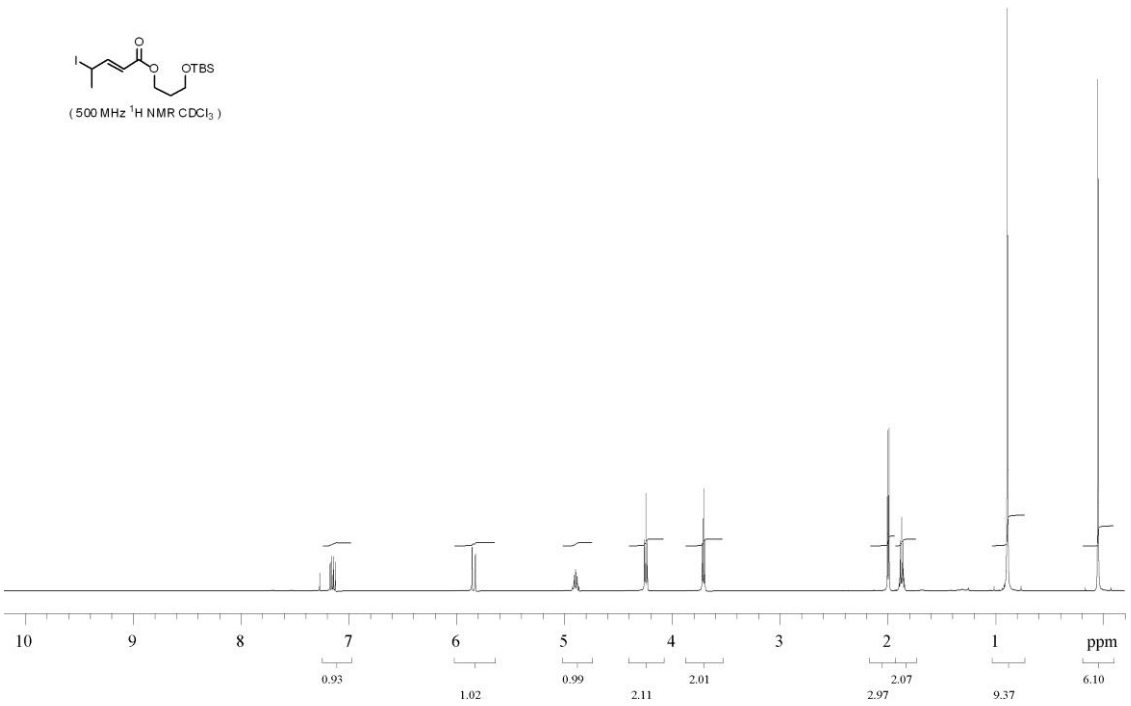

Cl
O
O
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.127
147.314
121.844
77.480
77.230
76.976
62.009
59.586
54.990
31.919
26.106
24.478
18.509
-5.198
220
200
180
160
140
120
100
80
60
40
20
ppm

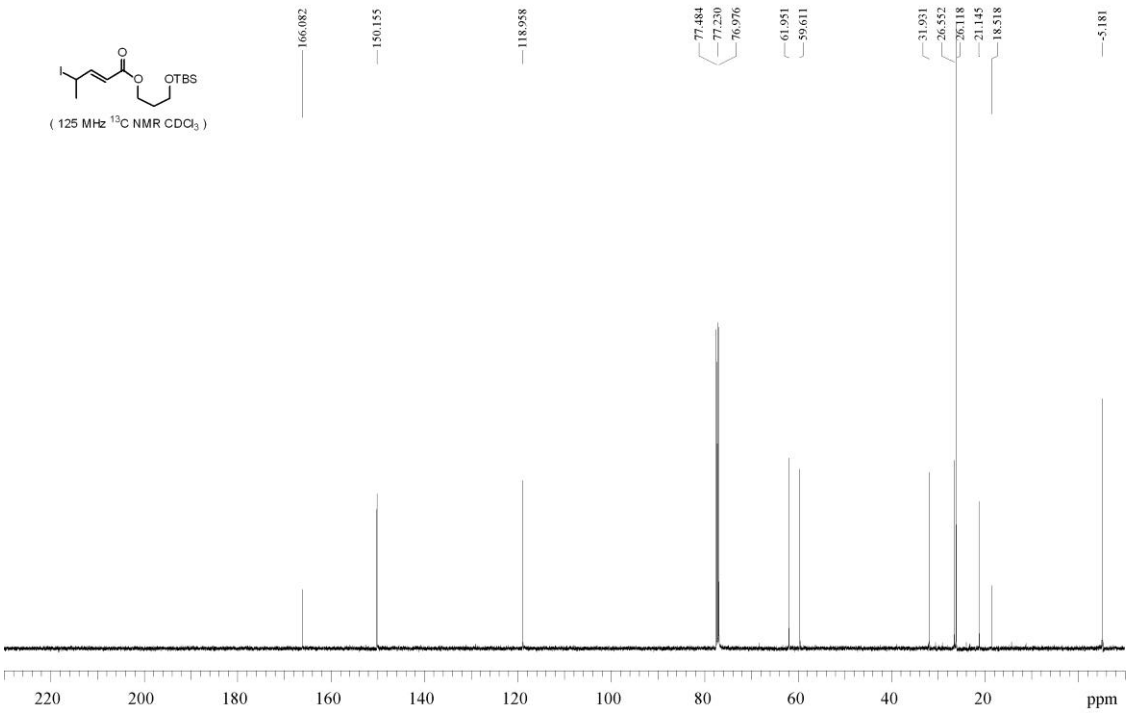

Cl
O
OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

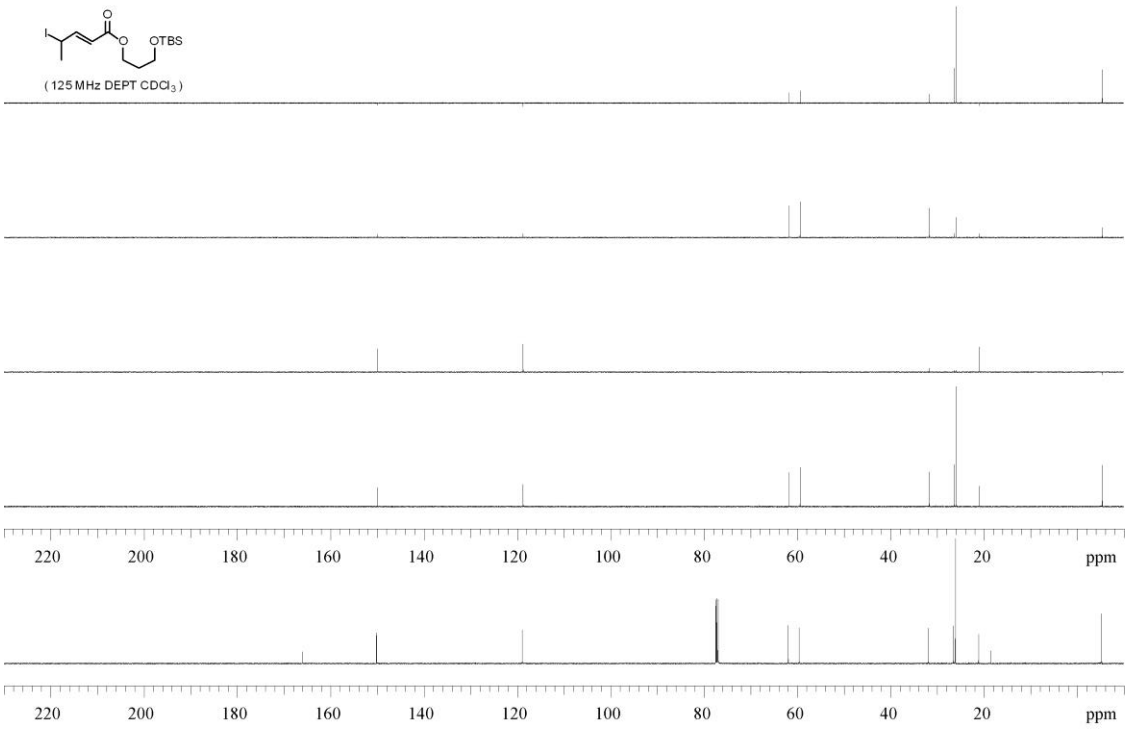

Br
O
OTBS
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
0.94
0.94
0.95
2.00
2.01
2.94
1.98
9.34
6.09

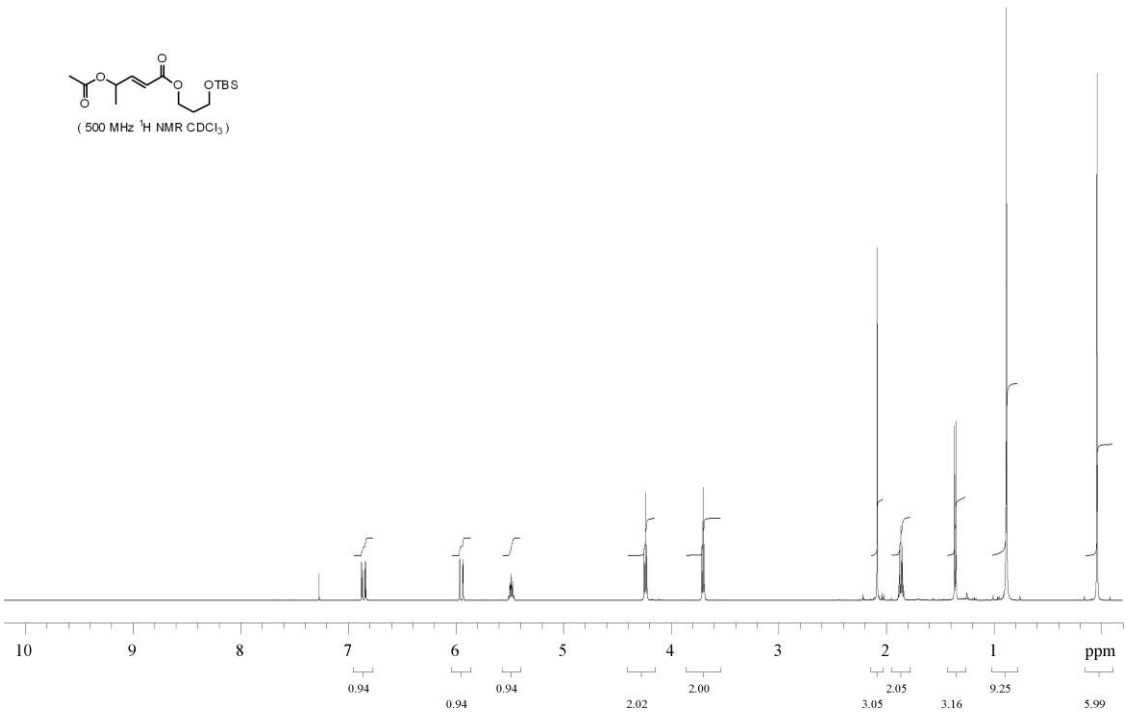

Br
O
O
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
165.979
147.687
121.189
77.484
77.230
76.976
61.984
59.553
45.045
31.894
26.085
24.863
18.477
-5.218
220
200
180
160
140
120
100
80
60
40
20
ppm

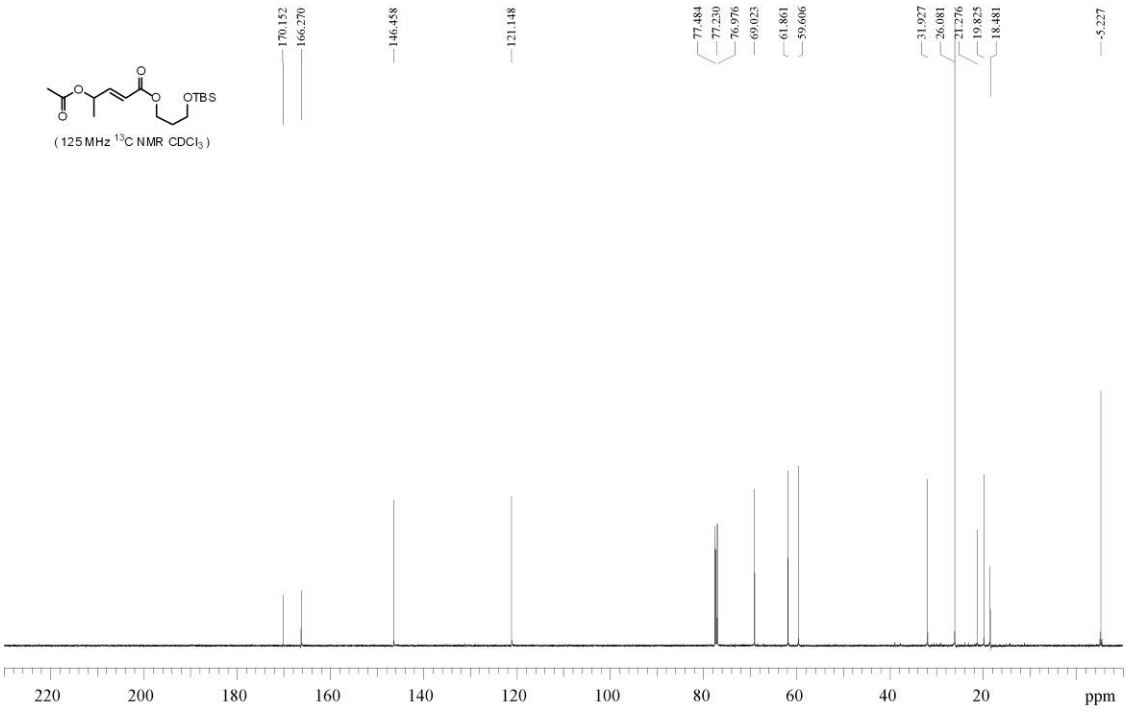

Br
O
O
OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

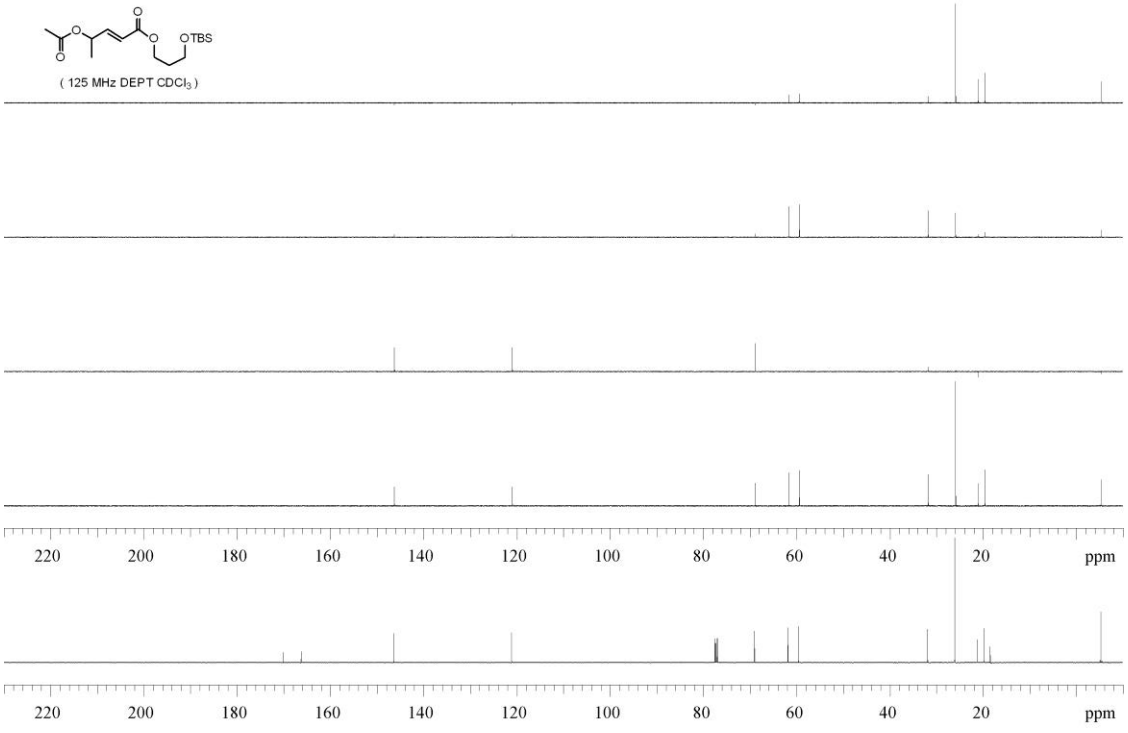

OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.93
1.02
0.99
2.11
2.01
2.97
2.07
9.37
6.10

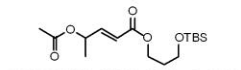

OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.082
150.155
118.958
77.484
77.230
76.976
61.951
59.611
31.931
26.552
26.118
21.145
18.518
-5.181
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

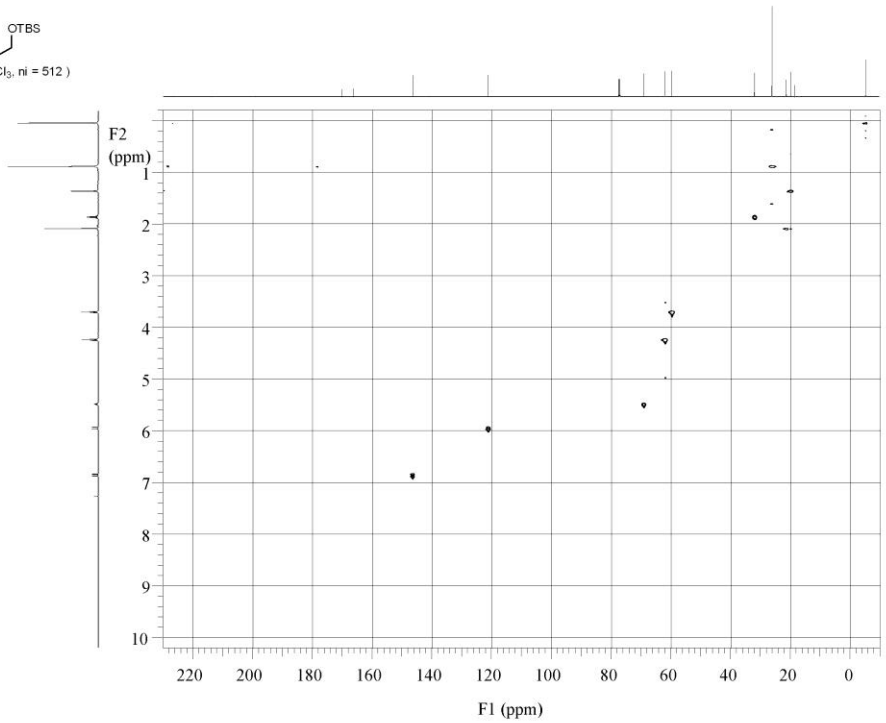

OTBS
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
0.94
0.94
0.94
2.02
2.00
3.05
2.05
3.16
9.25
5.99

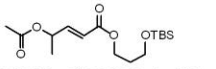

170.152
166.270
146.458
121.148
77.484
77.230
76.976
69.023
61.861
59.606
31.927
26.081
21.276
19.825
18.481
-5.227
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

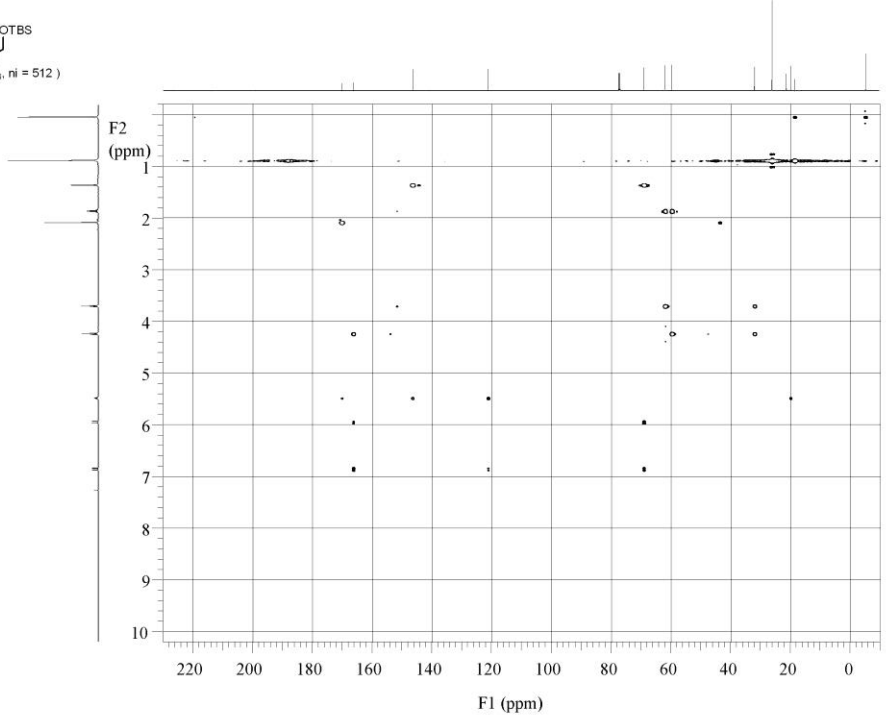


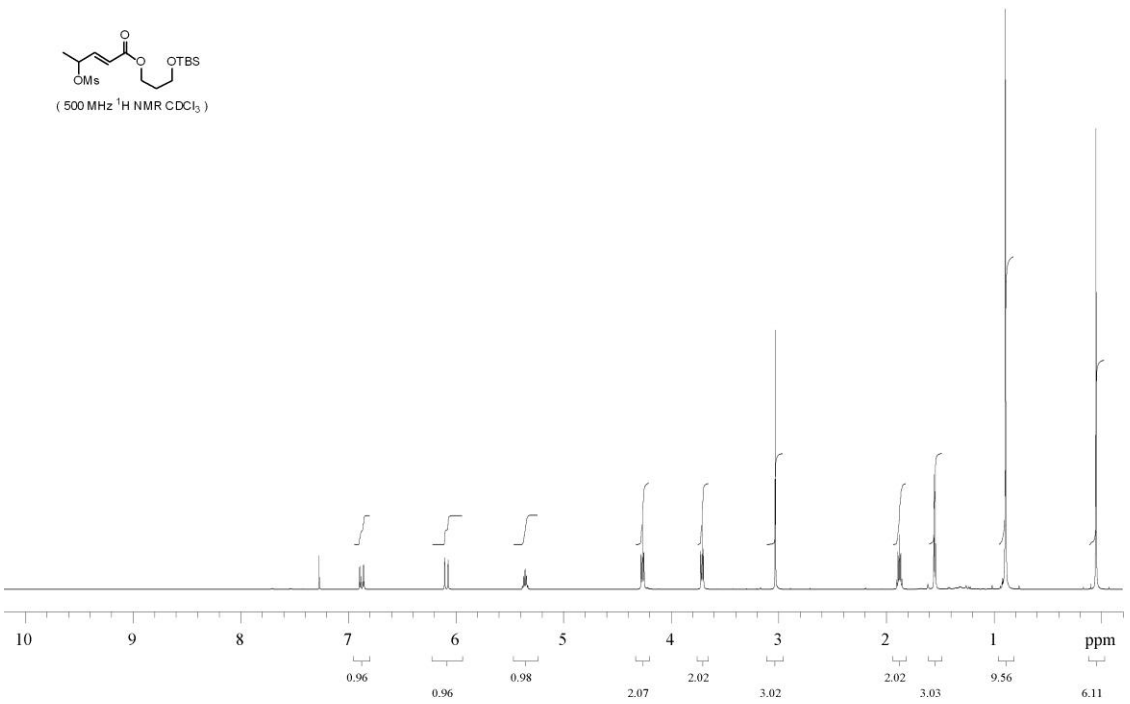
(500/125 MHz gHMQC $CDCl_3$, ni = 512)

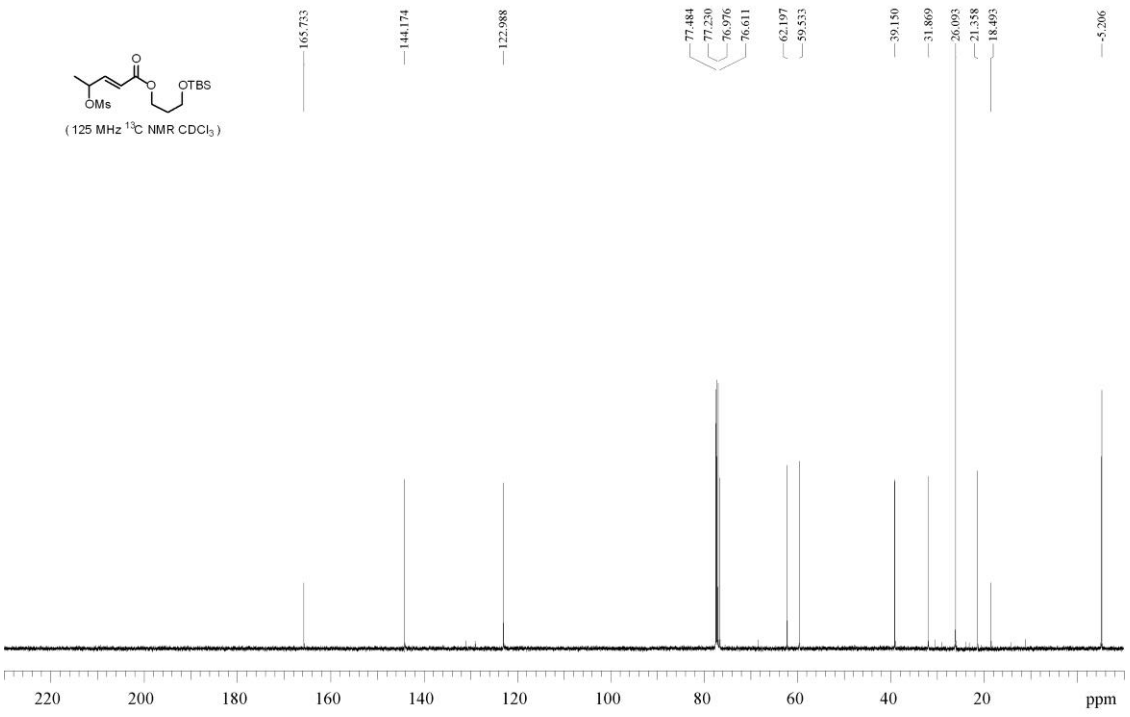


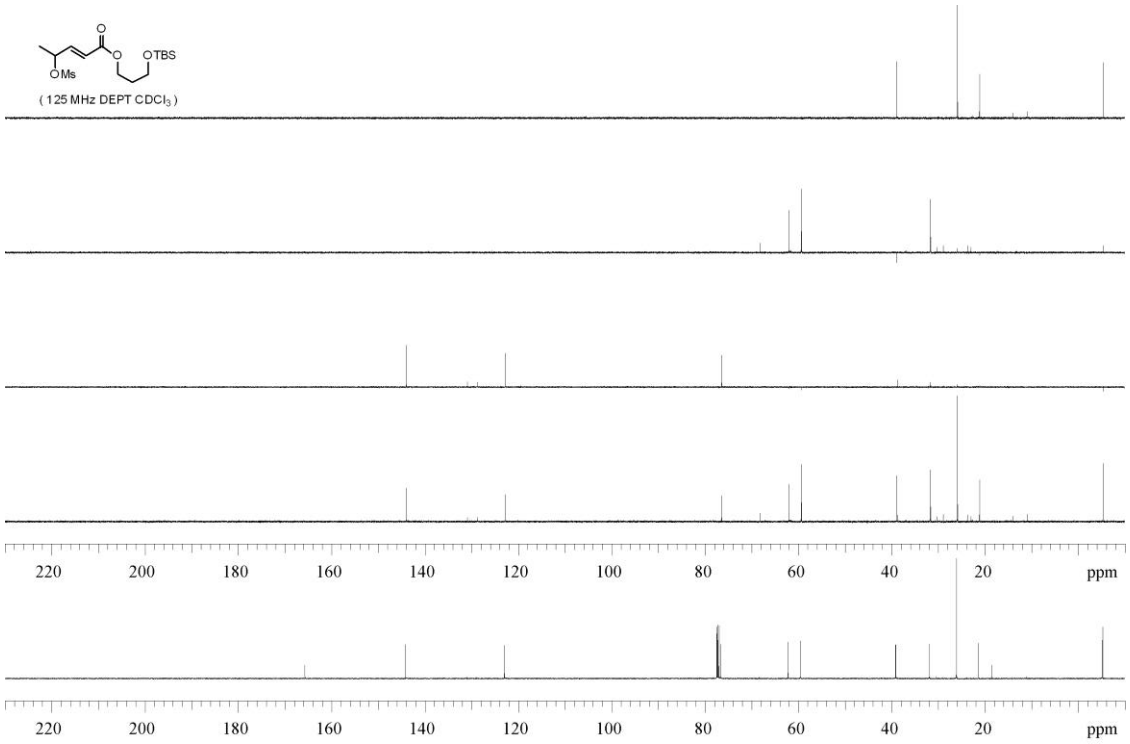


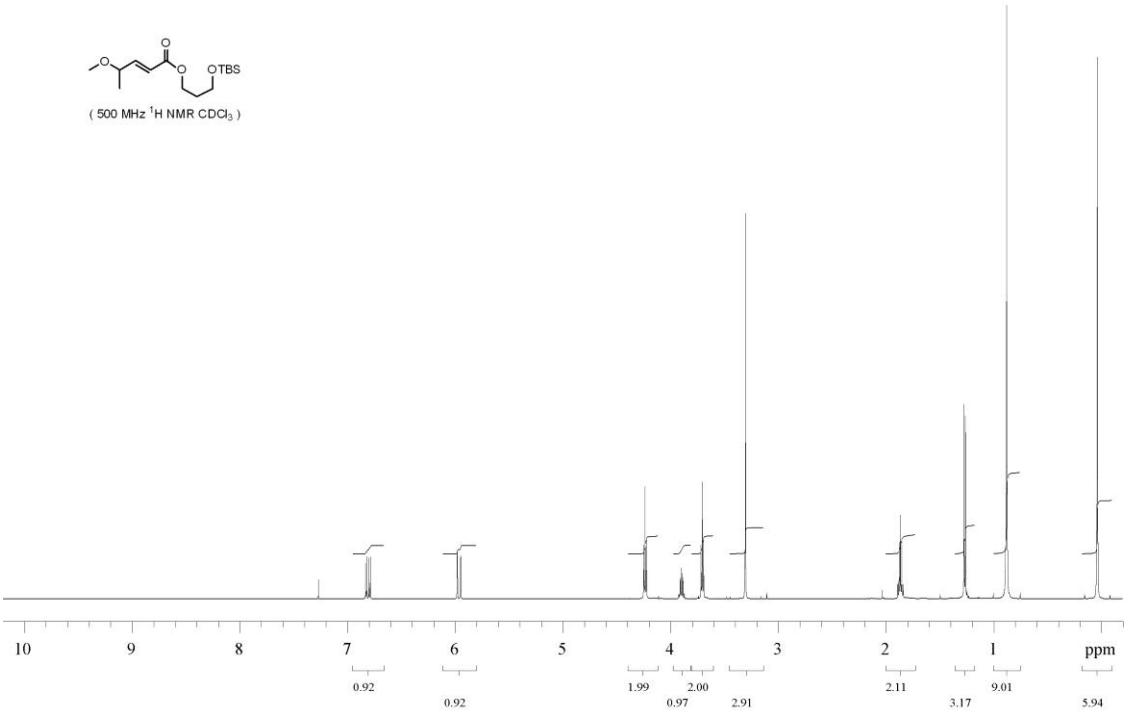
(500/125 MHz gHMBC $CDCl_3$, ni = 512)

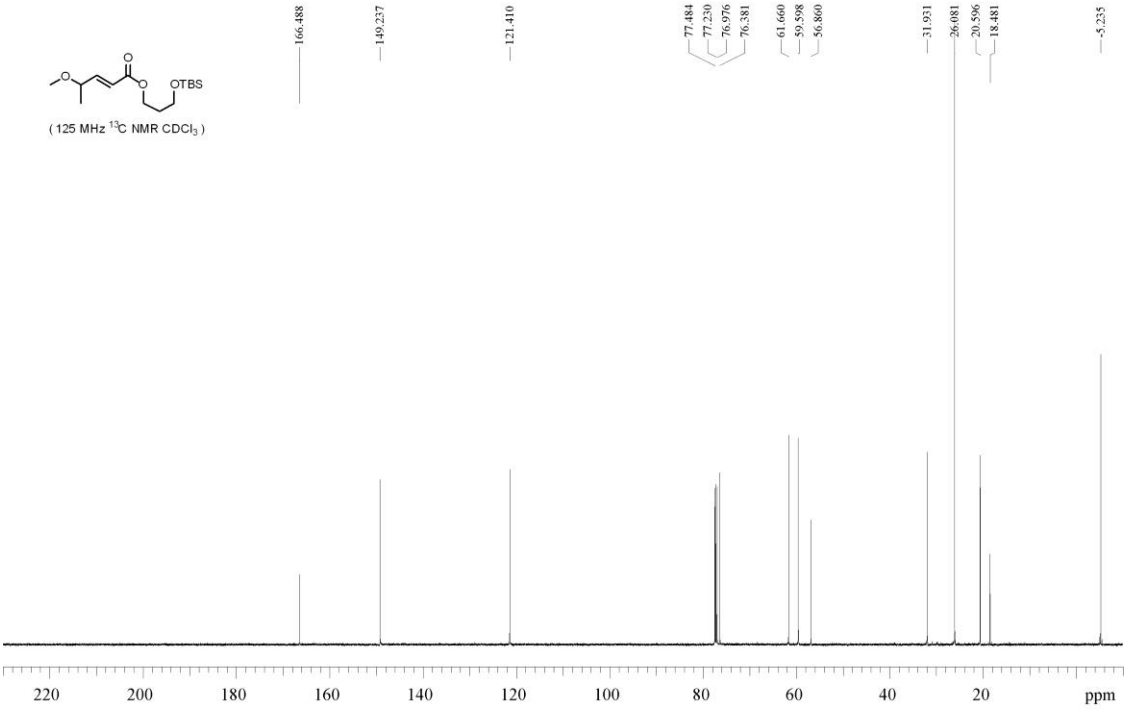


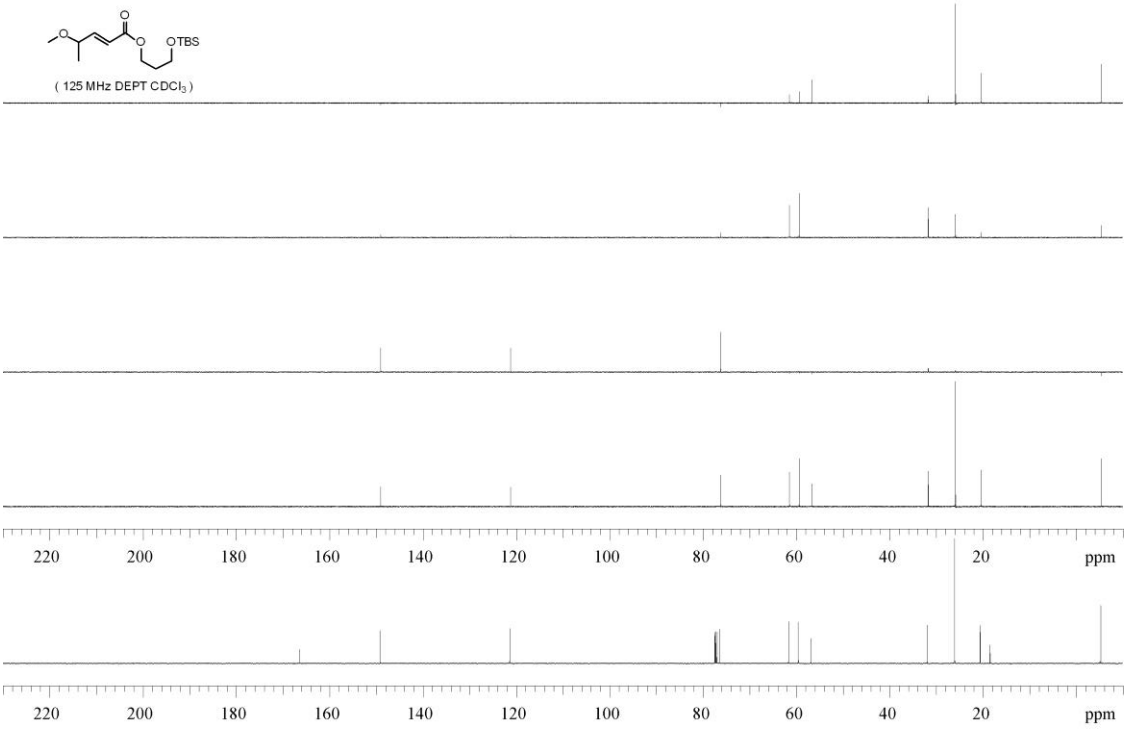

OMs
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.96
0.96
0.98
2.07
2.02
3.02
2.02
3.03
9.56
6.11

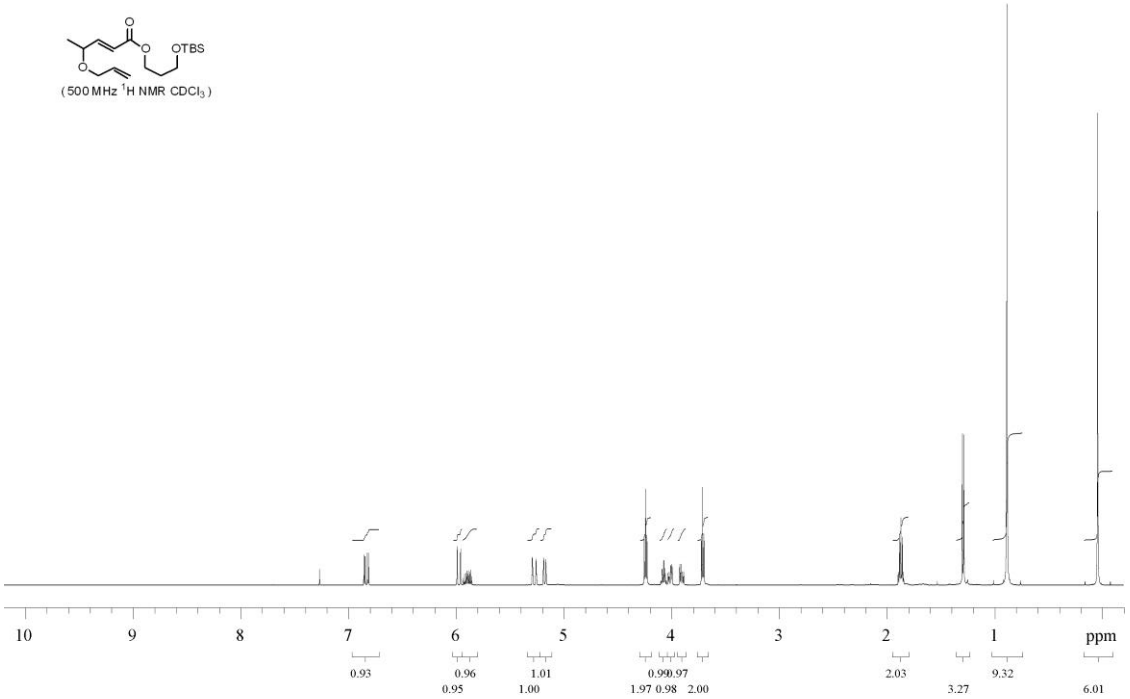

OMs
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
165.733
144.174
122.988
77.484
77.230
76.976
76.611
62.197
59.533
39.150
31.869
26.093
21.358
18.493
-5.206
220
200
180
160
140
120
100
80
60
40
20
ppm

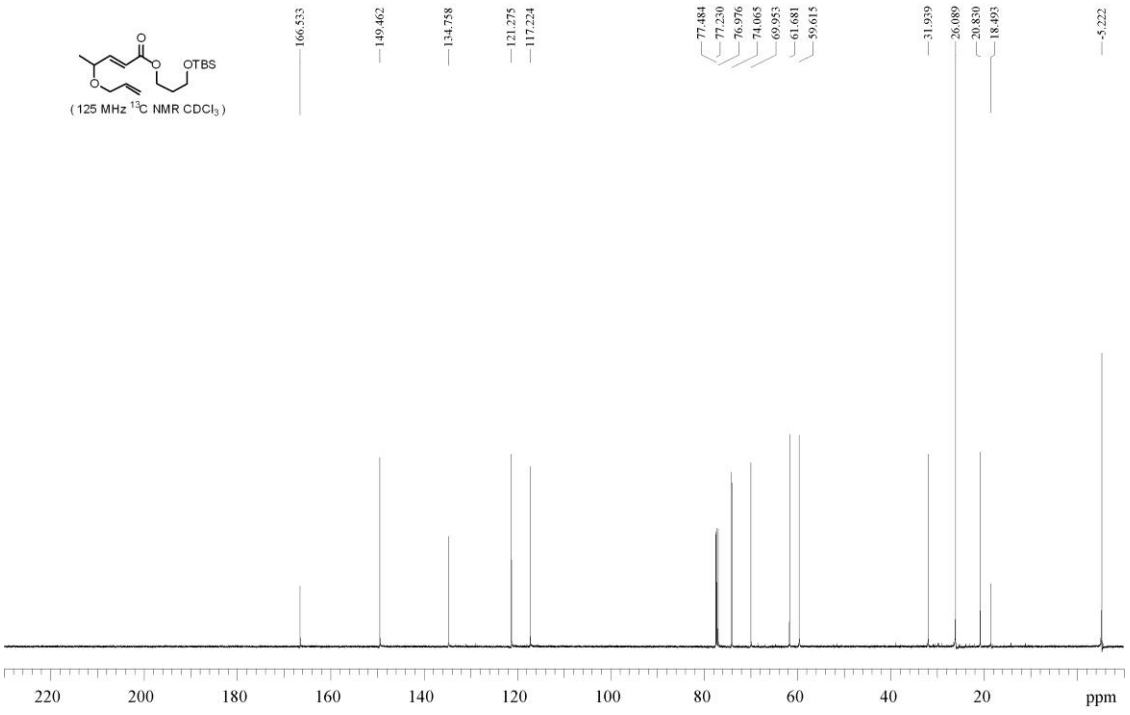

OTBS
OMs
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

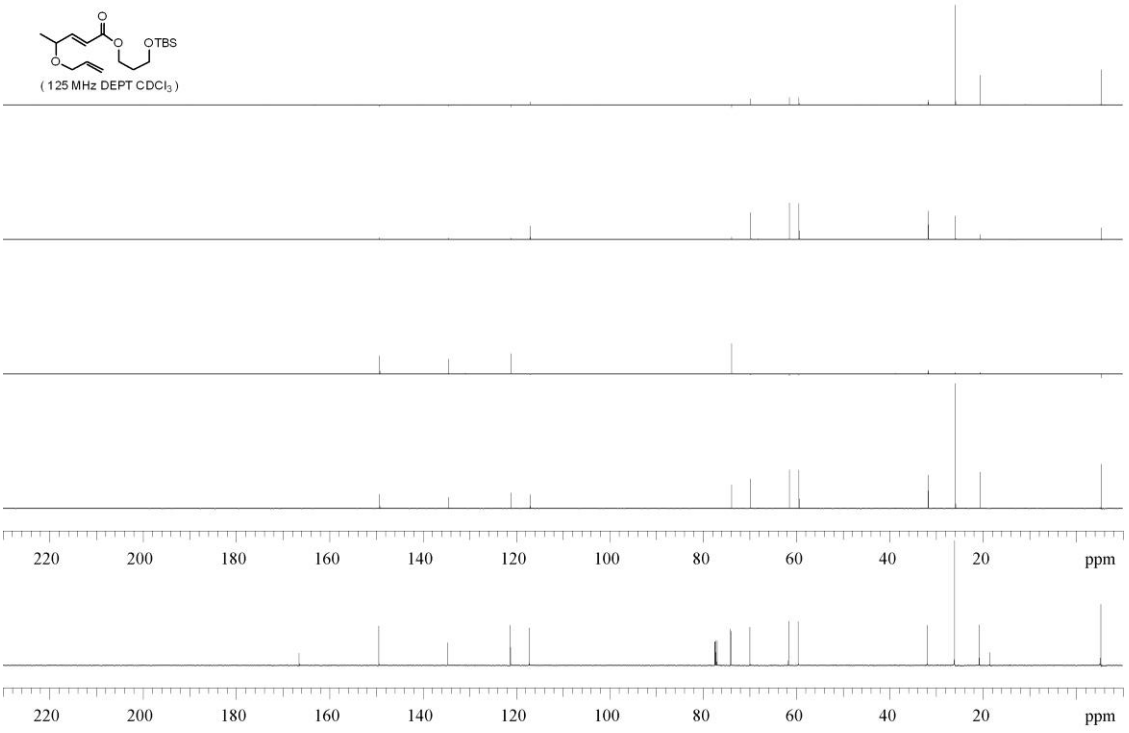

OTBS
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
0.92
0.92
1.99
0.97
2.00
2.91
2.11
3.17
9.01
5.94

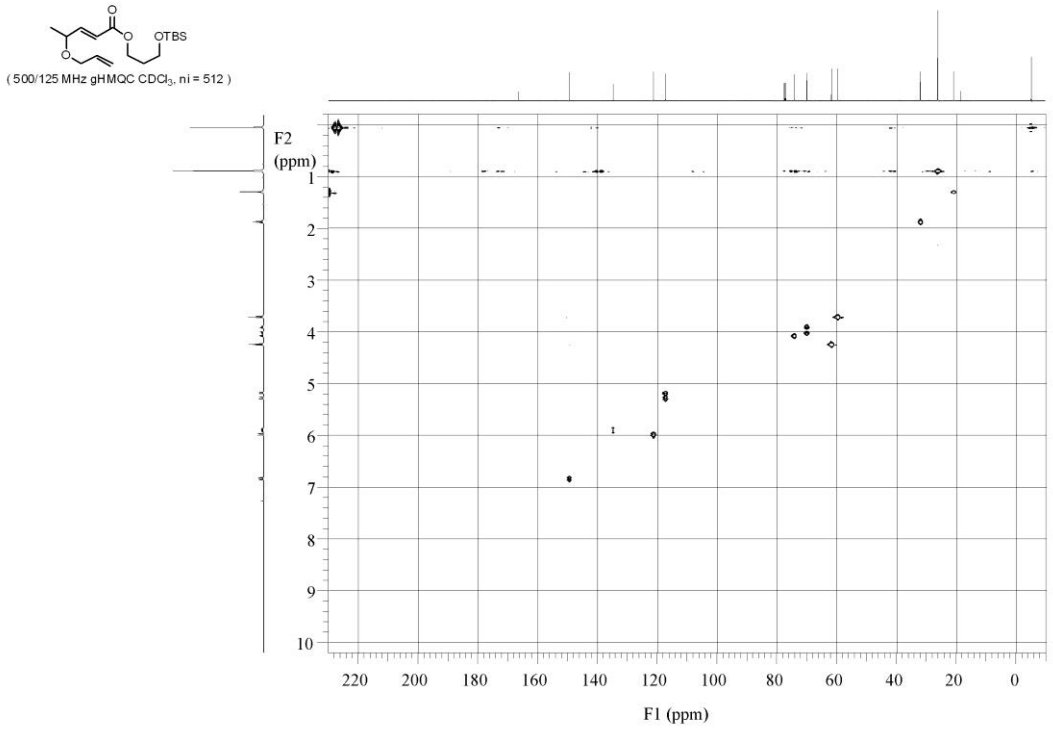

OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.488
149.237
121.410
77.484
77.230
76.976
76.381
61.660
59.598
56.860
31.931
26.081
20.596
18.481
-5.235
220
200
180
160
140
120
100
80
60
40
20
ppm

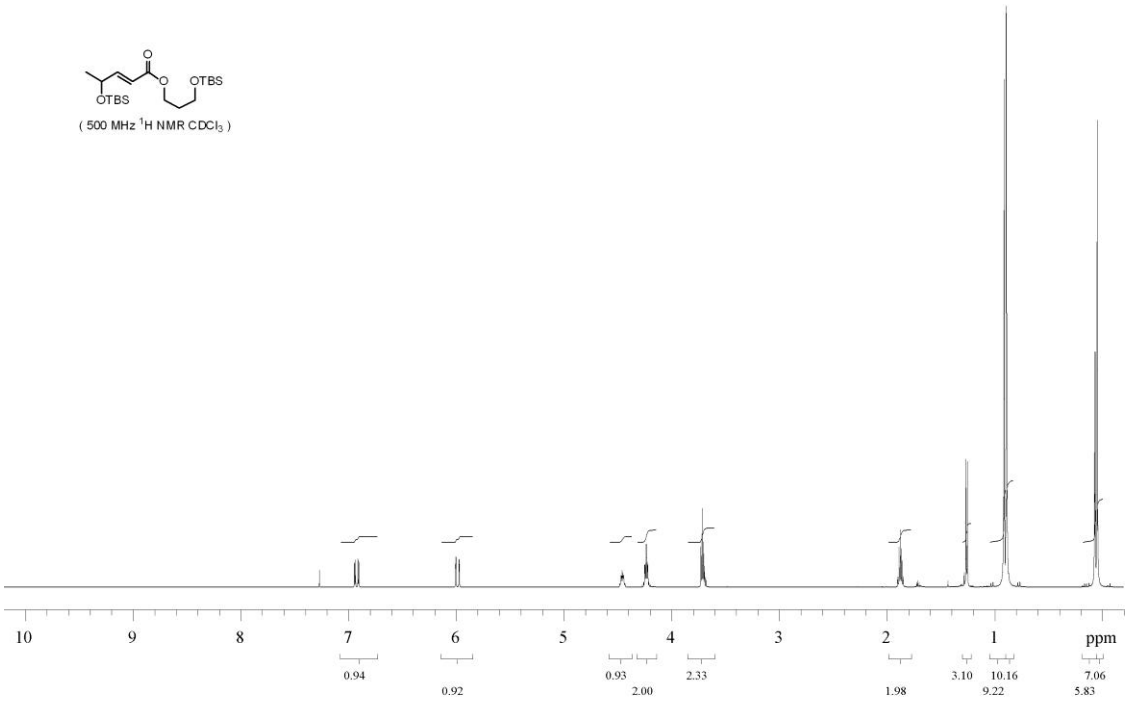

OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

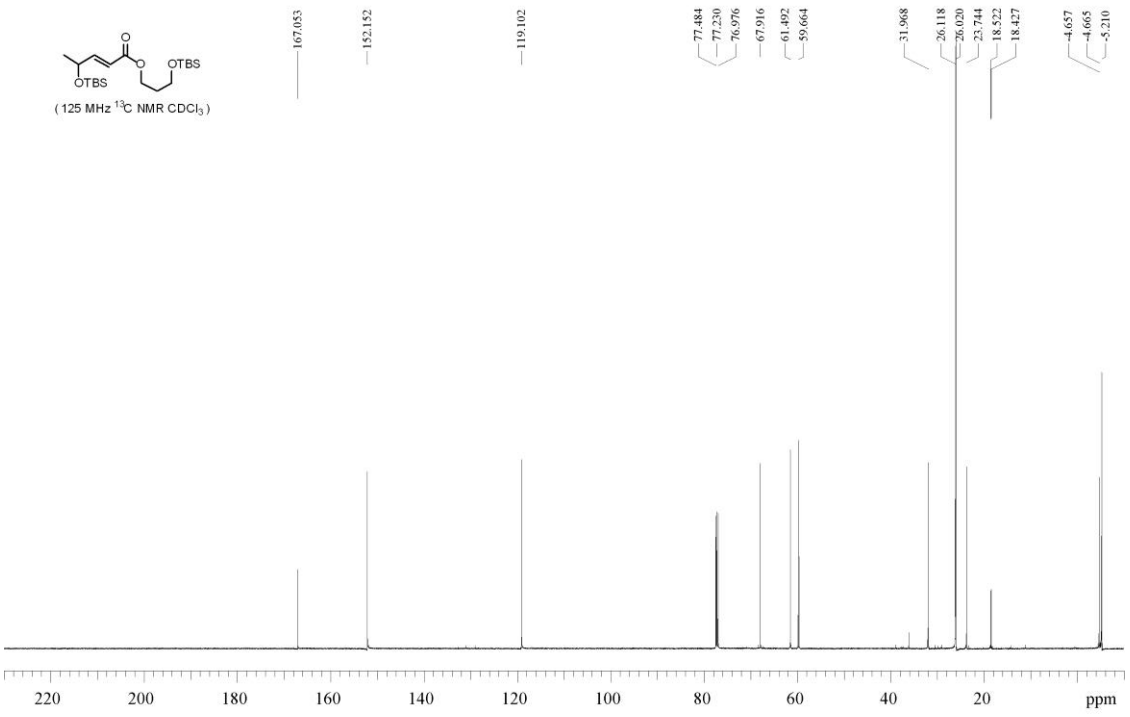

OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.93
0.96
0.95
1.01
1.00
0.99
0.97
1.97
0.98
2.00
2.03
3.27
9.32
6.01

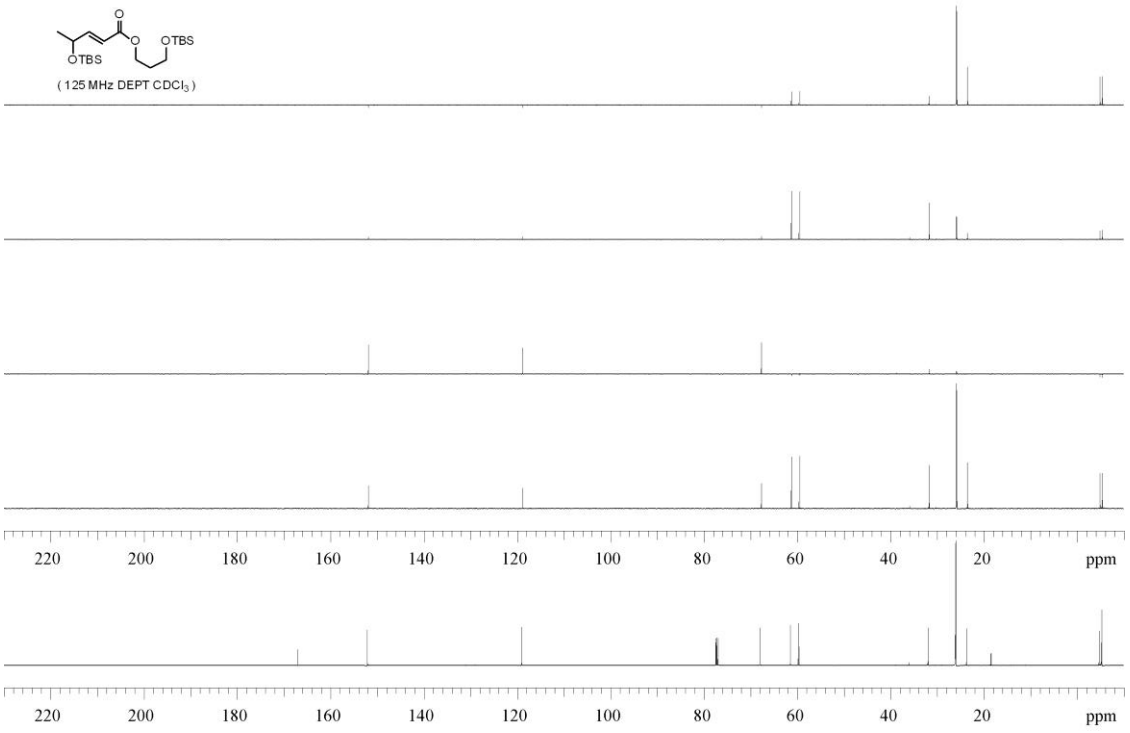

OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.533
149.462
134.758
121.275
117.224
77.484
77.230
76.976
74.065
69.953
61.681
59.615
31.939
26.089
20.830
18.493
-5.222
220
200
180
160
140
120
100
80
60
40
20
ppm

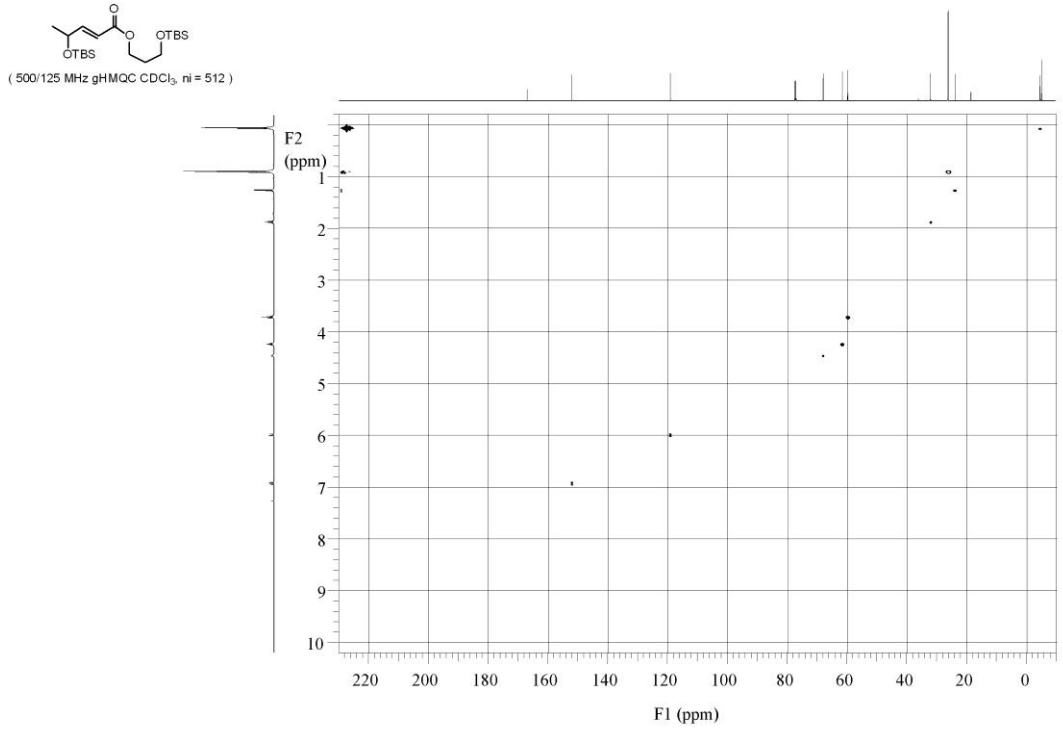

OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

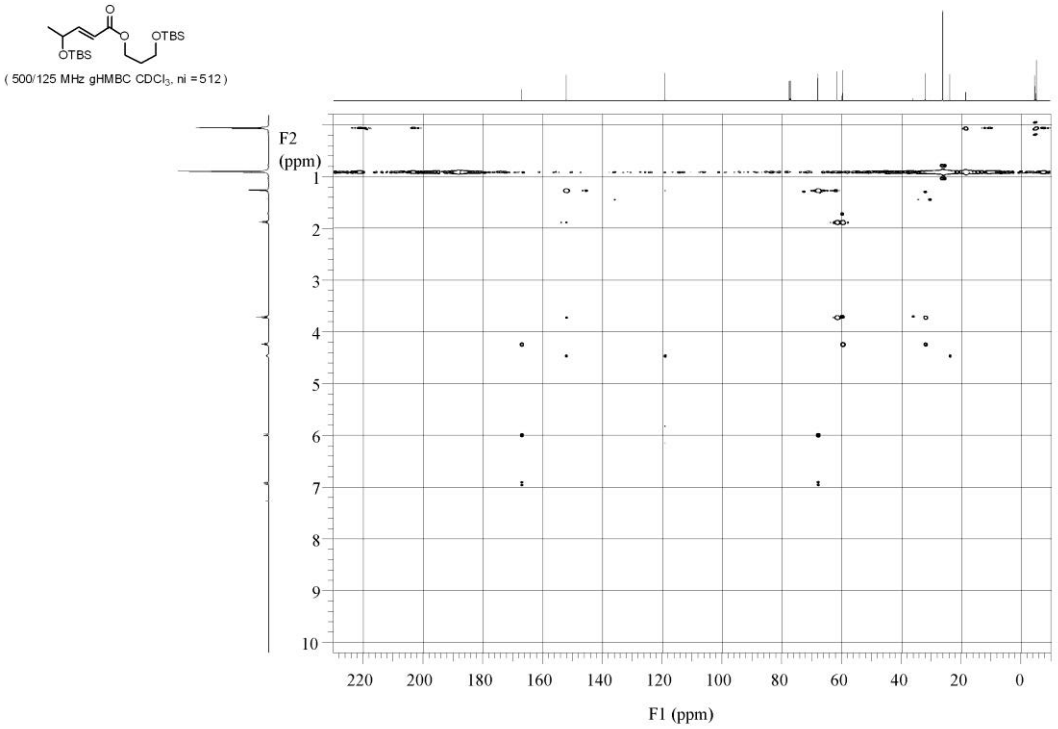

OTBS
(500/125 MHz gHMQC CDCl3, ni = 512)
F2
(ppm)
F1 (ppm)

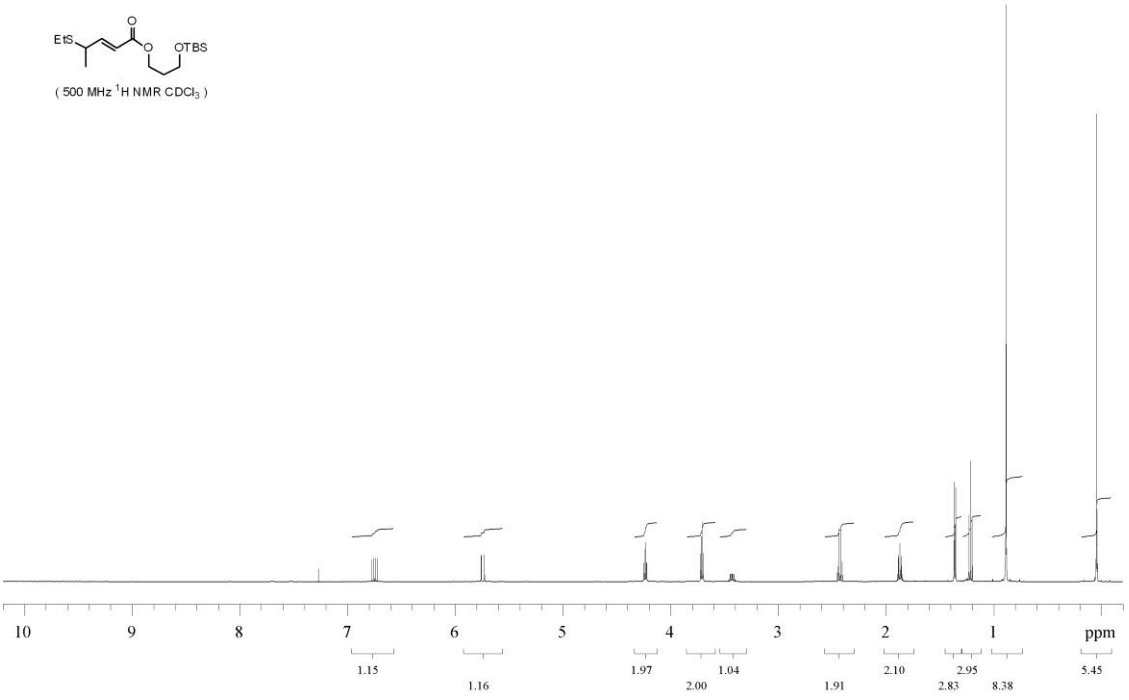

OTBS
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.94
0.92
0.93
2.00
2.33
1.98
3.10
10.16
9.22
7.06
5.83

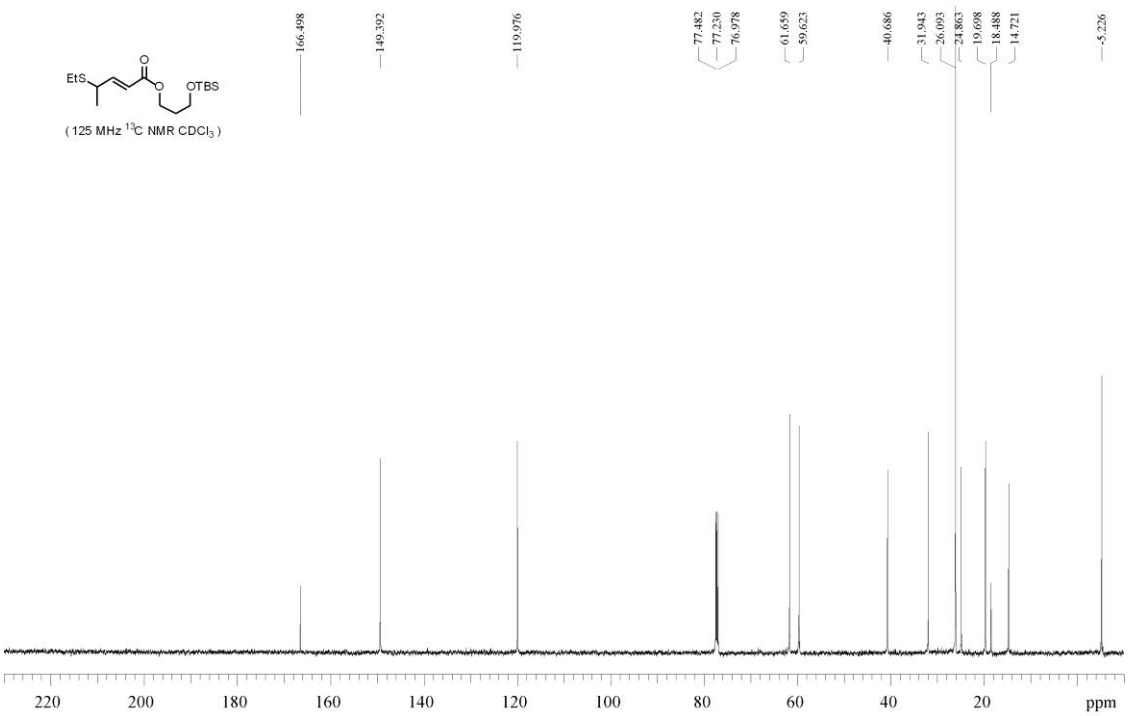

OTBS
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
167.053
152.152
119.102
77.484
77.230
76.976
67.916
61.492
59.664
31.968
26.118
26.020
23.744
18.522
18.427
-4.657
-4.665
-5.210
220
200
180
160
140
120
100
80
60
40
20
ppm

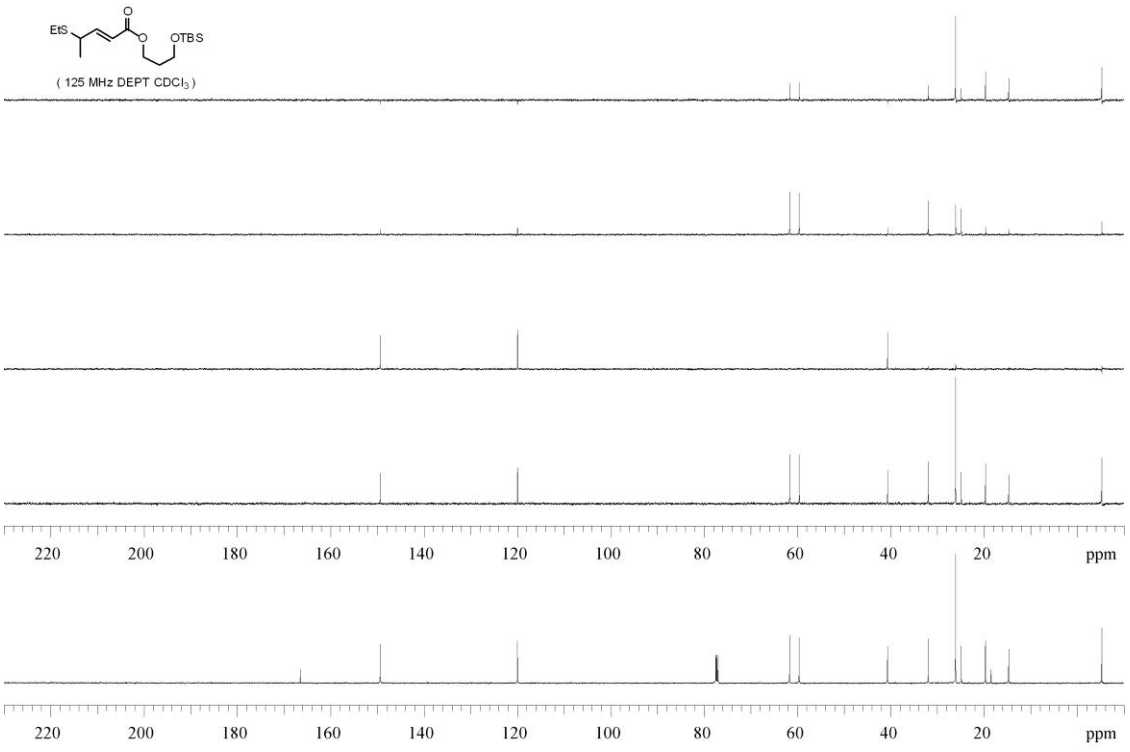

OTBS
OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

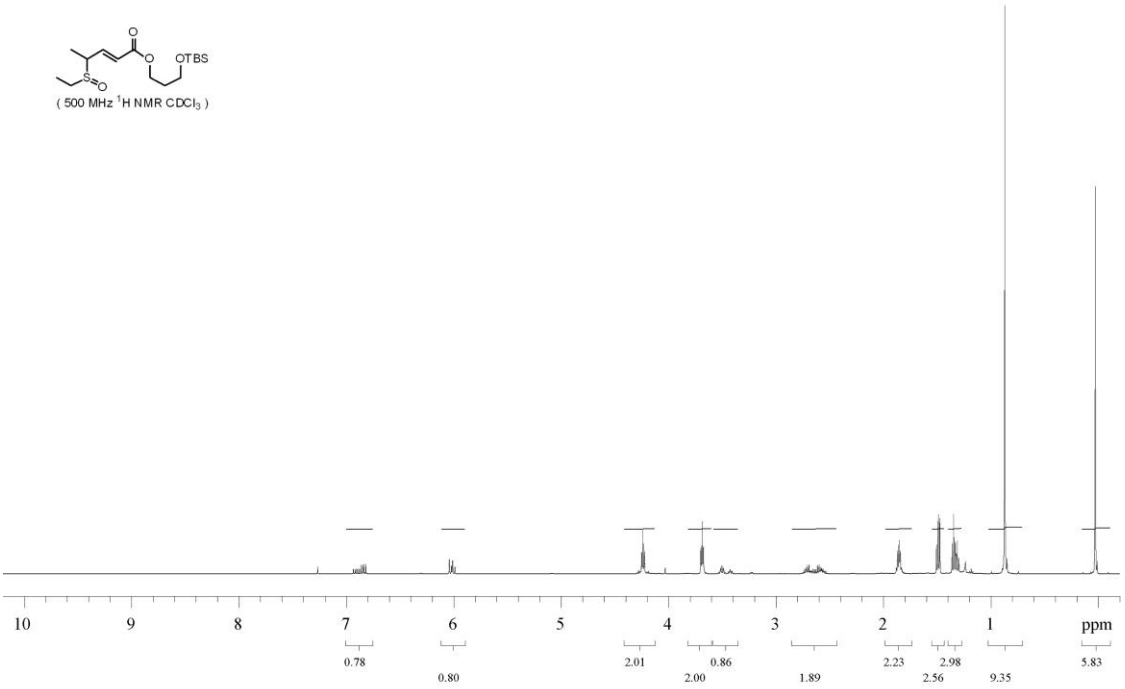

OTBS
OTBS
(500/125 MHz gHMQC CDCl3, ni = 512)
F2
(ppm)
F1 (ppm)

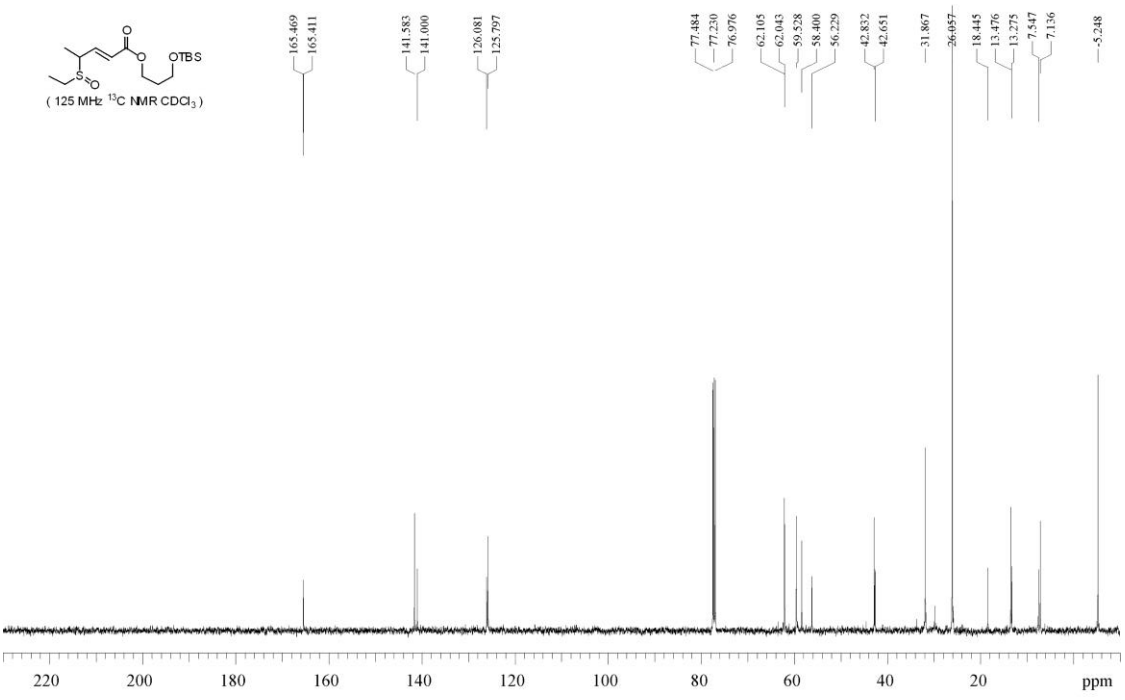

OTBS
OTBS
(500/125 MHz gHMBC CDCl3, ni = 512)
F2
(ppm)
F1 (ppm)

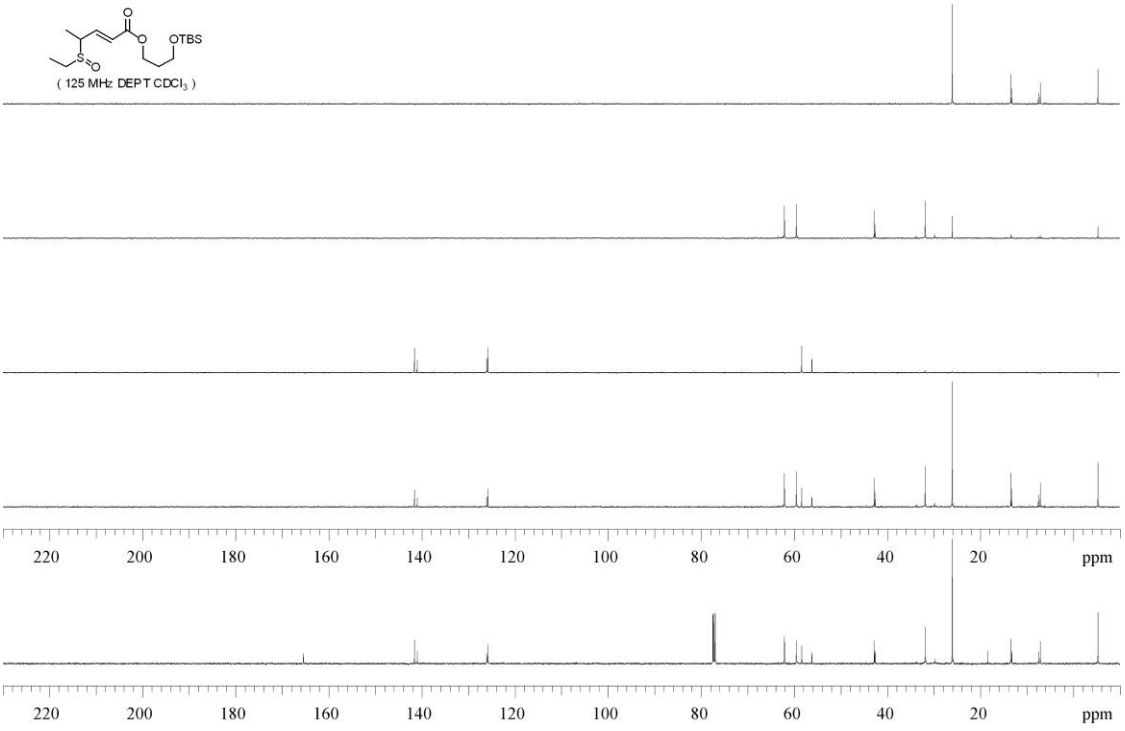

EtS
OTBS
(500 MHz 1H NMR CDCl3)
ppm
1.15
1.16
1.97
2.00
1.04
1.91
2.10
2.95
2.83
8.38
5.45

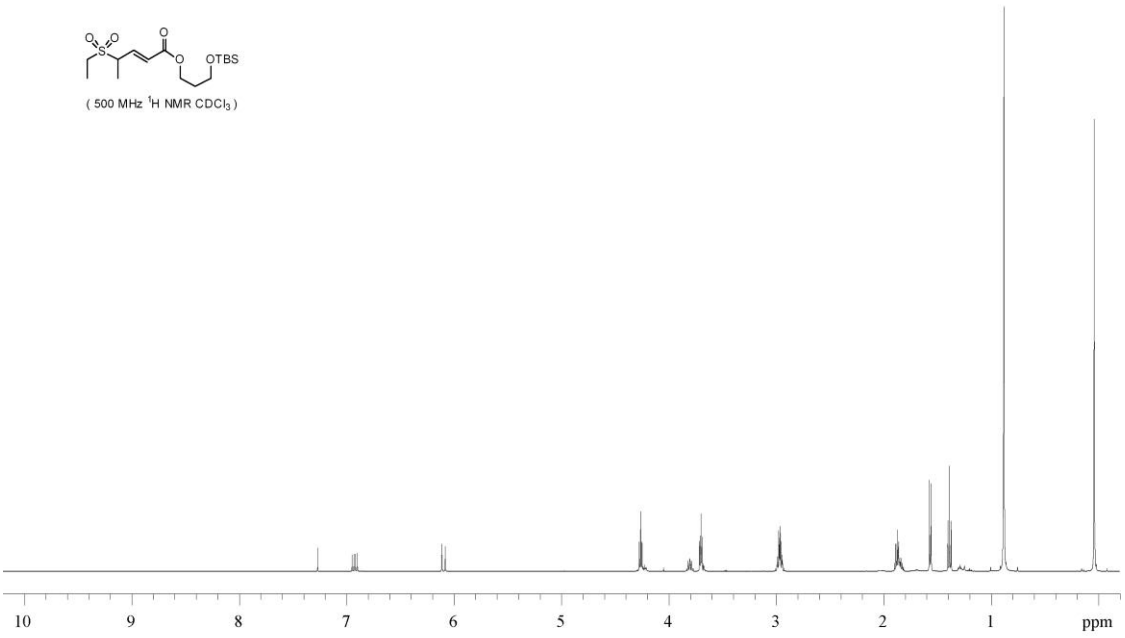

EtS
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.498
149.392
119.976
77.482
77.230
76.978
61.659
59.623
40.686
31.943
26.093
24.863
19.698
18.488
14.721
-5.226
220
200
180
160
140
120
100
80
60
40
20
ppm

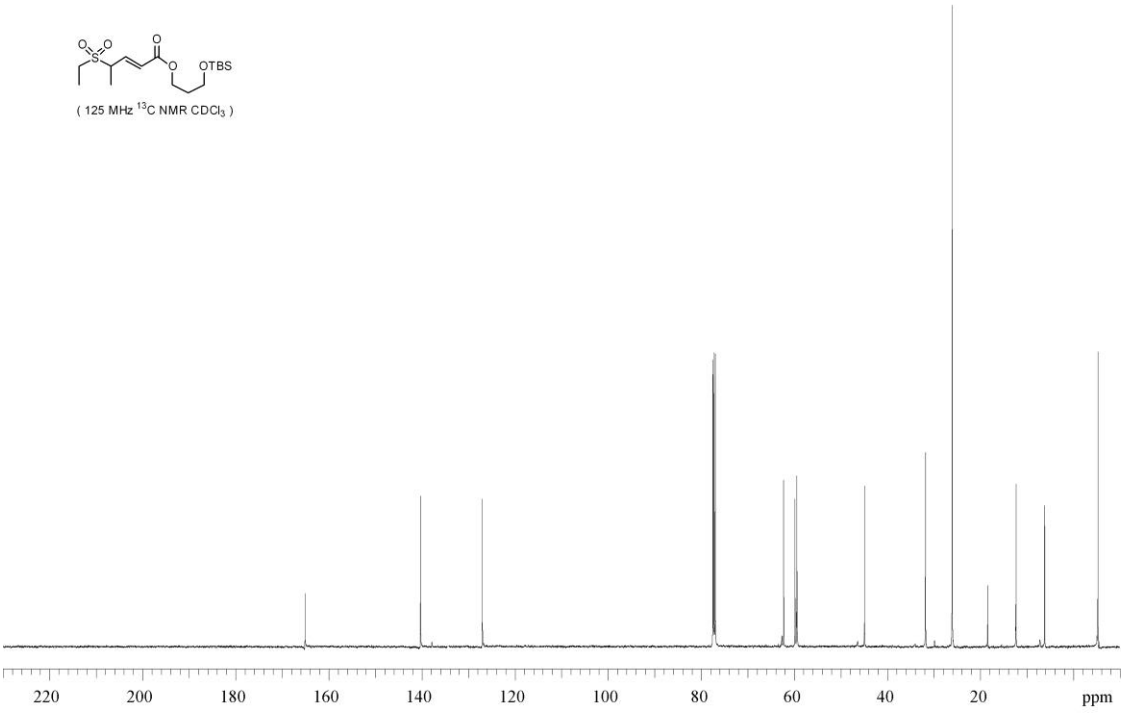

EtS
OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

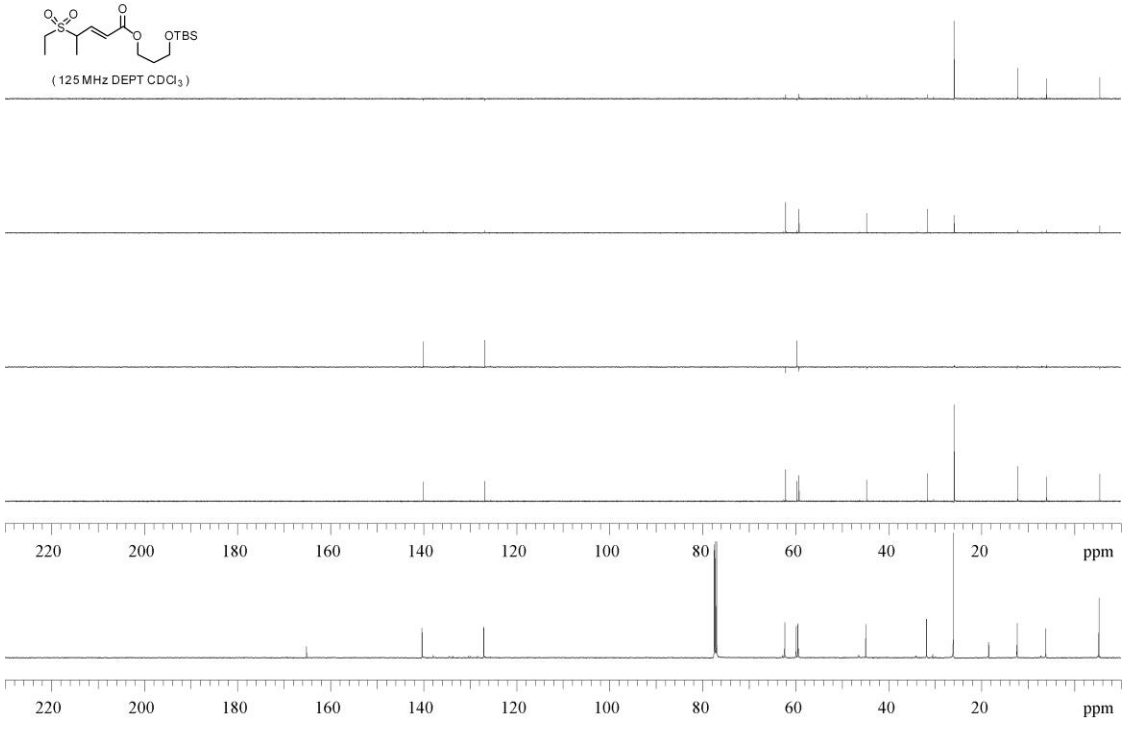

OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.78
0.80
2.01
0.86
2.00
1.89
2.23
2.98
2.56
9.35
5.83

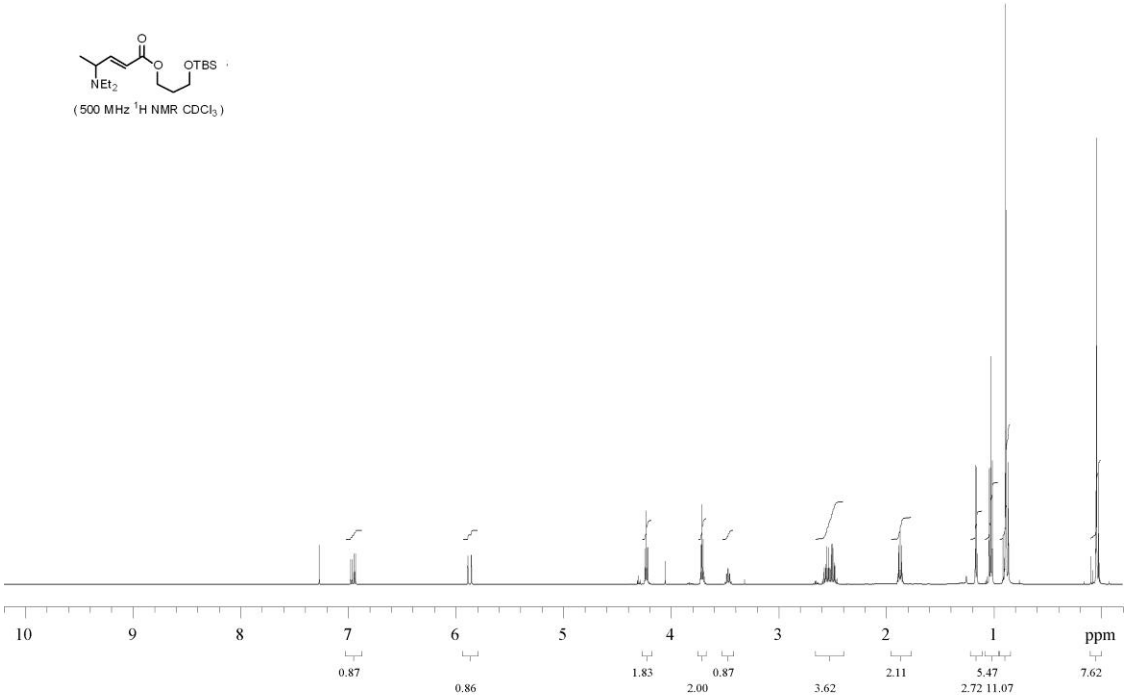

OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
165.469
165.411
141.583
141.000
126.081
125.797
77.484
77.230
76.976
62.105
62.043
59.528
58.400
56.229
42.832
42.651
31.867
26.057
18.445
13.476
13.275
7.547
7.136
-5.248
220
200
180
160
140
120
100
80
60
40
20
ppm

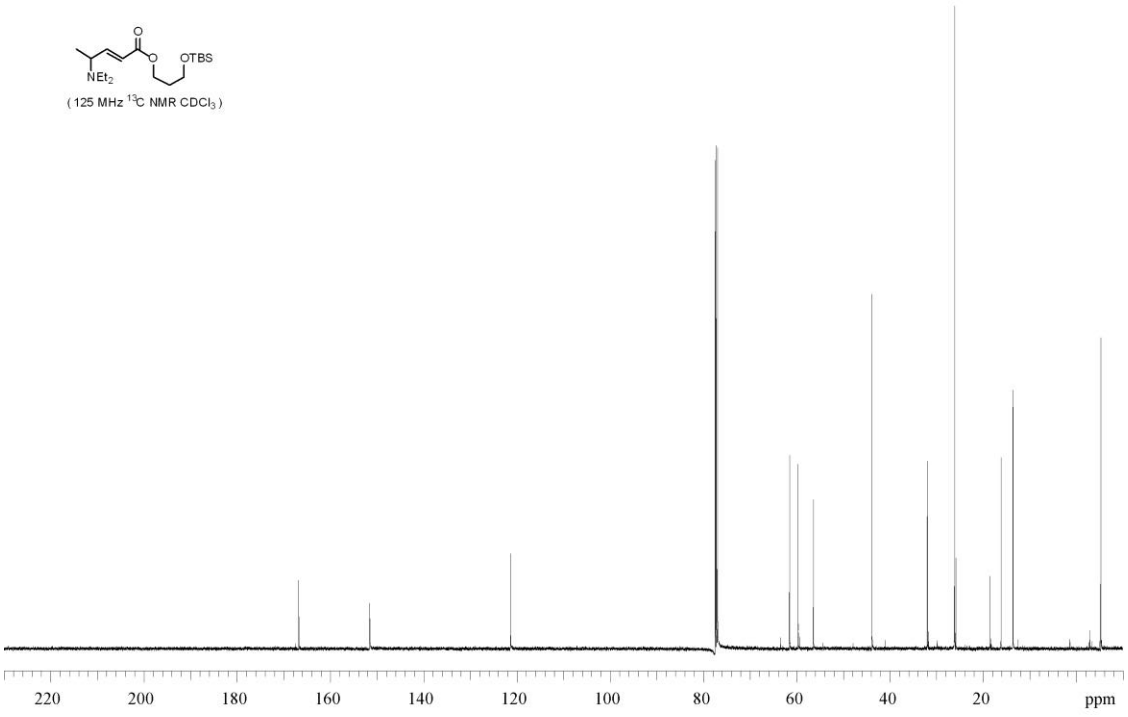

OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

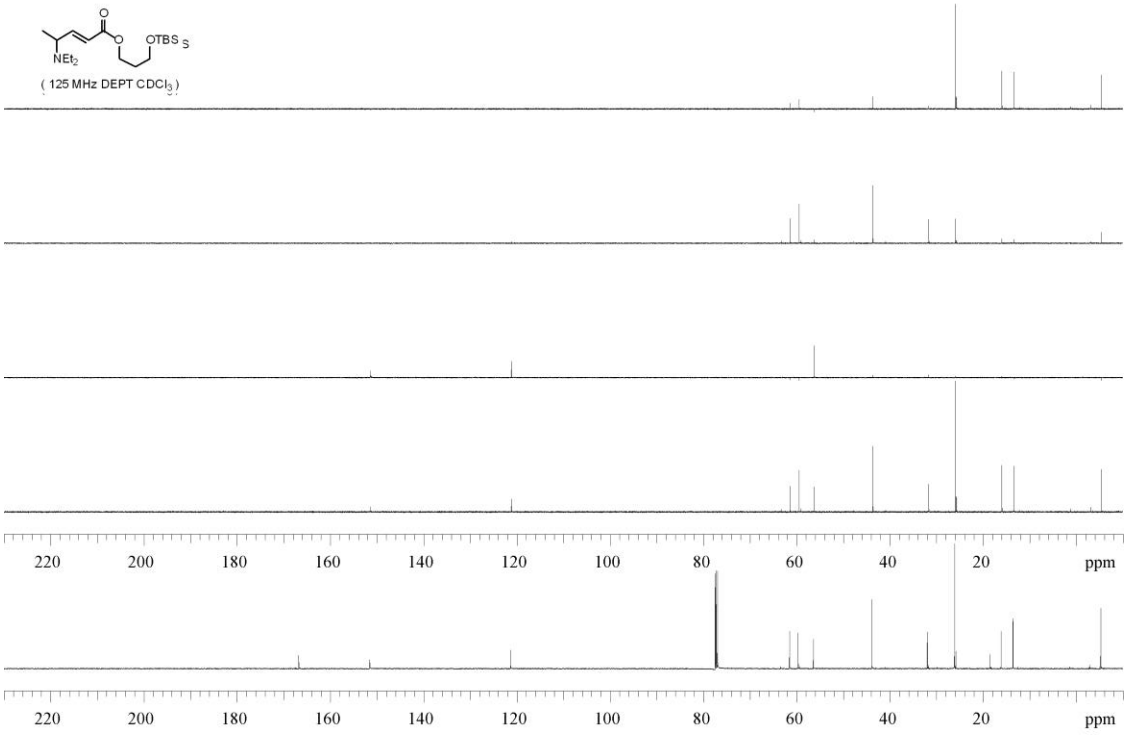

OTBS
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm

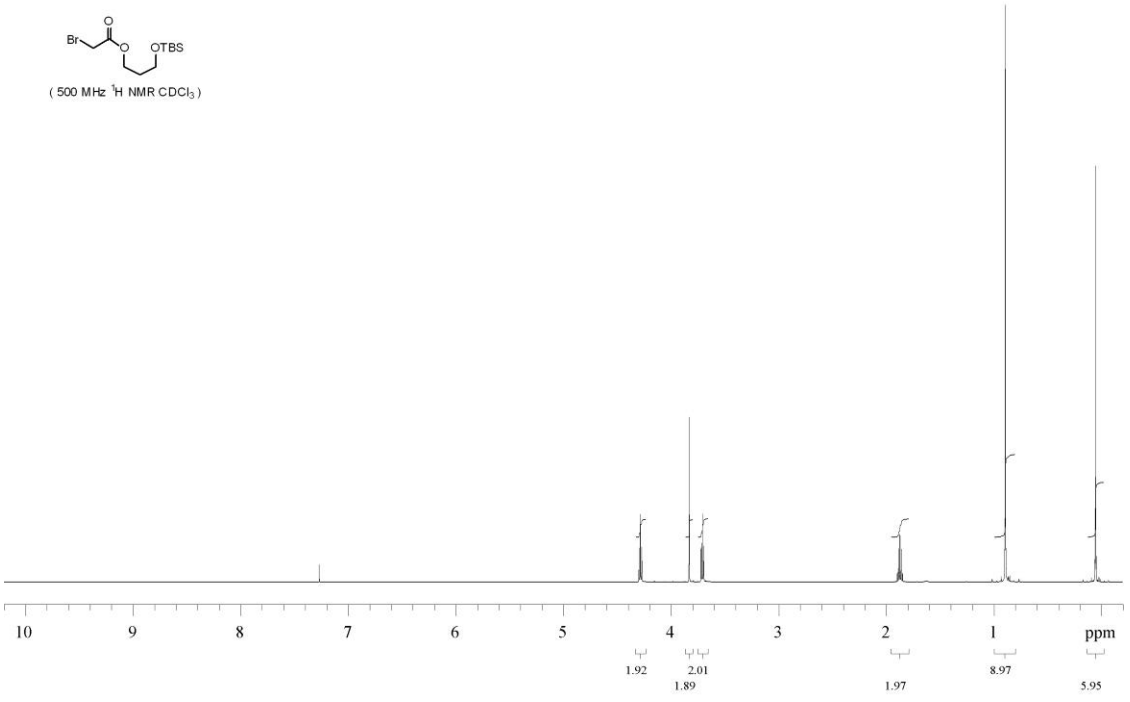

OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

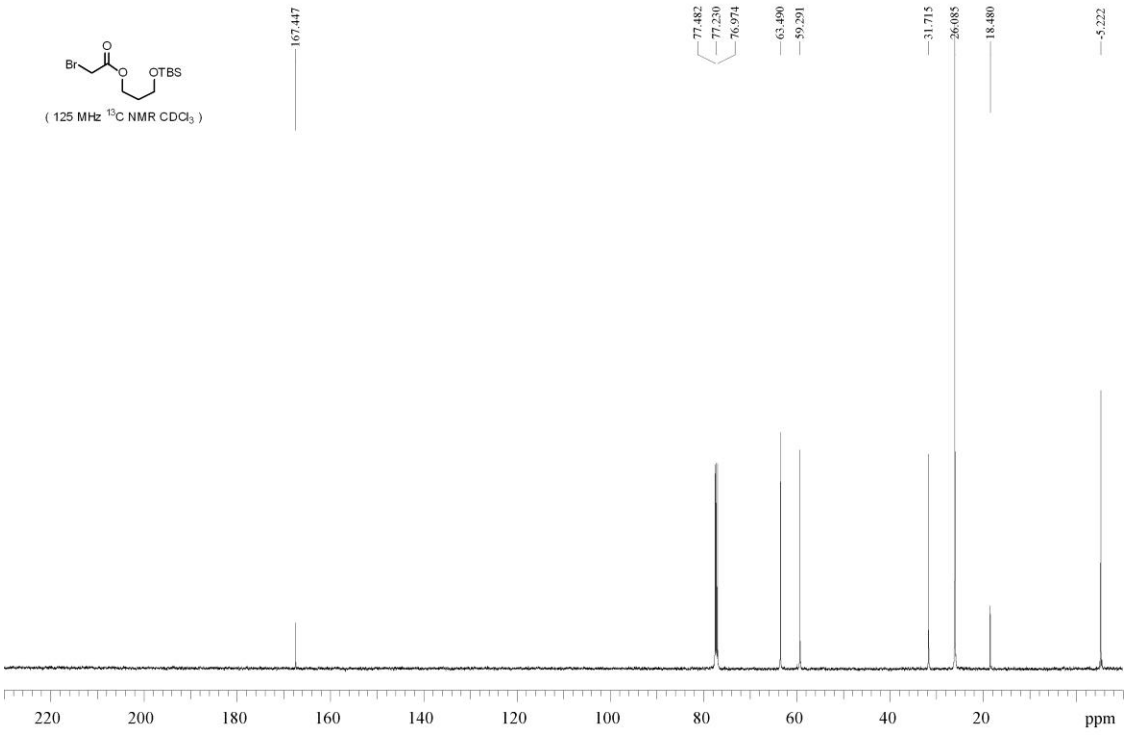

OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

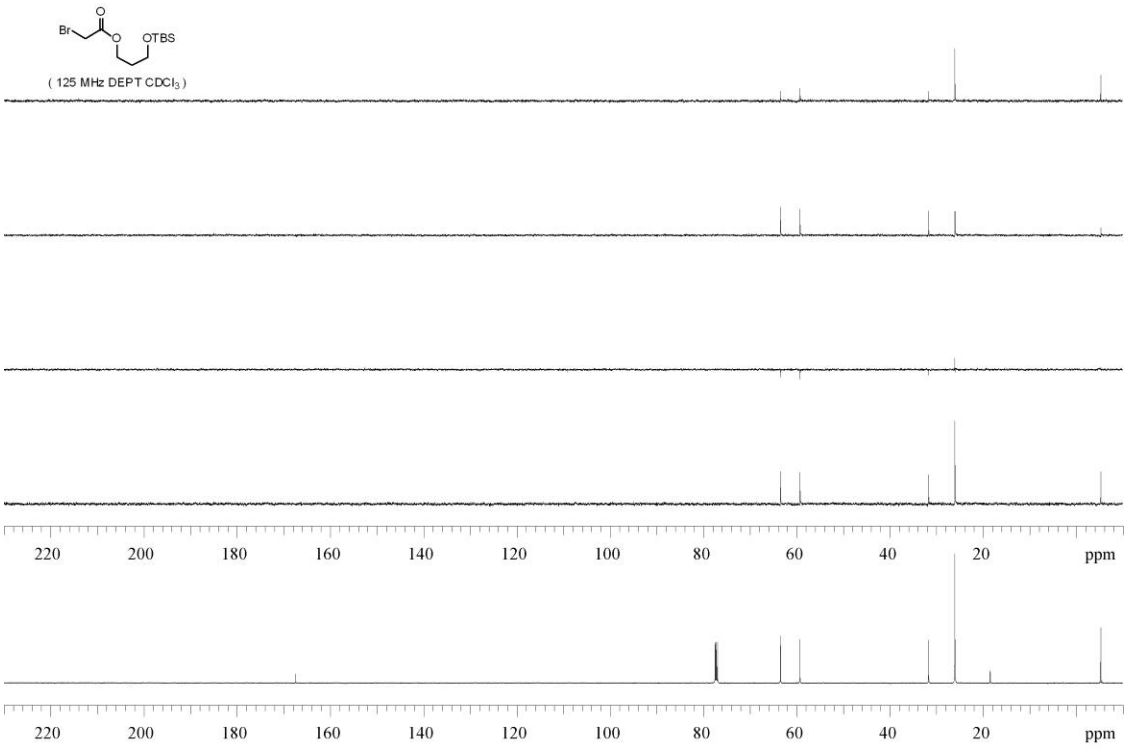

OTBS
NEt2
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
0.87
0.86
1.83
2.00
0.87
3.62
2.11
5.47
2.72 11.07
7.62

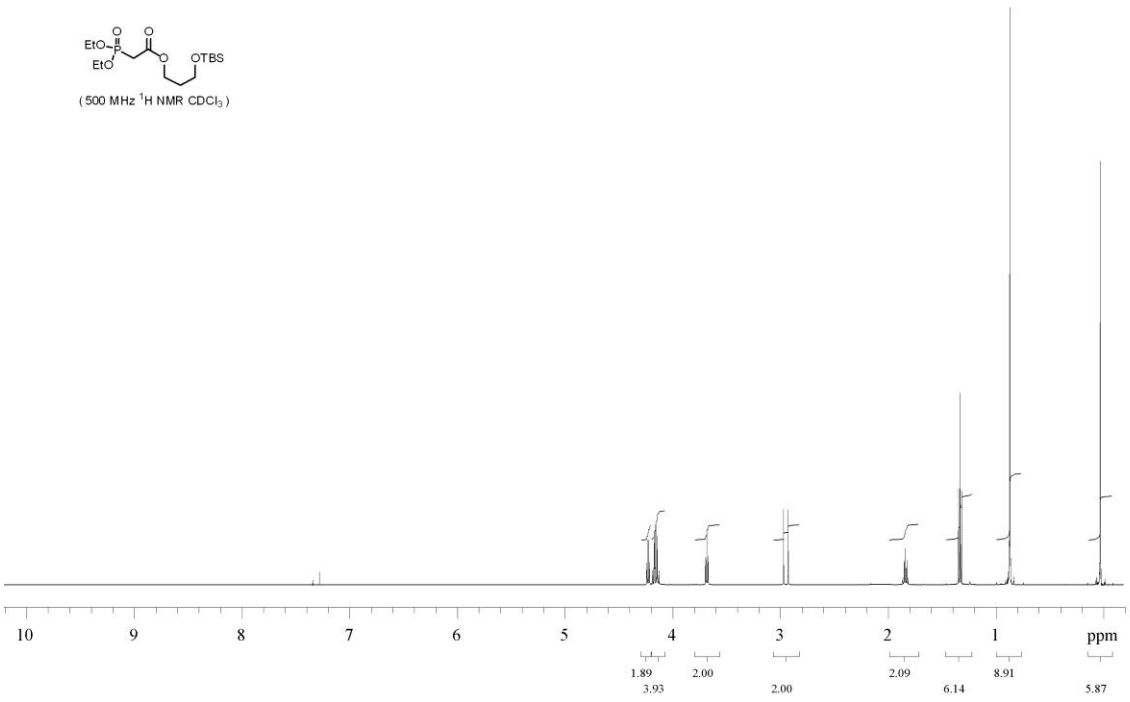

OTBS
NEt2
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

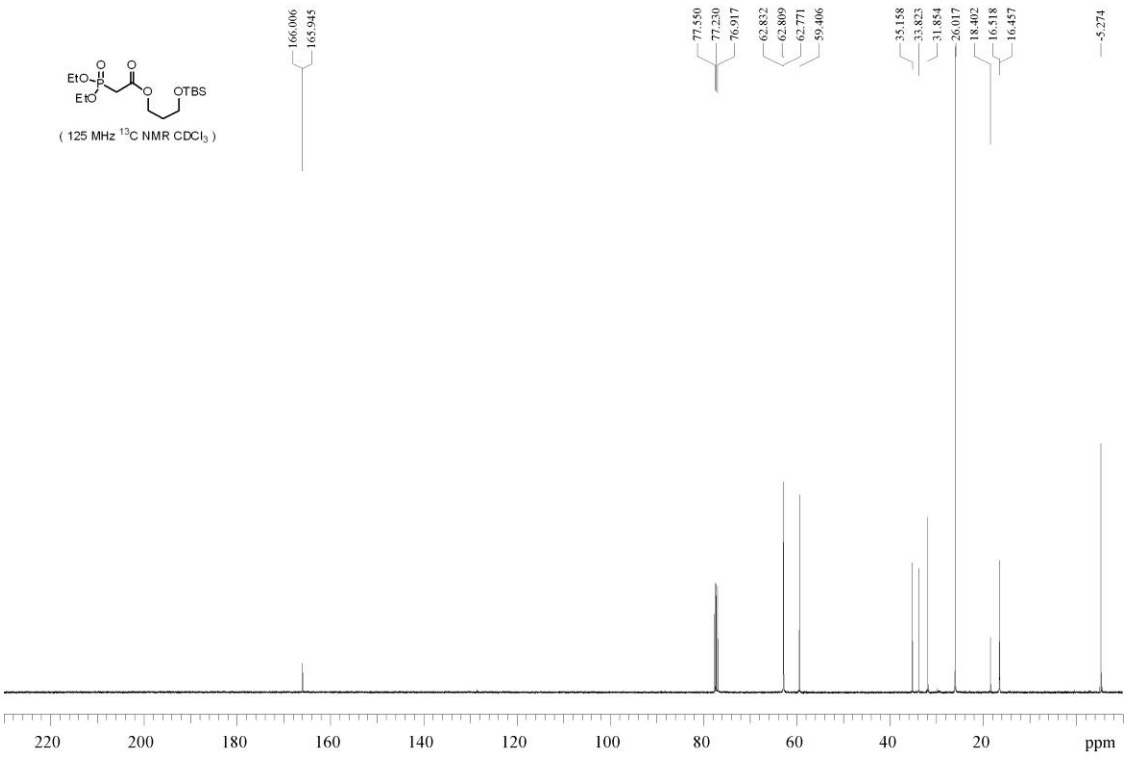

NEt2
OTBS
S
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

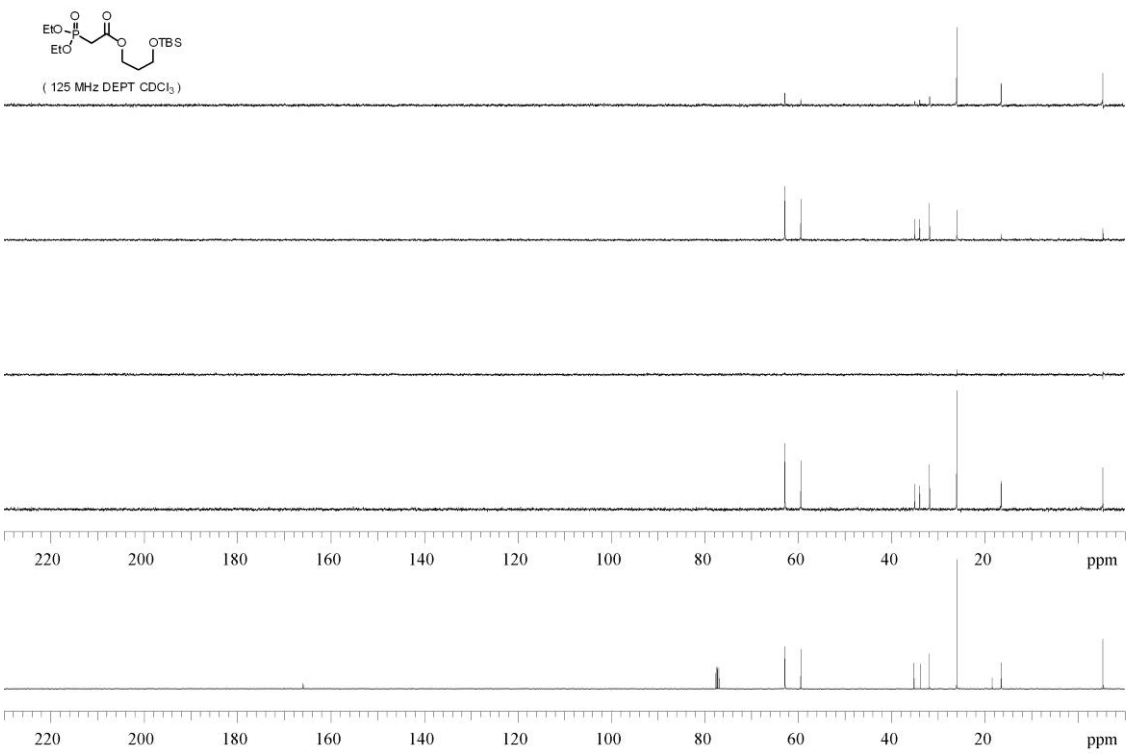

Br
OTBS
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
1.92
2.01
1.89
1.97
8.97
5.95

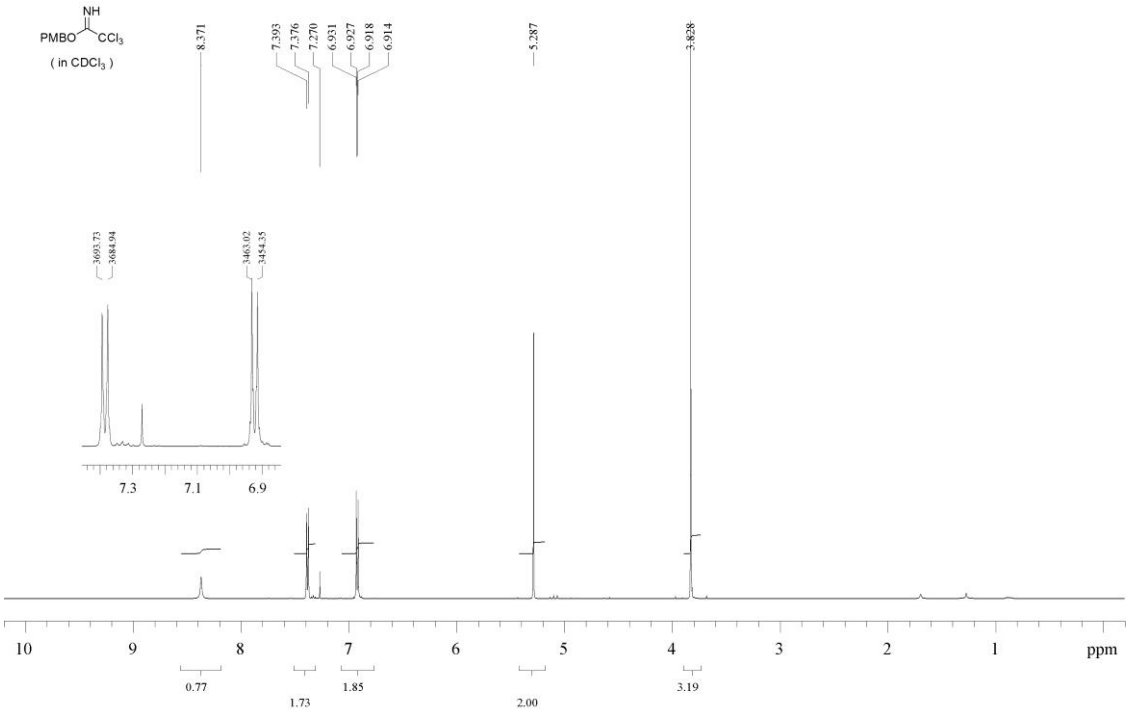

Br
O
O
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
167.447
77.482
77.230
76.974
63.490
59.291
31.715
26.085
18.480
-5.222
220
200
180
160
140
120
100
80
60
40
20
ppm

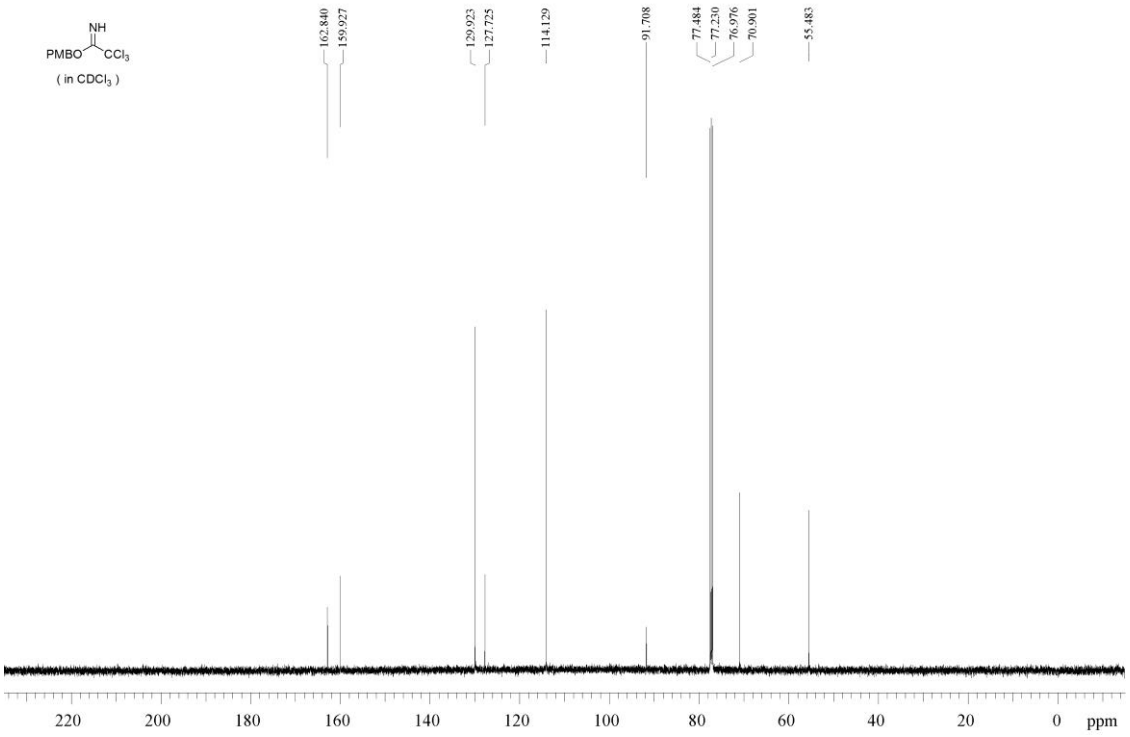

Br
O
O
OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

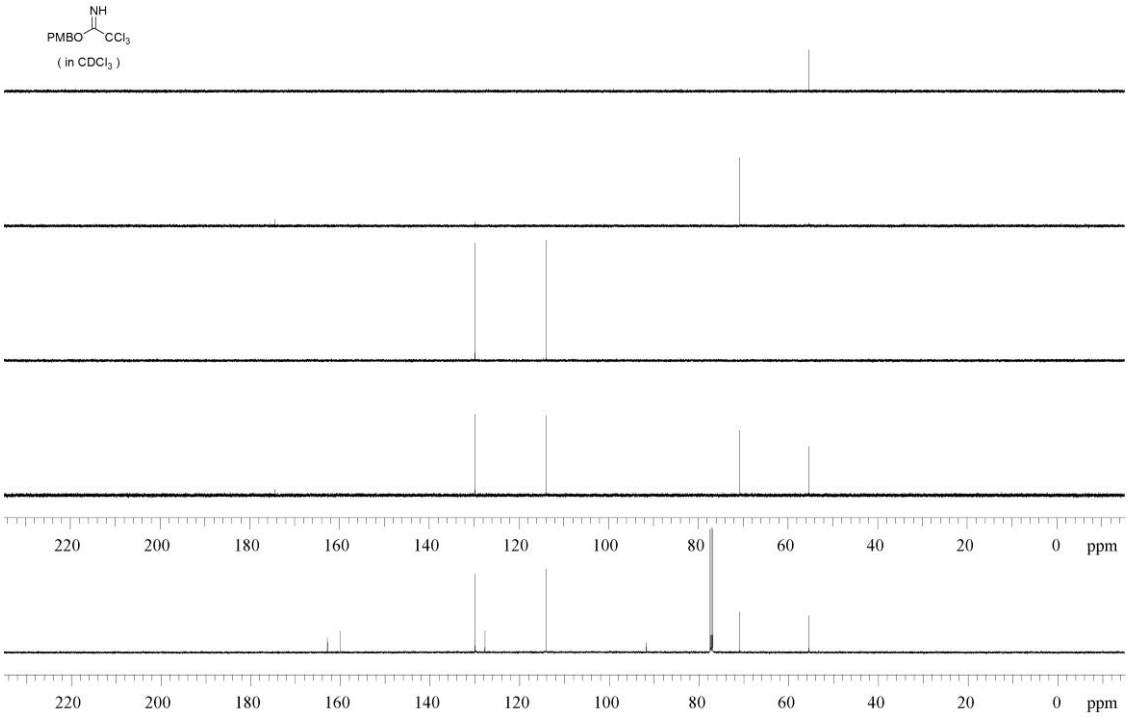

EtO
EtO
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
1.89
3.93
2.00
2.00
2.09
6.14
8.91
5.87

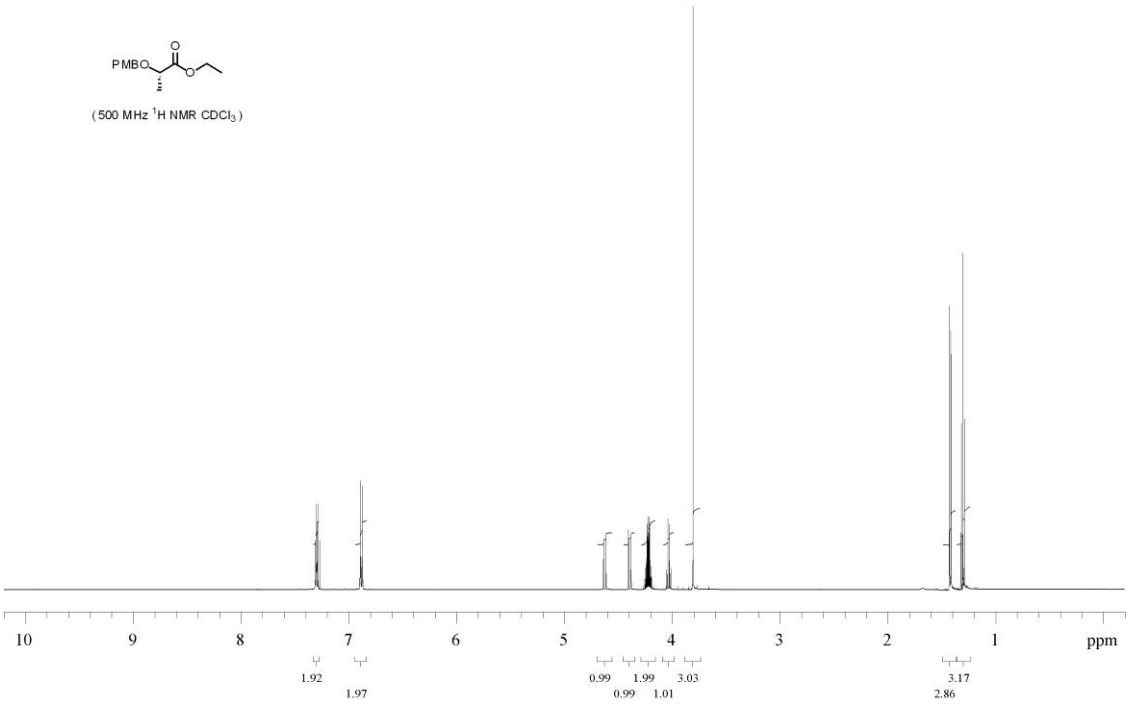

EtO
EtO
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.006
165.945
77.550
77.230
76.917
62.832
62.809
62.771
59.406
35.158
33.823
31.854
26.017
18.402
16.518
16.457
-5.274
220
200
180
160
140
120
100
80
60
40
20
ppm

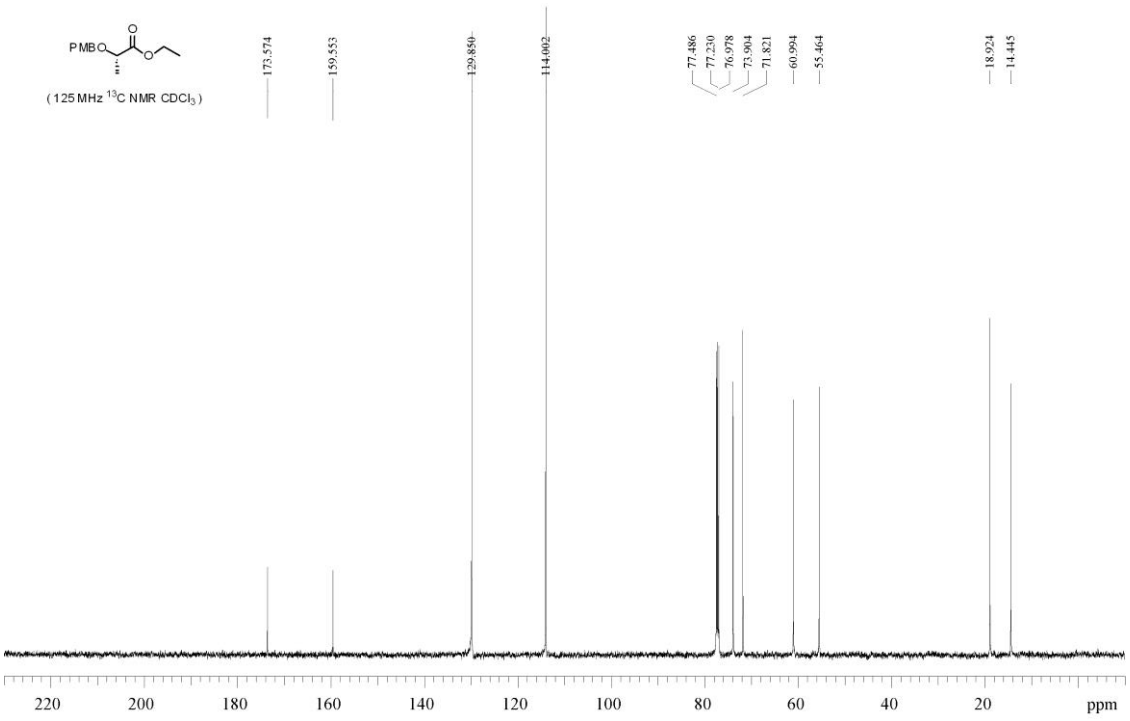

EtO
EtO
OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

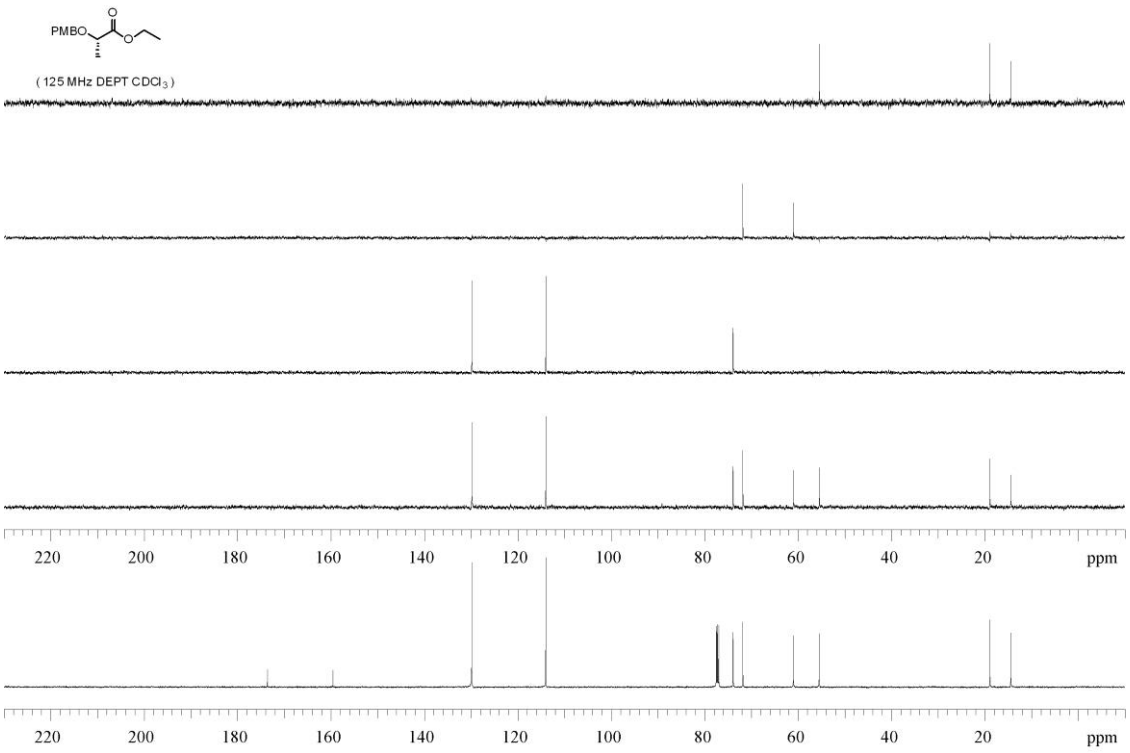

NH
PMBO
CCl3
(in CDCl3)
8.371
7.393
7.376
7.270
6.931
6.927
6.918
6.914
5.287
3.828
3693.73
3684.94
3465.02
3454.35
7.3
7.1
6.9
10
9
8
7
6
5
4
3
2
1
ppm
0.77
1.73
1.85
2.00
3.19

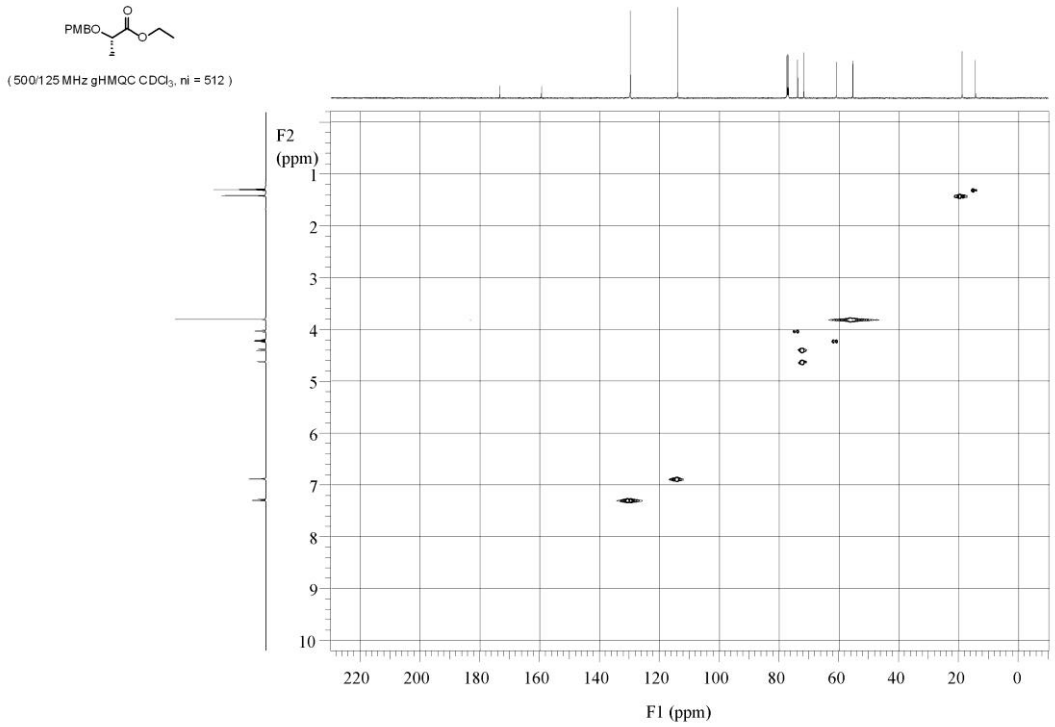

NH
PMBO
CCl3
(in CDCl3)
162.840
159.927
129.923
127.725
114.129
91.708
77.484
77.230
76.976
70.901
55.483
220
200
180
160
140
120
100
80
60
40
20
0
ppm

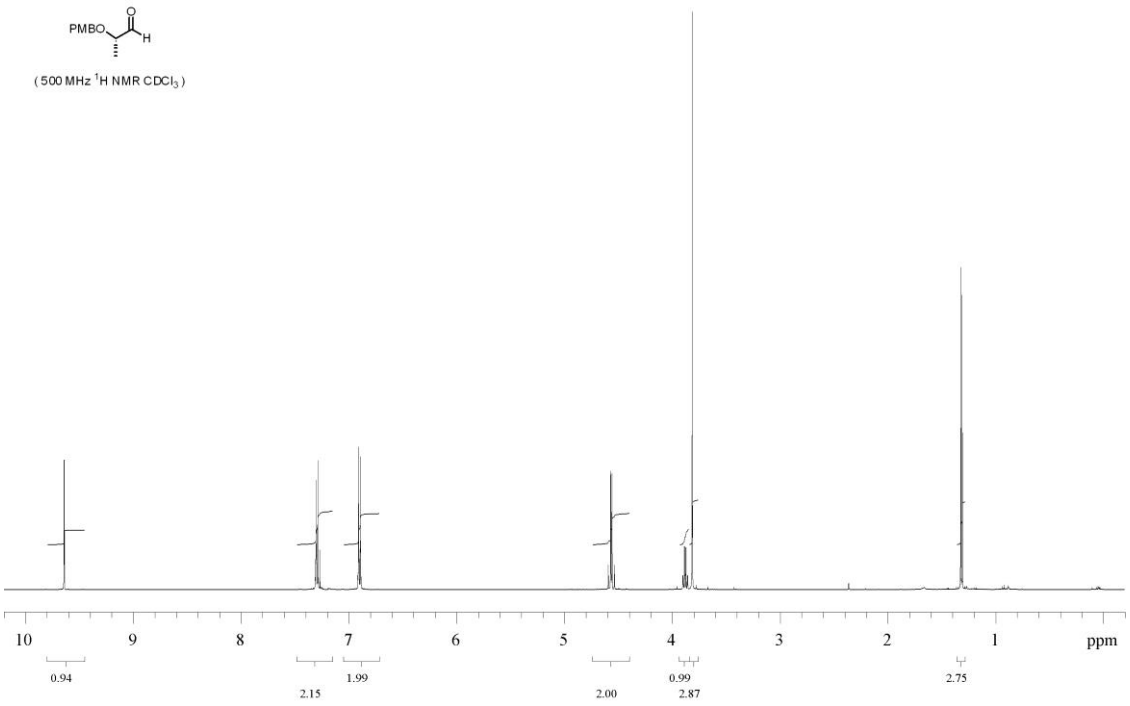

NH
PMBO
CCl3
(in CDCl3)
220
200
180
160
140
120
100
80
60
40
20
0
ppm
220
200
180
160
140
120
100
80
60
40
20
0
ppm

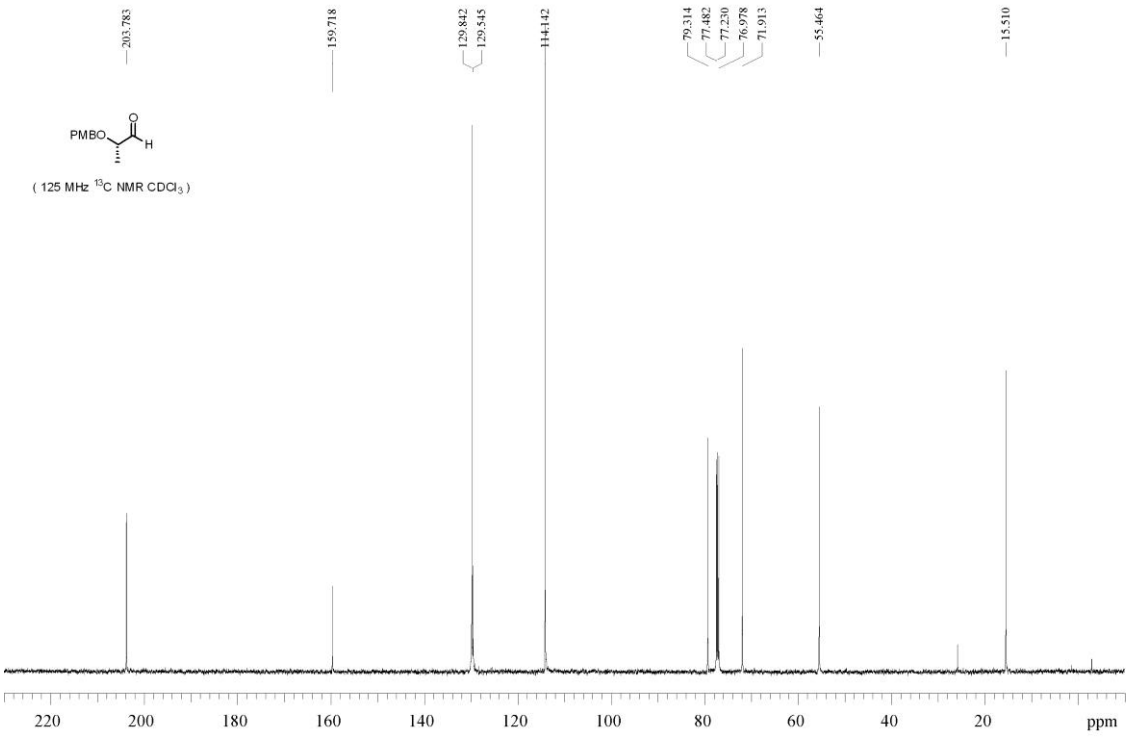

PMBO
O
O
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
1.92
1.97
0.99
1.99
3.03
0.99
1.01
3.17
2.86

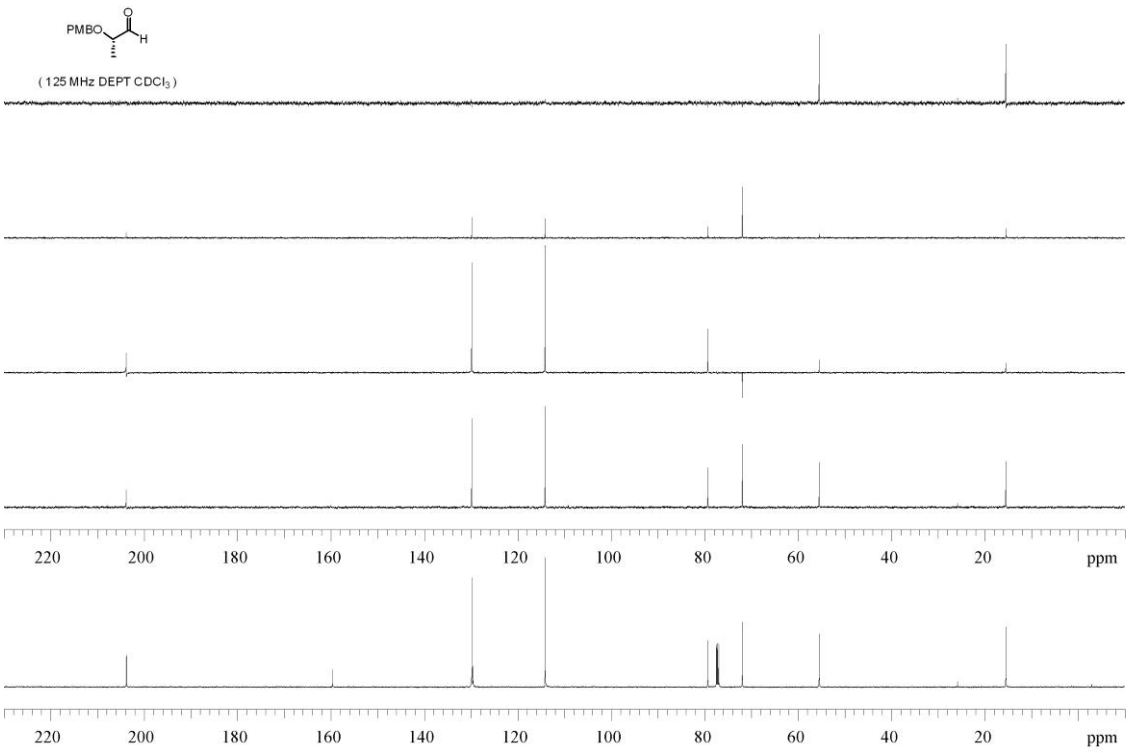

PMBO
O
O
(125 MHz ^{13}C NMR $CDCl_3$)
173.574
159.553
129.850
114.002
77.486
77.230
76.978
73.904
71.821
60.994
55.464
18.924
14.445
220
200
180
160
140
120
100
80
60
40
20
ppm

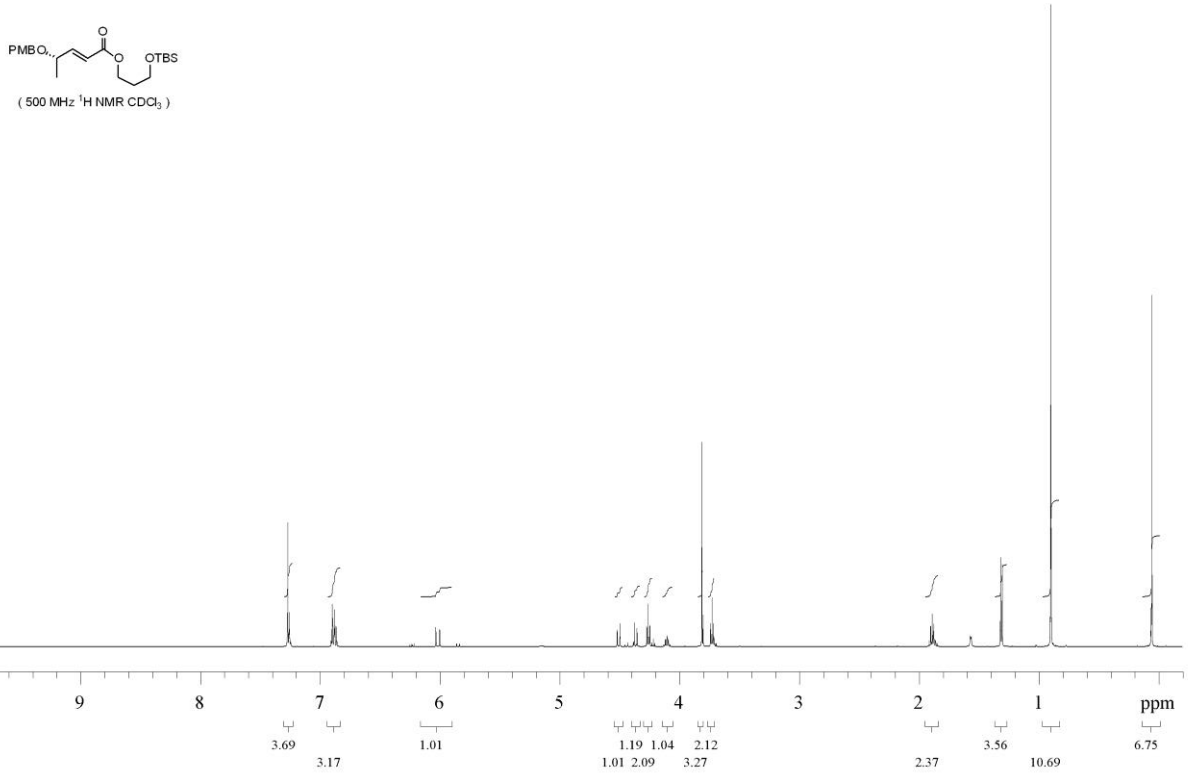

PMBO
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

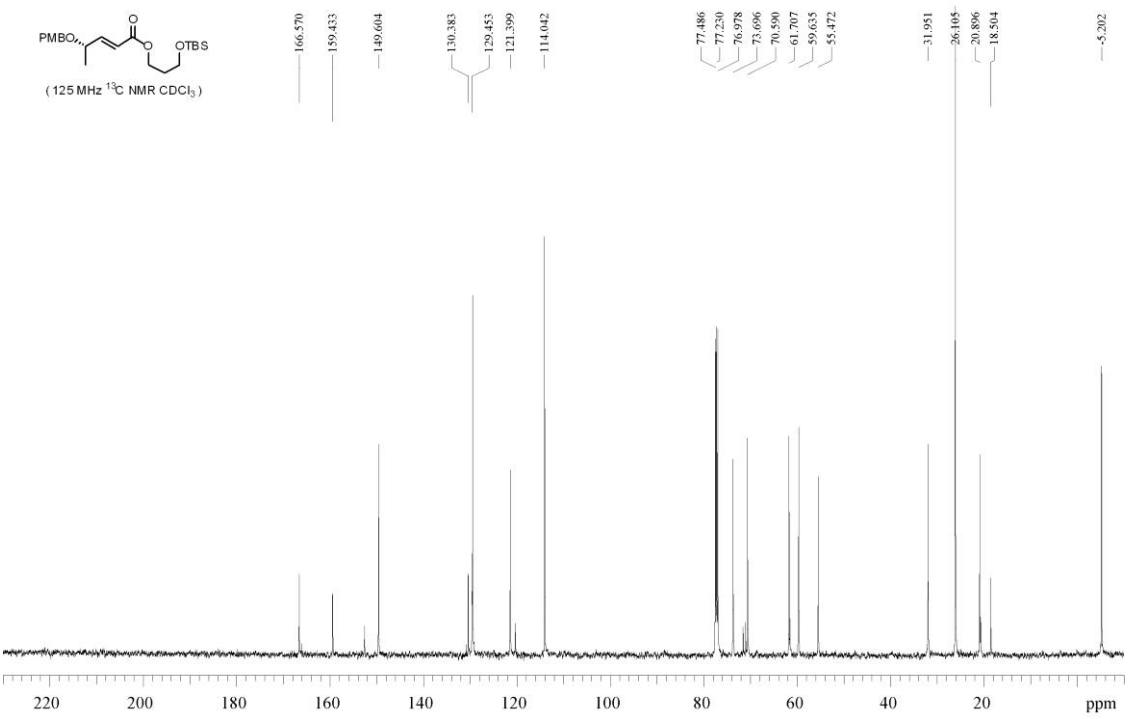

PMBO
(500/125 MHz gHMQC CDCl3, ni = 512)
F2
(ppm)
F1 (ppm)

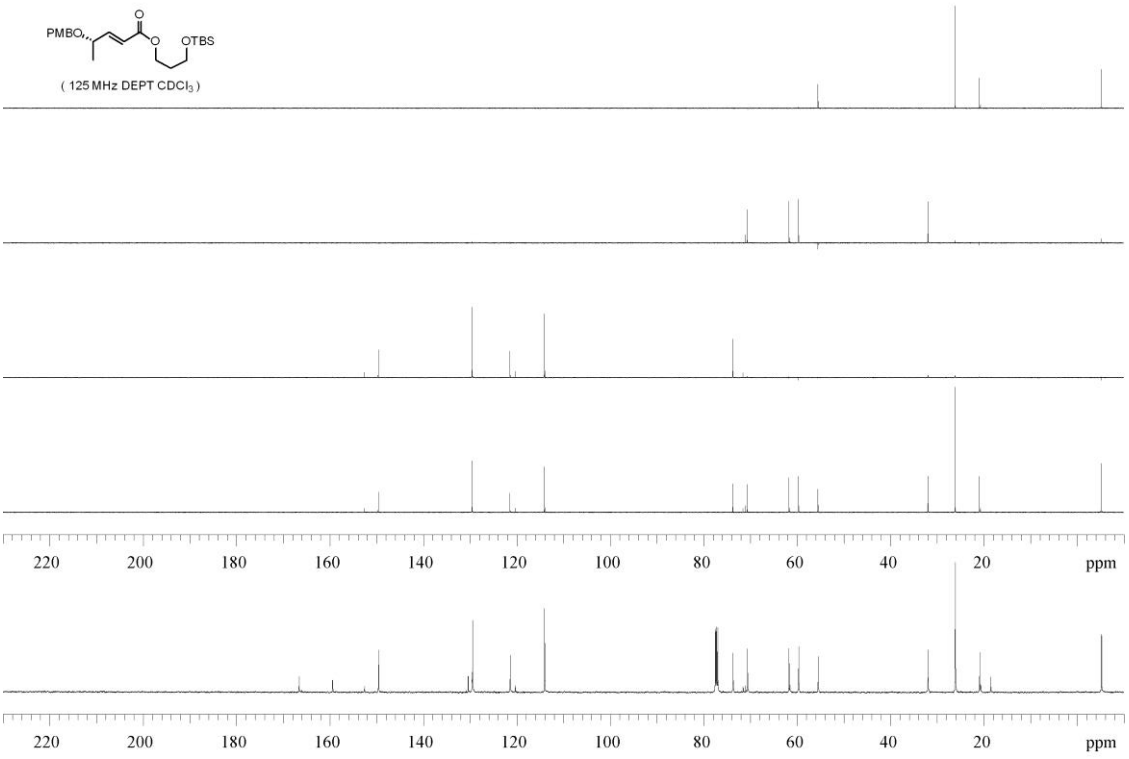

PMBO
H
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.94
2.15
1.99
2.00
0.99
2.87
2.75

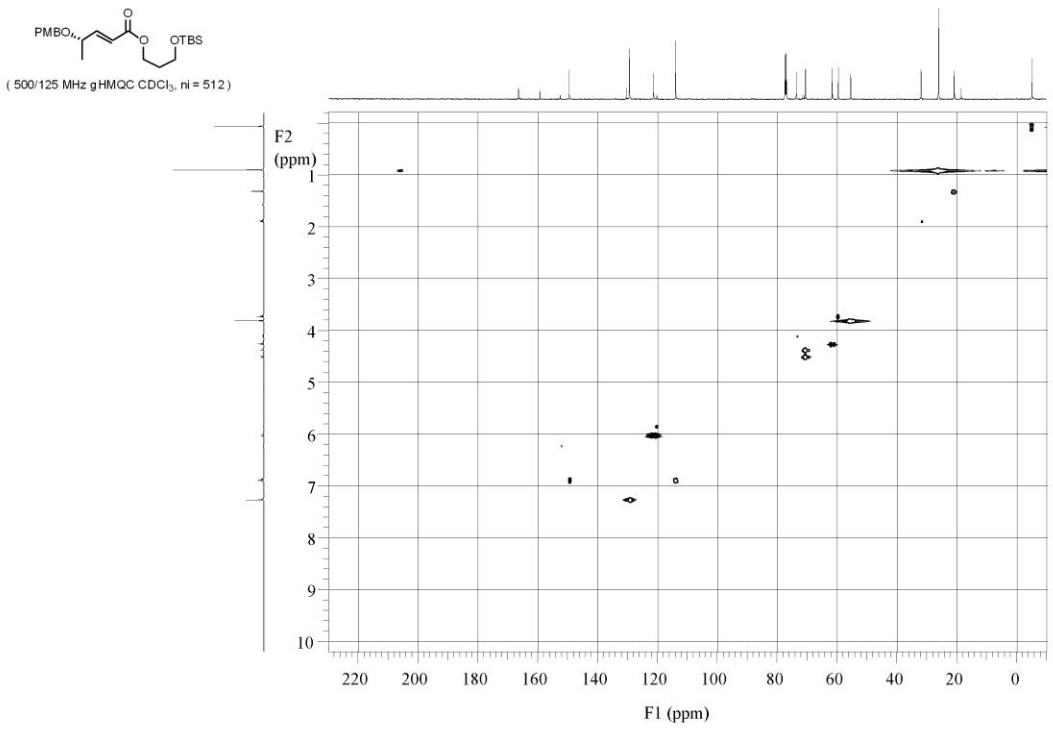

203.783
159.718
129.842
129.545
114.142
79.314
77.482
77.230
76.978
71.913
55.464
15.510
PMBO
H
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

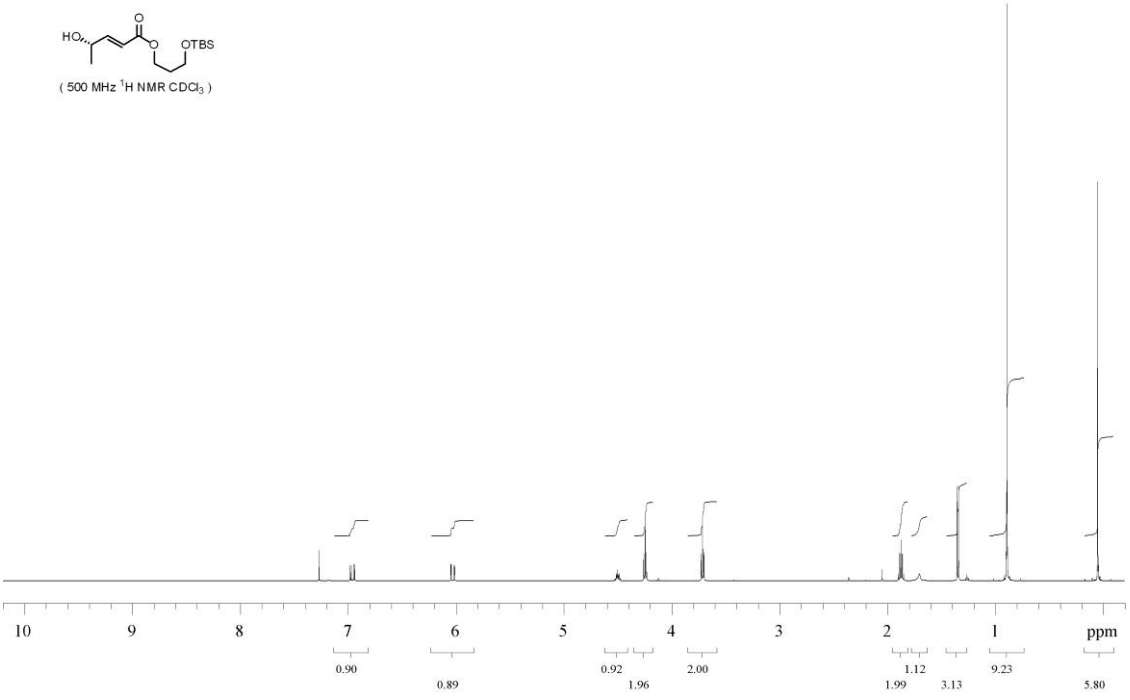

PMBO
H
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

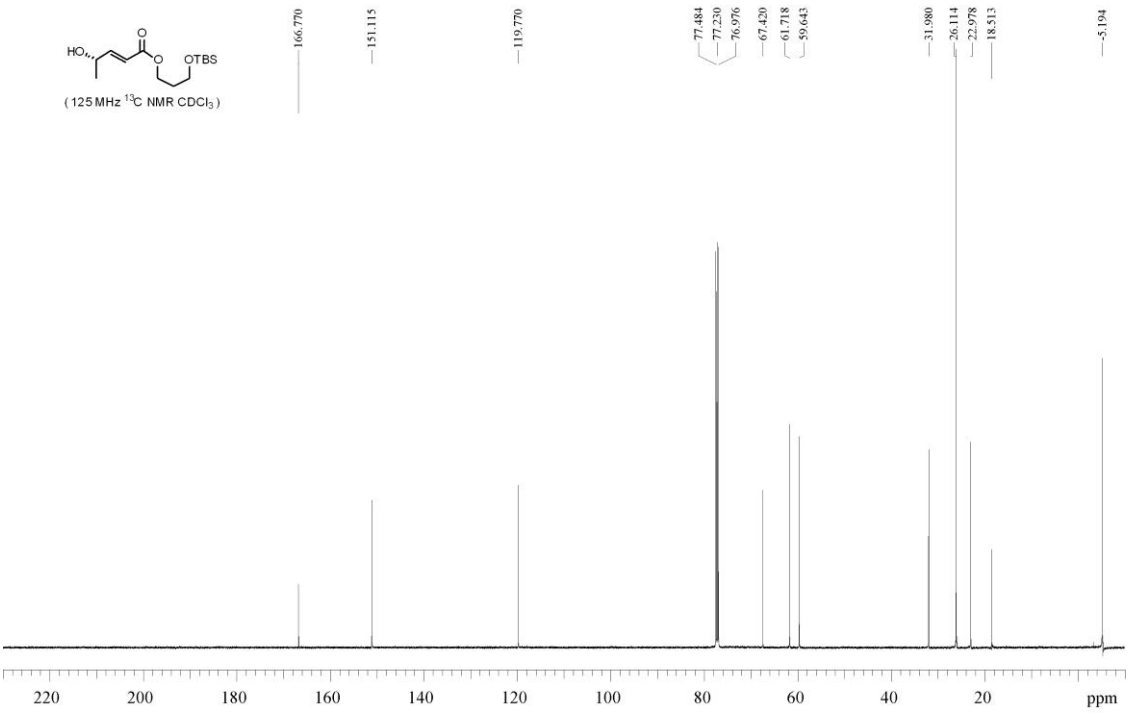

PMBO
OTBS
(500 MHz ^1H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
3.69
3.17
1.01
1.01
1.19
2.09
1.04
3.27
2.12
2.37
3.56
10.69
6.75

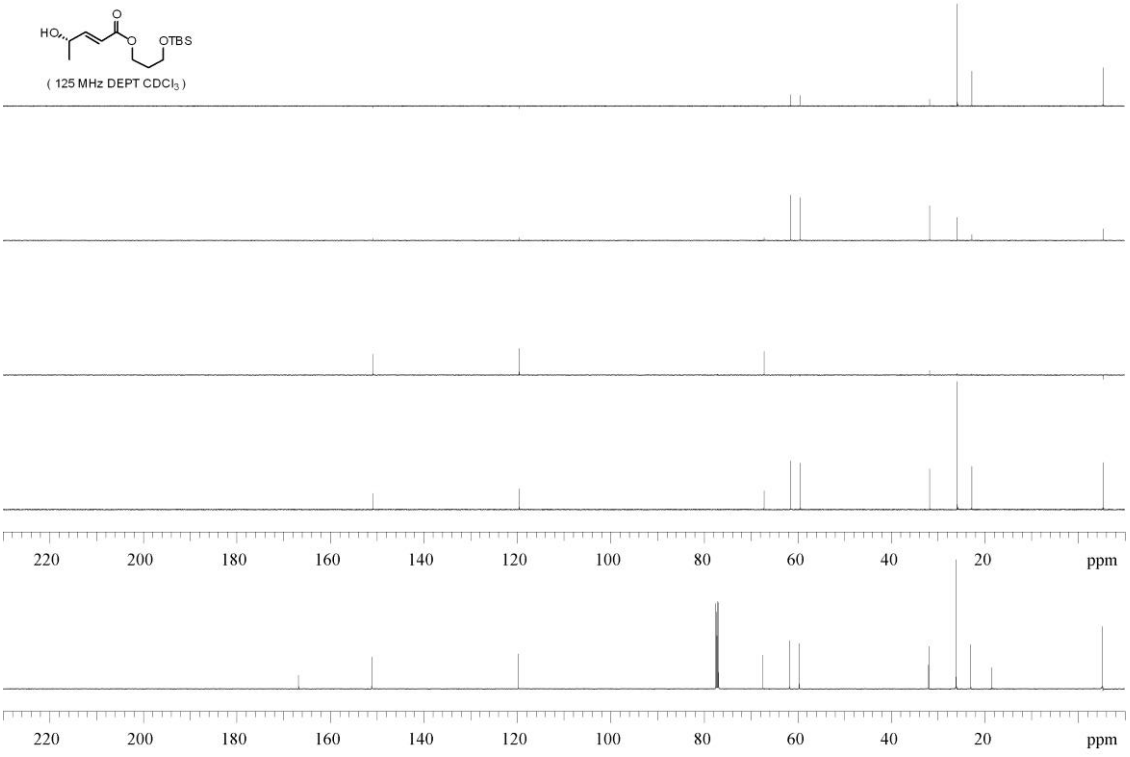

PMBO
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.570
159.433
149.604
130.383
129.453
121.399
114.042
77.486
77.230
76.978
73.696
70.590
61.707
59.635
55.472
31.951
26.105
20.896
18.504
-5.202
220
200
180
160
140
120
100
80
60
40
20
ppm

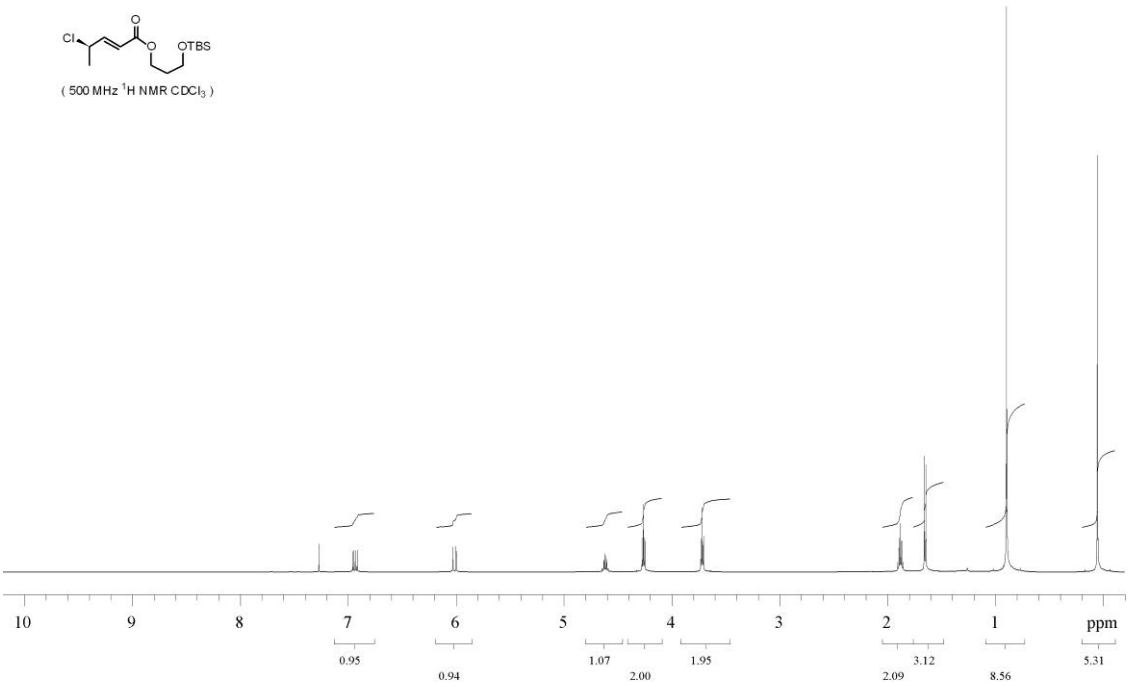

PMBO
OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

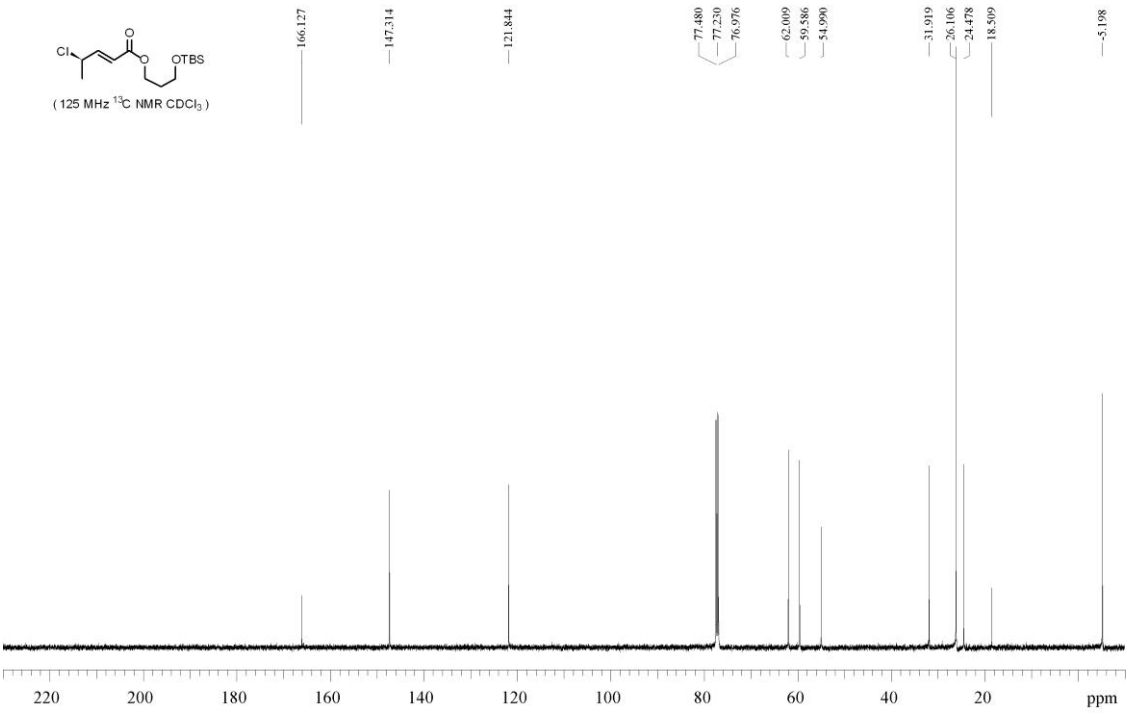

PMBO
OTBS
(500/125 MHz gHMQC CDCl3, ni = 512)
F2 (ppm)
F1 (ppm)

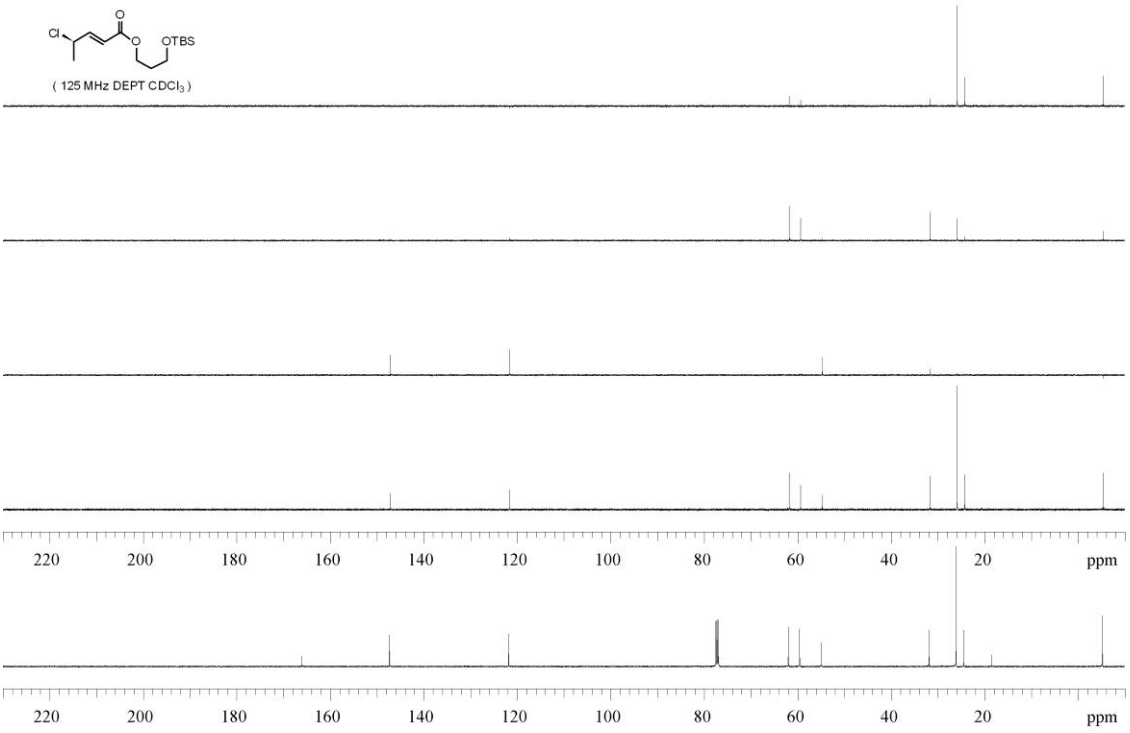

HO
OTBS
(500 MHz 1H NMR CDCl3)
ppm
0.90
0.89
0.92
1.96
2.00
1.99
1.12
3.13
9.23
5.80

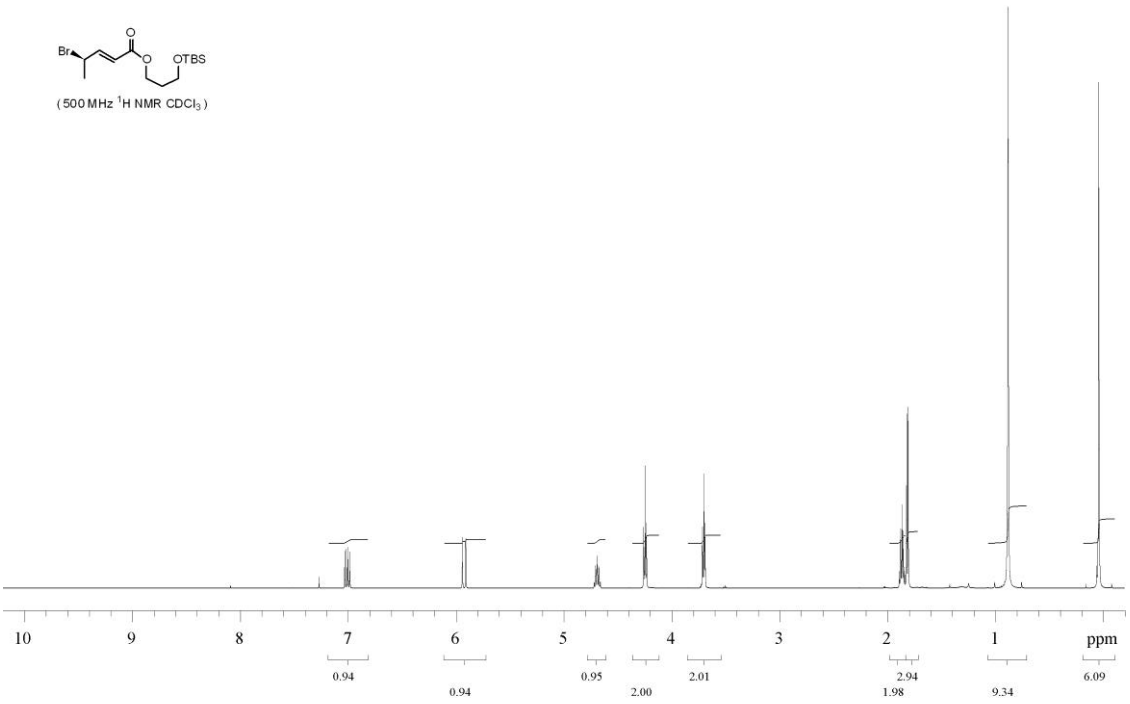

HO
O
O
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.770
151.115
119.770
77.484
77.230
76.976
67.420
61.718
59.643
31.980
26.114
22.978
18.513
-5.194
220
200
180
160
140
120
100
80
60
40
20
ppm

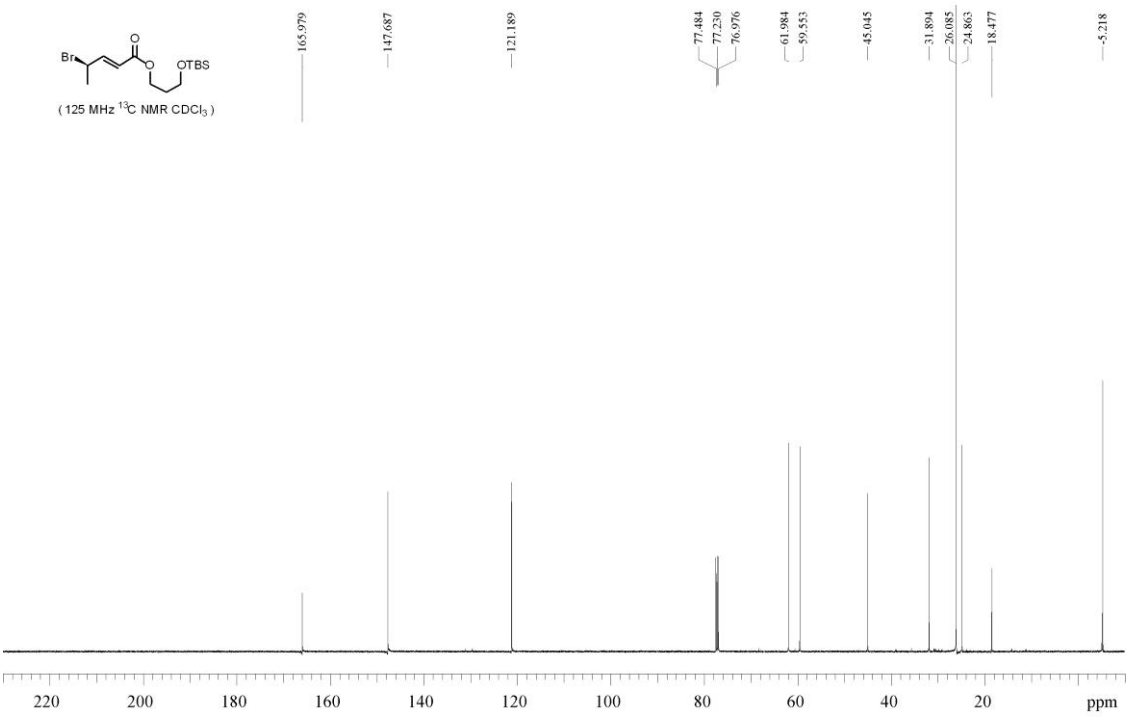

HO
O
O
OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

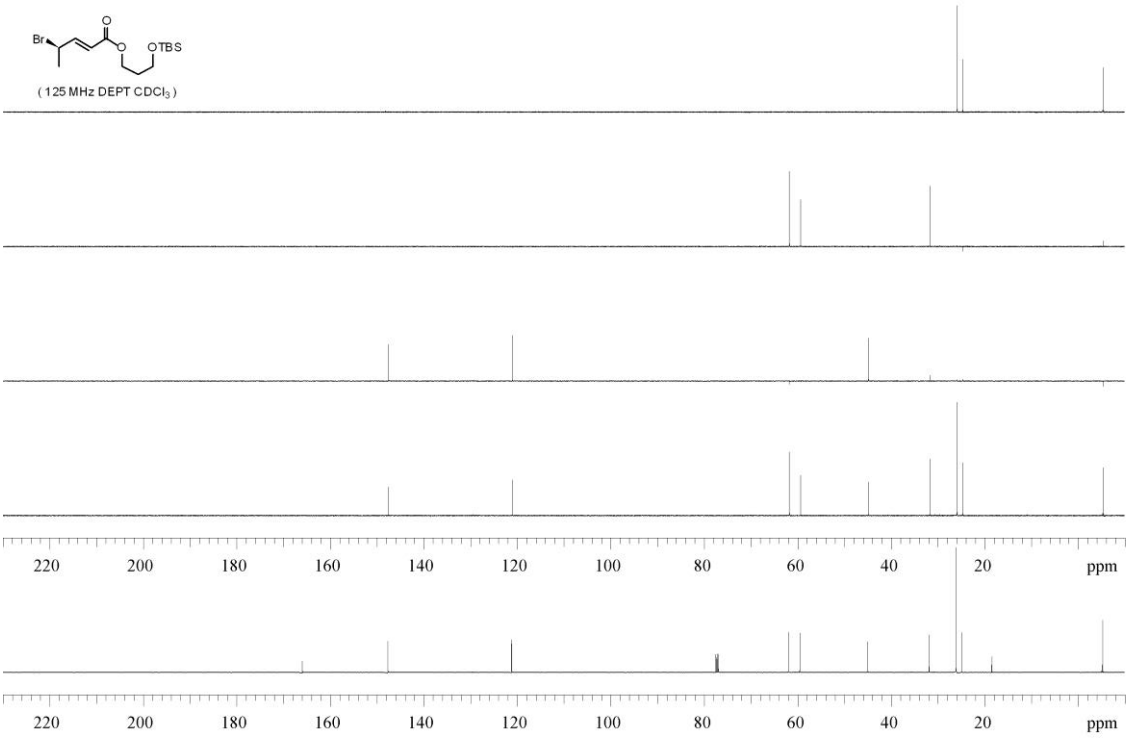

Cl
O
O
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.95
0.94
1.07
2.00
1.95
2.09
3.12
8.56
5.31

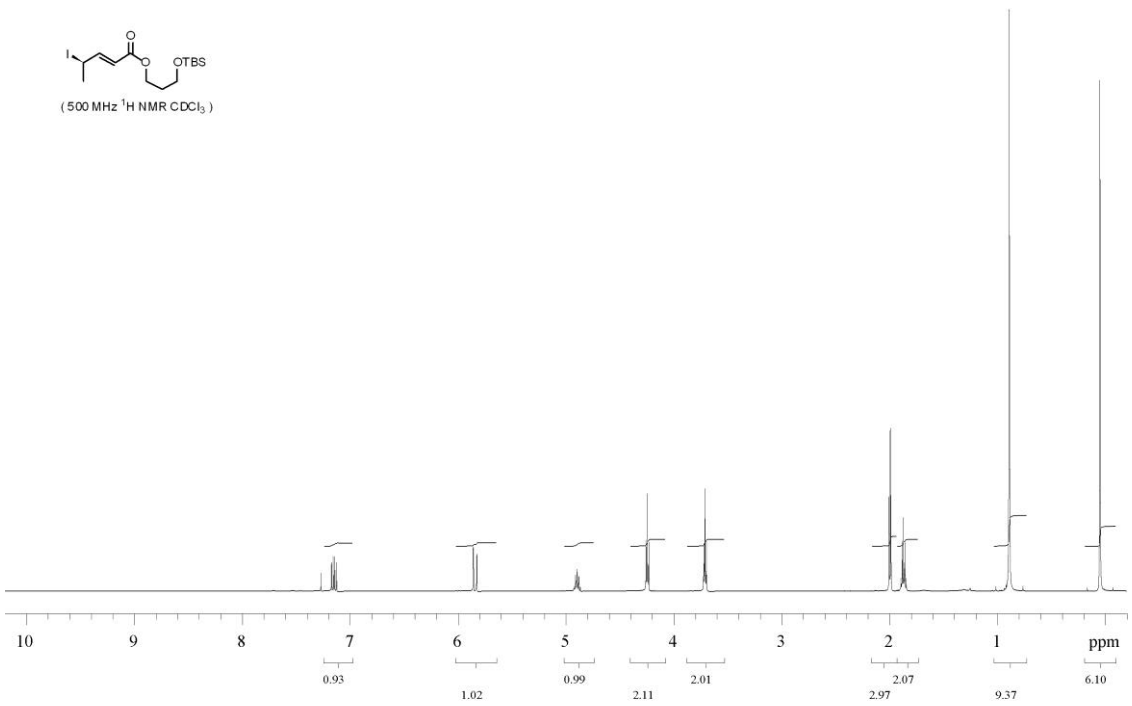

Cl
O
O
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
166.127
147.314
121.844
77.480
77.230
76.976
62.009
59.586
54.990
31.919
26.106
24.478
18.509
-5.198
220
200
180
160
140
120
100
80
60
40
20
ppm

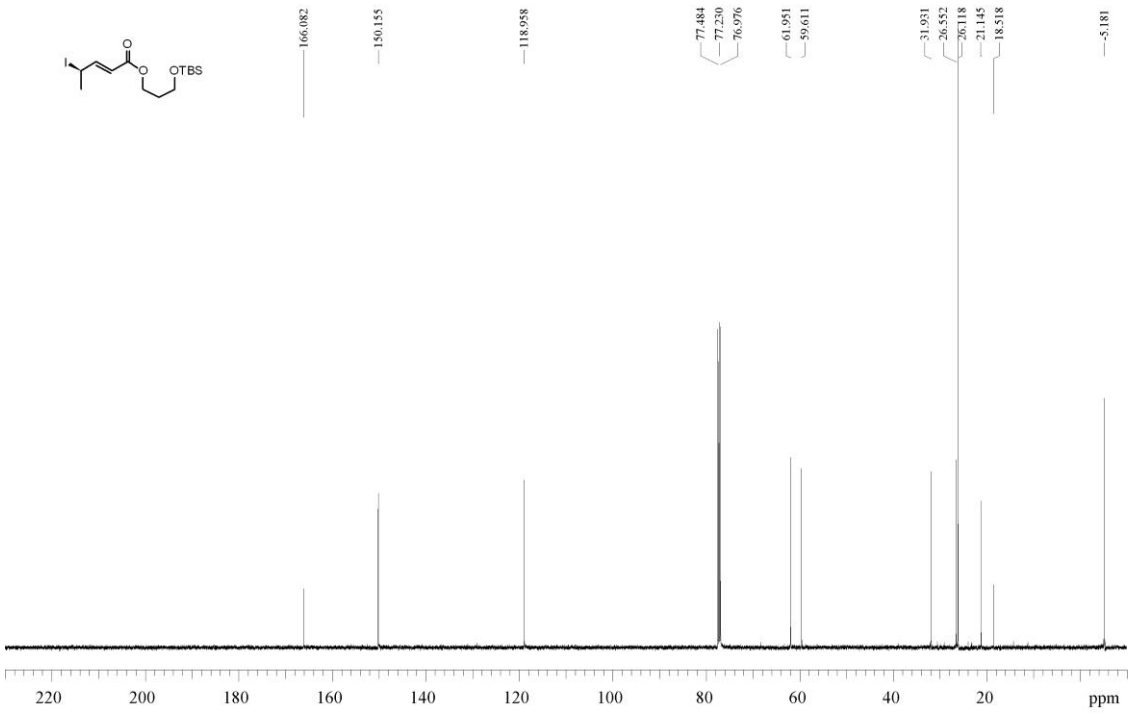

Cl
O
O
OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

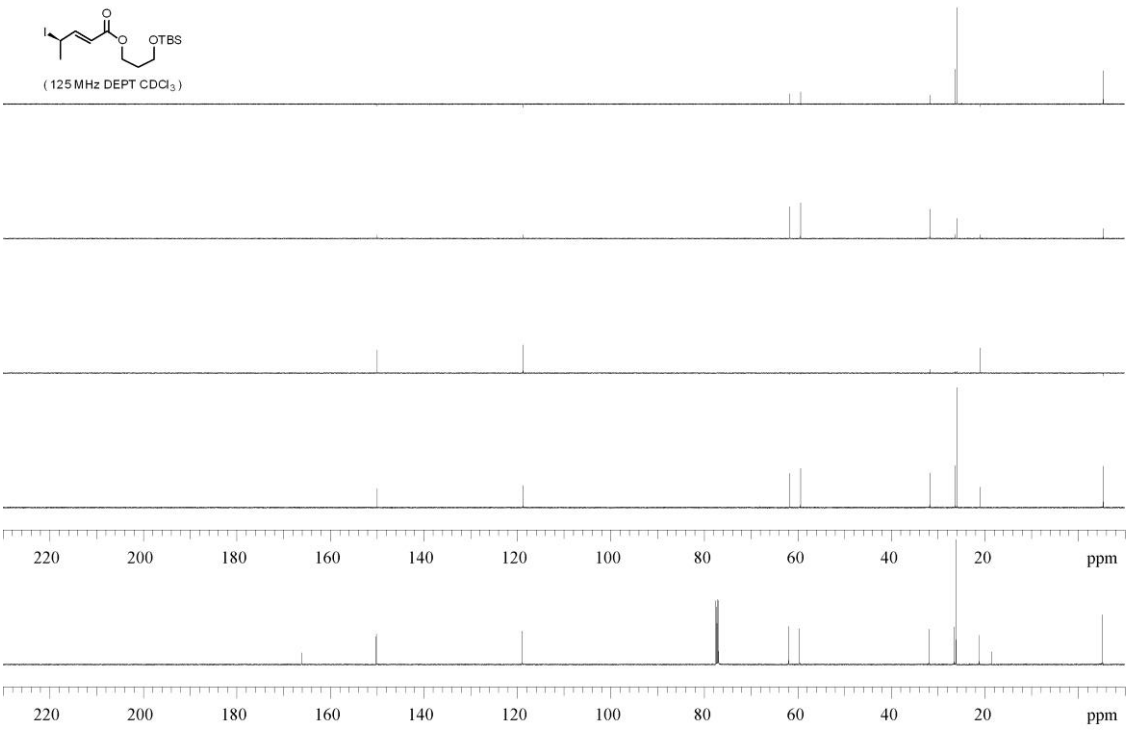

Br
O
O
OTBS
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
0.94
0.94
0.95
2.00
2.01
1.98
2.94
9.34
6.09

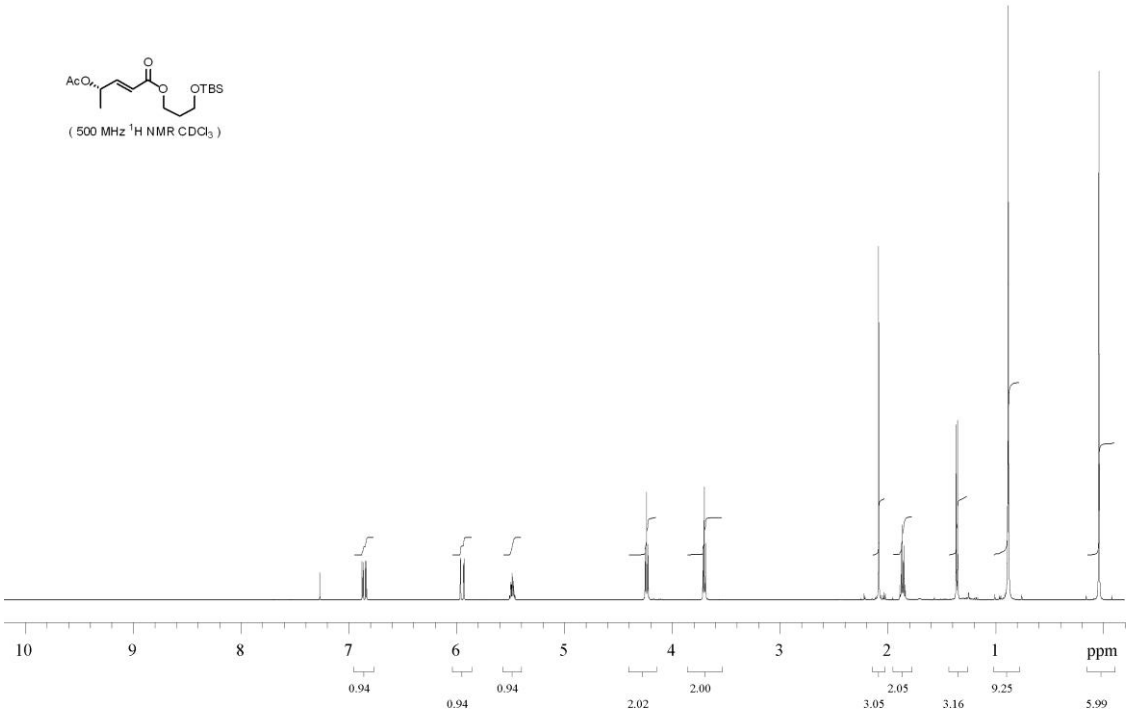

Br
O
O
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
165.979
147.687
121.189
77.484
77.230
76.976
61.984
59.553
45.045
31.894
26.085
24.863
18.477
-5.218
220
200
180
160
140
120
100
80
60
40
20
ppm

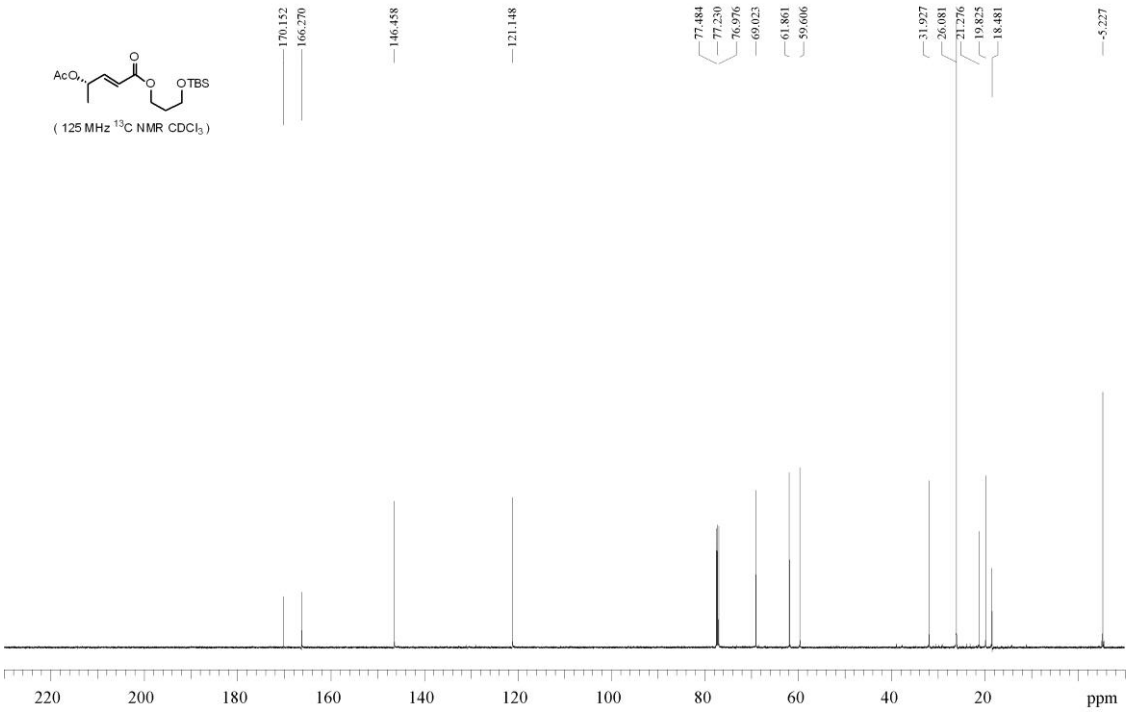

Br
O
O
OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

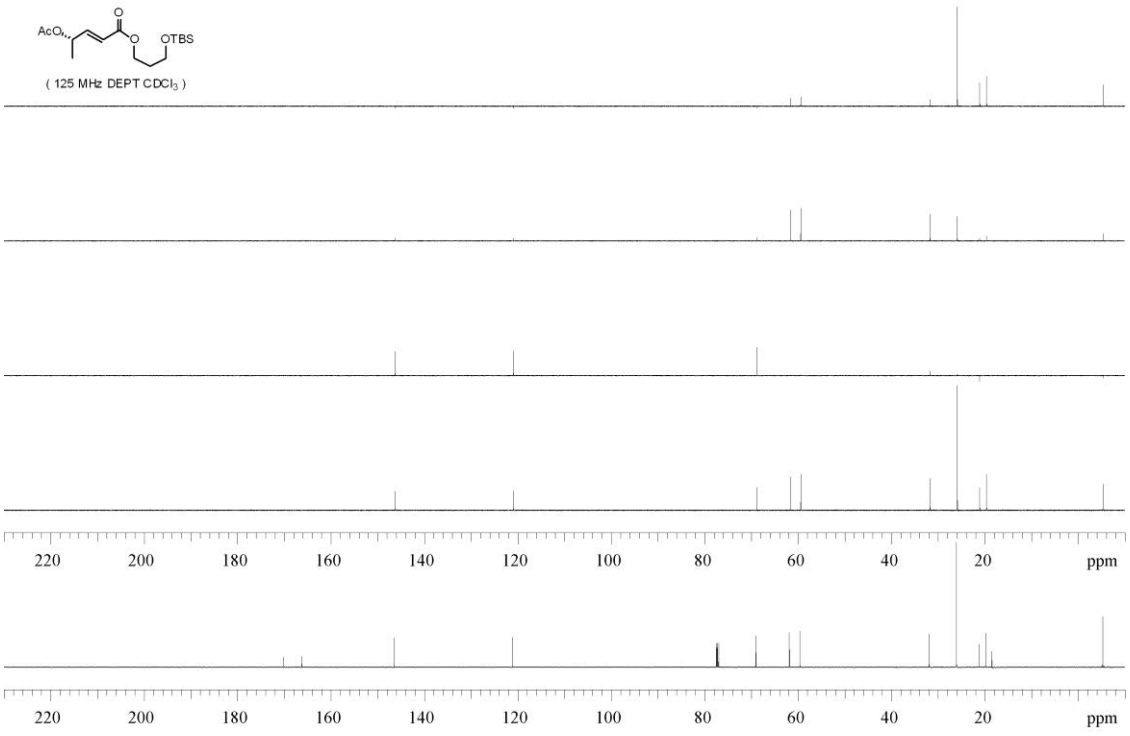

OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.93
1.02
0.99
2.11
2.01
2.97
2.07
9.37
6.10

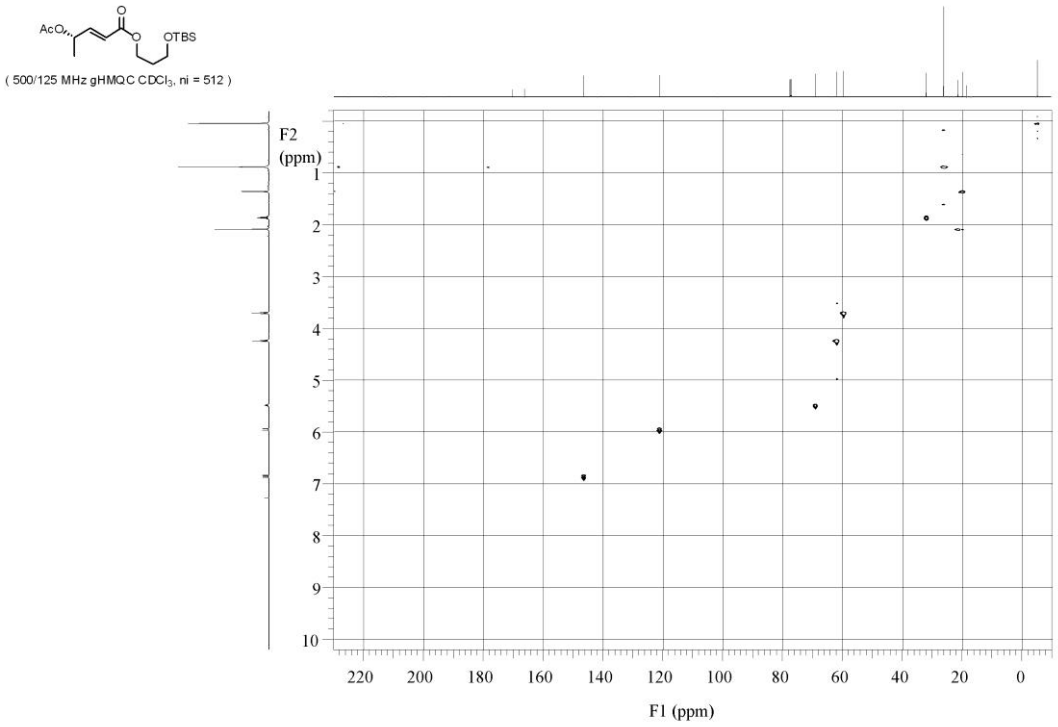

OTBS
166.082
150.155
118.958
77.484
77.230
76.976
61.951
59.611
31.931
26.552
26.118
21.145
18.518
-5.181
220
200
180
160
140
120
100
80
60
40
20
ppm

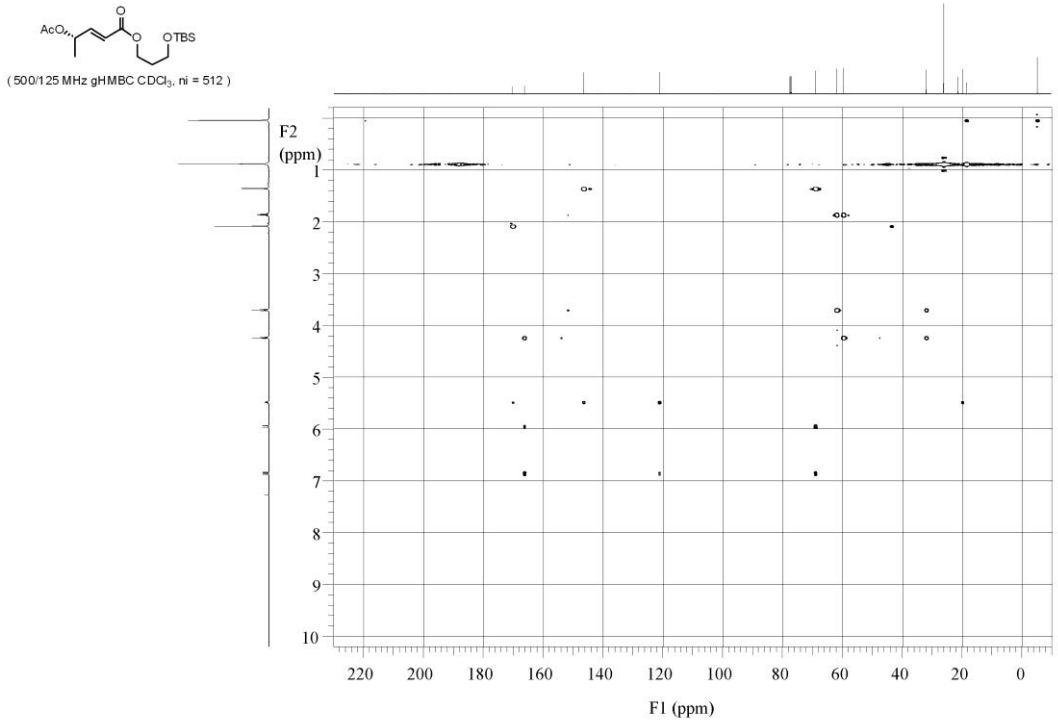

OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

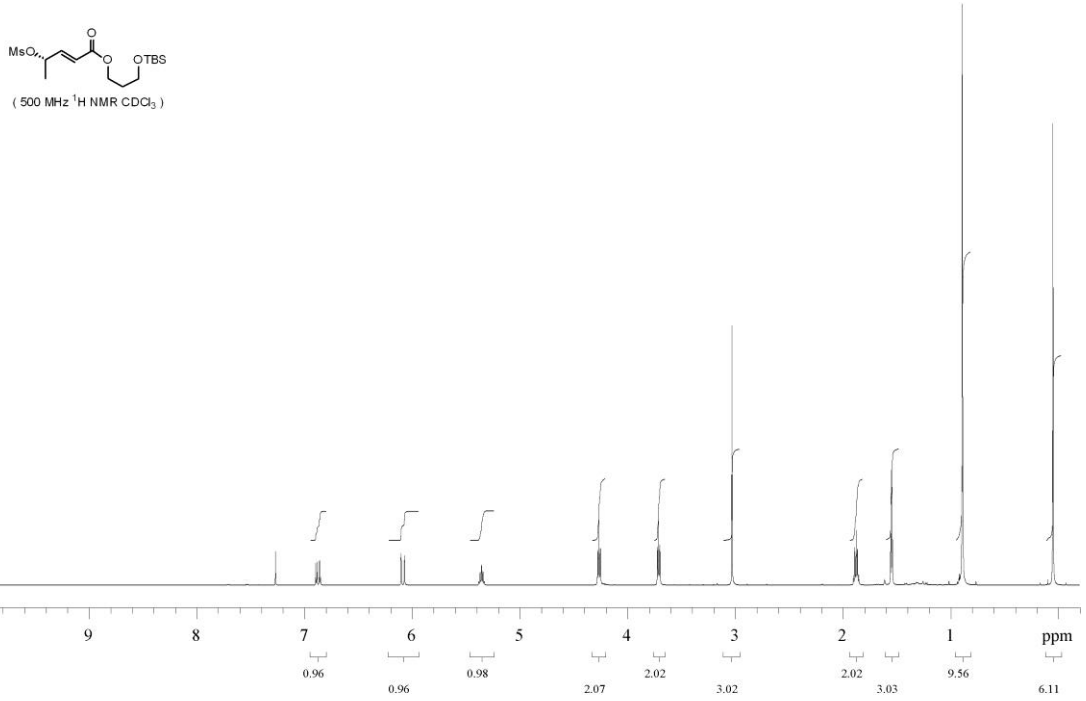

AcO
OTBS
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
0.94
0.94
0.94
2.02
2.00
3.05
2.05
3.16
9.25
5.99

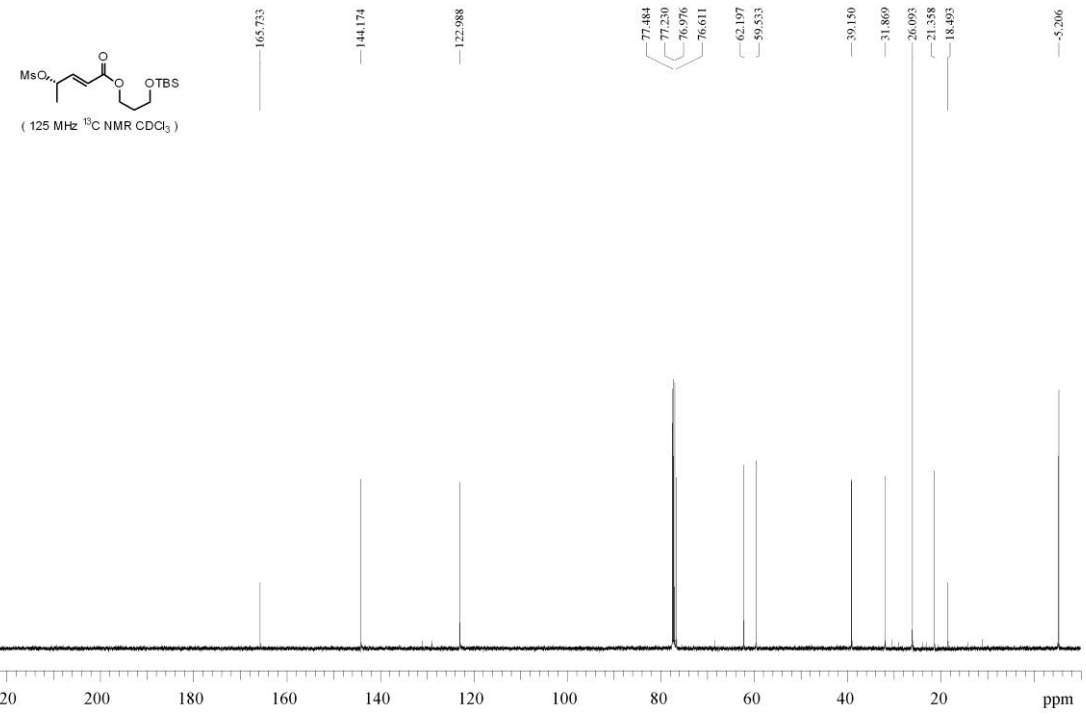

AcO
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
170.152
166.270
146.458
121.148
77.484
77.230
76.976
69.023
61.861
59.606
31.927
26.081
21.276
19.825
18.481
-5.227
220
200
180
160
140
120
100
80
60
40
20
ppm

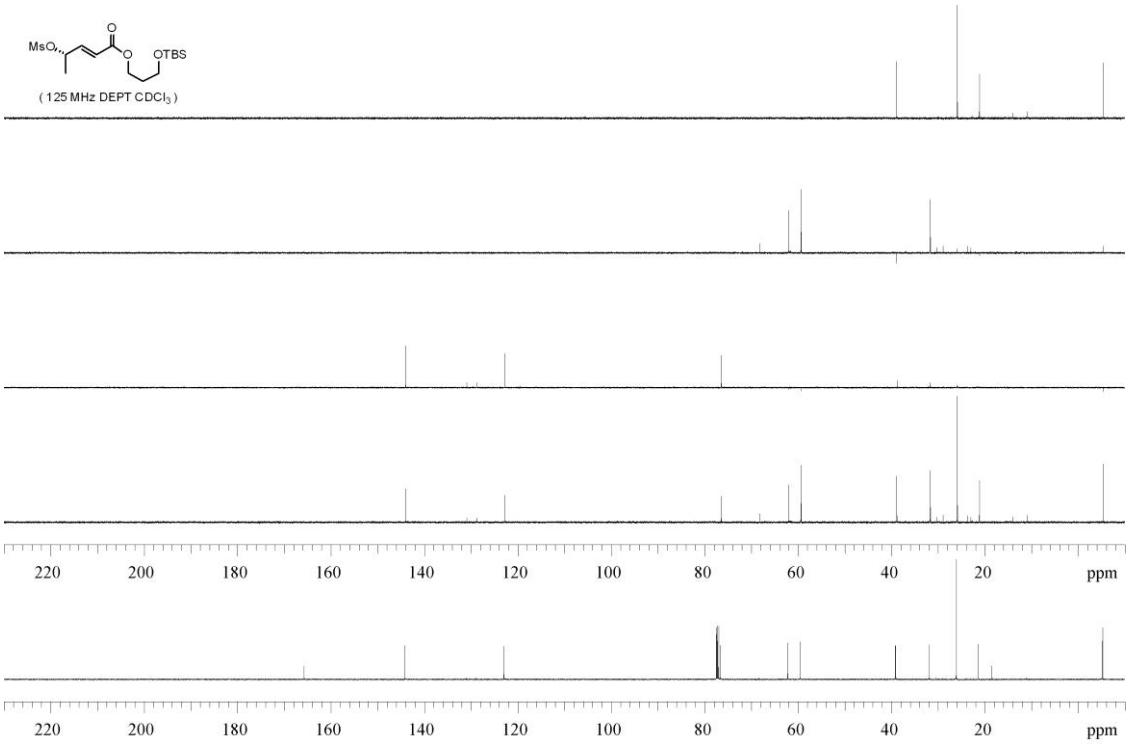

AcO
OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

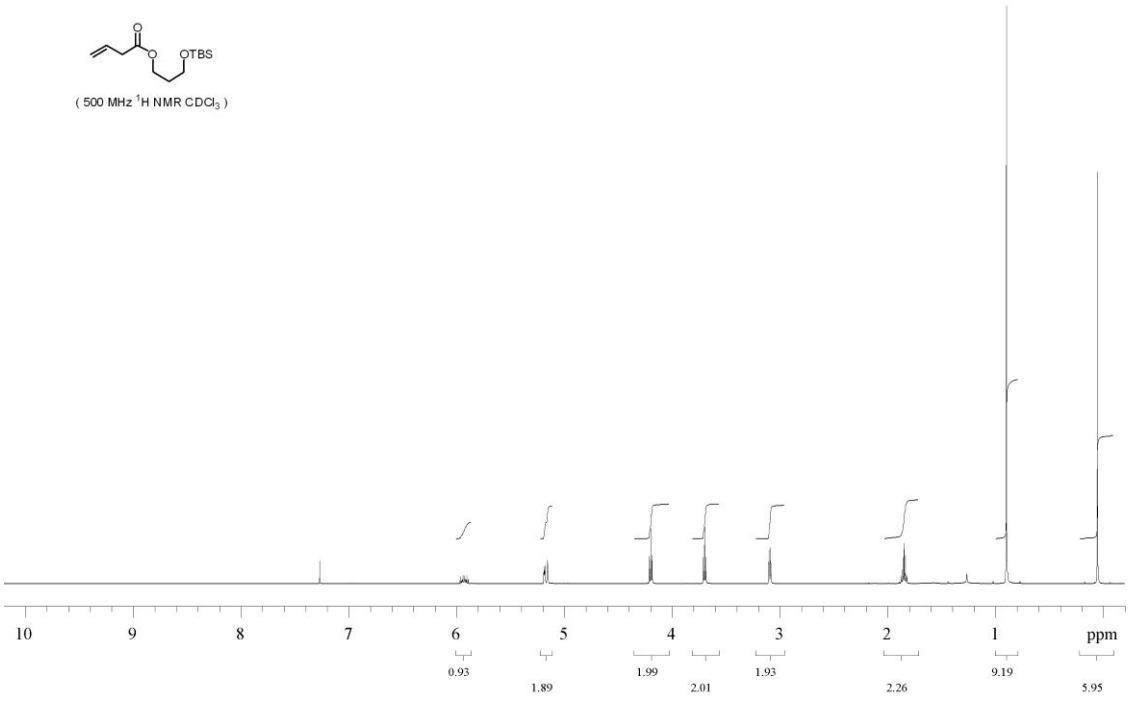

AcO
OTBS
(500/125 MHz gHMQC CDCl3, ni = 512)
F2 (ppm)
F1 (ppm)

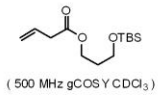

AcO
OTBS
(500/125 MHz gHMBC CDCl3, ni = 512)
F2 (ppm)
F1 (ppm)


MsO
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.96
0.96
0.98
2.07
2.02
3.02
2.02
3.03
9.56
6.11

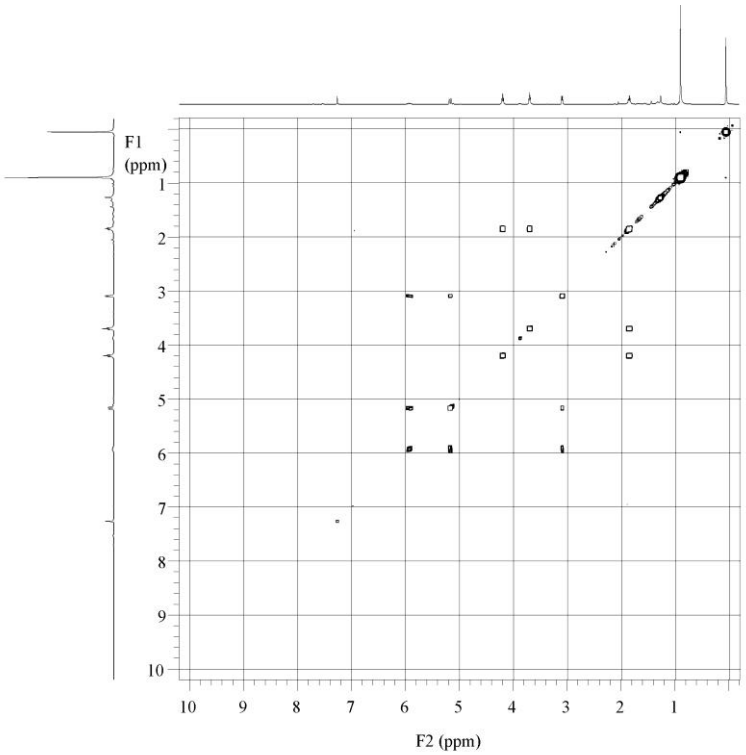

MsO
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
165.733
144.174
122.988
77.484
77.230
76.976
76.611
62.197
59.533
39.150
31.869
26.093
21.358
18.493
-5.206
220
200
180
160
140
120
100
80
60
40
20
ppm

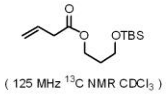

MsO
OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
0.93
1.89
1.99
2.01
1.93
2.26
9.19
5.95

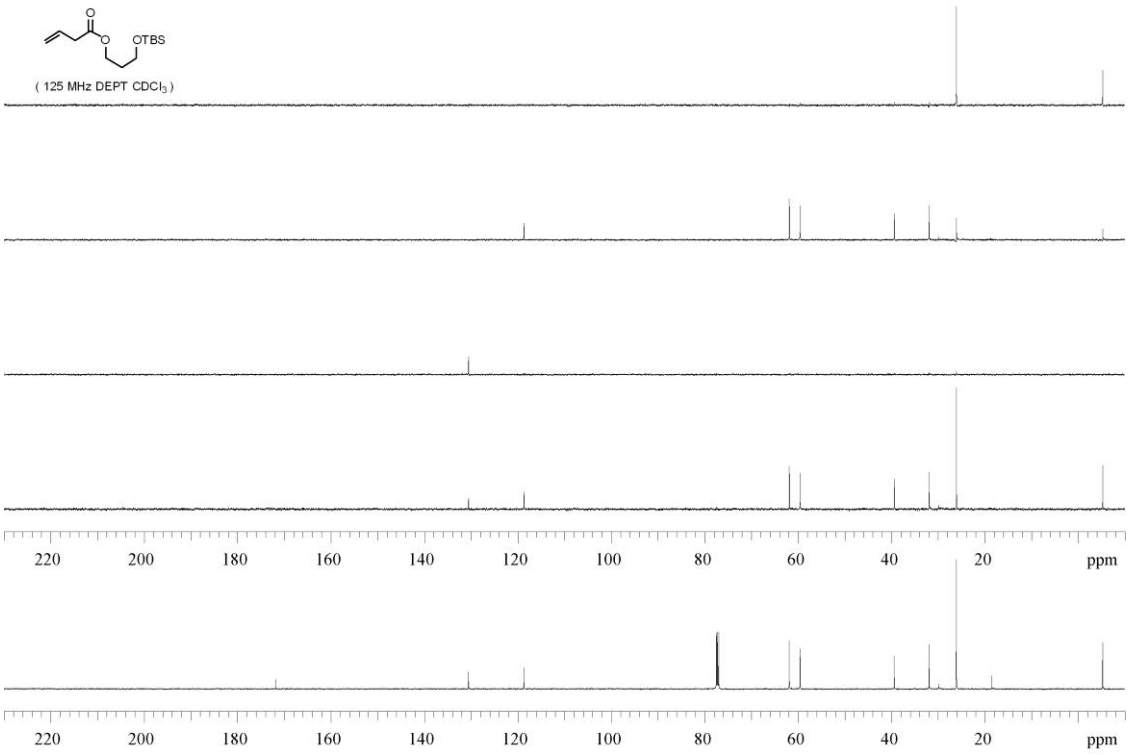


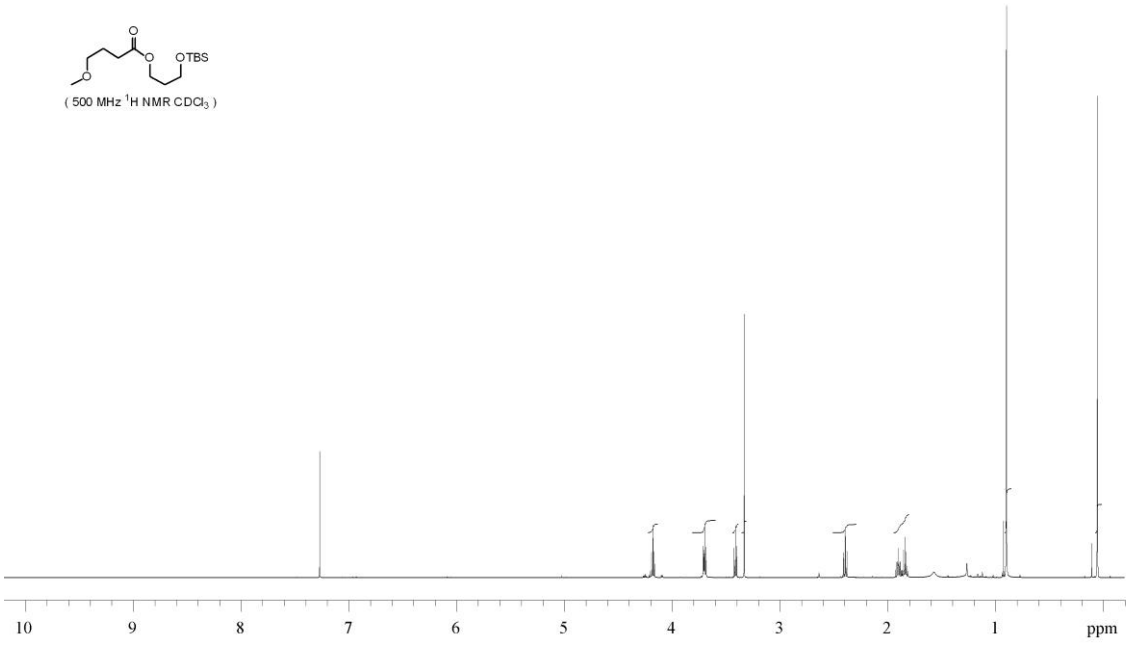
(500 MHz gCOSY $CDCl_3$)

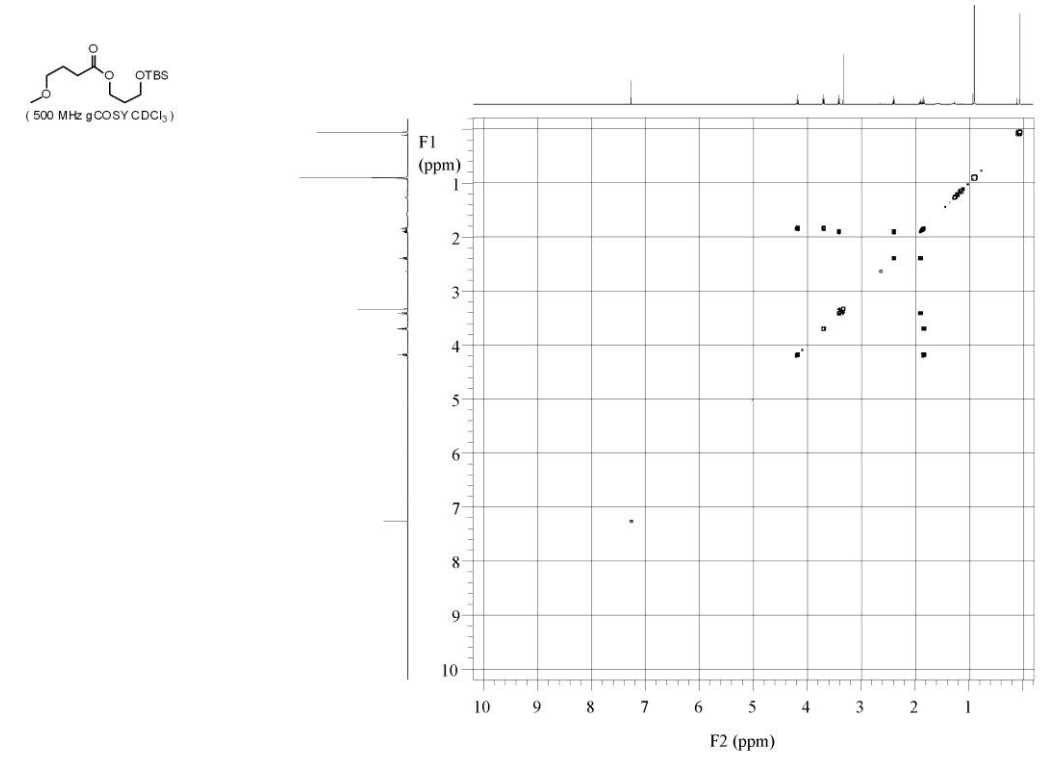


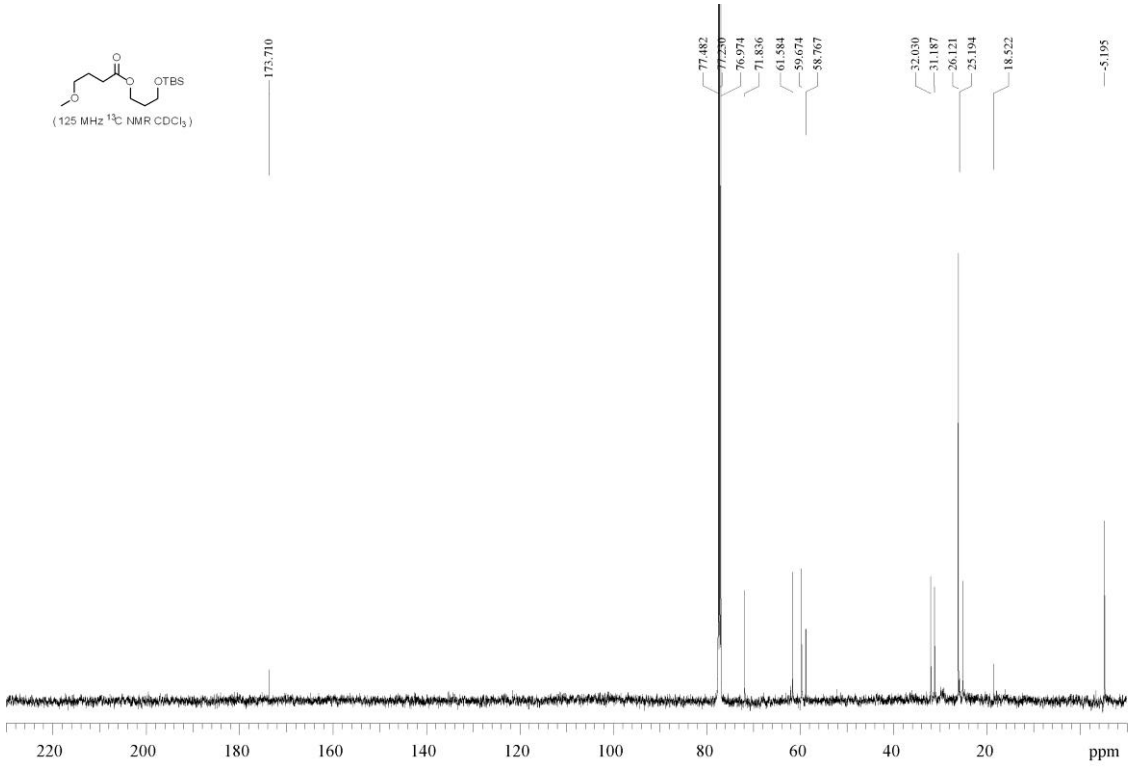


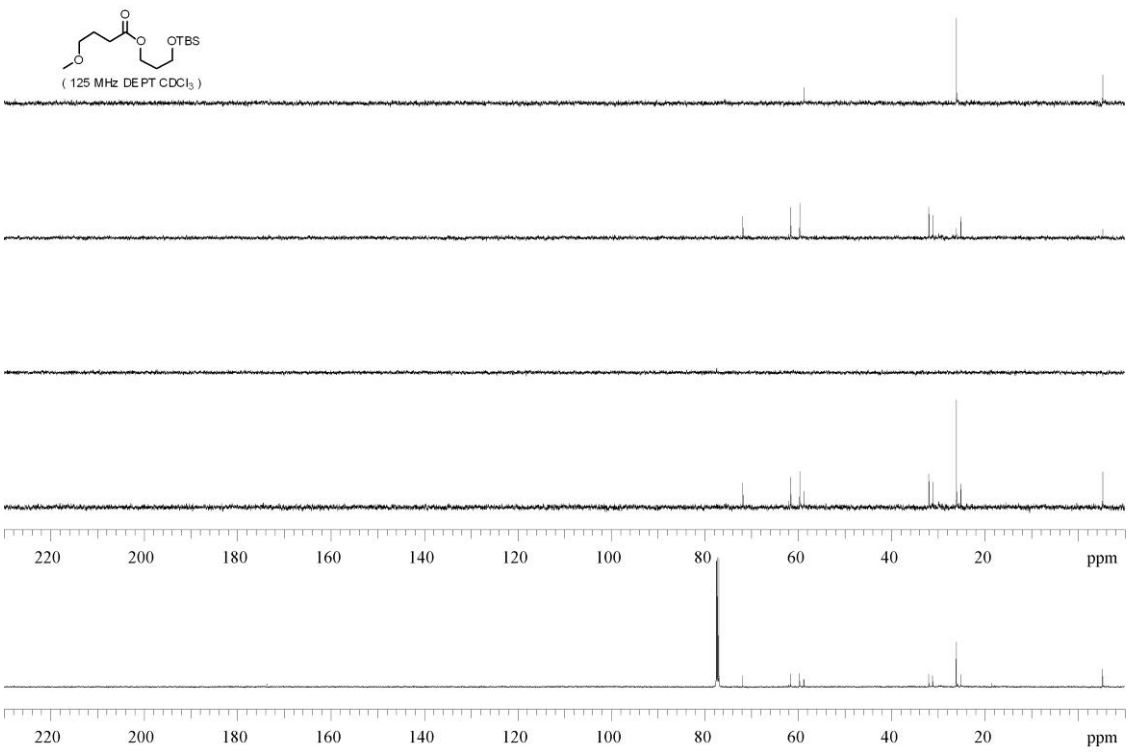
(125 MHz ^{13}C NMR $CDCl_3$)

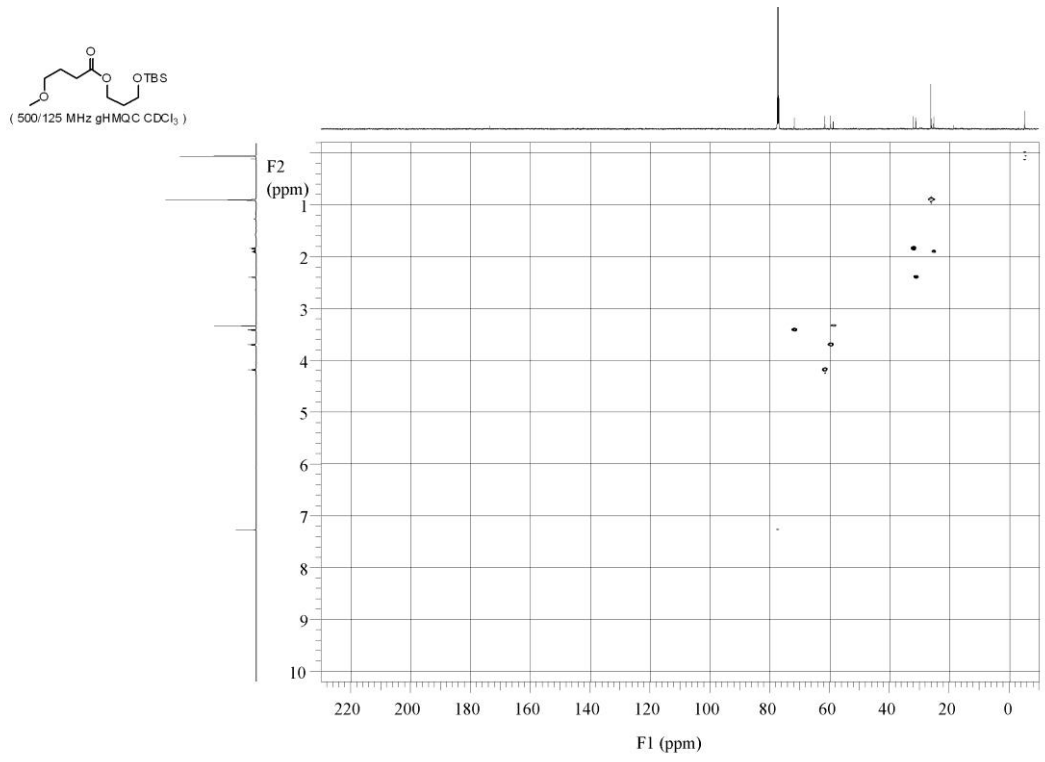

OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

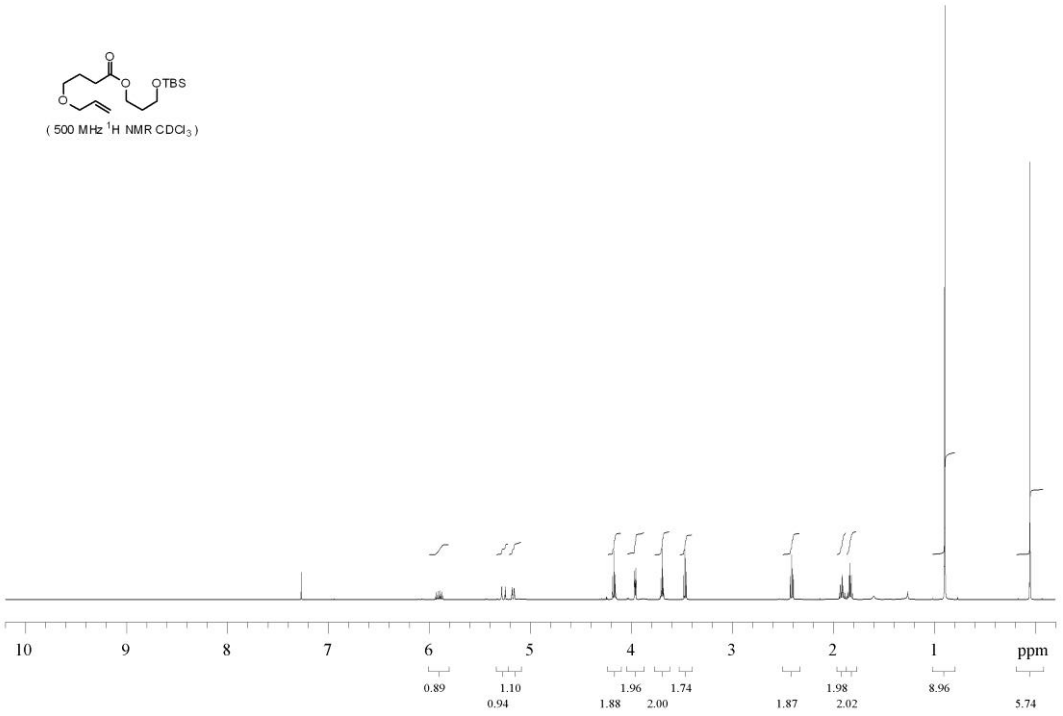

OTBS
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm

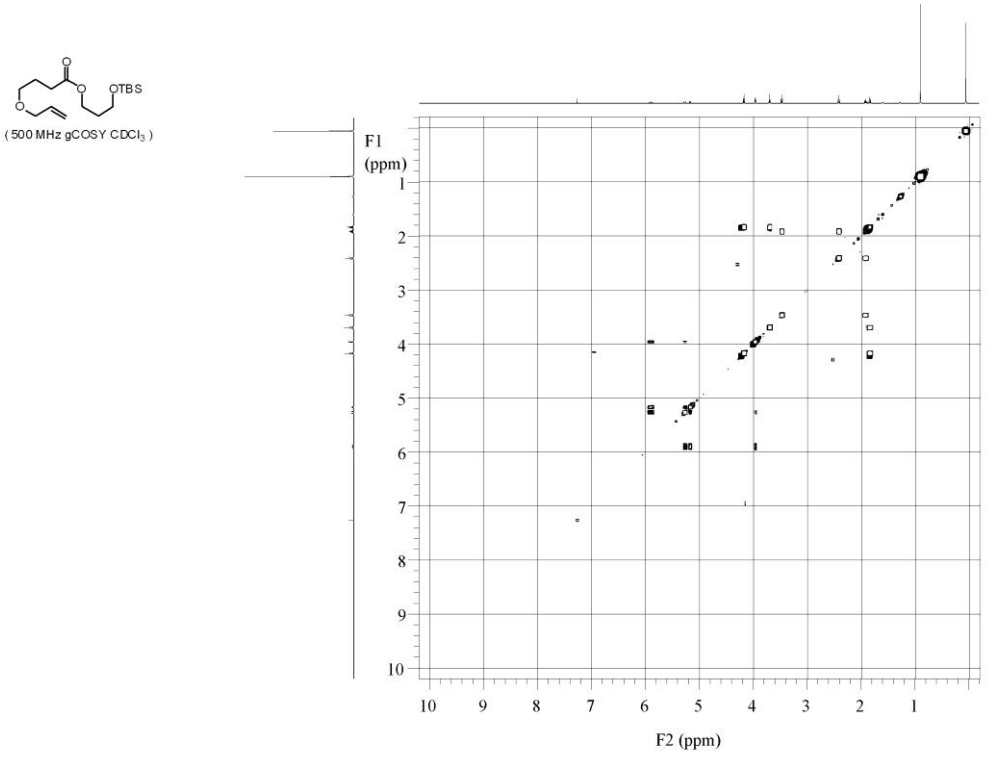

OTBS
(500 MHz gCOSY CDCl3)
F1
(ppm)
F2 (ppm)

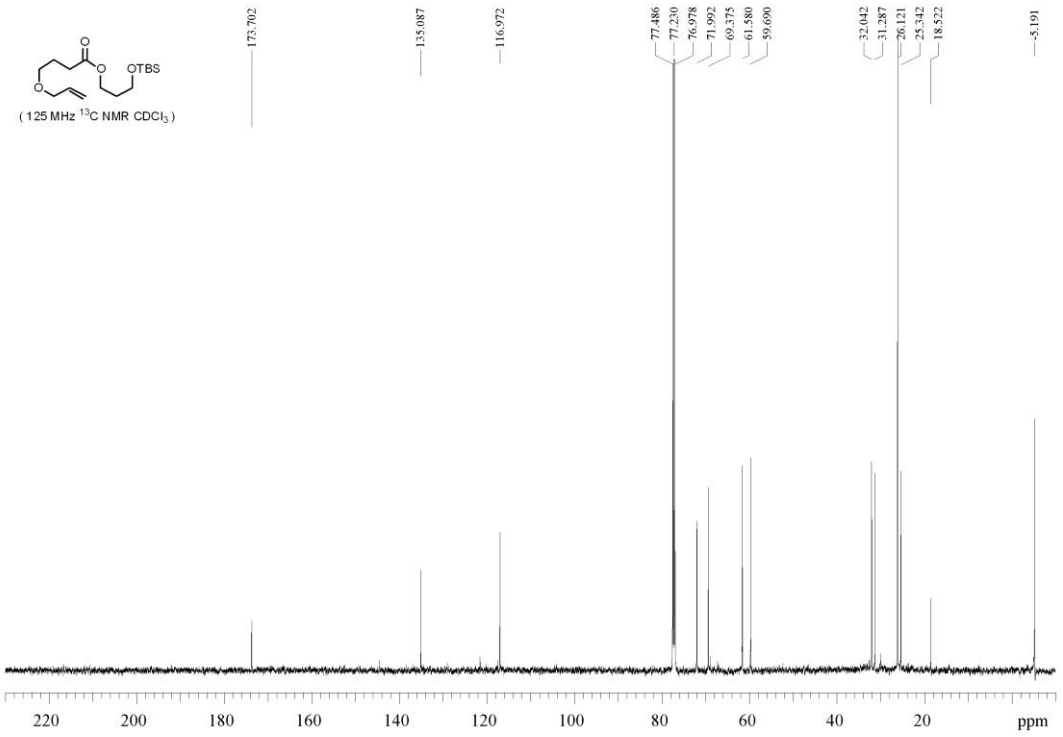

OTBS
(125 MHz 13C NMR CDCl3)
173.710
77.482
77.259
76.974
71.836
61.584
59.674
58.767
32.030
31.187
26.121
25.194
18.522
-5.195
ppm

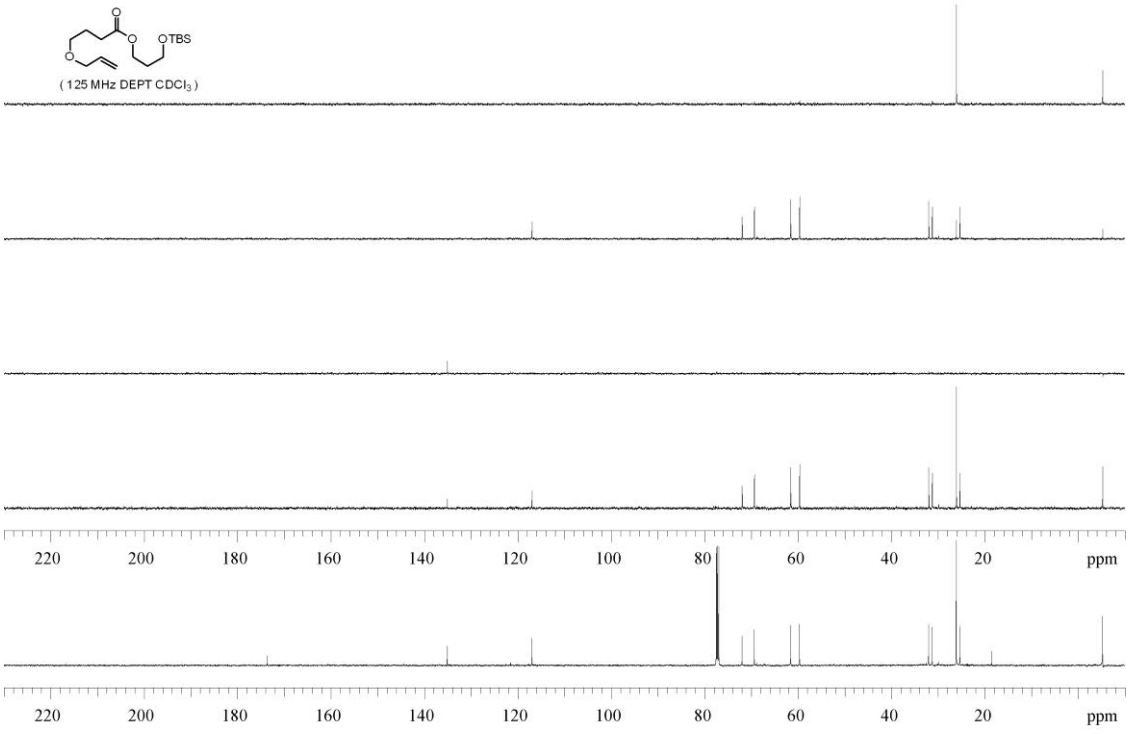

OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

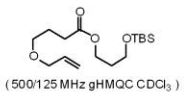

OTBS
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)


OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.89
1.10
0.94
1.96
1.74
1.88
2.00
1.87
1.98
2.02
8.96
5.74

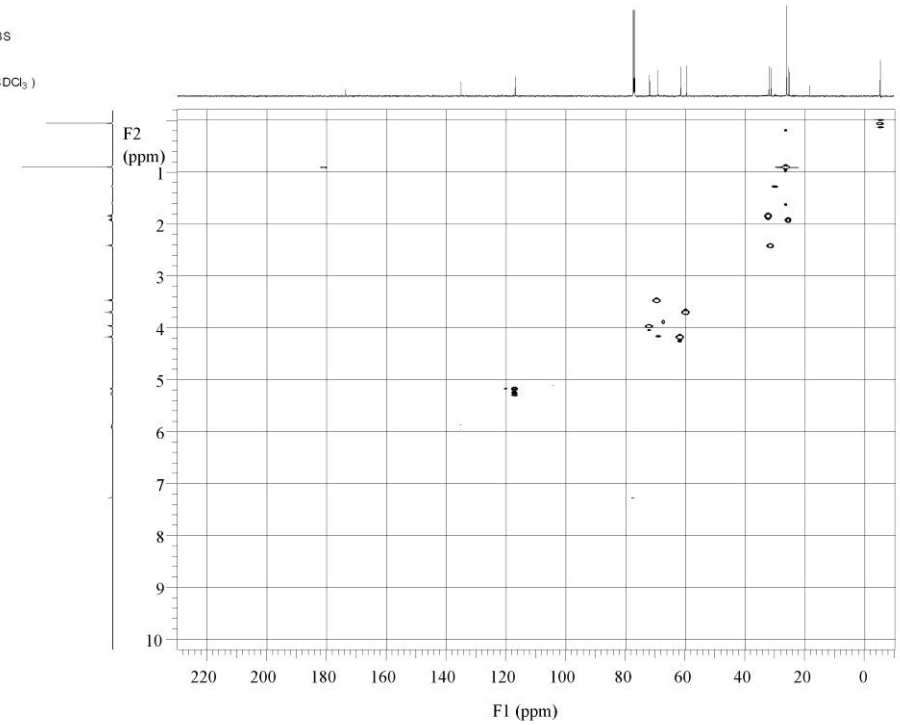

OTBS
(500 MHz gCOSY $CDCl_3$)
F1
(ppm)
1
2
3
4
5
6
7
8
9
10
10
9
8
7
6
5
4
3
2
1
F2 (ppm)

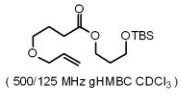

OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
173.702
135.087
116.972
77.486
77.230
76.978
71.992
69.375
61.580
59.690
32.042
31.287
26.121
25.342
18.522
-5.191
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

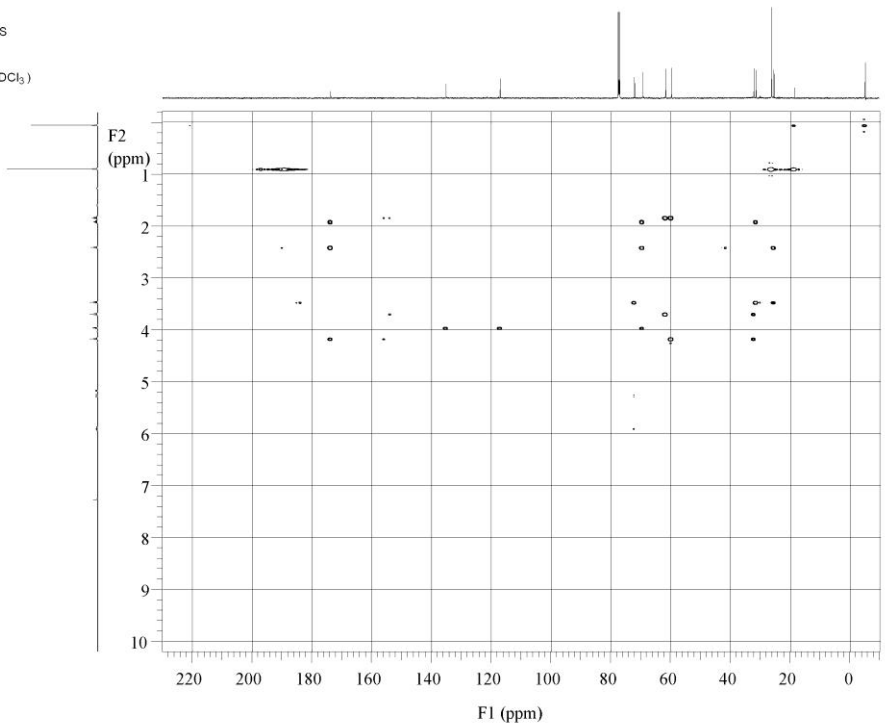


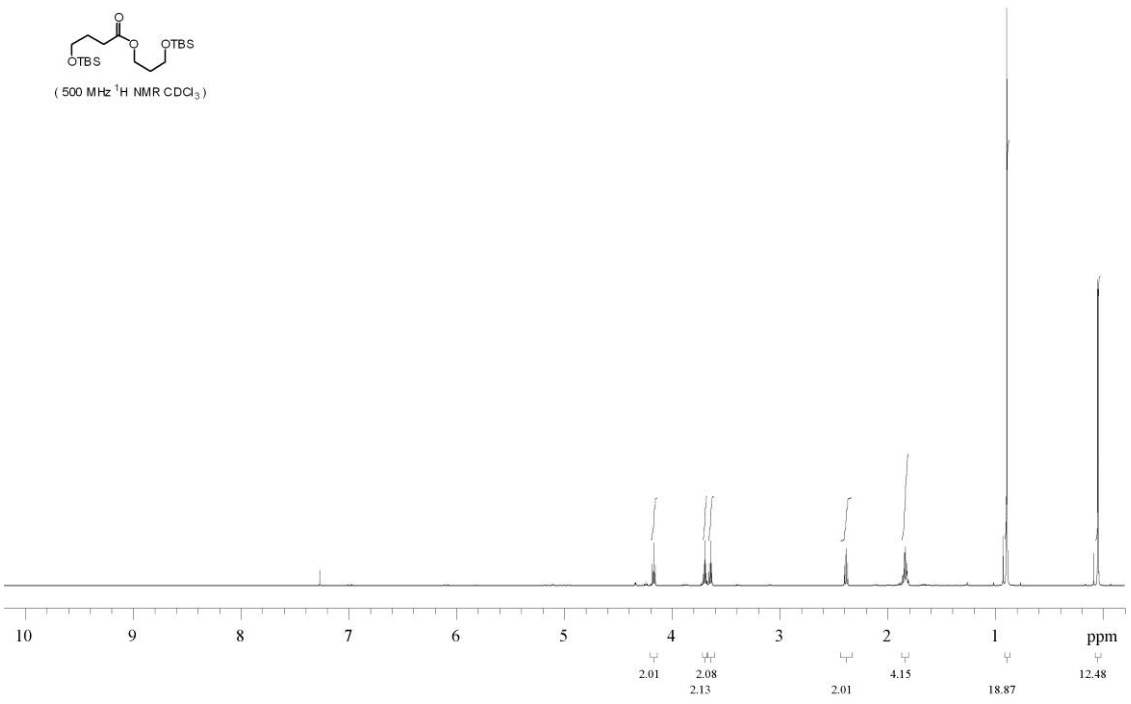
(500/125 MHz gHMQC $CDCl_3$)

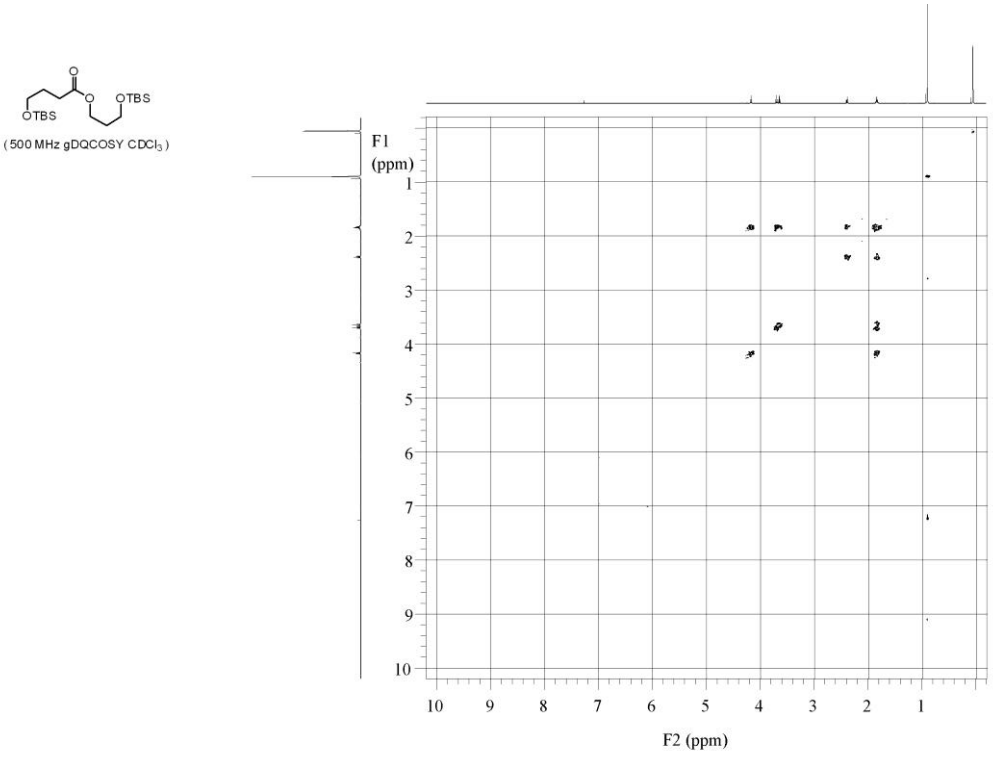


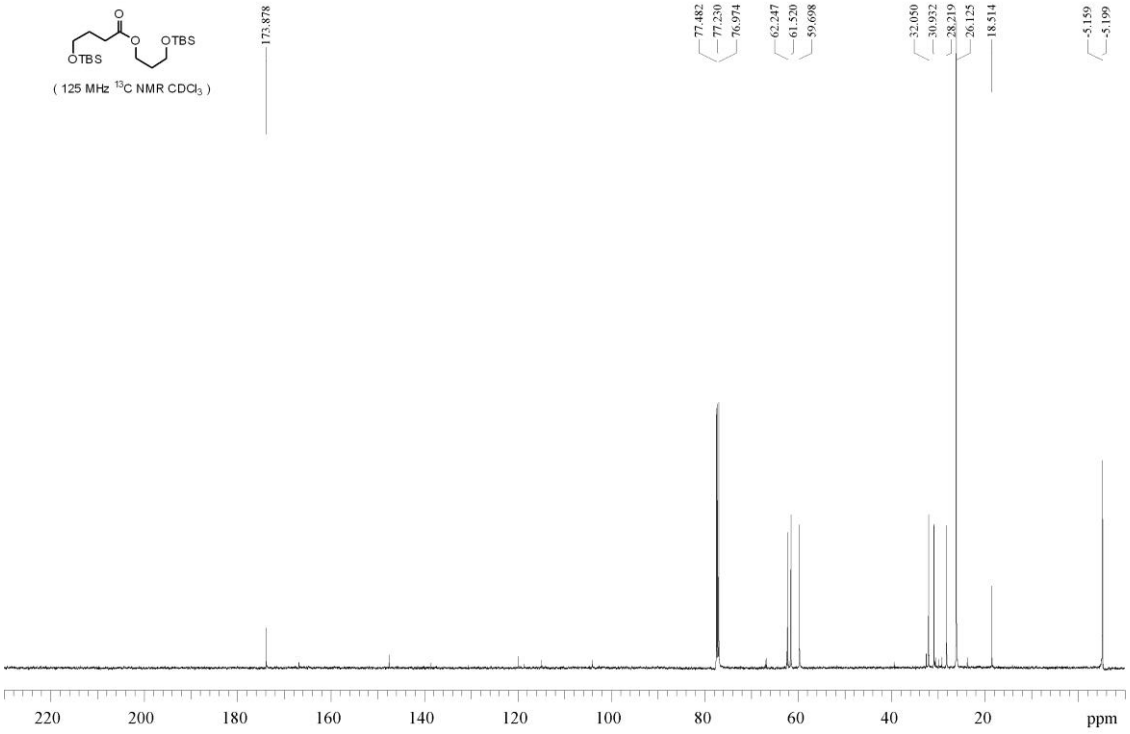


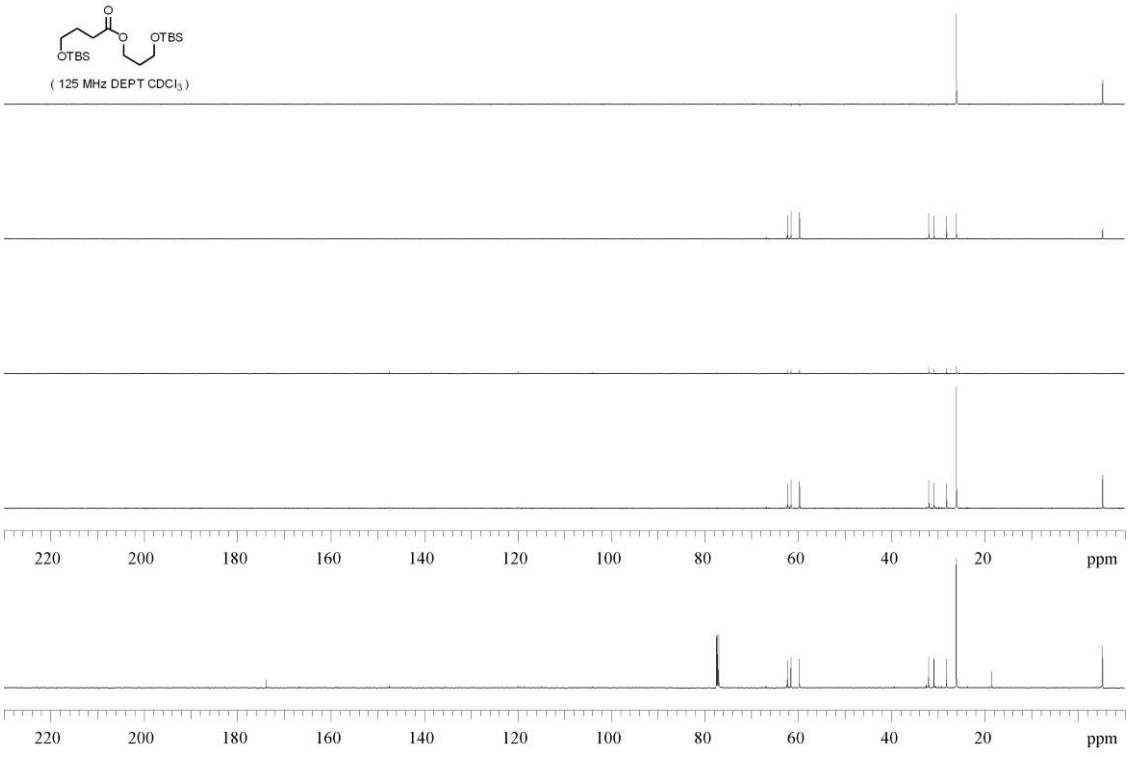
(500/125 MHz gHMBC $CDCl_3$)

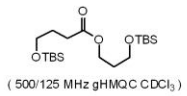



OTBS
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
2.01
2.08
2.13
2.01
4.15
18.87
12.48

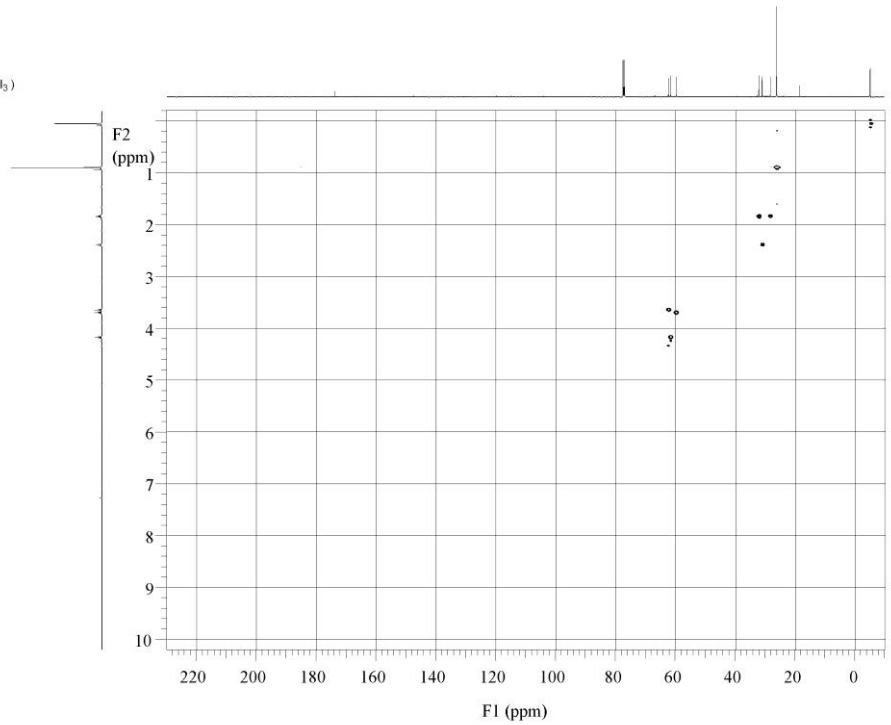

OTBS
OTBS
(500 MHz gDQCOSY $CDCl_3$)
F1
(ppm)
1
2
3
4
5
6
7
8
9
10
10
9
8
7
6
5
4
3
2
1
F2 (ppm)

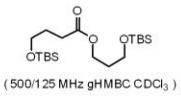

OTBS
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
173.878
77.482
77.230
76.974
62.247
61.520
59.698
32.050
30.932
28.219
26.125
18.514
-5.159
-5.199
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

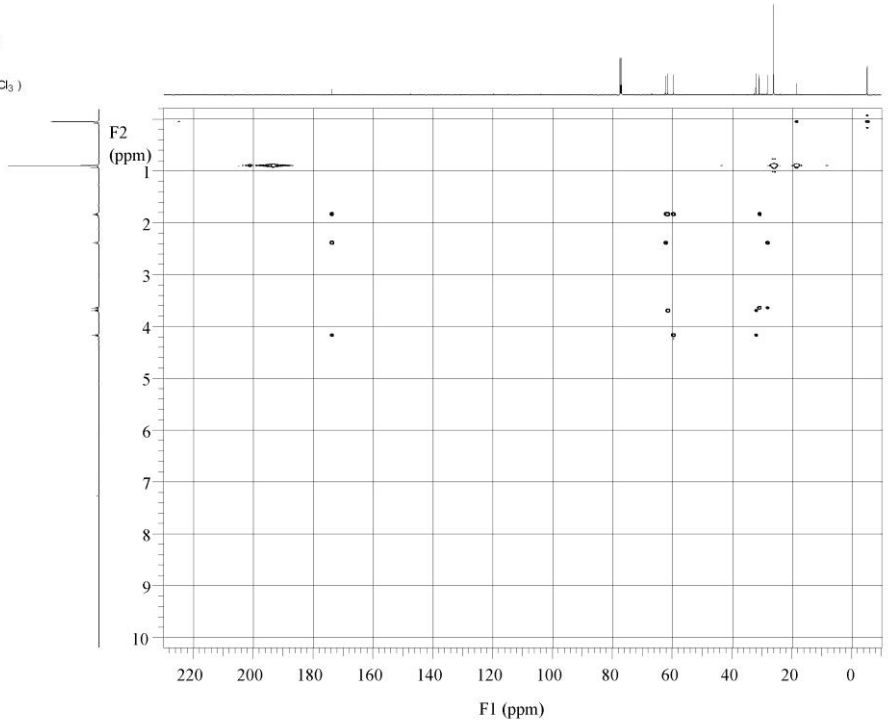


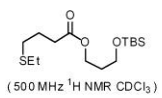
(500/125 MHz gHMQC $CDCl_3$)



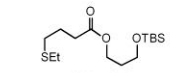


(500/125 MHz gHMBC $CDCl_3$)

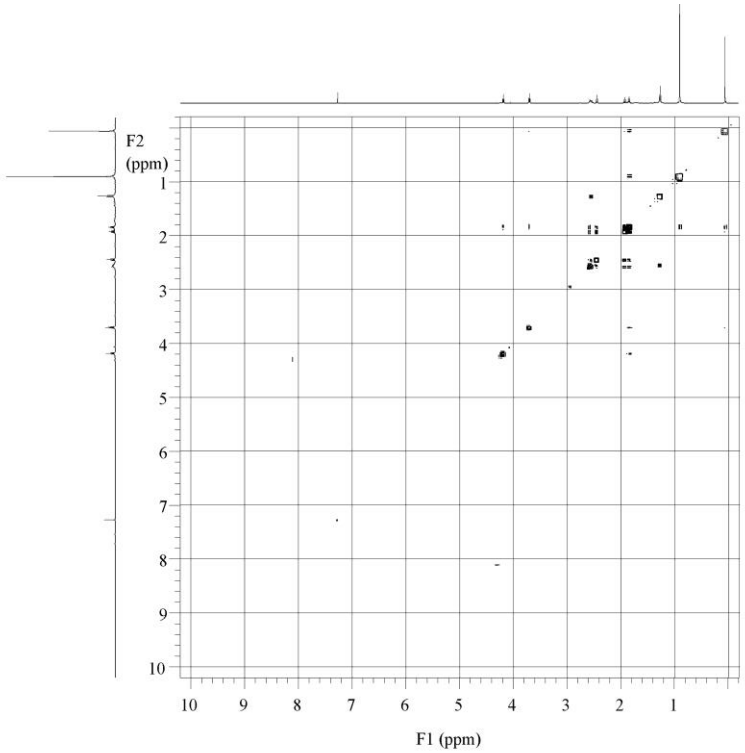


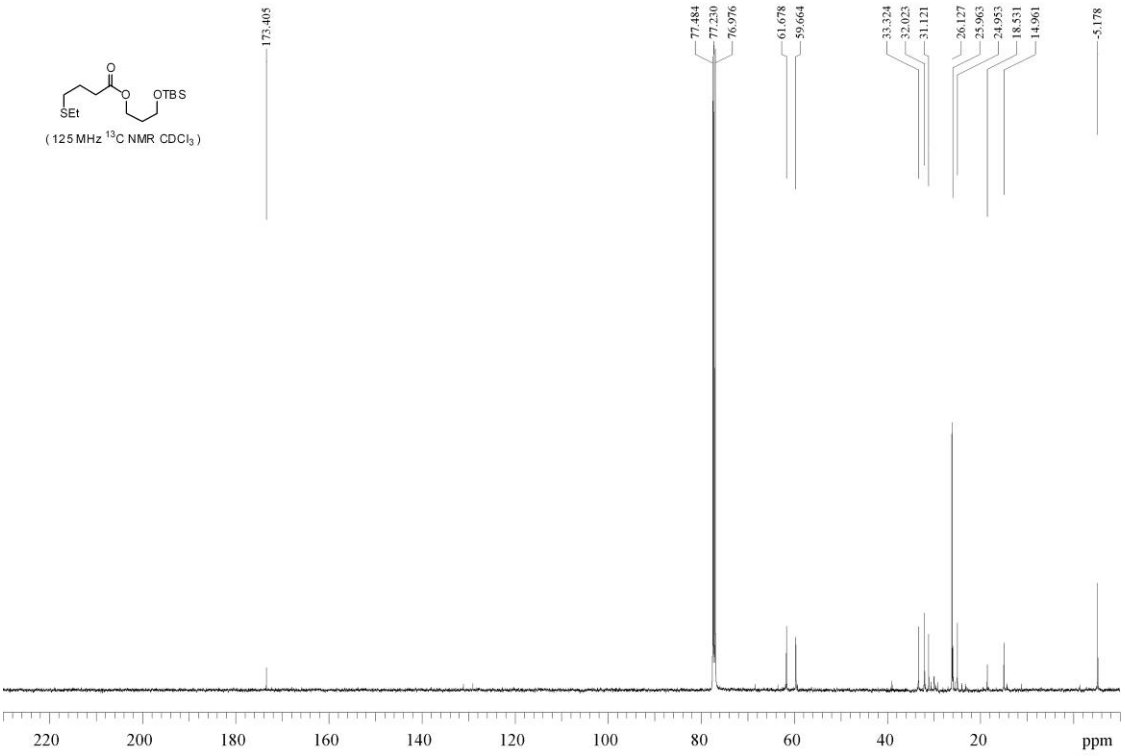


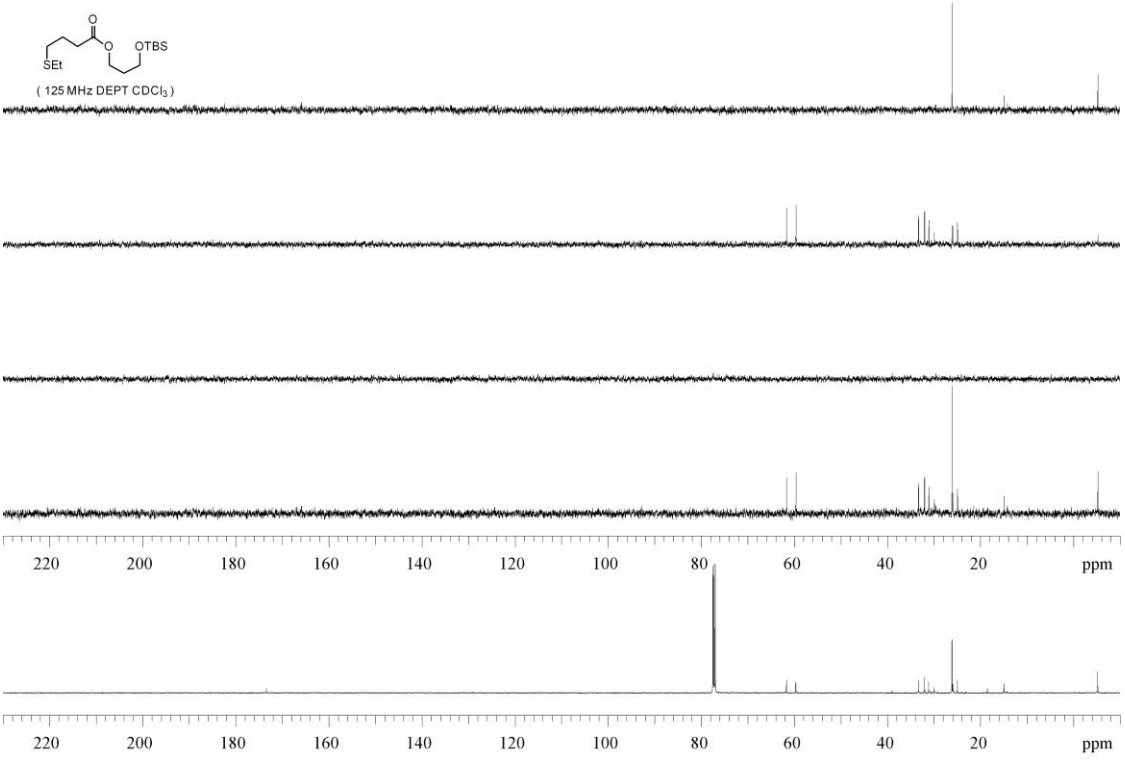
(500 MHz ^{1}H NMR $CDCl_3$)

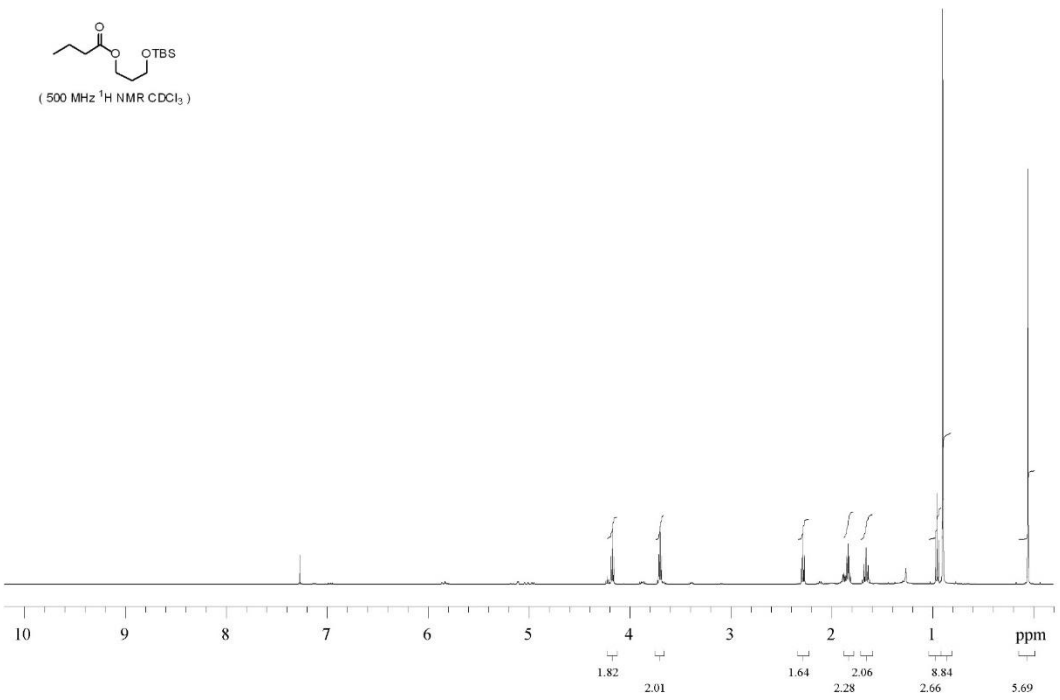


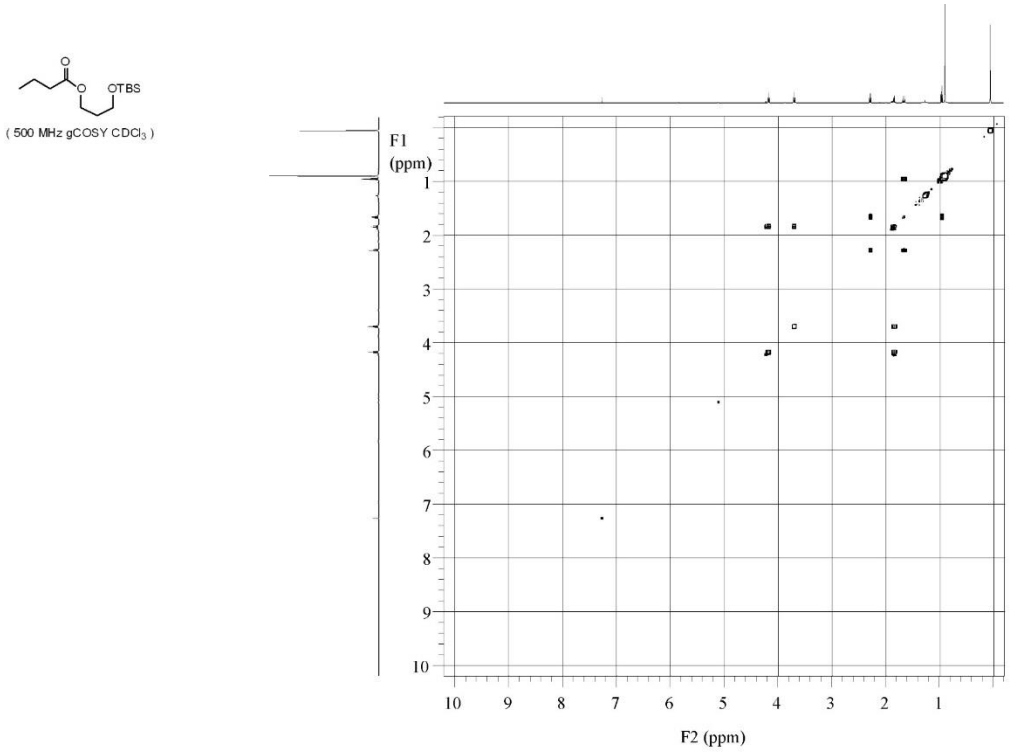
(500 MHz gCOSY $CDCl_3$, ni = 512)

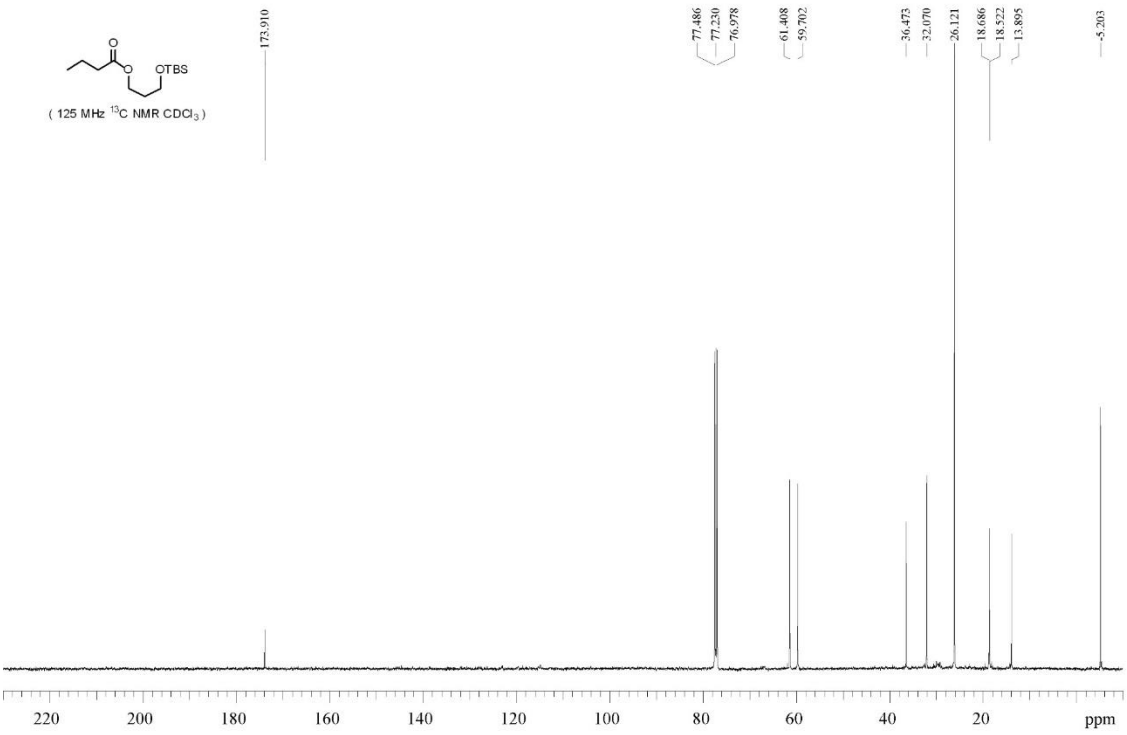


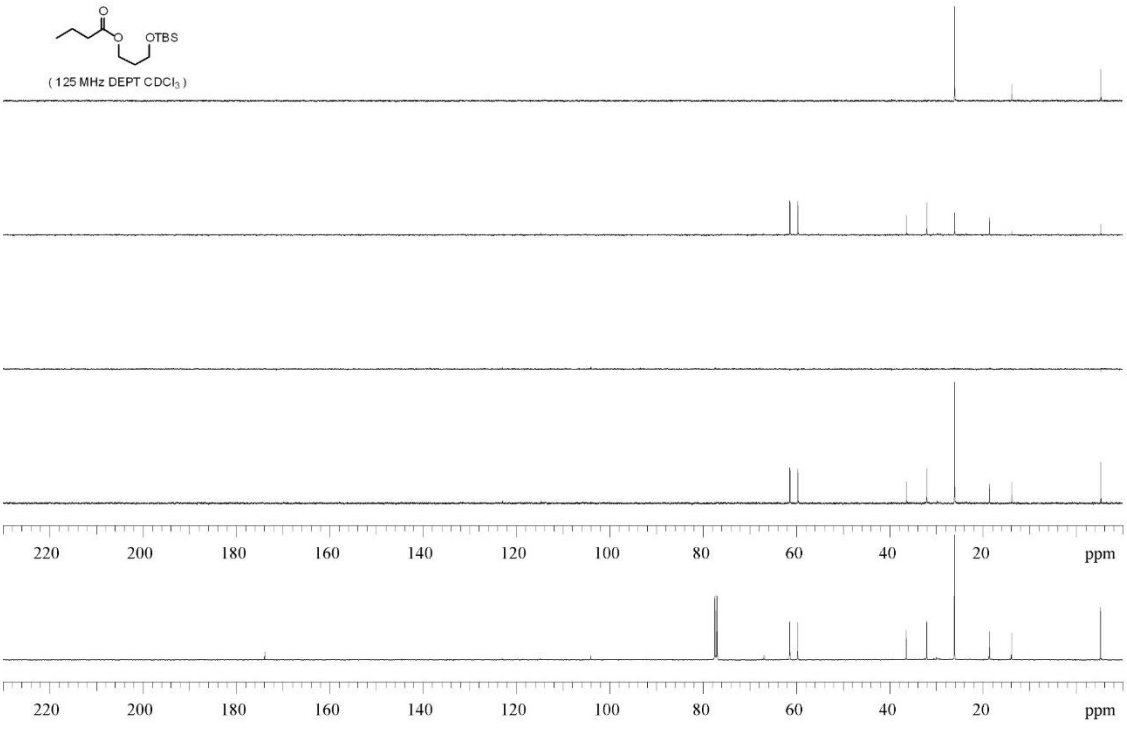

173.405
77.484
77.230
76.976
61.678
59.664
33.324
32.023
31.121
26.127
25.963
24.953
18.531
14.961
-5.178
SEt
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

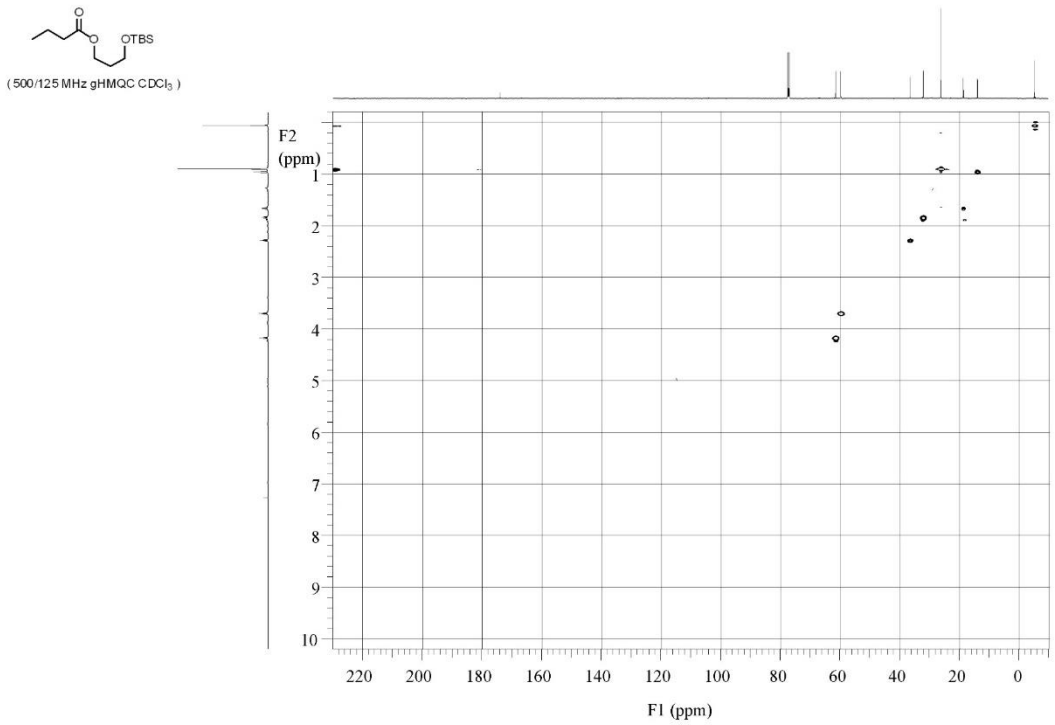

SEt
OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

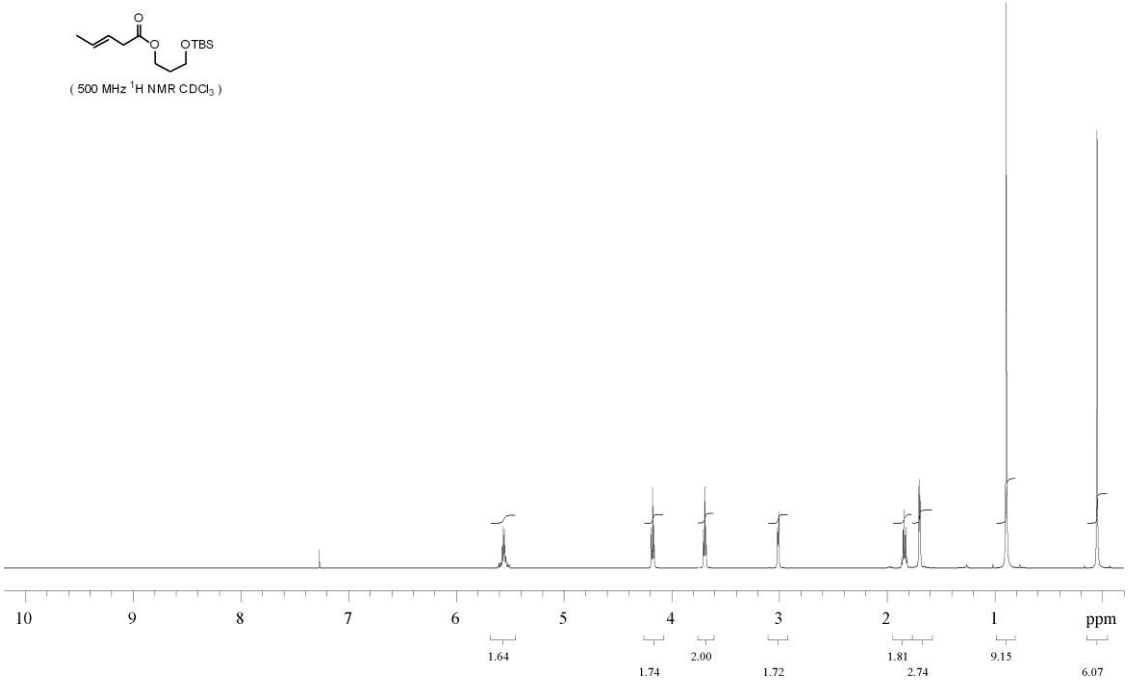

OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
1.82
2.01
1.64
2.06
2.28
8.84
2.66
5.69

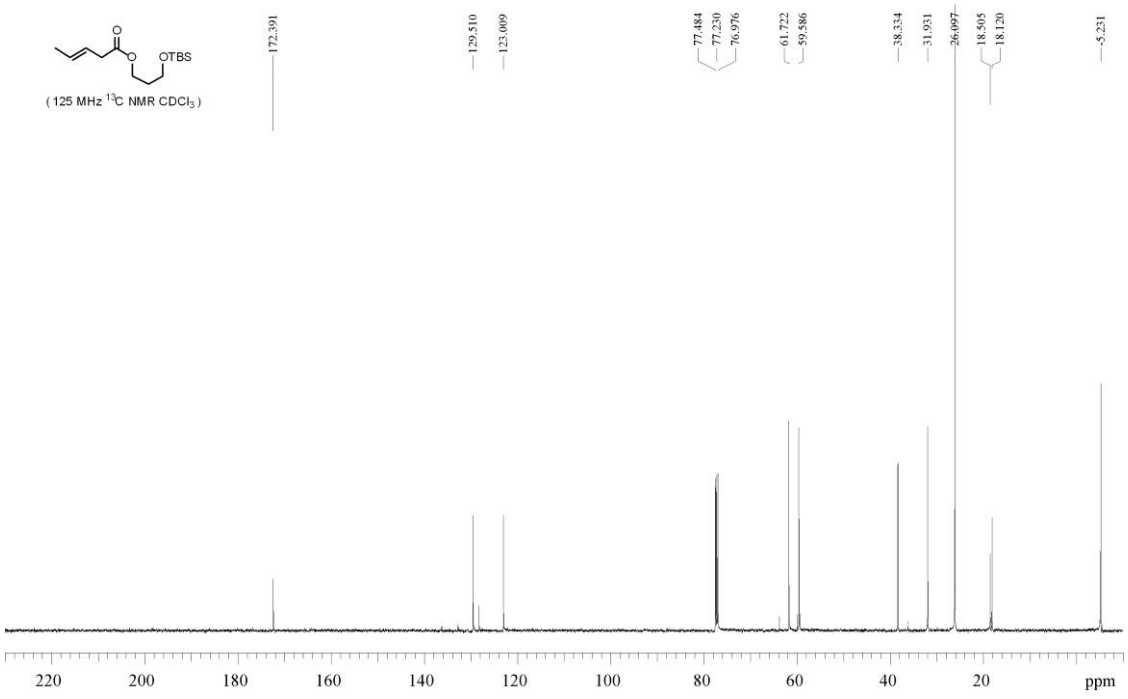

OTBS
(500 MHz gCOSY $CDCl_3$)
F1
(ppm)
1
2
3
4
5
6
7
8
9
10
10
9
8
7
6
5
4
3
2
1
F2 (ppm)

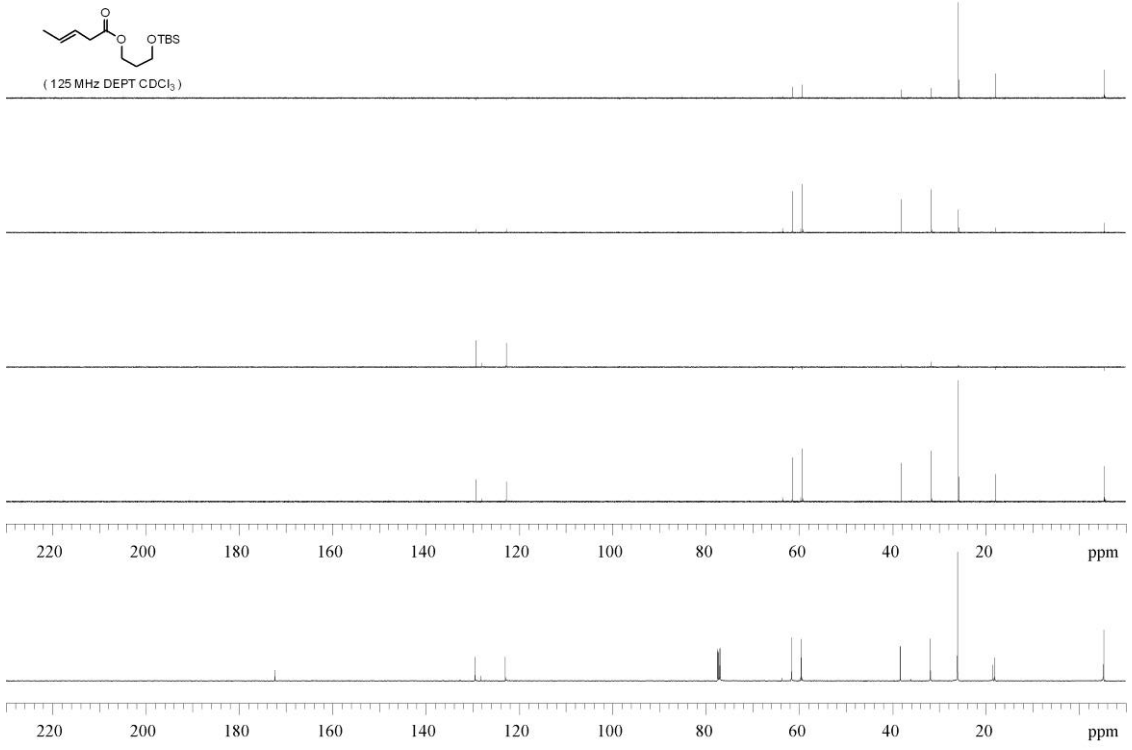

OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
173.910
77.486
77.230
76.978
61.408
59.702
36.473
32.070
26.121
18.686
18.522
13.895
-5.203
220
200
180
160
140
120
100
80
60
40
20
ppm

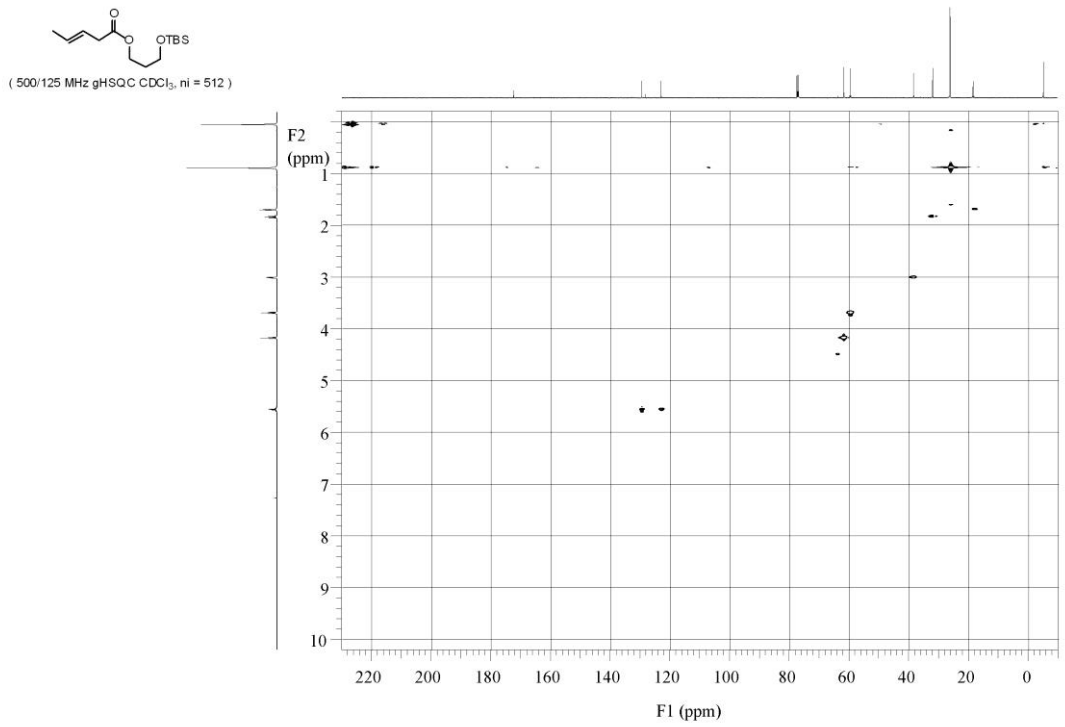

OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

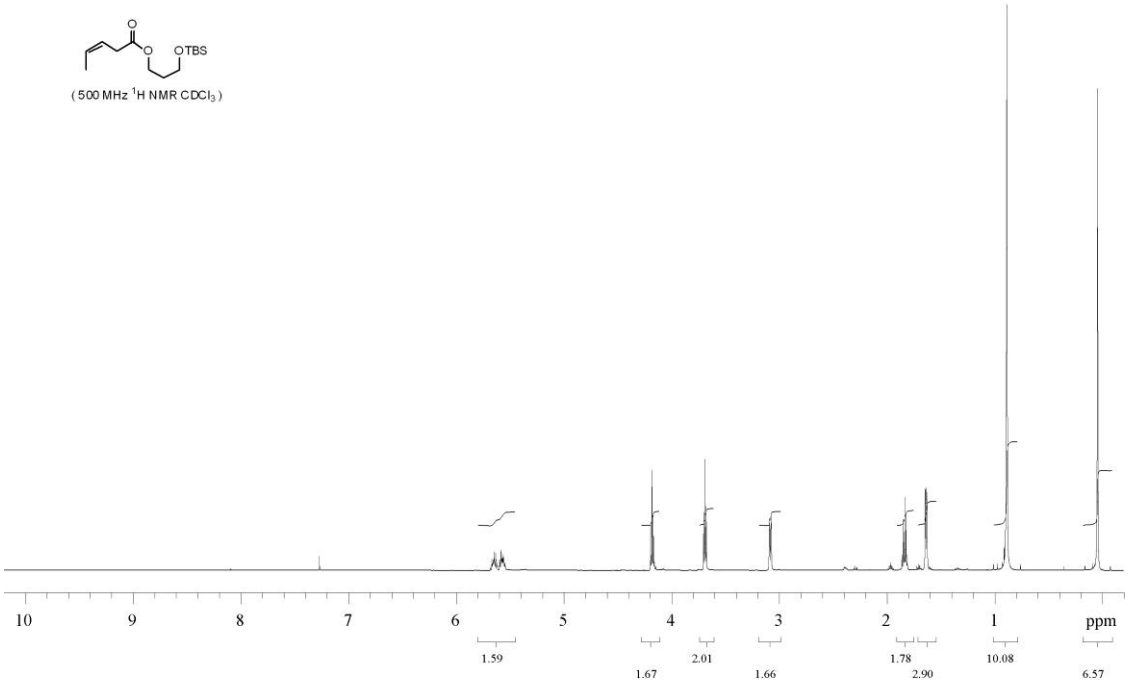

OTBS
(500/125 MHz gHMQC $CDCl_3$)
F2
(ppm)
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

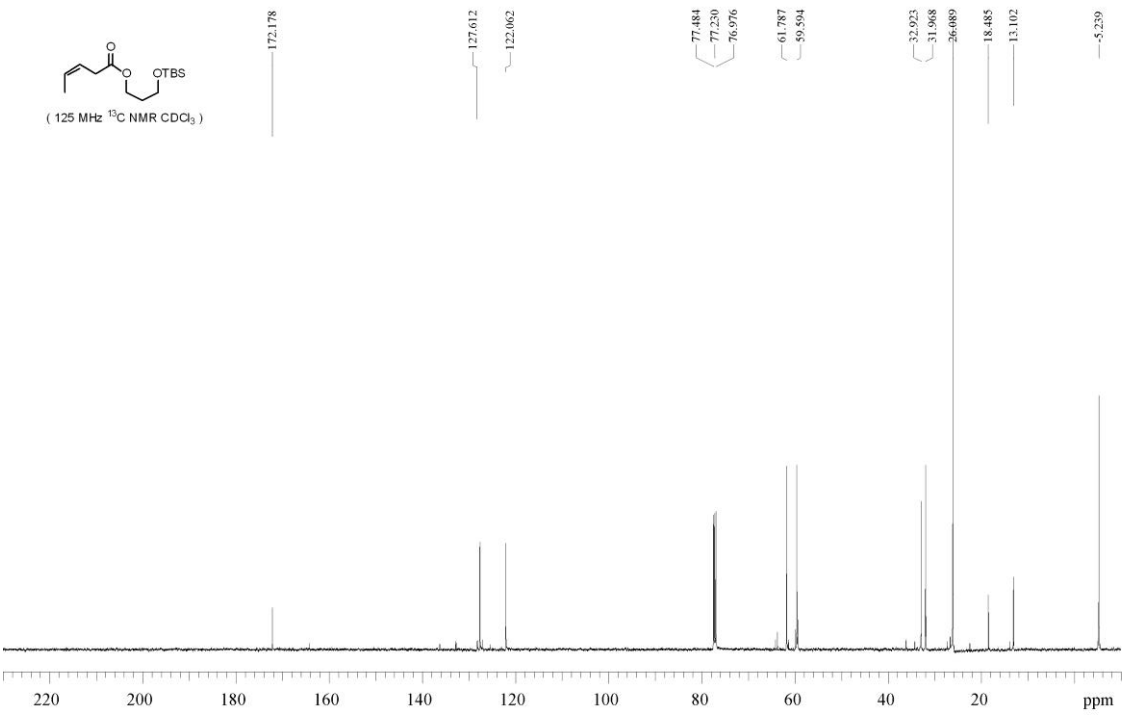

OTBS
(500 MHz ^1H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
1.64
1.74
2.00
1.72
1.81
2.74
9.15
6.07

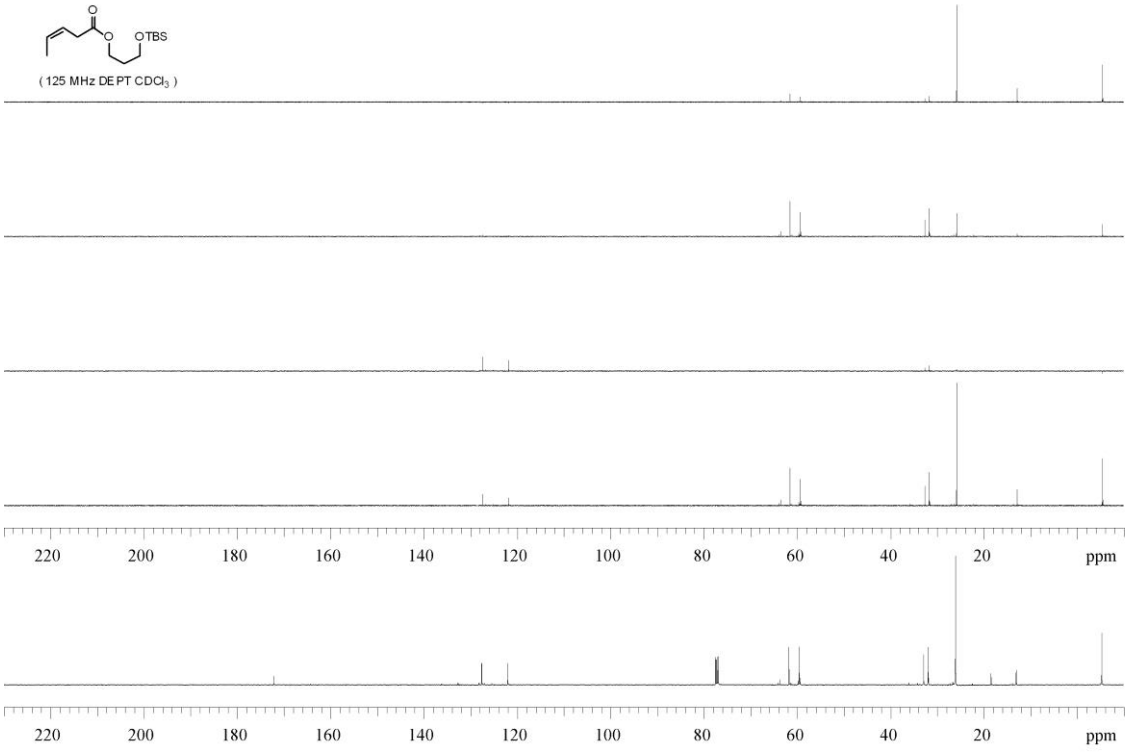

OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
172.391
129.510
123.009
77.484
77.230
76.976
61.722
59.586
38.334
31.931
26.097
18.505
18.120
-5.231
220
200
180
160
140
120
100
80
60
40
20
ppm

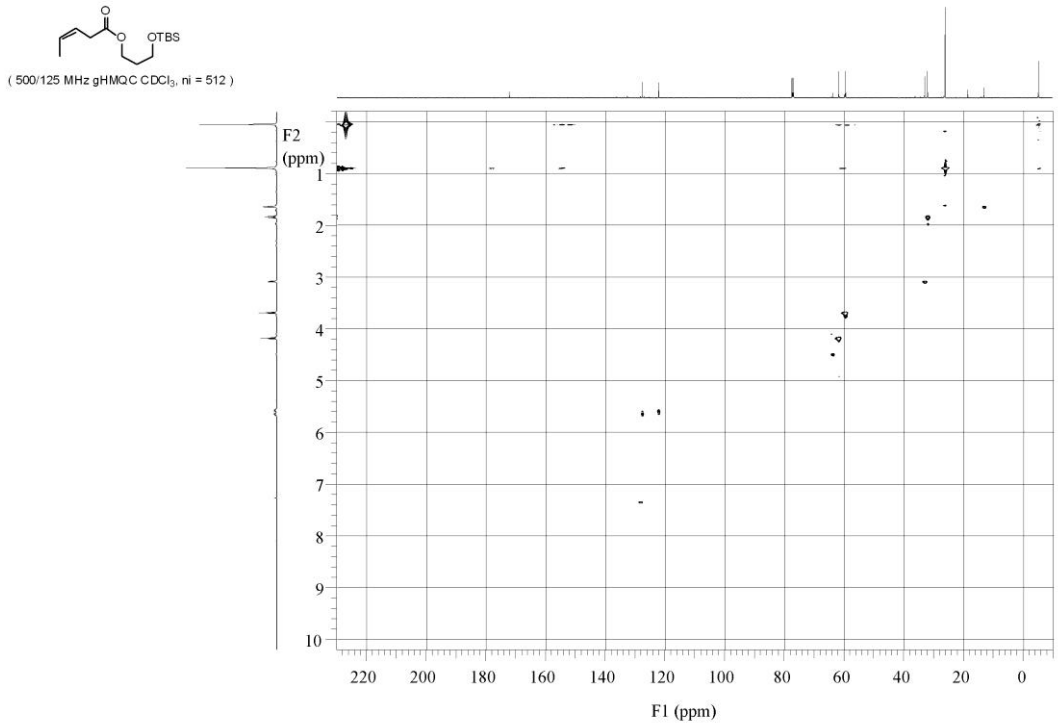

OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

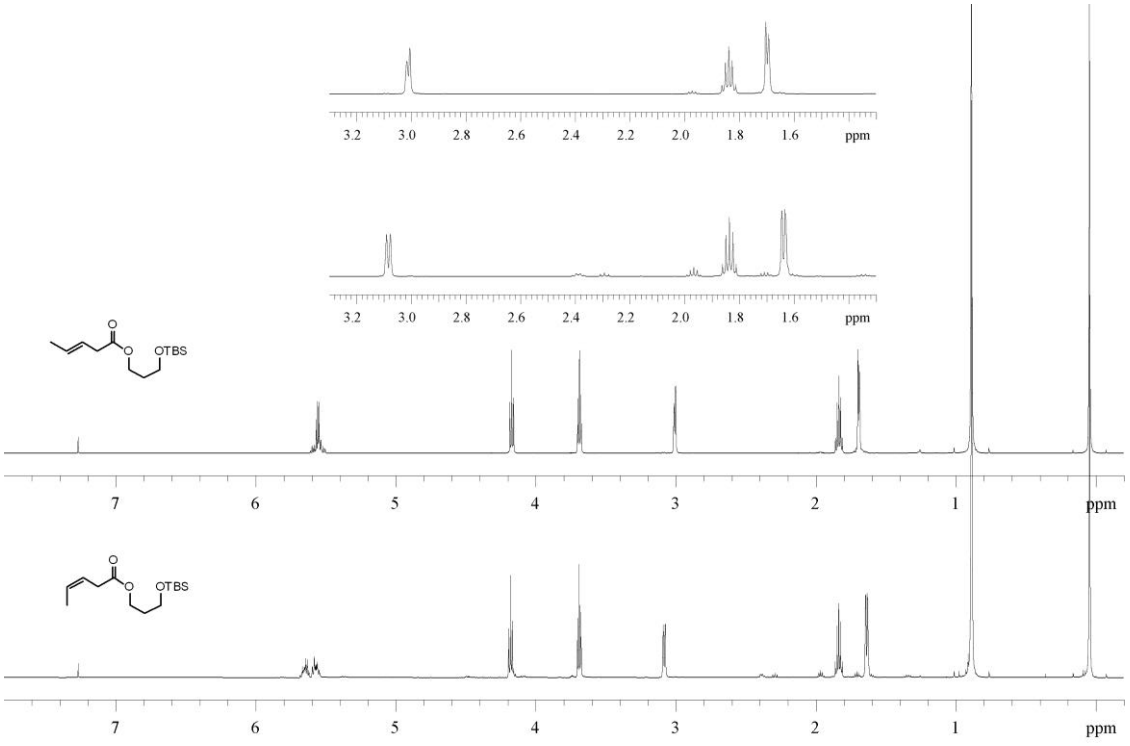

OTBS
(500/125 MHz gHSQC CDCl3, ni = 512)
F2
(ppm)
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

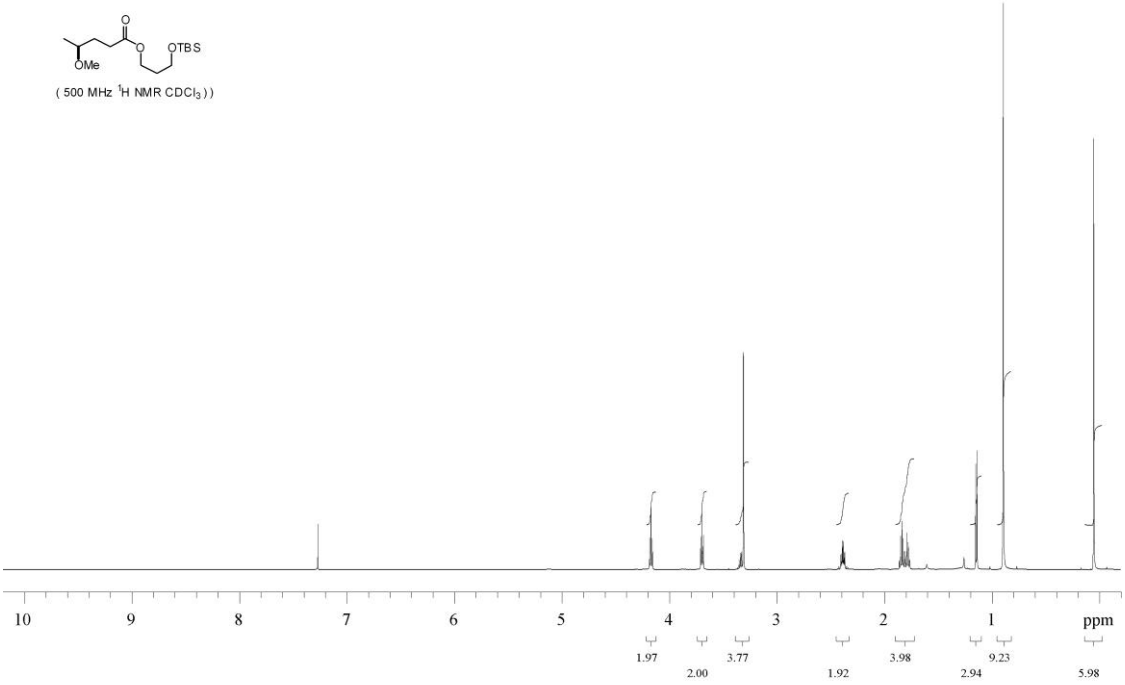

OTBS
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
1.59
1.67
2.01
1.66
1.78
2.90
10.08
6.57

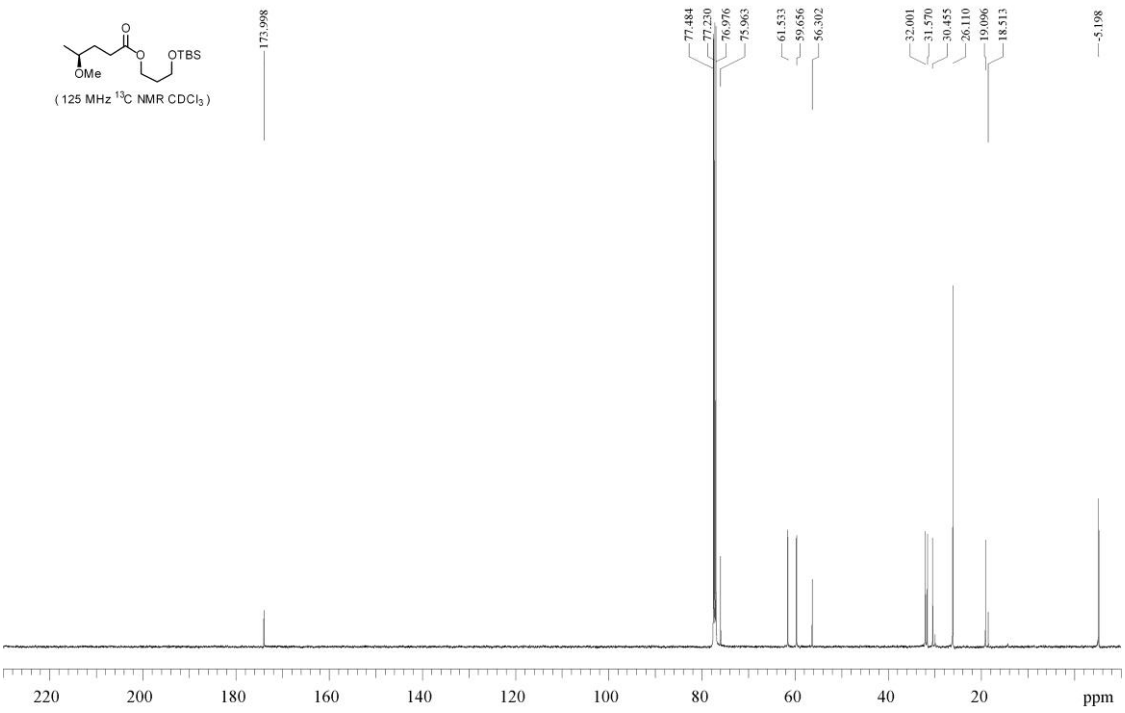

OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
172.178
127.612
122.062
77.484
77.230
76.976
61.787
59.594
32.923
31.968
26.089
18.485
13.102
-5.239
220
200
180
160
140
120
100
80
60
40
20
ppm

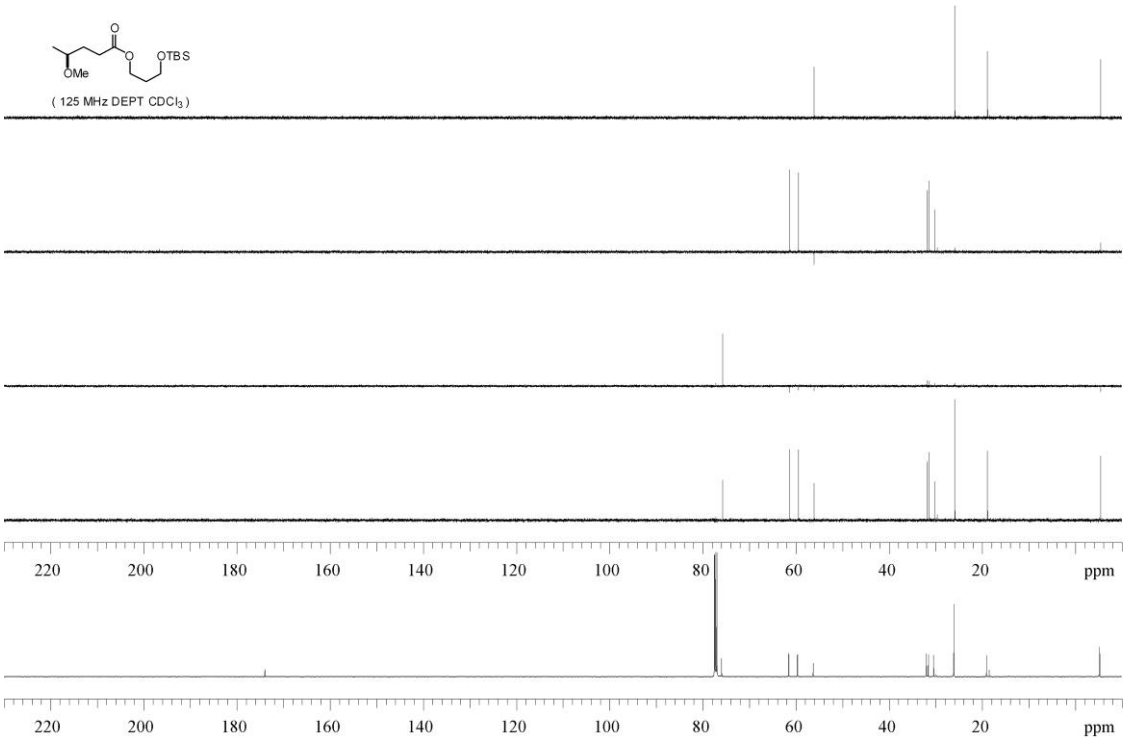

OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

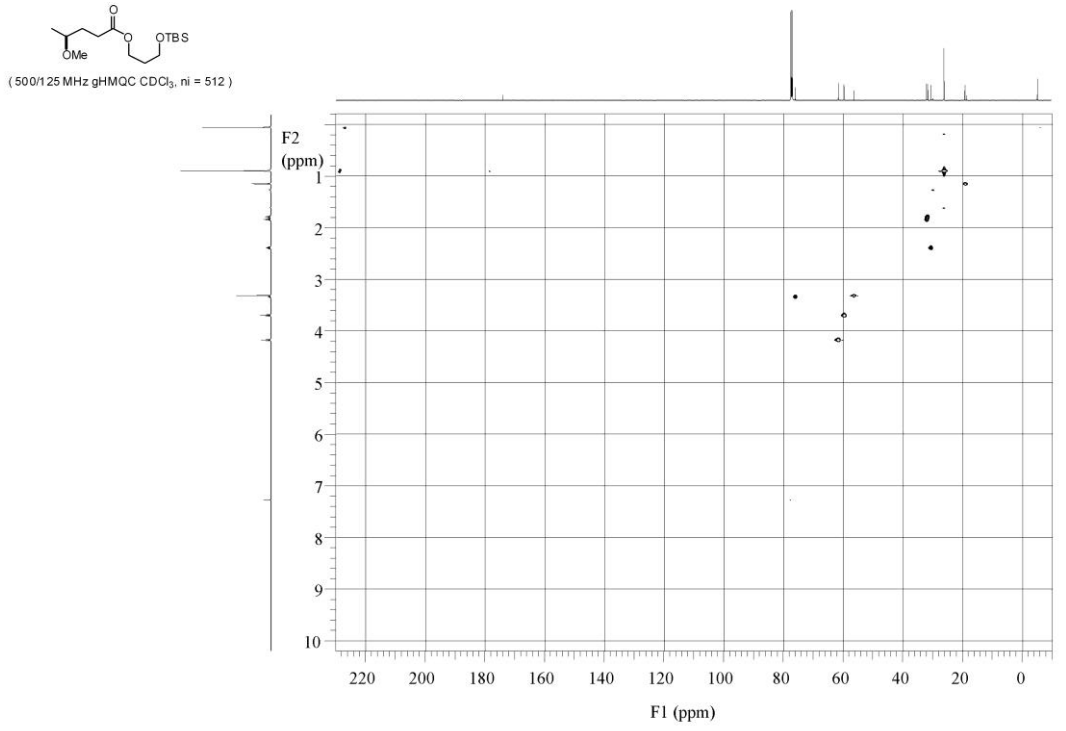

OTBS
(500/125 MHz gHMQC CDCl3, ni = 512)
F2
(ppm)
F1 (ppm)

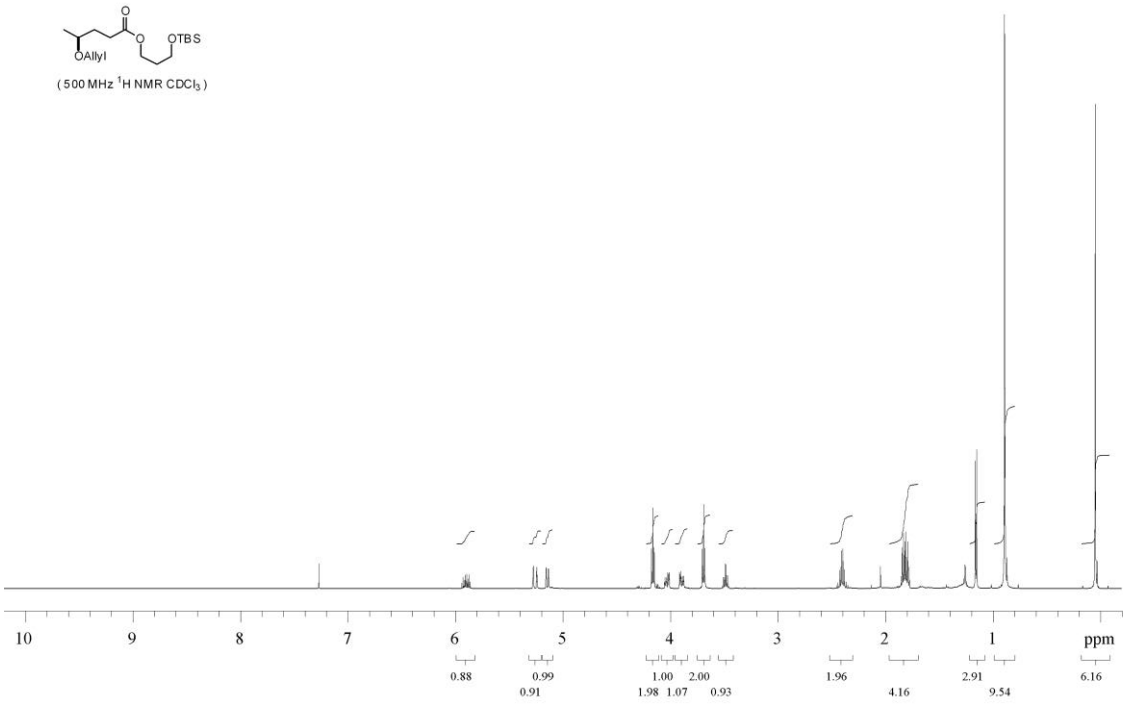

OTBS
ppm
OTBS
ppm

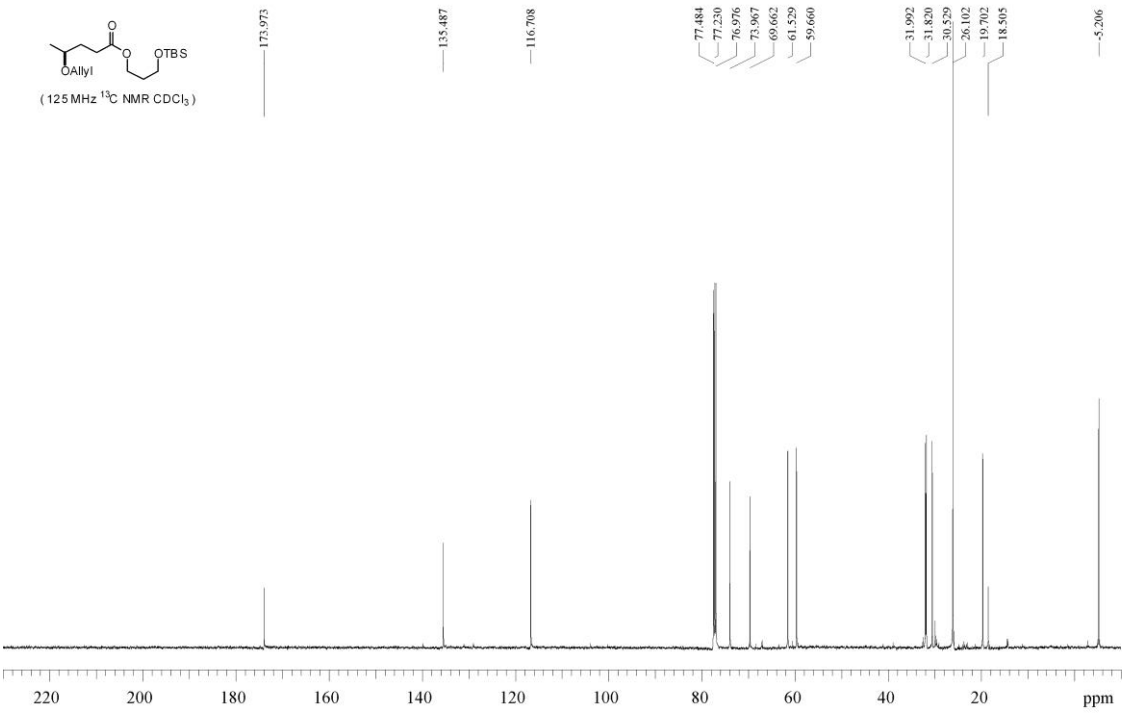

OMe
OTBS
(500 MHz ^{1}H NMR $CDCl_3$))
10
9
8
7
6
5
4
3
2
1
ppm
1.97
2.00
3.77
1.92
3.98
2.94
9.23
5.98

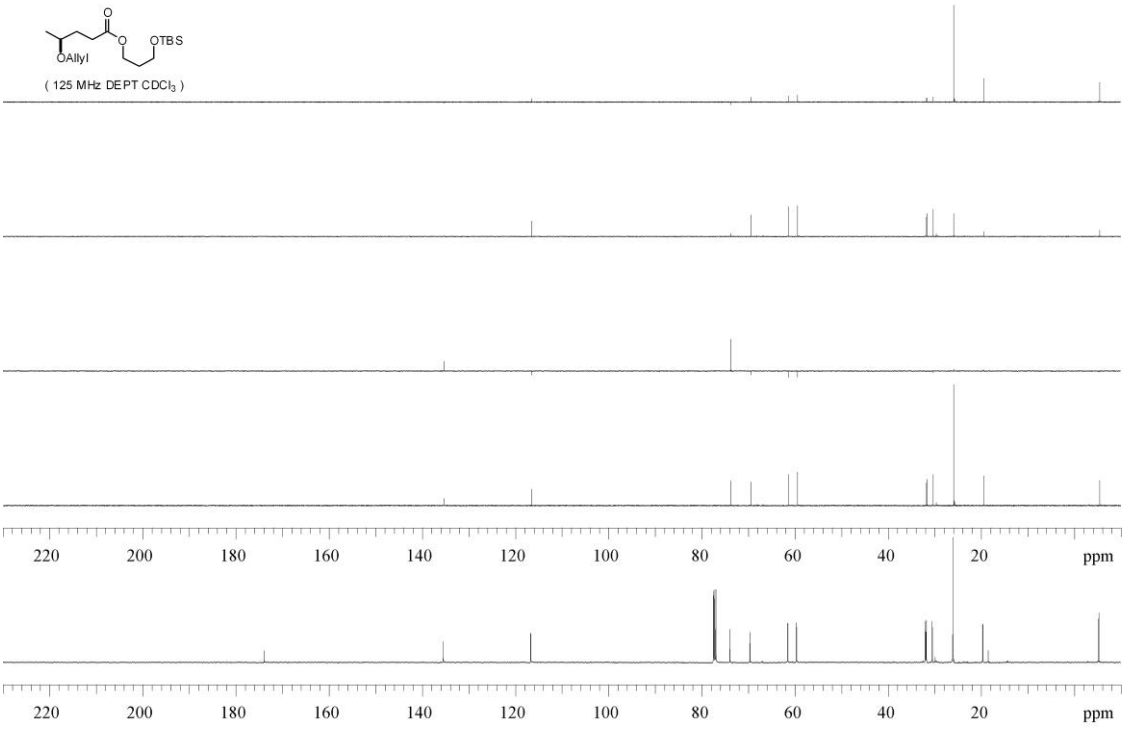

OMe
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
173.998
77.484
77.230
76.976
75.963
61.533
59.656
56.302
32.001
31.570
30.455
26.110
19.096
18.513
-5.198
220
200
180
160
140
120
100
80
60
40
20
ppm

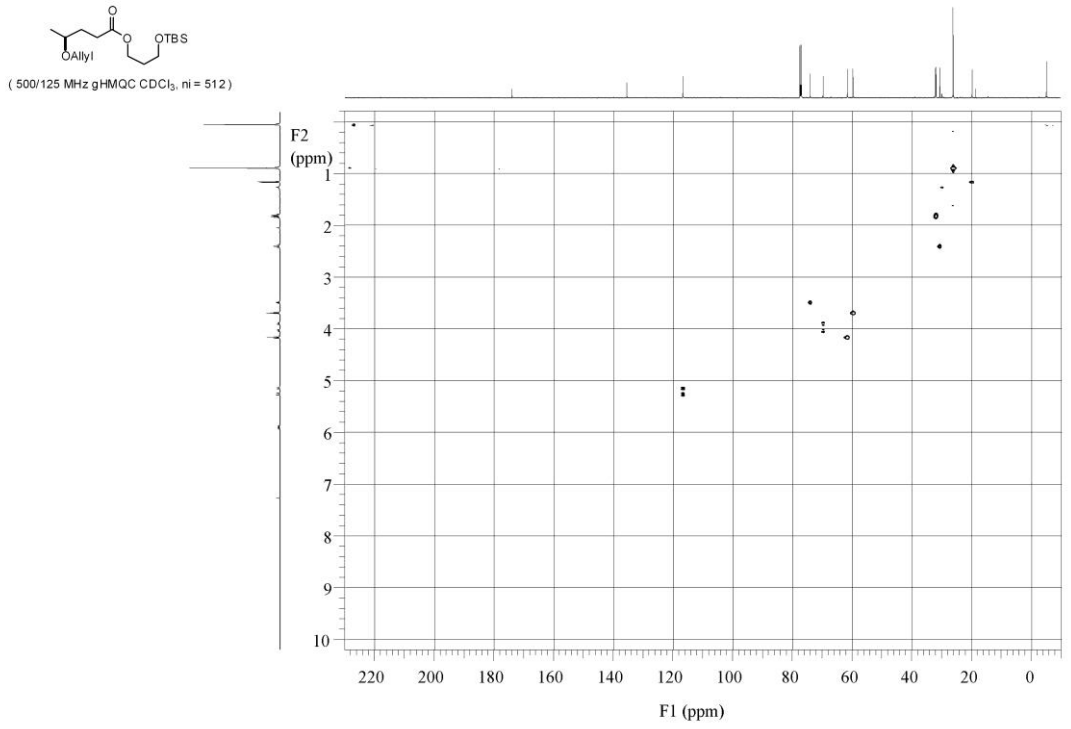

OTBS
OMe
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

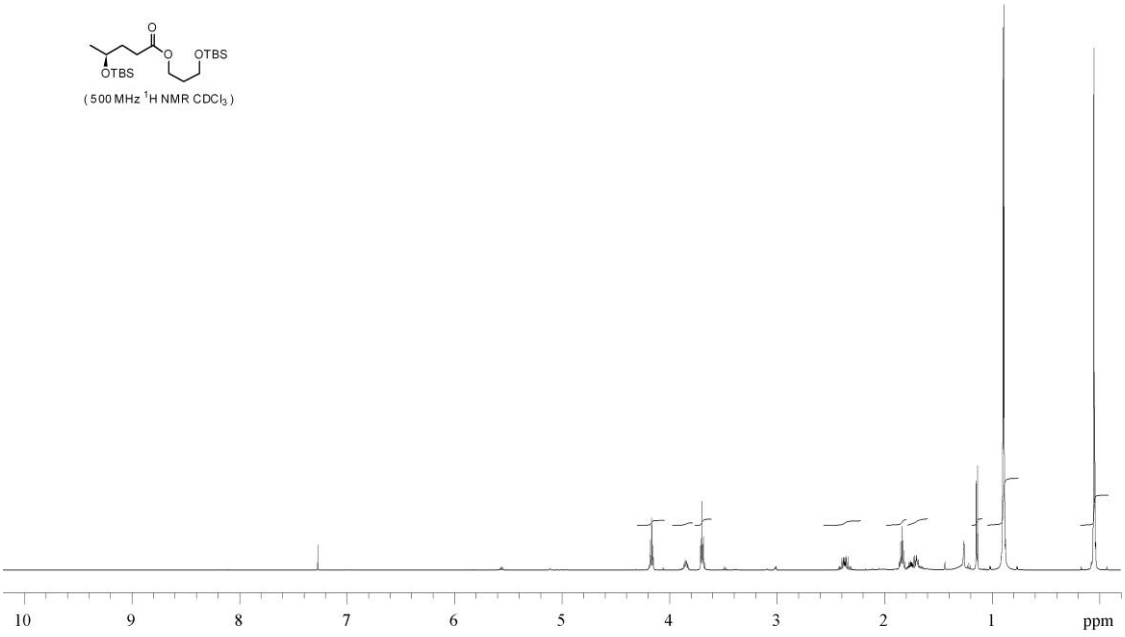

OTBS
OMe
(500/125 MHz gHMQC CDCl3, ni = 512)
F2
(ppm)
F1 (ppm)

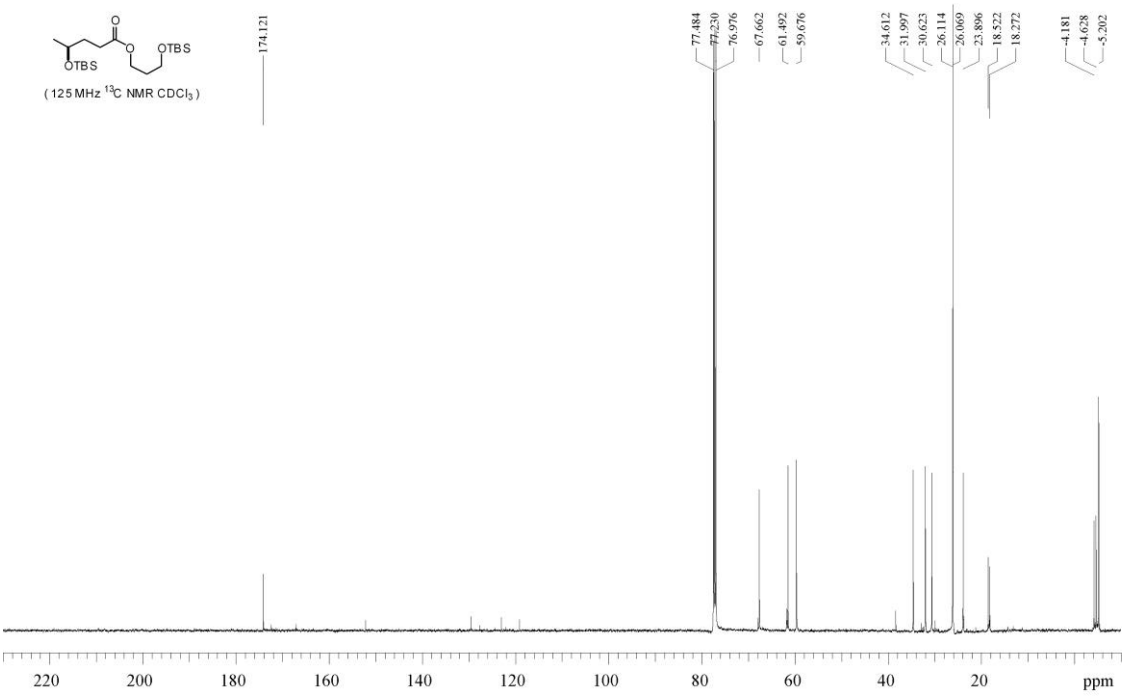

OAllyl
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.88
0.99
0.91
1.00
2.00
1.98
1.07
0.93
1.96
4.16
2.91
9.54
6.16

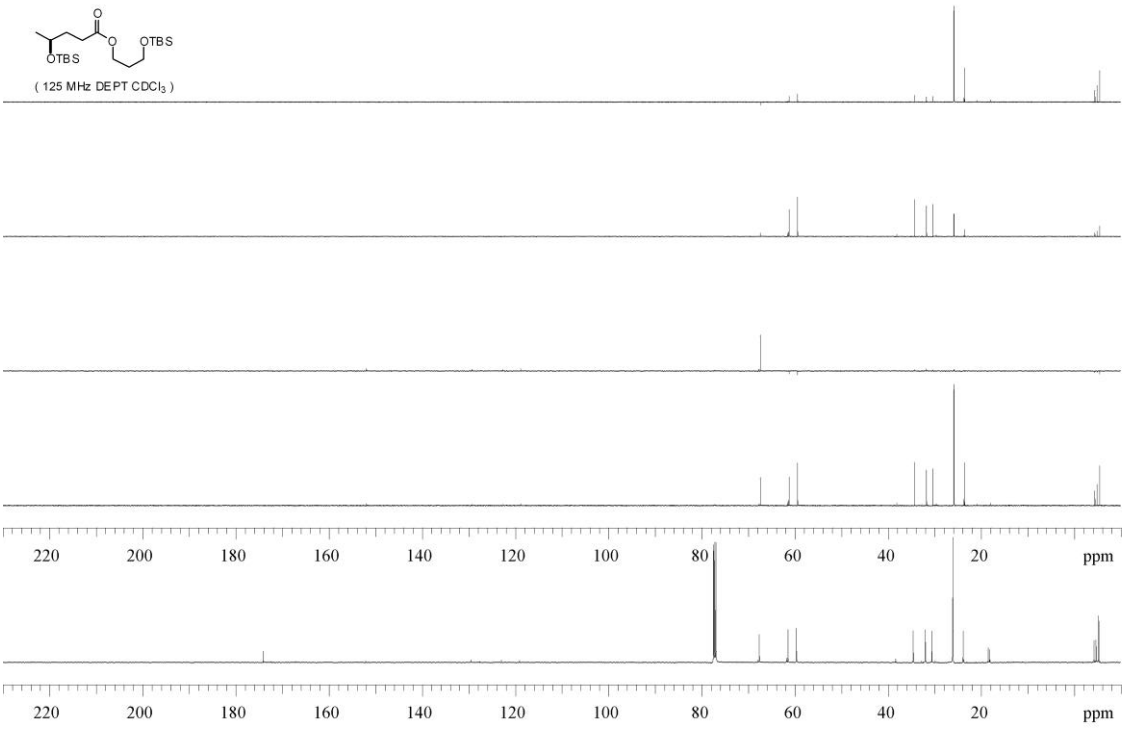

OAllyl
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
173.973
135.487
116.708
77.484
77.230
76.976
73.967
69.662
61.529
59.660
31.992
31.820
30.529
26.102
19.702
18.505
-5.206
220
200
180
160
140
120
100
80
60
40
20
ppm

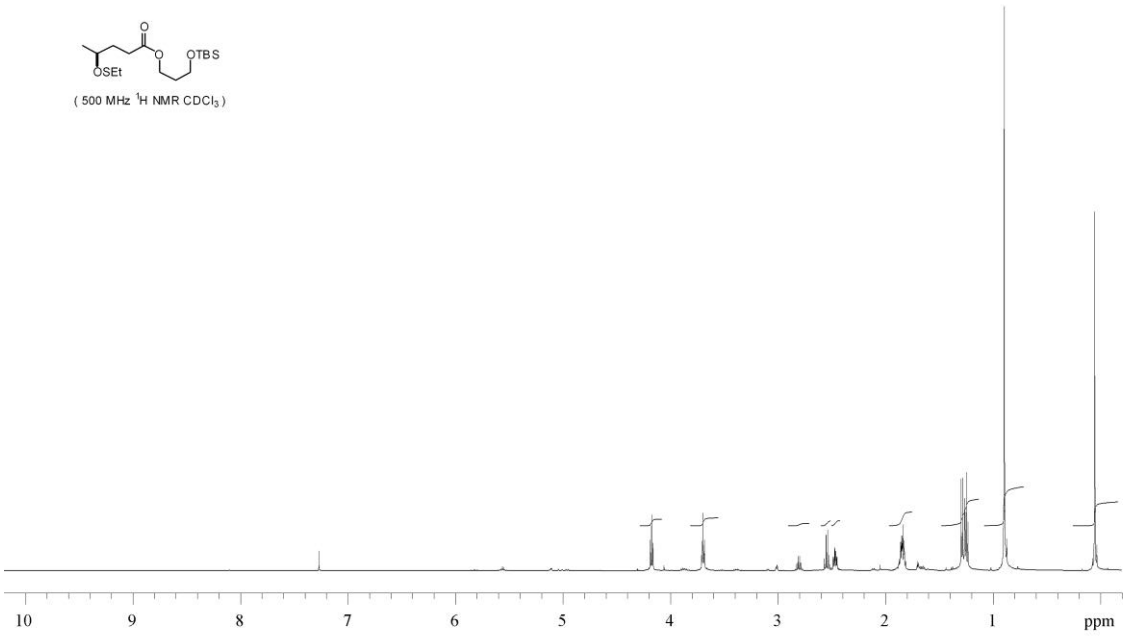

OAllyl
OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

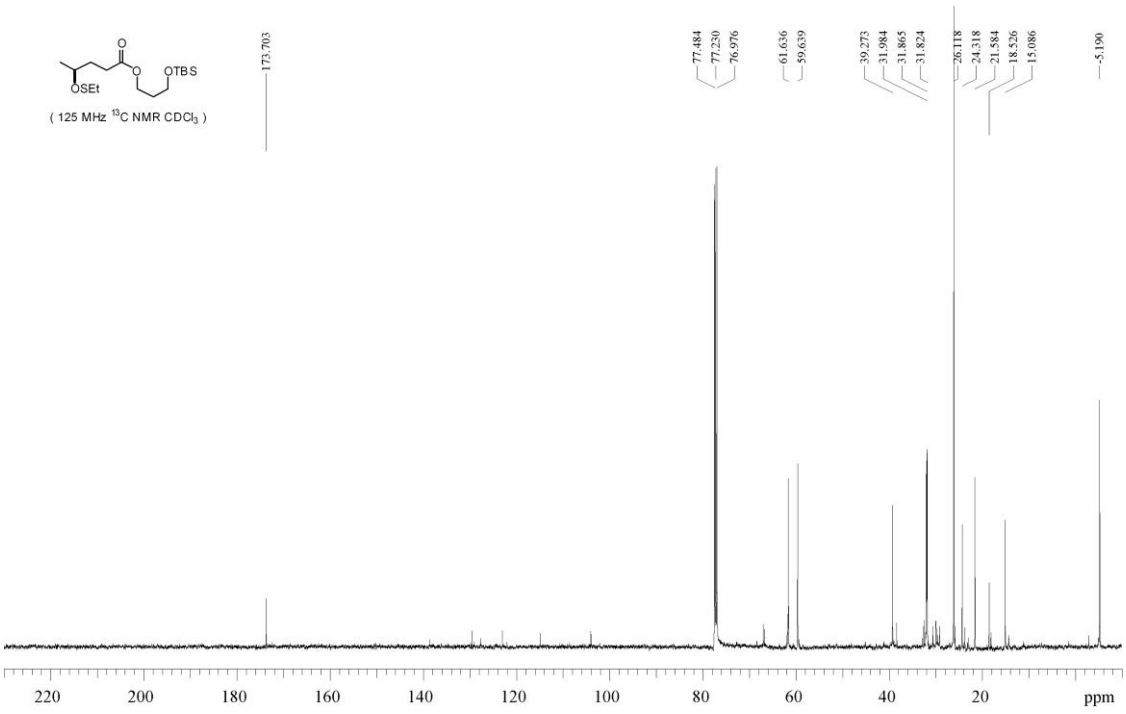

OAllyl
OTBS
(500/125 MHz gHMQC CDCl3, ni = 512)
F2
(ppm)
F1 (ppm)

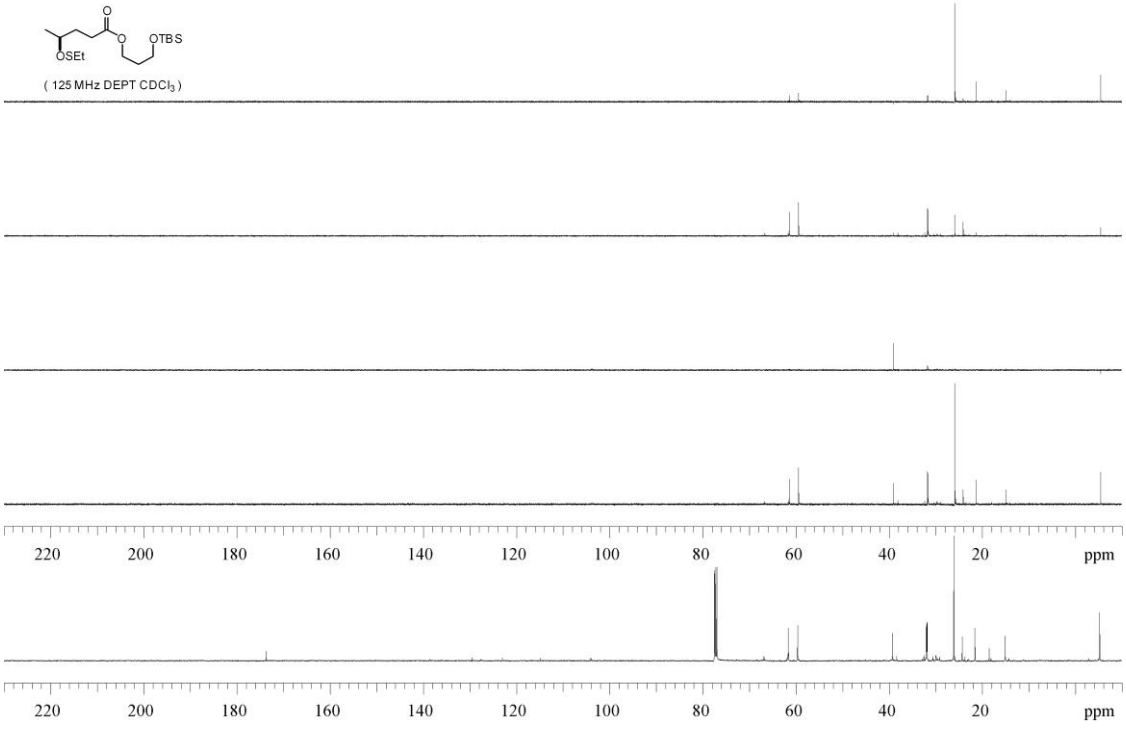

OTBS
OTBS
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm


OTBS
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
174.121
77.484
77.230
76.976
67.662
61.492
59.676
34.612
31.997
30.623
26.114
26.069
23.896
18.522
18.272
-4.181
-4.628
-5.202
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
OTBS
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

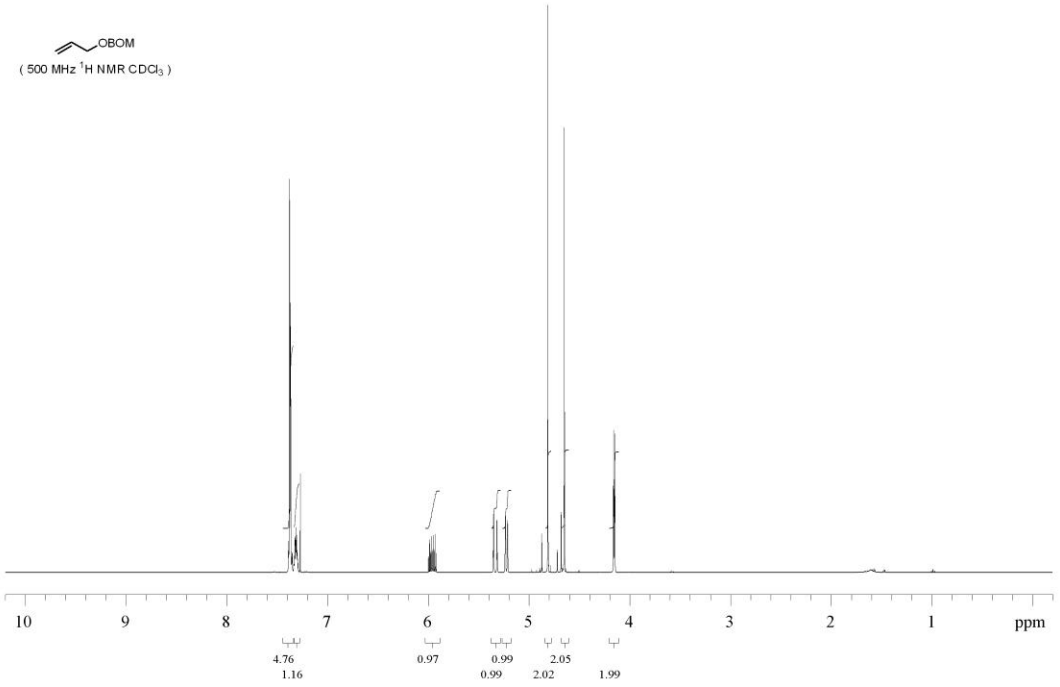

OTBS
OSEt
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm

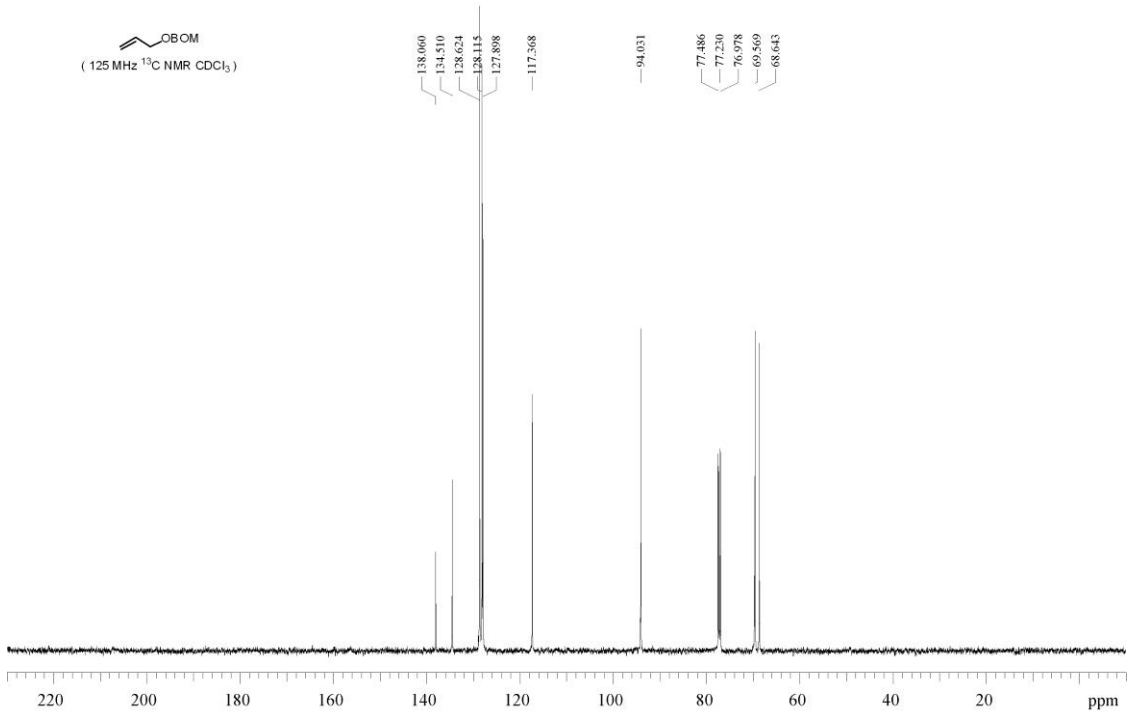

OSEt
OTBS
(125 MHz ^{13}C NMR $CDCl_3$)
173.703
77.484
77.230
76.976
61.636
59.639
39.273
31.984
31.865
31.824
26.118
24.318
21.584
18.526
15.086
-5.190
220
200
180
160
140
120
100
80
60
40
20
ppm

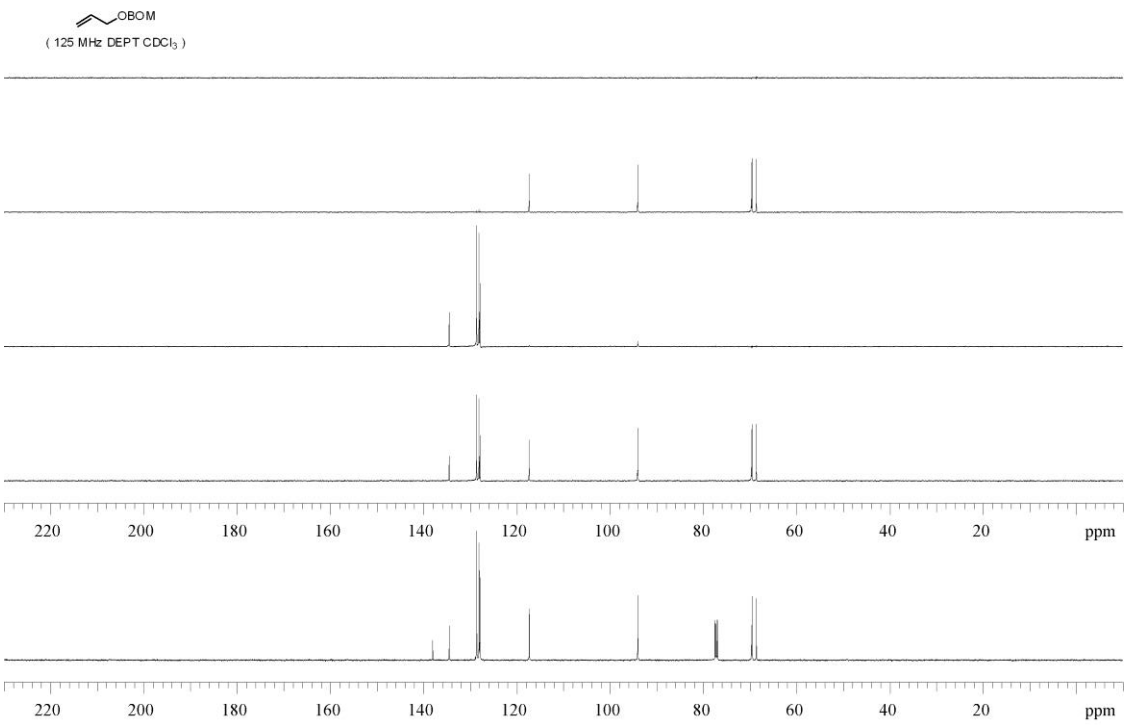

OSEt
OTBS
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

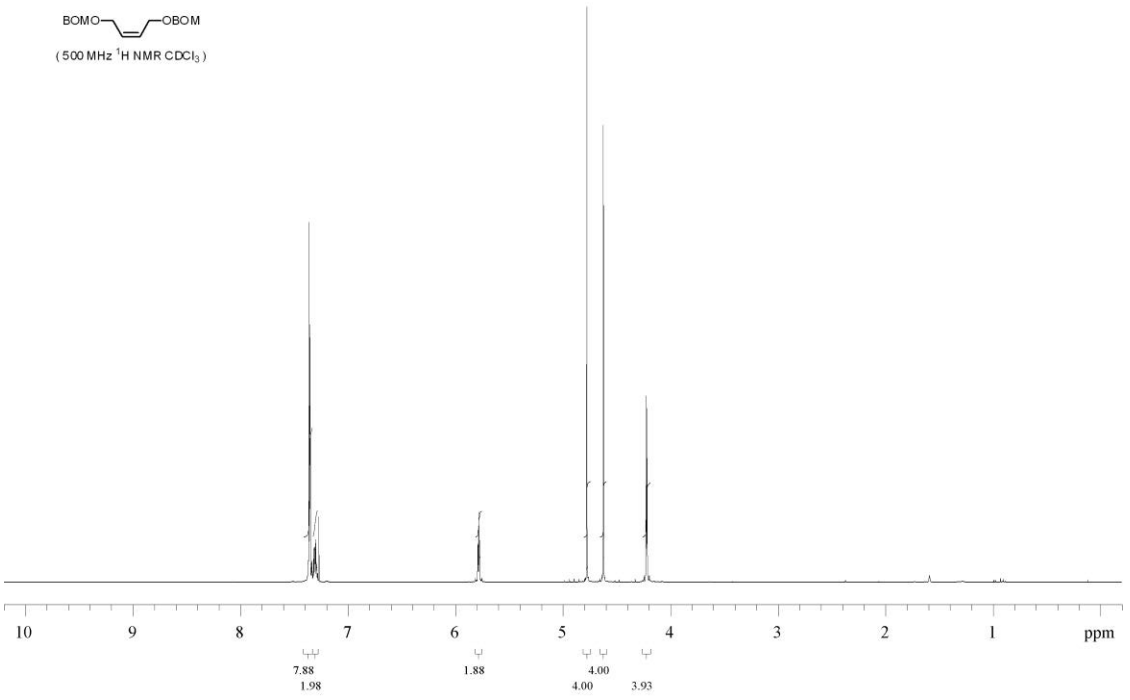
APPENDIX B

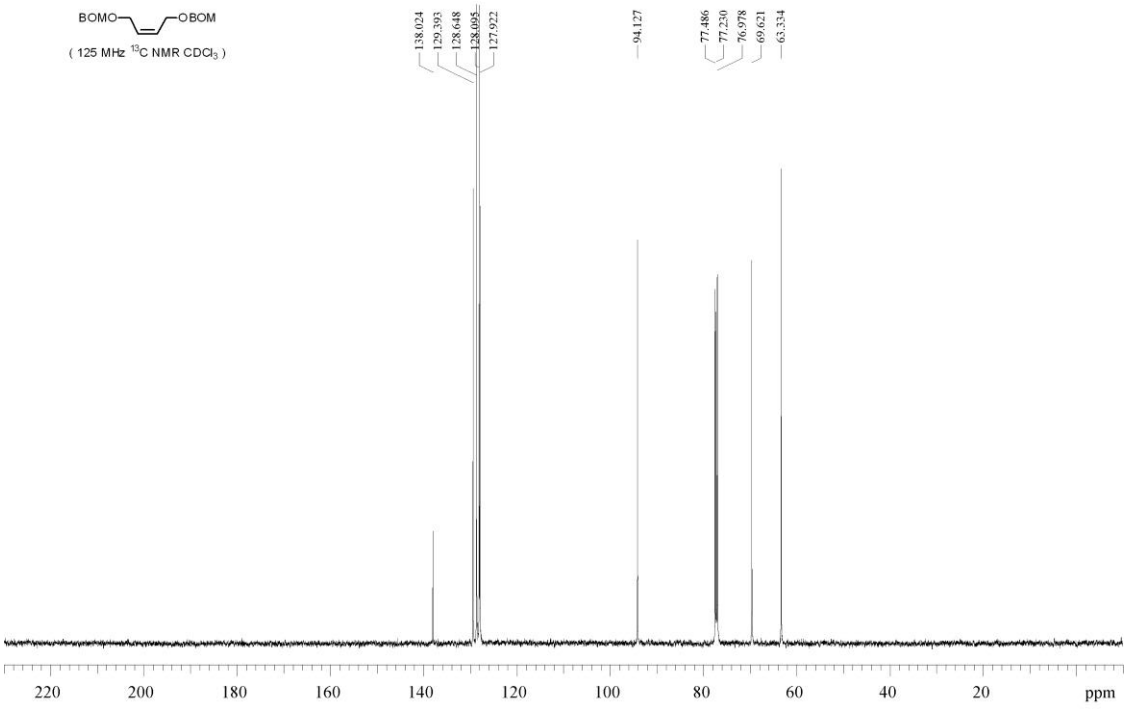
NMR SPECTRUM OF CHAPTER 2

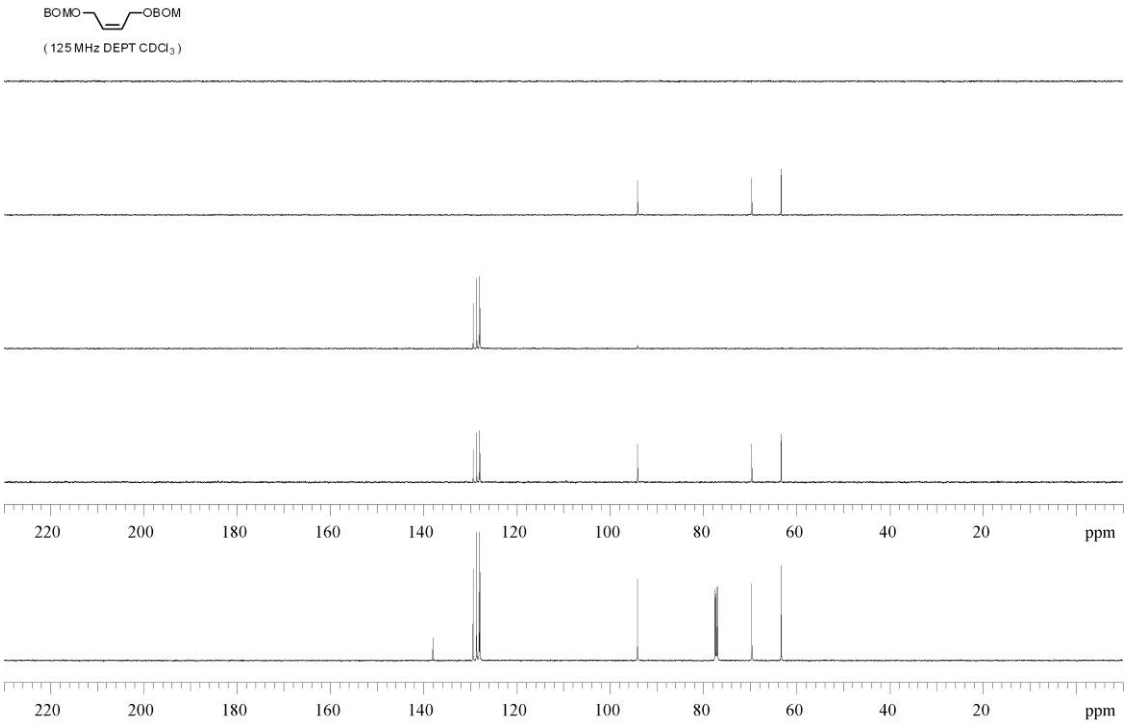

OBOM
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
4.76
1.16
0.97
0.99
0.99
2.02
1.99

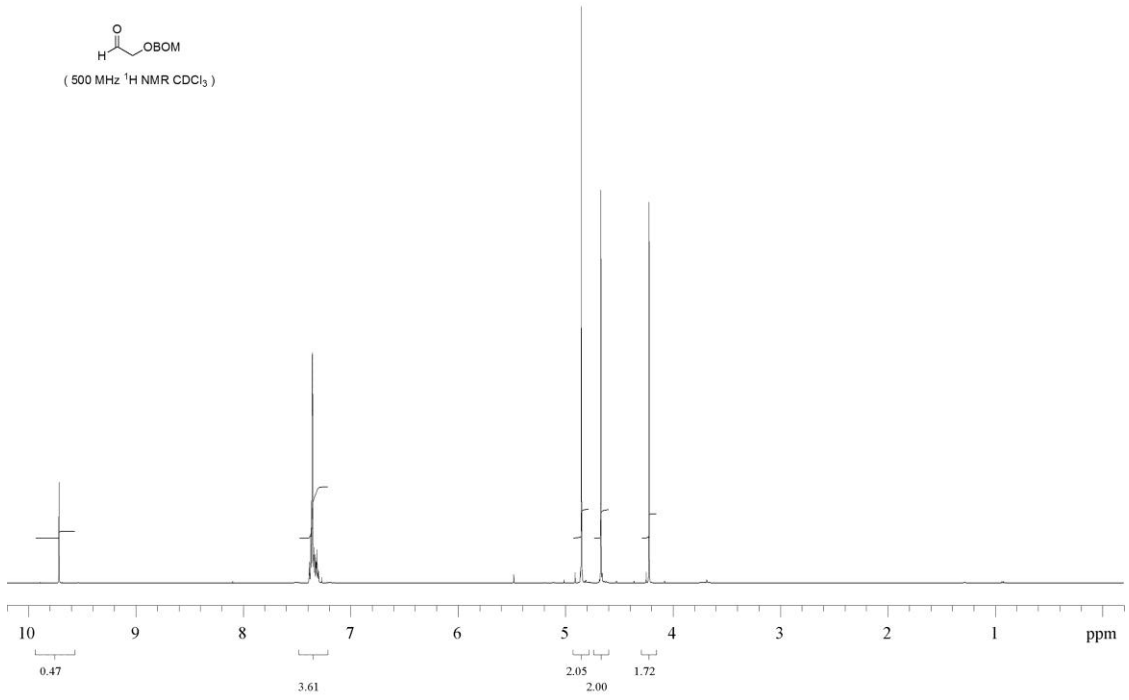

OBOM
(125 MHz ^{13}C NMR $CDCl_3$)
138.060
134.510
128.624
128.115
127.898
117.368
94.031
77.486
77.230
76.978
69.569
68.643
220
200
180
160
140
120
100
80
60
40
20
ppm

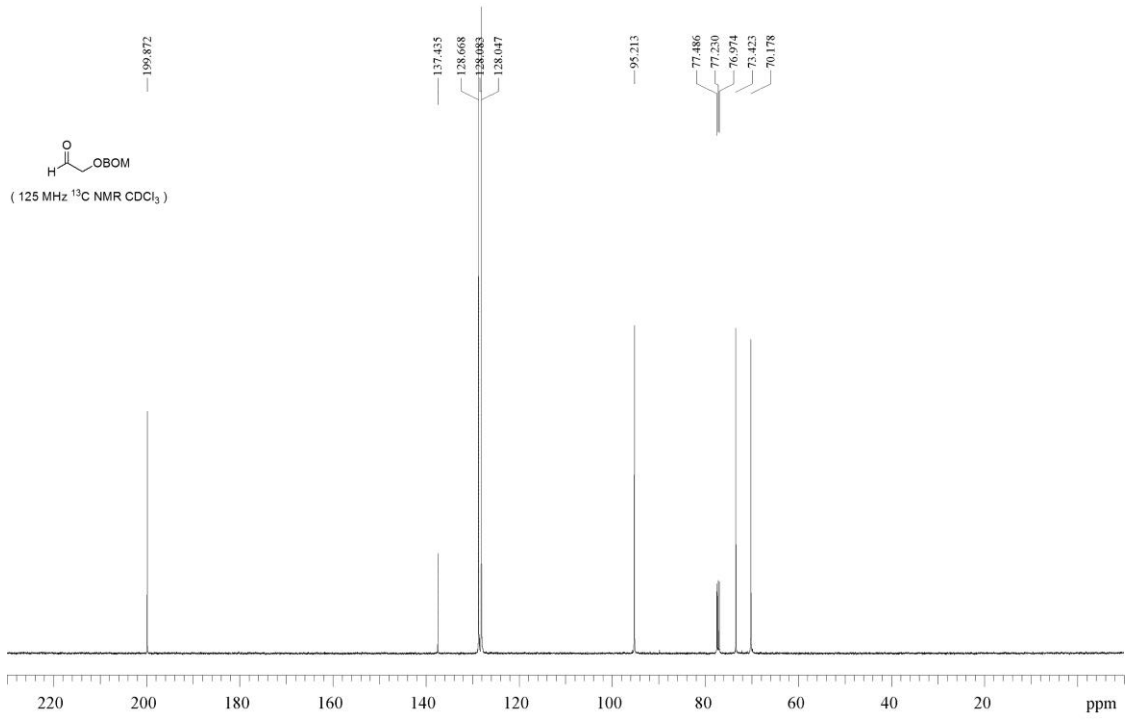

OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

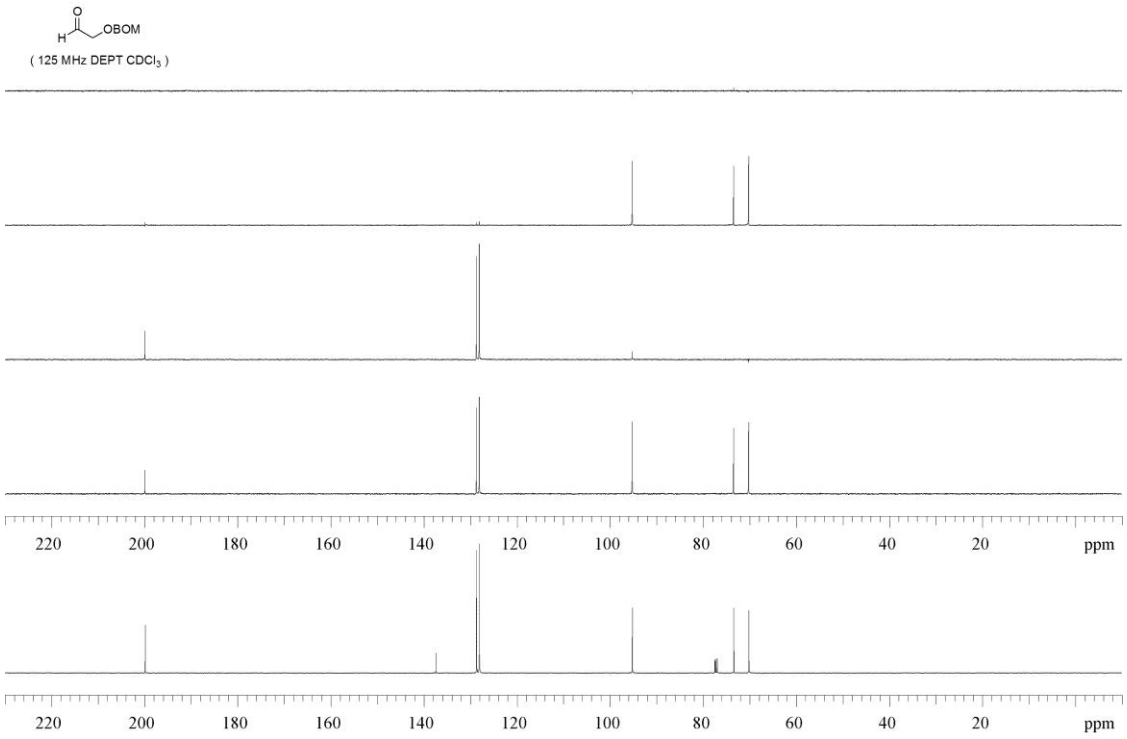

BOMO
OBOM
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
7.88
1.98
1.88
4.00
4.00
3.93

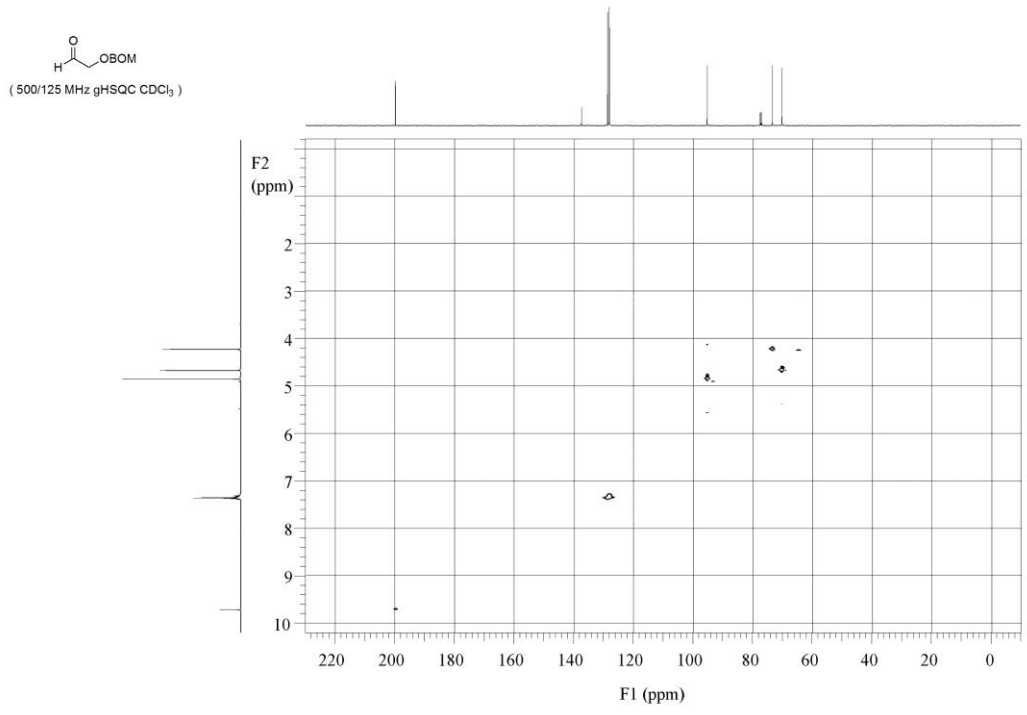

BOMO
OBOM
(125 MHz ^{13}C NMR $CDCl_3$)
138.024
129.393
128.648
128.095
127.922
94.127
77.486
77.230
76.978
69.621
63.334
220
200
180
160
140
120
100
80
60
40
20
ppm

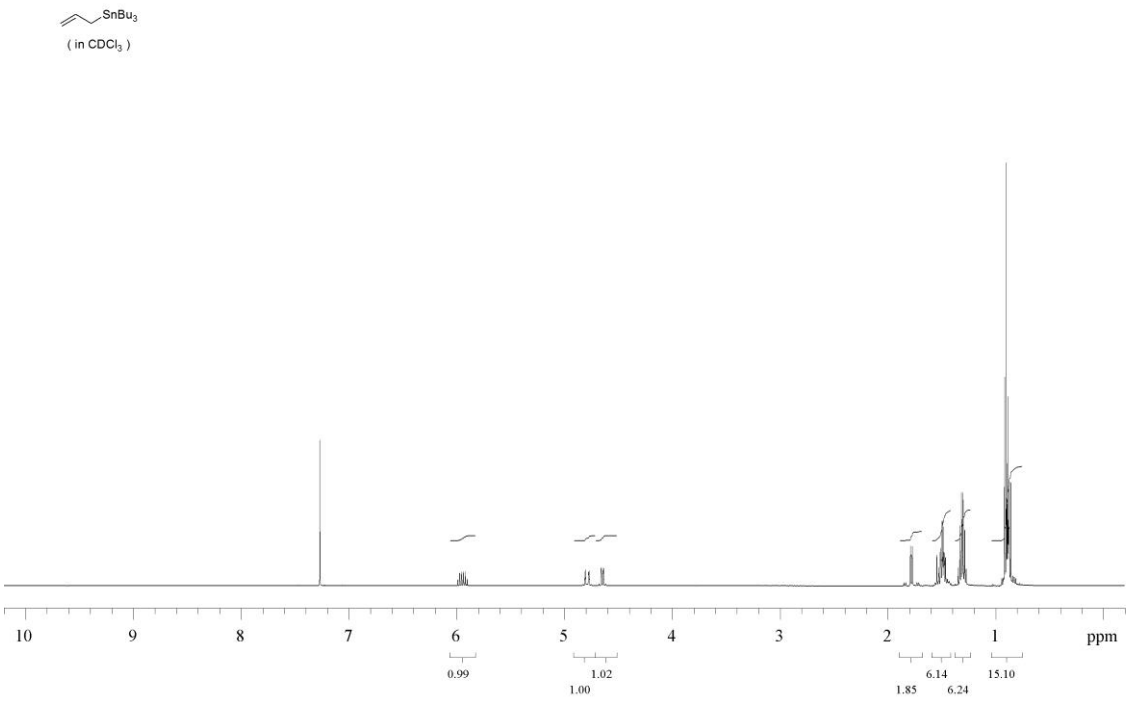

BOMO
OBOM
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

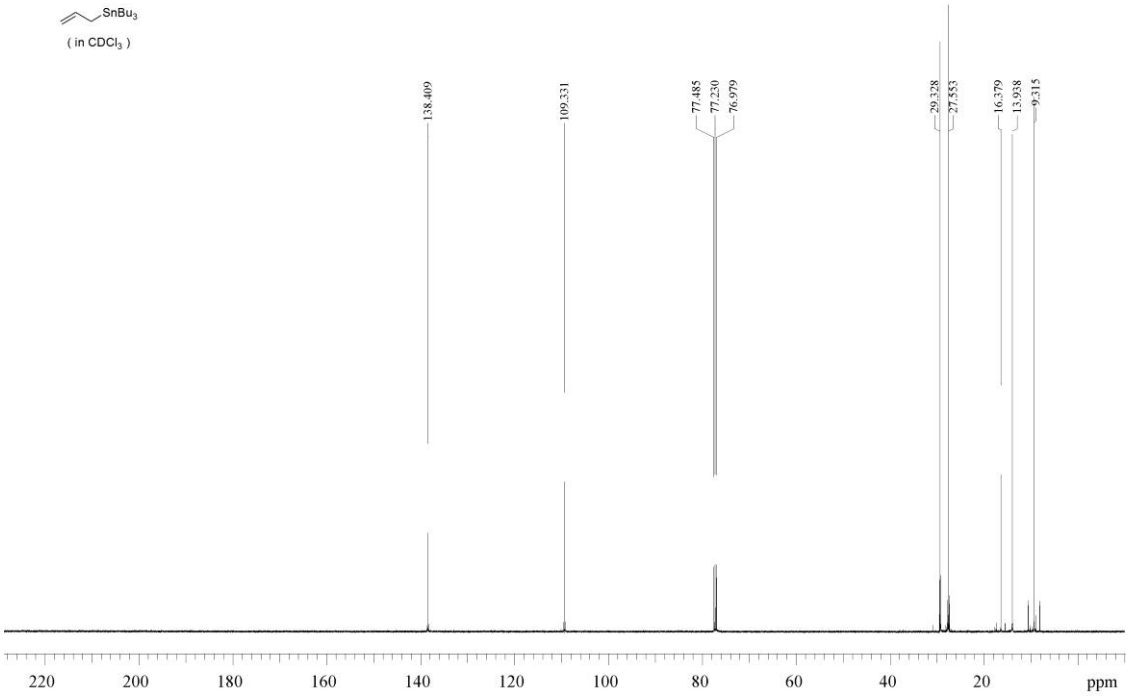

OBOM
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.47
3.61
2.05
2.00
1.72

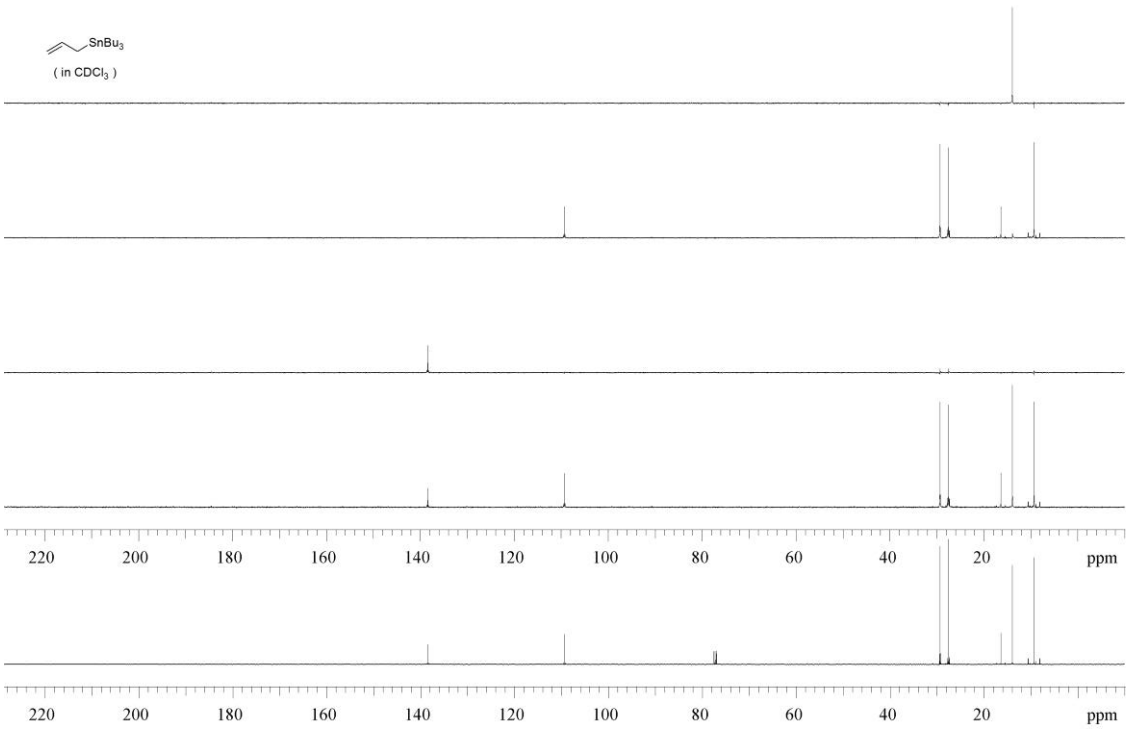

199.872
137.435
128.668
128.083
128.047
95.213
77.486
77.220
76.974
73.423
70.178
OBOM
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

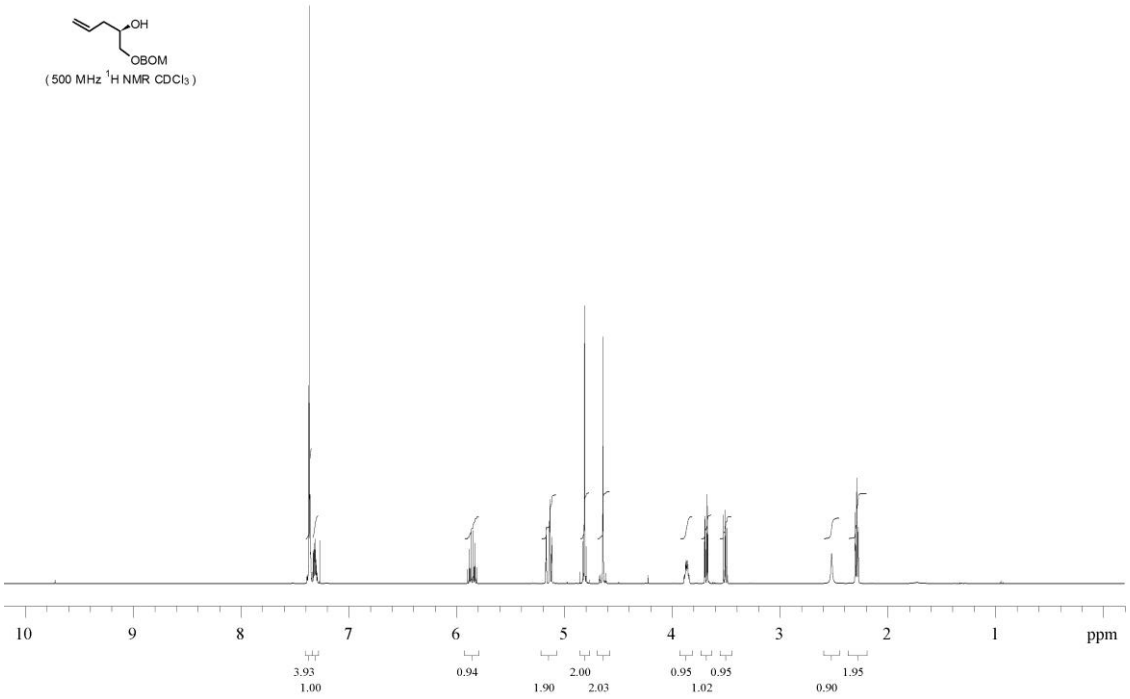

OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

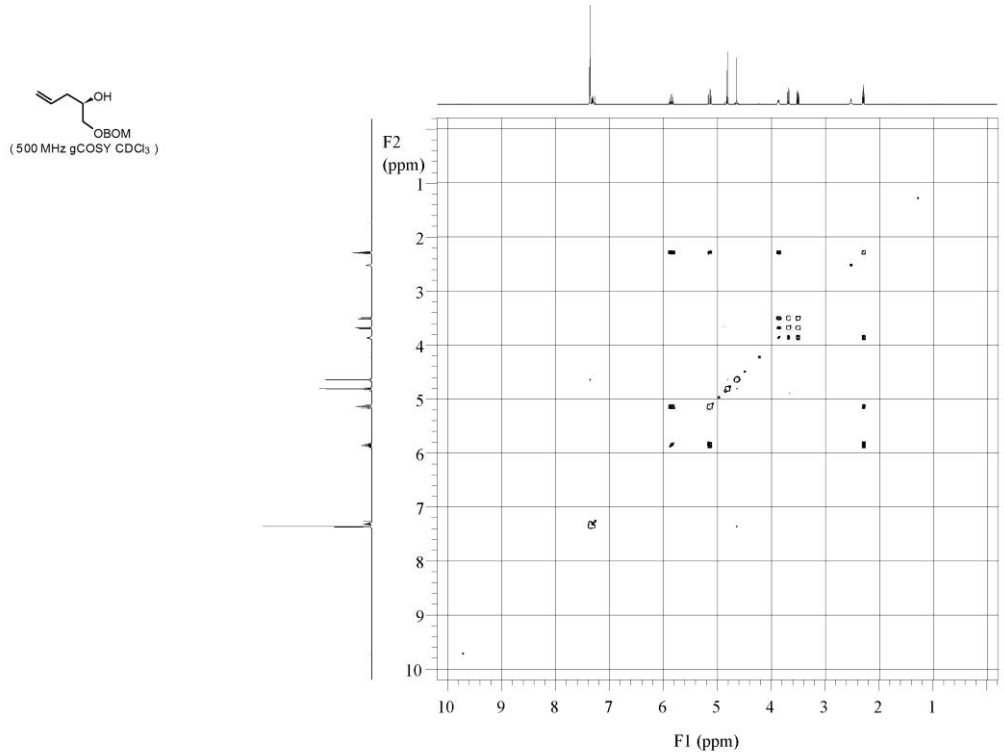

OBOM
(500/125 MHz gHSQC CDCl3)
F2
(ppm)
F1 (ppm)

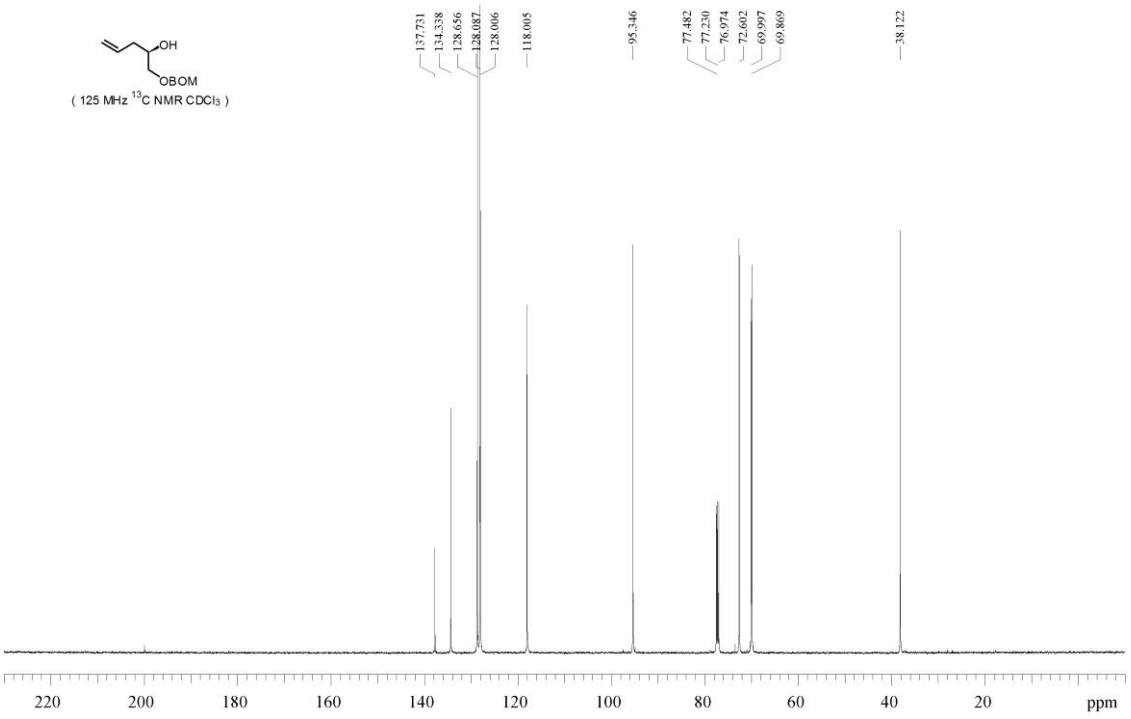

SnBu3
(in CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
0.99
1.02
1.00
1.85
6.14
6.24
15.10

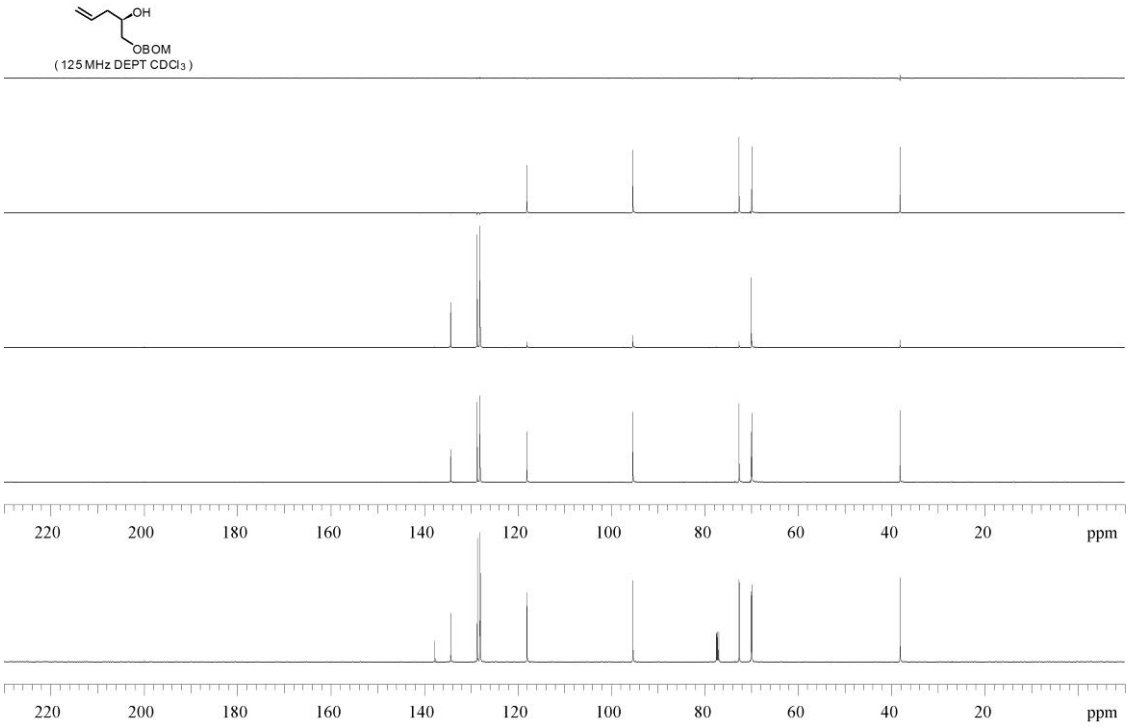

SnBu3
(in CDCl3)
138.409
109.331
77.485
77.230
76.979
29.328
27.553
16.379
13.938
9.315
220
200
180
160
140
120
100
80
60
40
20
ppm

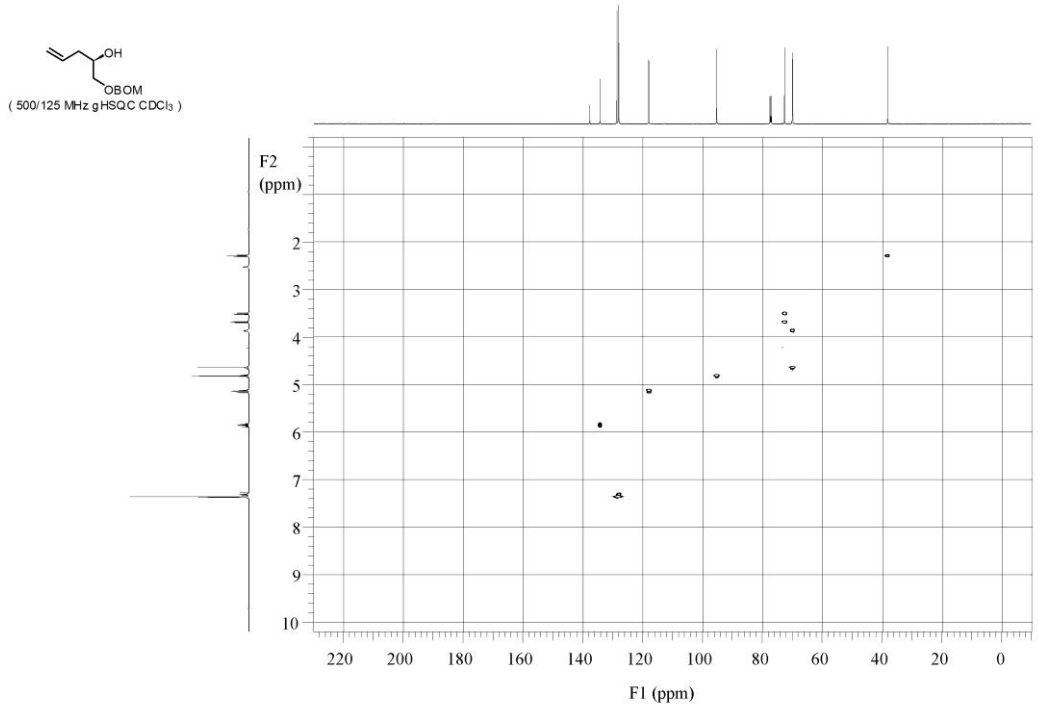

SnBu3
(in CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

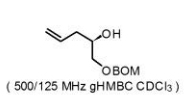

OH
OBOM
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
3.93
1.00
0.94
1.90
2.00
2.03
0.95
0.95
1.02
1.95
0.90


OH
OBOM
(500 MHz gCOSY CDCl3)
F2
(ppm)
F1 (ppm)

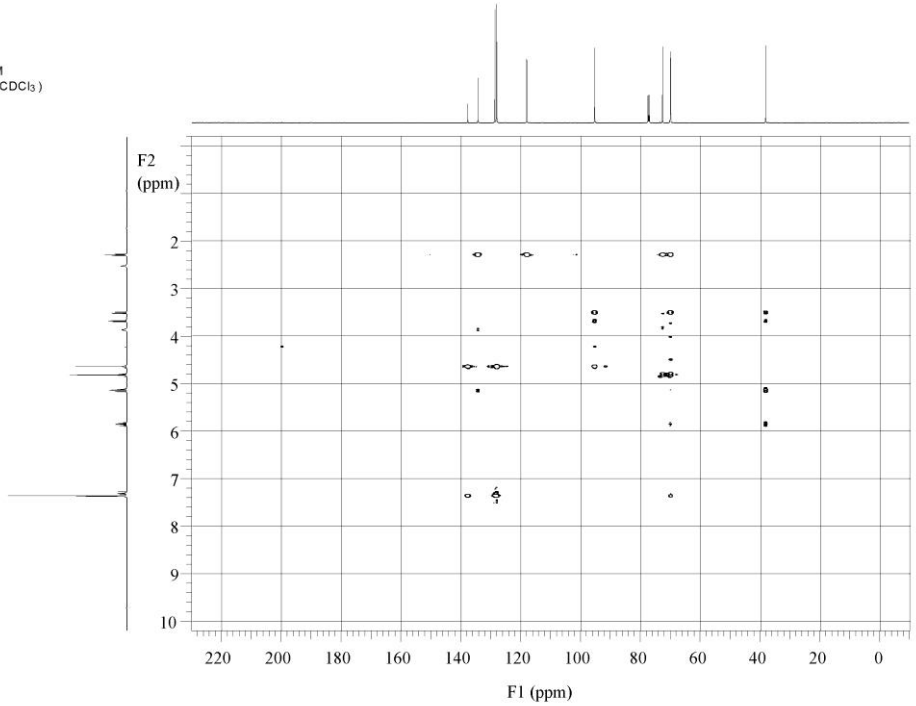

OH
OBOM
(125 MHz 13C NMR CDCl3)
137.731
134.338
128.656
128.087
128.006
118.005
95.346
77.482
77.230
76.974
72.602
69.997
69.869
38.122
ppm

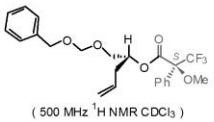

OH
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm


OH
OBOM
(500/125 MHz gHSQC CDCl3)
F2
(ppm)
F1 (ppm)

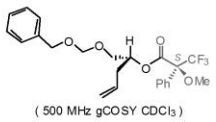


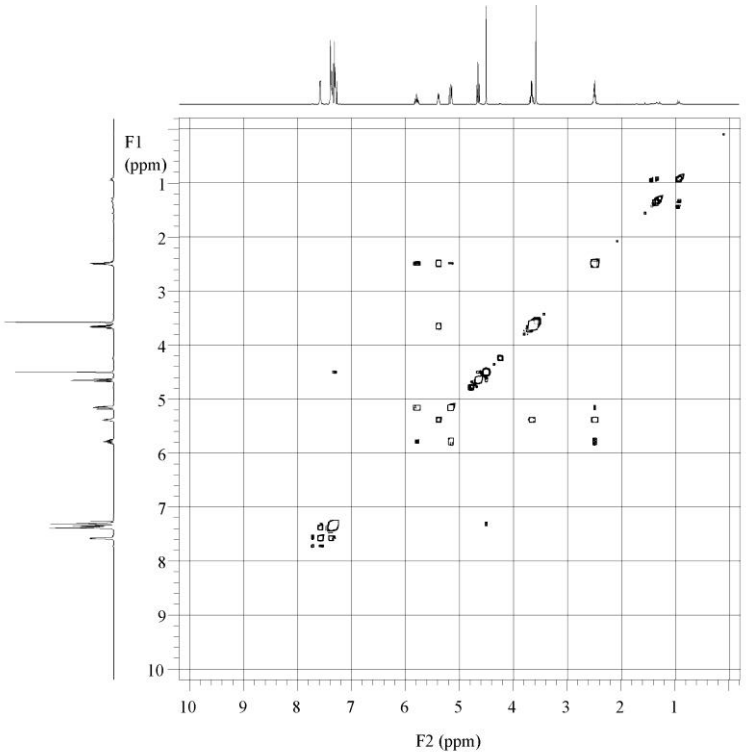
(500/125 MHz gHMBC $CDCl_3$)

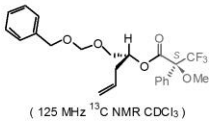




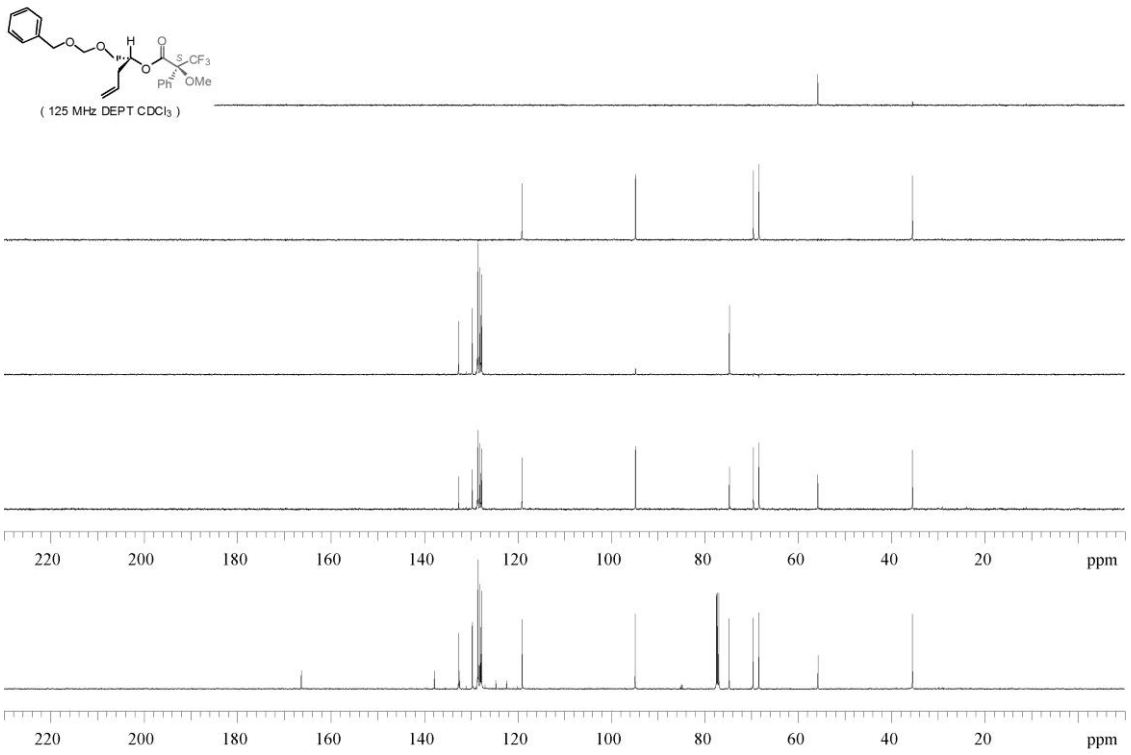
(500 MHz ^1H NMR $CDCl_3$)

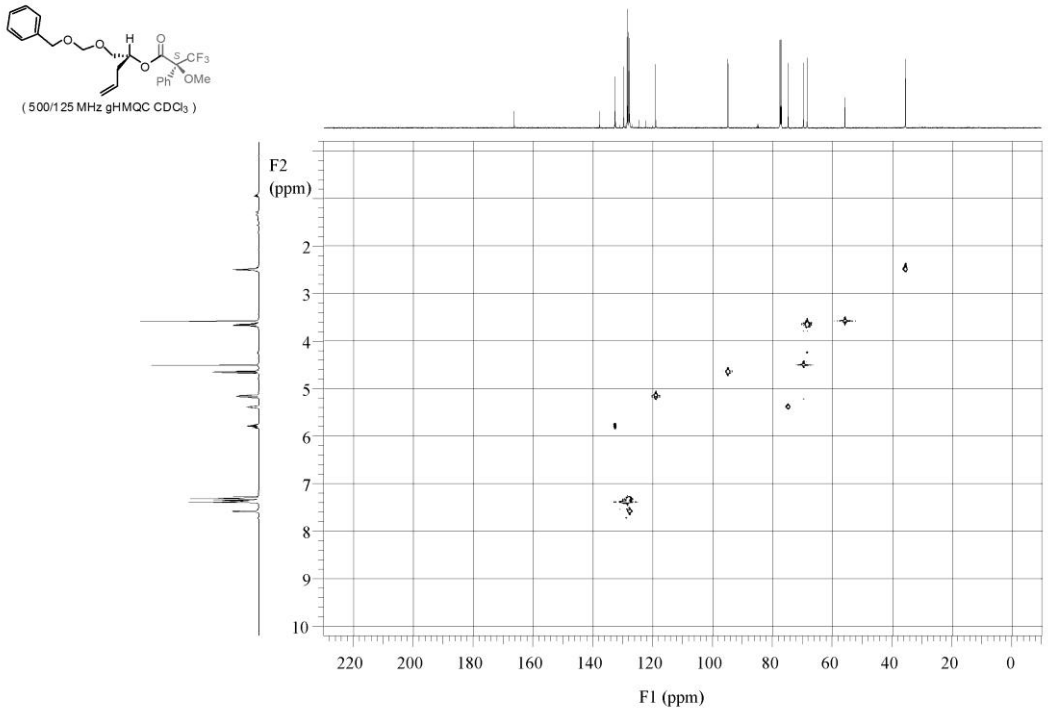

(500 MHz gCOSY CDCl3)

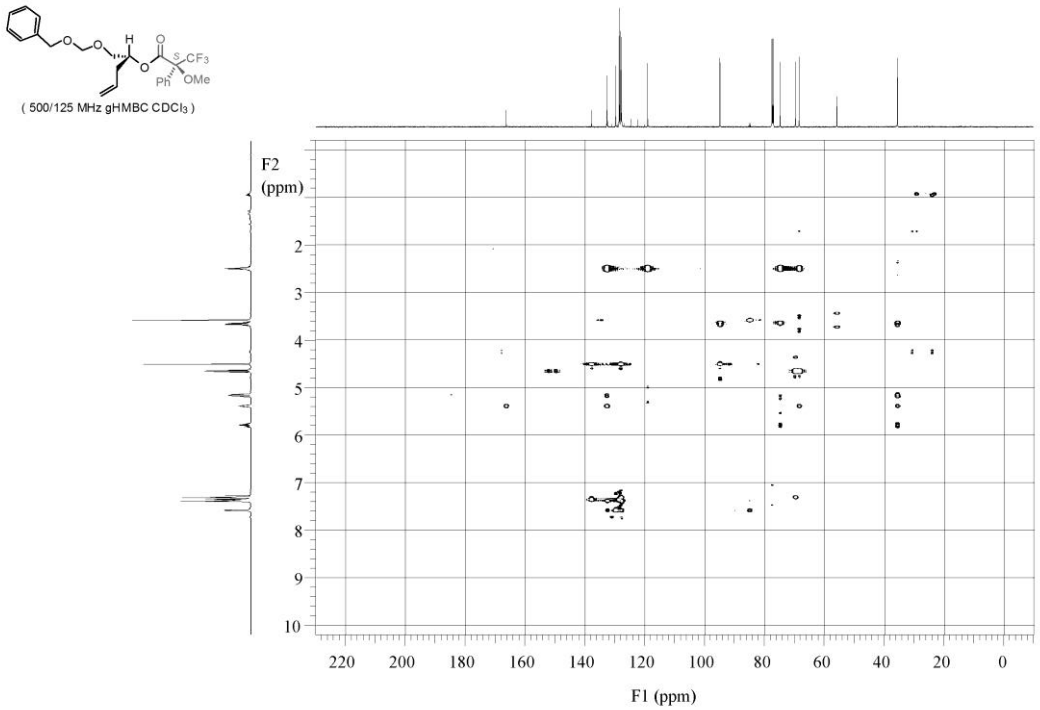

F1
(ppm)
F2 (ppm)

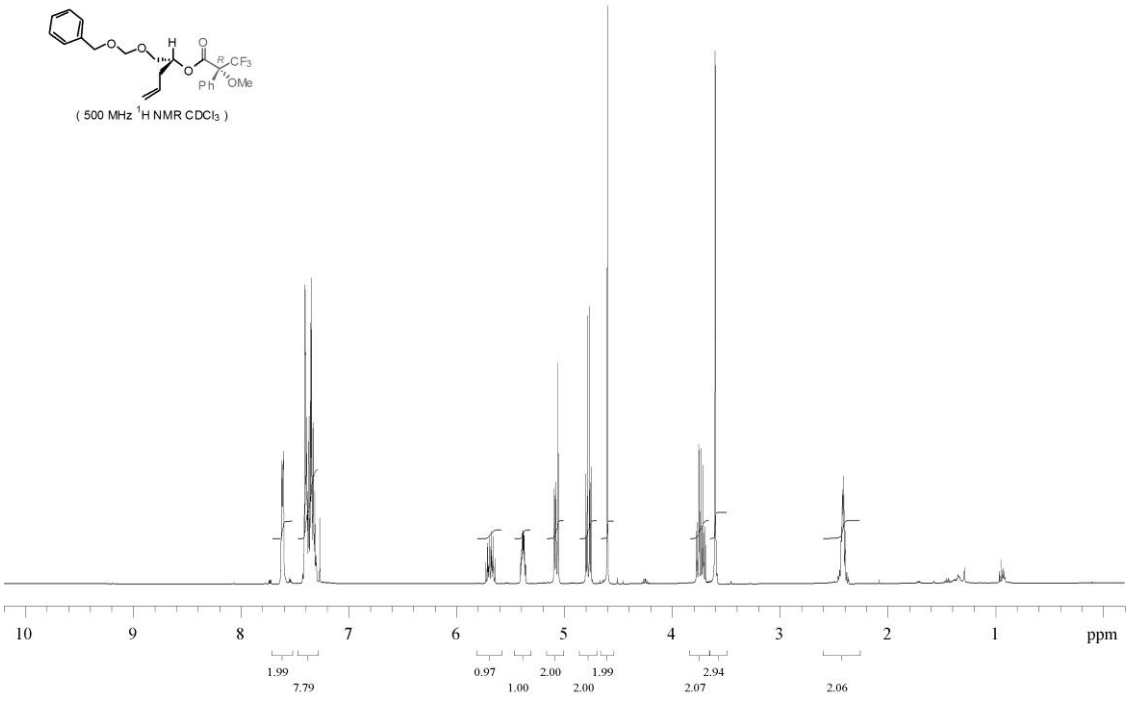

(125 MHz 13C NMR CDCl3)

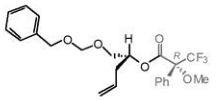
166.347
137.860
132.702
132.518
129.729
128.635
128.459
128.079
127.955
127.752
119.058
94.870
77.482
77.230
76.974
74.753
69.603
68.380
55.731
35.510
ppm


(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

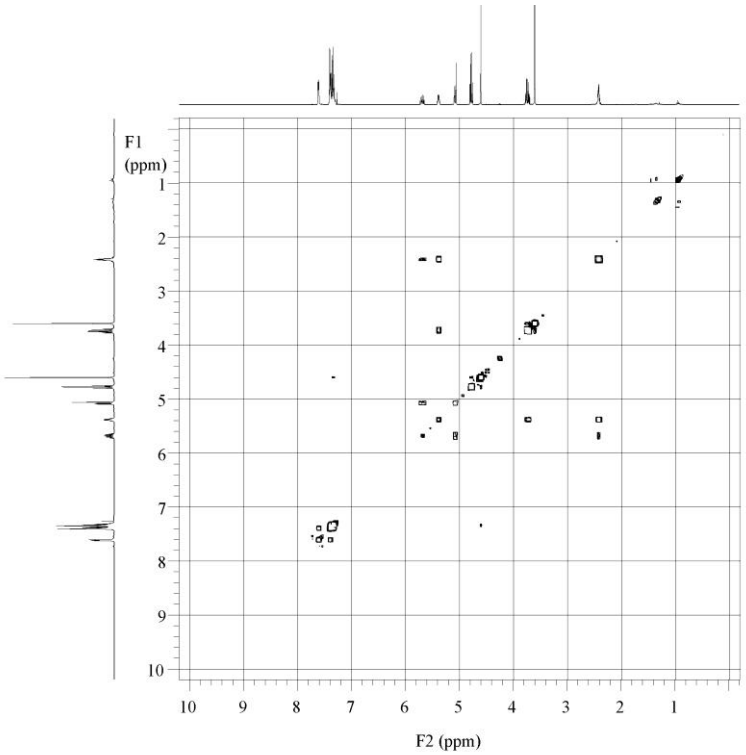

(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

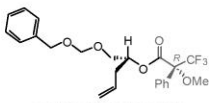

(500/125 MHz gHMBC $CDCl_3$)
F2
(ppm)
F1 (ppm)


(500 MHz ^1H NMR $CDCl_3$)
ppm
1.99
7.79
0.97
1.00
2.00
2.00
1.99
2.07
2.94
2.06

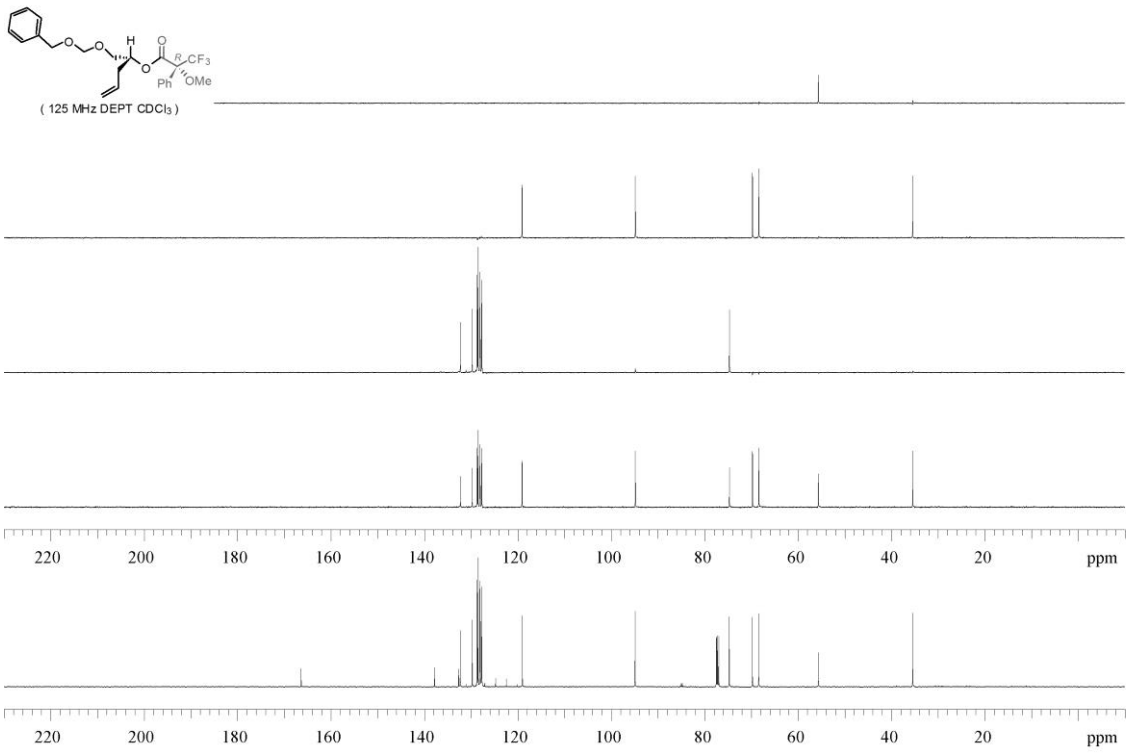


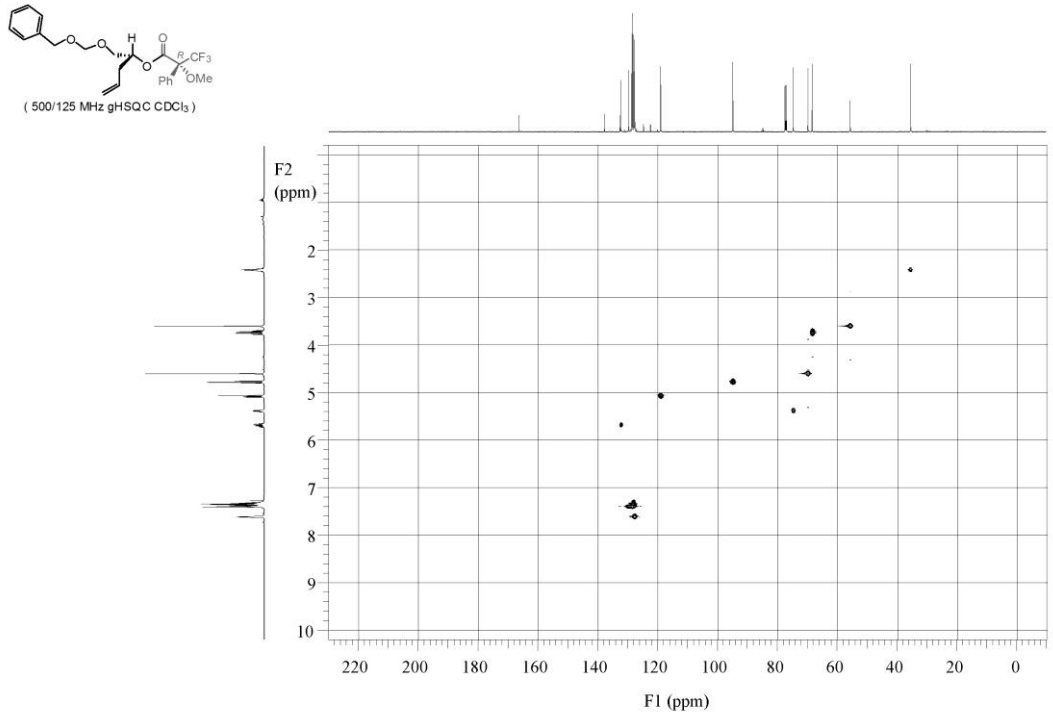
(500 MHz gCOSY $CDCl_3$)

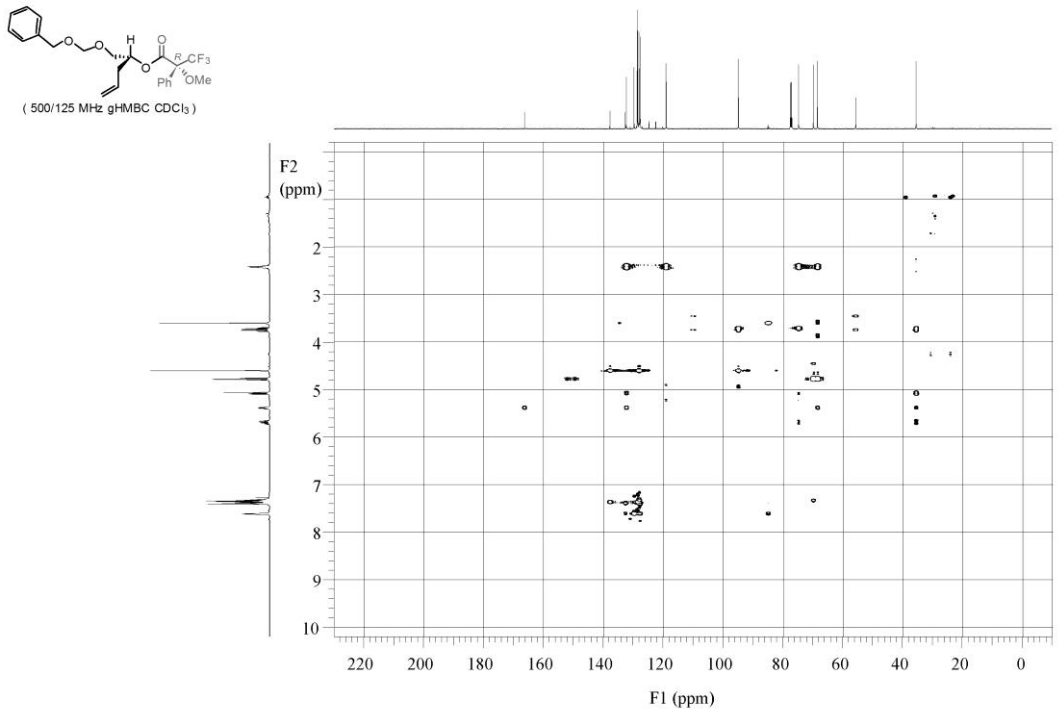


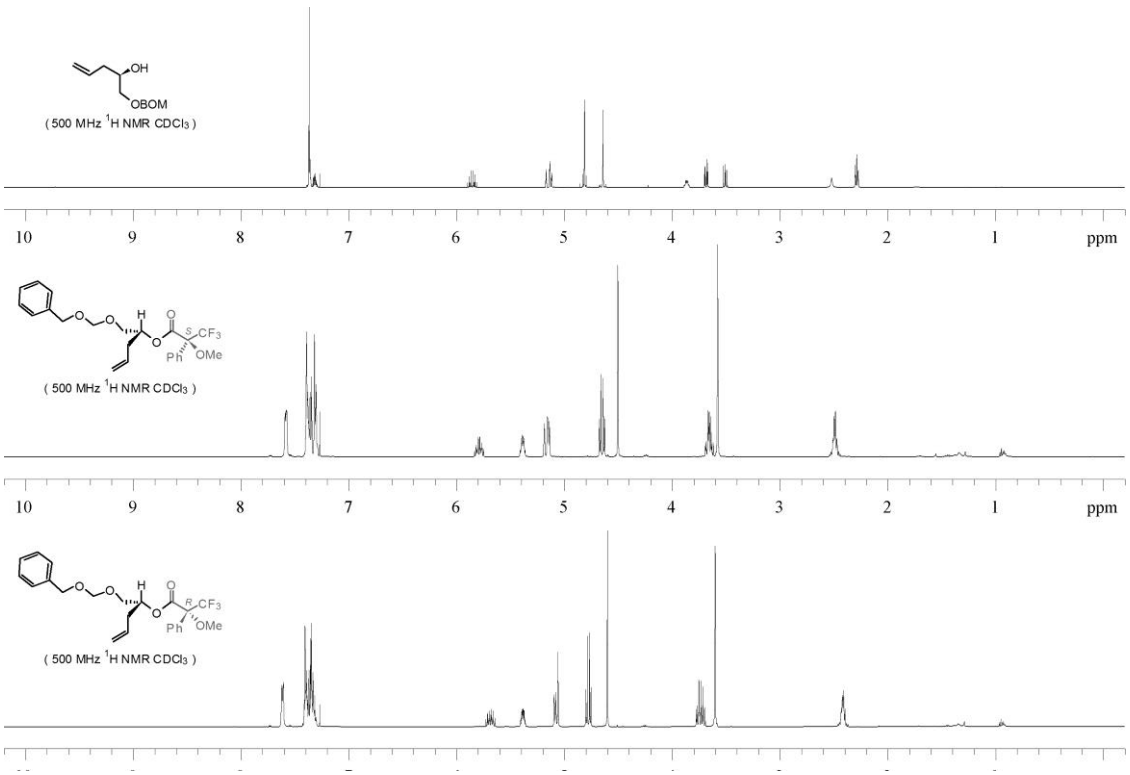


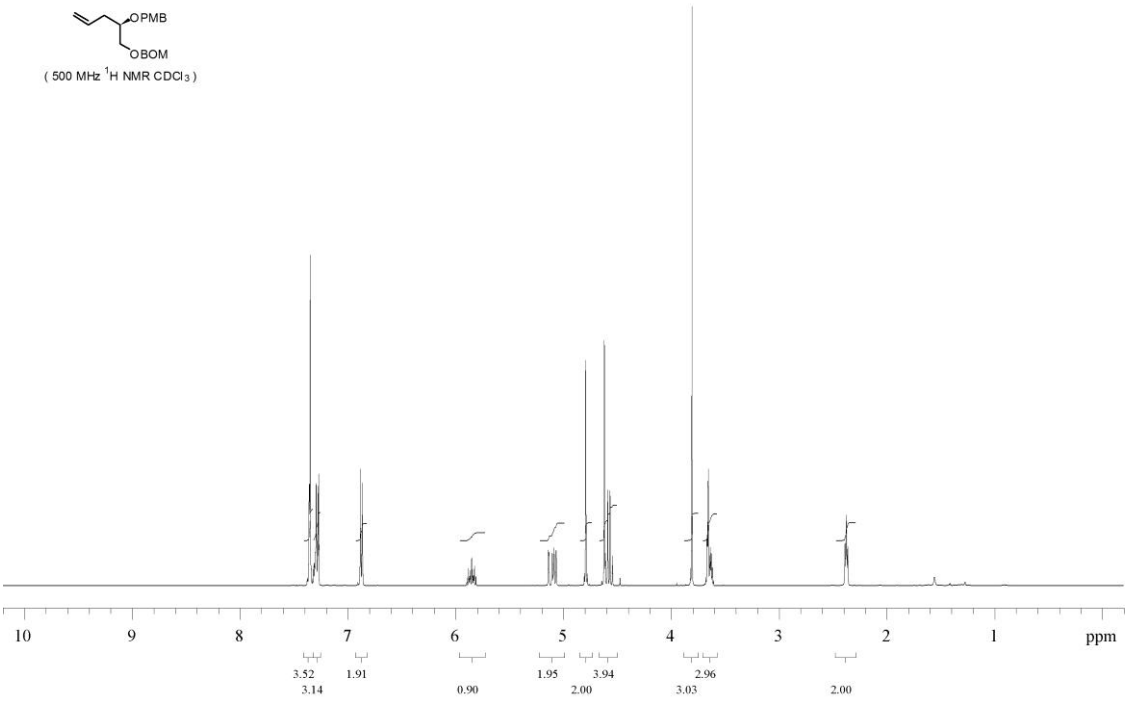
(125 MHz ^{13}C NMR $CDCl_3$)

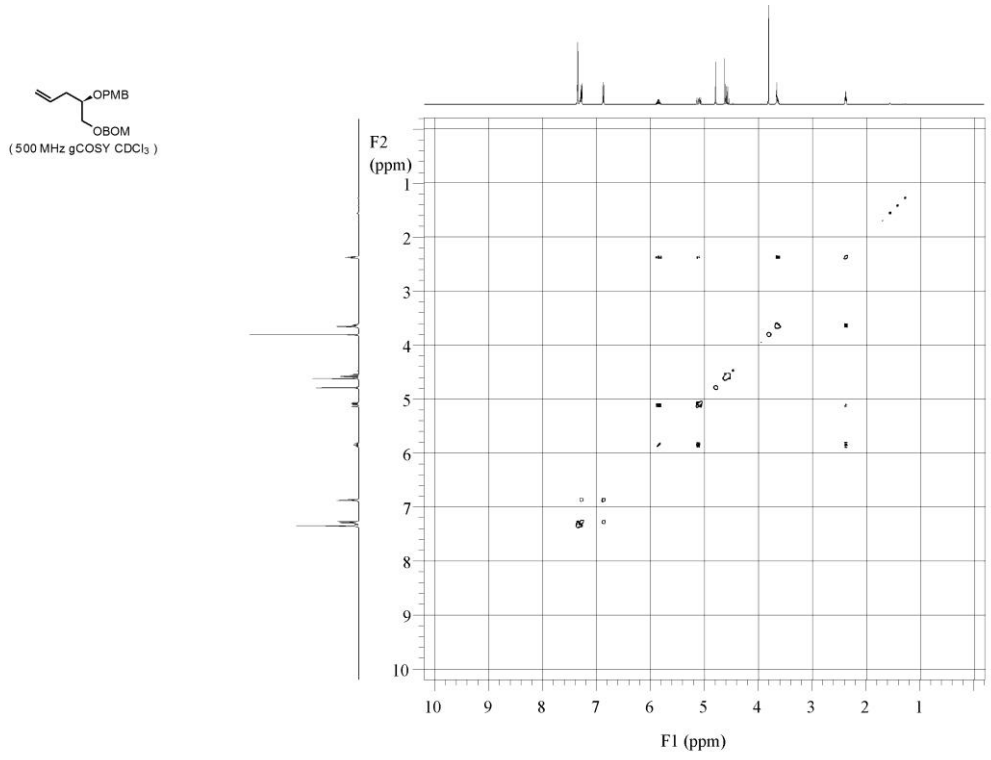

(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

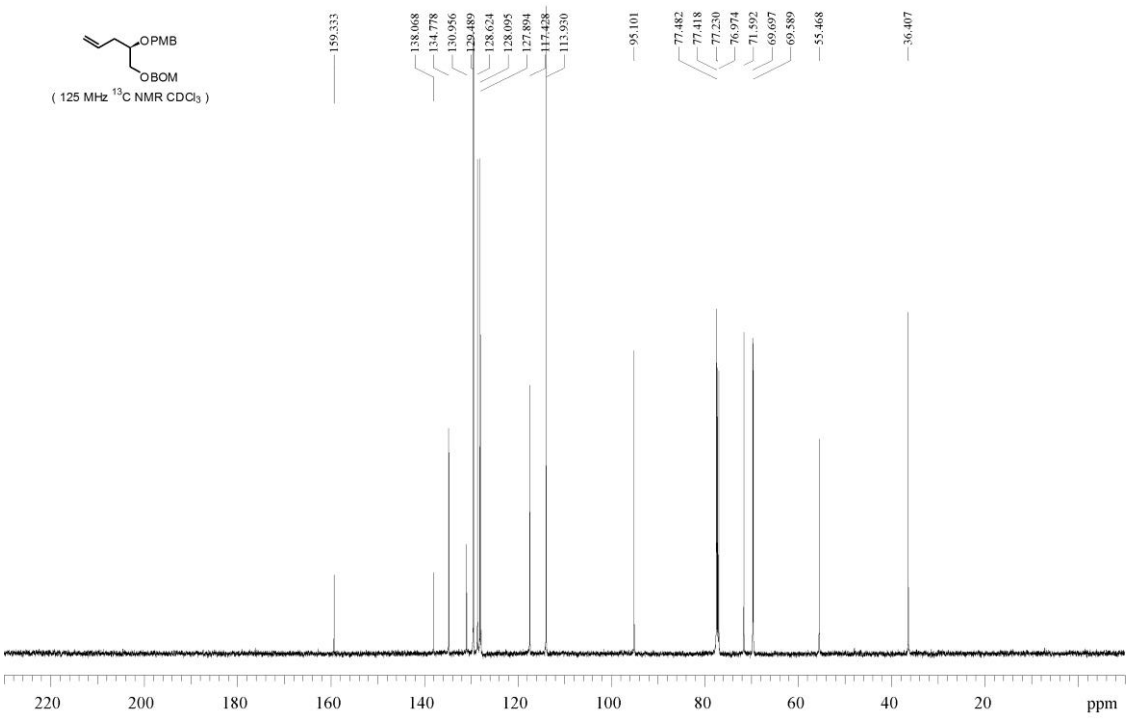

(500/125 MHz gHSQC CDCl3)
F2
(ppm)
F1 (ppm)

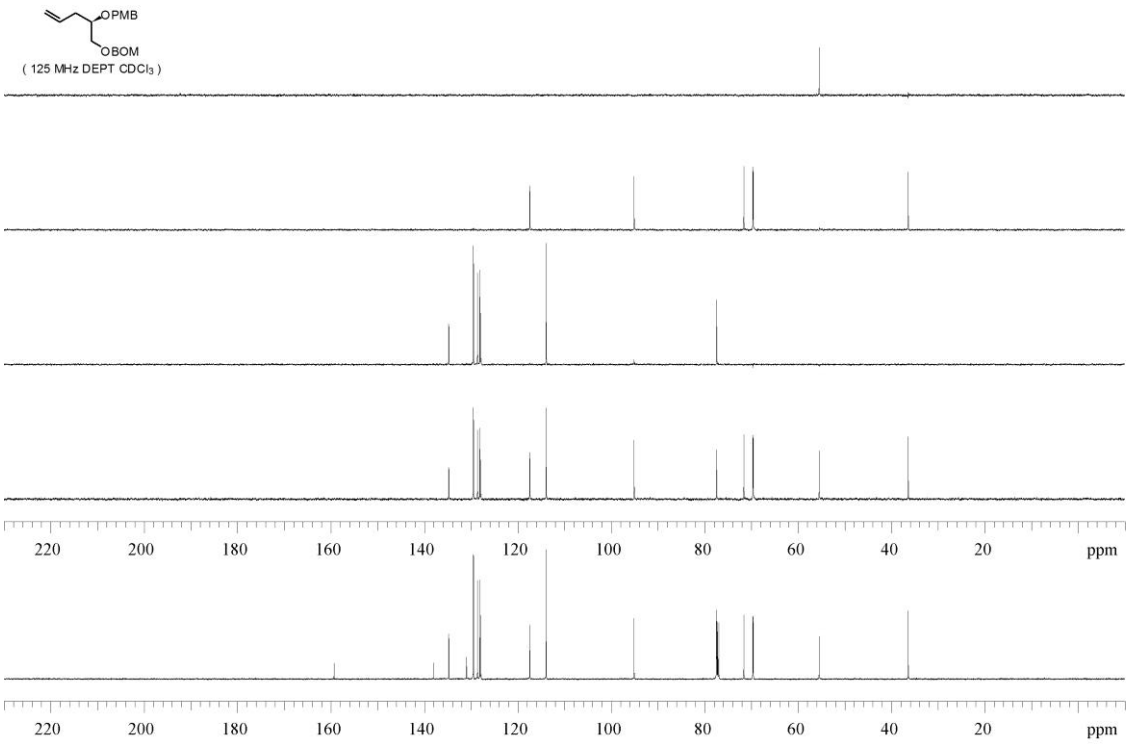

(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

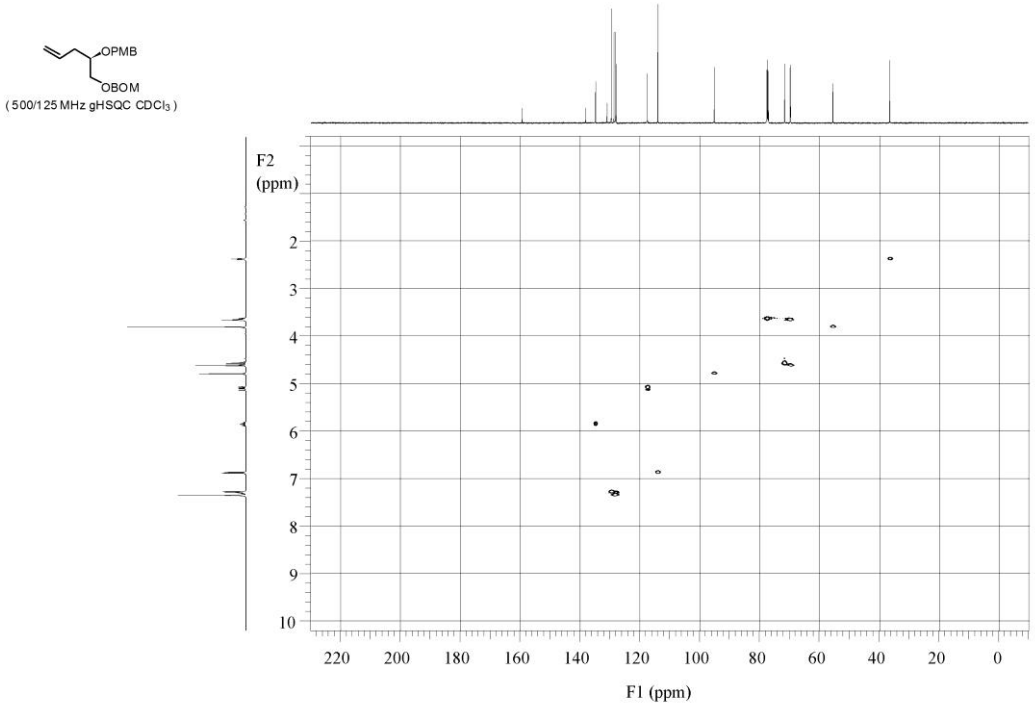

OH
OBOM
(500 MHz 1H NMR CDCl3)
ppm
(500 MHz 1H NMR CDCl3)
ppm
(500 MHz 1H NMR CDCl3)

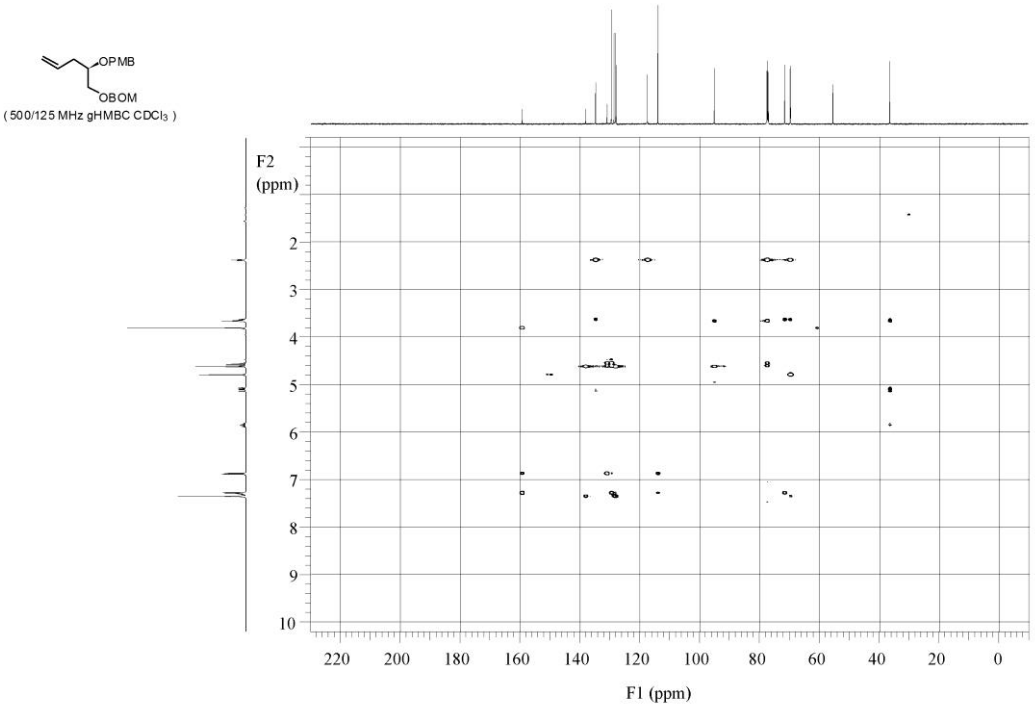

OPMB
OBOM
(500 MHz ^{1}H NMR CDCl$_3$)
10
9
8
7
6
5
4
3
2
1
ppm
3.52
3.14
1.91
0.90
1.95
2.00
3.94
2.96
3.03
2.00

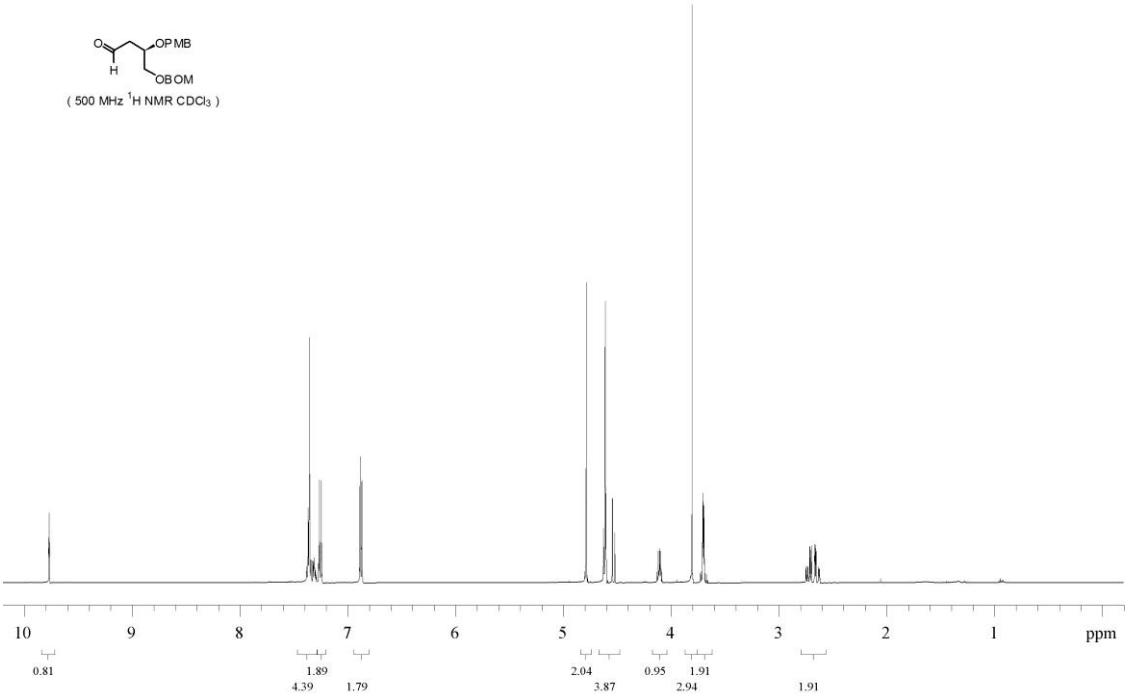

OPMB
OBOM
(500 MHz gCOSY CDCl$_3$)
F2
(ppm)
F1 (ppm)

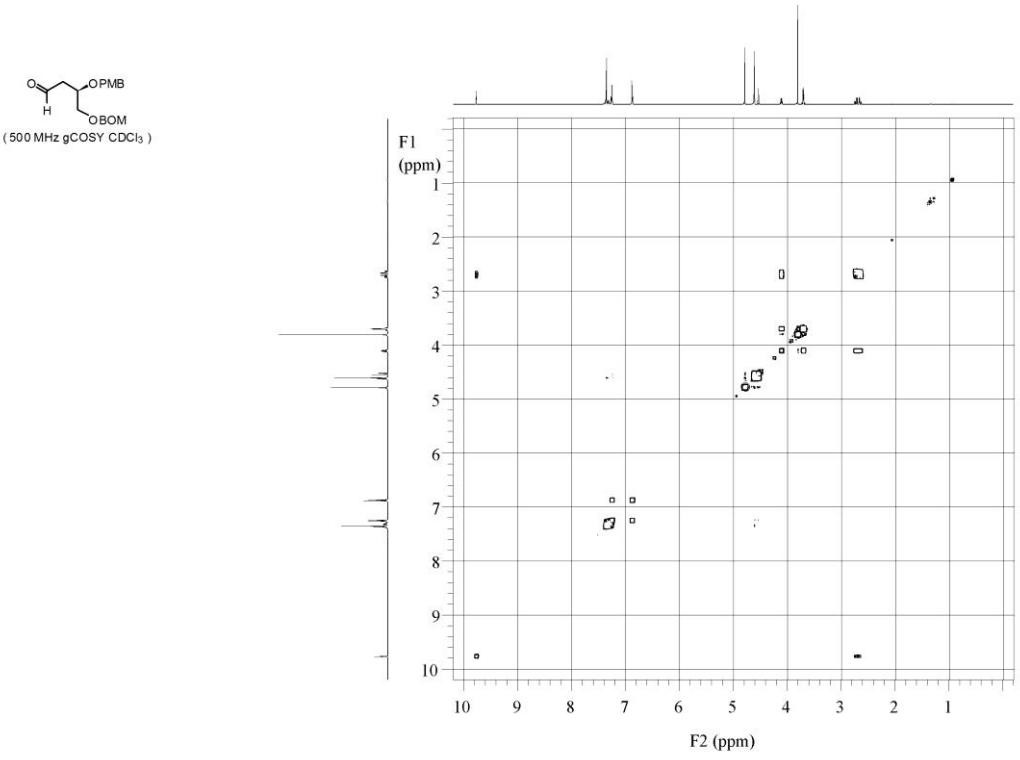

OPMB
OBOM
(125 MHz ^{13}C NMR $CDCl_3$)
159.333
138.068
134.778
130.956
129.489
128.624
128.095
127.894
117.428
113.930
95.101
77.482
77.418
77.230
76.974
71.592
69.697
69.589
55.468
36.407
220
200
180
160
140
120
100
80
60
40
20
ppm

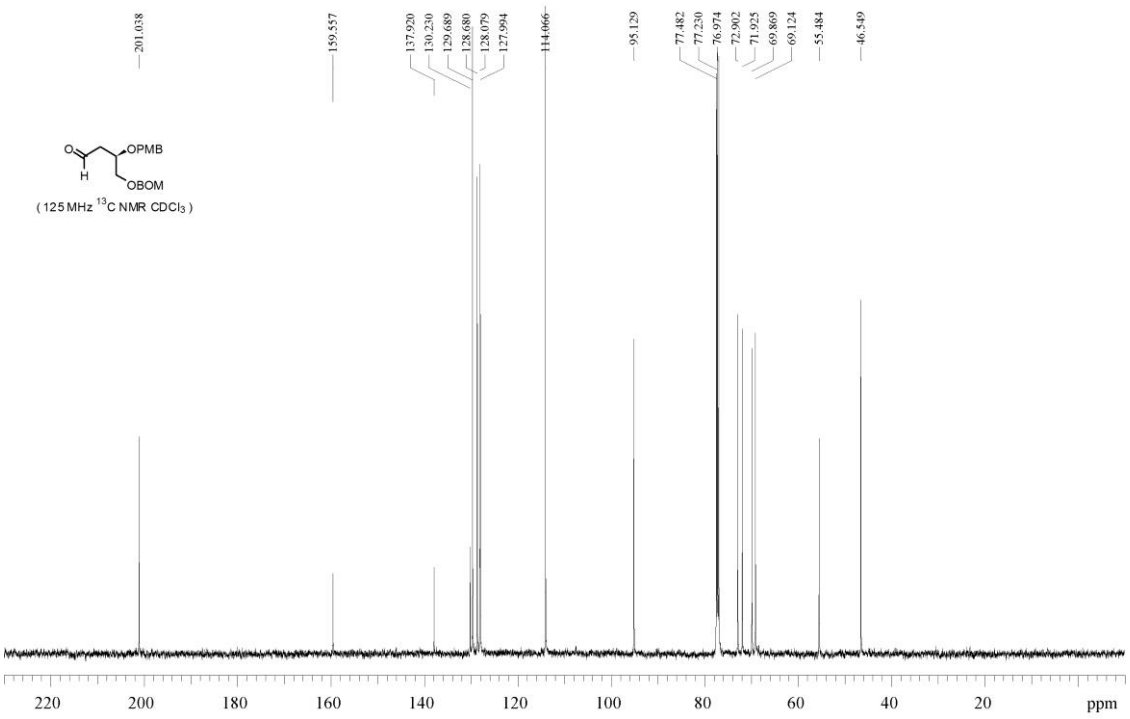

OPMB
OBOM
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

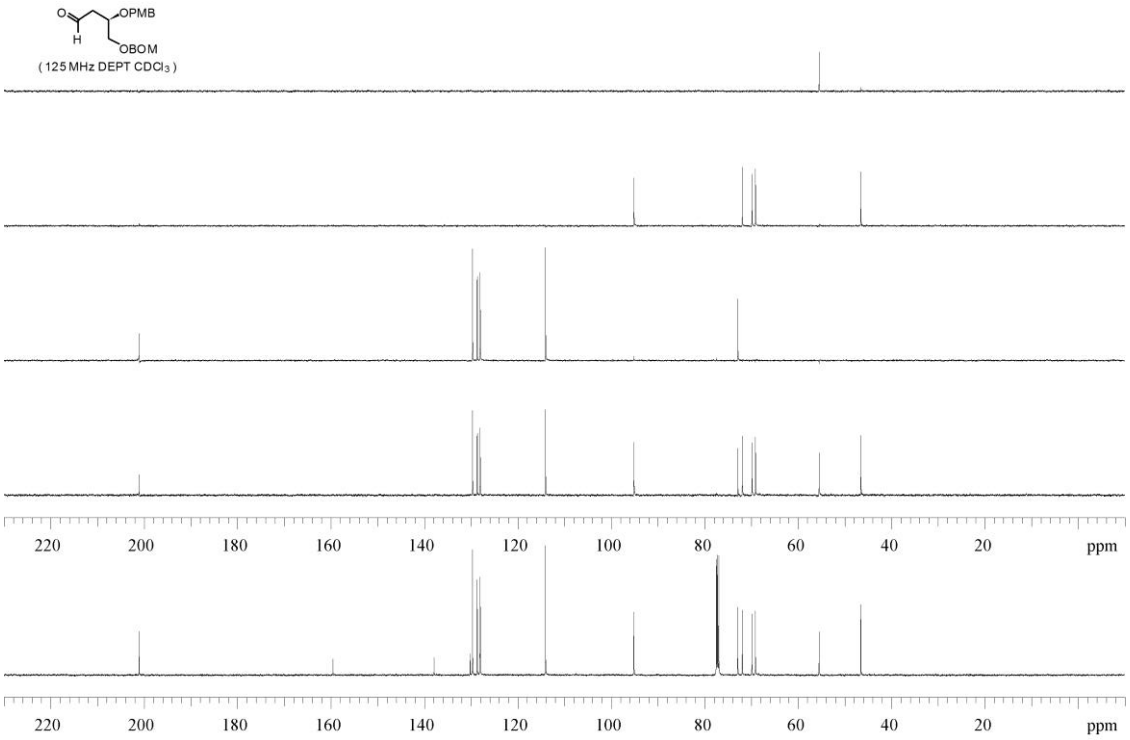

OPMB
OBOM
(500/125 MHz gHSQC CDCl3)
F2
(ppm)
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

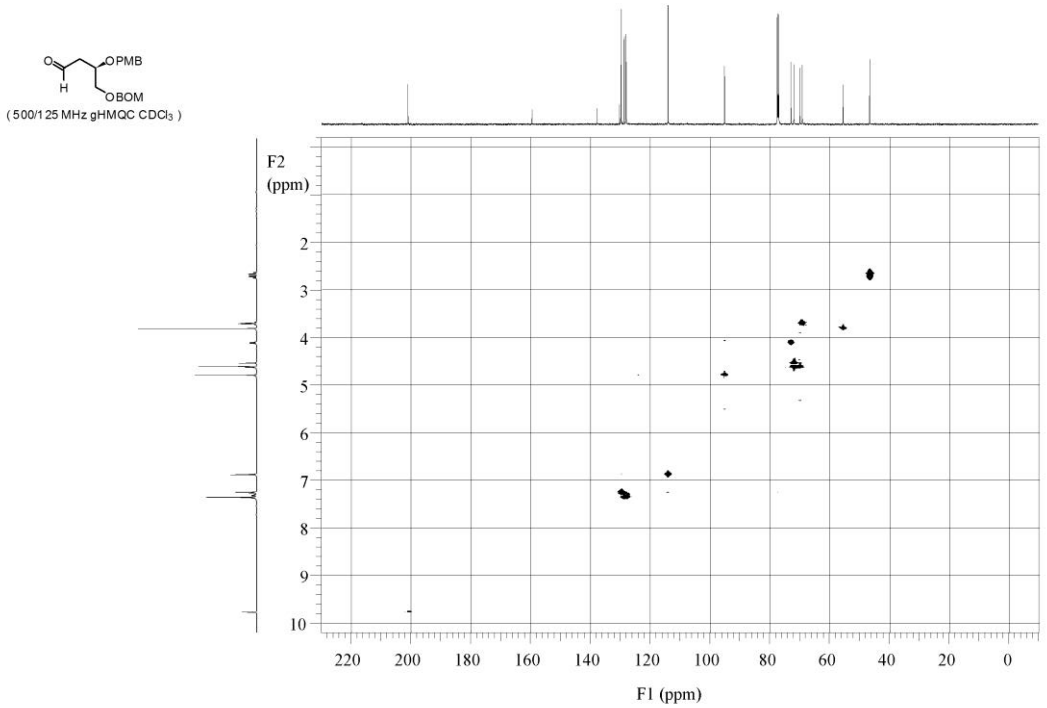

OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

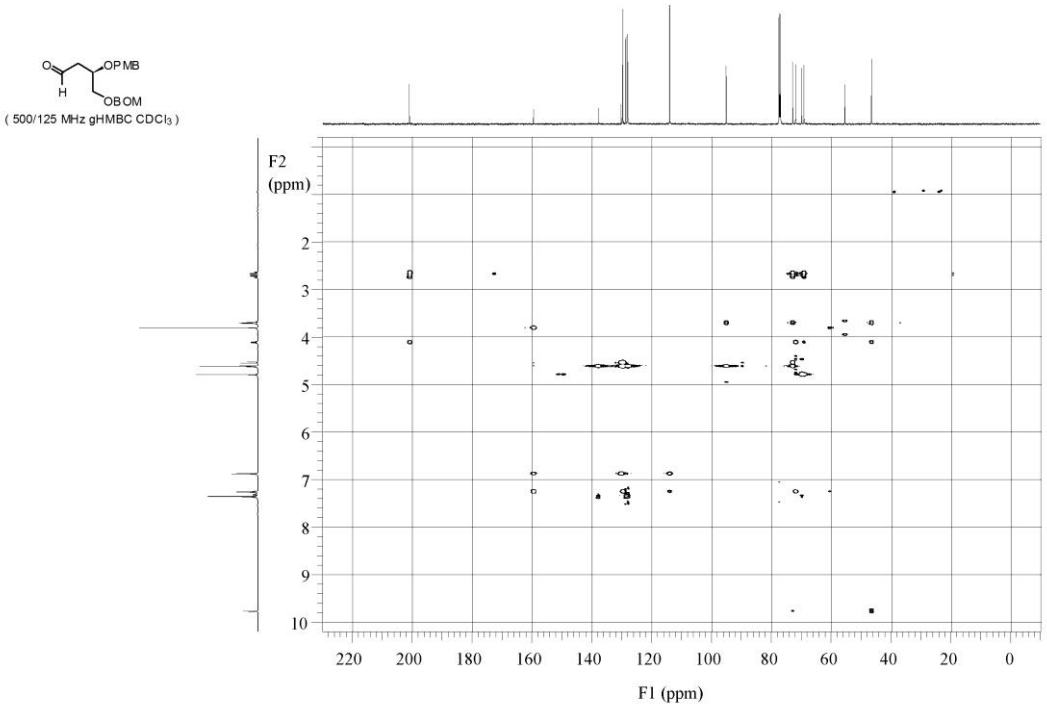

OPMB
OBOM
H
O
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.81
1.89
4.39
1.79
2.04
3.87
0.95
1.91
2.94
1.91

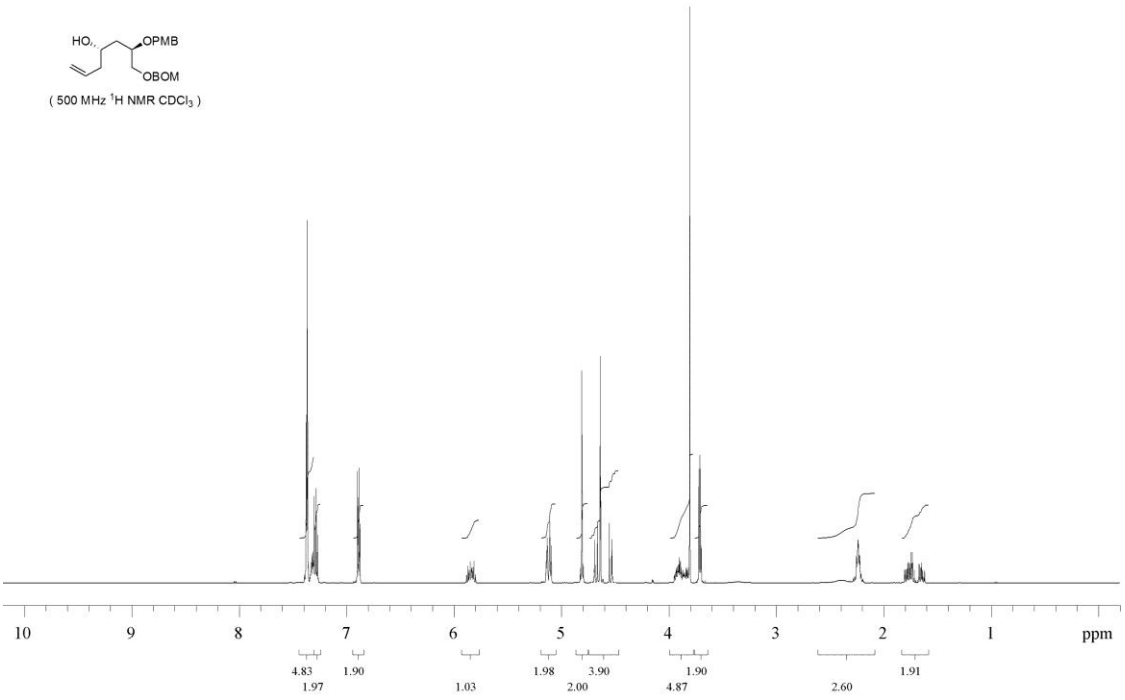

OPMB
OBOM
H
O
(500 MHz gCOSY $CDCl_3$)
F1
(ppm)
F2 (ppm)

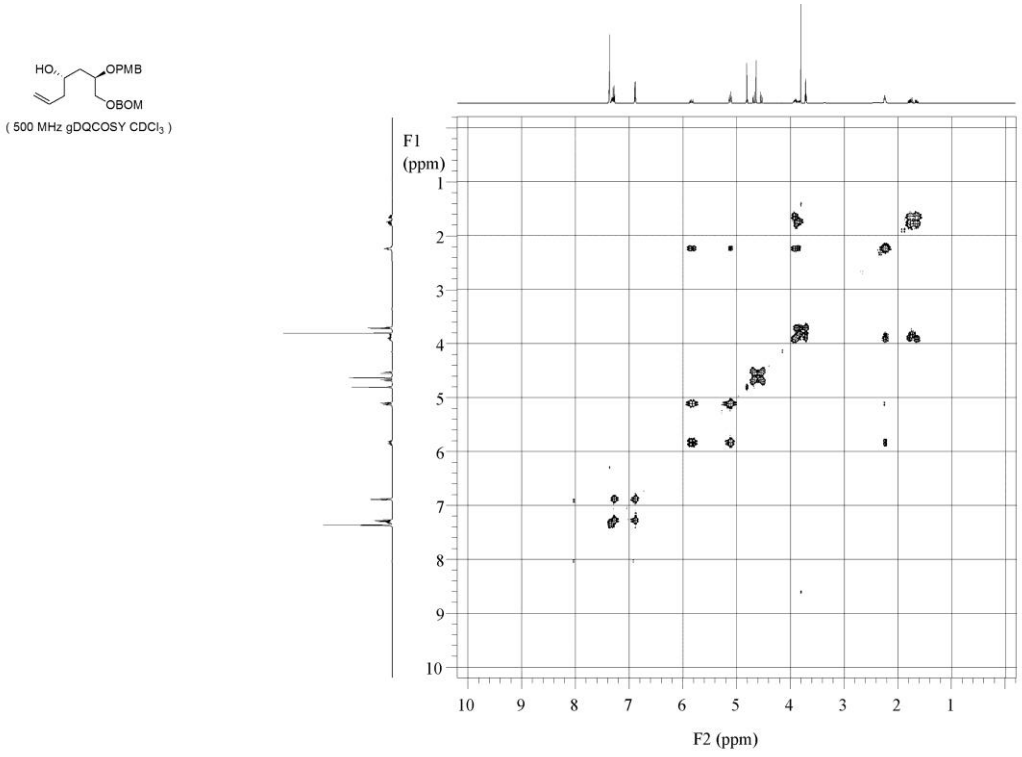

201.038
159.557
137.920
130.230
129.689
128.680
128.079
127.994
114.066
95.129
77.482
77.230
76.974
72.902
71.925
69.869
69.124
55.484
46.549
OPMB
OBOM
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

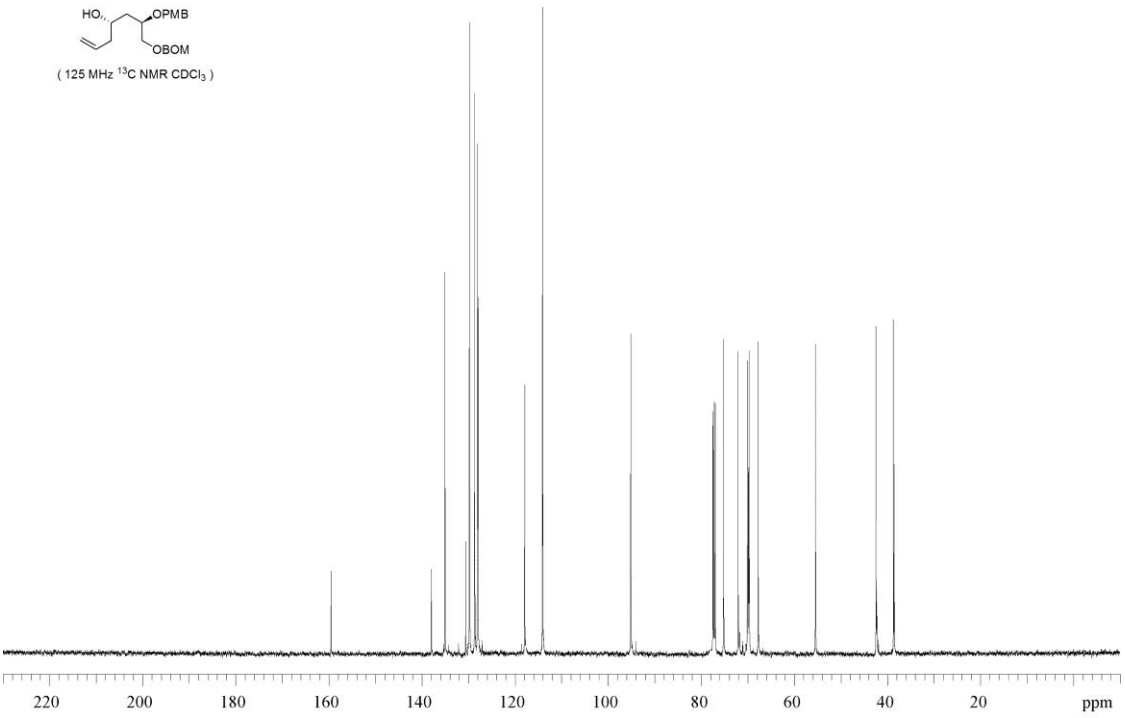

OPMB
OBOM
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

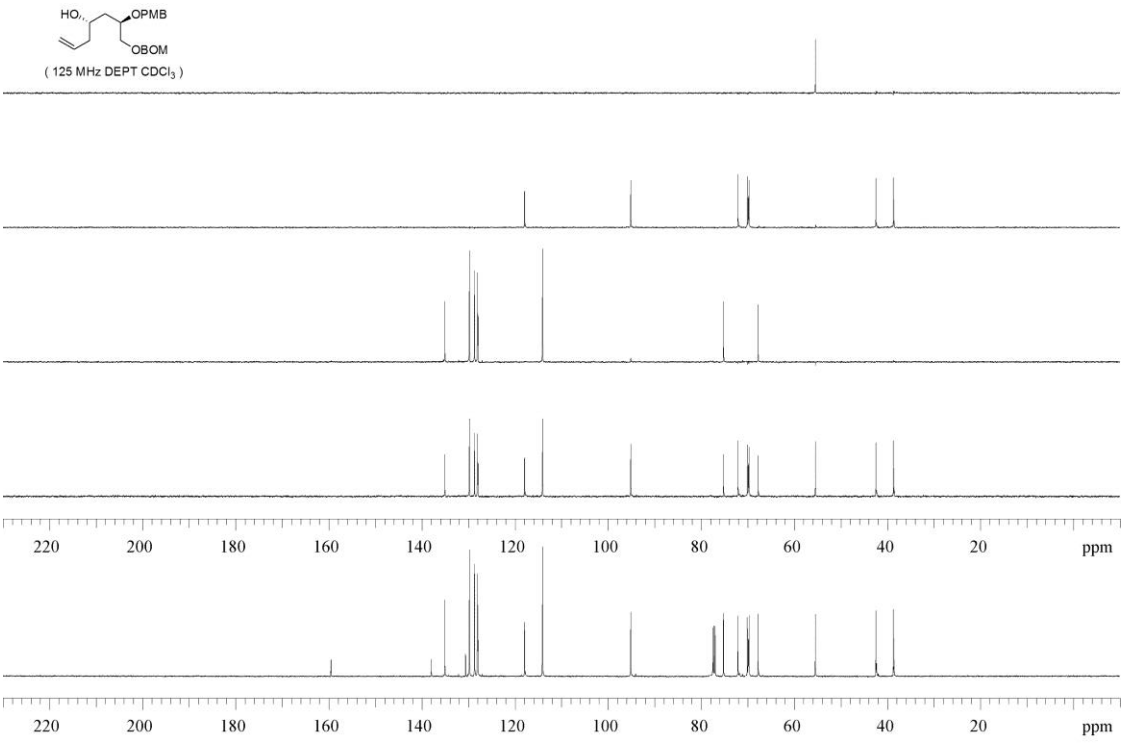

OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

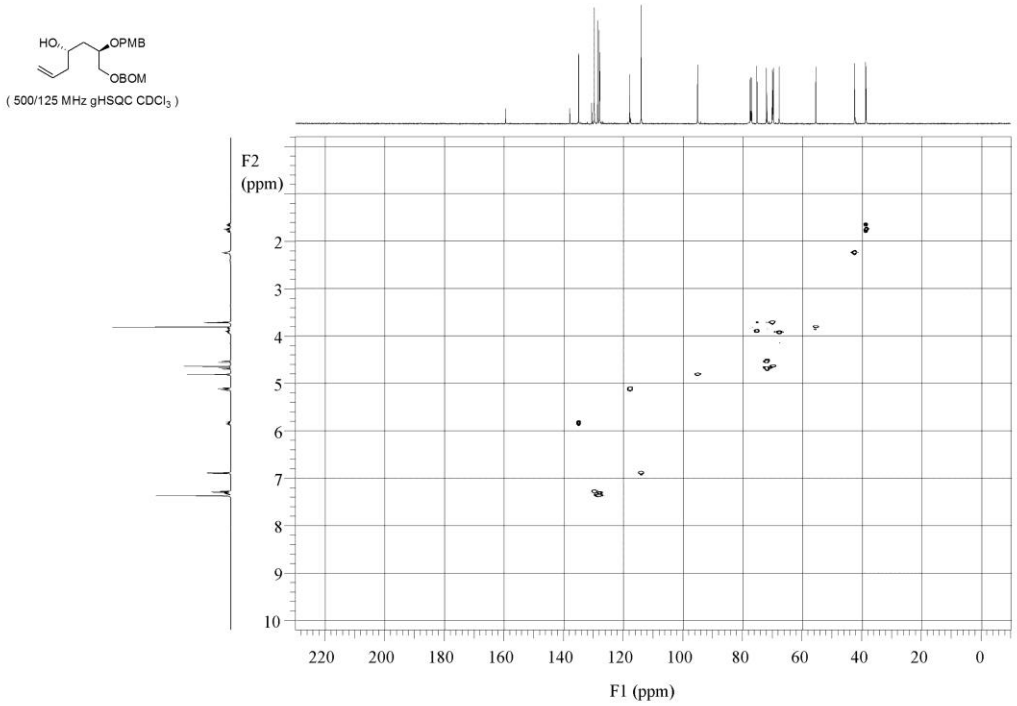

OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

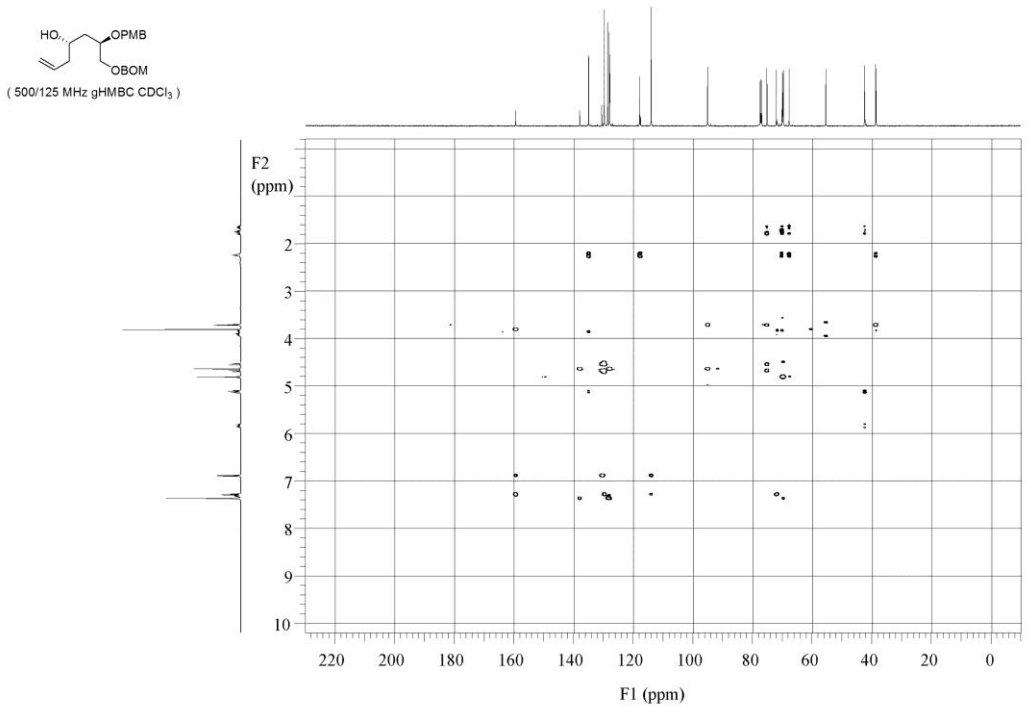

HO
OPMB
OBOM
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
4.83
1.90
1.98
3.90
1.90
1.91
1.97
1.03
2.00
4.87
2.60

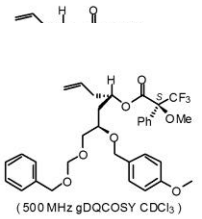

HO
OPMB
OBOM
(500 MHz gDQCOSY $CDCl_3$)
F1
(ppm)
F2 (ppm)


HO
OPMB
OBOM
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

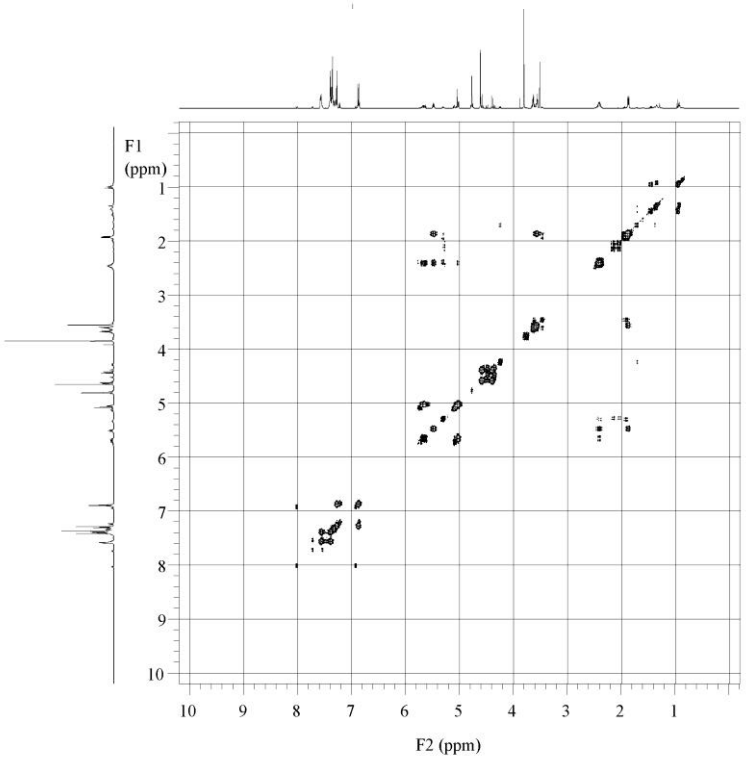

HO
OPMB
OBOM
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

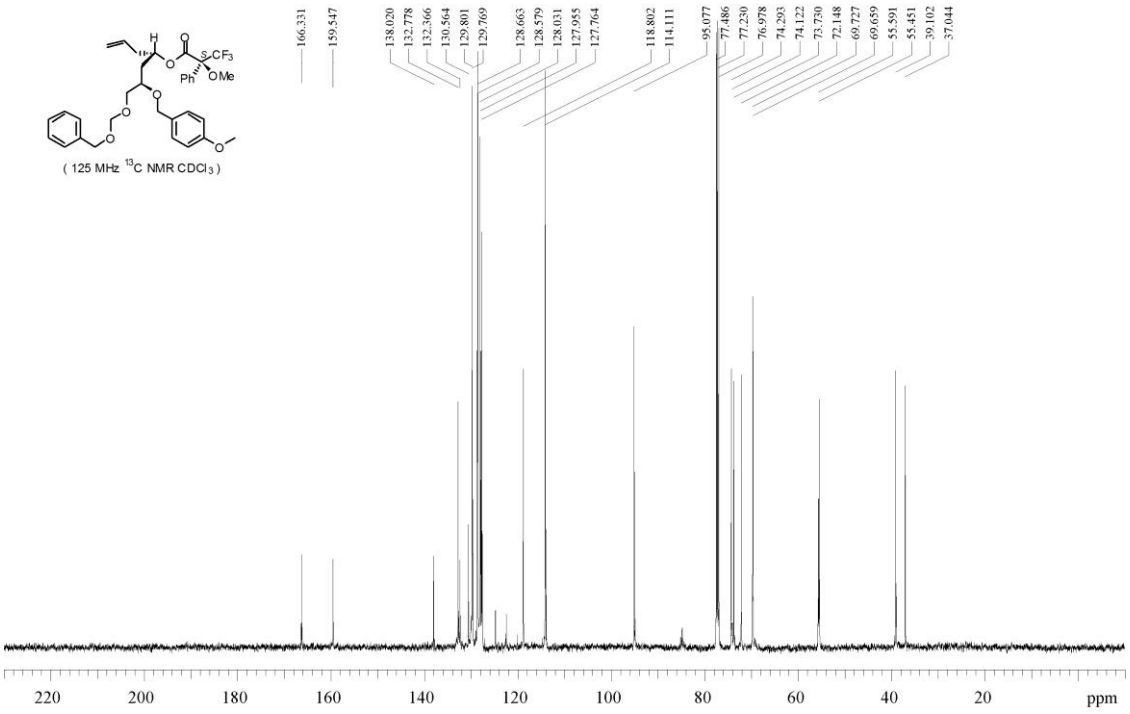

HO
OPMB
OBOM
(500/125 MHz gHSQC CDCl3)
F2
(ppm)
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

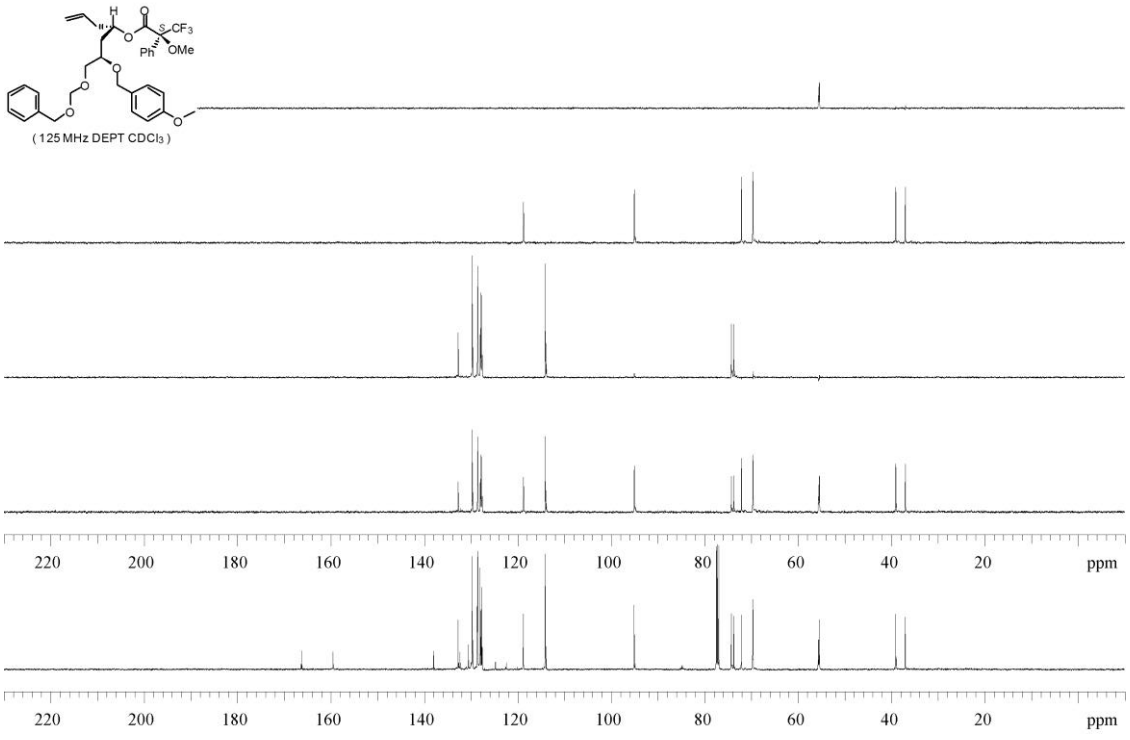

HO
OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

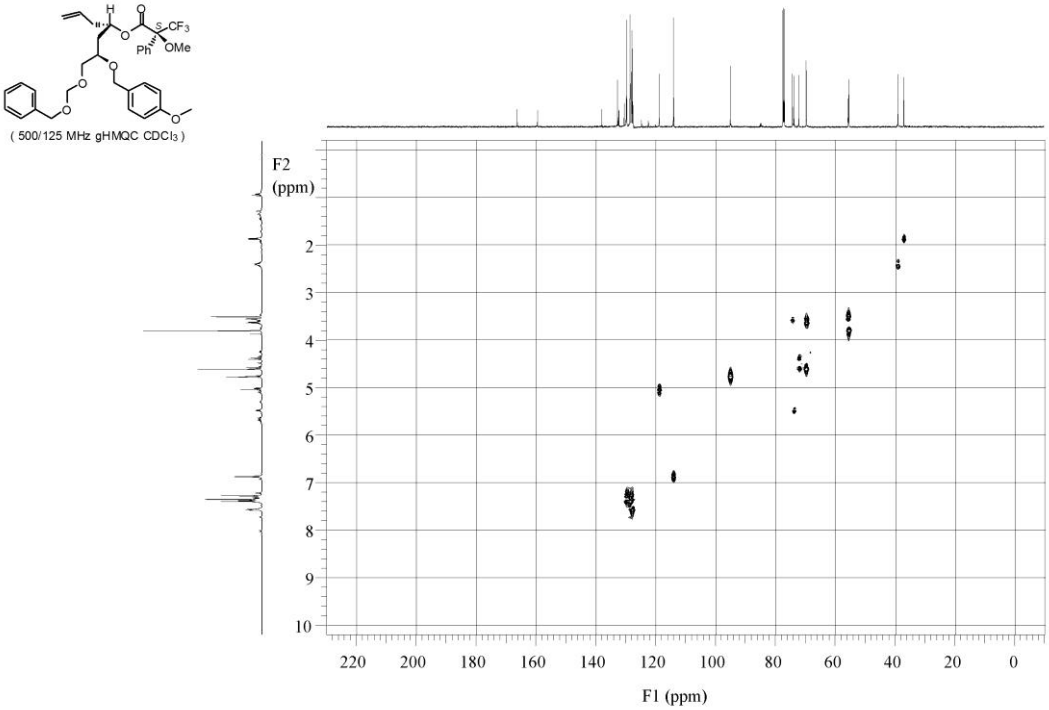


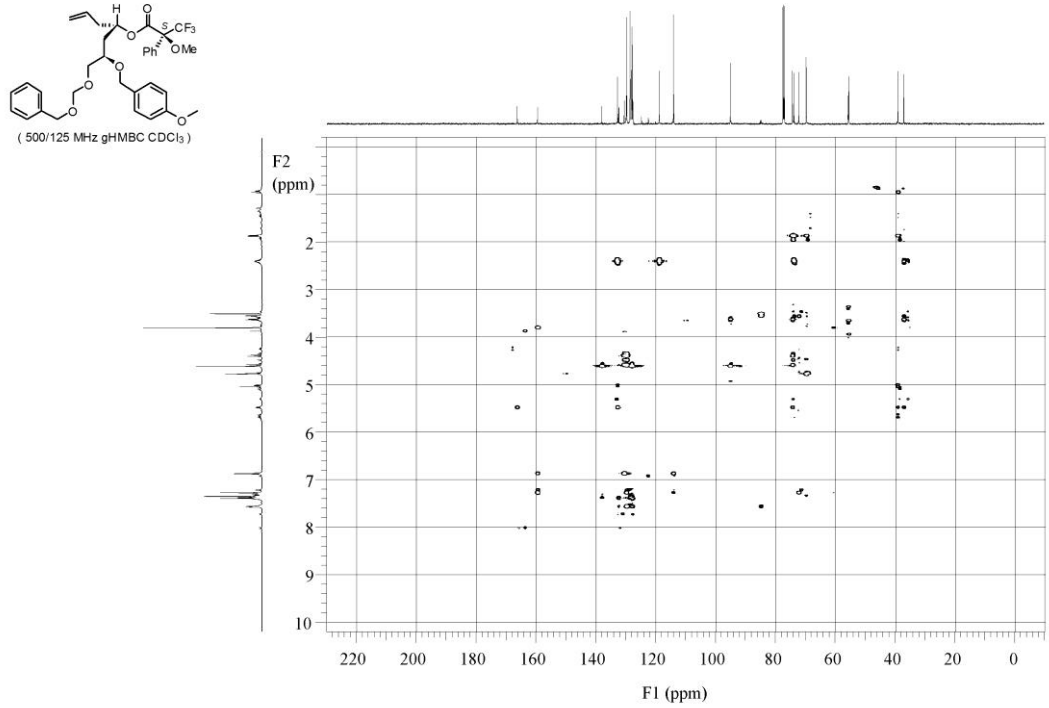
(500 MHz gDQCOSY $CDCl_3$)

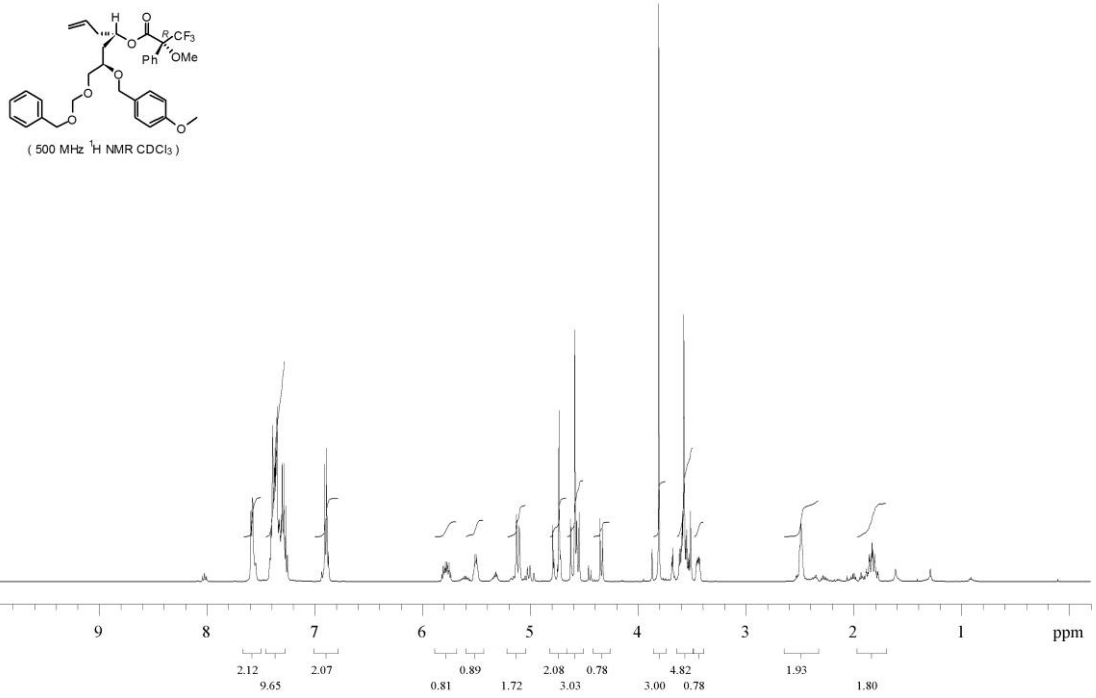


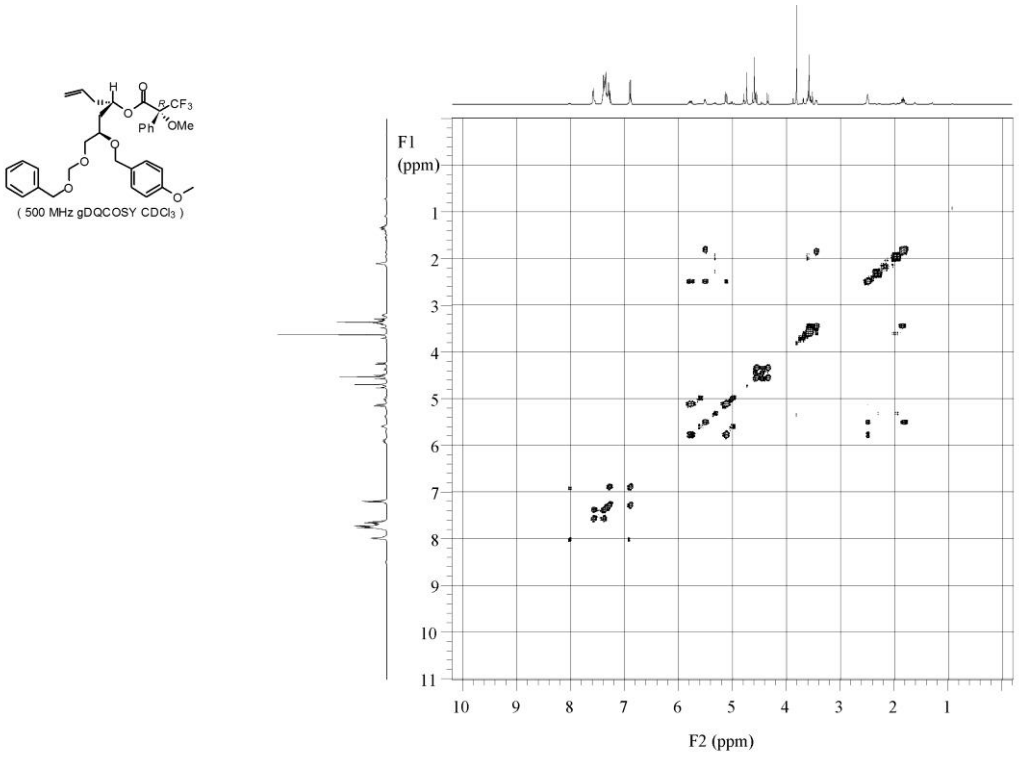

166.331
159.547
138.020
132.778
132.366
130.564
129.801
129.769
128.663
128.579
128.031
127.955
127.764
118.802
114.111
95.077
77.486
77.230
76.978
74.293
74.122
73.730
72.148
69.727
69.659
55.591
55.451
39.102
37.044
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

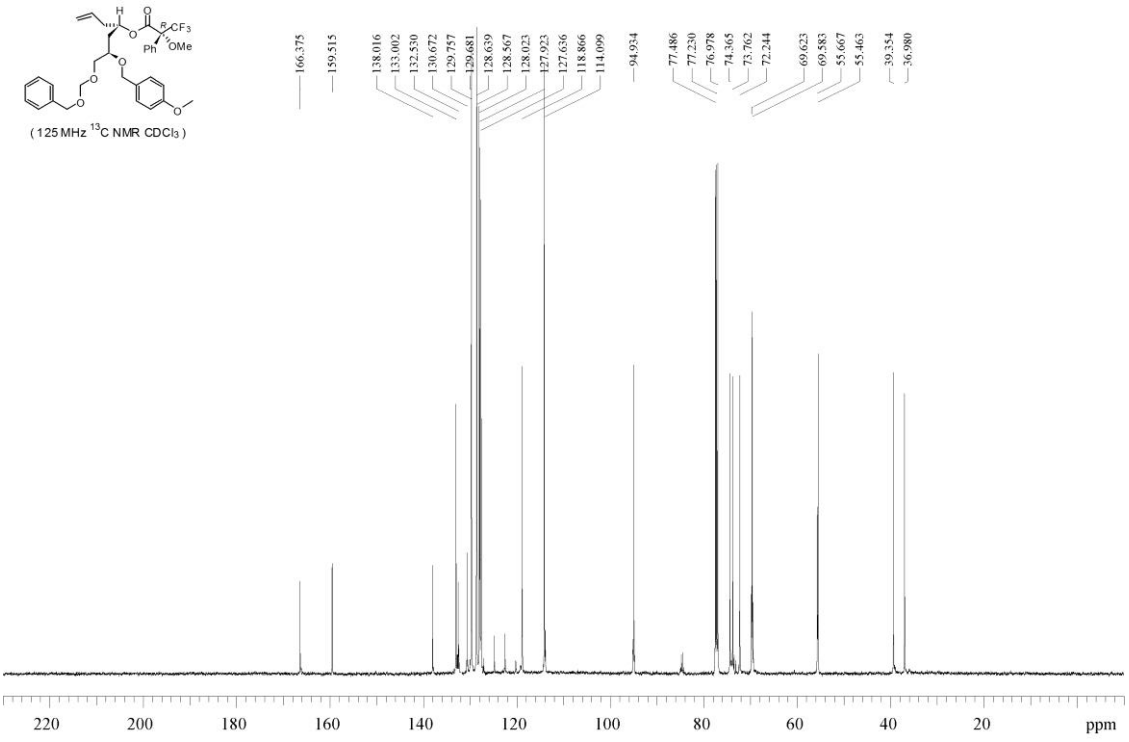

(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

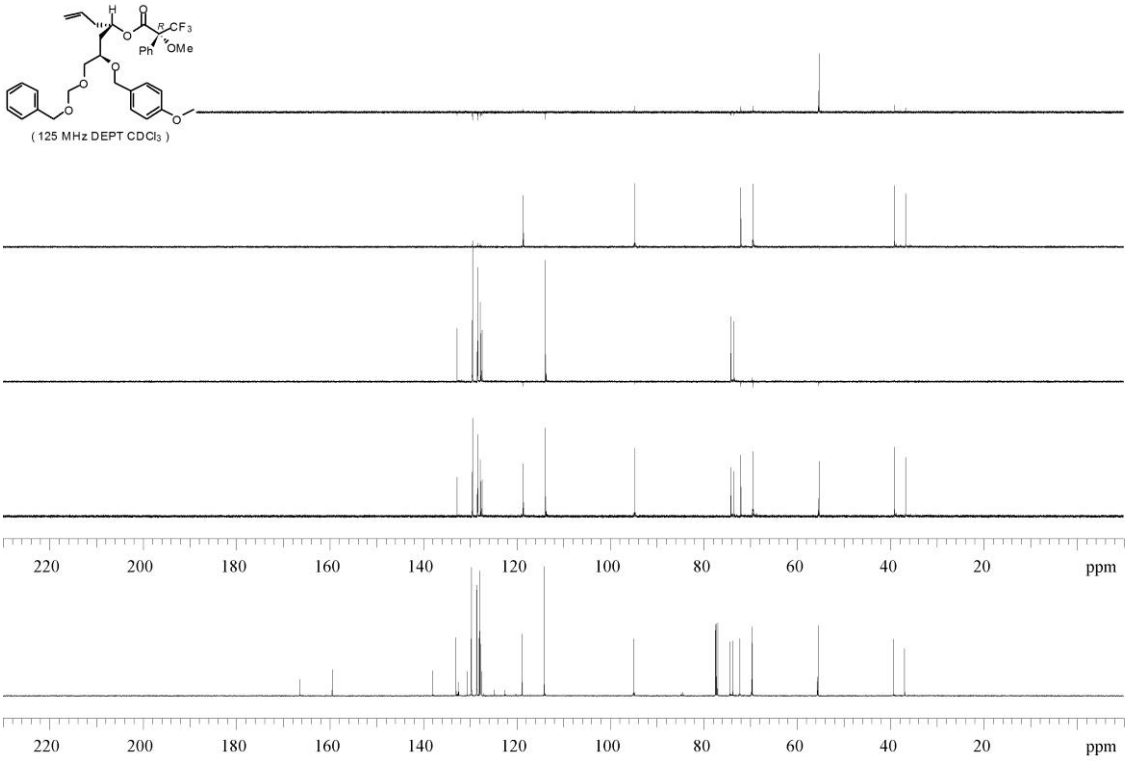

(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

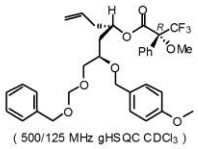

(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)


(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
2.12
2.07
0.89
2.08
0.78
4.82
1.93
9.65
0.81
1.72
3.03
3.00
0.78
1.80

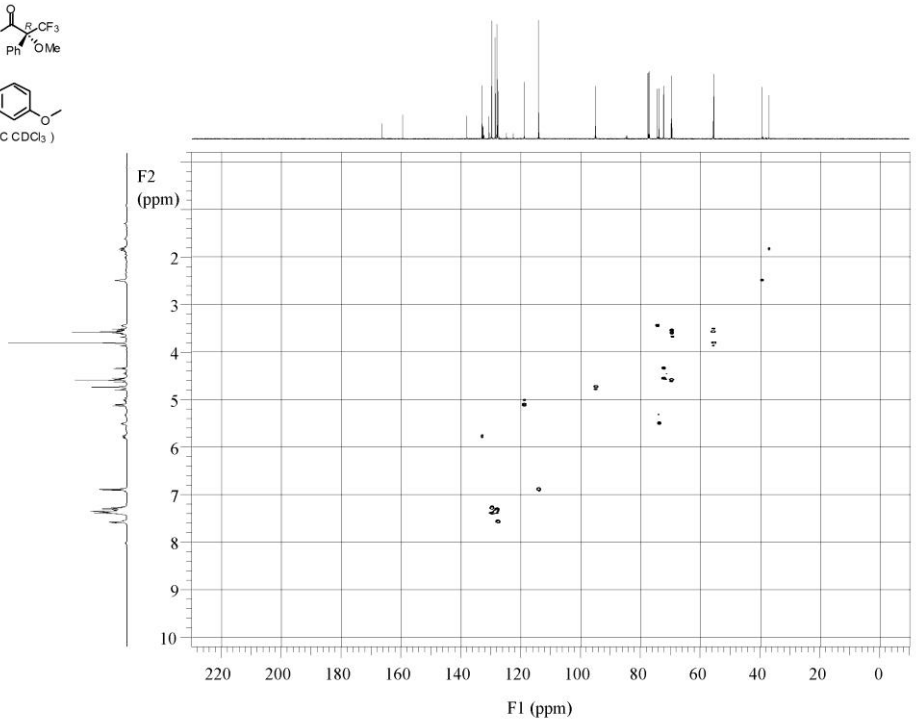

(500 MHz gDQCOSY $CDCl_3$)
F1
(ppm)
F2 (ppm)

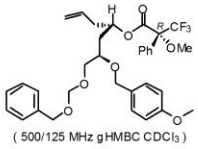

(125 MHz ^{13}C NMR $CDCl_3$)
166.375
159.515
138.016
133.002
132.530
130.672
129.757
129.681
128.639
128.567
128.023
127.923
127.636
118.866
114.099
94.934
77.486
77.230
76.978
74.365
73.762
72.244
69.623
69.583
55.667
55.463
39.354
36.980
220
200
180
160
140
120
100
80
60
40
20
ppm


(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

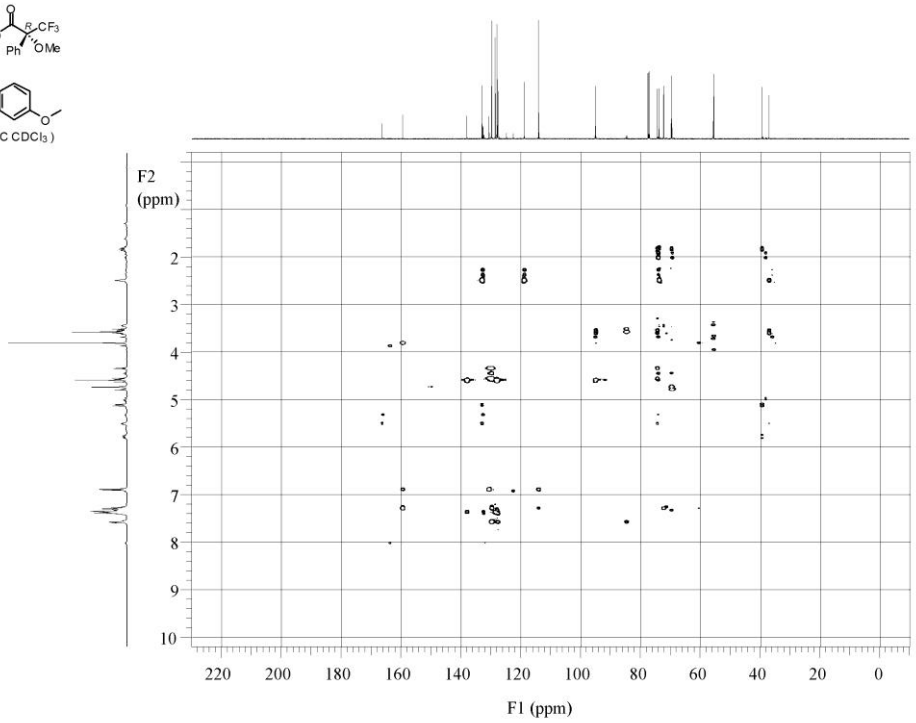


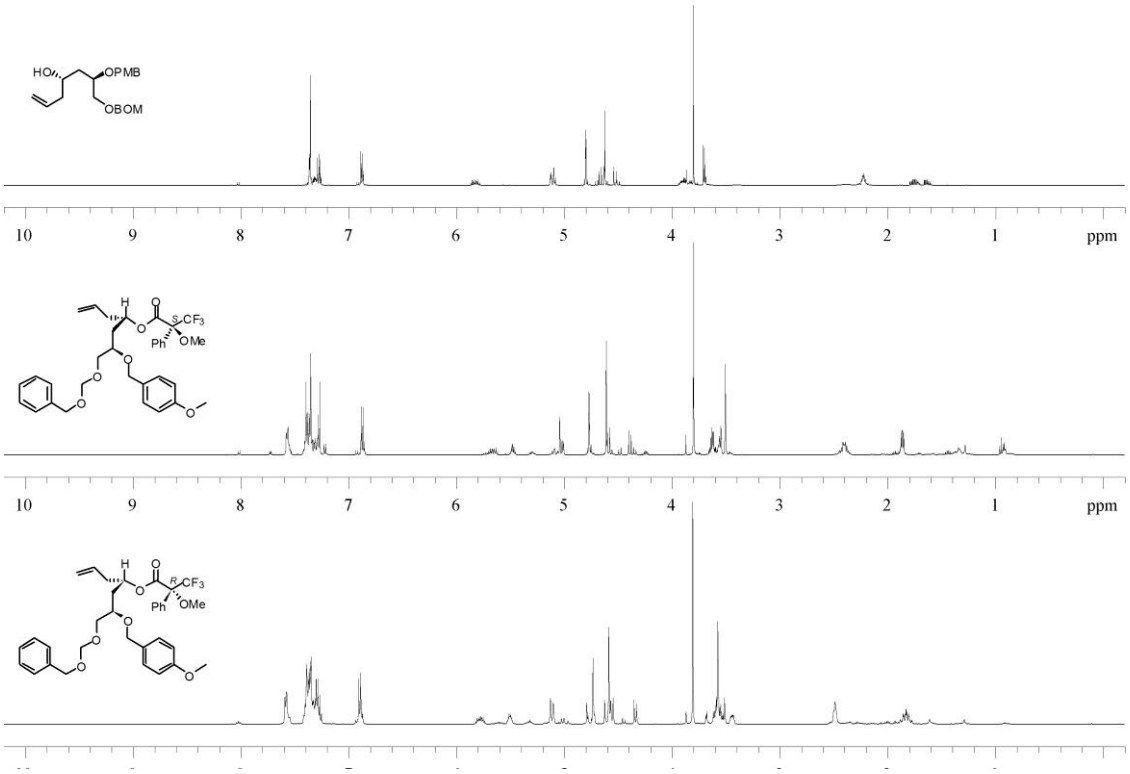
(500/125 MHz gHSQC $CDCl_3$)

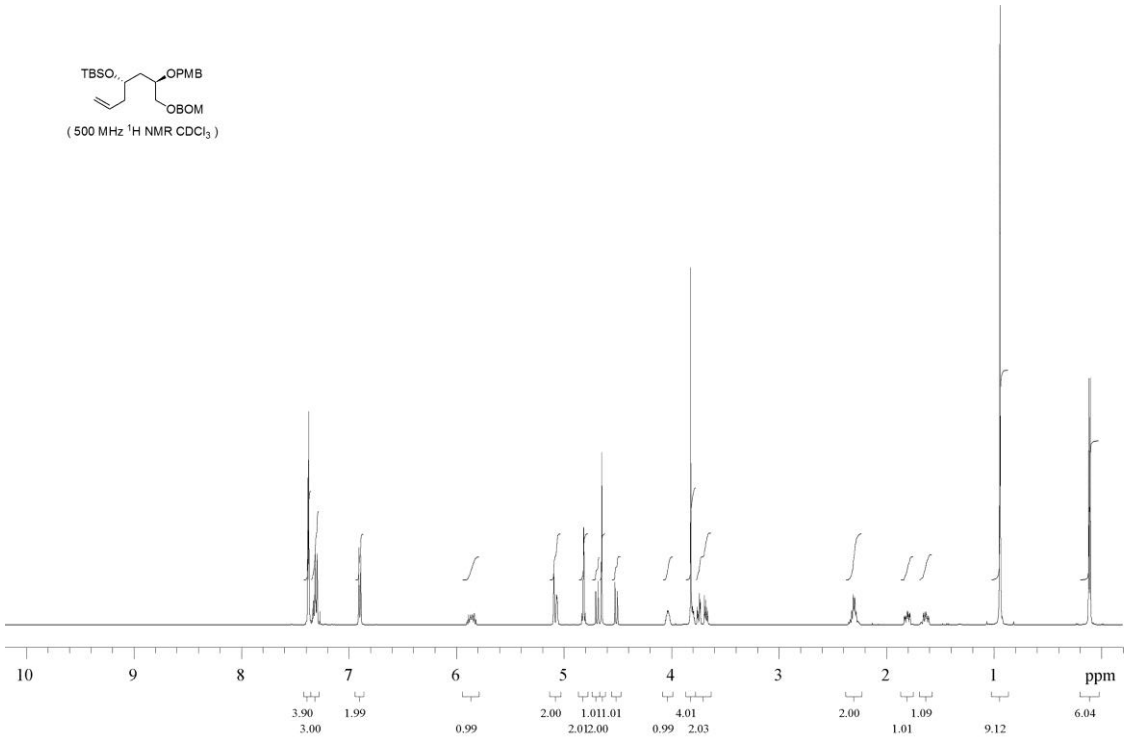


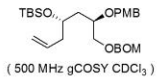


(500/125 MHz gHMBC $CDCl_3$)

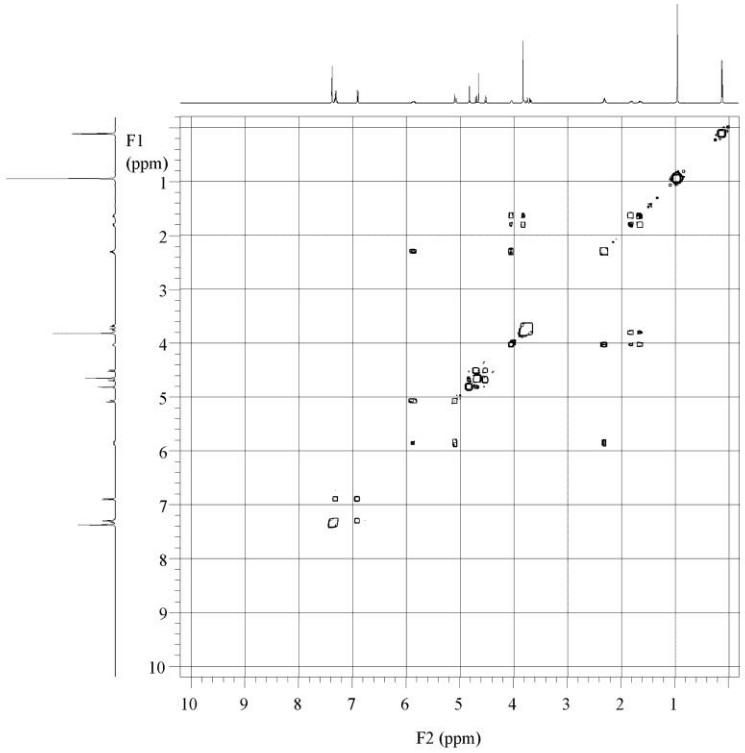


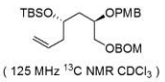

HO
OPMB
OBOM
10 9 8 7 6 5 4 3 2 1 ppm
H
O
S
CF3
Ph
OMe
O
O
O
10 9 8 7 6 5 4 3 2 1 ppm
H
O
R
CF3
Ph
OMe
O
O
O


TBSO
OPMB
OBOM
(500 MHz ^{1}H NMR $CDCl_3$)
10 9 8 7 6 5 4 3 2 1 ppm
3.90 1.99 0.99 2.00 1.01 1.01 4.01 2.00 1.09 6.04
3.00 2.01 2.00 0.99 2.03 1.01 9.12

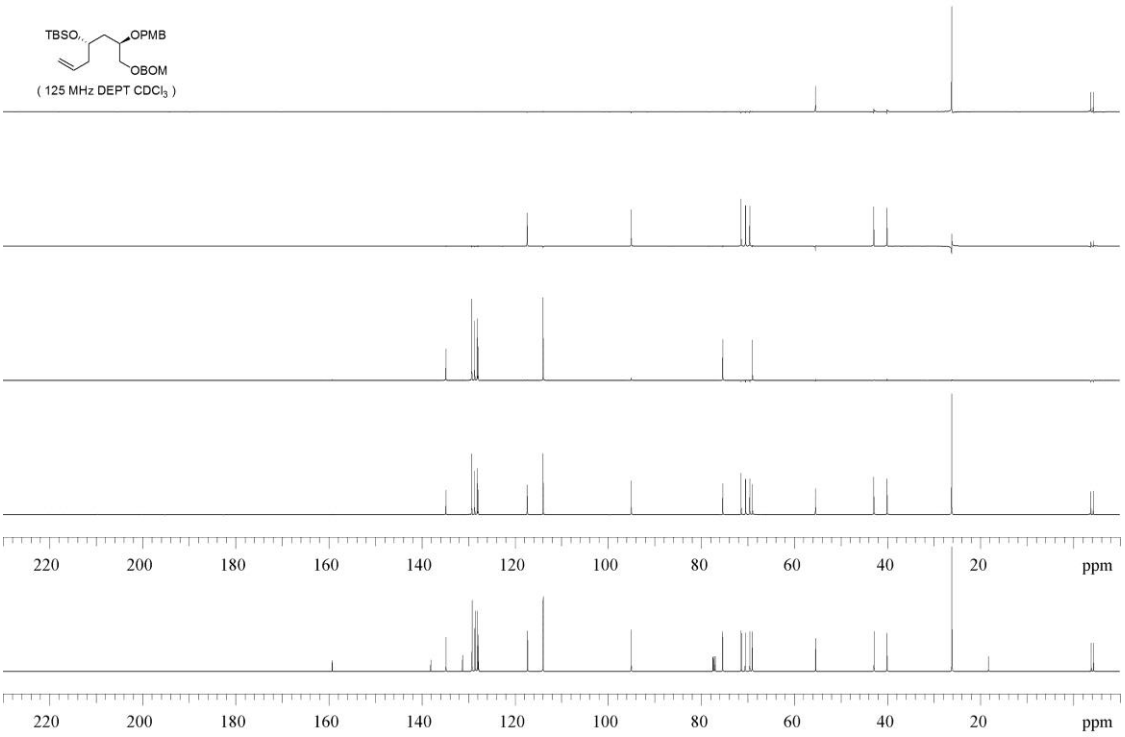


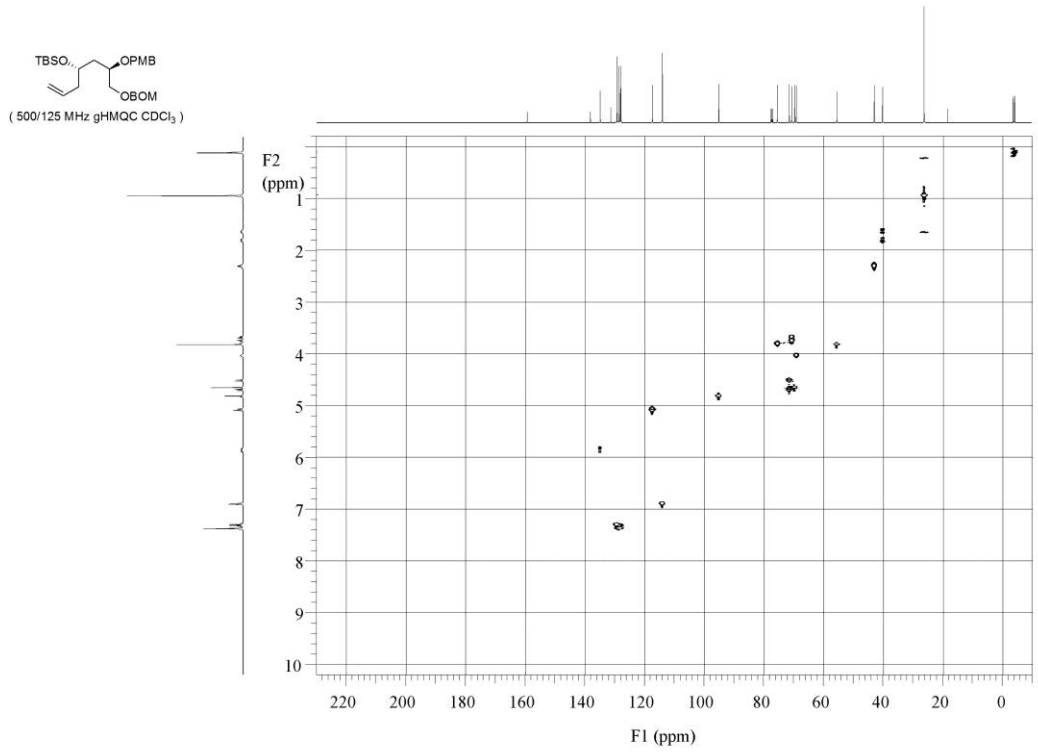
(500 MHz gCOSY $CDCl_3$)

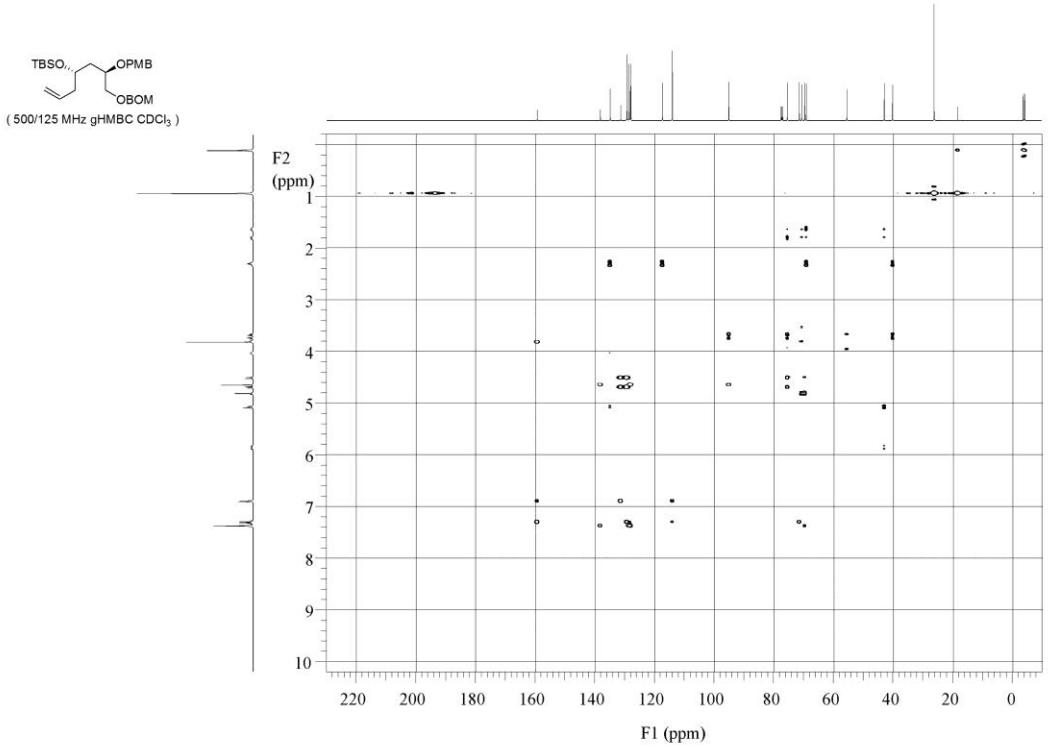


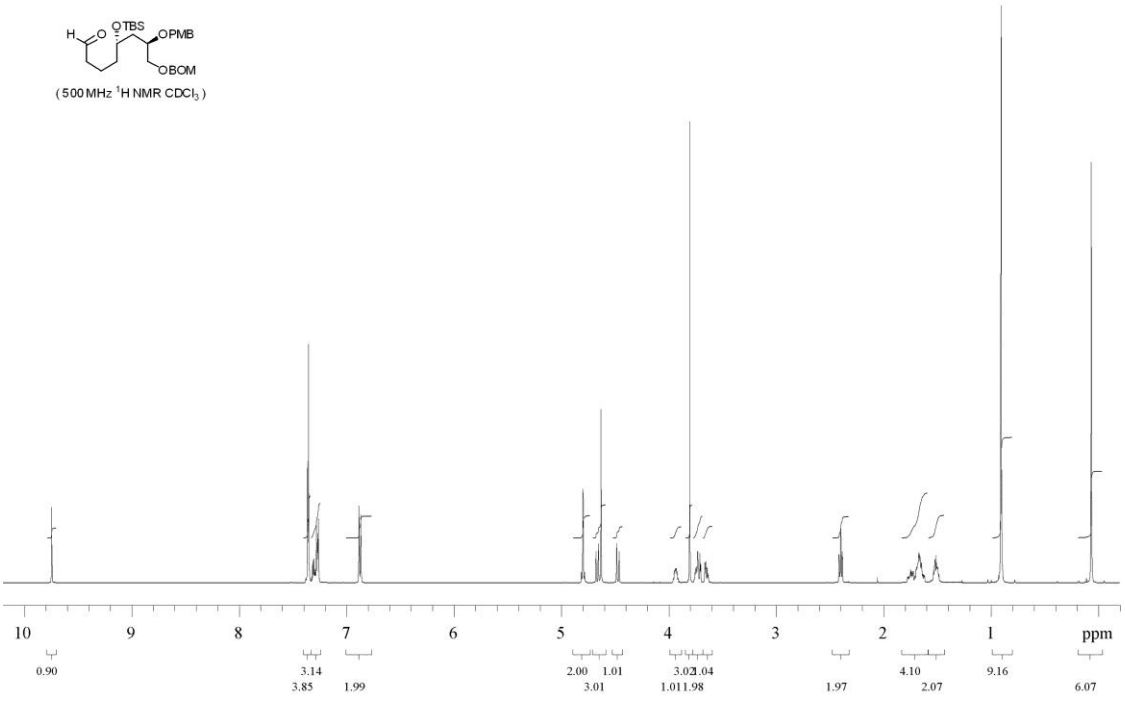


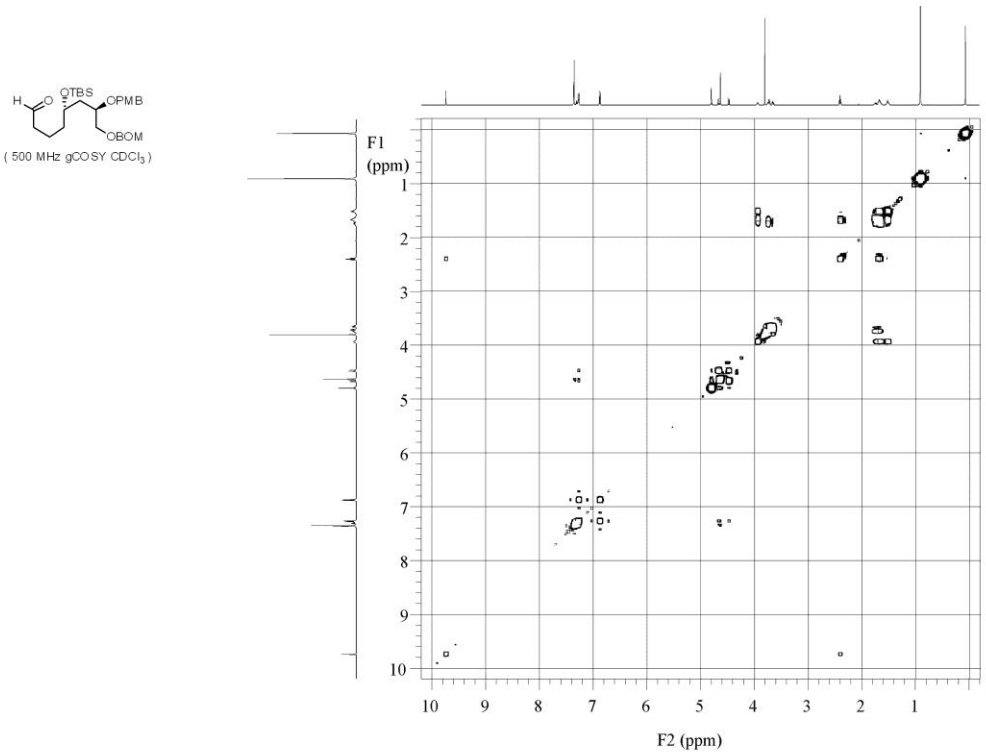
(125 MHz ^{13}C NMR $CDCl_3$)

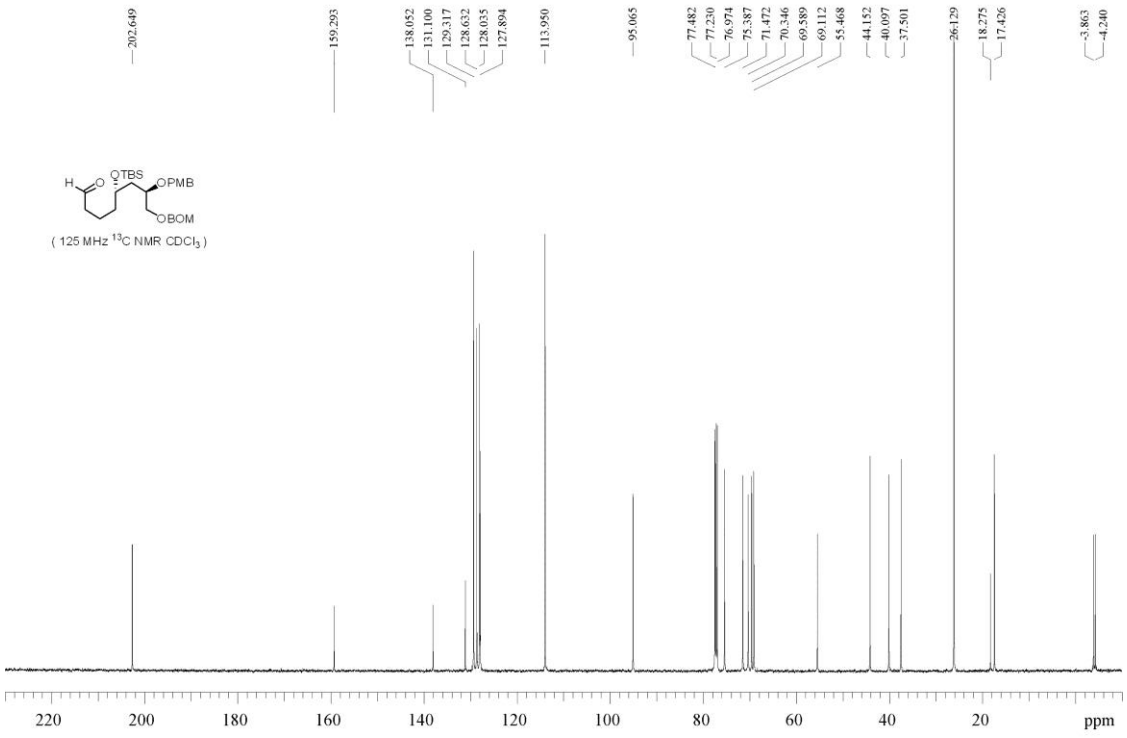

TBSO
OPMB
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

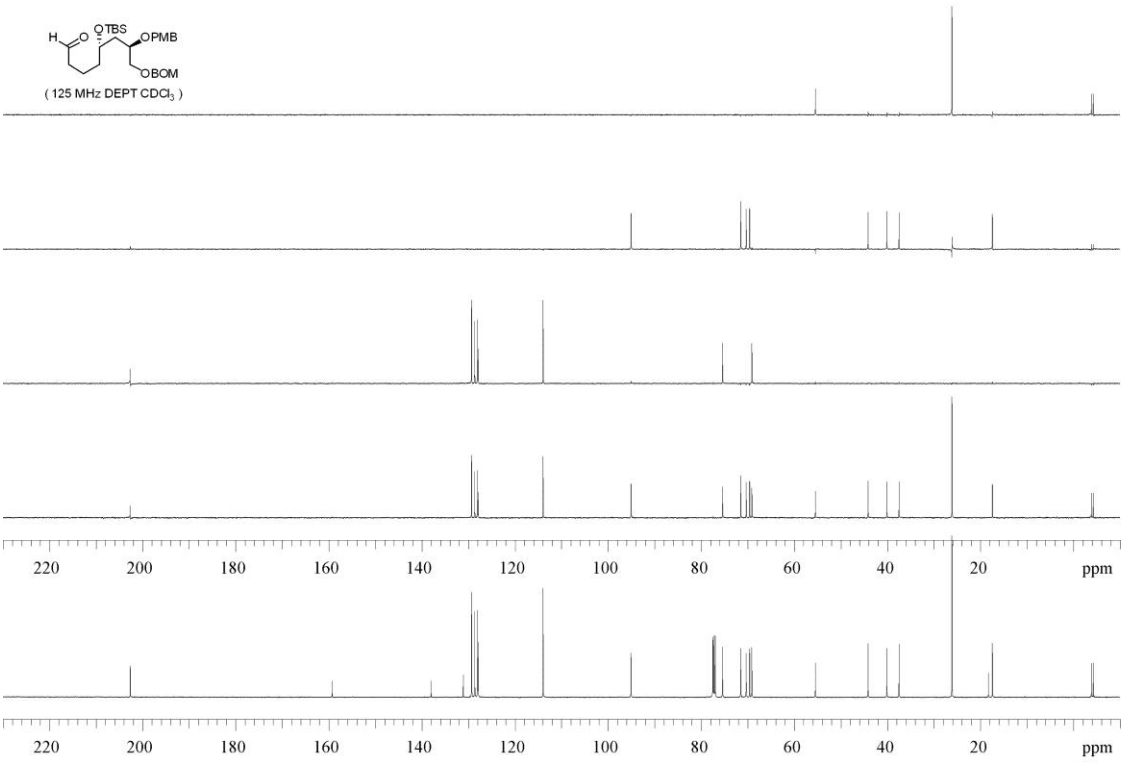

TBSO
OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

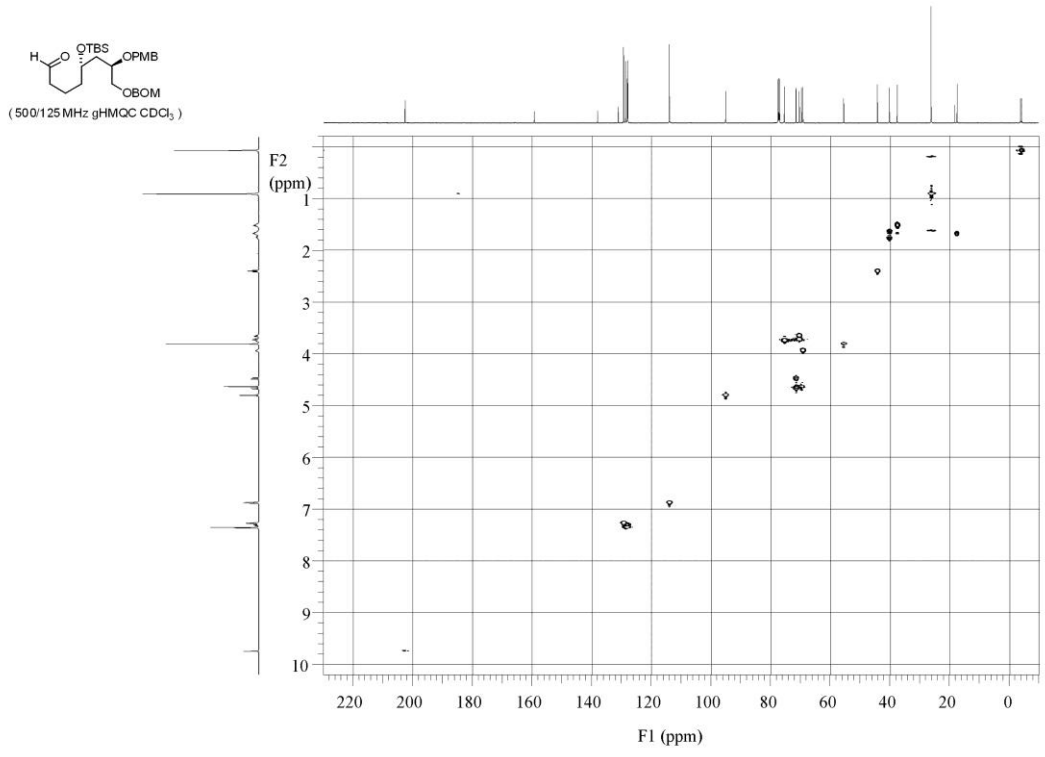

TBSO
OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

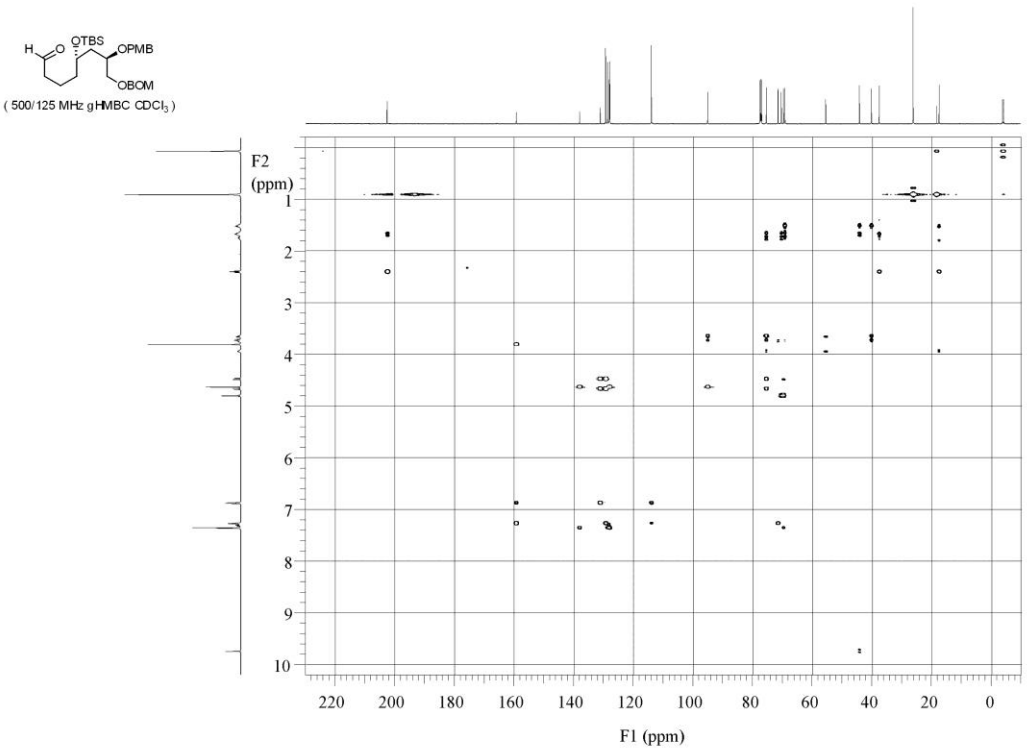

OTBS
OPMB
OBOM
(500 MHz 1H NMR CDCl3)
ppm
0.90
3.14
3.85
1.99
2.00
1.01
3.01
3.02
1.04
1.01
1.98
1.97
4.10
2.07
9.16
6.07

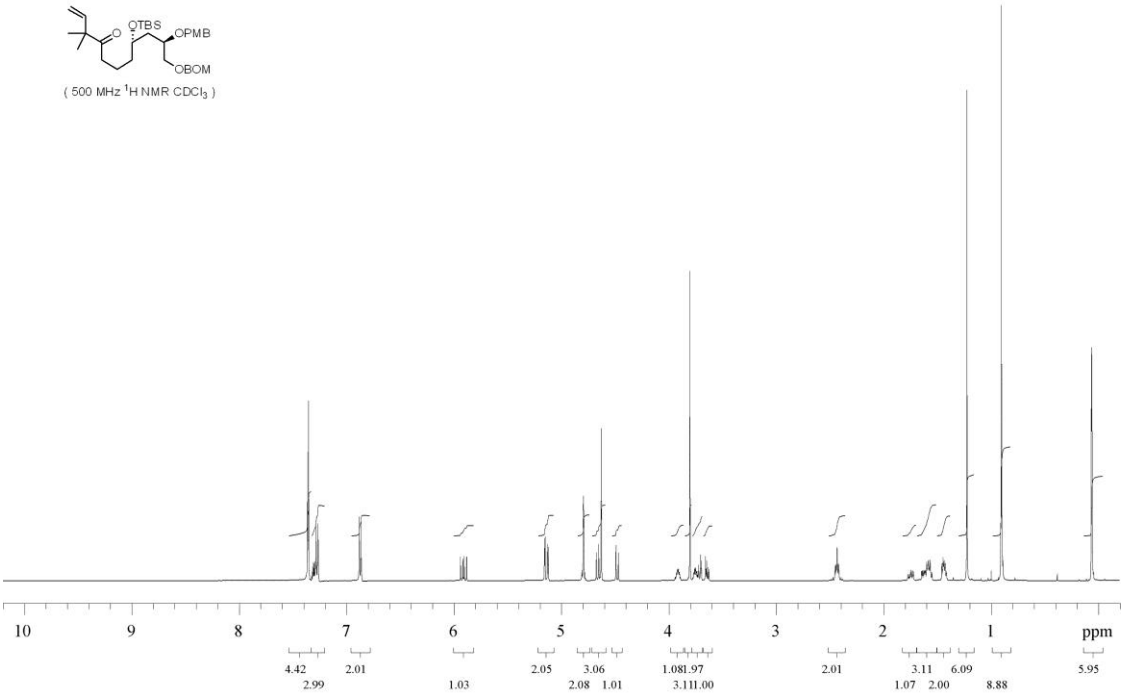

OTBS
OPMB
OBOM
(500 MHz gCOSY $CDCl_3$)
F1 (ppm)
F2 (ppm)


202.649
159.293
138.052
131.100
129.317
128.632
128.035
127.894
113.950
95.065
77.482
77.230
76.974
75.387
71.472
70.346
69.589
69.112
55.468
44.152
40.097
37.501
26.129
18.275
17.426
-3.863
-4.240
OTBS
OPMB
OBOM
(125 MHz ^{13}C NMR $CDCl_3$)
ppm


OTBS
OPMB
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)


OTBS
OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)


OTBS
OPMB
OBOM
(500 MHz 1H NMR CDCl3)
ppm
4.42
2.99
2.01
1.03
2.05
3.06
2.08
1.01
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1.97
3.11
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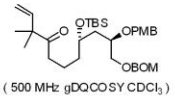
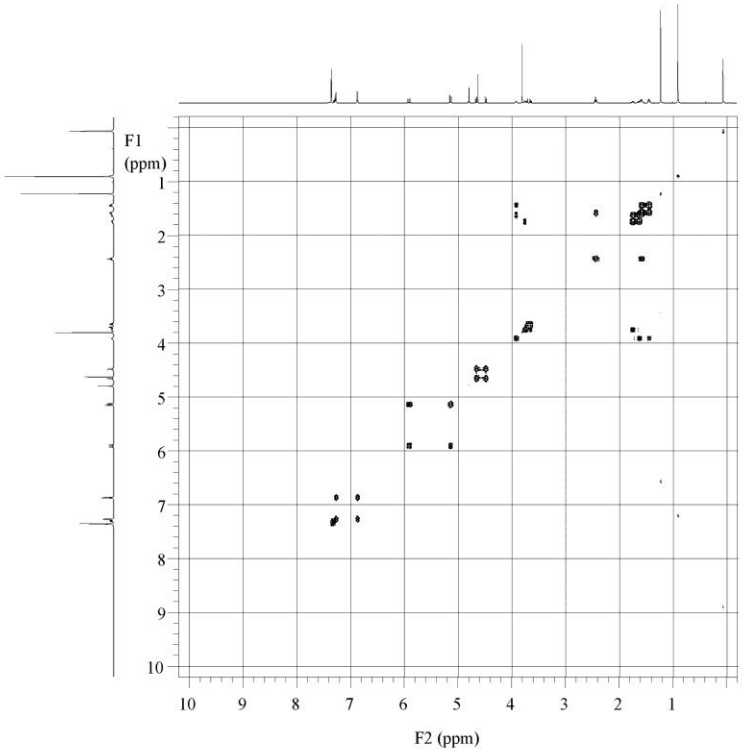
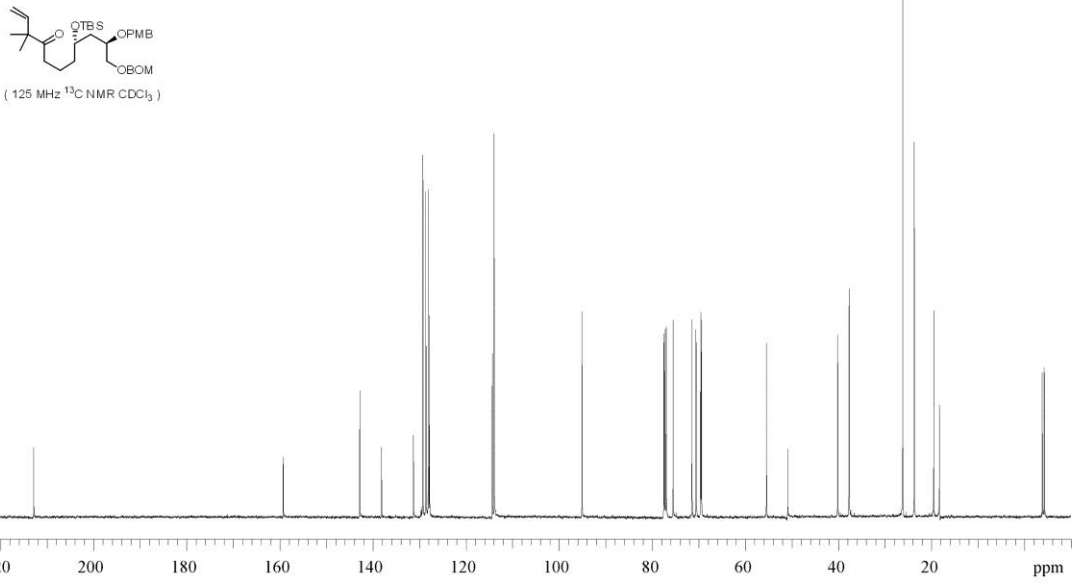
3.11
1.07
2.00
6.09
8.88
5.95

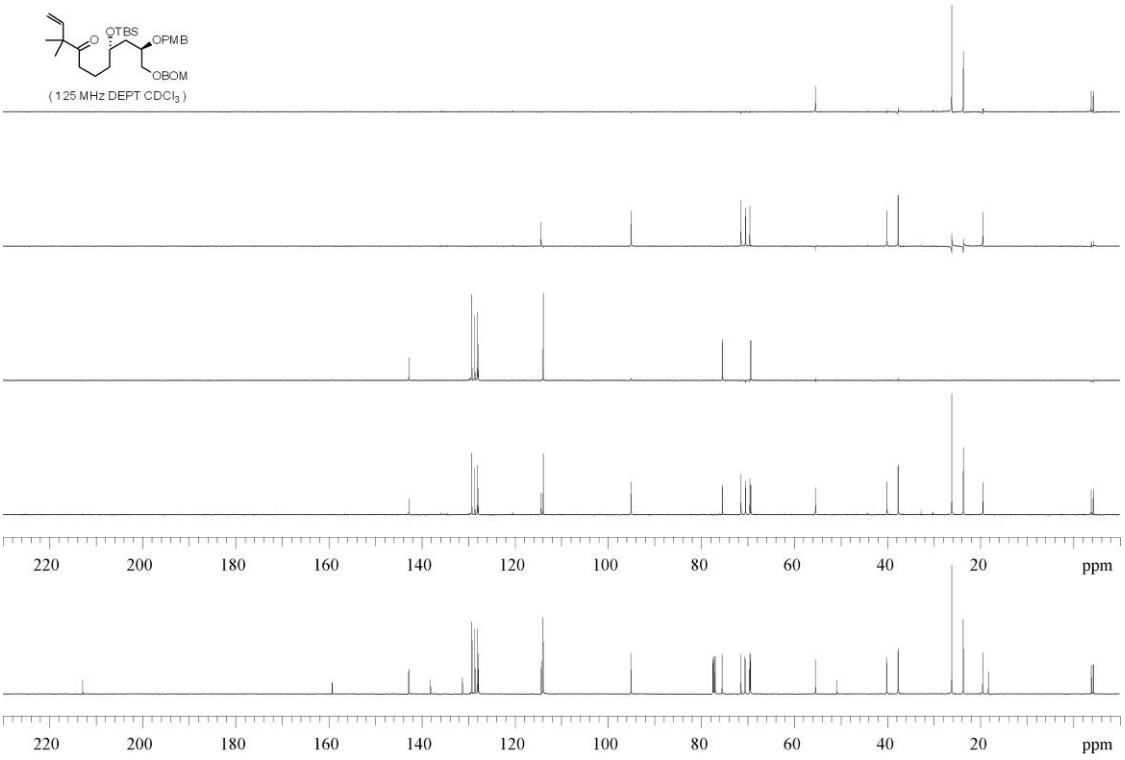


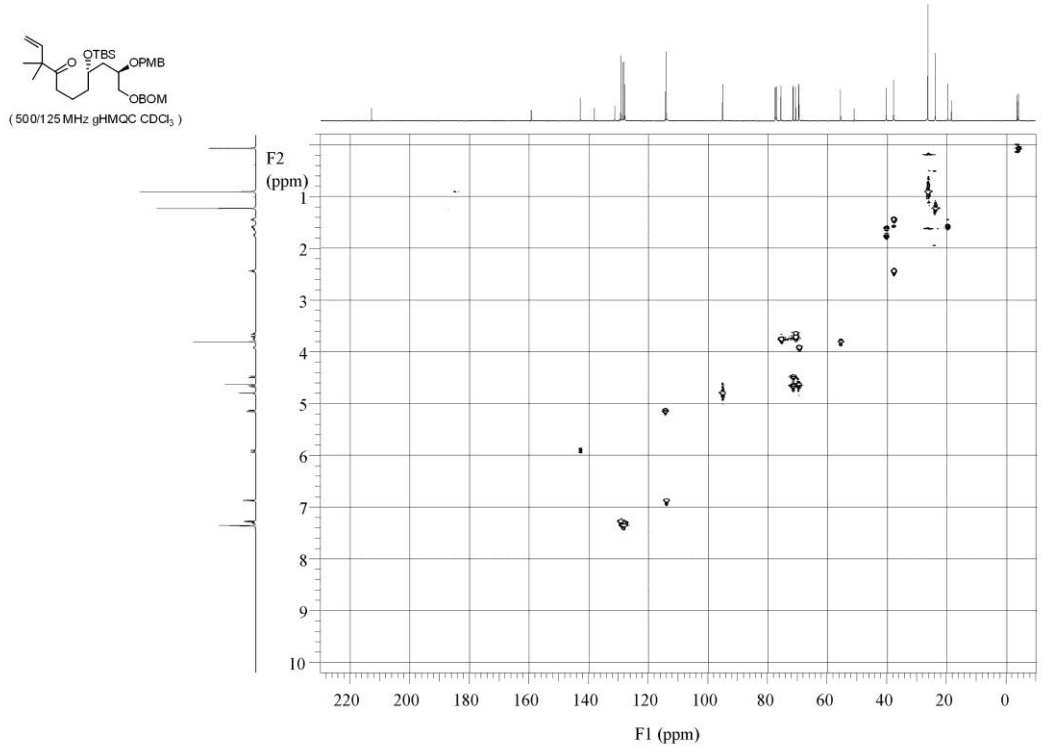
(500 MHz gDQCOSY $CDCl_3$)

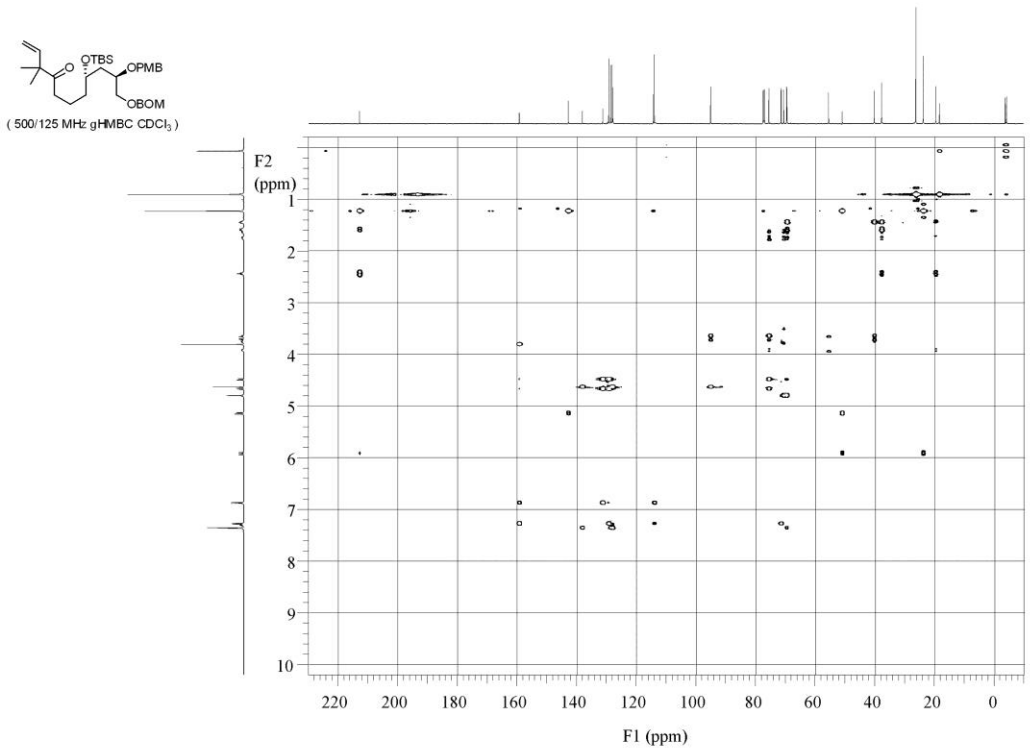


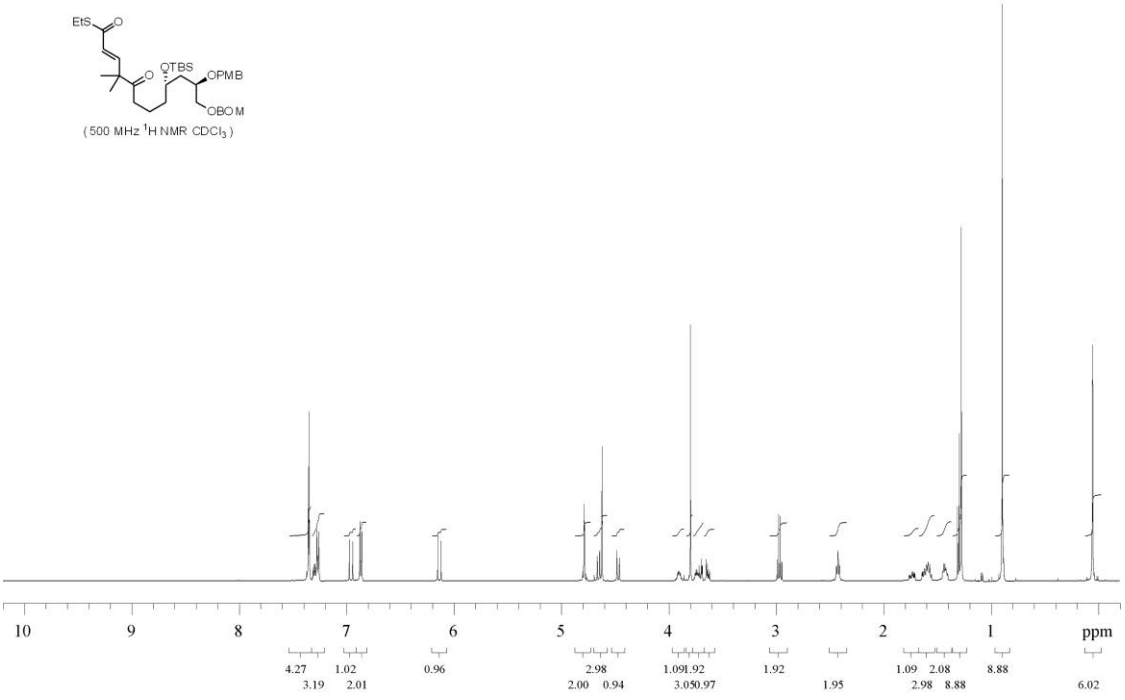


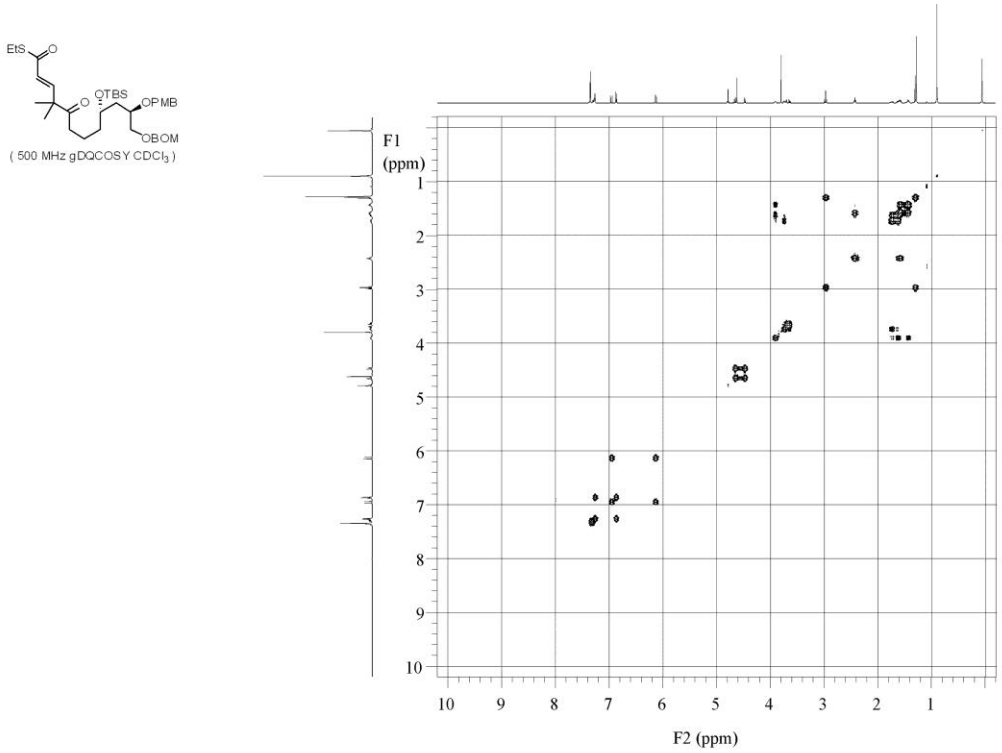
(125 MHz ^{13}C NMR $CDCl_3$)

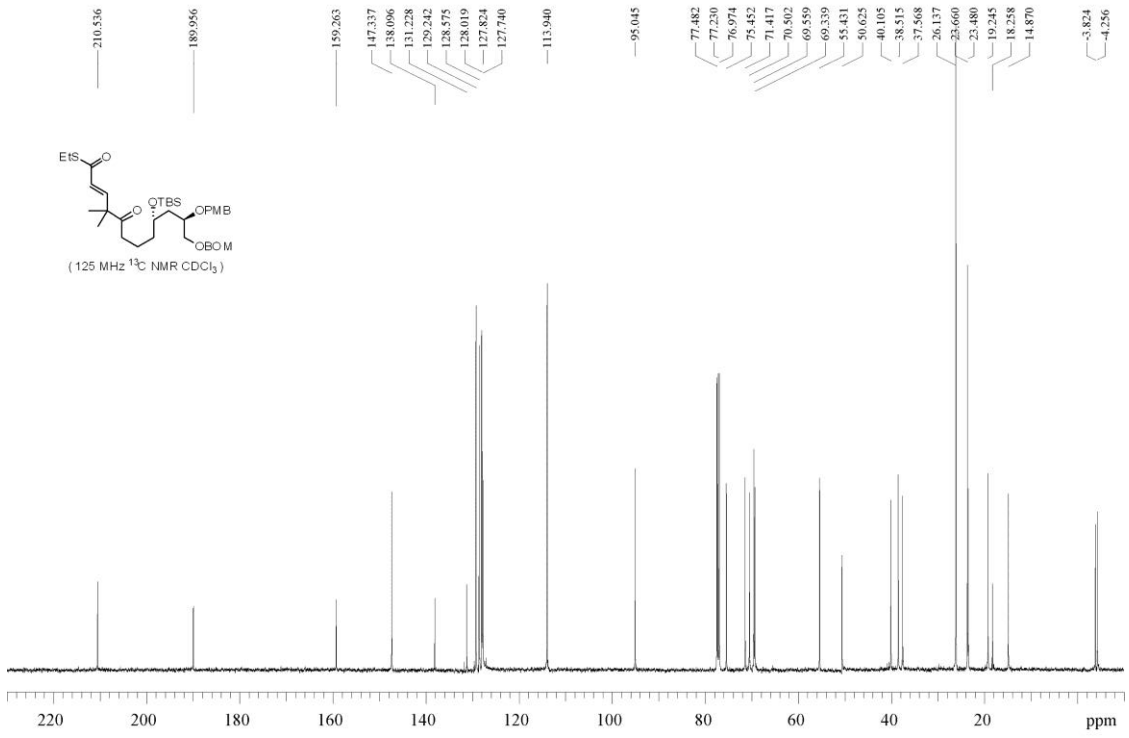

OTBS
OPMB
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

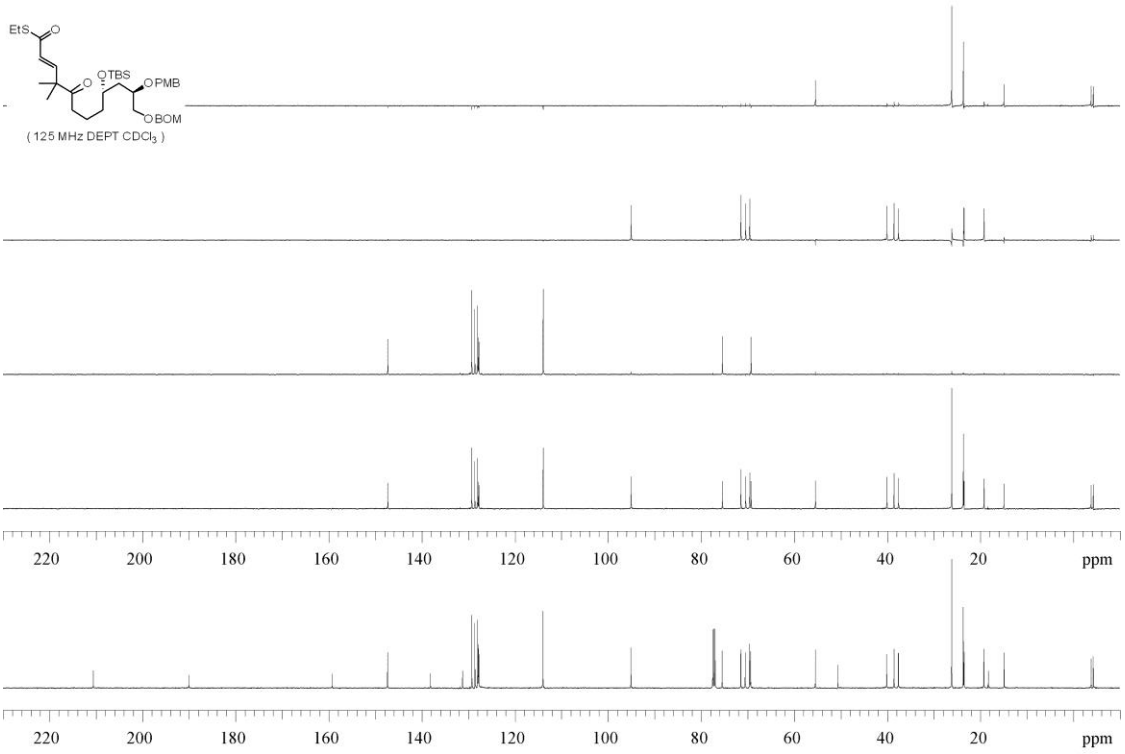

OTBS
OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

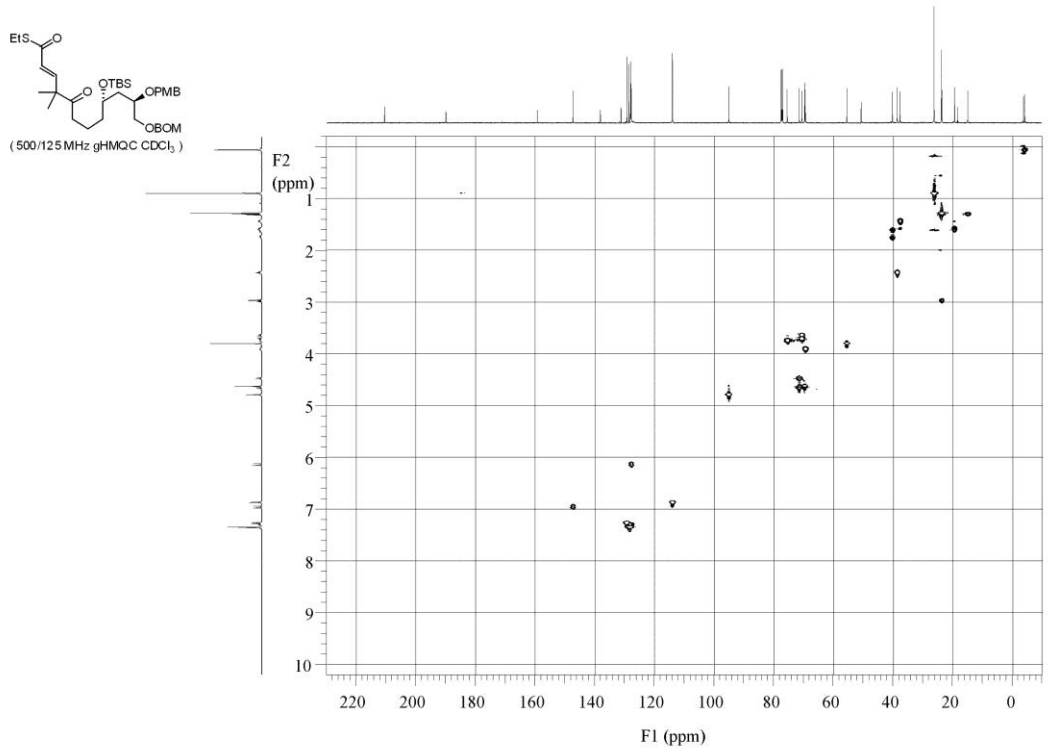

OTBS
OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

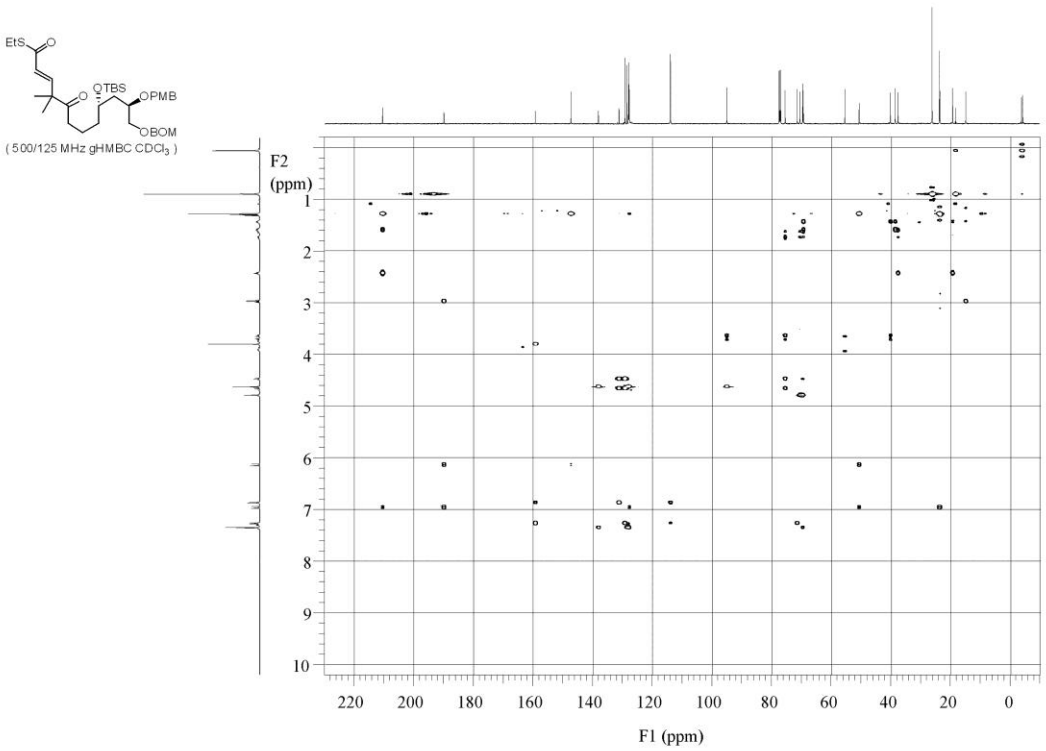

EtS
OTBS
OPMB
OBOM
(500 MHz 1H NMR CDCl3)
ppm
4.27
3.19
1.02
2.01
0.96
2.98
2.00
0.94
1.09
1.92
3.05
0.97
1.92
1.95
1.09
2.08
2.98
8.88
6.02

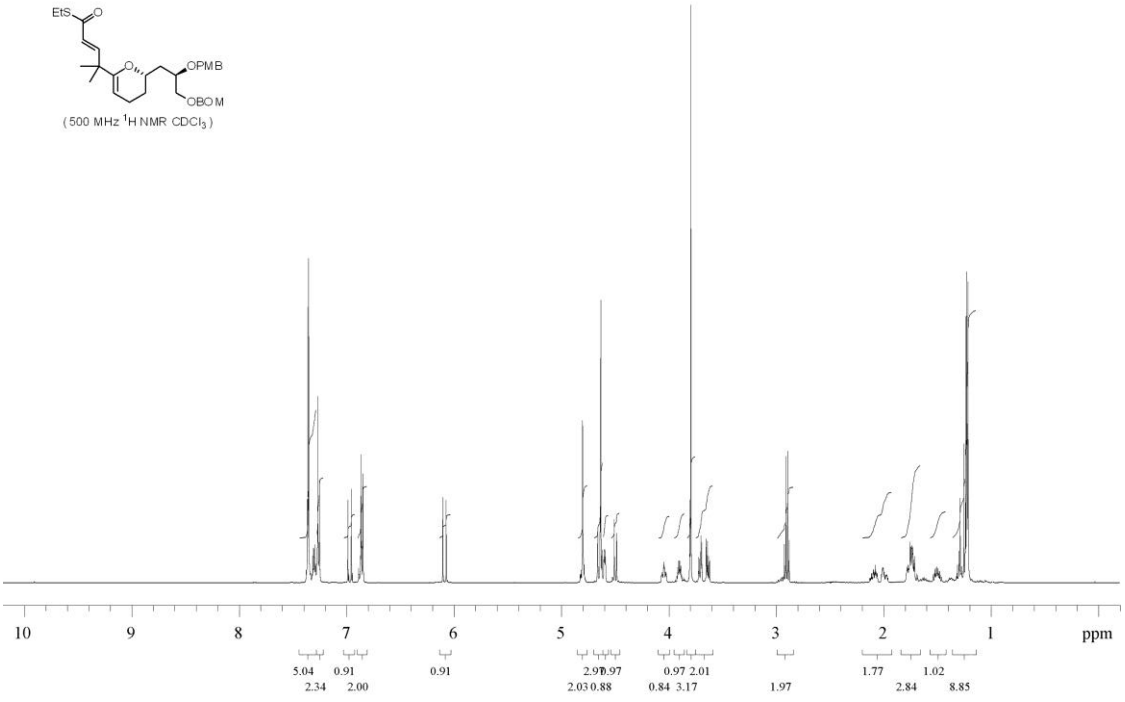

EtS
O
OTBS
O
OPMB
OBOM
(500 MHz gDQCOSY $CDCl_3$)
F1
(ppm)
F2 (ppm)

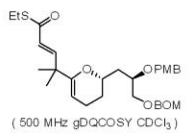

210.536
189.956
159.263
147.337
138.096
131.228
129.242
128.575
128.019
127.824
127.740
113.940
95.045
77.482
77.230
76.974
75.452
71.417
70.502
69.559
69.339
55.431
50.625
40.105
38.515
37.568
26.137
25.660
23.480
19.245
18.258
14.870
-3.824
-4.256
EtS
O
OTBS
O
OPMB
OBOM
(125 MHz ^{13}C NMR $CDCl_3$)
ppm


EtS
O
OTBS
O
OPMB
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

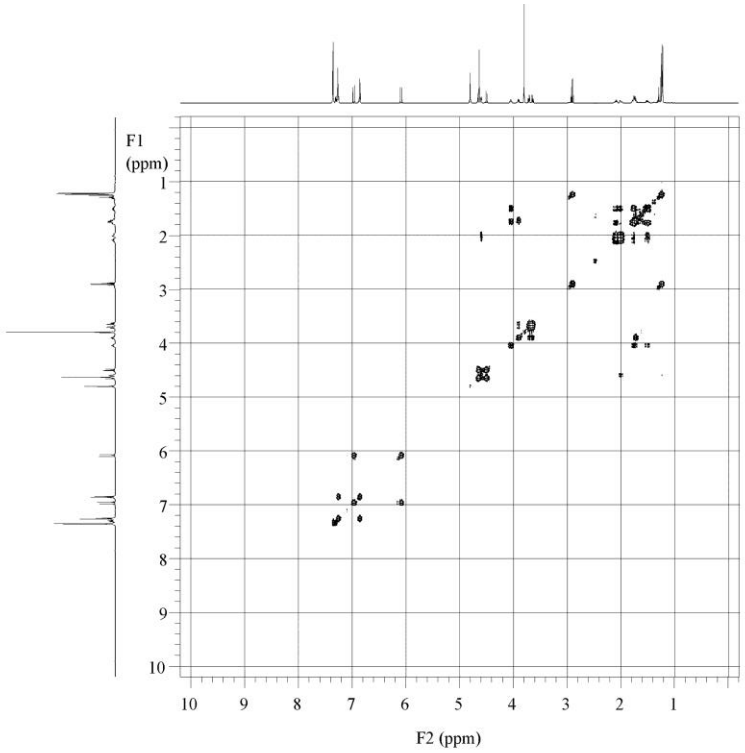

EtS
O
OTBS
O
OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

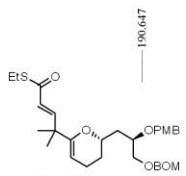

EtS
O
OTBS
OPMB
OBOM
(500/125 MHz gHMBC $CDCl_3$)
F2
(ppm)
F1 (ppm)


EtS
O
OPMB
OBOM
(500 MHz ^{1}H NMR $CDCl_3$)
ppm
5.04
2.34
0.91
2.00
0.91
2.03
2.97
0.88
1.97
0.84
0.97
3.17
2.01
1.97
1.77
2.84
1.02
8.85

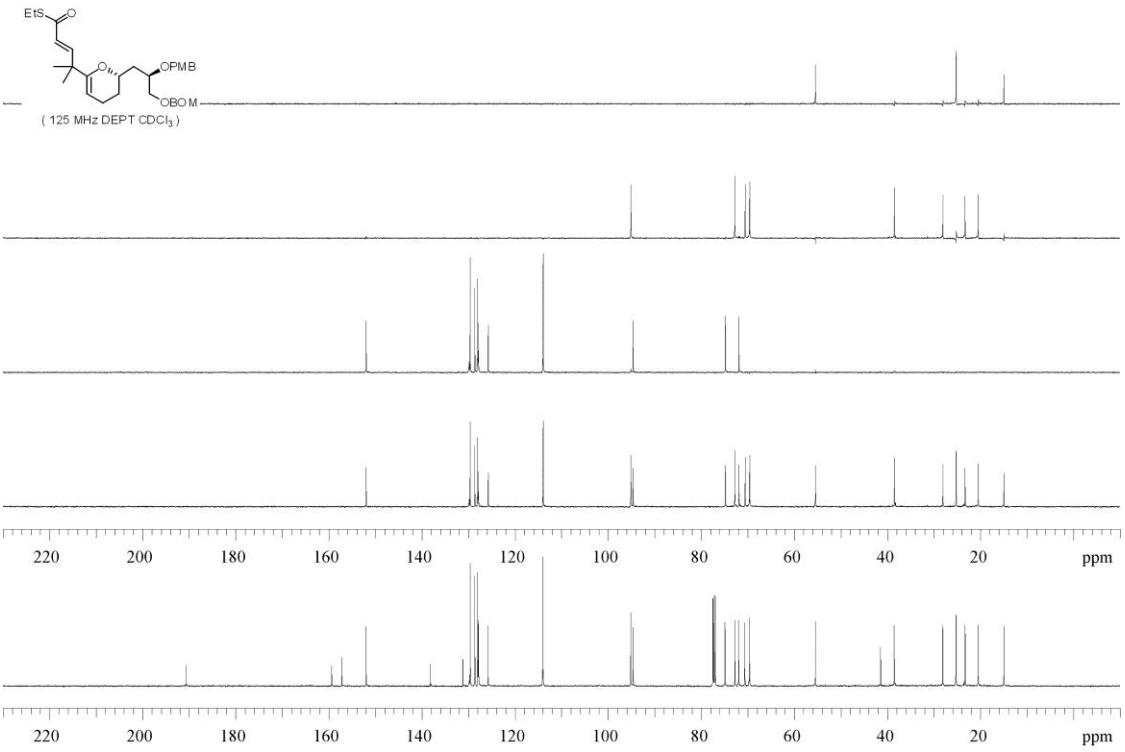


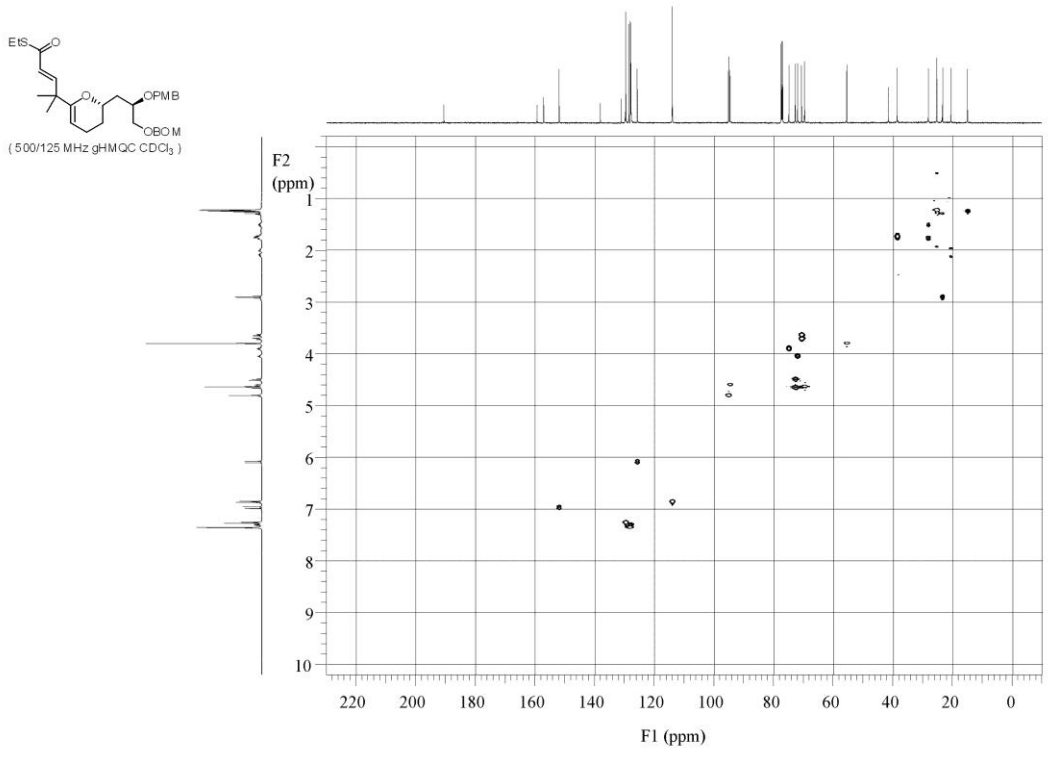
(500 MHz gDQCOSY $CDCl_3$)

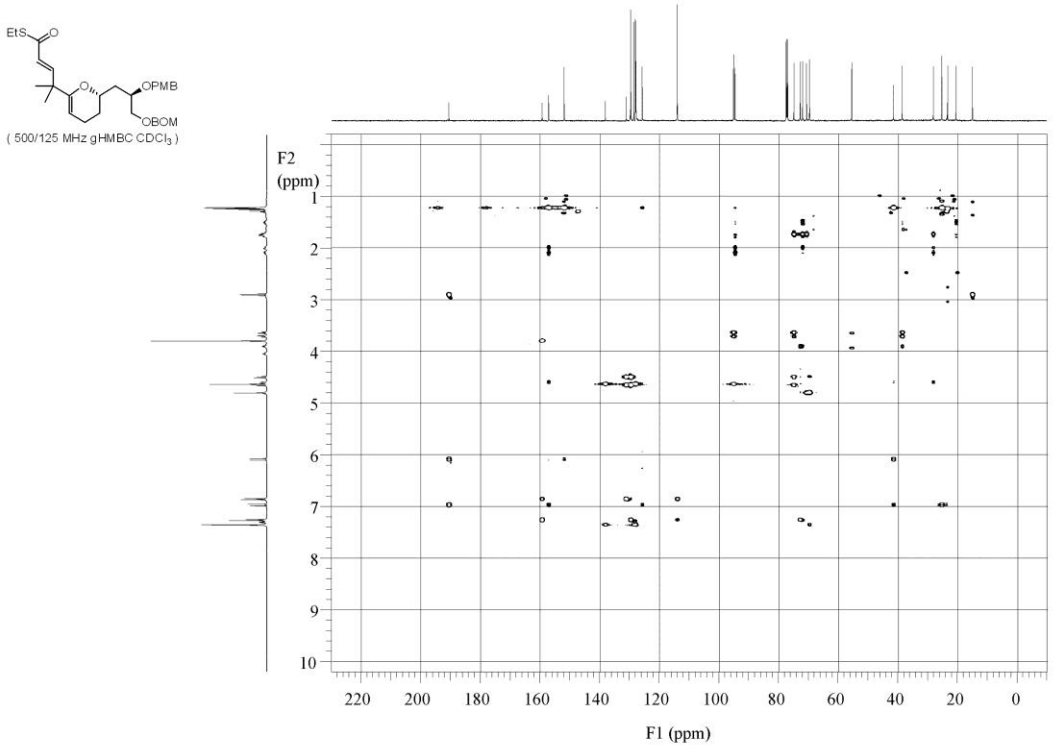


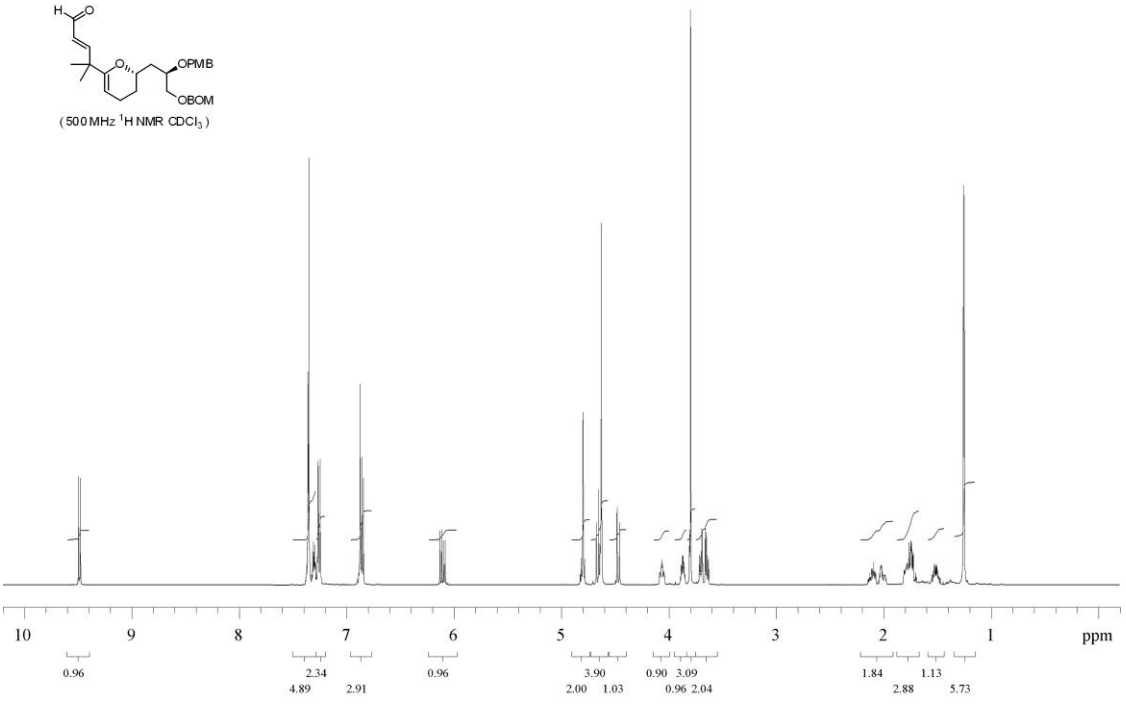


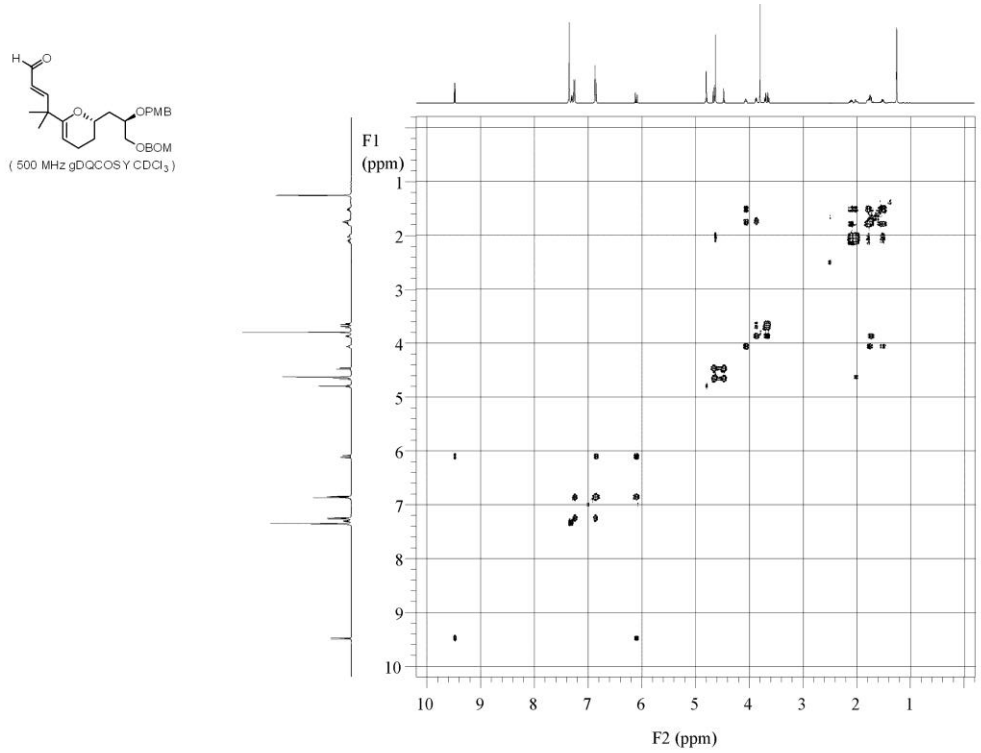
(125 MHz ^{13}C NMR $CDCl_3$)

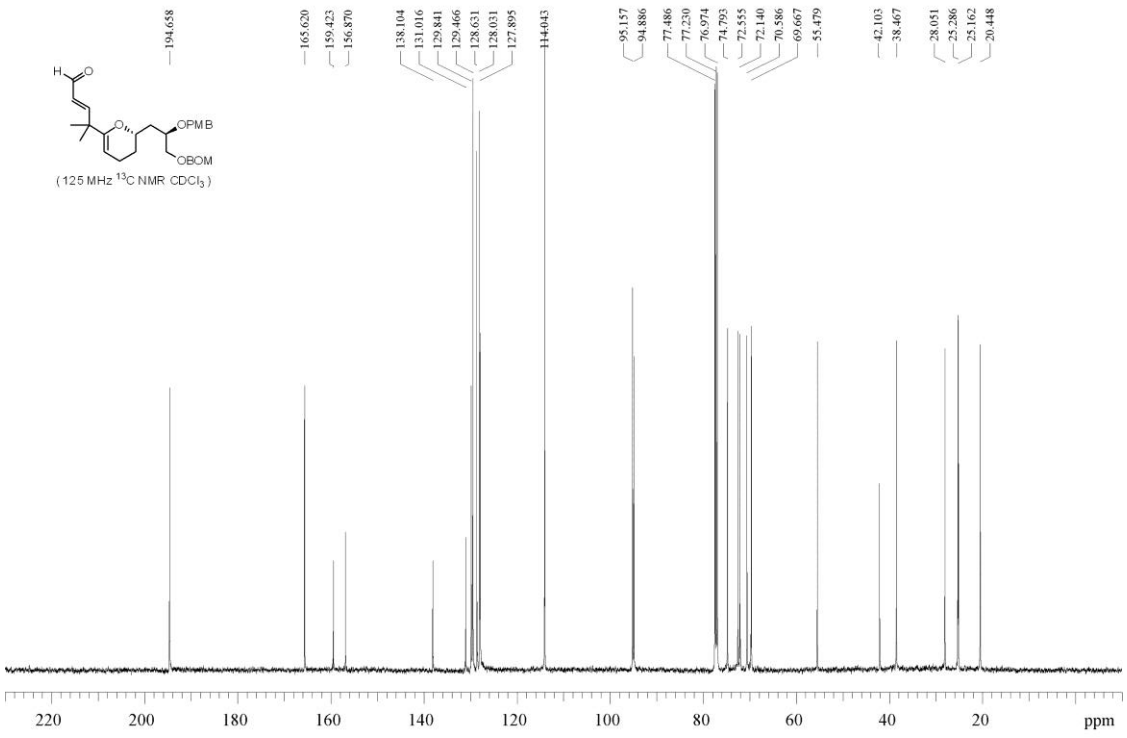

EtS
O
OPMB
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

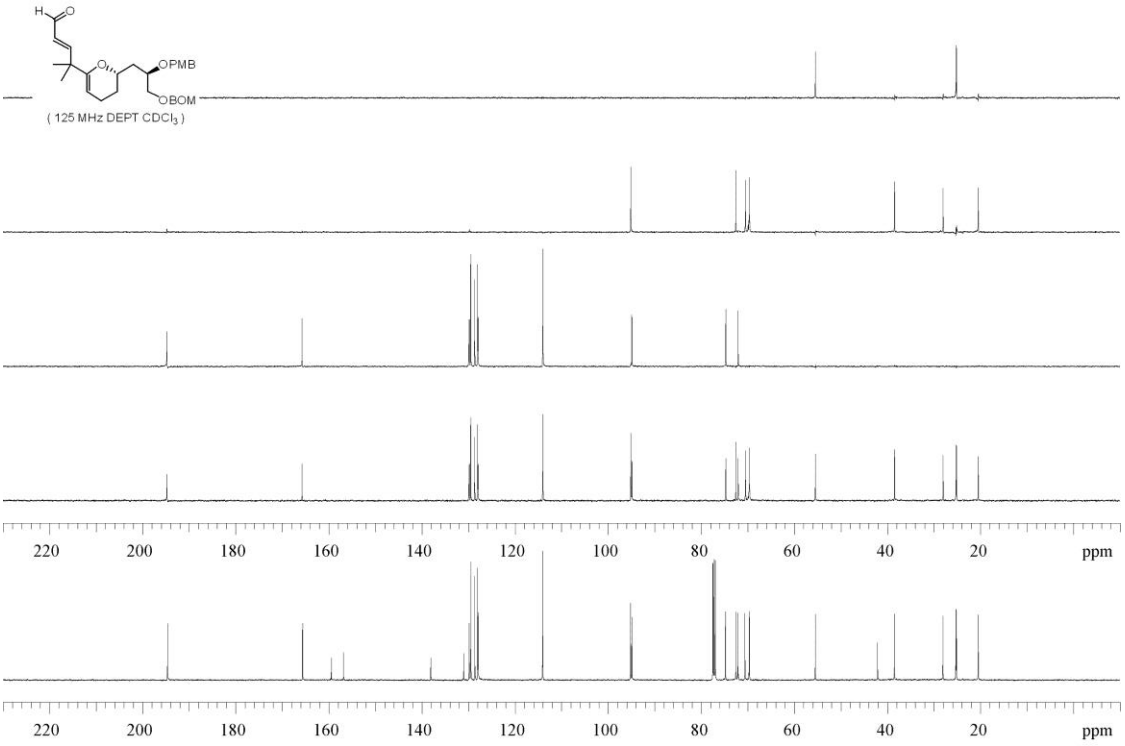

EtS
O
OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

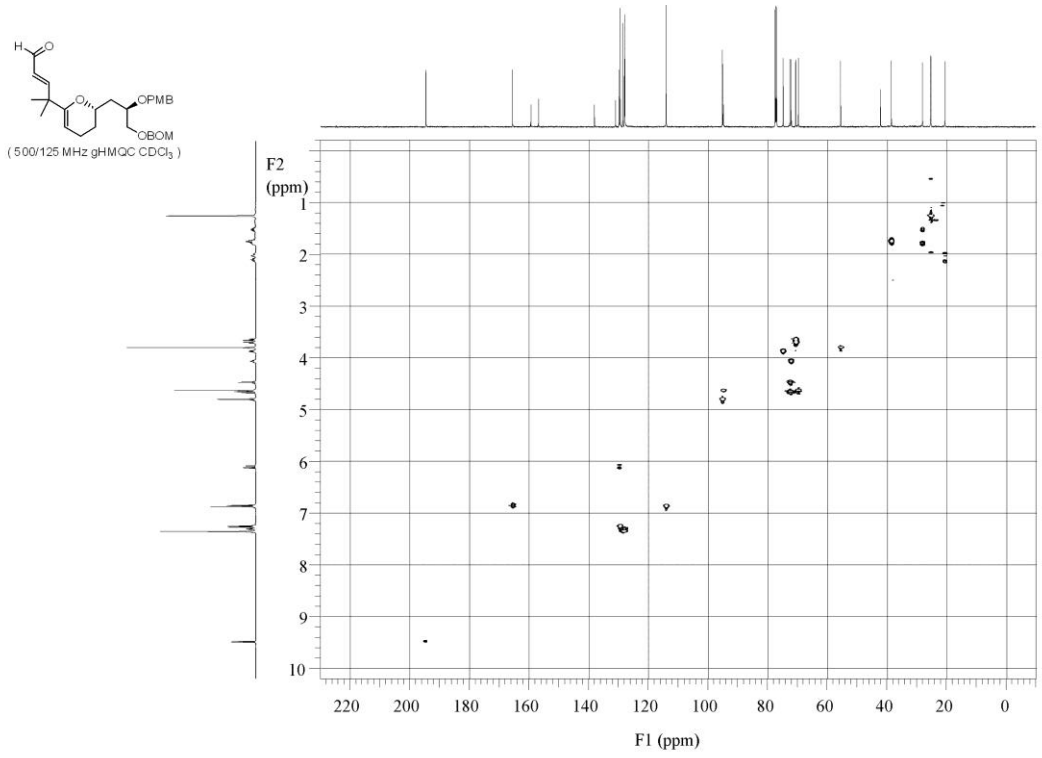

EtS
O
OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

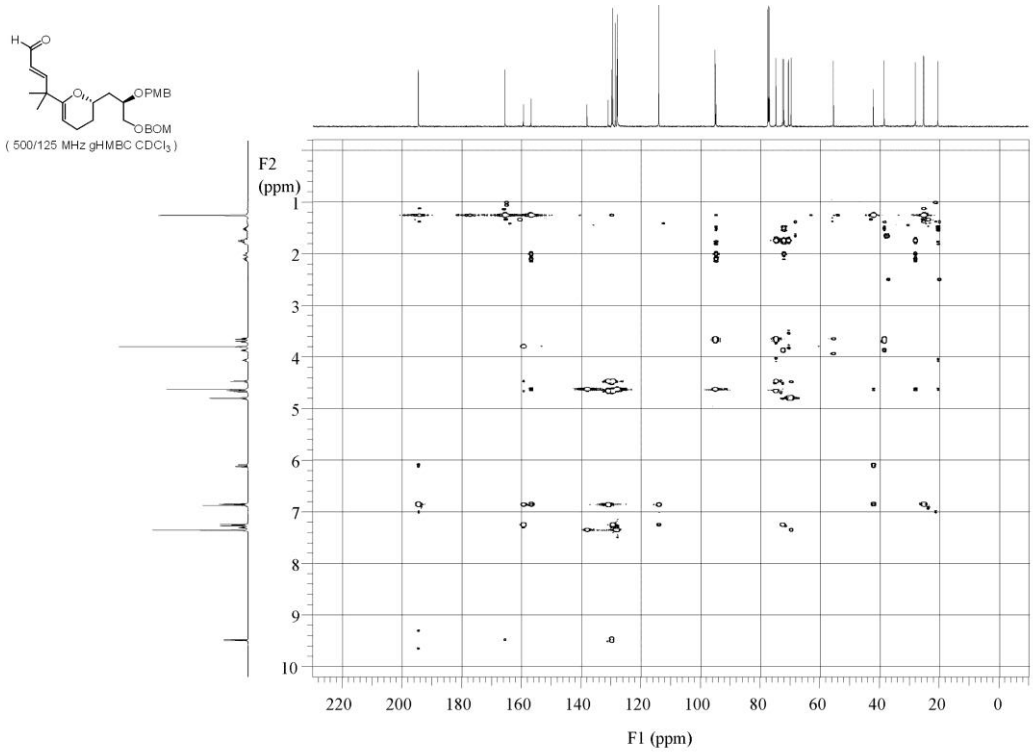

H
O
OPMB
OBOM
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
0.96
2.34
4.89
2.91
0.96
3.90
2.00
1.03
0.90
3.09
0.96
2.04
1.84
2.88
1.13
5.73

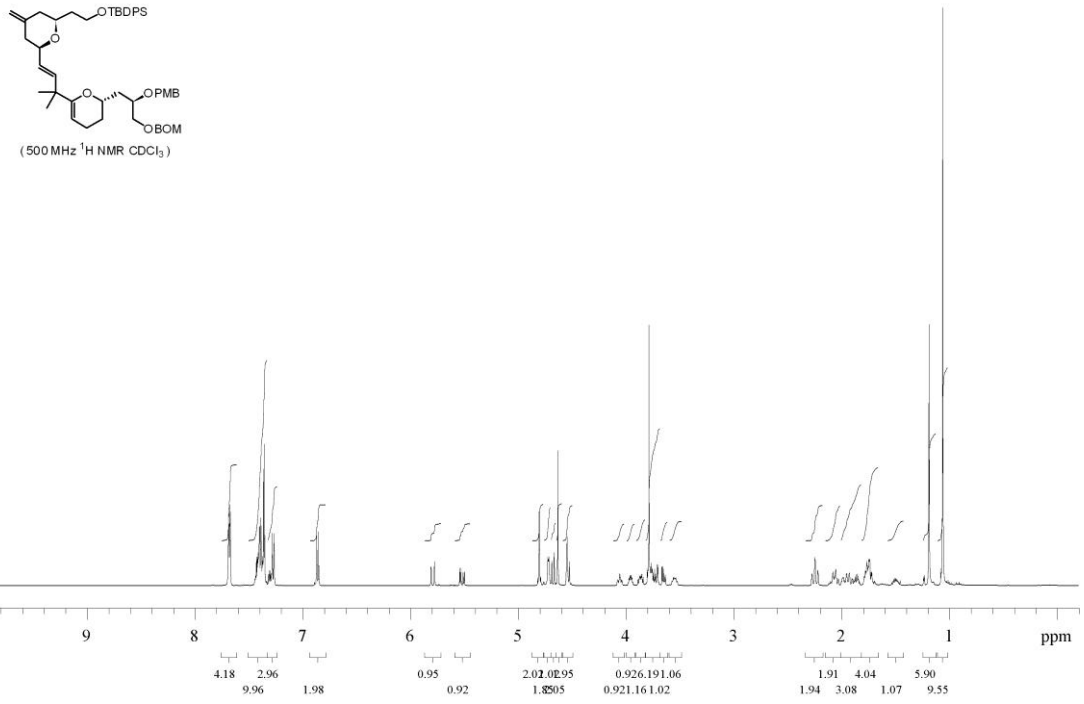

OPMB
OBOM
(500 MHz gDQCOSY CDCl3)
F1
(ppm)
F2 (ppm)

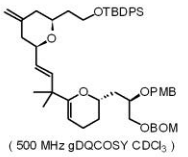

194.658
165.620
159.423
156.870
138.104
131.016
129.841
129.466
128.631
128.031
127.895
114.043
95.157
94.886
77.486
77.230
76.974
74.793
72.555
72.140
70.586
69.667
55.479
42.103
38.467
28.051
25.286
25.162
20.448
OPMB
OBOM
(125 MHz 13C NMR CDCl3)
ppm


OPMB
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

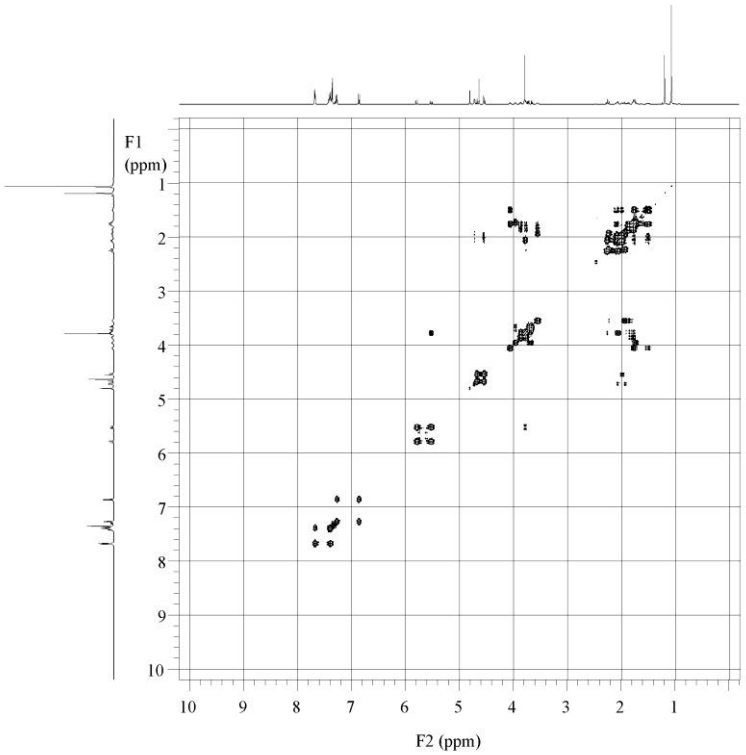

OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

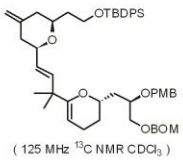

OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)


OTBDPS
OPMB
OBOM
(500 MHz 1H NMR CDCl3)
ppm

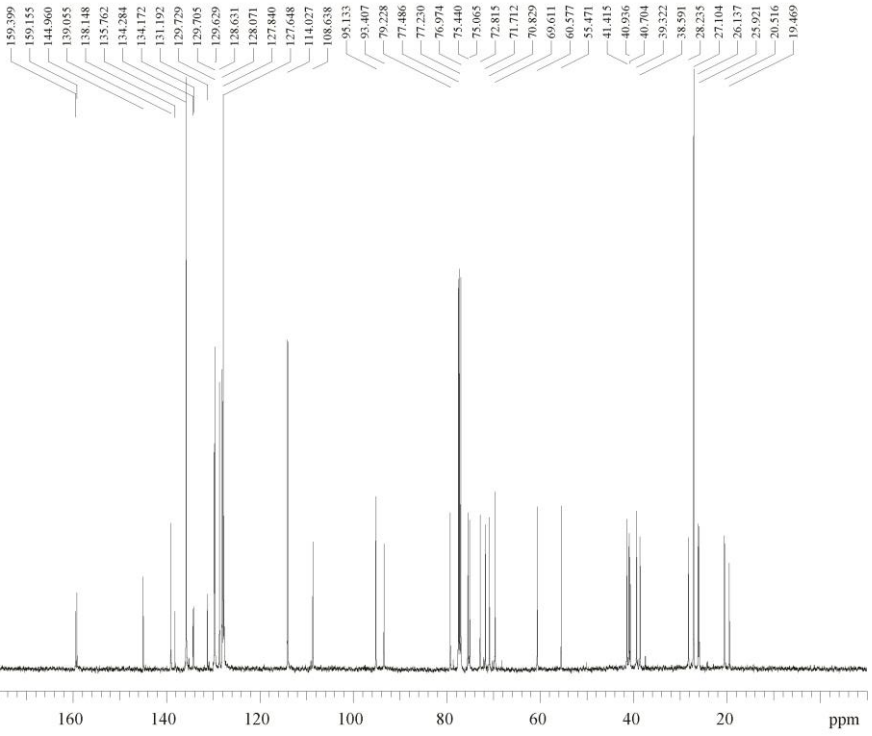


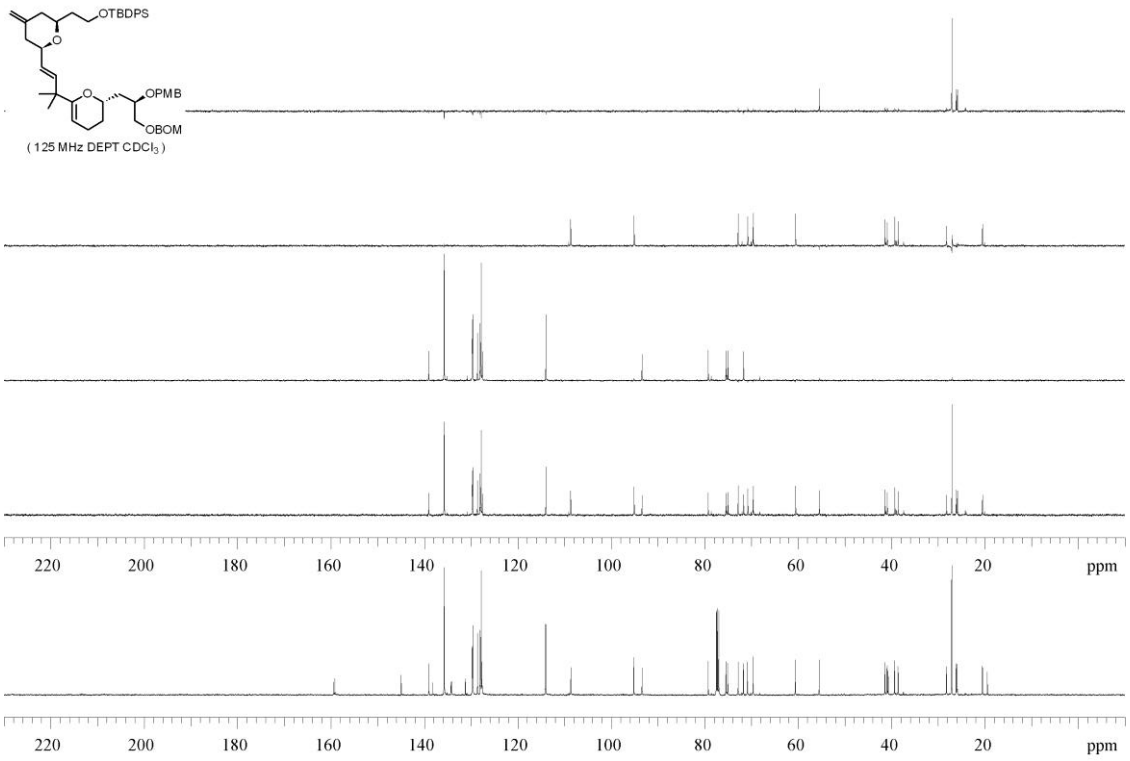
(500 MHz gDQCOSY $CDCl_3$)

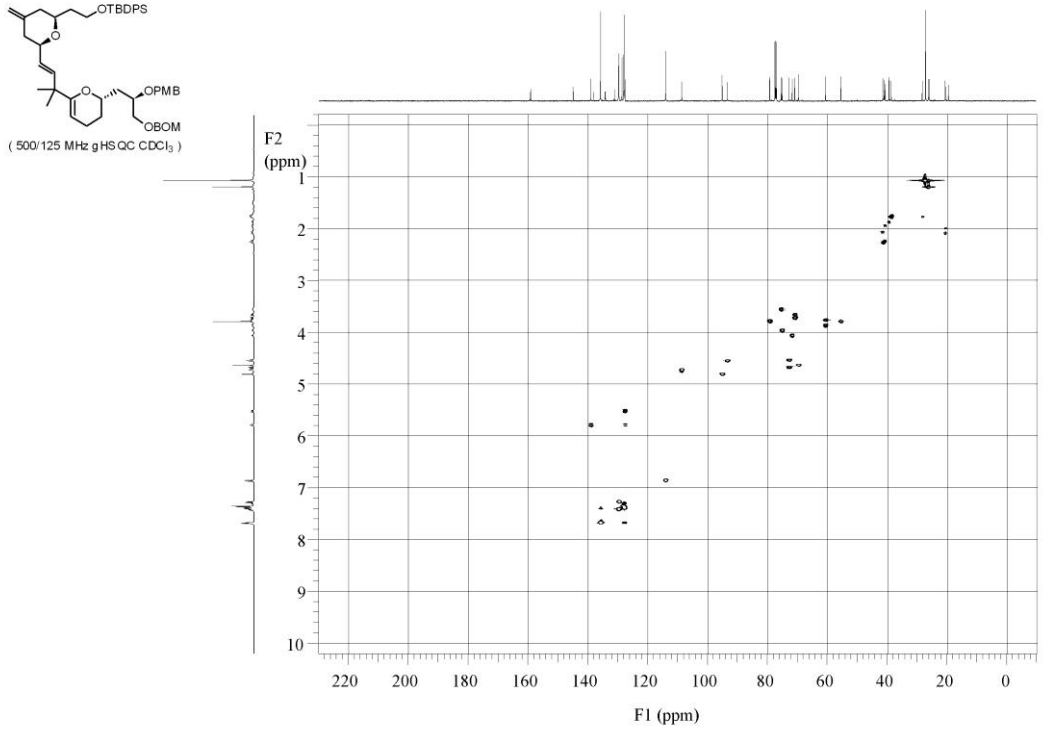


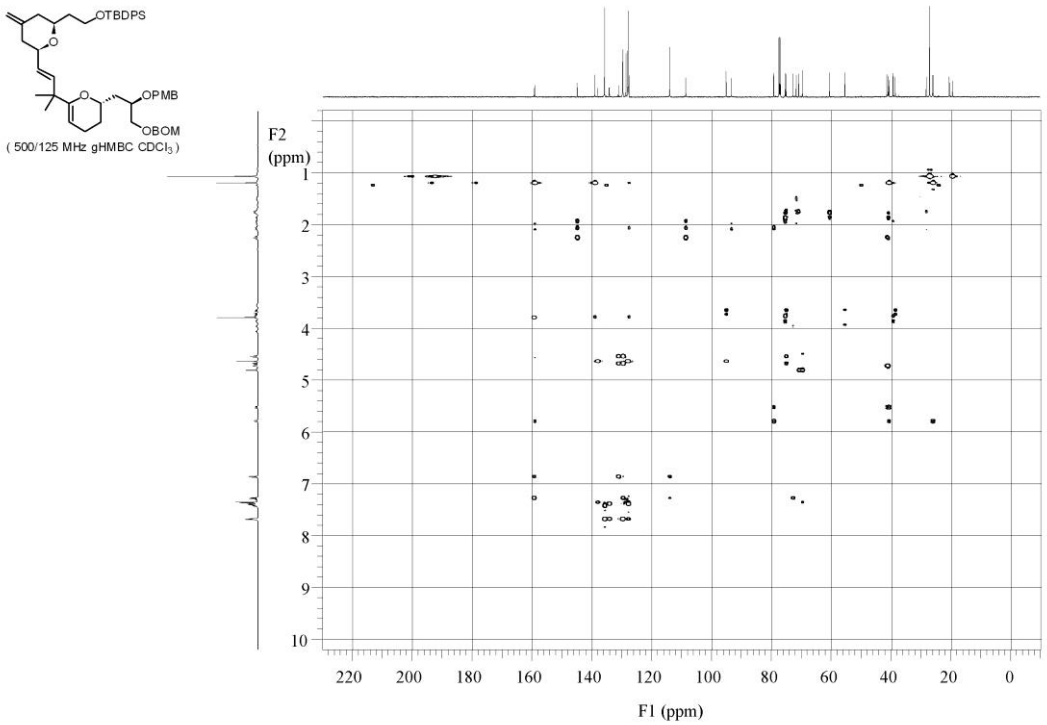


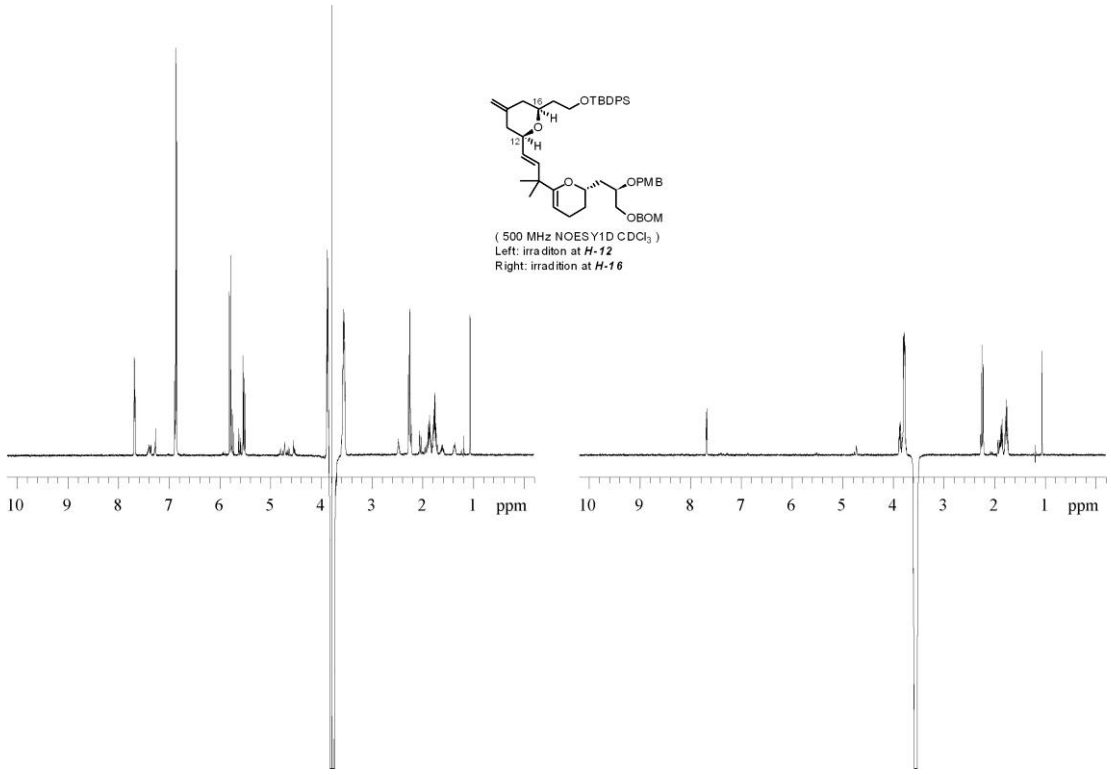
(125 MHz ^{13}C NMR $CDCl_3$)

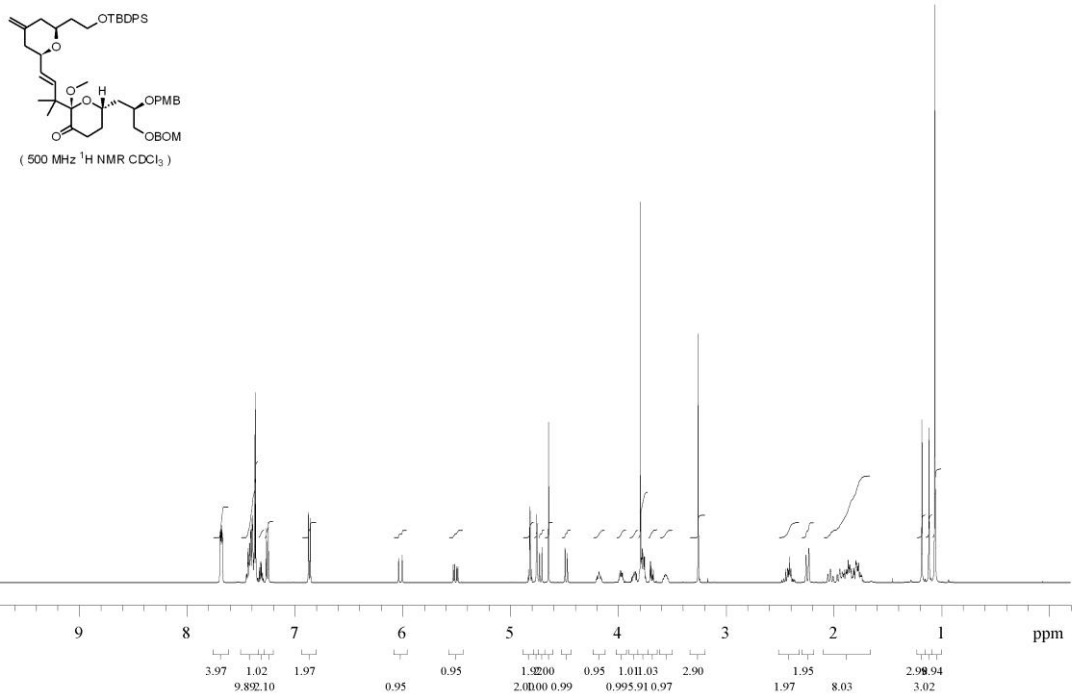


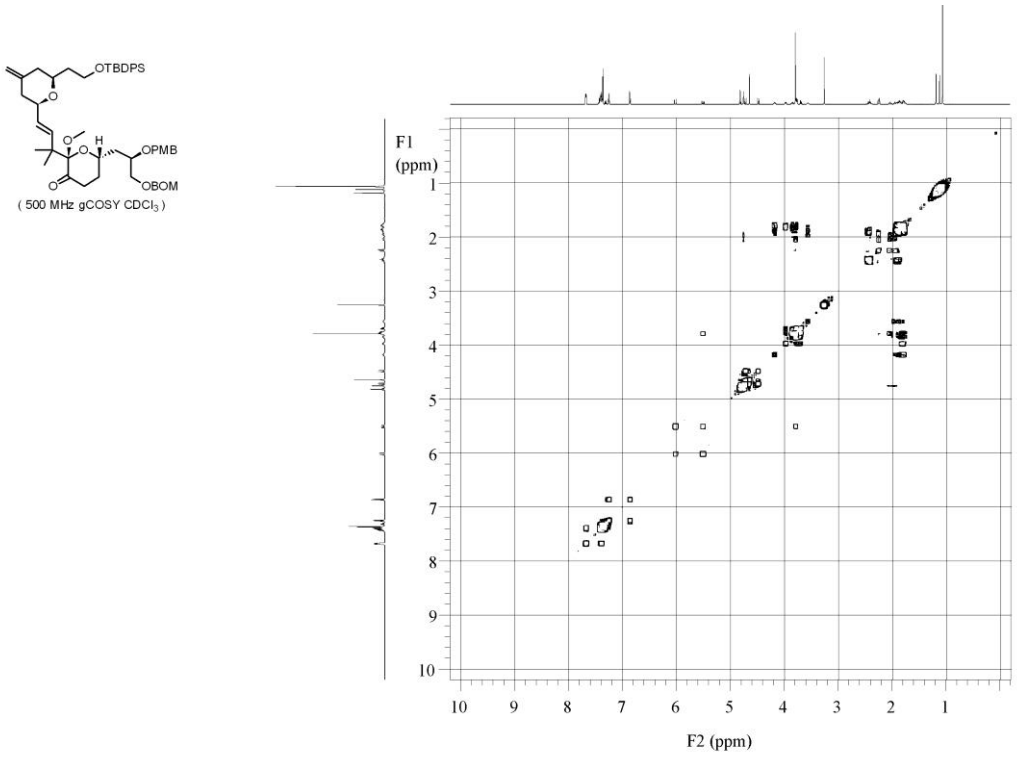

OTBDPS
OPMB
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

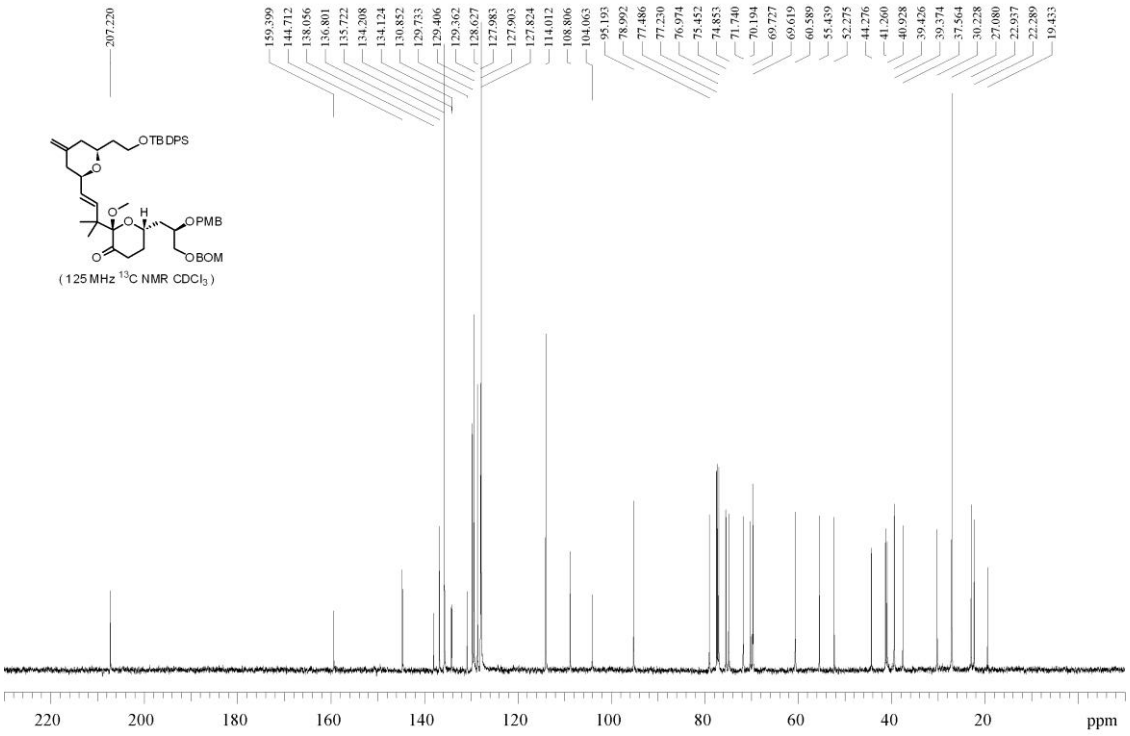

OTBDPS
OPMB
OBOM
(500/125 MHz gHSQC CDCl3)
F2
(ppm)
F1 (ppm)

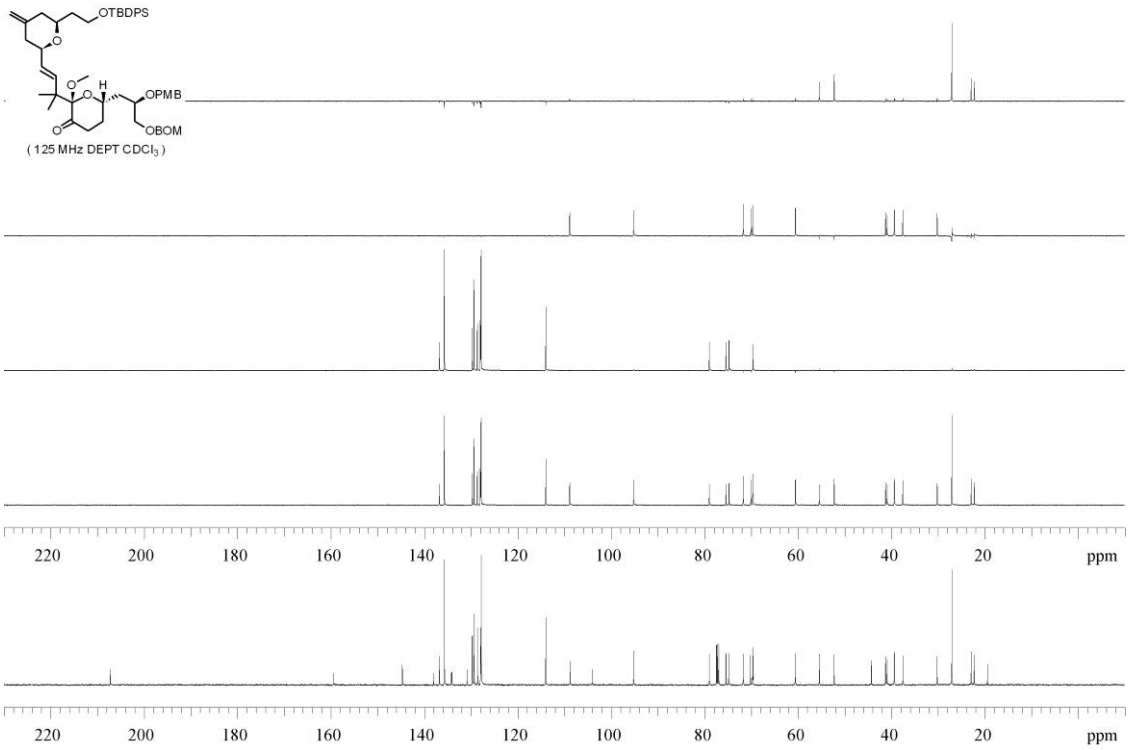

OTBDPS
OPMB
OBOM
(500/125 MHz gHMBC $CDCl_3$)
F2 (ppm)
F1 (ppm)

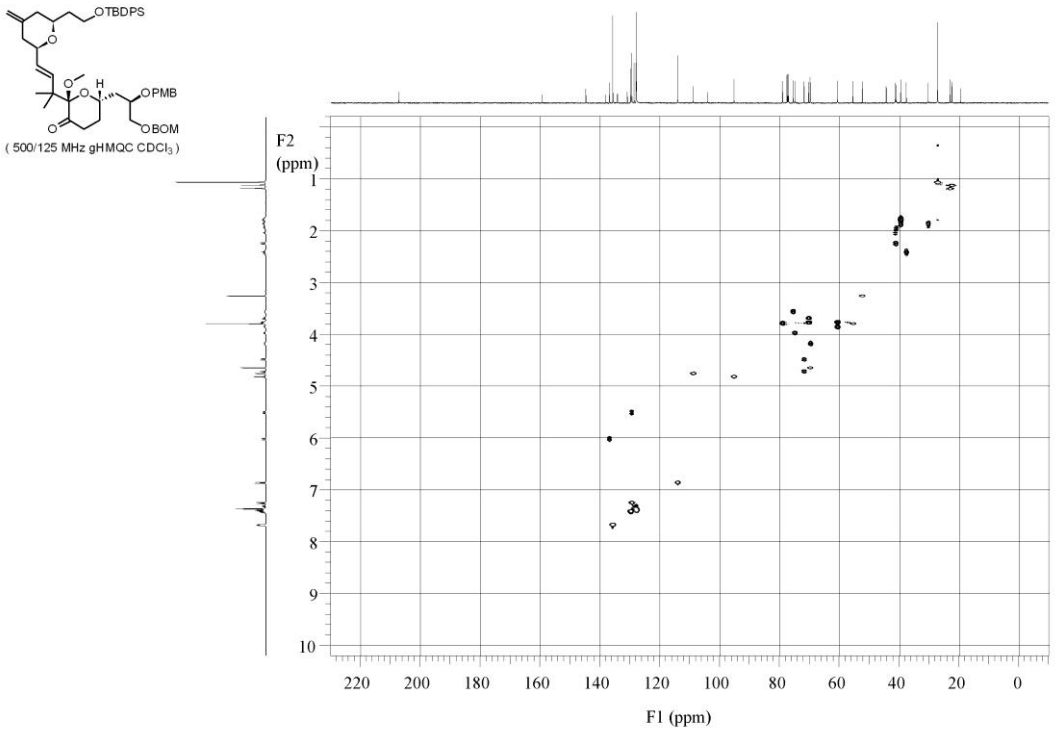

OTBDPS
OPMB
OBOM
(500 MHz NOESY1D $CDCl_3$)
Left: irraditon at H-12
Right: irradition at H-16
ppm
ppm

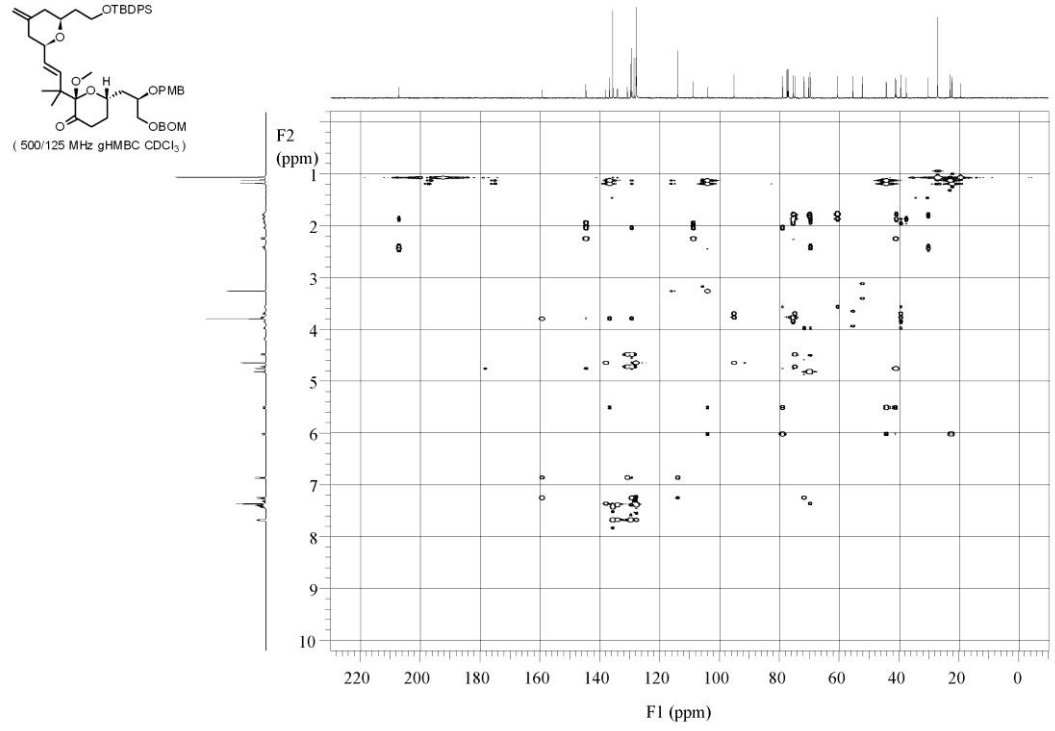

OTBDPS
OPMB
OBOM
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm

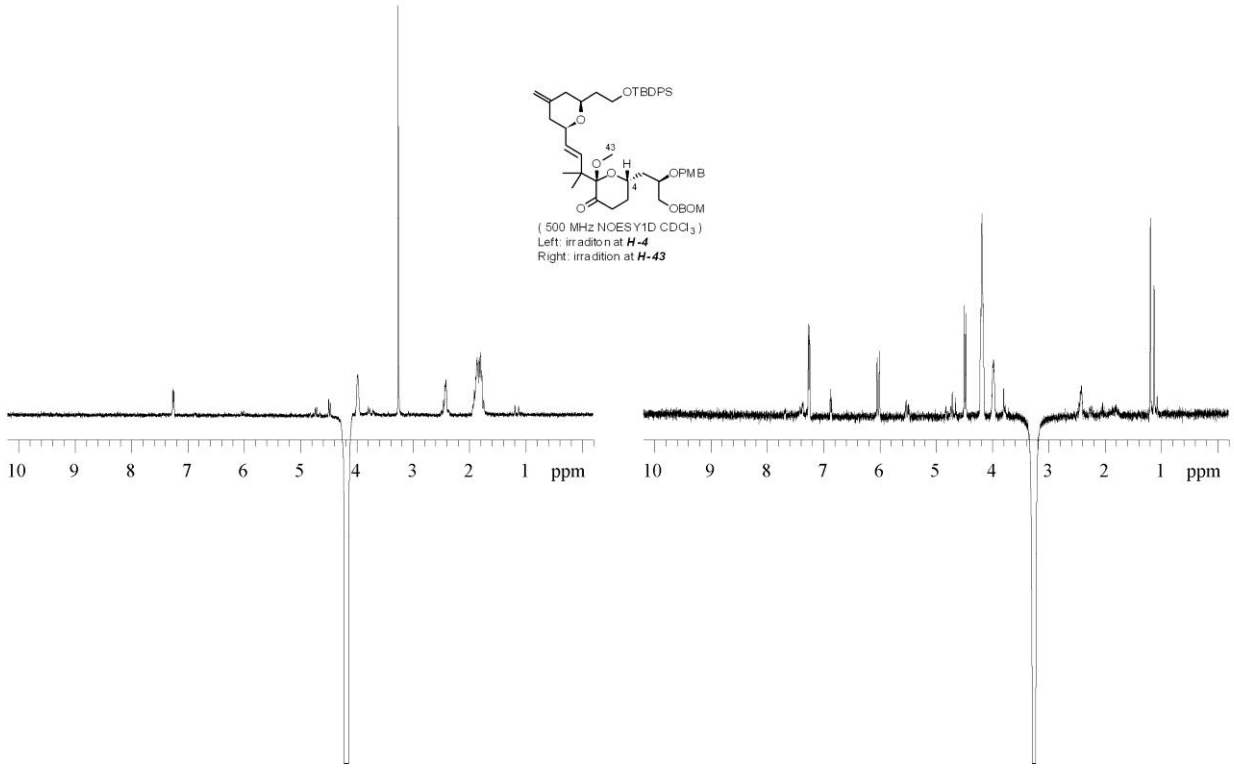

OTBDPS
OPMB
OBOM
(500 MHz gCOSY $CDCl_3$)
F1 (ppm)
F2 (ppm)

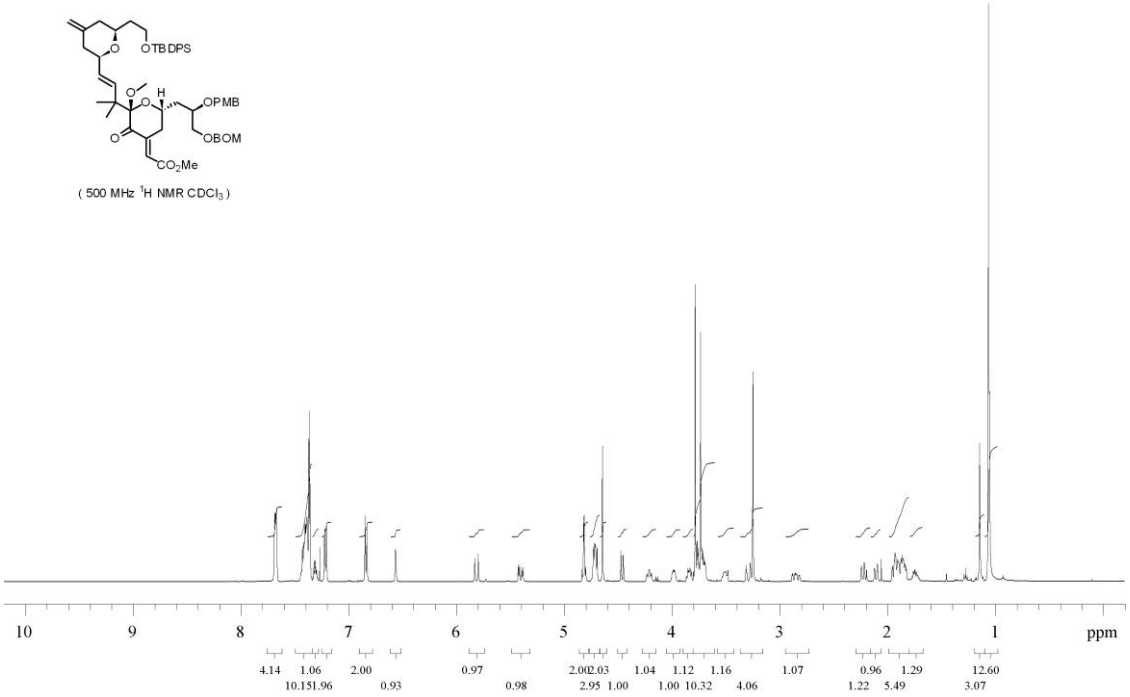

207.220
159.399
144.712
138.056
136.801
135.722
134.208
134.124
130.852
129.733
129.406
129.362
128.627
127.983
127.903
127.824
114.012
108.806
104.063
95.193
78.992
77.486
77.230
76.974
75.452
74.853
71.740
70.194
69.727
69.619
60.589
55.439
52.275
44.276
41.260
40.928
39.426
39.374
37.564
30.228
27.080
22.937
22.289
19.433
OTBDPS
OPMB
OBOM
H
O
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

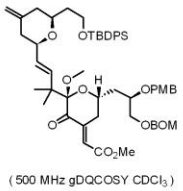

OTBDPS
OPMB
OBOM
H
O
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBDPS
OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2 (ppm)
F1 (ppm)

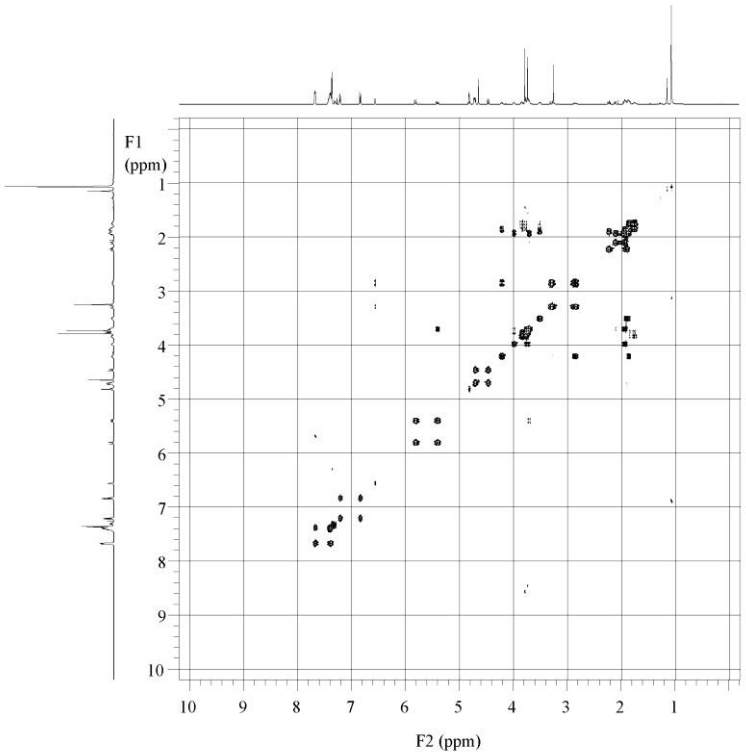

OTBDPS
OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2 (ppm)
F1 (ppm)

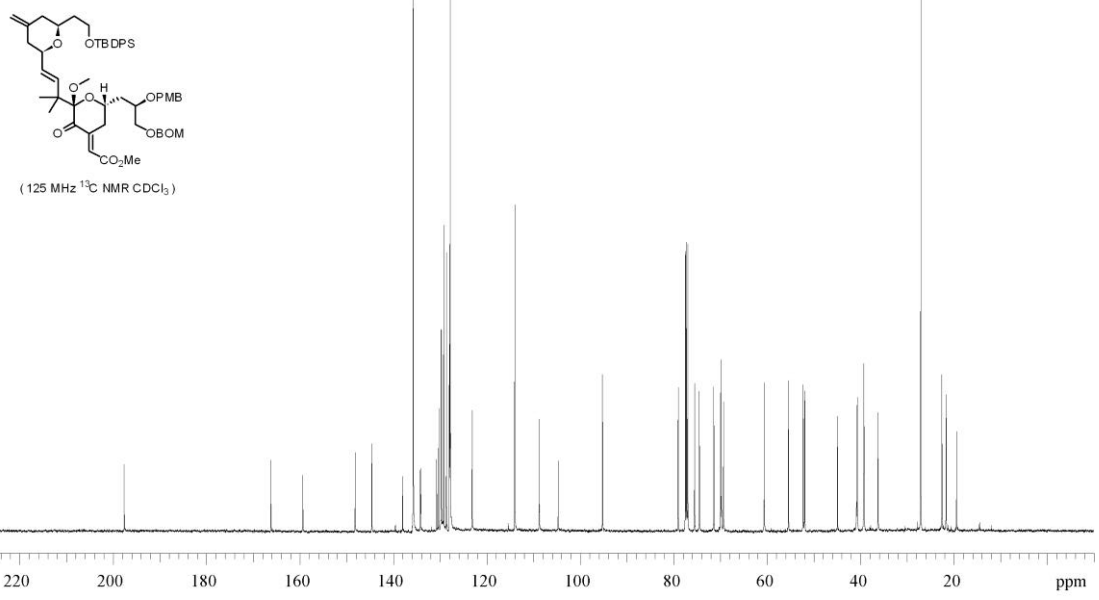

OTBDPS
43
H
4
OPMB
OBOM
(500 MHz NOESY1D CDCl3)
Left: irraditon at H-4
Right: irradition at H-43
10 9 8 7 6 5 4 3 2 1 ppm
10 9 8 7 6 5 4 3 2 1 ppm


OTBDPS
H
OPMB
OBOM
CO2Me
(500 MHz 1H NMR CDCl3)
10 9 8 7 6 5 4 3 2 1 ppm
4.14 1.06 2.00 0.97 2.00 2.03 1.04 1.12 1.16 1.07 0.96 1.29 12.60
10.15 1.96 0.93 0.98 2.95 1.00 1.00 10.32 4.06 1.22 5.49 3.07

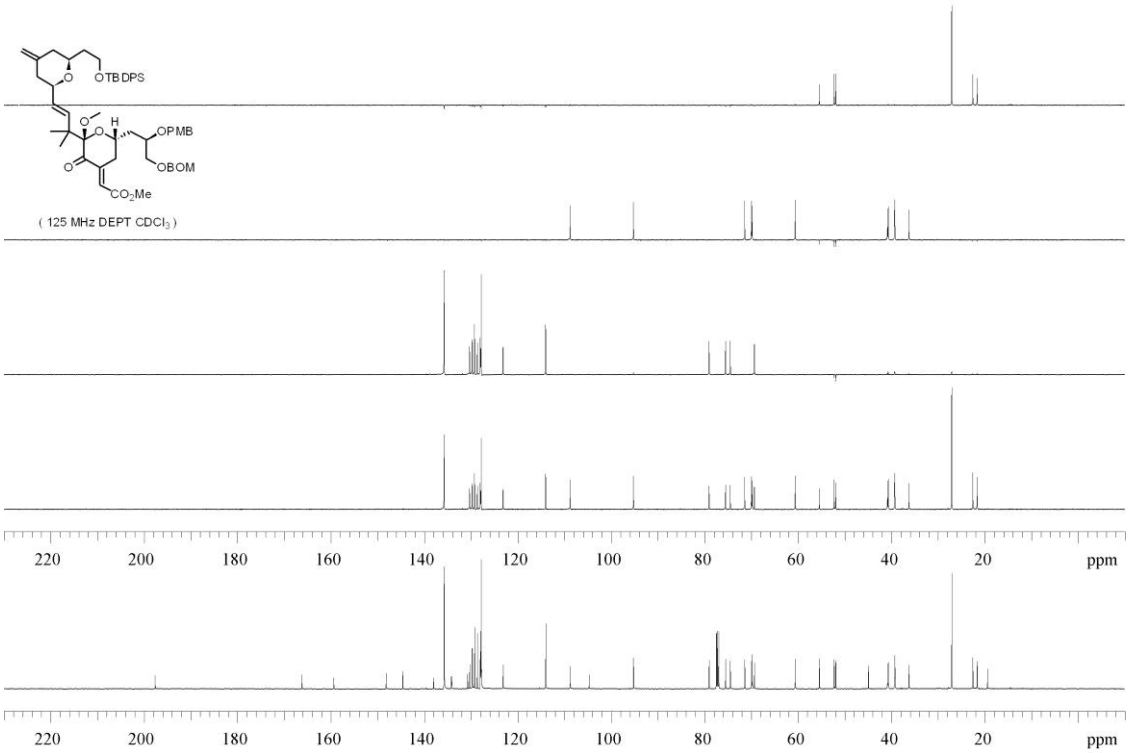


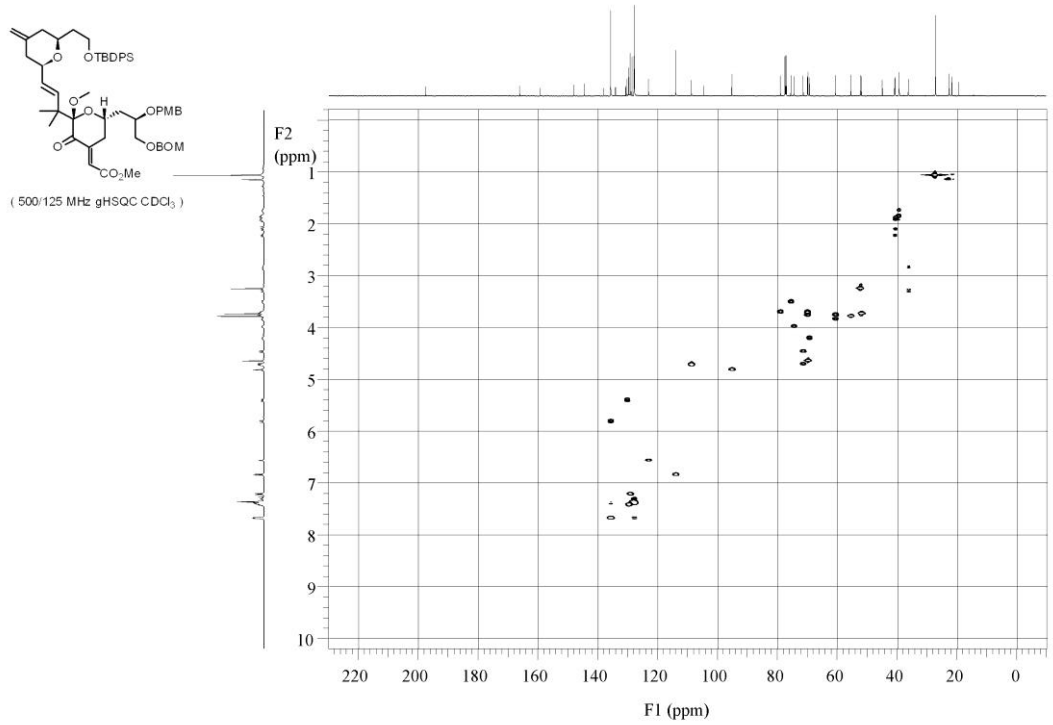
(500 MHz gDQCOSY $CDCl_3$)

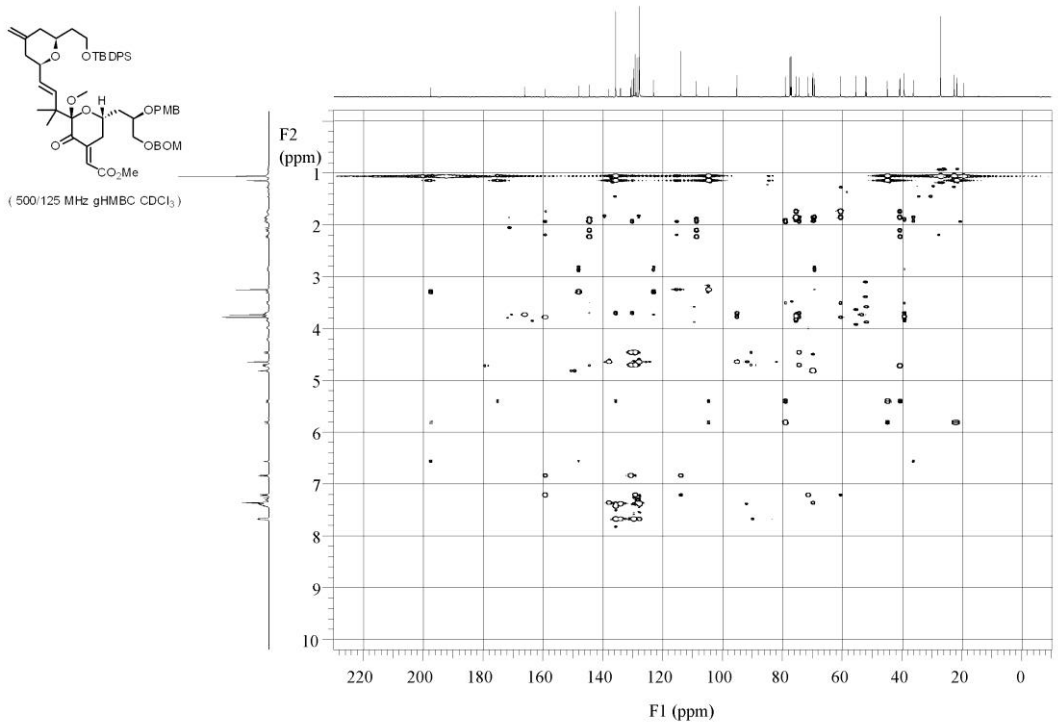


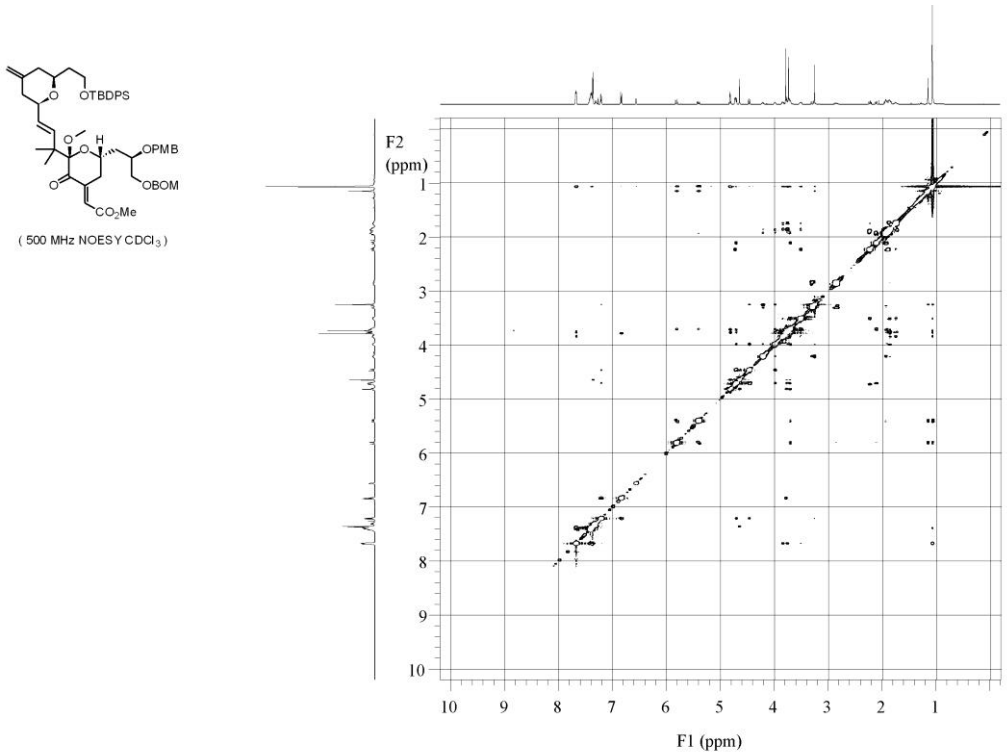


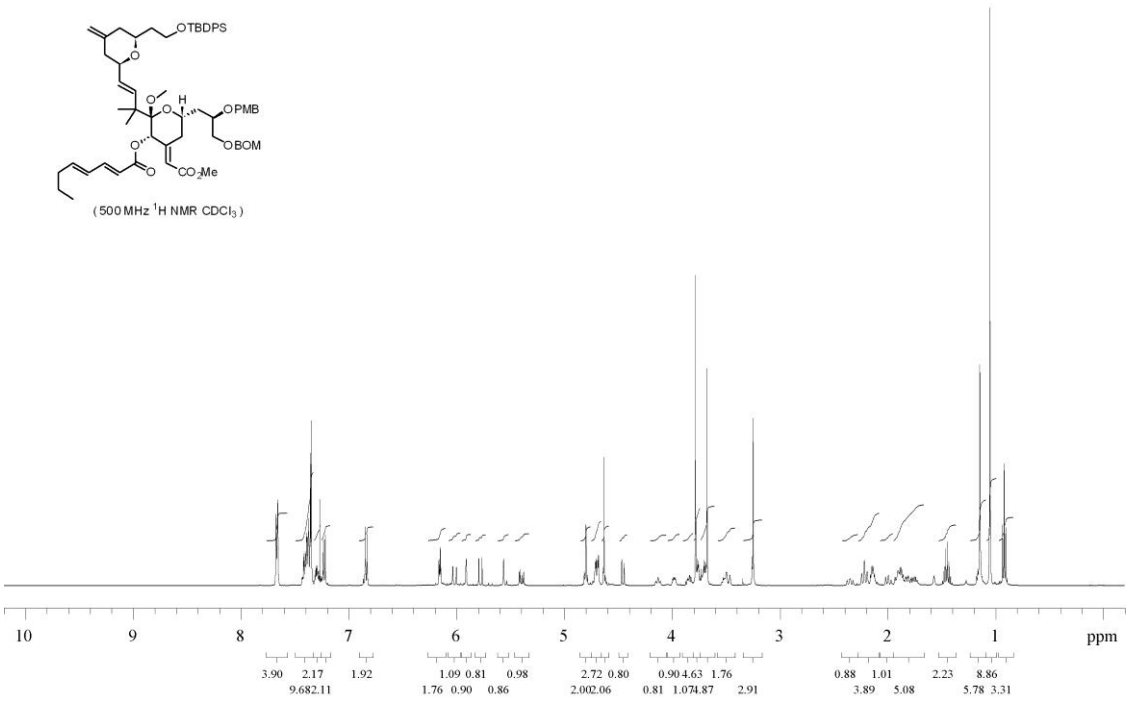
(125 MHz ^{13}C NMR $CDCl_3$)

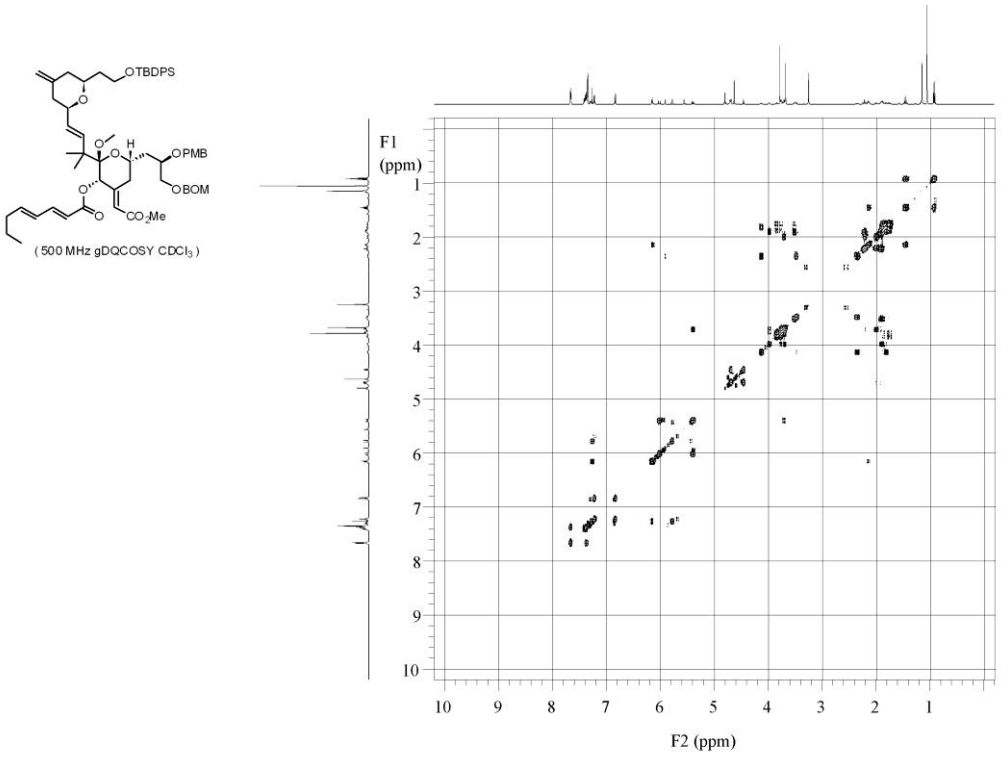

OTBDPS
OPMB
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

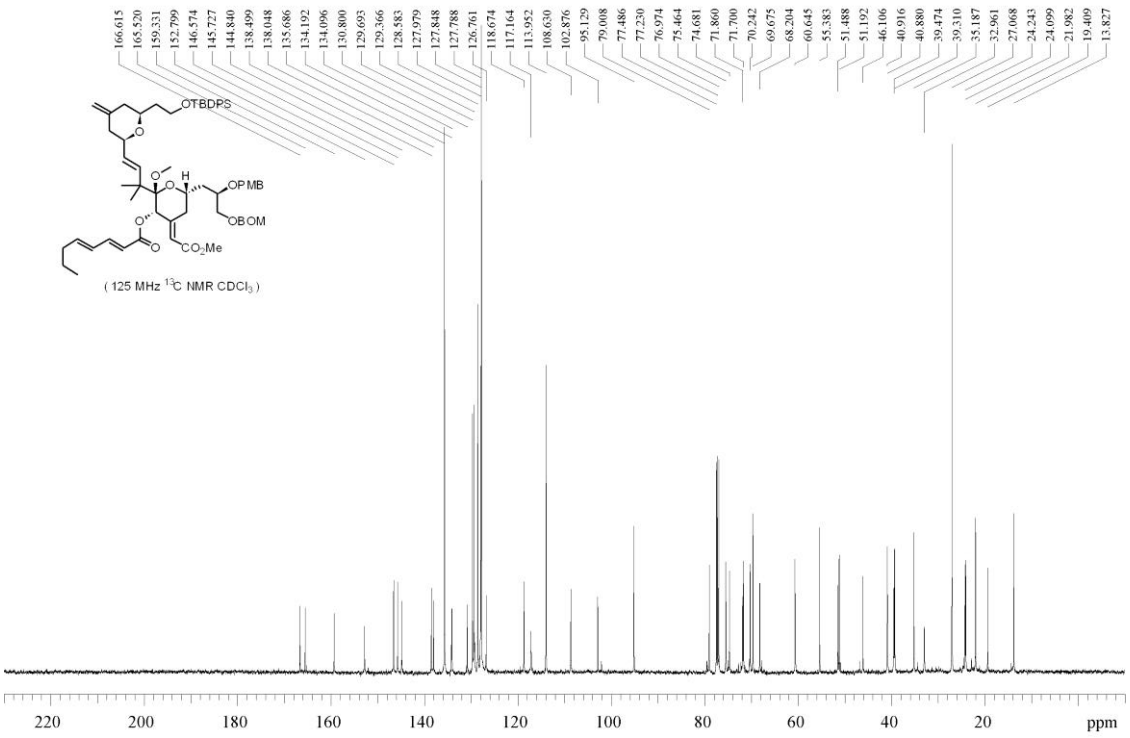

OTBDPS
OPMB
OBOM
CO2Me
(500/125 MHz gHSQC CDCl3)
F2
(ppm)
F1 (ppm)

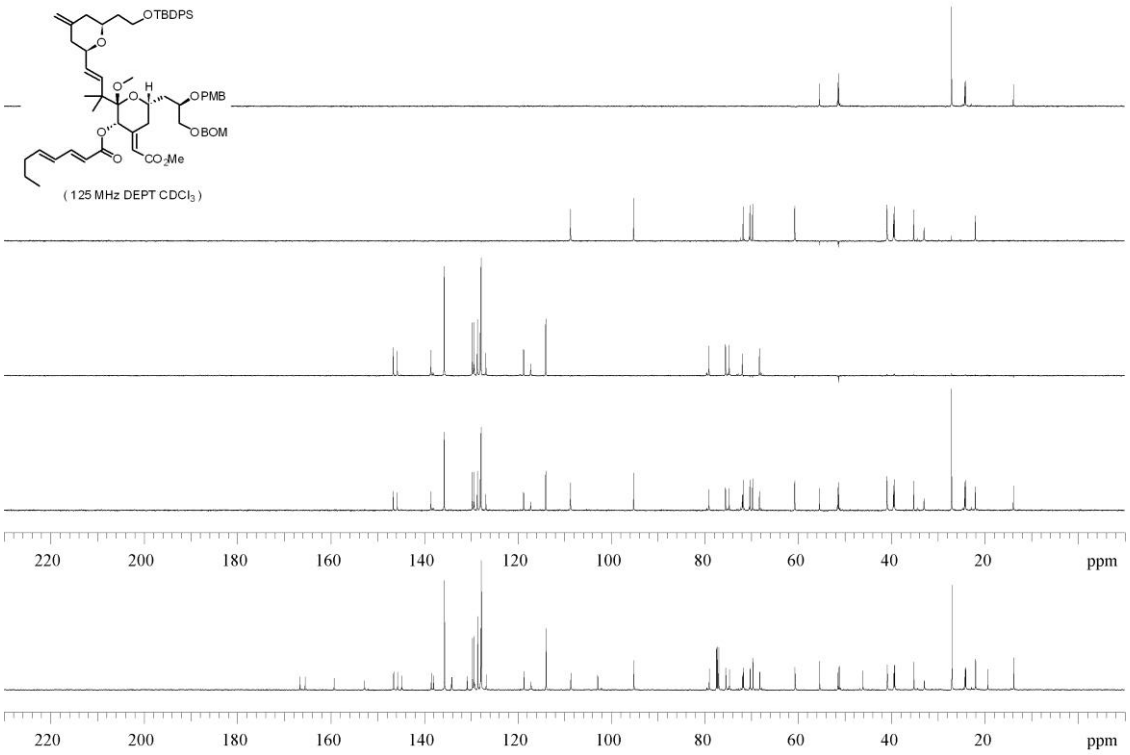

OTBDPS
OPMB
OBOM
CO2Me
H
O
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

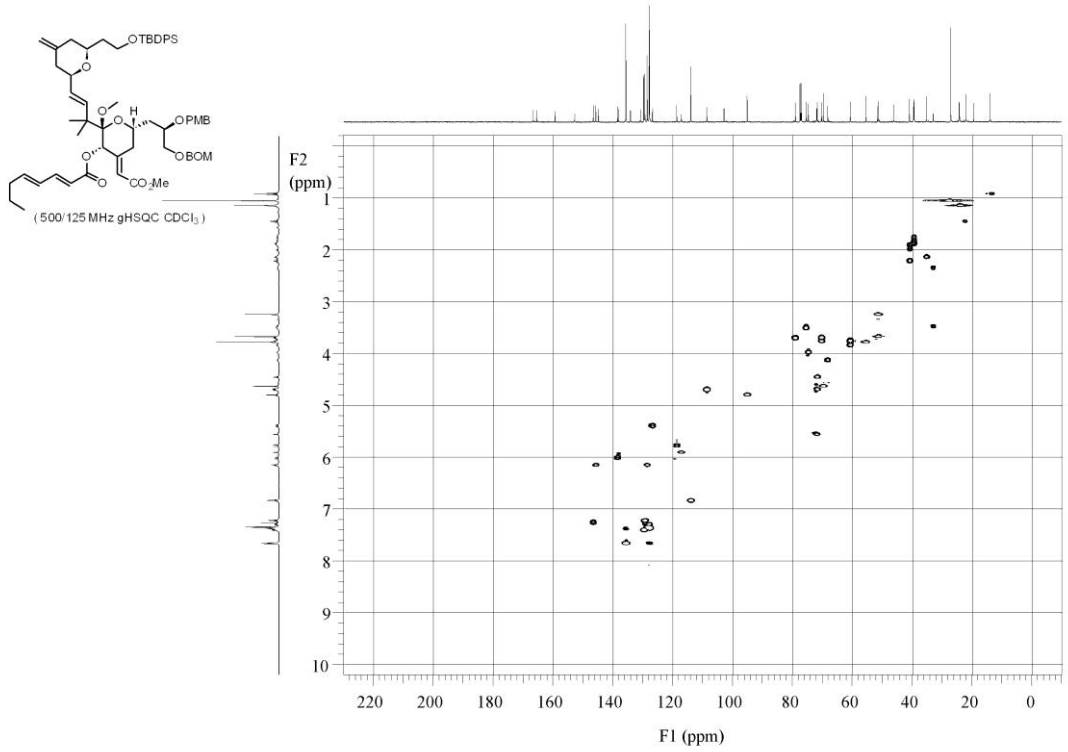

OTBDPS
OPMB
OBOM
CO2Me
H
O
(500 MHz NOESY CDCl3)
F2
(ppm)
F1 (ppm)

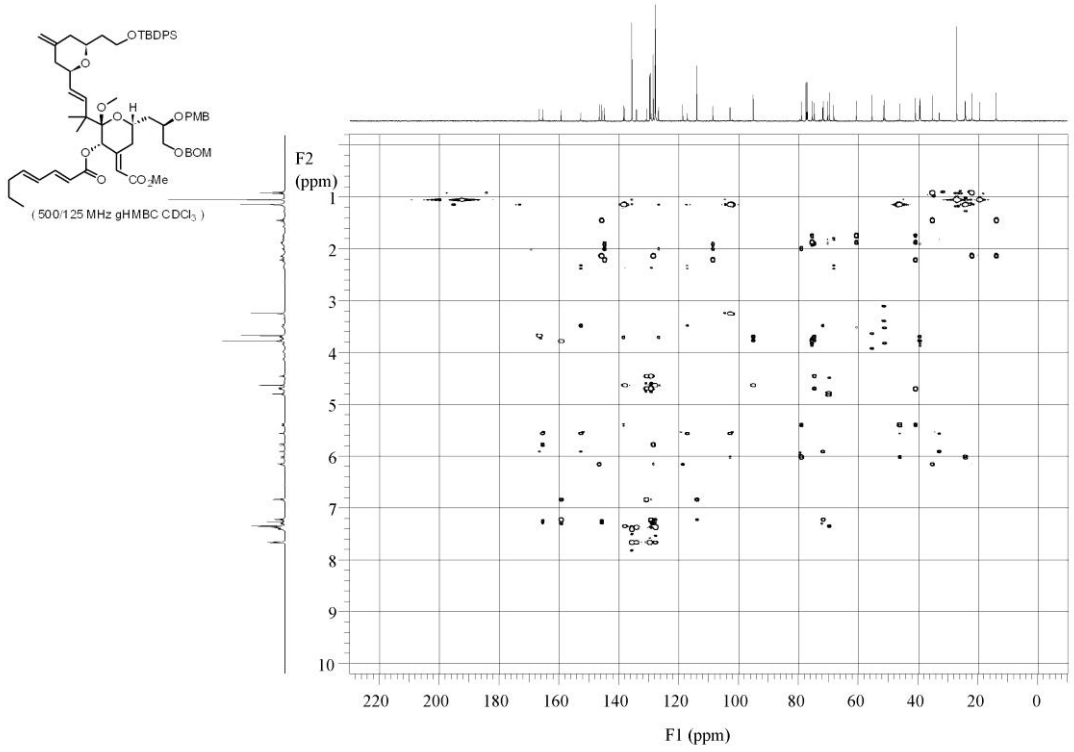

OTBDPS
OPMB
OBOM
CO2Me
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
3.90 2.17 1.92 1.09 0.81 0.98 2.72 0.80 0.90 4.63 1.76 0.88 1.01 2.23 8.86
9.68 2.11 1.76 0.90 0.86 2.00 2.06 0.81 1.07 4.87 2.91 3.89 5.08 5.78 3.31

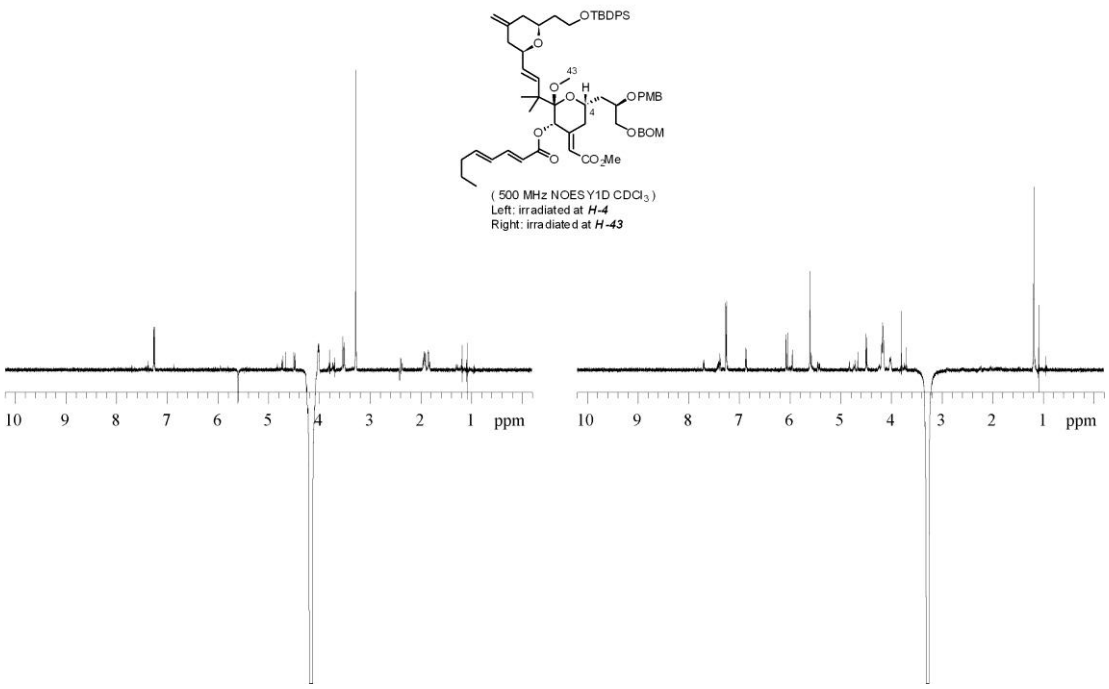

OTBDPS
OPMB
OBOM
CO2Me
(500 MHz gDQCOSY CDCl3)
F1 (ppm)
F2 (ppm)
1
2
3
4
5
6
7
8
9
10

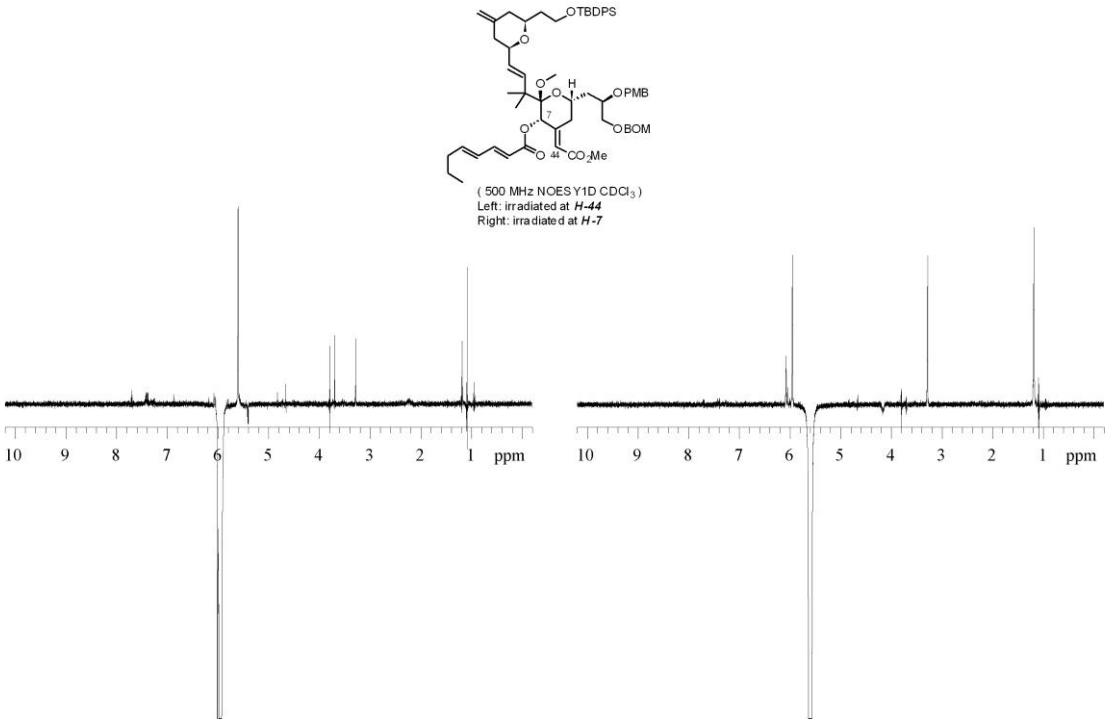

166.615
165.520
159.331
152.799
146.574
145.727
144.840
138.499
138.048
135.686
134.192
134.096
130.800
129.693
129.366
128.583
127.979
127.848
127.788
126.761
118.674
117.164
113.952
108.630
102.876
95.129
79.008
77.486
77.220
76.974
75.464
74.681
71.860
71.700
70.242
69.675
68.204
60.645
55.383
51.488
51.192
46.106
40.916
40.880
39.474
39.310
35.187
32.961
27.068
24.243
24.099
21.982
19.409
13.827
OTBDPS
OPMB
OBOM
CO2Me
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

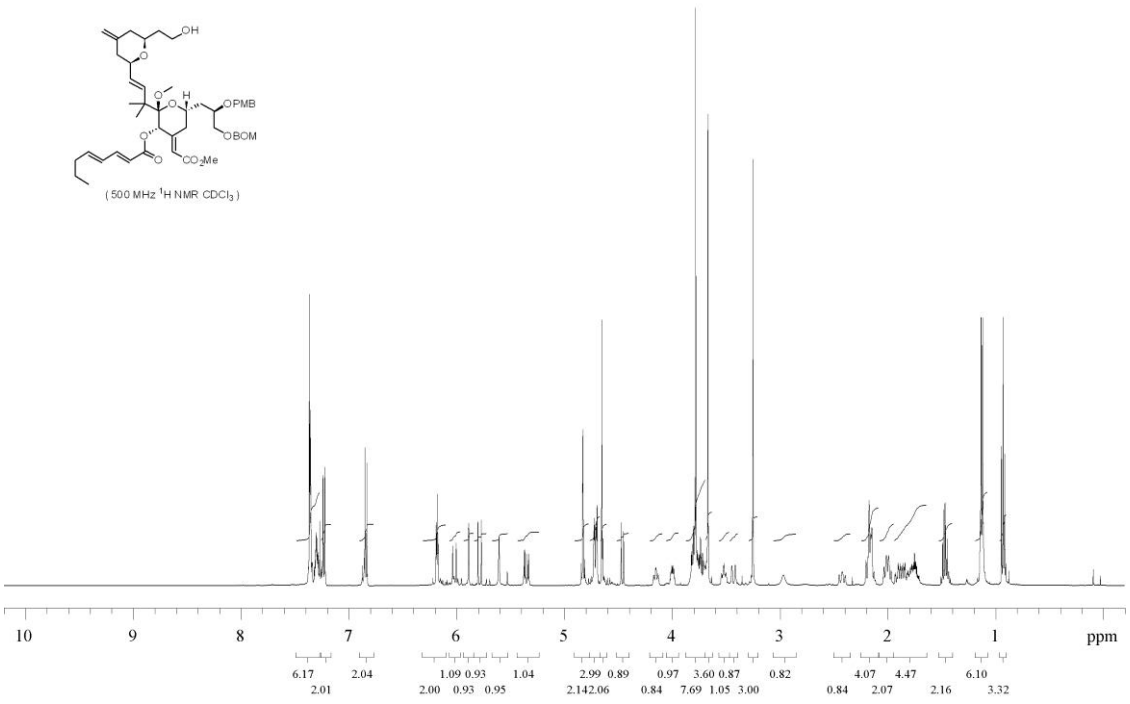

OTBDPS
OPMB
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

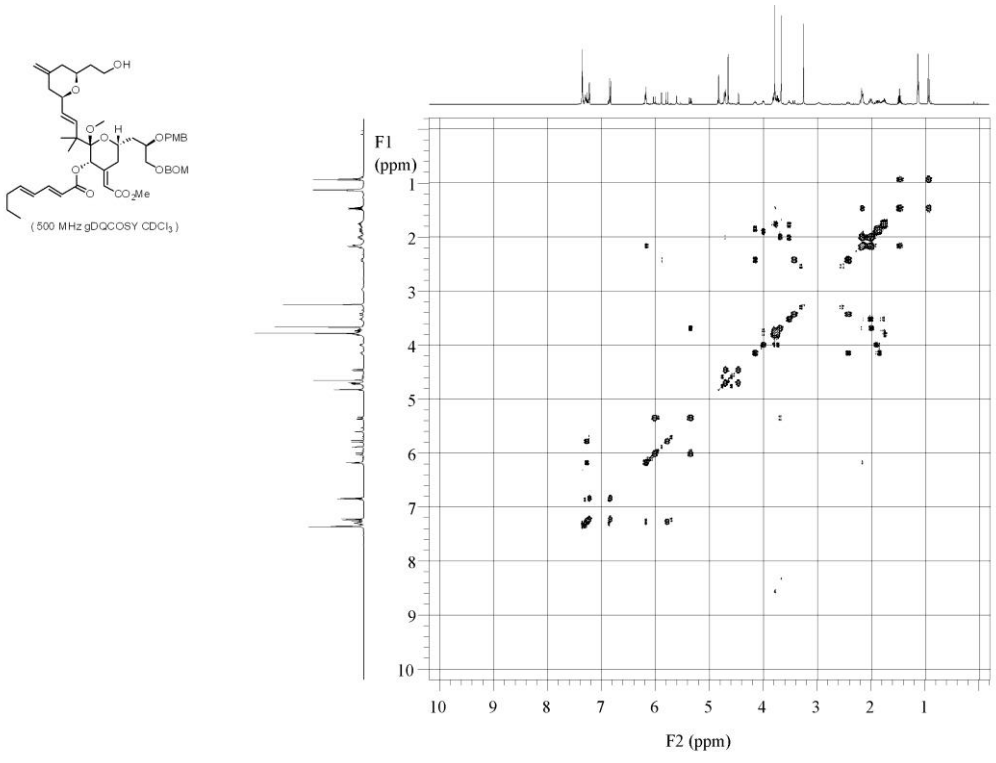

OTBDPS
OPMB
OBOM
CO2Me
(500/125 MHz gHSQC CDCl3)
F2 (ppm)
F1 (ppm)

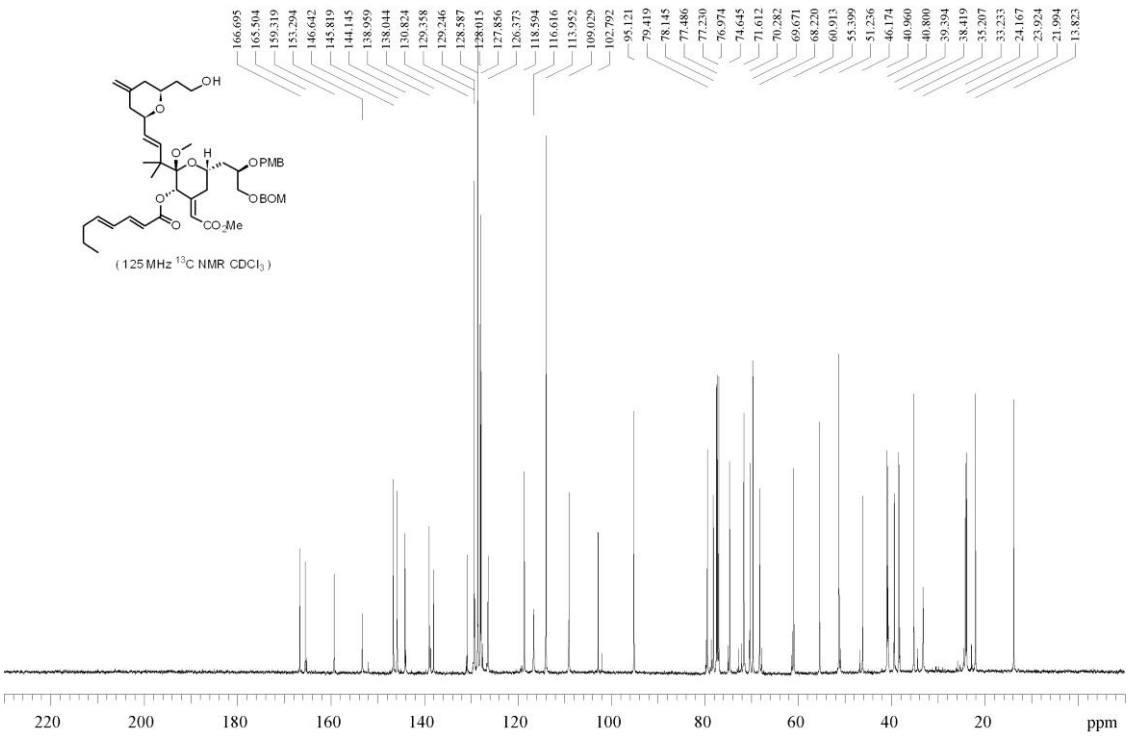

OTBDPS
OPMB
OBOM
CO2Me
(500/125 MHz gHMBC CDCl3)
F2 (ppm)
F1 (ppm)


OTBDPS
43
H
OPMB
4
OBOM
CO2Me
(500 MHz NOESY1D CDCl3)
Left: irradiated at H-4
Right: irradiated at H-43
10 9 8 7 6 5 4 3 2 1 ppm
10 9 8 7 6 5 4 3 2 1 ppm


OTBDPS
H
OPMB
7
OBOM
44
CO2Me
(500 MHz NOESY1D CDCl3)
Left: irradiated at H-44
Right: irradiated at H-7
10 9 8 7 6 5 4 3 2 1 ppm
10 9 8 7 6 5 4 3 2 1 ppm


OH
OPMB
OBOM
CO2Me
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
6.17
2.01
2.04
1.09 0.93
2.00 0.93 0.95
1.04
2.99 0.89
2.142.06
0.97
0.84
3.60 0.87
7.69 1.05 3.00
0.82
4.07 4.47
0.84 2.07
2.16
6.10
3.32


OH
OPMB
OBOM
CO2Me
(500 MHz gDQCOSY CDCl3)
F1
(ppm)
F2 (ppm)


166.695
165.504
159.319
153.294
146.642
145.819
144.145
138.959
138.044
130.824
129.358
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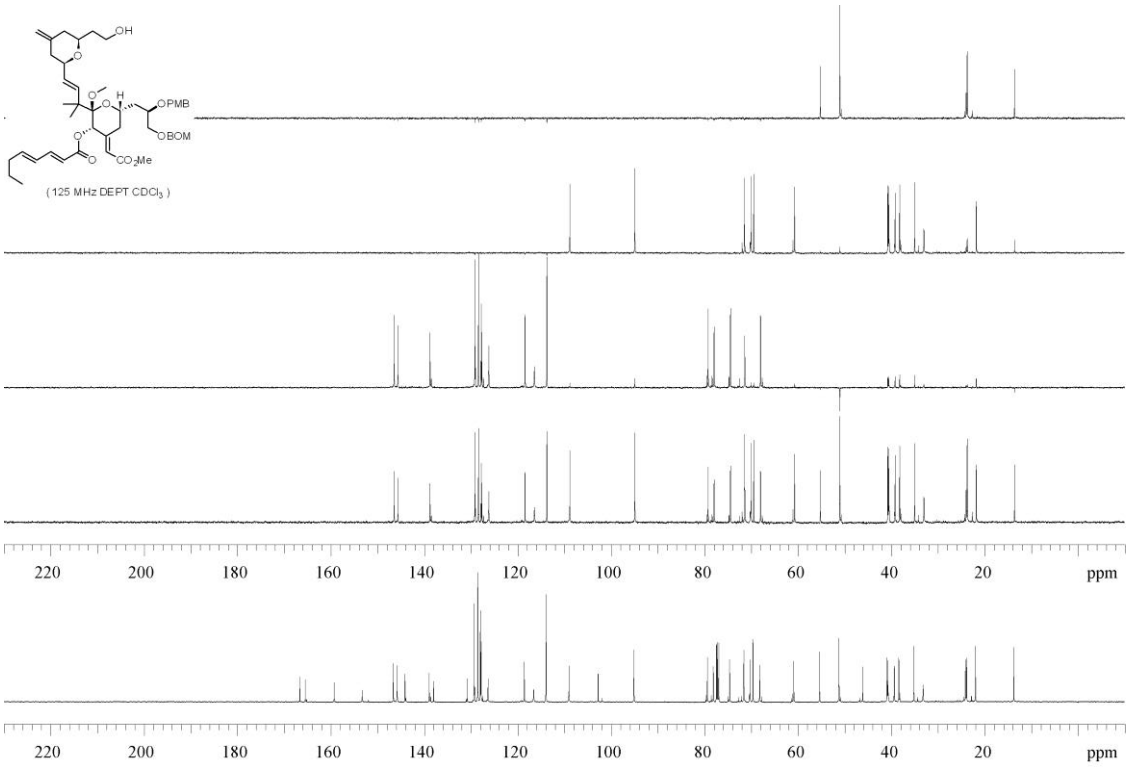
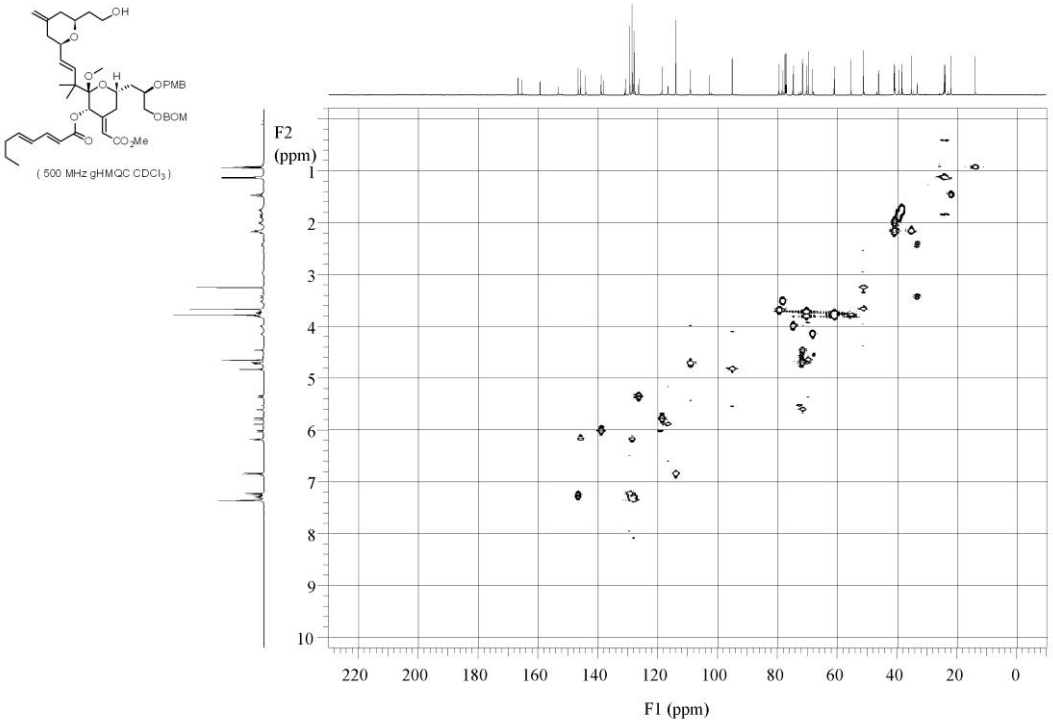
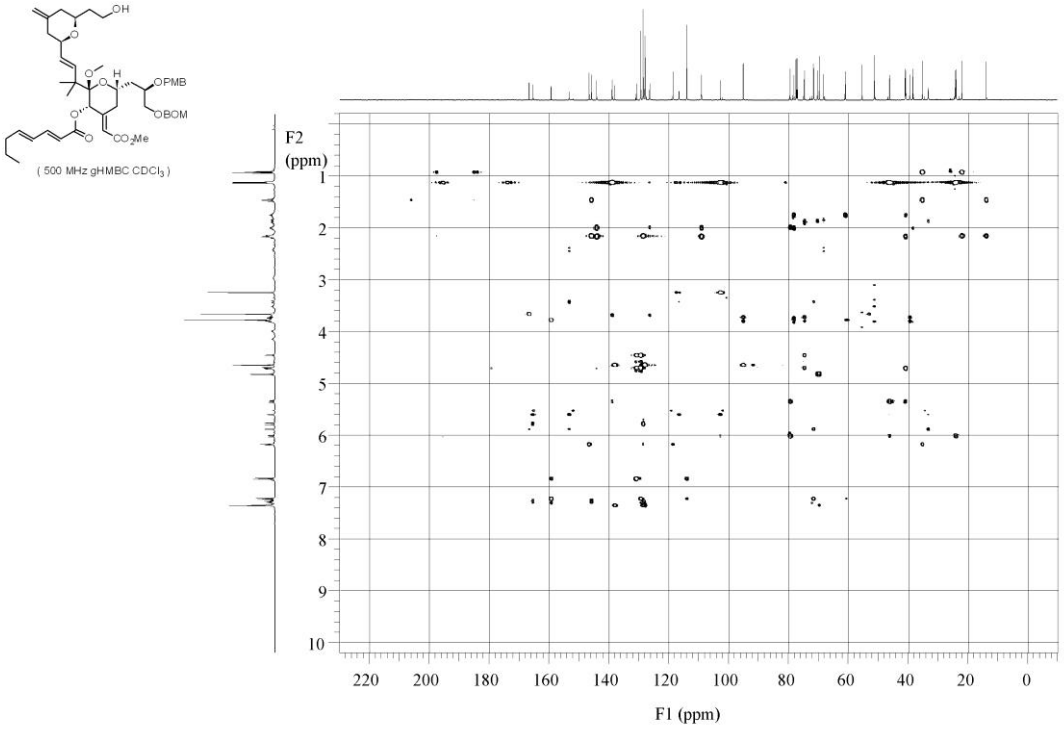
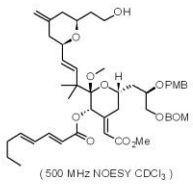
128.587
128.015
127.856
126.373
118.594
116.616
113.952
109.029
102.792
95.121
79.419
78.145
77.486
77.230
76.974
74.645
71.612
70.282
69.671
68.220
60.913
55.399
51.236
46.174
40.960
40.800
39.394
38.419
35.207
33.233
24.167
23.924
21.994
13.823
OH
OPMB
OBOM
CO2Me
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

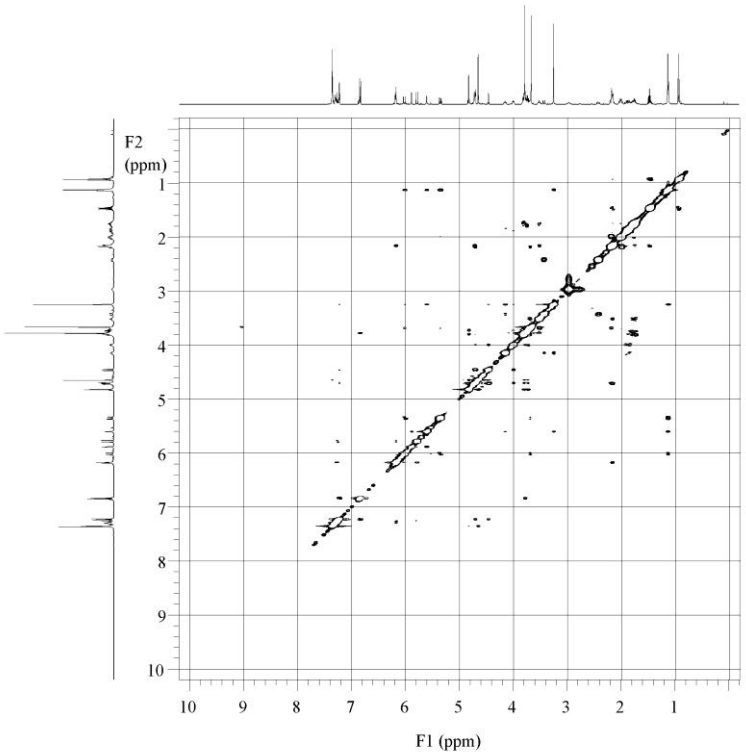

OH
OPMB
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

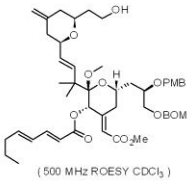

OH
OPMB
OBOM
CO2Me
(500 MHz gHMQC CDCl3)
F2
(ppm)
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)


OH
OPMB
OBOM
CO2Me
(500 MHz gHMBC CDCl3)
F2
(ppm)
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

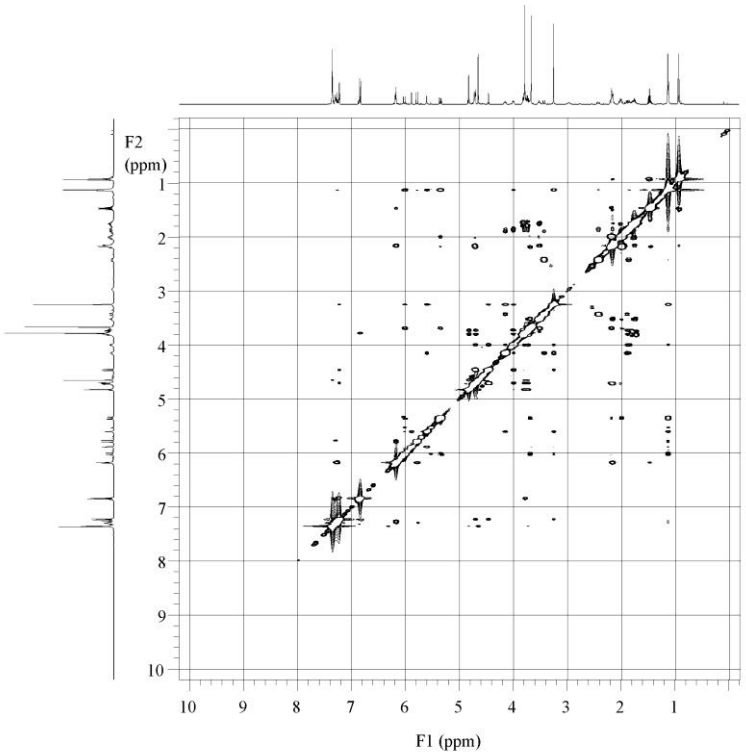


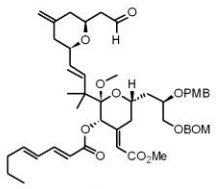
(500 MHz NOESY $CDCl_3$)



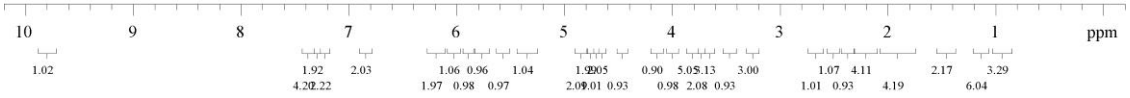


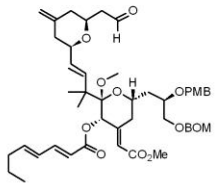
(500 MHz ROESY $CDCl_3$)



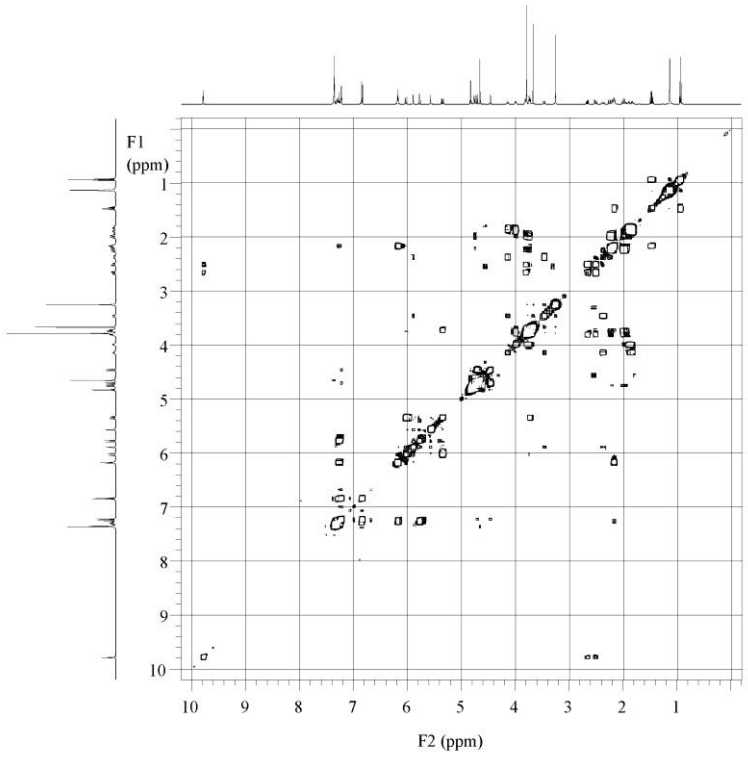


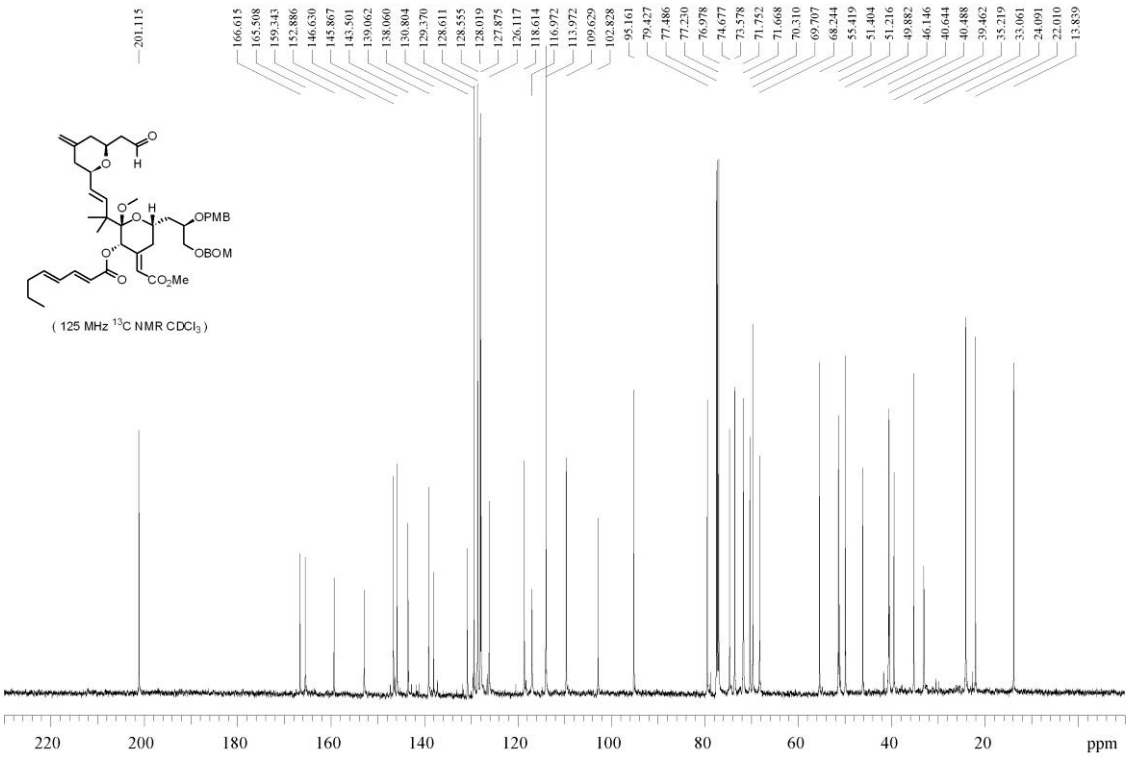
(500 MHz ^{1}H NMR $CDCl_3$)

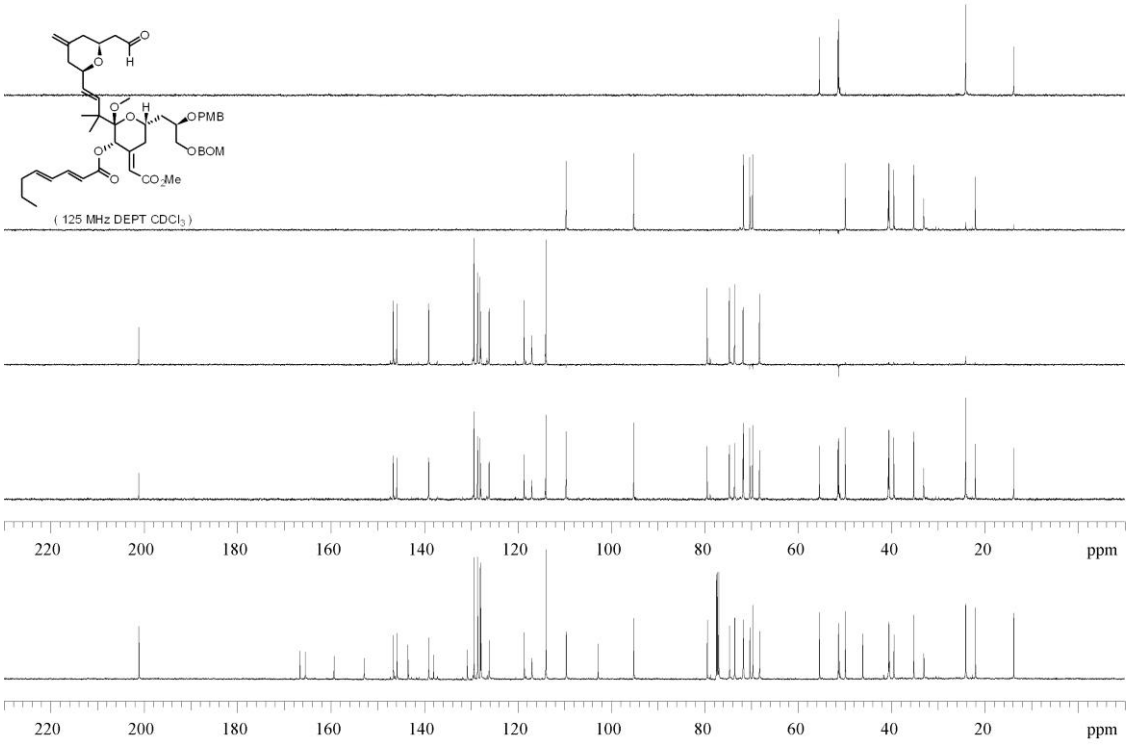


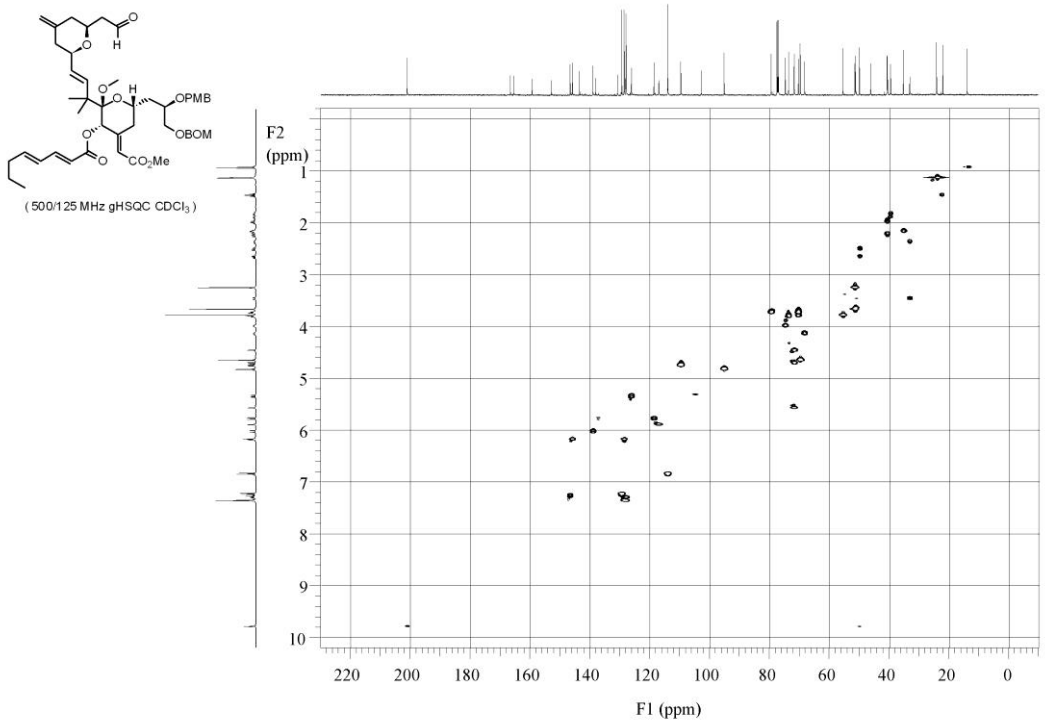


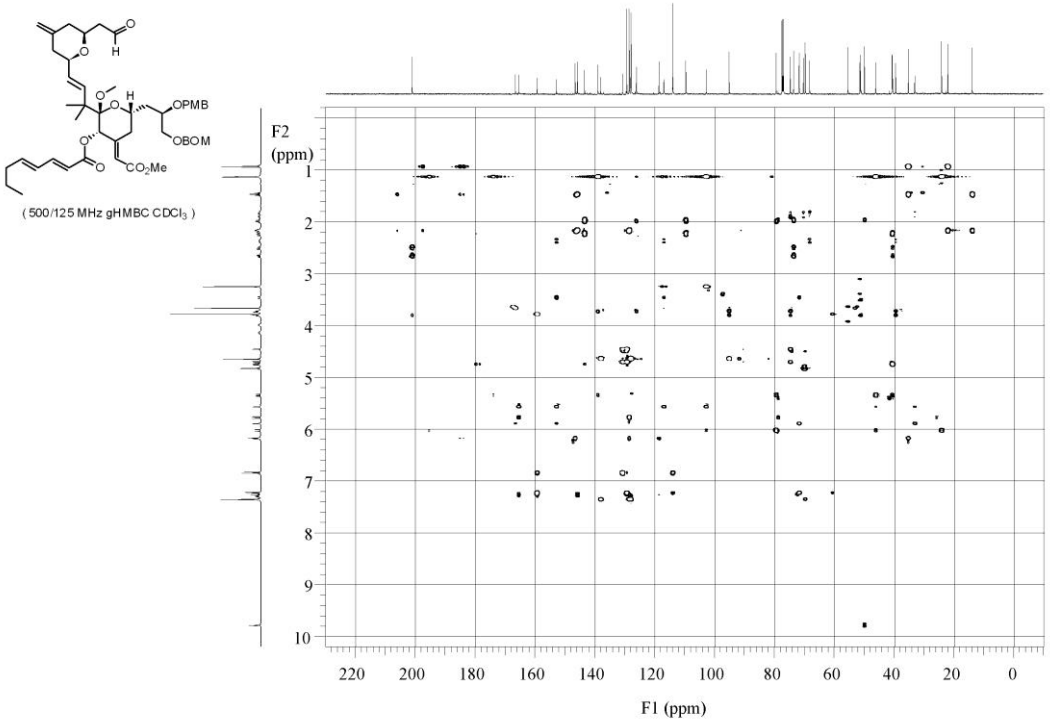
(500 MHz gCOSY $CDCl_3$)

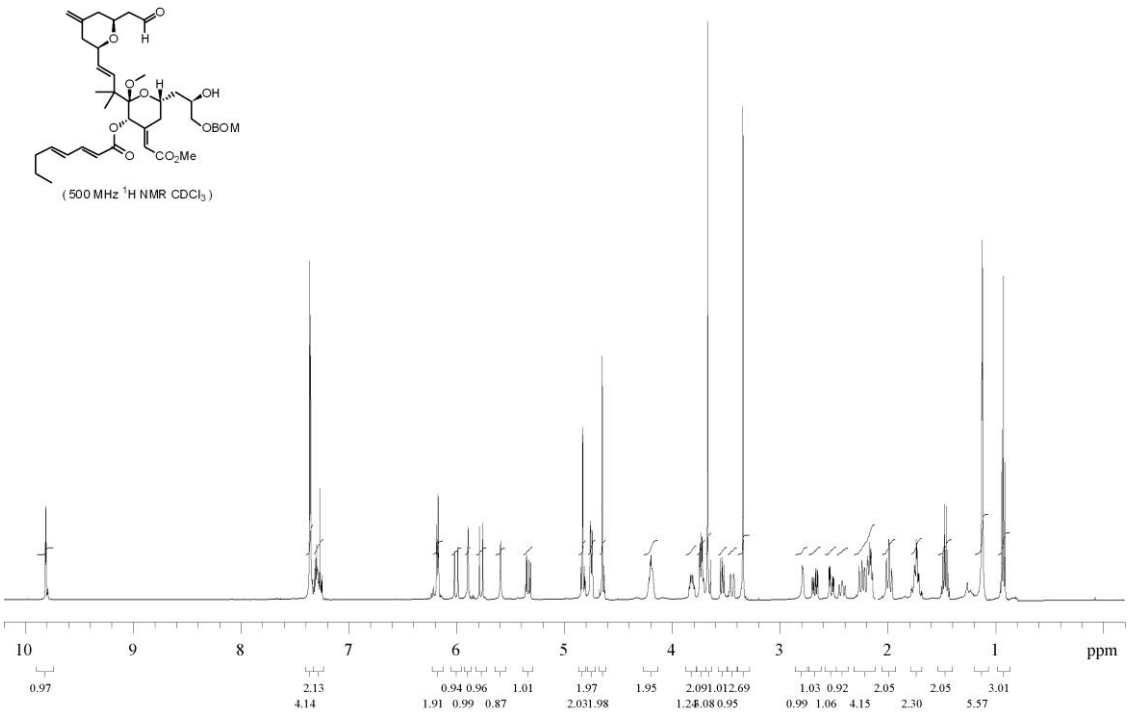


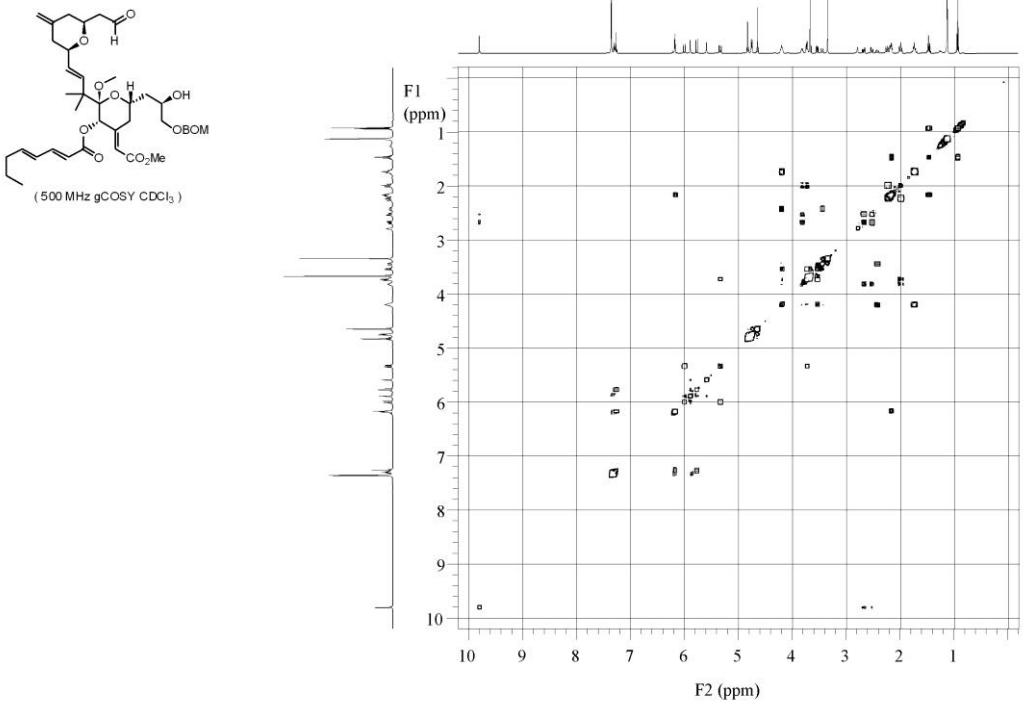

201.115
166.615
165.508
159.343
152.886
146.630
145.867
143.501
139.062
138.060
130.804
129.370
128.611
128.555
128.019
127.875
126.117
118.614
116.972
113.972
109.629
102.828
95.161
79.427
77.486
77.230
76.978
74.677
73.578
71.752
71.668
70.310
69.707
68.244
55.419
51.404
51.216
49.882
46.146
40.644
40.488
39.462
35.219
33.061
24.091
22.010
13.839
OPMB
OBOM
CO2Me
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

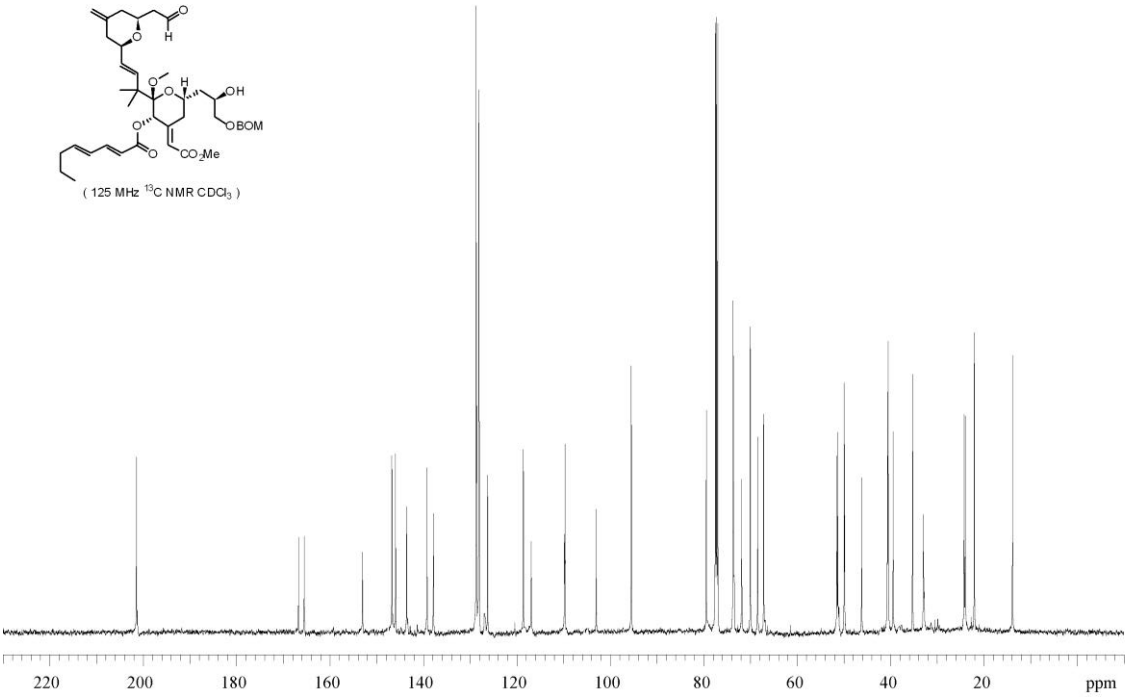

OPMB
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

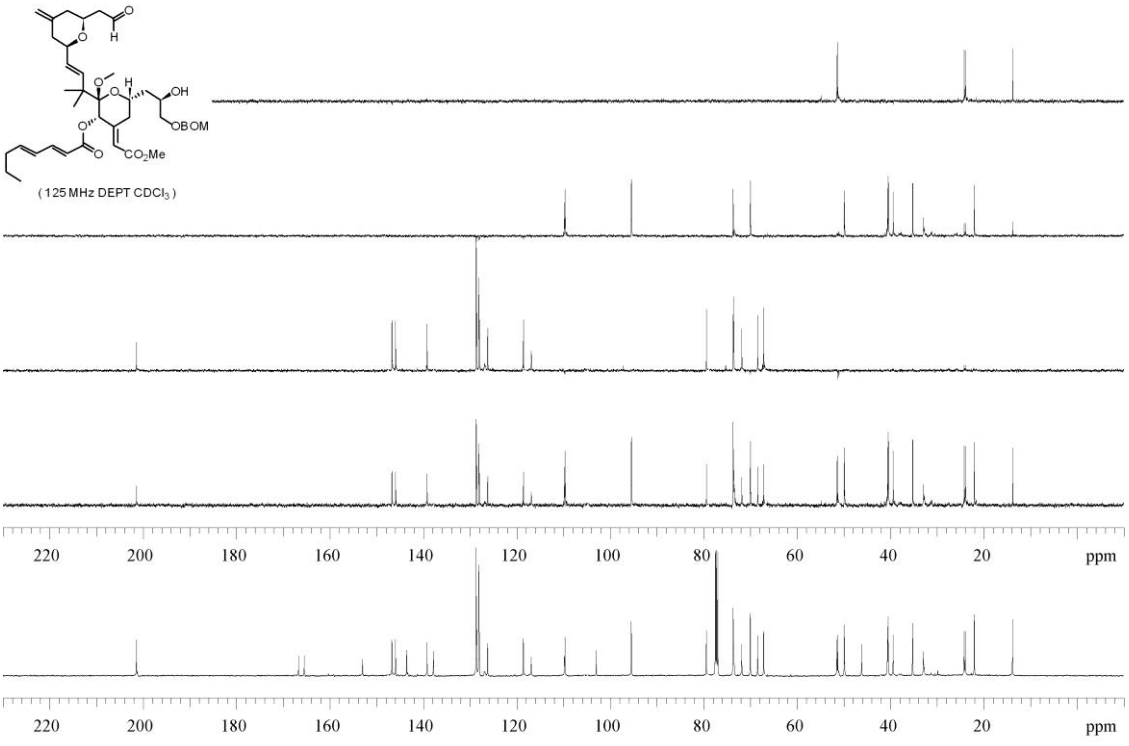

OPMB
OBOM
CO2Me
(500/125 MHz gHSQC CDCl3)
F2 (ppm)
F1 (ppm)

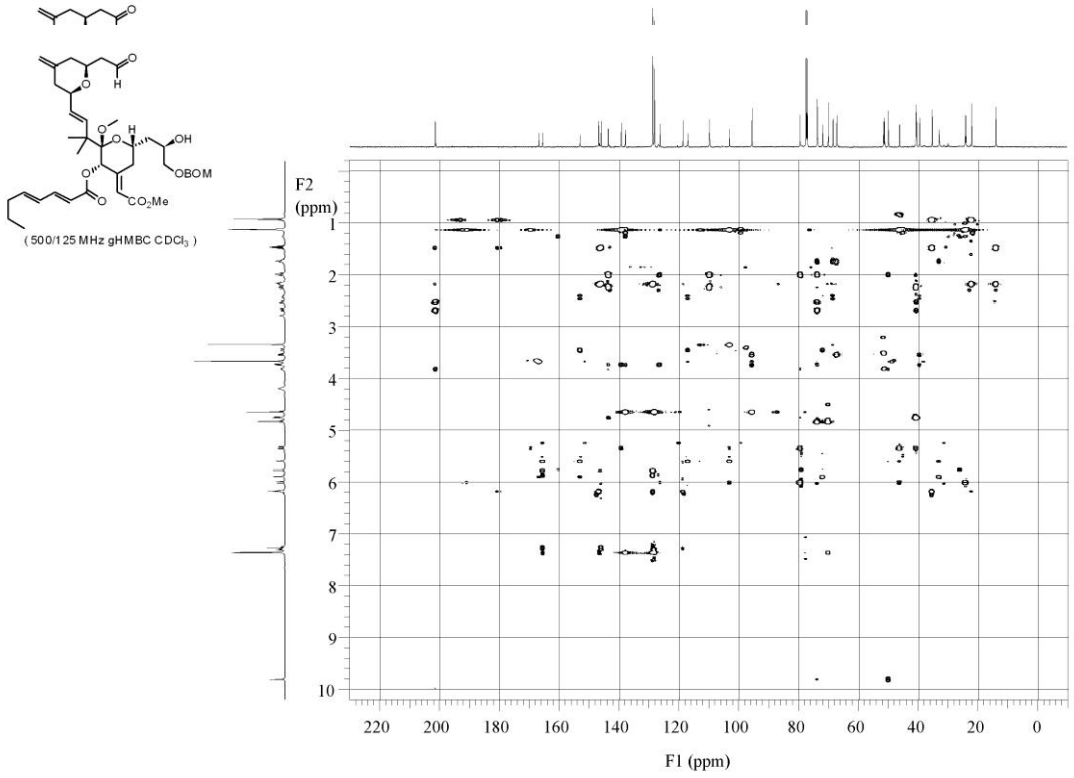

OPMB
OBOM
CO2Me
(500/125 MHz gHMBC CDCl3)
F2 (ppm)
F1 (ppm)

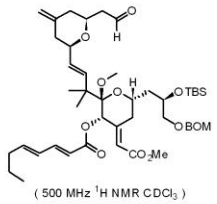

(500 MHz ^{1}H NMR $CDCl_3$)
OH
OBOM
CO_2Me
10
9
8
7
6
5
4
3
2
1
ppm
0.97
2.13
4.14
0.94 0.96
1.91 0.99 0.87
1.01
1.97
2.03 1.98
1.95
2.09 1.01 2.69
1.24 1.08 0.95
1.03 0.92
0.99 1.06 4.15
2.05
2.30
2.05
3.01
5.57


(500 MHz gCOSY $CDCl_3$)
OH
OBOM
CO_2Me
F1
(ppm)
F2 (ppm)
1
2
3
4
5
6
7
8
9
10

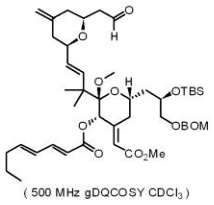

(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm


(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

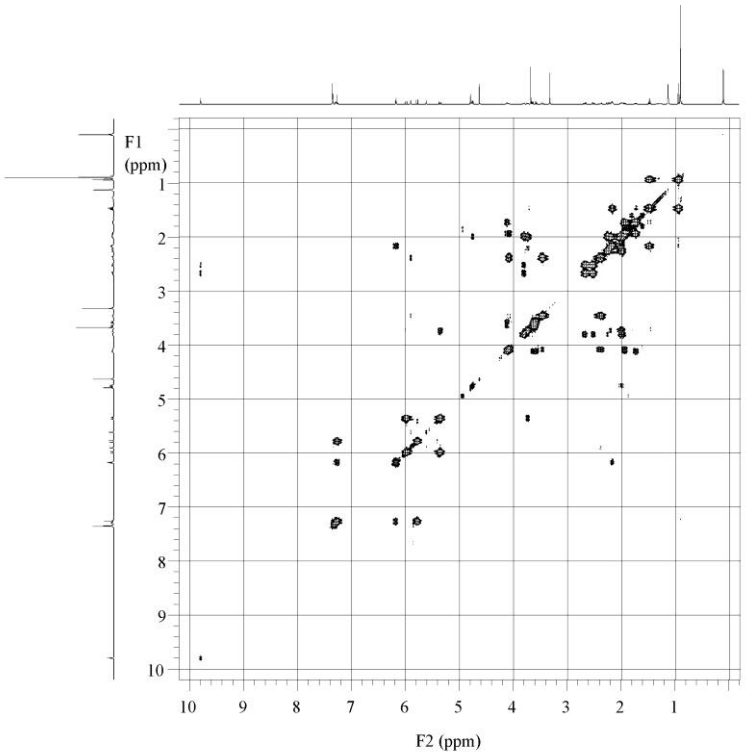

OH
OBOM
CO_2Me
(500/125 MHz gHMBC $CDCl_3$)
F2
(ppm)
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

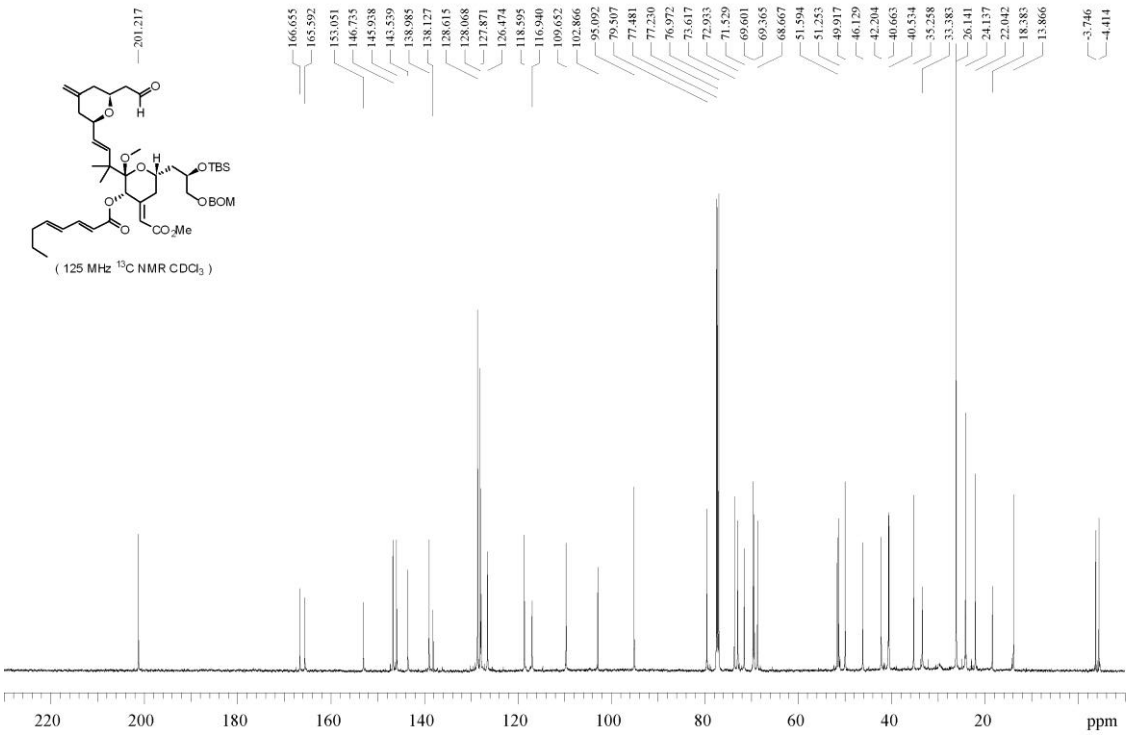


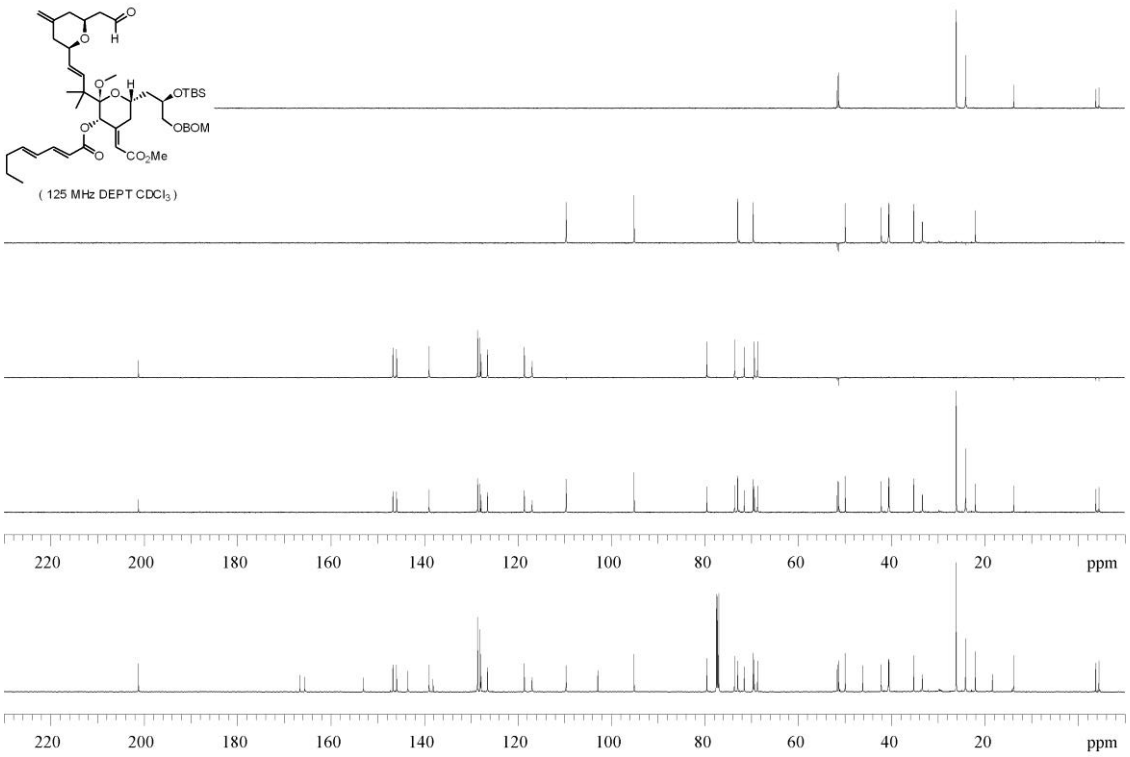
(500 MHz ^{1}H NMR $CDCl_3$)

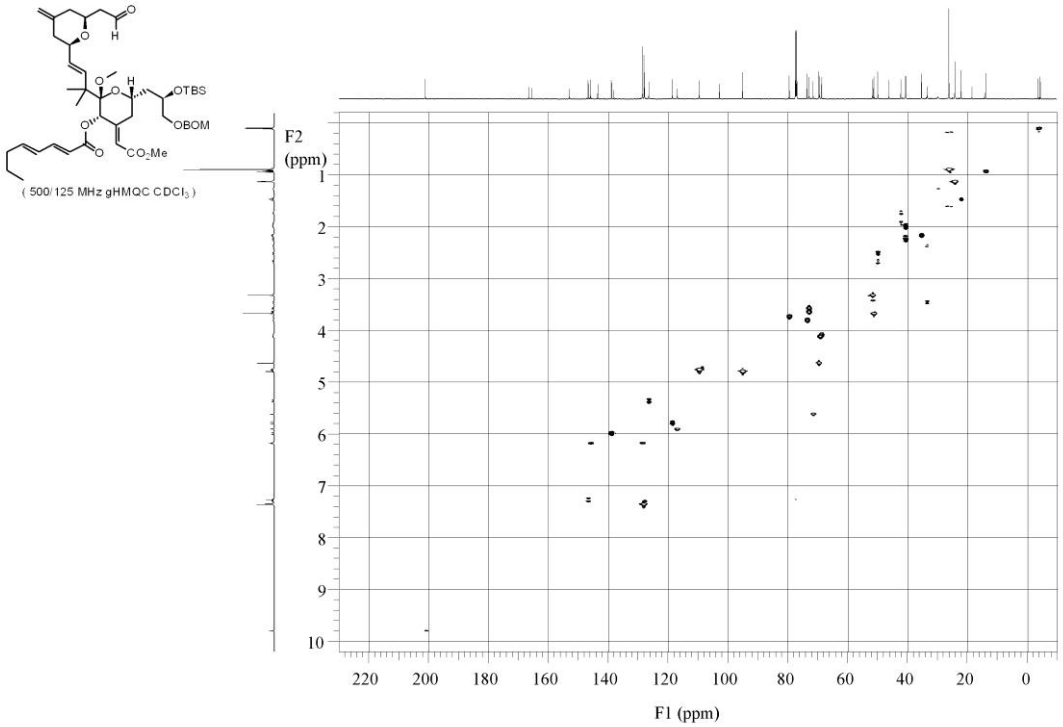


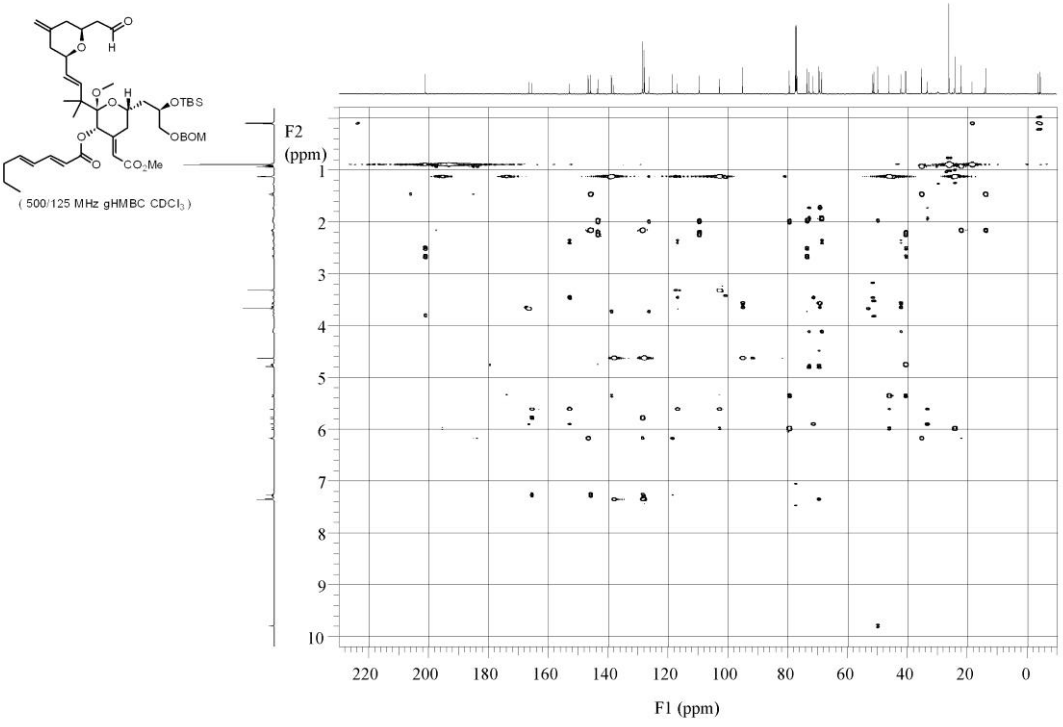
(500 MHz gDQCOSY $CDCl_3$)

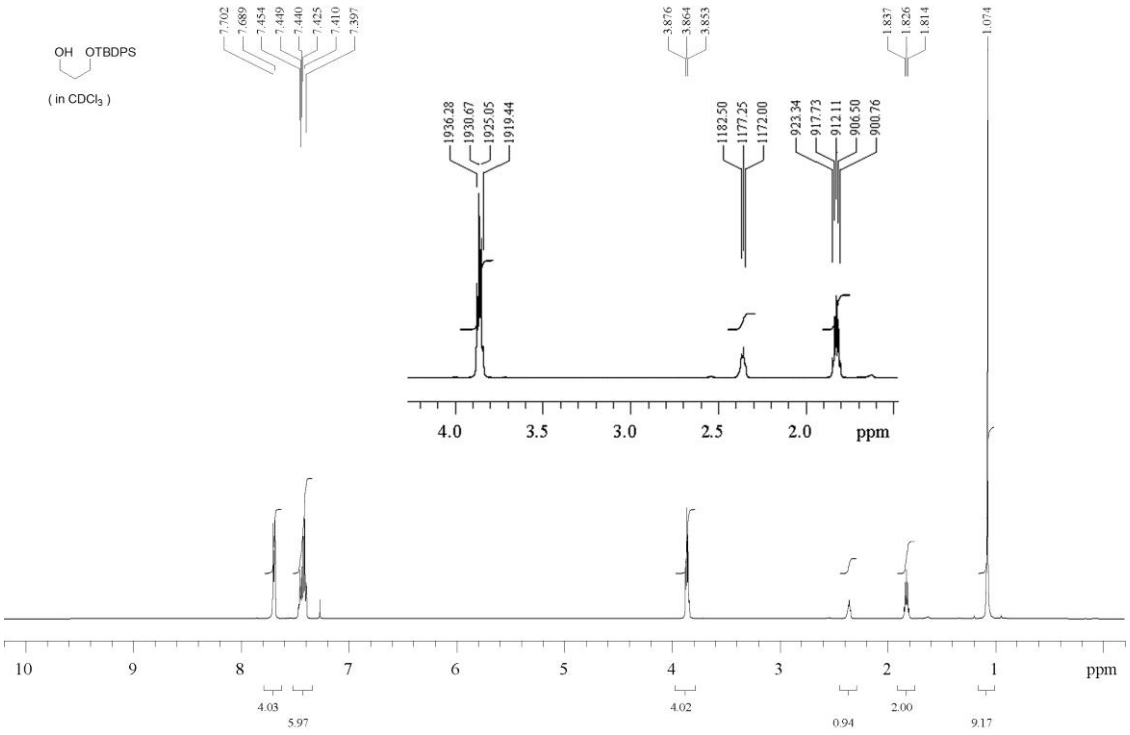


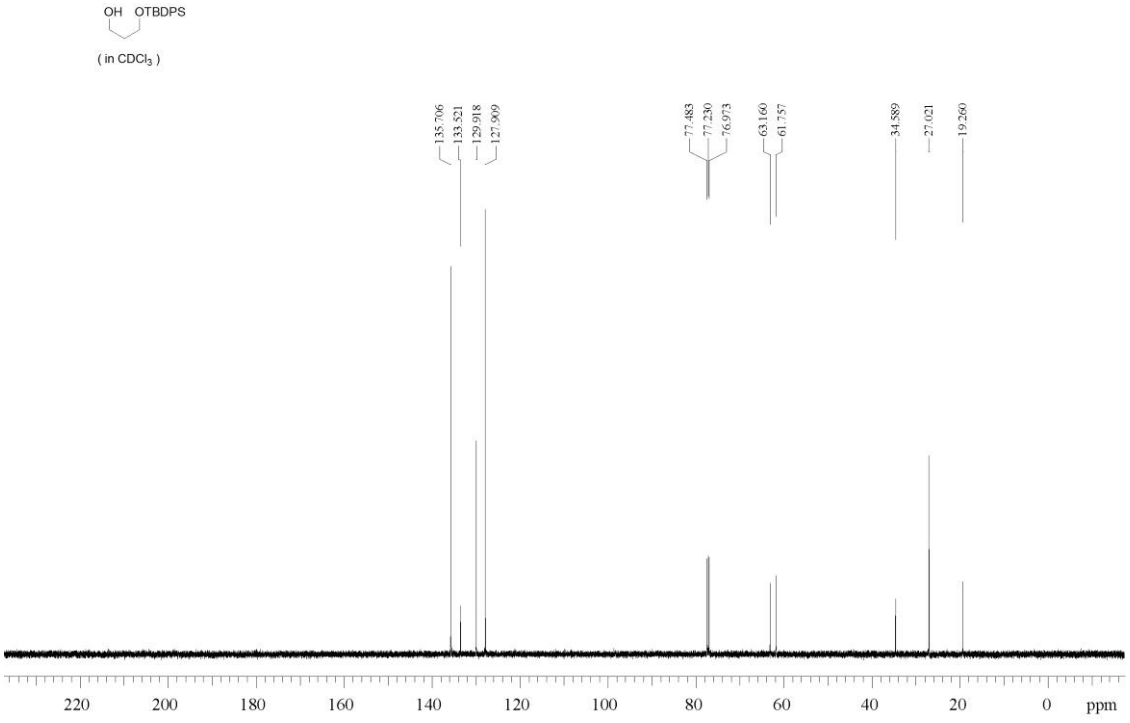

201.217
166.655
165.592
153.051
146.735
145.938
143.539
138.985
138.127
128.615
128.068
127.871
126.474
118.595
116.940
109.652
102.866
95.092
79.507
77.481
77.230
76.972
73.617
72.933
71.529
69.601
69.365
68.667
51.594
51.253
49.917
46.129
42.204
40.663
40.534
35.258
33.383
26.141
24.137
22.042
18.383
13.866
-3.746
-4.414
OTBS
OBOM
CO2Me
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

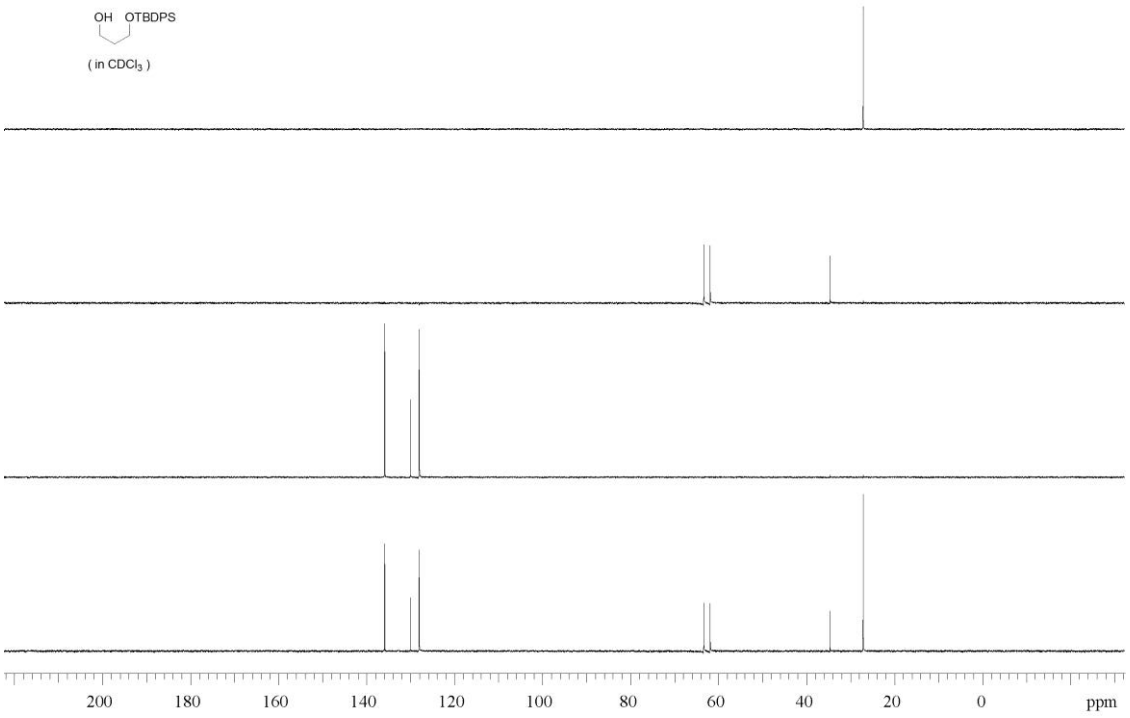

OTBS
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

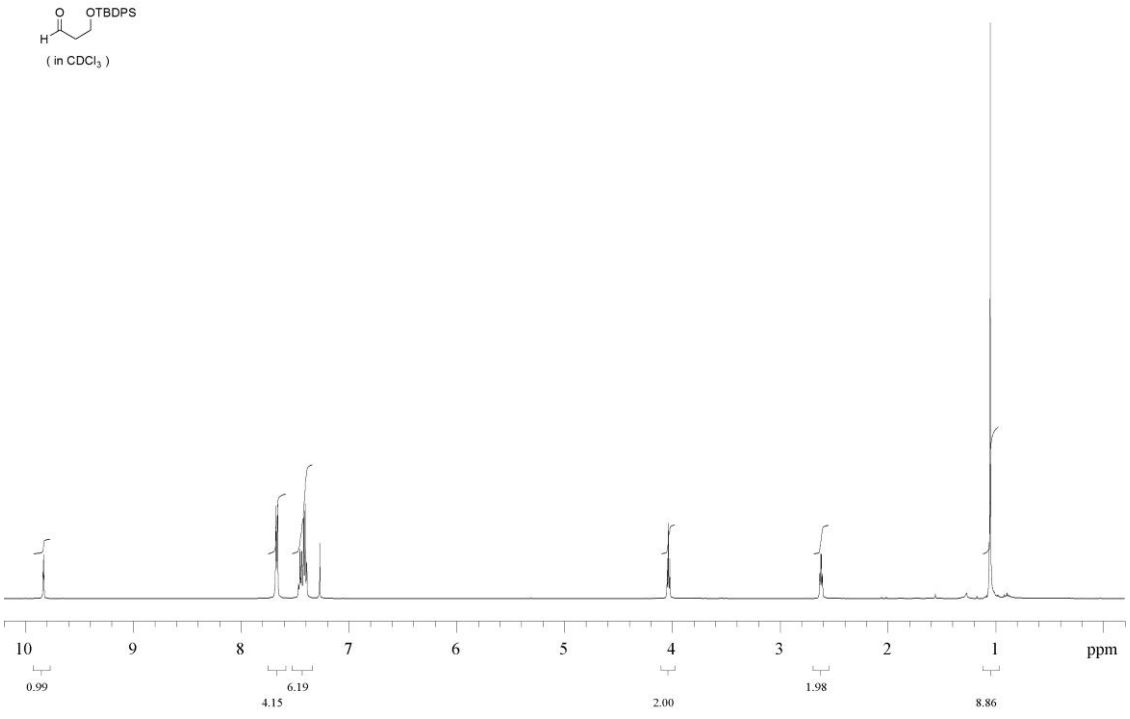

OTBS
OBOM
CO2Me
(500/125 MHz gHMQC CDCl3)
F2 (ppm)
F1 (ppm)

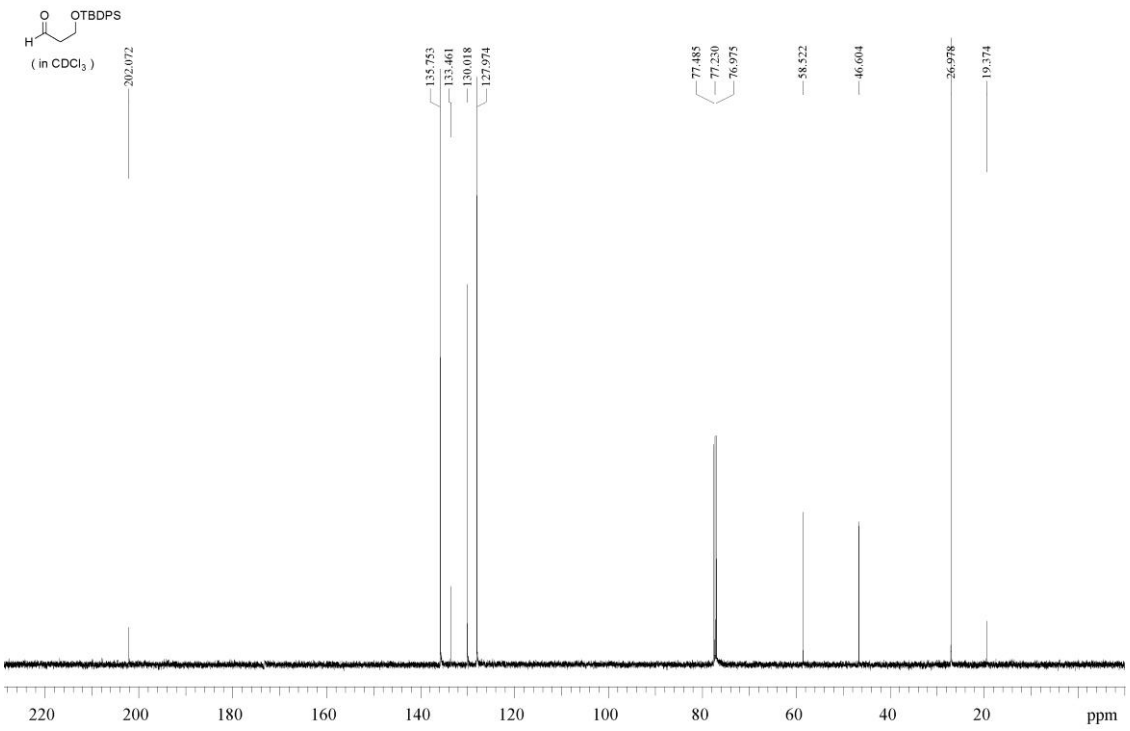

OTBS
OBOM
CO2Me
(500/125 MHz gHMBC CDCl3)
F2 (ppm)
F1 (ppm)

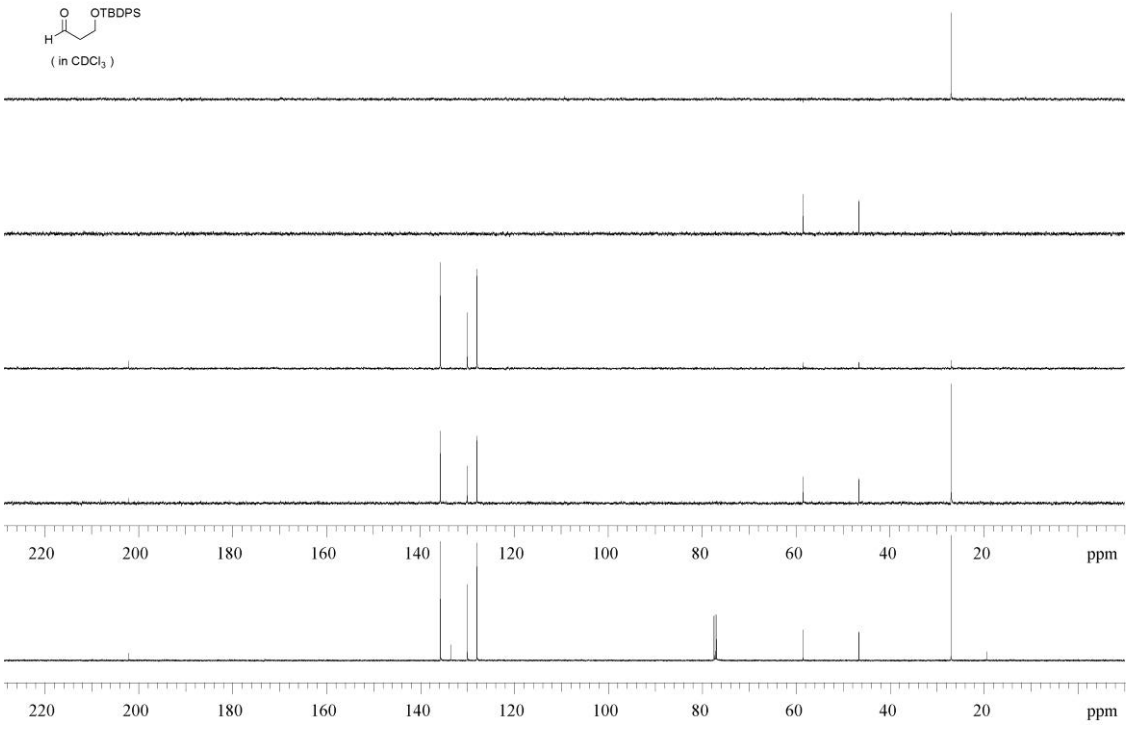

OH OTBDPS
(in CDCl3)
7.702
7.689
7.454
7.449
7.440
7.425
7.410
7.397
3.876
3.864
3.853
1.837
1.826
1.814
1.074
1936.28
1930.67
1925.05
1919.44
1182.50
1177.25
1172.00
923.34
917.73
912.11
906.50
900.76
4.0
3.5
3.0
2.5
2.0
ppm
10
9
8
7
6
5
4
3
2
1
ppm
4.03
5.97
4.02
0.94
2.00
9.17

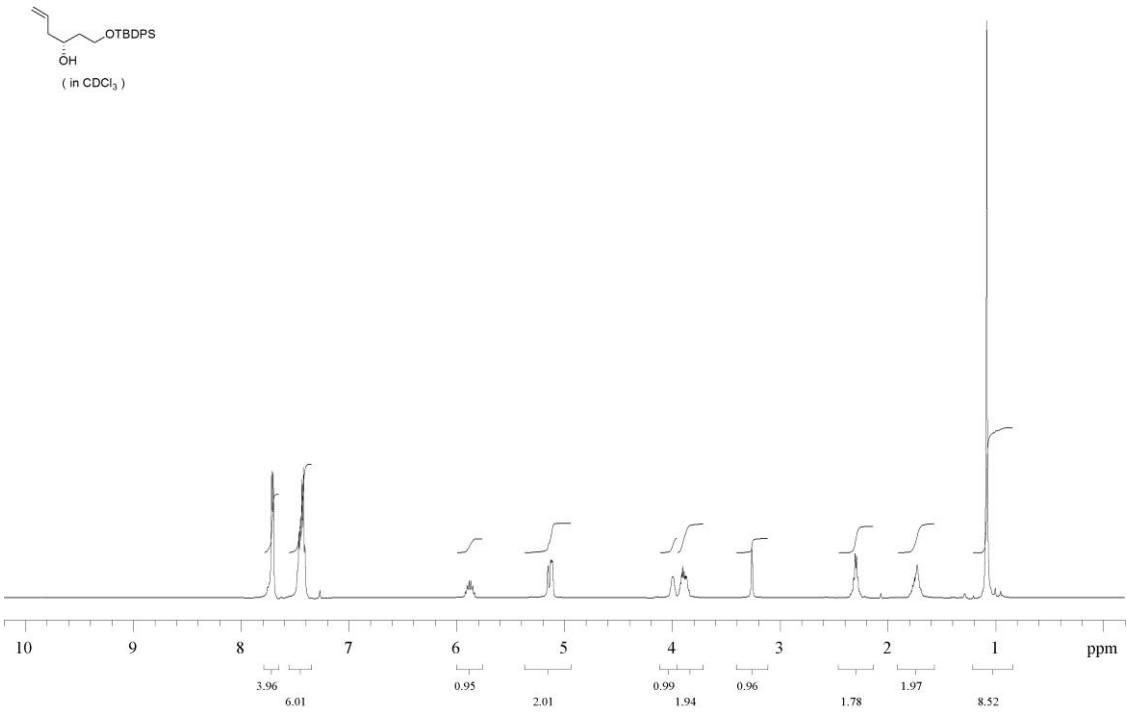

OH OTBDPS
(in CDCl3)
135.706
133.521
129.918
127.909
77.483
77.230
76.973
63.160
61.757
34.589
27.021
19.260
220
200
180
160
140
120
100
80
60
40
20
0
ppm

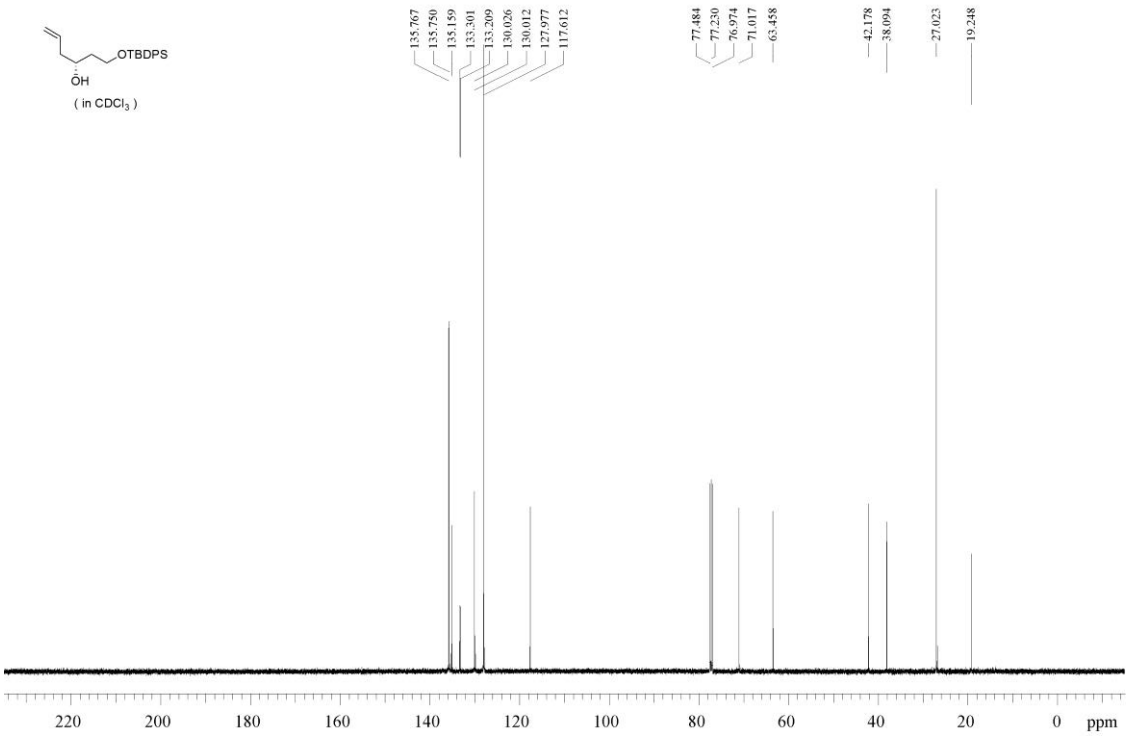

OH OTBDPS
(in CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm

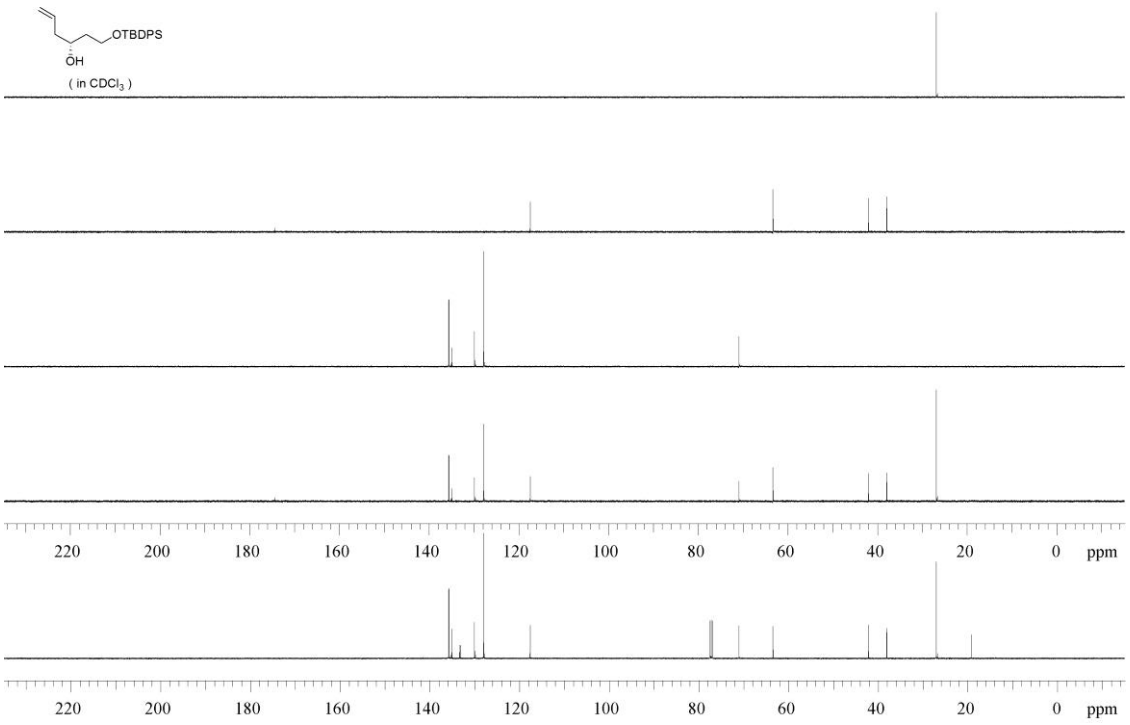

O OTBDPS
H
(in CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
0.99
4.15
6.19
2.00
1.98
8.86

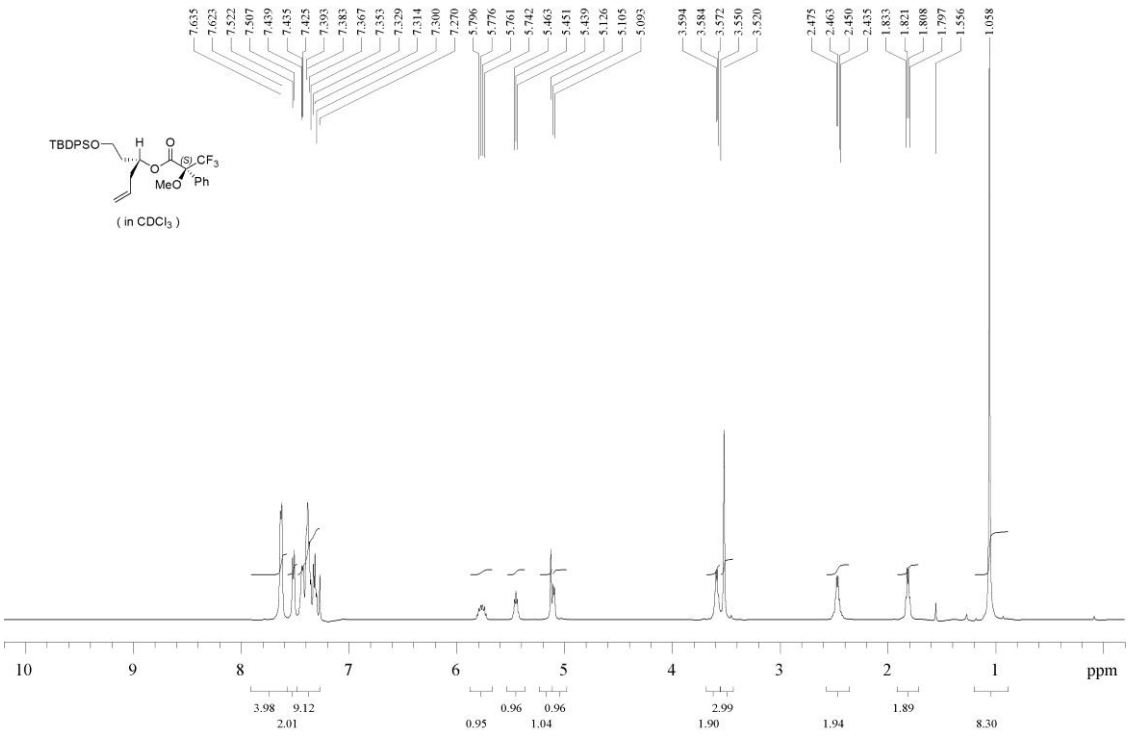

O
OTBDPS
H
(in CDCl3)
202.072
135.753
133.461
130.018
127.974
77.485
77.230
76.975
58.522
46.604
26.978
19.374
220
200
180
160
140
120
100
80
60
40
20
ppm

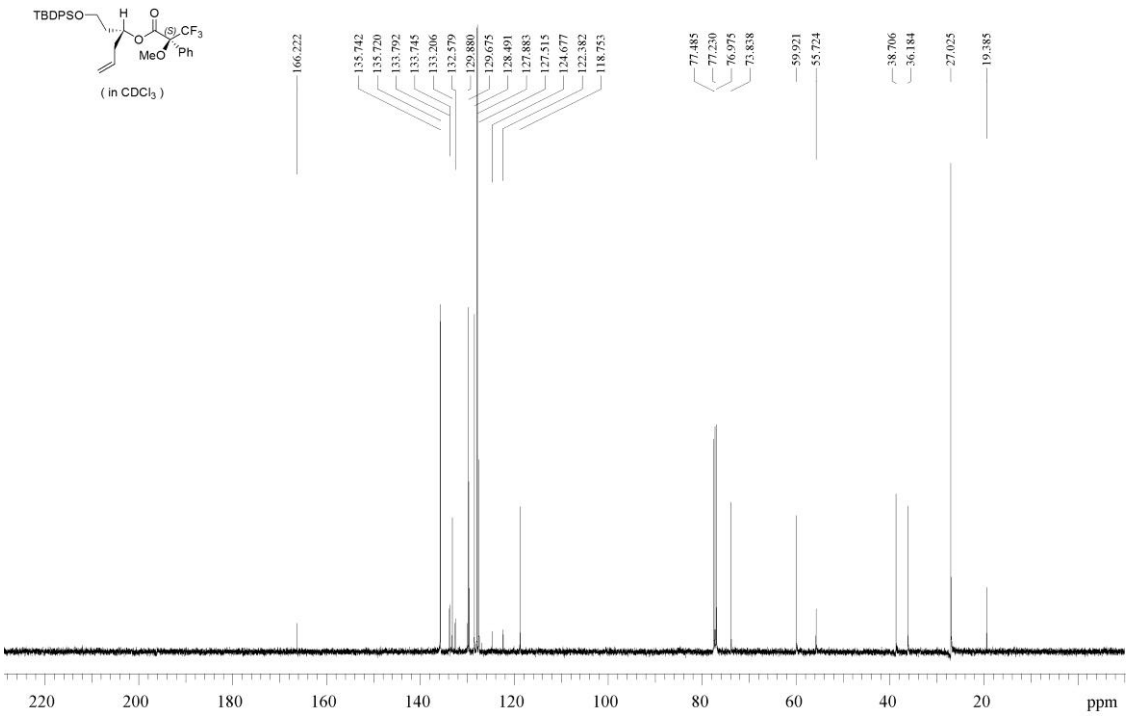

O
OTBDPS
H
(in CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

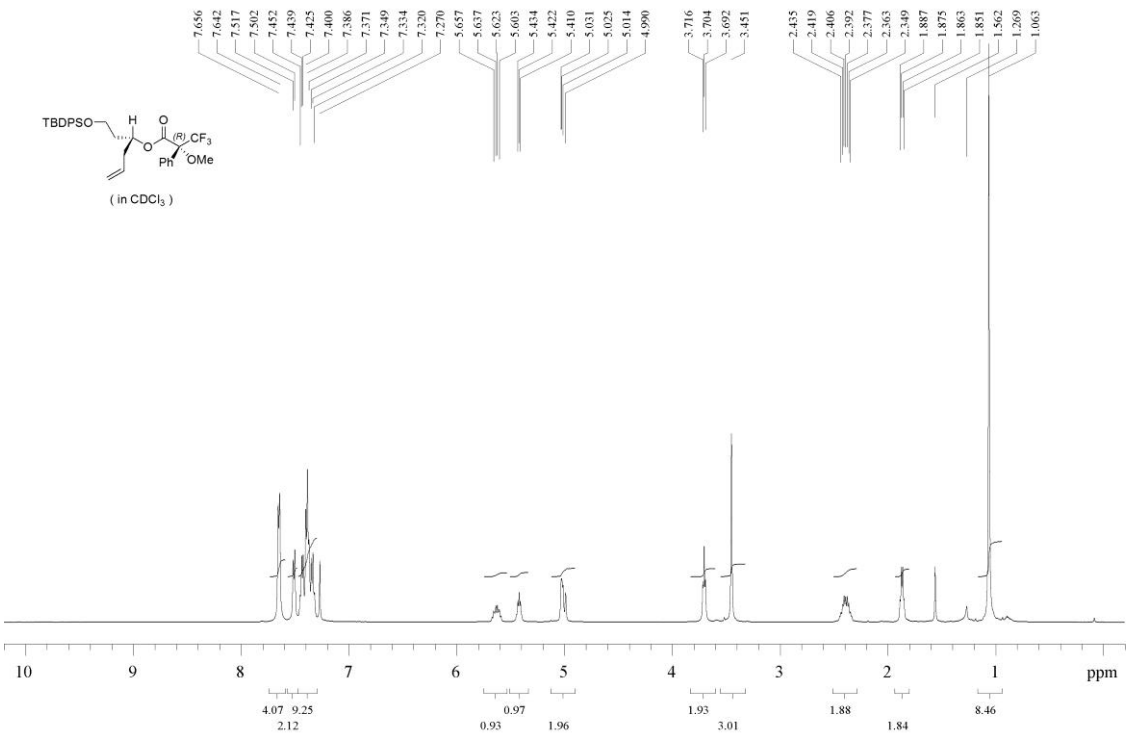

OTBDPS
OH
(in CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
3.96
6.01
0.95
2.01
0.99
1.94
0.96
1.78
1.97
8.52

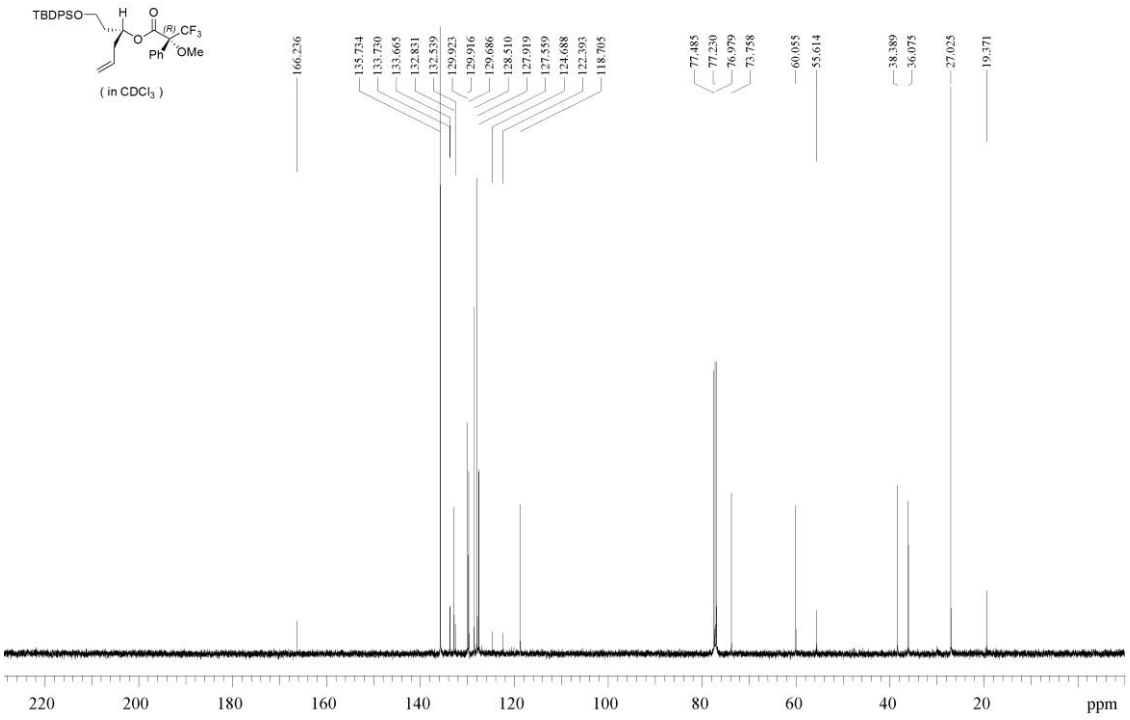

OTBDPS
OH
(in CDCl3)
135.767
135.750
135.159
133.301
133.209
130.026
130.012
127.977
117.612
77.484
77.230
76.974
71.017
63.458
42.178
38.094
27.023
19.248
220
200
180
160
140
120
100
80
60
40
20
0
ppm

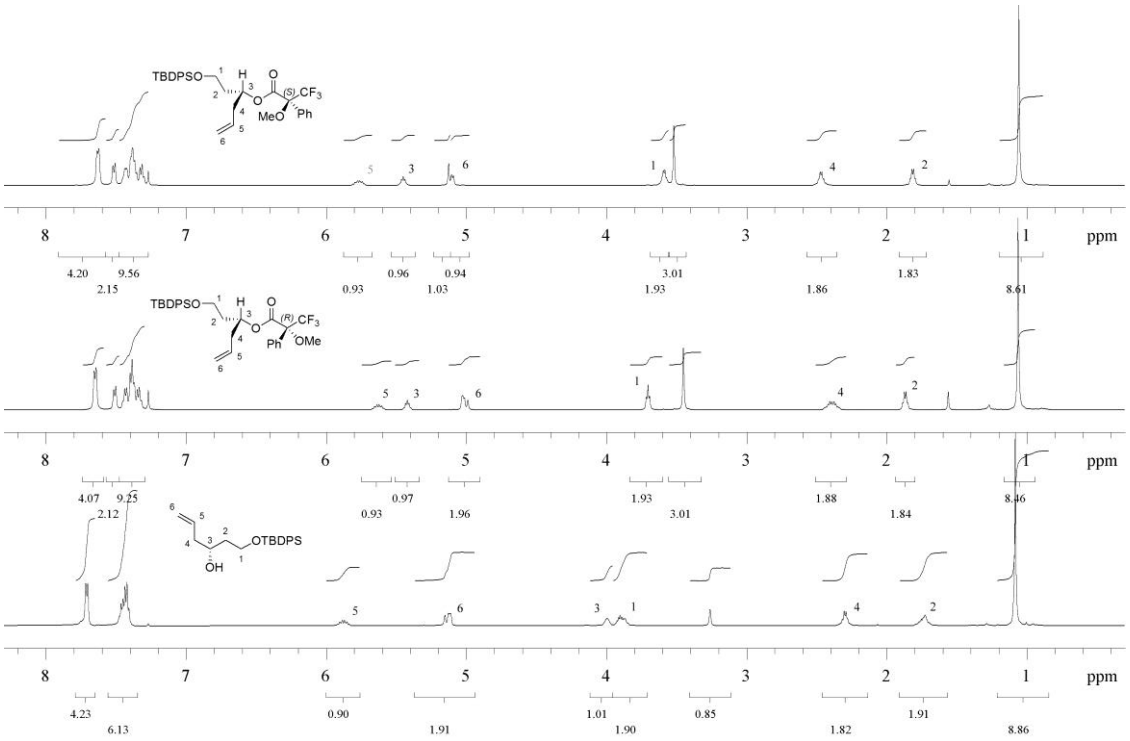

OTBDPS
OH
(in CDCl3)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

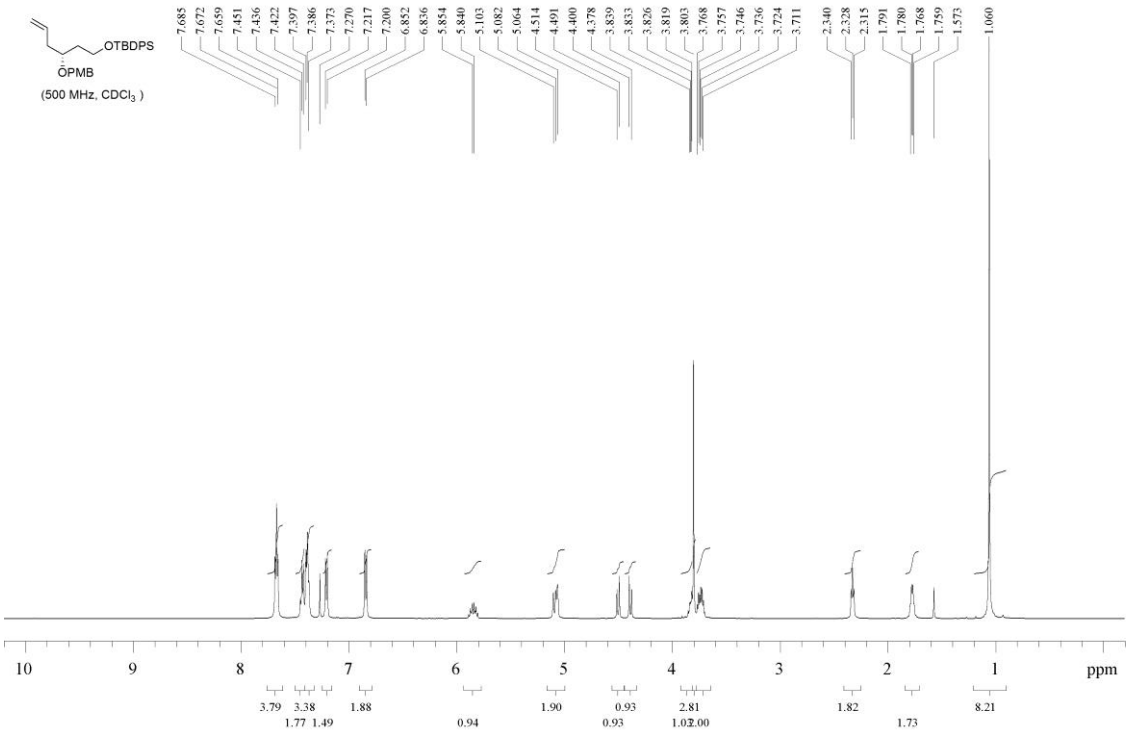

7.635
7.623
7.522
7.507
7.439
7.435
7.425
7.393
7.383
7.367
7.353
7.329
7.314
7.300
7.270
5.796
5.776
5.761
5.742
5.463
5.451
5.439
5.126
5.105
5.093
3.594
3.584
3.572
3.550
3.520
2.475
2.463
2.450
2.435
1.833
1.821
1.808
1.797
1.556
1.058
TBDPSO
H
O
O
(S)
CF3
MeO
Ph
(in CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
3.98
9.12
2.01
0.95
0.96
1.04
0.96
2.99
1.90
1.94
1.89
8.30

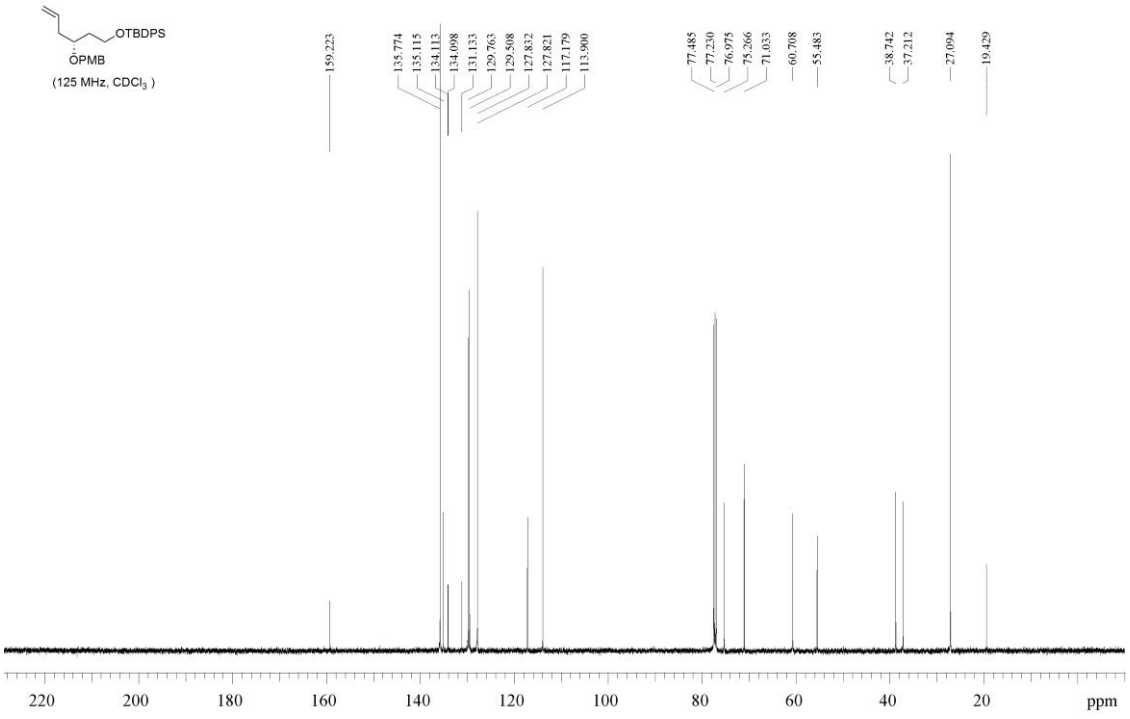

TBDPSO
H
O
O
(S)
CF3
MeO
Ph
(in CDCl3)
166.222
135.742
135.720
133.792
133.745
133.206
132.579
129.880
129.675
128.491
127.883
127.515
124.677
122.382
118.753
77.485
77.230
76.975
73.838
59.921
55.724
38.706
36.184
27.025
19.385
220
200
180
160
140
120
100
80
60
40
20
ppm

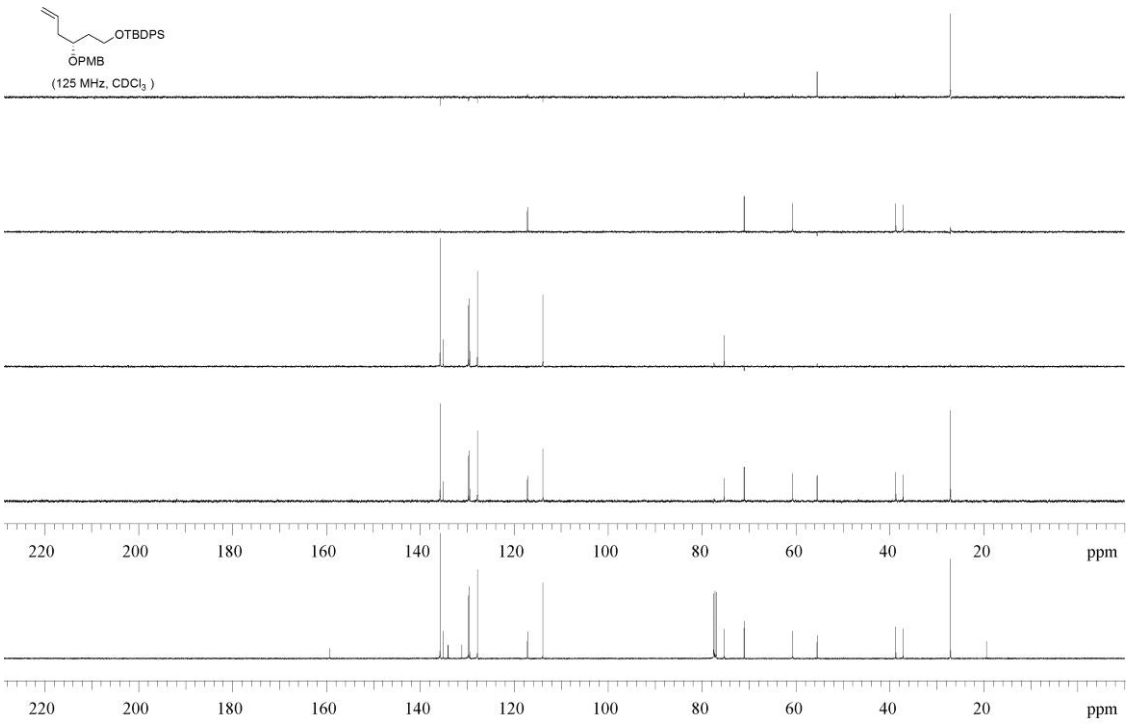

7.656
7.642
7.517
7.502
7.452
7.439
7.425
7.400
7.386
7.371
7.349
7.334
7.320
7.270
5.657
5.637
5.623
5.603
5.434
5.422
5.410
5.031
5.025
5.014
4.990
3.716
3.704
3.692
3.451
2.435
2.419
2.406
2.392
2.377
2.363
2.349
1.887
1.875
1.863
1.851
1.562
1.269
1.063
TBDPSO
H
O
O
(R)
CF3
Ph
OMe
(in CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
4.07
9.25
2.12
0.93
0.97
1.96
1.93
3.01
1.88
1.84
8.46

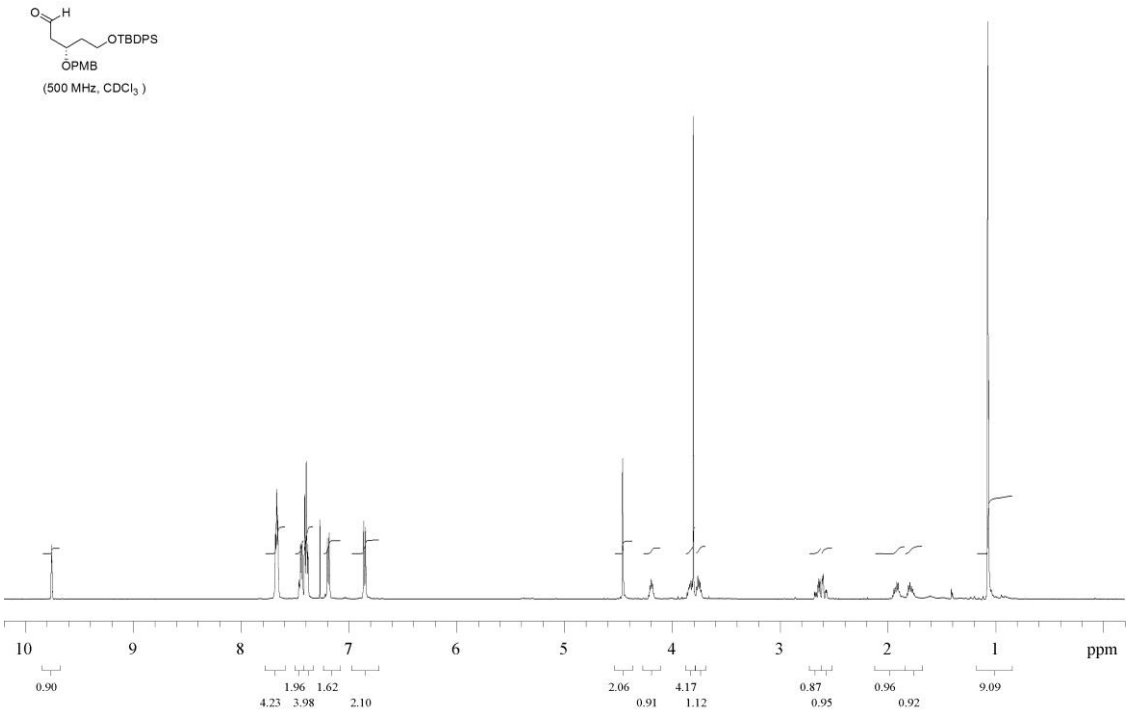

TBDPSO
(in $CDCl_3$)
166.236
135.734
133.730
133.665
132.831
132.539
129.923
129.916
129.686
128.510
127.919
127.559
124.688
122.393
118.705
77.485
77.230
76.979
73.758
60.055
55.614
38.389
36.075
27.025
19.371
220
200
180
160
140
120
100
80
60
40
20
ppm

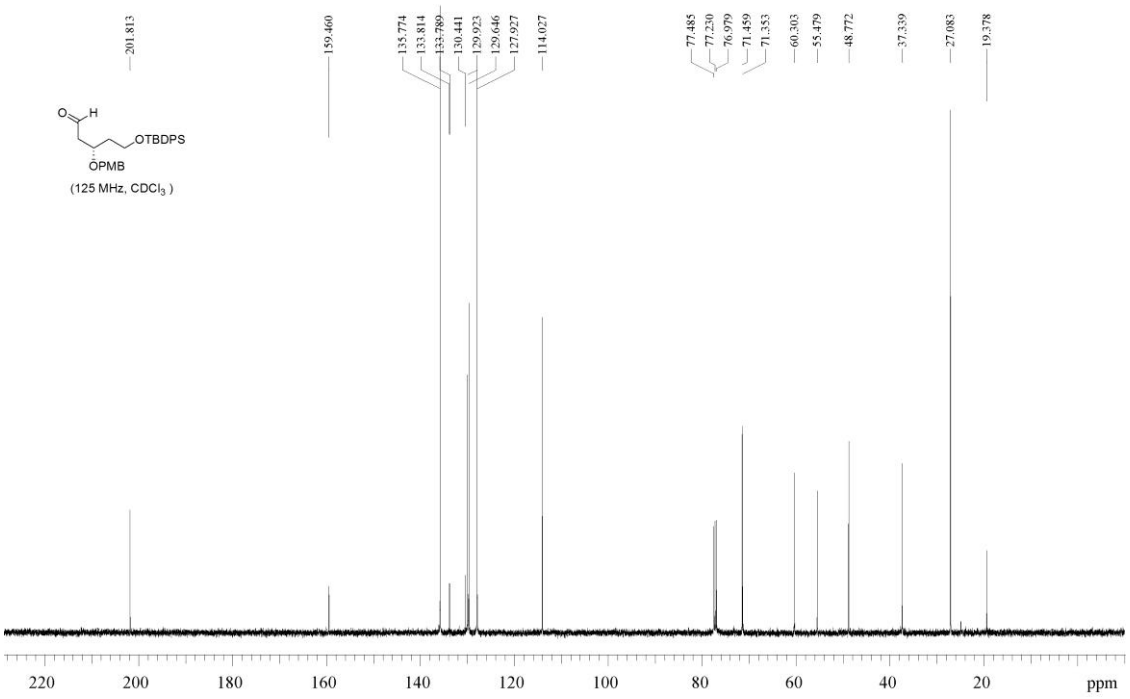

TBDPSO
MeO
Ph
CF_3
8
7
6
5
4
3
2
1
ppm
4.20
9.56
2.15
0.93
0.96
1.03
0.94
3.01
1.93
1.86
1.83
8.61
TBDPSO
Ph
OMe
CF_3
4.07
9.25
2.12
0.93
0.97
1.96
1.93
3.01
1.88
1.84
8.46
OTBDPS
OH
4.23
6.13
0.90
1.91
1.01
1.90
0.85
1.82
1.91
8.86

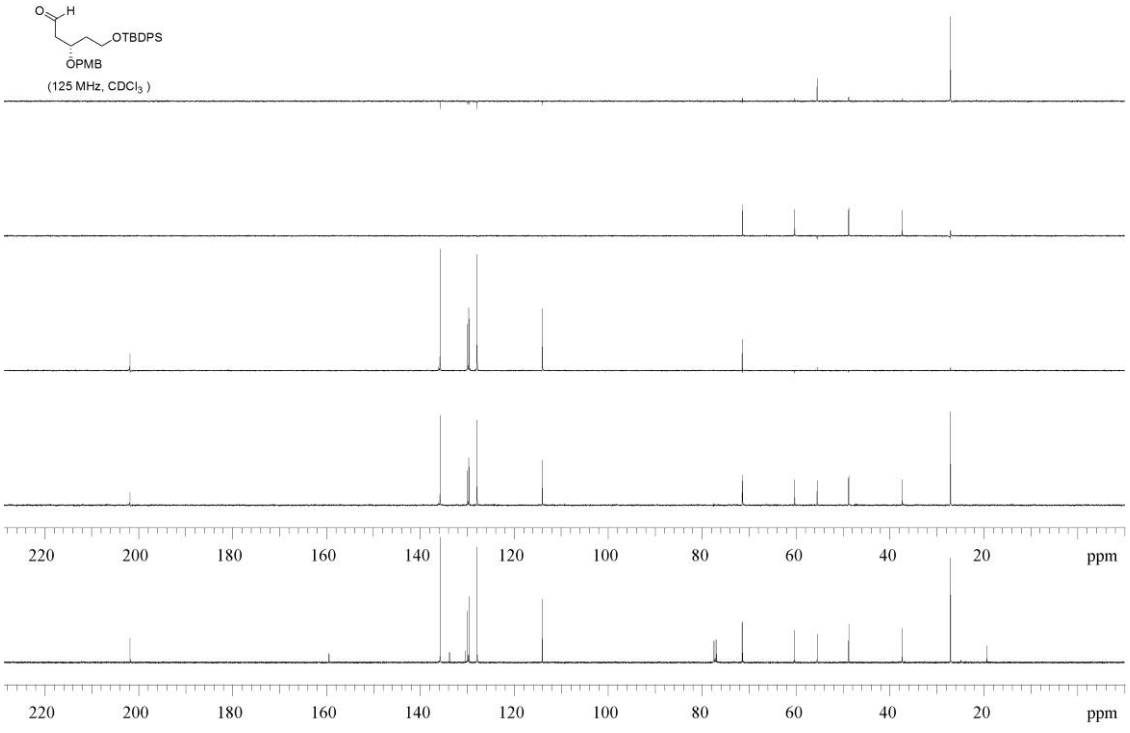

OTBDPS
OPMB
(500 MHz, CDCl3)
7.685
7.672
7.659
7.451
7.436
7.422
7.397
7.386
7.373
7.270
7.217
7.200
6.852
6.836
5.854
5.840
5.103
5.082
5.064
4.514
4.491
4.400
4.378
3.839
3.833
3.826
3.819
3.803
3.768
3.757
3.746
3.736
3.724
3.711
2.340
2.328
2.315
1.791
1.780
1.768
1.759
1.573
1.060
10
9
8
7
6
5
4
3
2
1
ppm
3.79
3.38
1.77
1.49
1.88
0.94
1.90
0.93
0.93
2.81
1.02
2.00
1.82
1.73
8.21

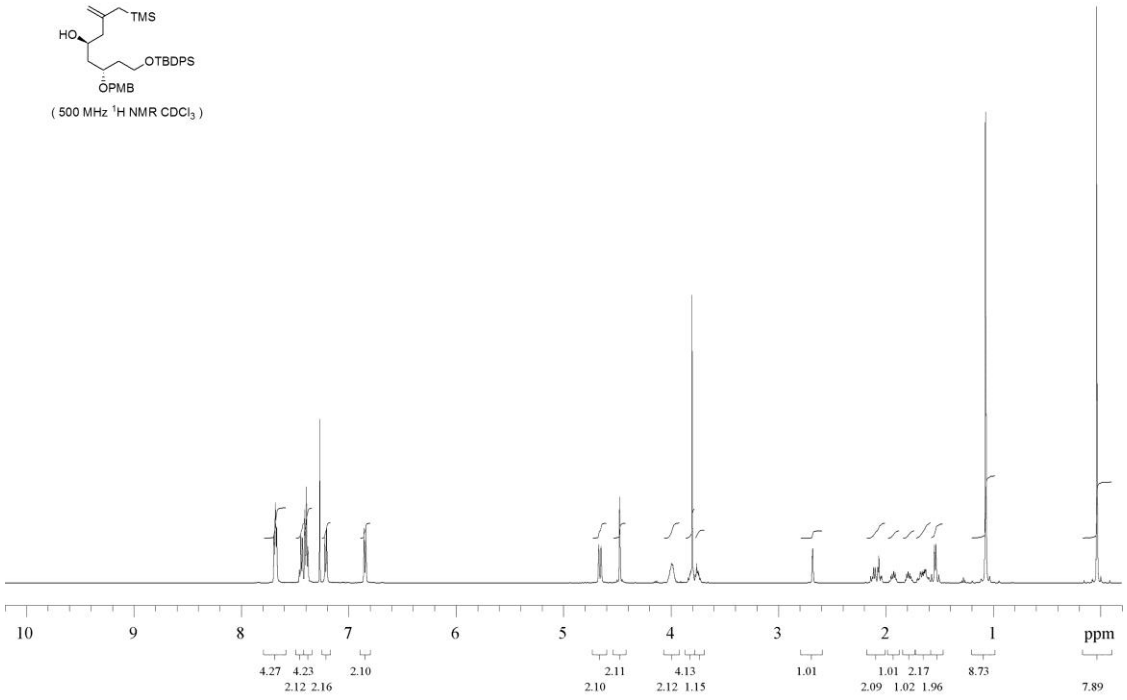

OTBDPS
OPMB
(125 MHz, CDCl3)
159.223
135.774
135.115
134.113
134.098
131.133
129.763
129.508
127.832
127.821
117.179
113.900
77.485
77.230
76.975
75.266
71.033
60.708
55.483
38.742
37.212
27.094
19.429
220
200
180
160
140
120
100
80
60
40
20
ppm

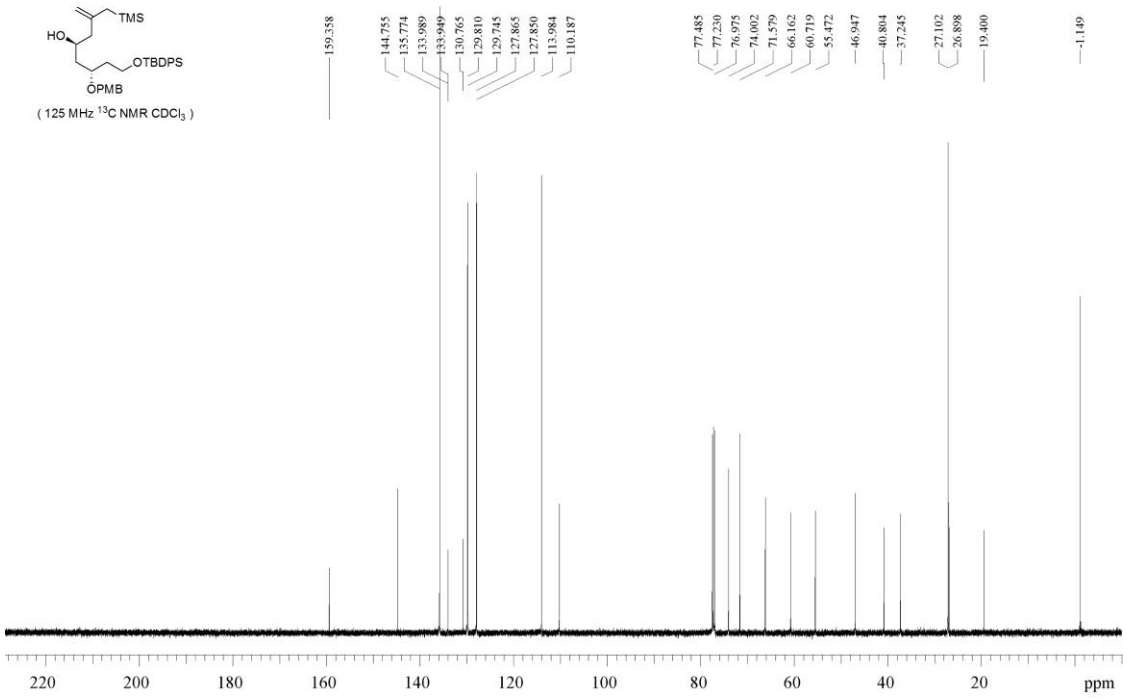

OTBDPS
OPMB
(125 MHz, CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

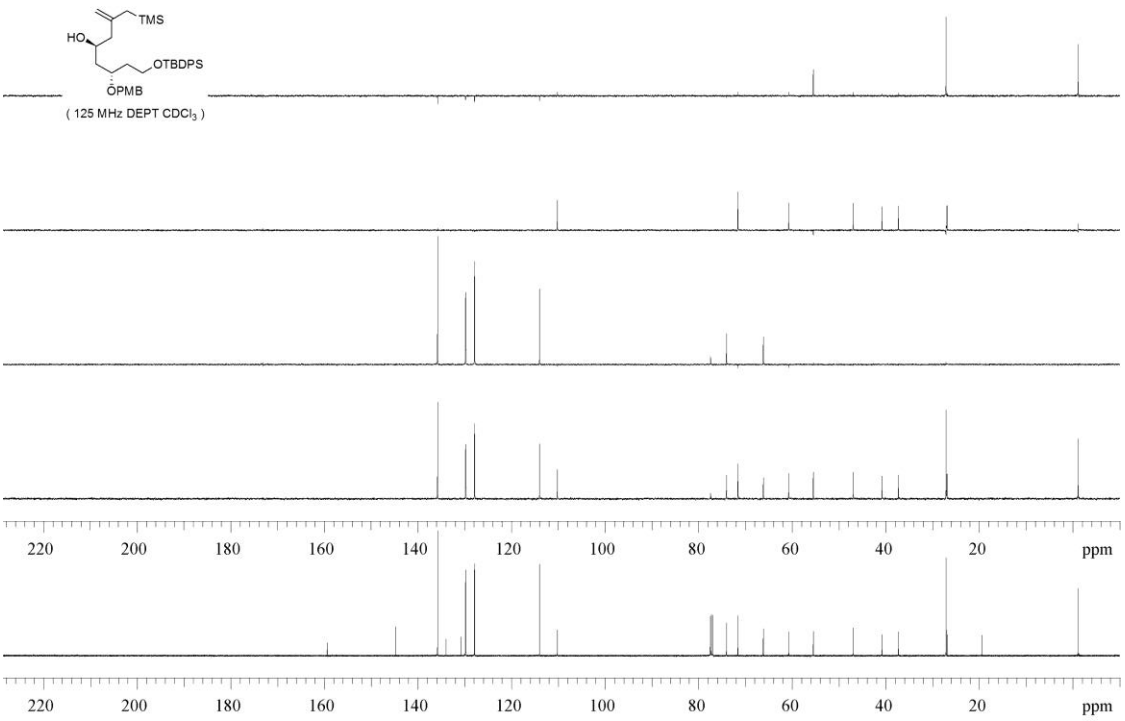

O
H
OTBDPS
OPMB
(500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
0.90
4.23
1.96
3.98
1.62
2.10
2.06
0.91
4.17
1.12
0.87
0.95
0.96
0.92
9.09

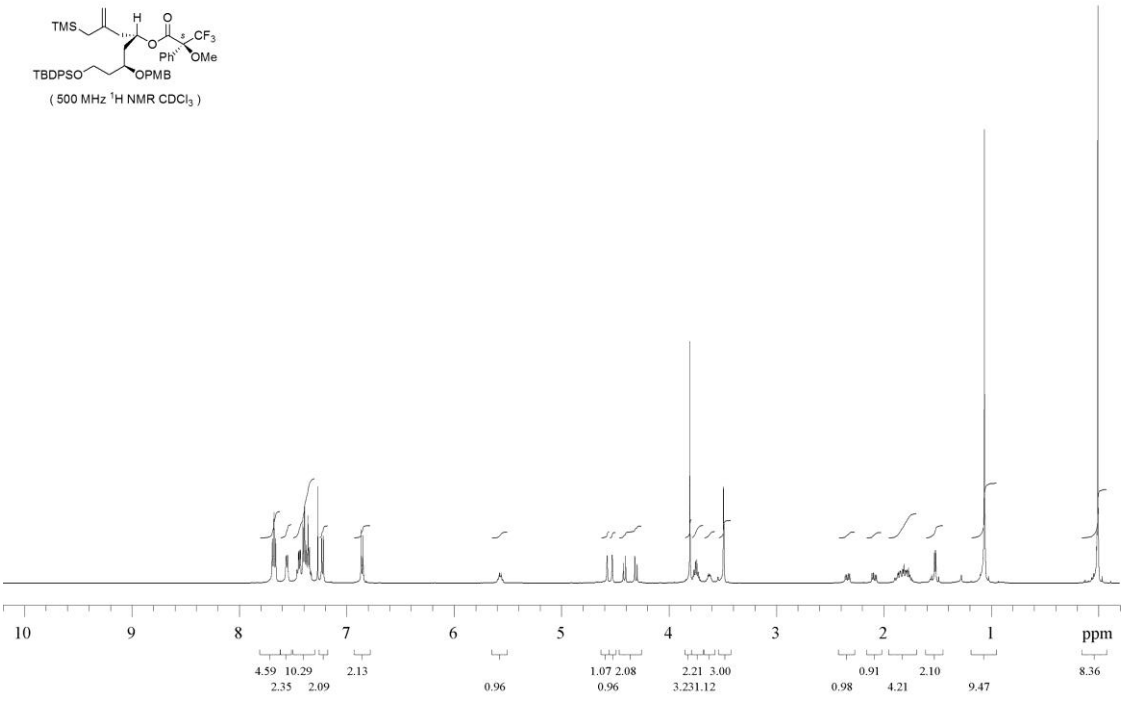

201.813
159.460
135.774
133.814
133.789
130.441
129.923
129.646
127.927
114.027
77.485
77.230
76.979
71.459
71.353
60.303
55.479
48.772
37.339
27.083
19.378
O
H
OTBDPS
OPMB
(125 MHz, CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

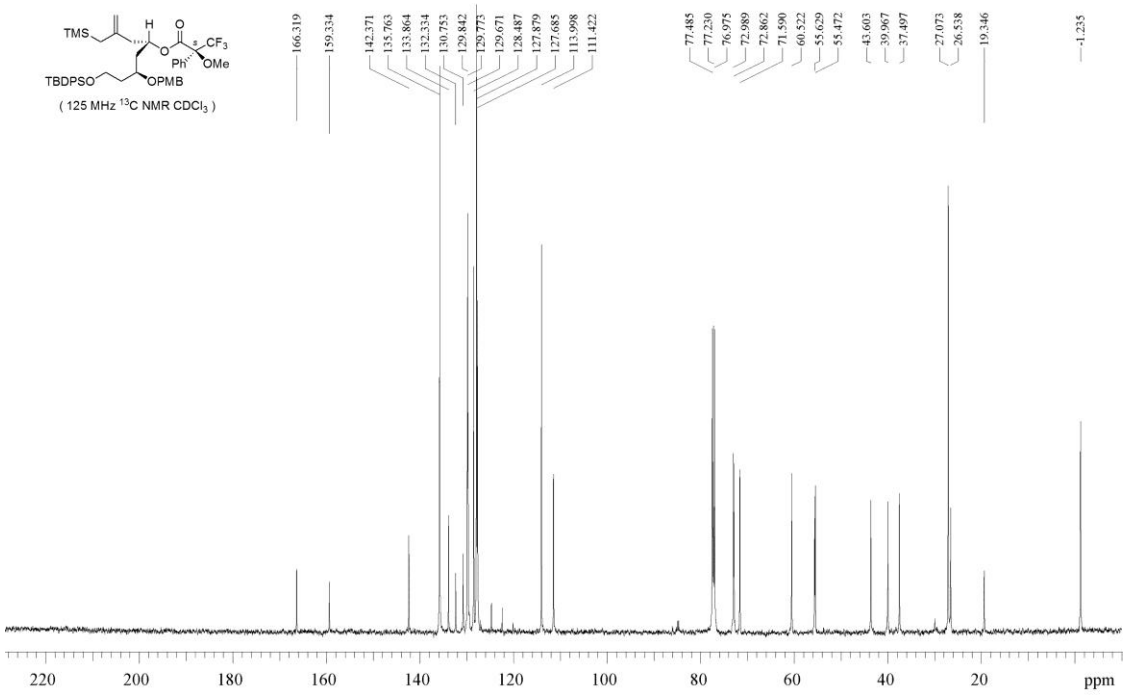

O
H
OTBDPS
OPMB
(125 MHz, CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

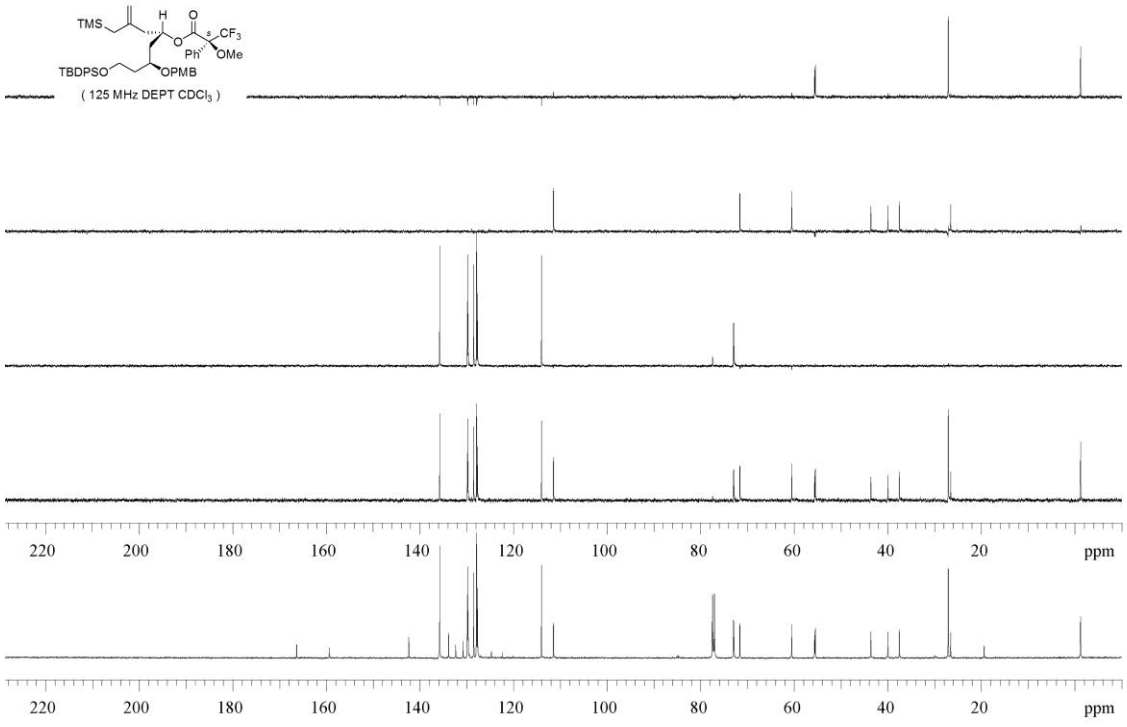

TMS
HO
OTBDPS
OPMB
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
4.27
4.23
2.12
2.16
2.10
2.11
2.10
4.13
2.12
1.15
1.01
1.01
2.09
2.17
1.02
1.96
8.73
7.89

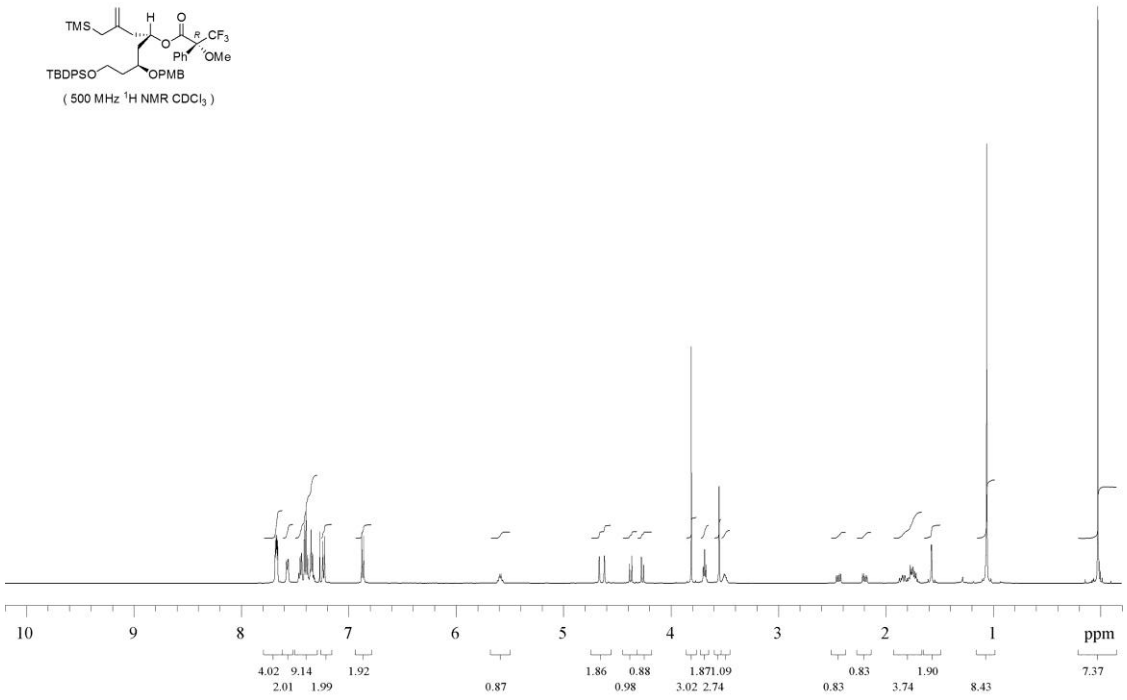

TMS
HO
OTBDPS
OPMB
(125 MHz ^{13}C NMR $CDCl_3$)
159.358
144.755
135.774
133.989
133.949
130.765
129.810
129.745
127.865
127.850
113.984
110.187
77.485
77.230
76.975
74.002
71.579
66.162
60.719
55.472
46.947
40.804
37.245
27.102
26.898
19.400
-1.149
220
200
180
160
140
120
100
80
60
40
20
ppm

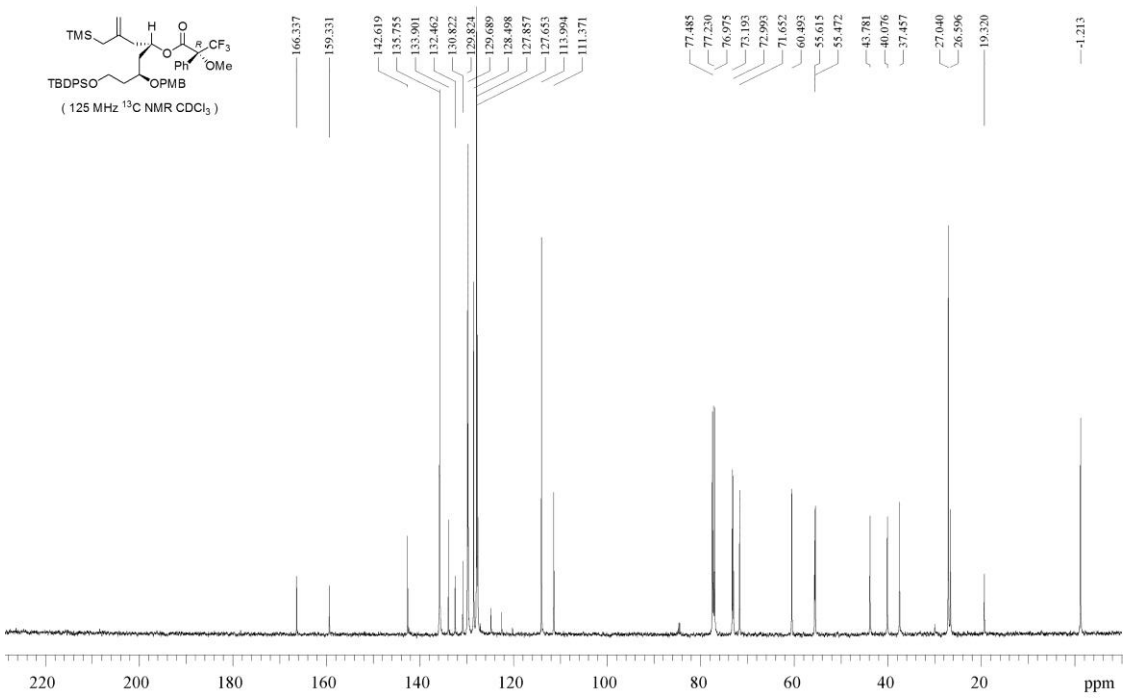

TMS
HO
OTBDPS
OPMB
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

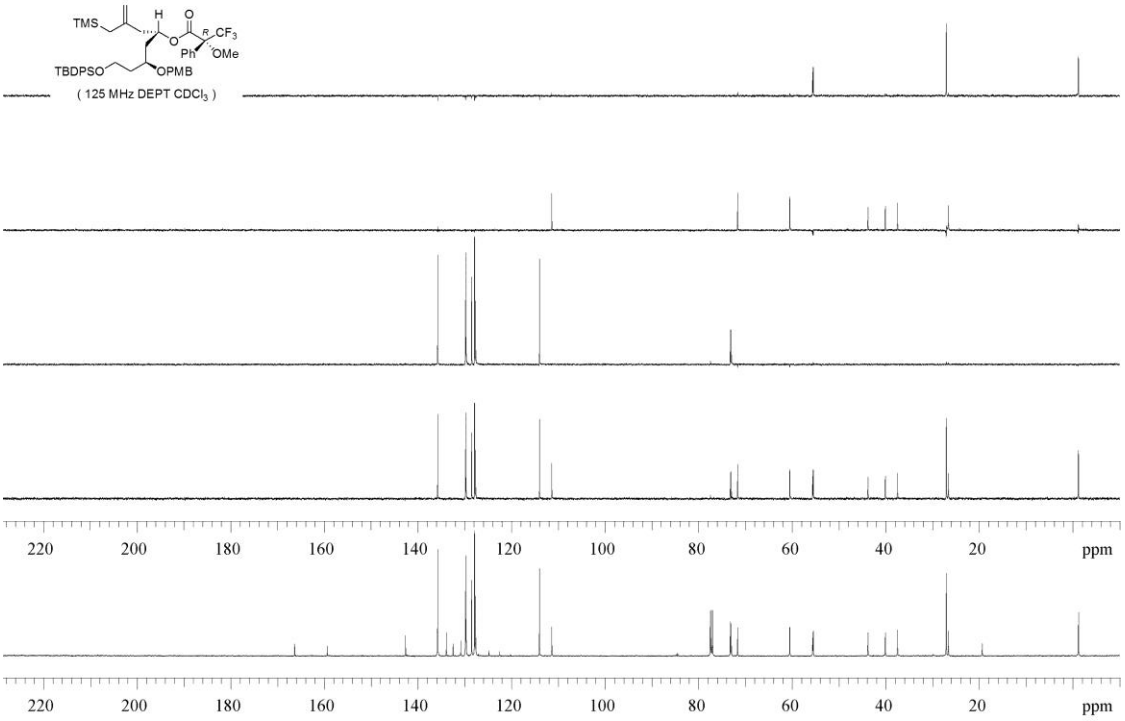

TMS
H
O
CF3
Ph
OMe
TBDPSO
OPMB
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
4.59 10.29 2.13
2.35 2.09
0.96
1.07 2.08
0.96
2.21 3.00
3.23 1.12
0.91
0.98 4.21
2.10
9.47
8.36

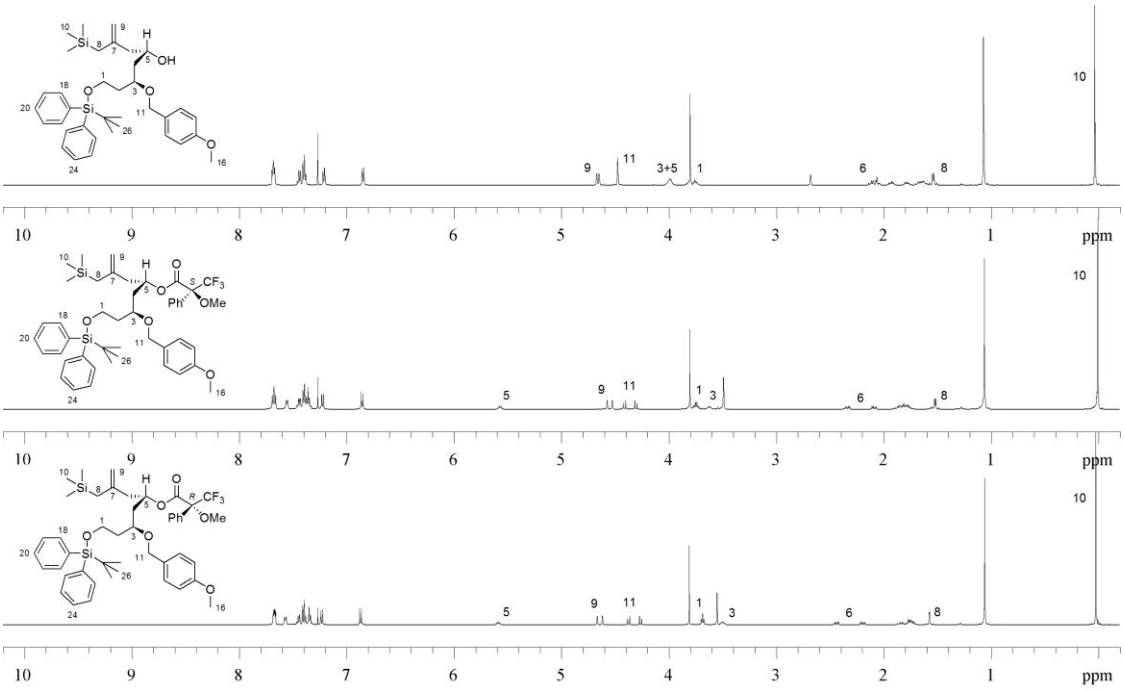

TMS
H
O
O
s
CF3
Ph
OMe
TBDPSO
OPMB
(125 MHz 13C NMR CDCl3)
166.319
159.334
142.371
135.763
133.864
132.334
130.753
129.842
129.773
129.671
128.487
127.879
127.685
113.998
111.422
77.485
77.230
76.975
72.989
72.862
71.590
60.522
55.629
55.472
43.603
39.967
37.497
27.073
26.538
19.346
-1.235
220
200
180
160
140
120
100
80
60
40
20
ppm

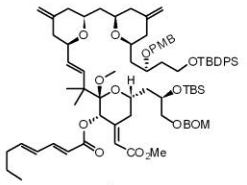

TMS
H
O
O
s
CF3
Ph
OMe
TBDPSO
OPMB
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm


TMS
H
O
O
R
CF3
Ph
OMe
TBDPSO
OPMB
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
4.02
9.14
1.92
0.87
1.86
0.88
1.87
1.09
0.83
1.90
7.37
2.01
1.99
0.98
3.02
2.74
0.83
3.74
8.43

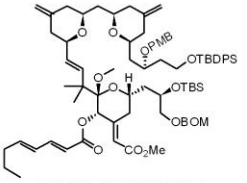

TMS
H
O
O
R
CF3
Ph
OMe
TBDPSO
OPMB
(125 MHz 13C NMR CDCl3)
166.337
159.331
142.619
135.755
133.901
132.462
130.822
129.824
129.689
128.498
127.857
127.653
113.994
111.371
77.485
77.230
76.975
73.193
72.993
71.652
60.493
55.615
55.472
43.781
40.076
37.457
27.040
26.596
19.320
-1.213
220
200
180
160
140
120
100
80
60
40
20
ppm


TMS
TBDPSO
OPMB
Ph
CF3
OMe
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

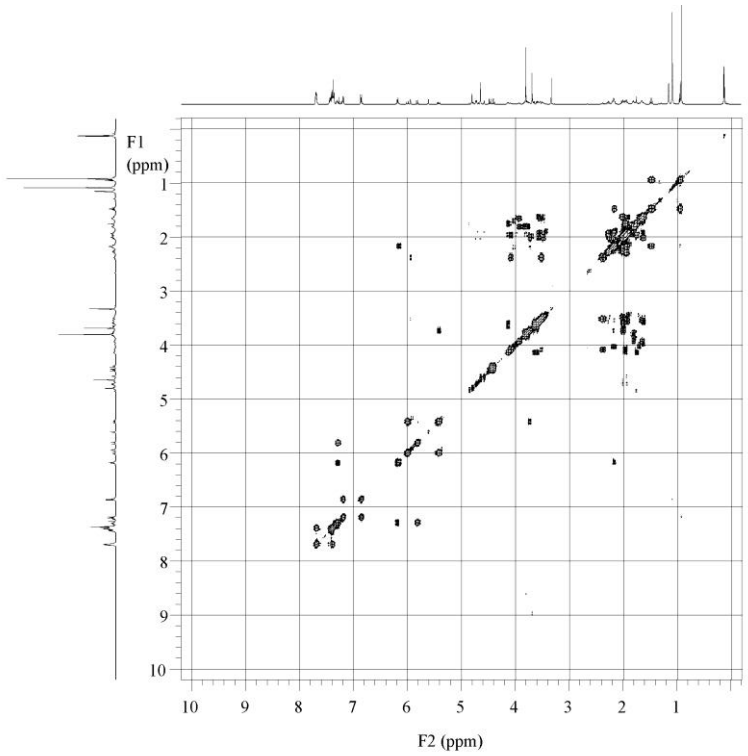

OH
Ph
CF3
OMe
10
9
11
3+5
1
6
8
5
3
ppm

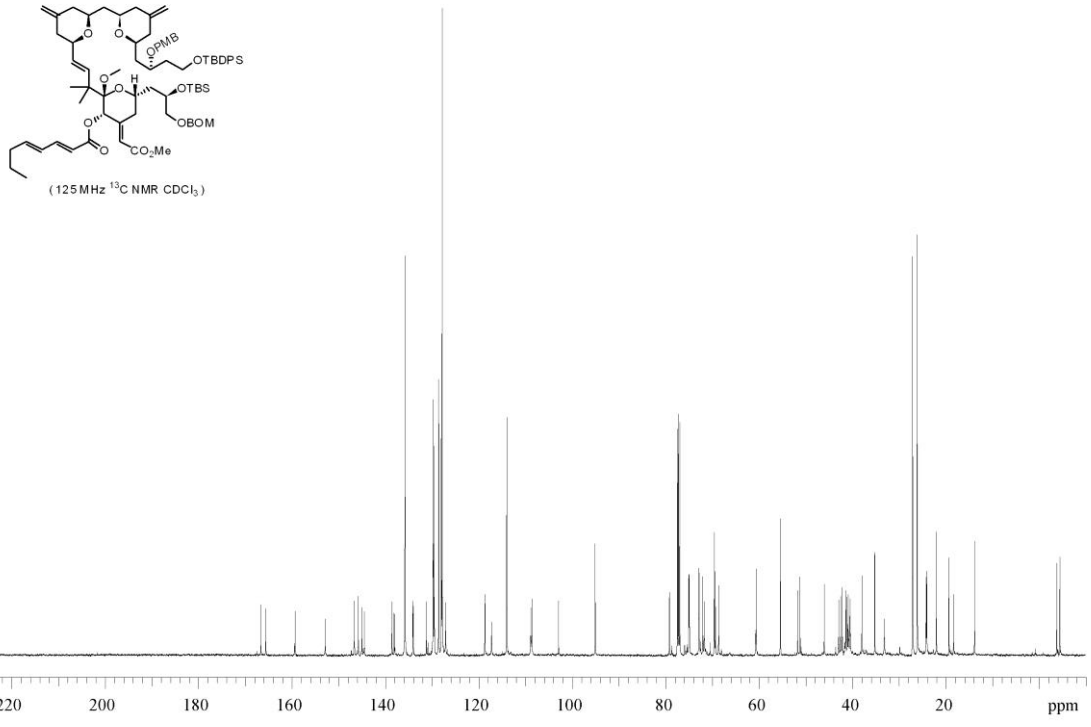


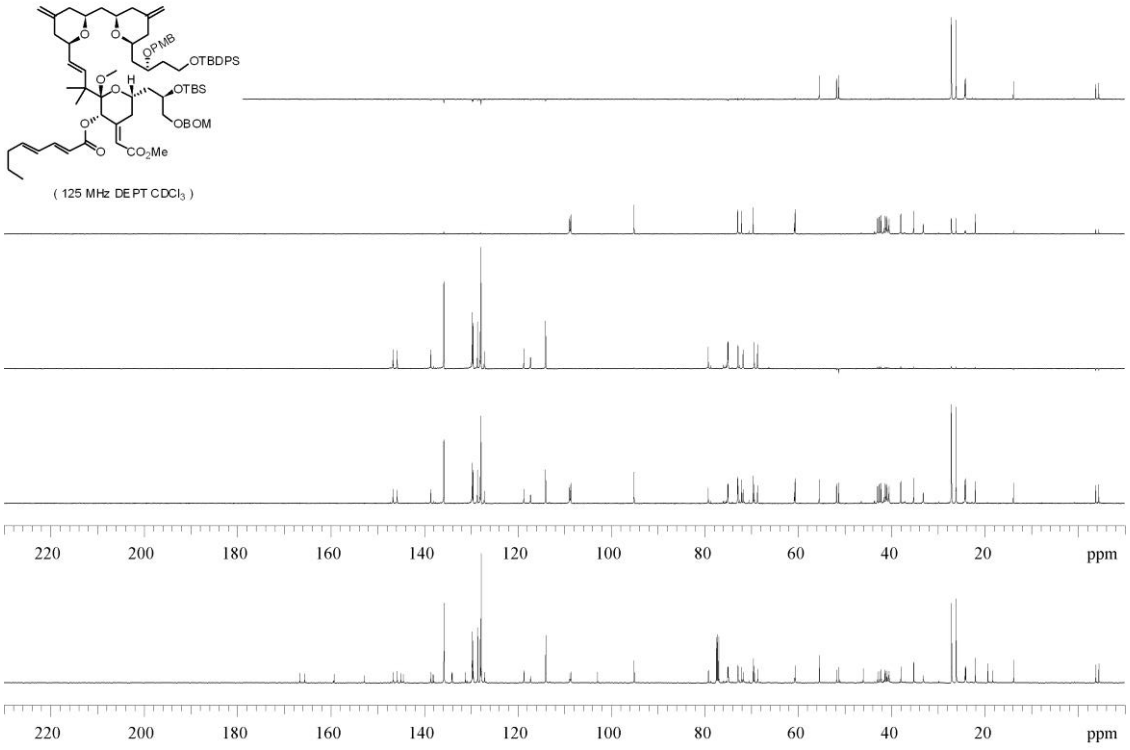
(500 MHz ^{1}H NMR $CDCl_3$)

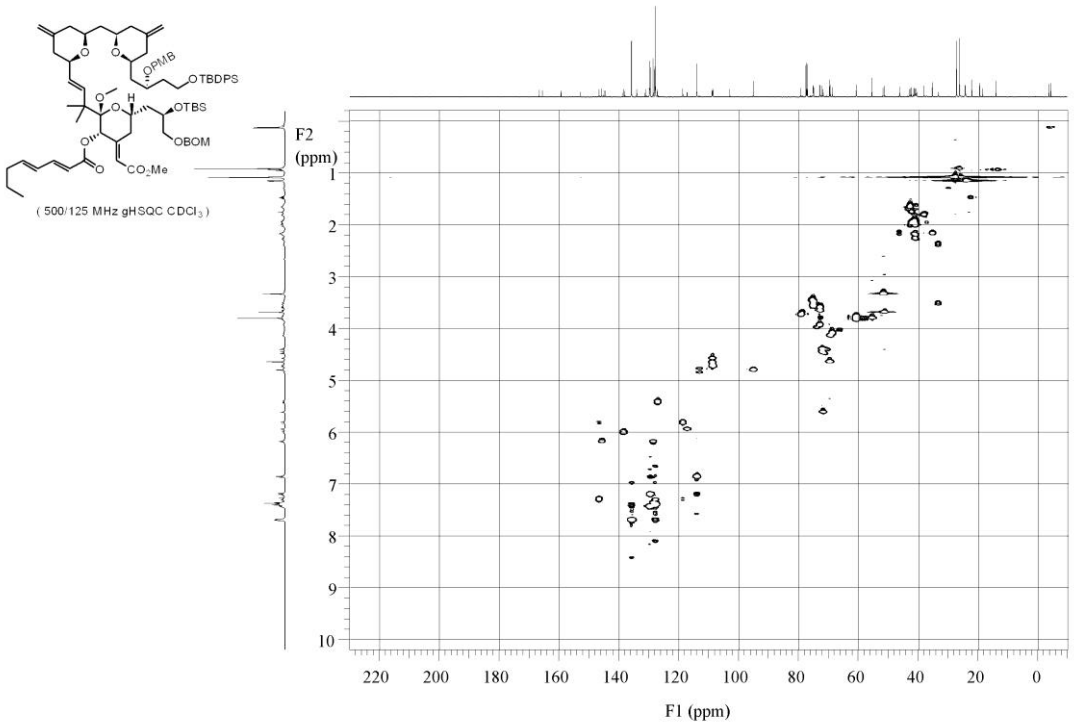


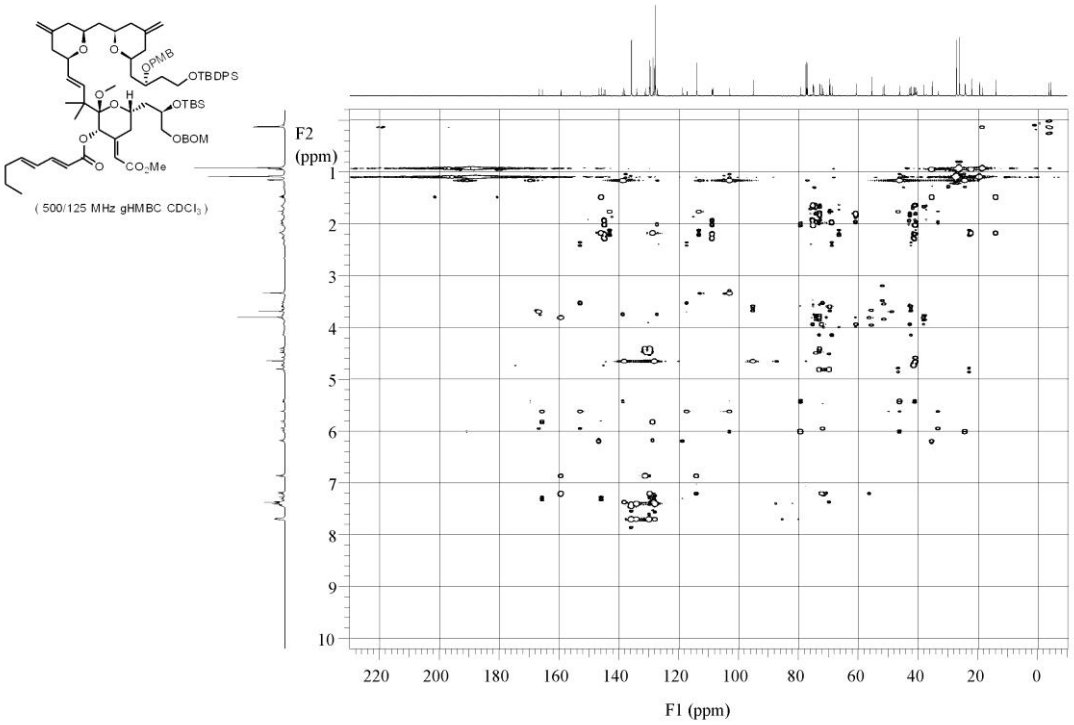
(500 MHz gDQCOSY $CDCl_3$)

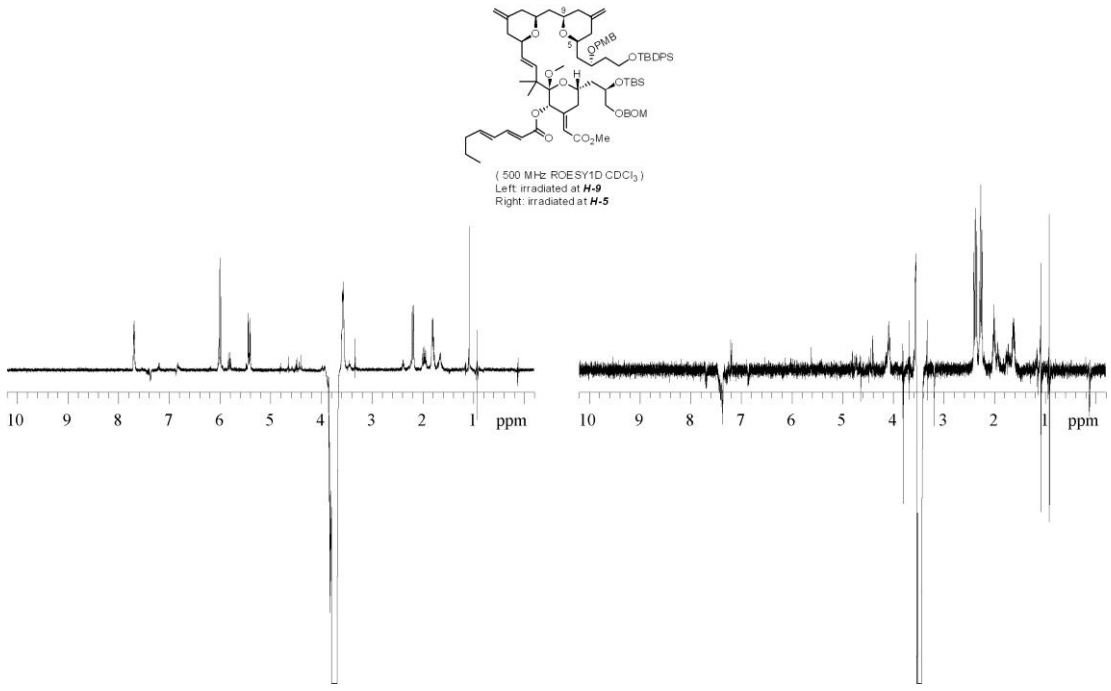


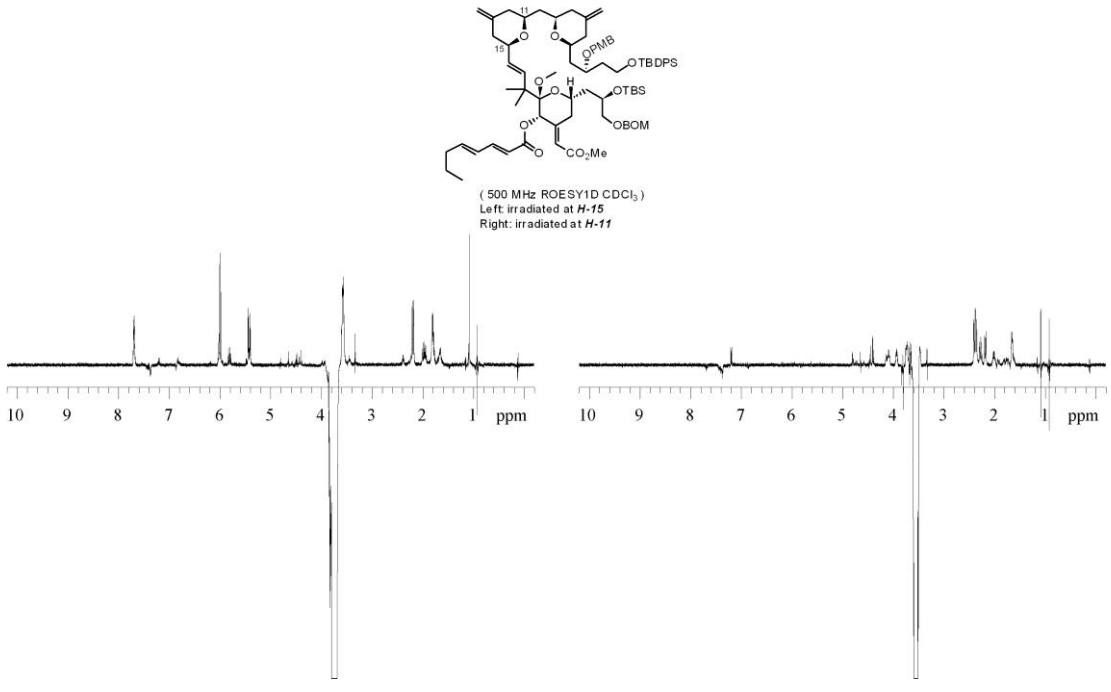

OPMB
OTBDPS
OTBS
OBOM
CO_2Me
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

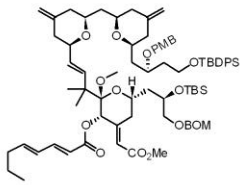

OPMB
OTBDPS
OTBS
OBOM
CO_2Me
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm


OPMB
OTBDPS
OTBS
OBOM
CO2Me
(500/125 MHz gHSQC CDCl3)
F2 (ppm)
F1 (ppm)

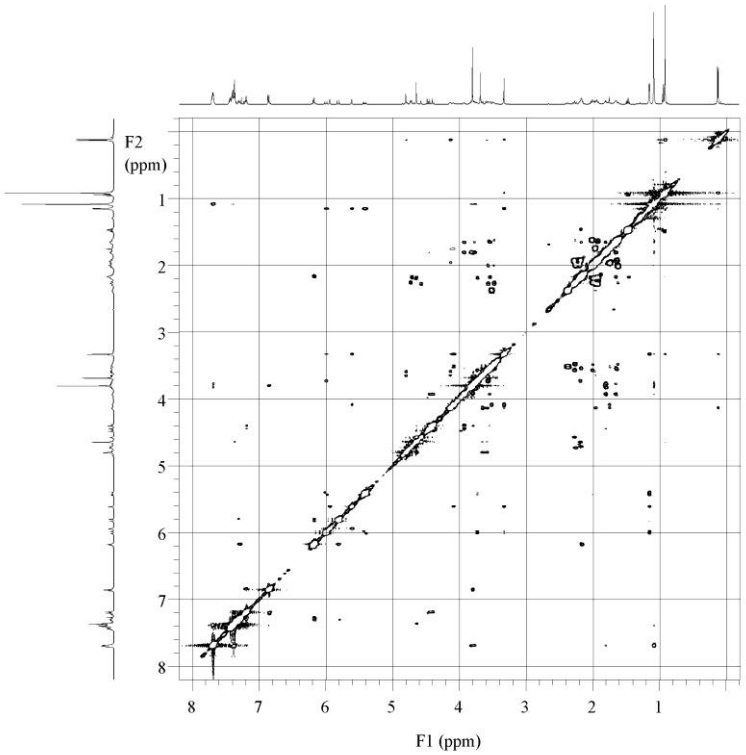

OPMB
OTBDPS
OTBS
OBOM
CO2Me
(500/125 MHz gHMBC CDCl3)
F2 (ppm)
F1 (ppm)

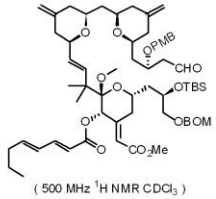

OPMB
OTBDPS
OTBS
OBOM
CO2Me
(500 MHz ROESY1D CDCl3)
Left: irradiated at H-9
Right: irradiated at H-5
10 9 8 7 6 5 4 3 2 1 ppm
10 9 8 7 6 5 4 3 2 1 ppm


OPMB
OTBDPS
OTBS
OBOM
CO2Me
(500 MHz ROESY1D CDCl3)
Left: irradiated at H-15
Right: irradiated at H-11
10 9 8 7 6 5 4 3 2 1 ppm
10 9 8 7 6 5 4 3 2 1 ppm

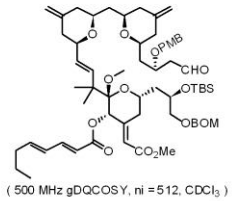


(500 MHz ROESY $CDCl_3$)

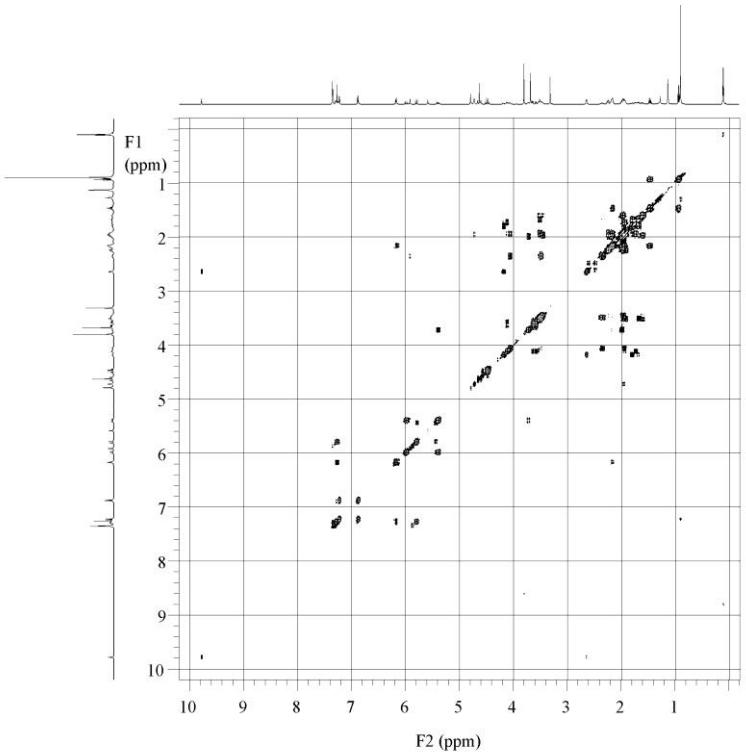


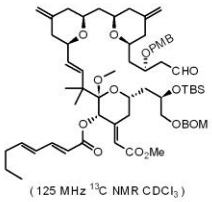


(500 MHz ^1H NMR $CDCl_3$)

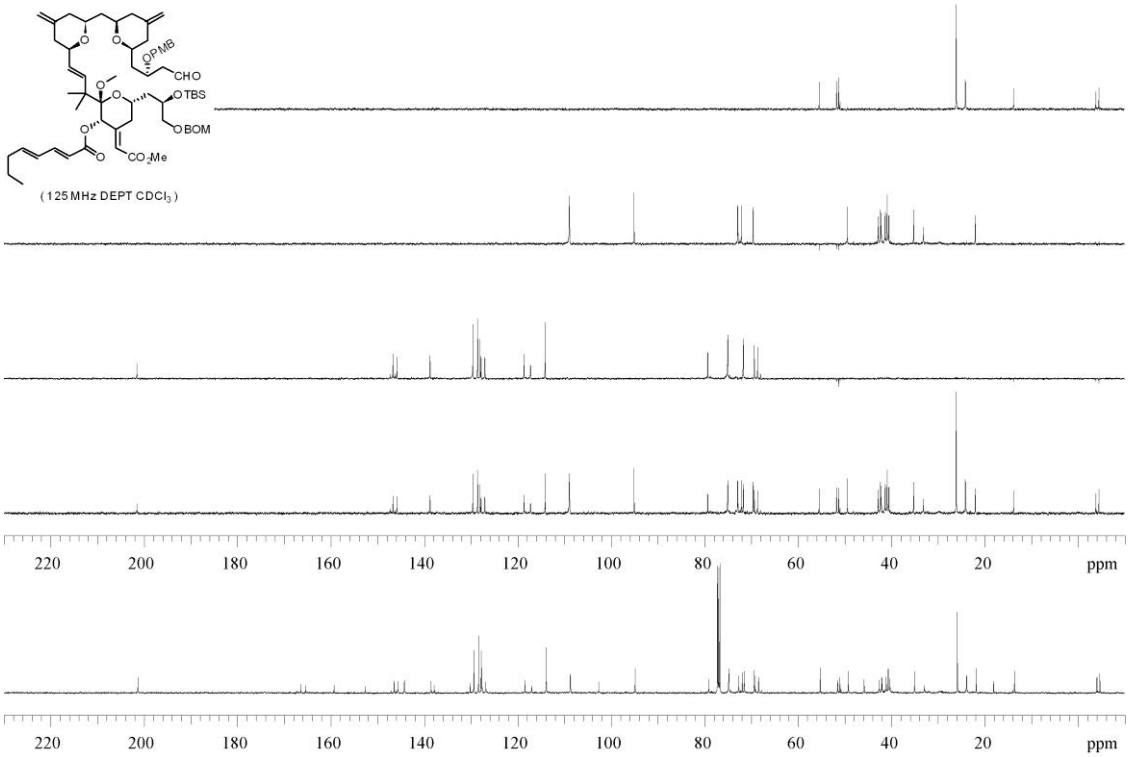


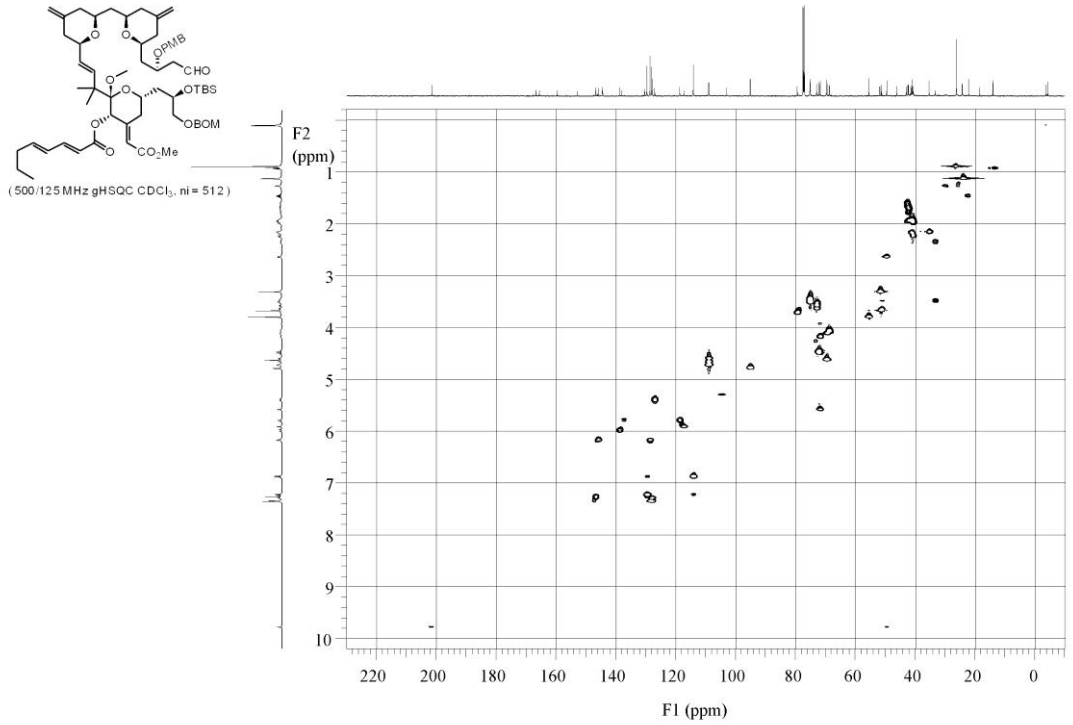
(500 MHz gDQCOSY, ni = 512, $CDCl_3$)

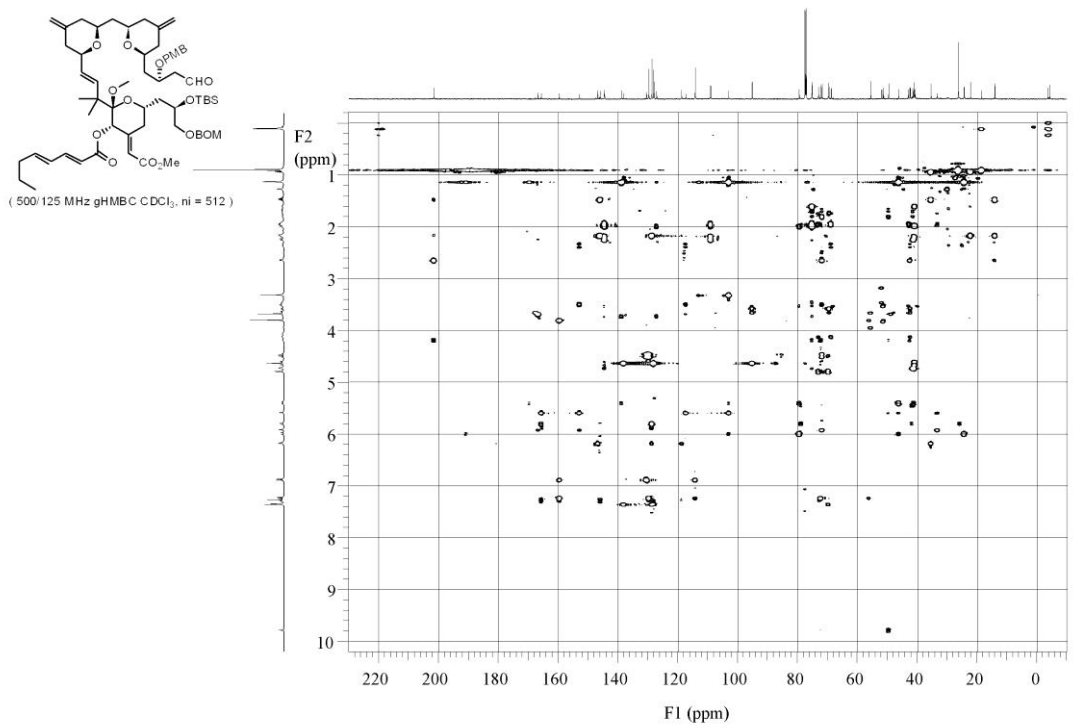


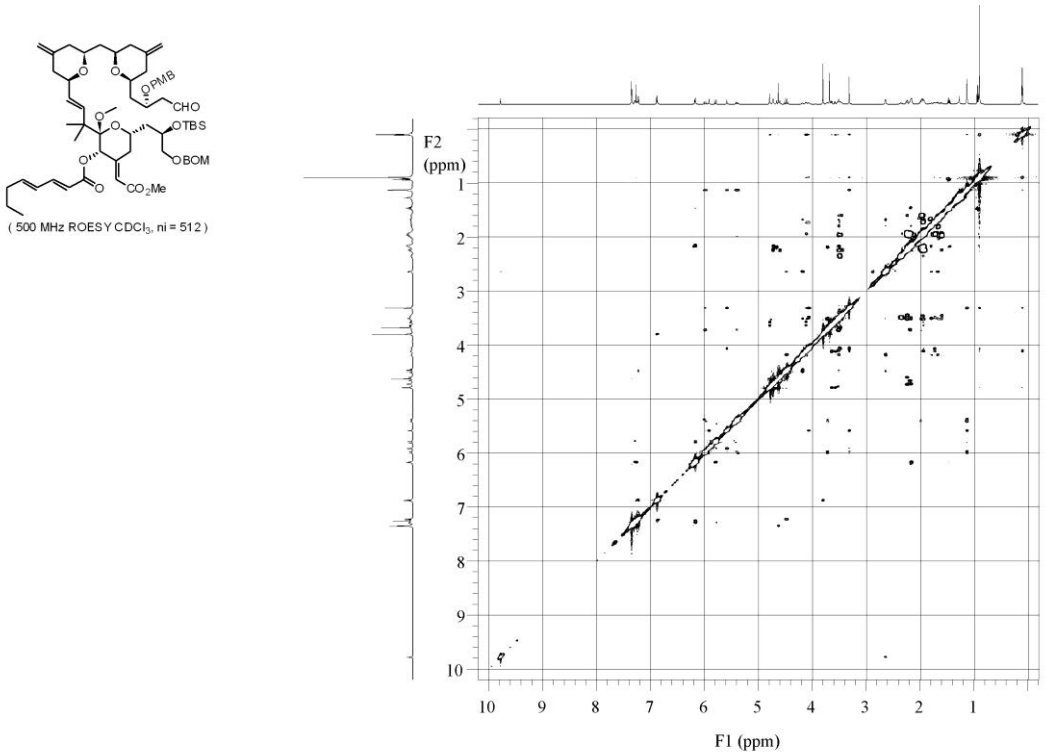


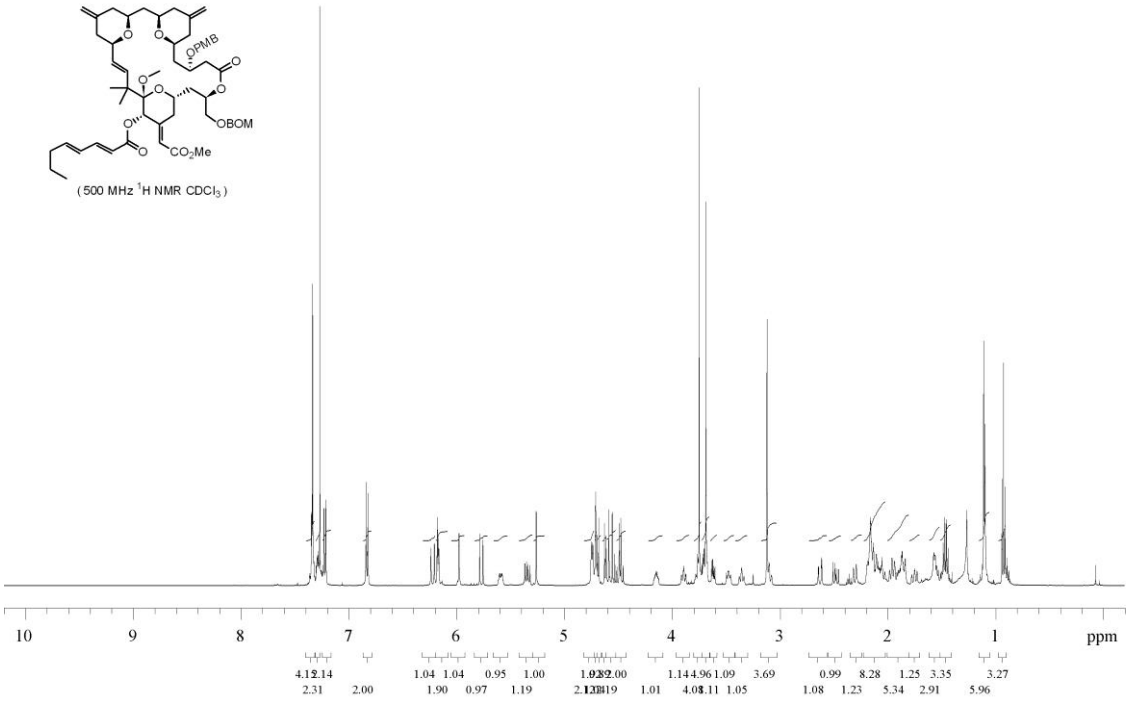
(125 MHz ^{13}C NMR $CDCl_3$)

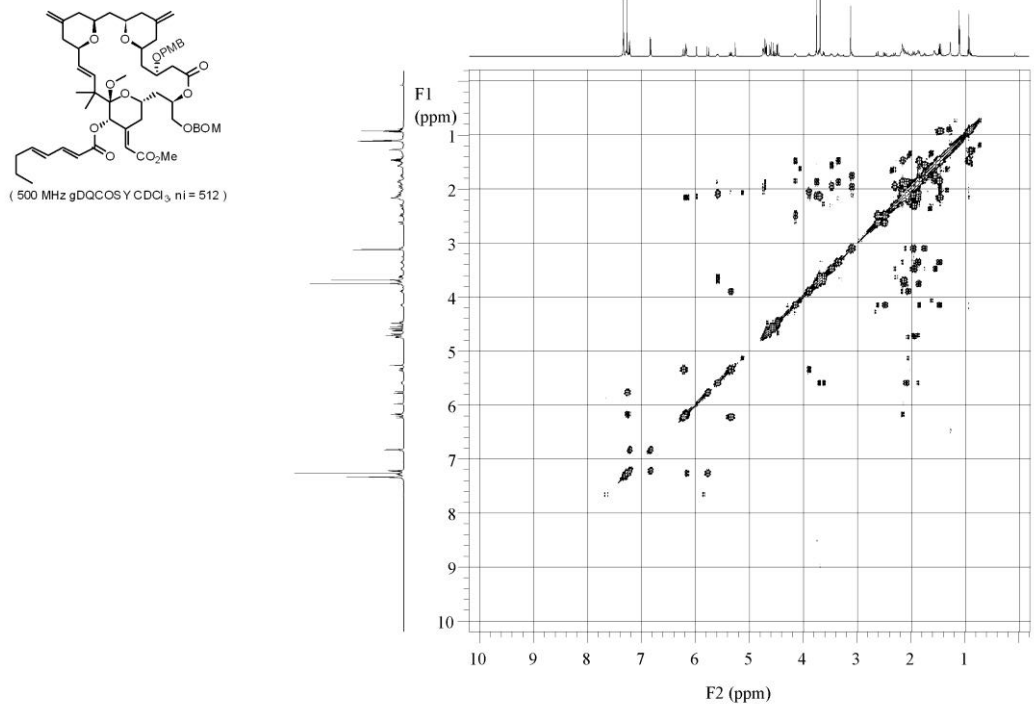

OPMB
CHO
OTBS
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

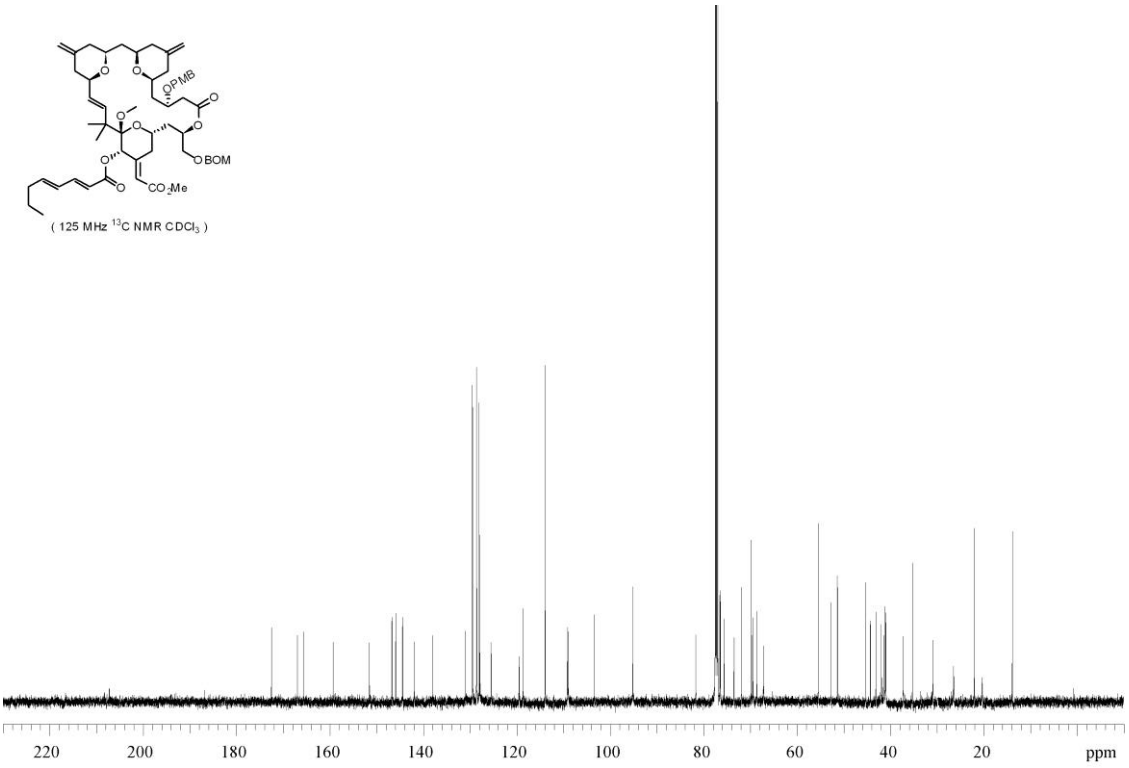

OPMB
CHO
OTBS
OBOM
CO2Me
(500/125 MHz gHSQC CDCl3, ni = 512)
F2 (ppm)
F1 (ppm)

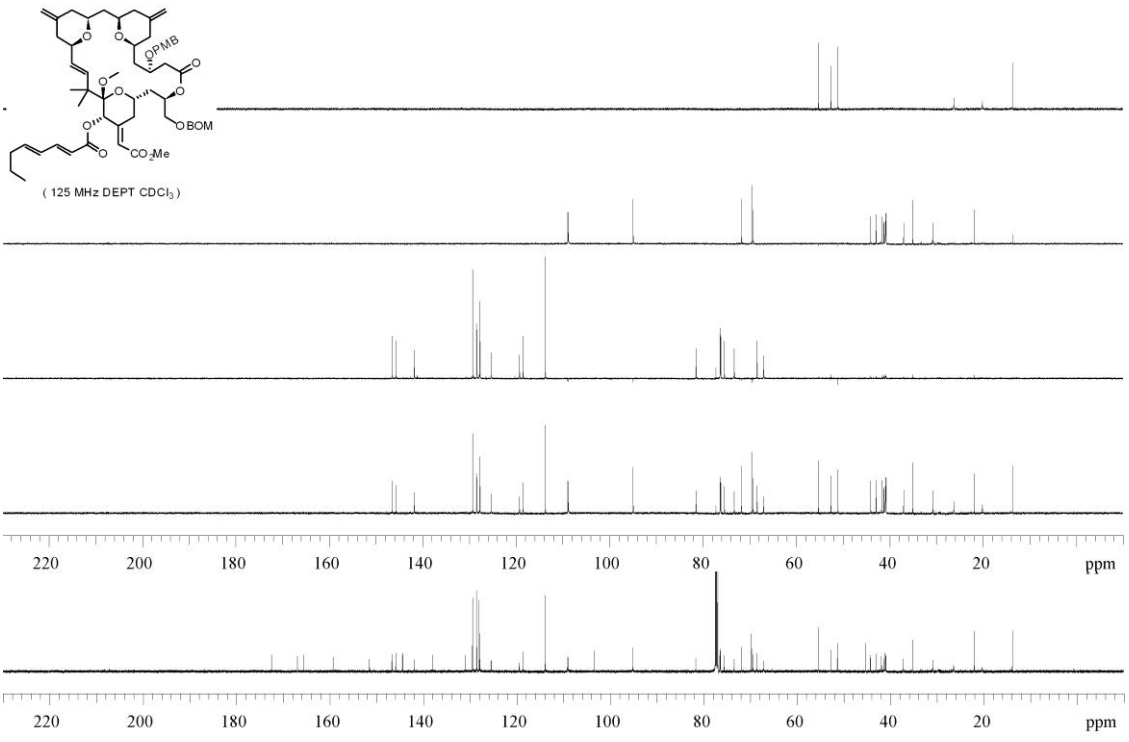

OPMB
CHO
OTBS
OBOM
CO2Me
(500/125 MHz gHMBC CDCl3, ni = 512)
F2
(ppm)
F1 (ppm)

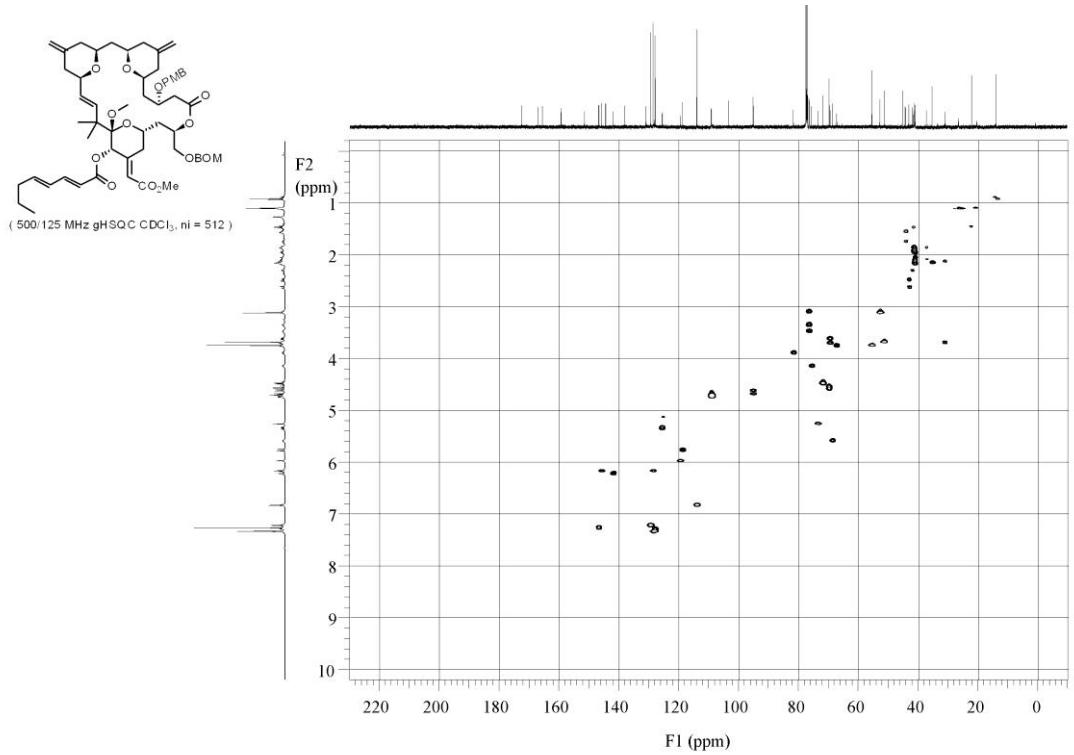

OPMB
CHO
OTBS
OBOM
CO2Me
(500 MHz ROESY CDCl3, ni = 512)
F2
(ppm)
F1 (ppm)

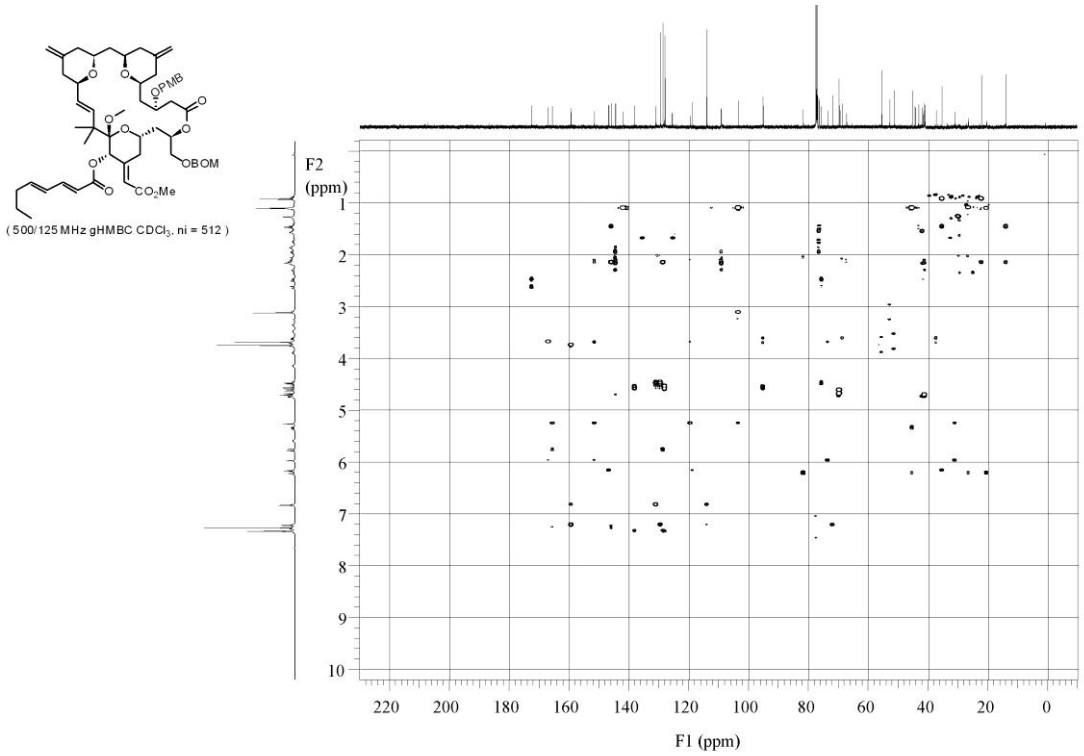

OPMB
OBOM
CO2Me
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm

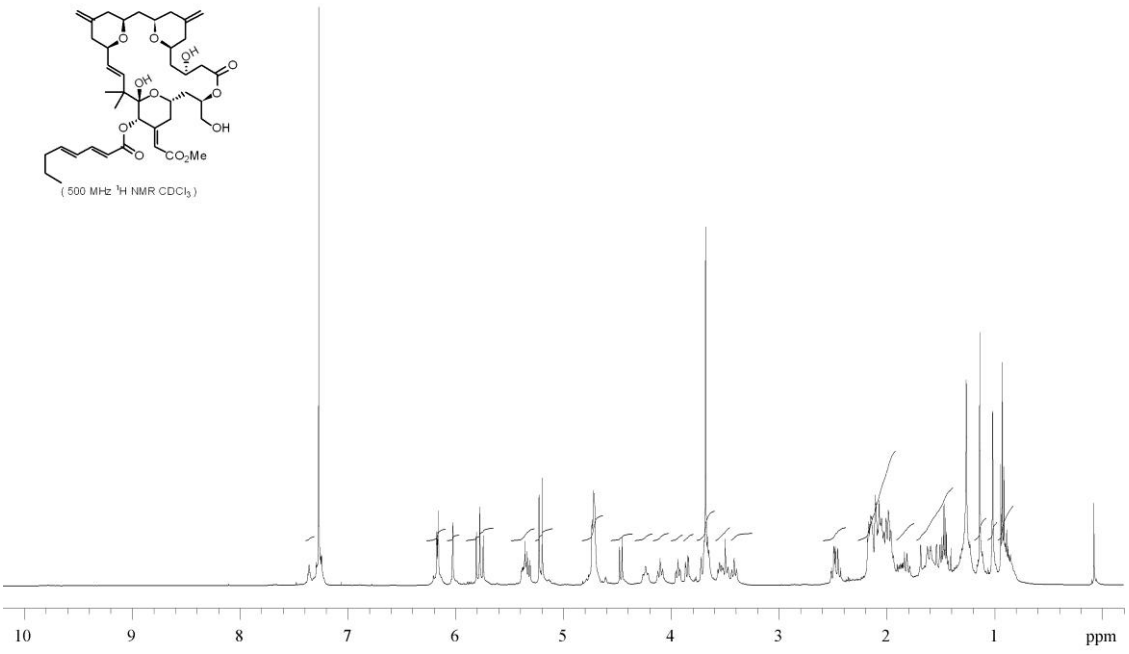

OPMB
OBOM
CO2Me
(500 MHz gDQCOSY CDCl3, ni = 512)
F1
(ppm)
F2 (ppm)

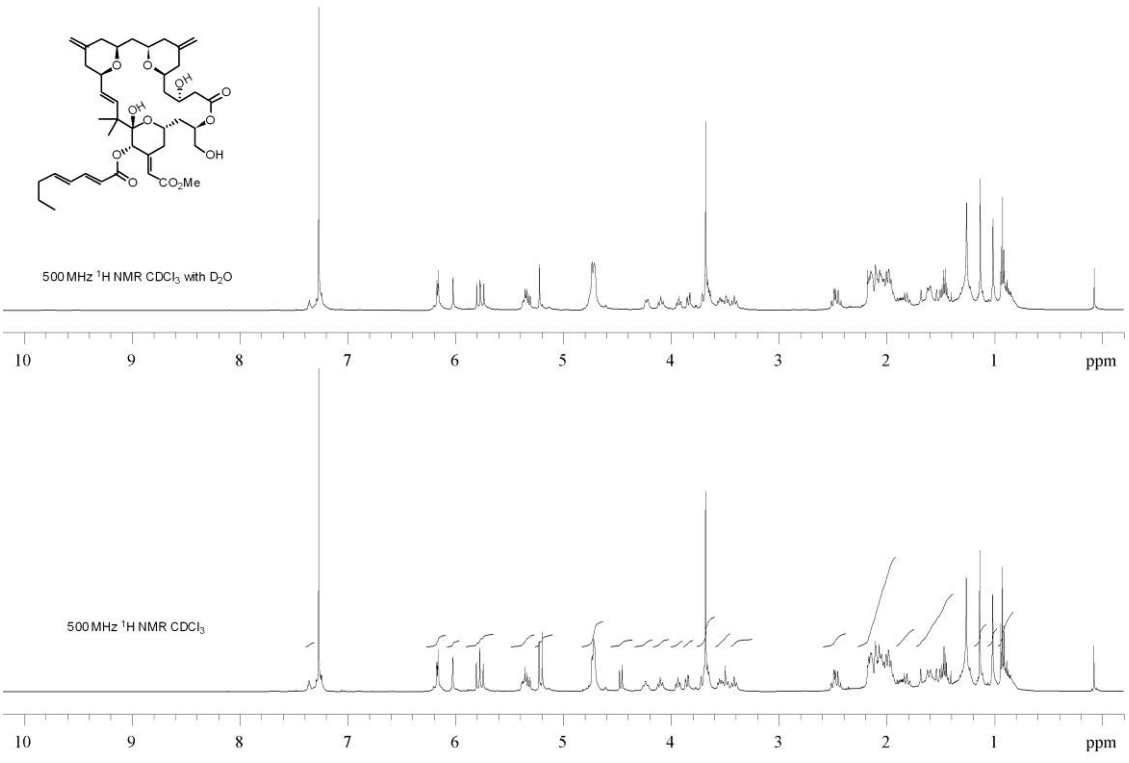

OPMB
OBOM
CO2Me
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm


OPMB
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

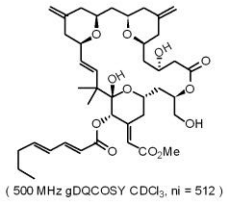

OPMB
OBOM
CO2Me
(500/125 MHz gHSQC CDCl3, ni = 512)
F2 (ppm)
F1 (ppm)


OPMB
OBOM
CO2Me
(500/125 MHz gHMBC CDCl3, ni = 512)
F2 (ppm)
F1 (ppm)

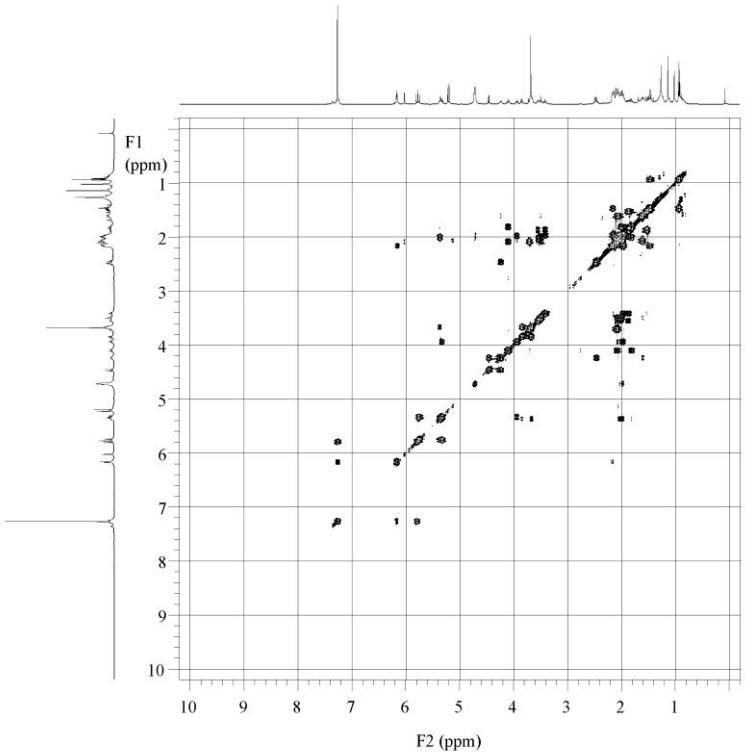

(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm

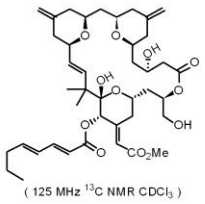

500 MHz ^{1}H NMR $CDCl_3$ with D_2O
10
9
8
7
6
5
4
3
2
1
ppm

500 MHz ^{1}H NMR $CDCl_3$
10
9
8
7
6
5
4
3
2
1
ppm

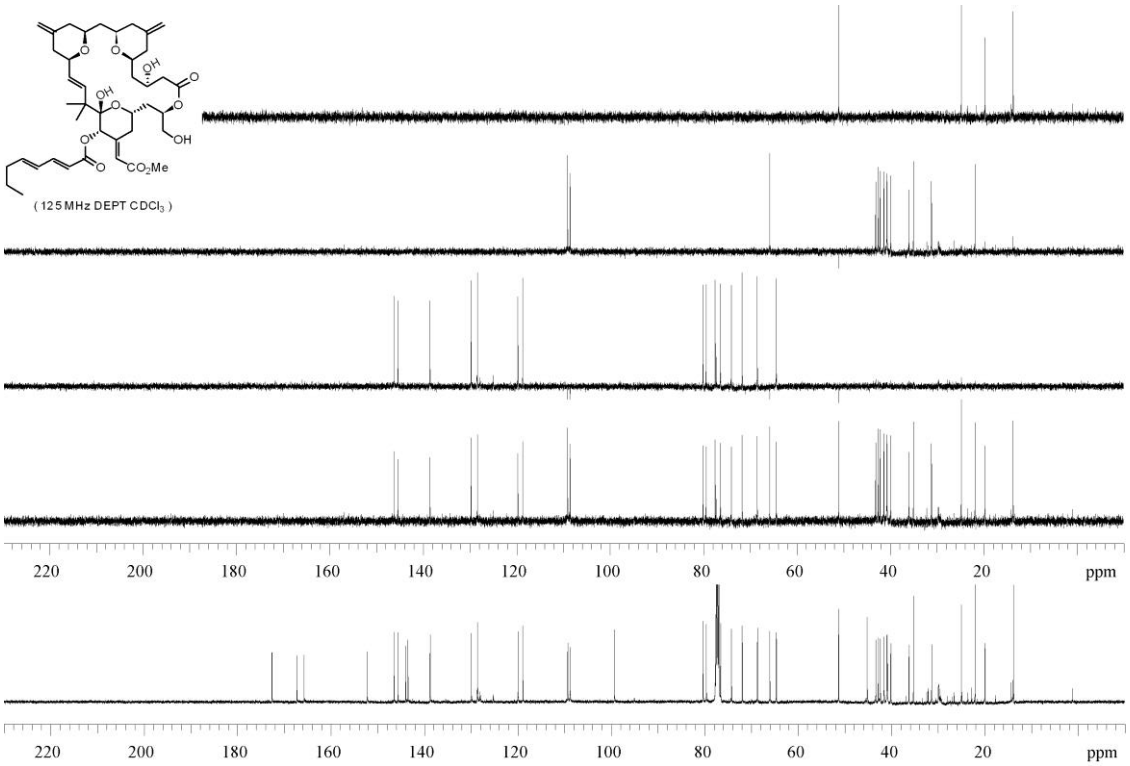


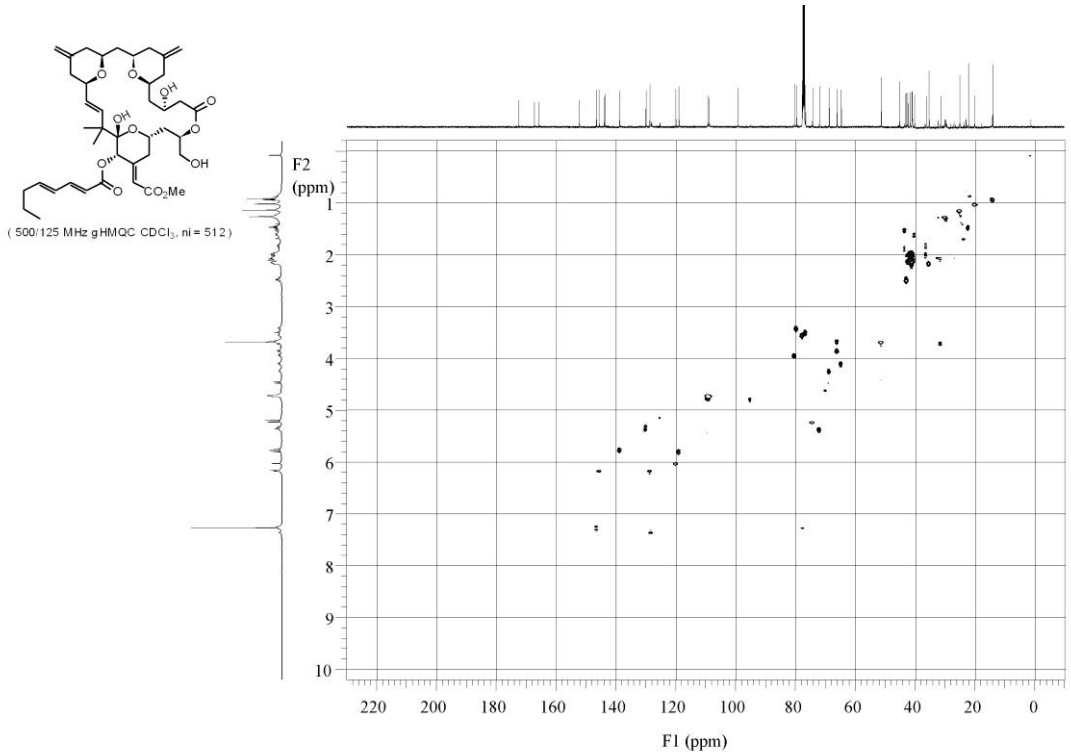
(500 MHz gDQCOSY $CDCl_3$, ni = 512)

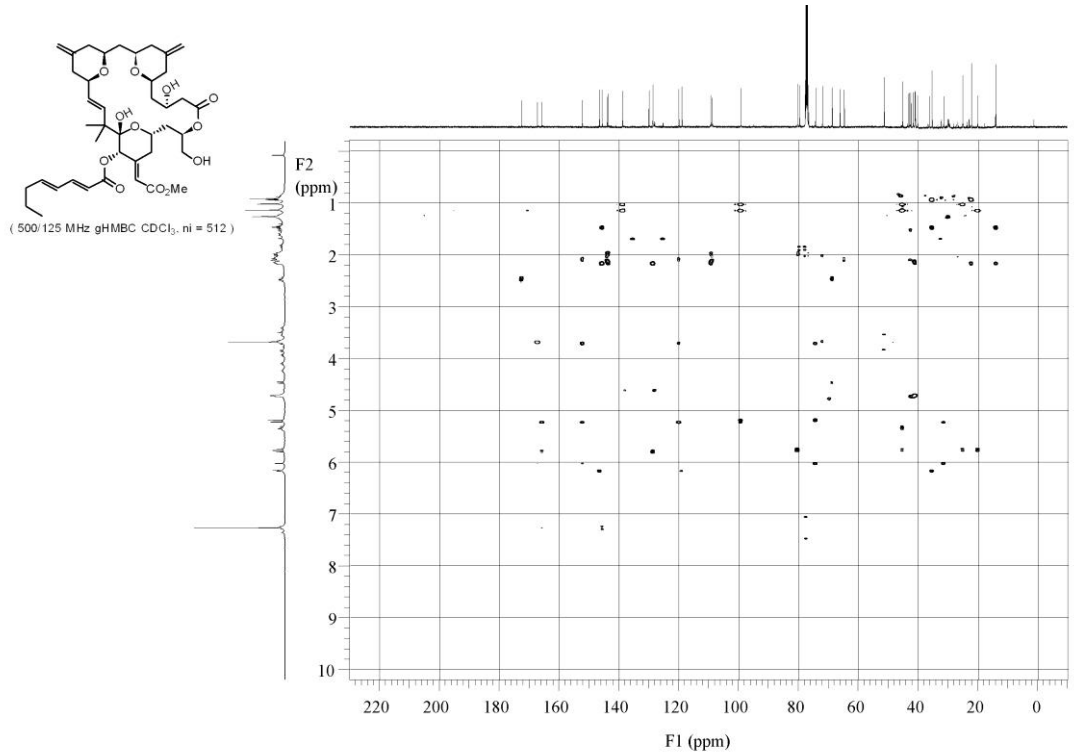


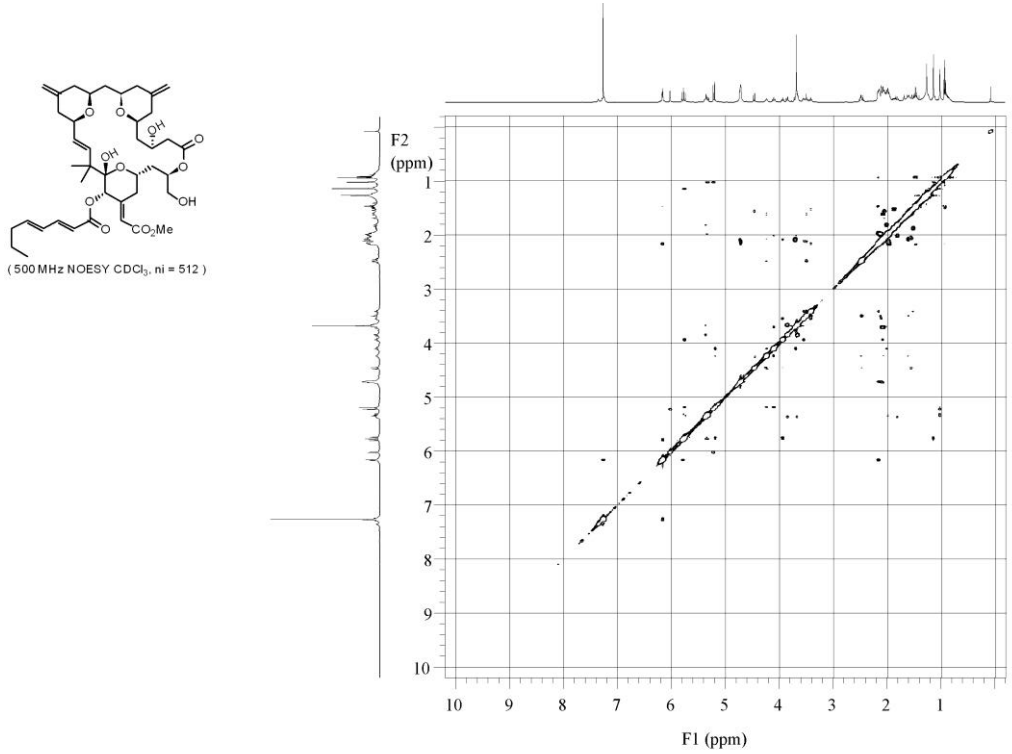


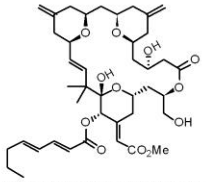
(125 MHz ^{13}C NMR $CDCl_3$)


(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

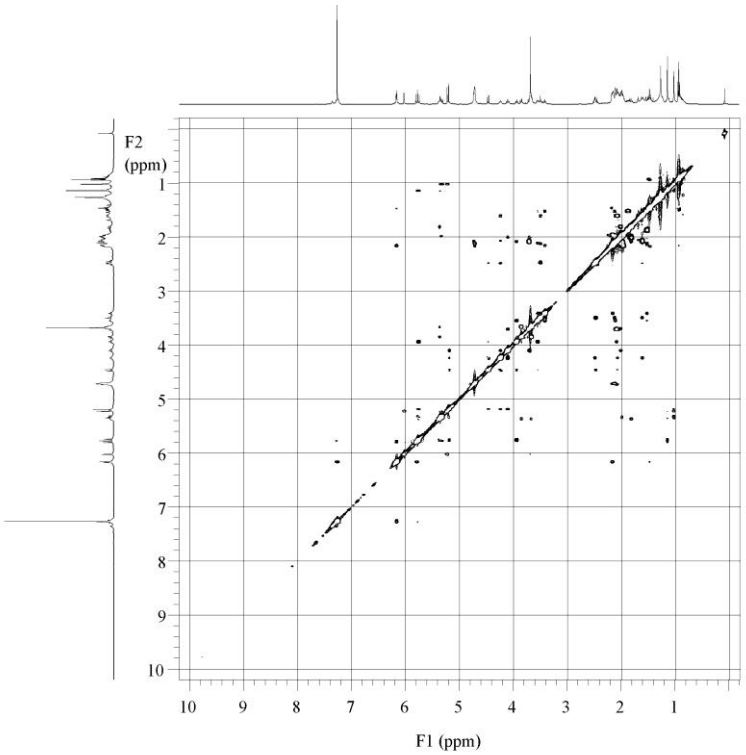

(500/125 MHz gHMQC CDCl3, ni = 512)
F2 (ppm)
F1 (ppm)

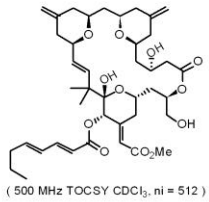

(500/125 MHz gHMBC $CDCl_3$, ni = 512)
F2
(ppm)
F1 (ppm)


(500 MHz NOESY $CDCl_3$, ni = 512)
F2
(ppm)
F1 (ppm)

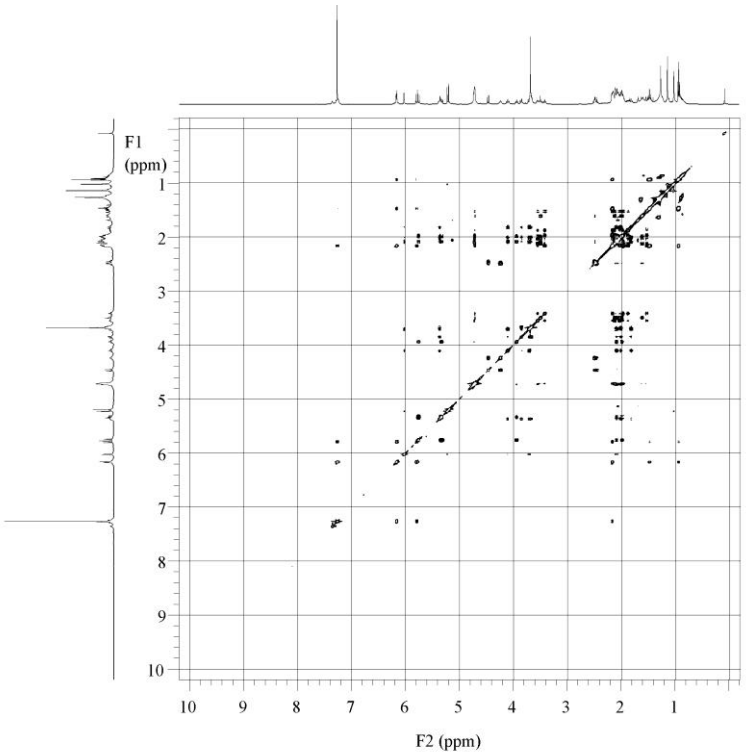


(500 MHz ROESY $CDCl_3$, ni = 512)



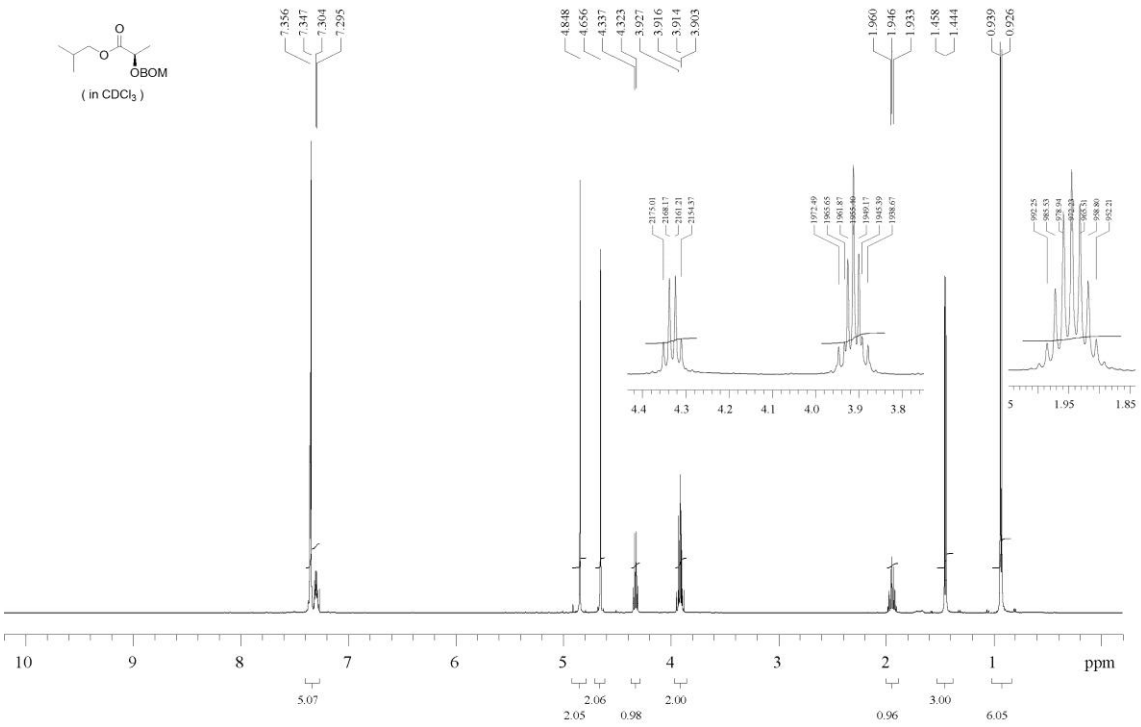


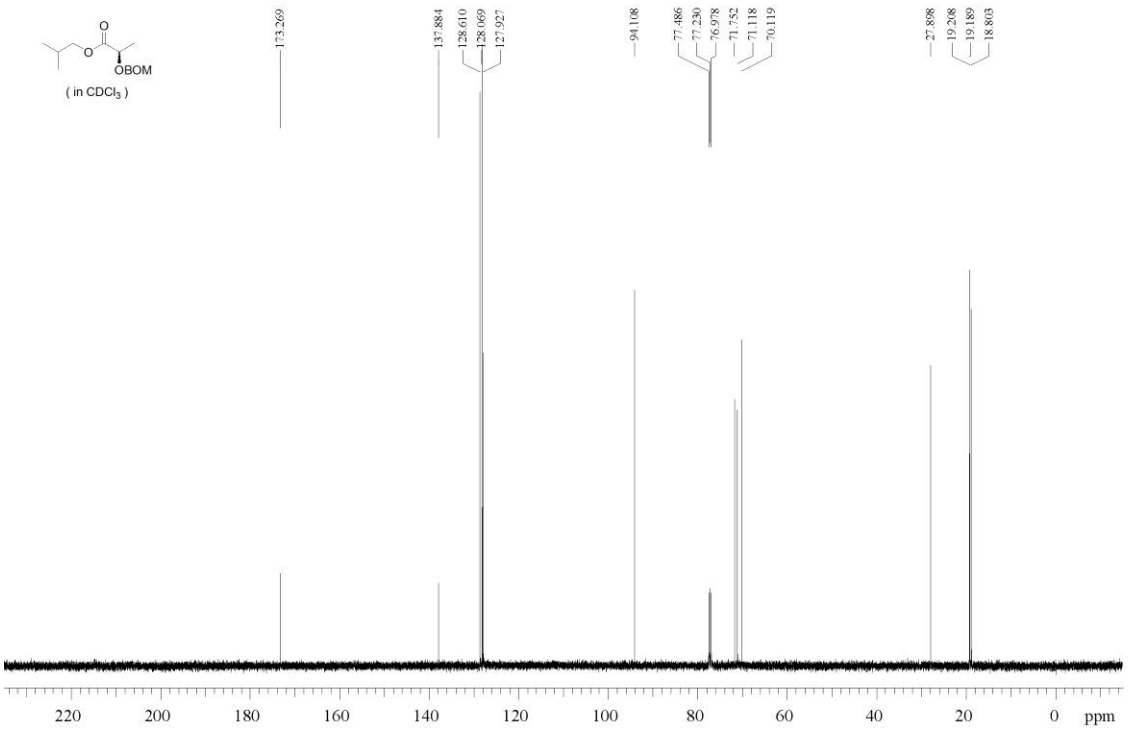
(500 MHz TOCSY $CDCl_3$, ni = 512)

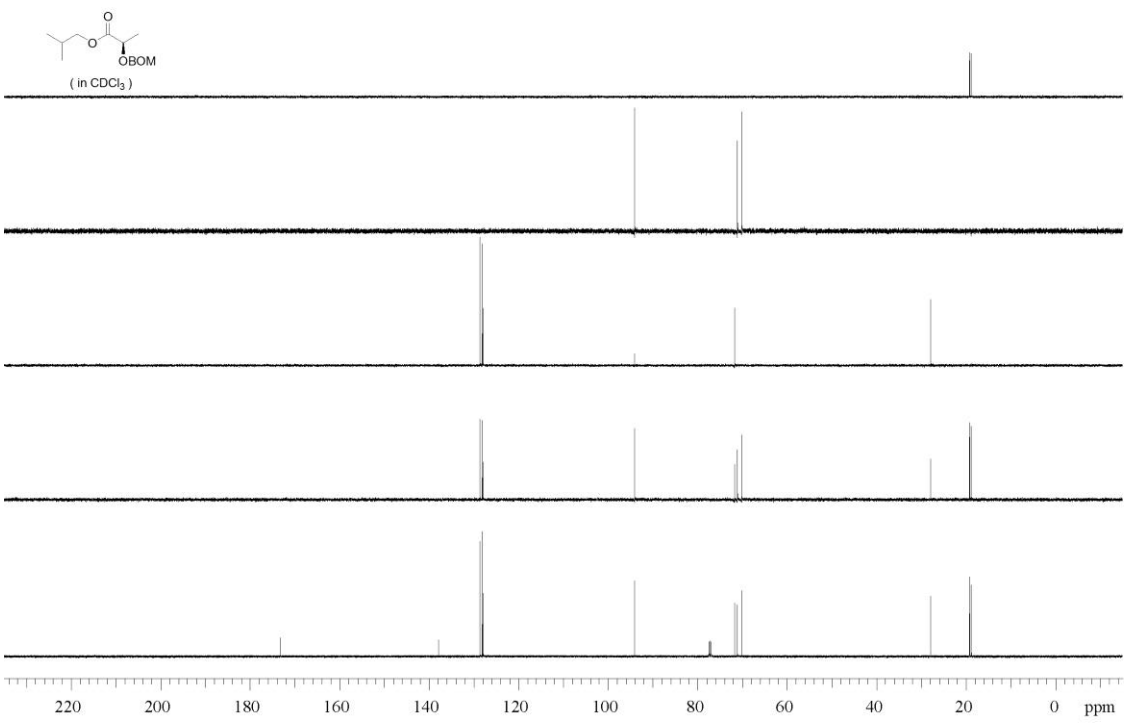


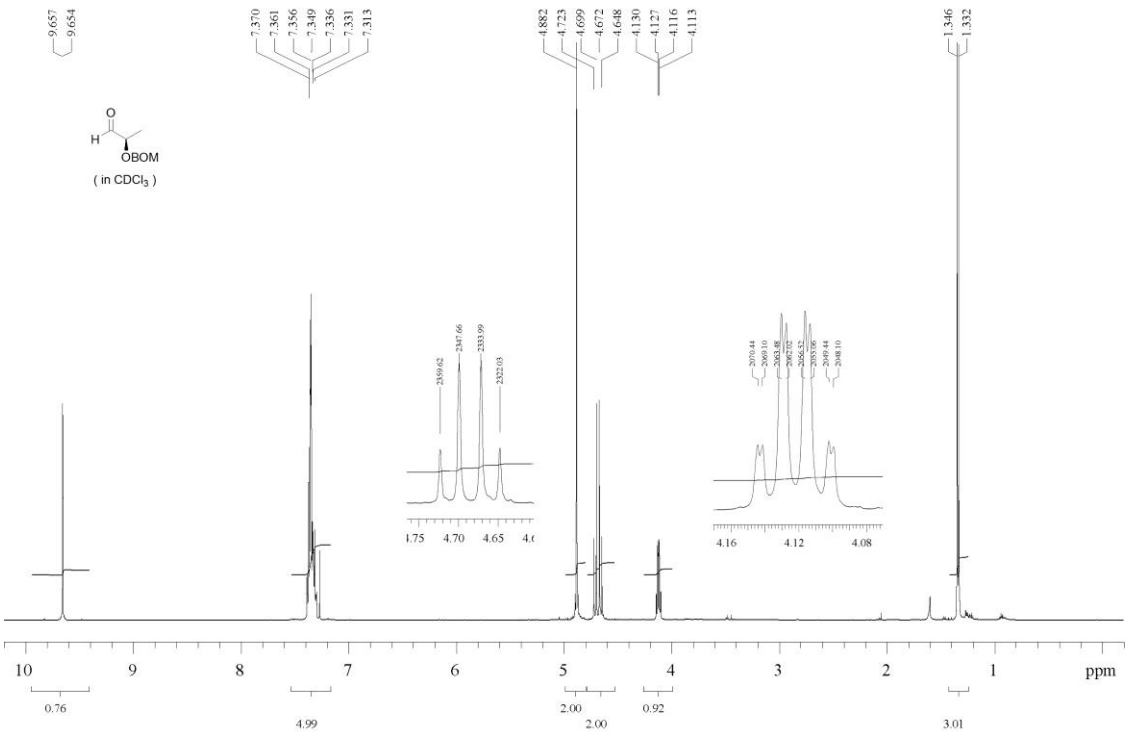
APPENDIX C

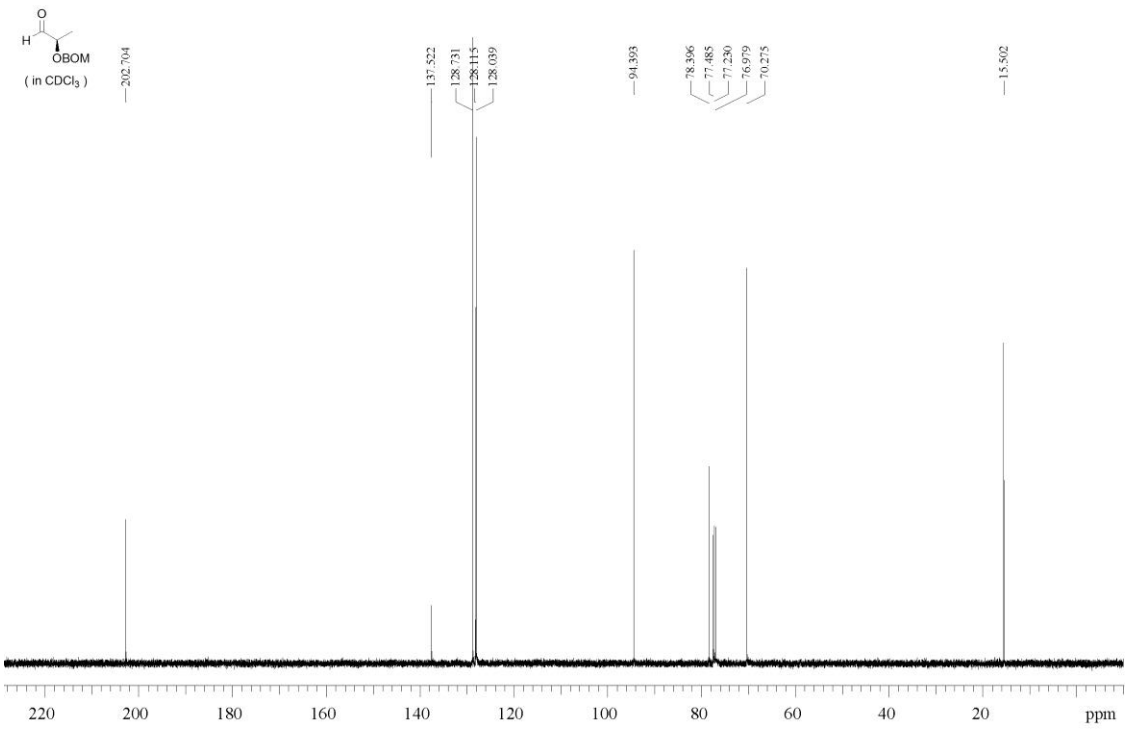
NMR SPECTRUM OF CHAPTER 3

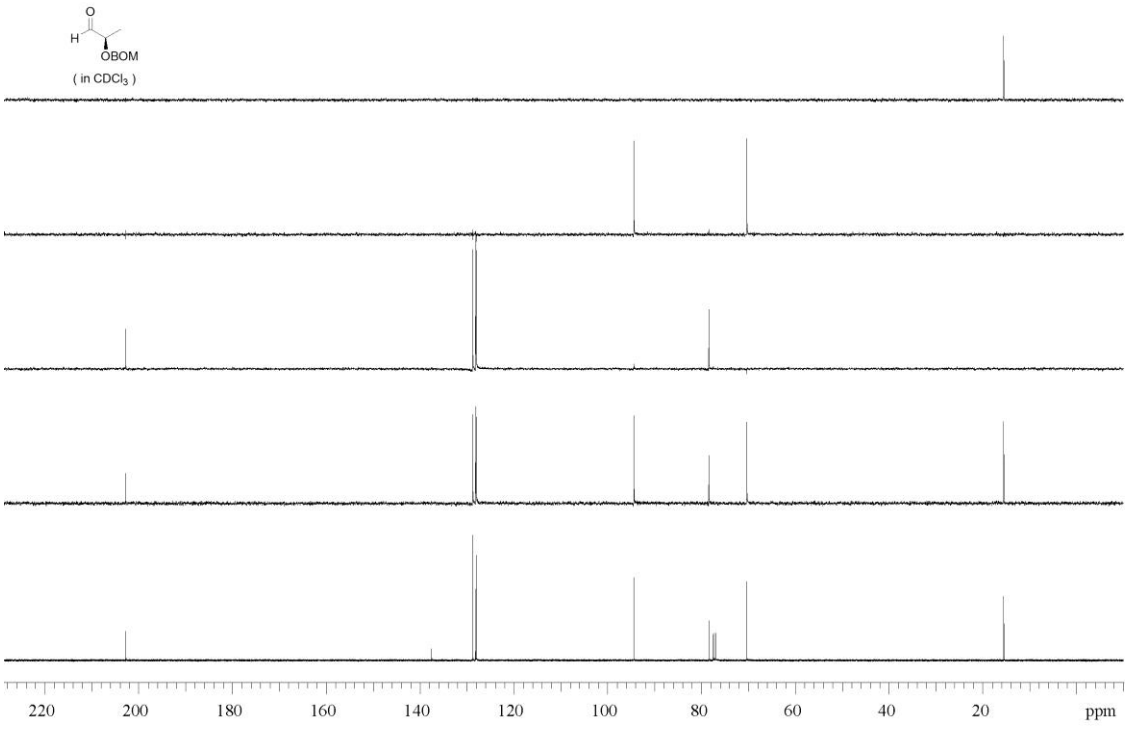

OBOM
(in CDCl3)
7.356
7.347
7.304
7.295
4.848
4.656
4.337
4.323
3.927
3.916
3.914
3.903
1.960
1.946
1.933
1.458
1.444
0.939
0.926
10
9
8
7
6
5
4
3
2
1
ppm
5.07
2.06
2.05
0.98
2.00
0.96
3.00
6.05

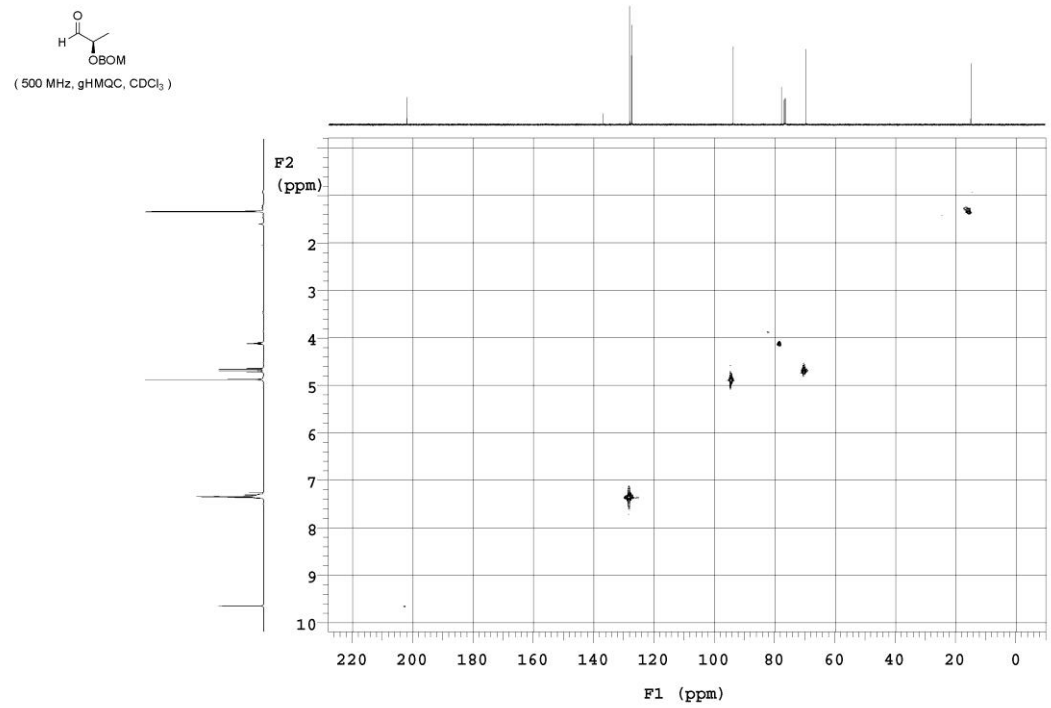

OBOM
(in CDCl3)
173.269
137.884
128.610
128.069
127.927
94.108
77.486
77.230
76.978
71.752
71.118
70.119
27.898
19.208
19.189
18.803
220
200
180
160
140
120
100
80
60
40
20
0
ppm

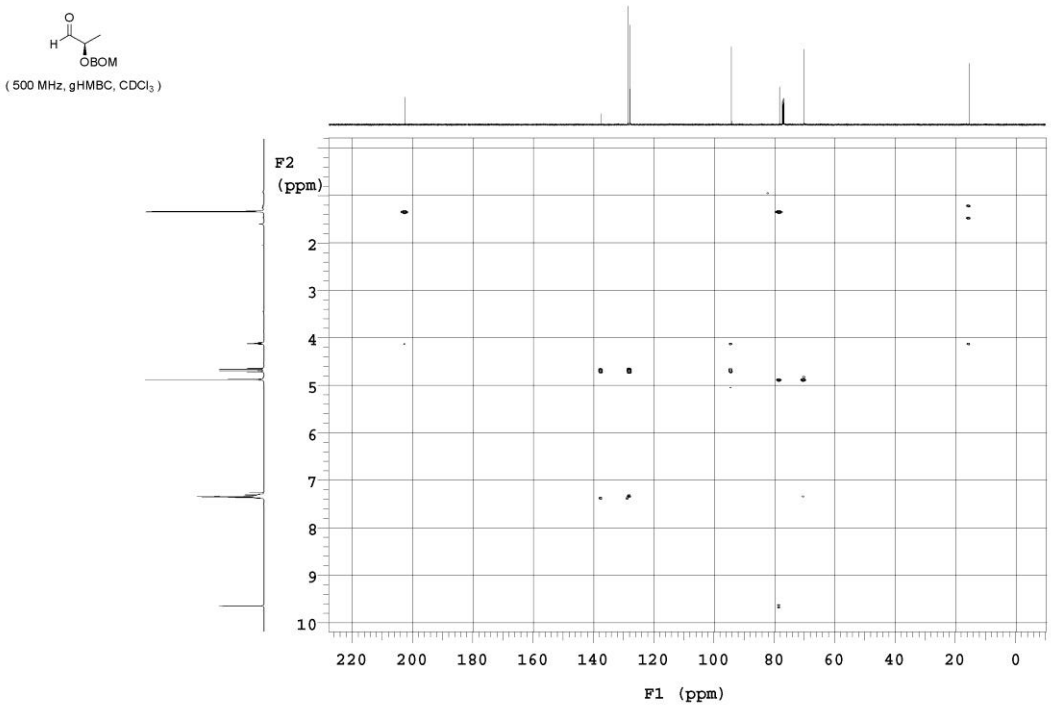

OBOM
(in CDCl3)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

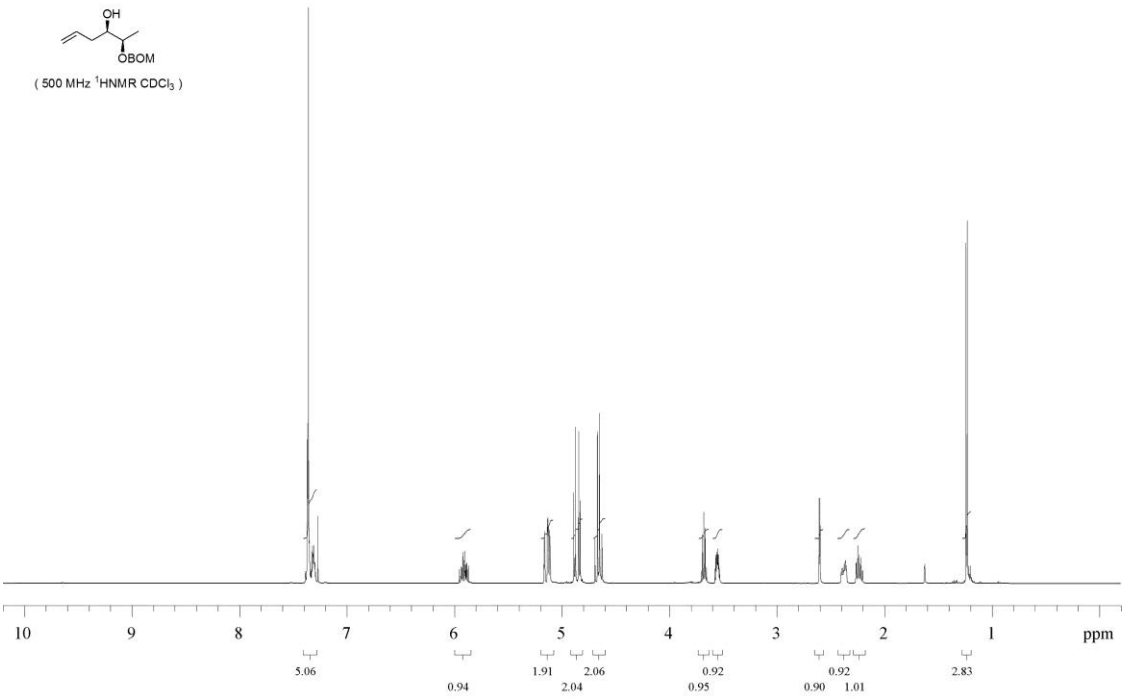

9.657
9.654
7.370
7.361
7.356
7.349
7.336
7.331
7.313
4.882
4.723
4.699
4.672
4.648
4.130
4.127
4.116
4.113
1.346
1.332
OBOM
(in CDCl3)
2859.62
2847.66
2833.99
2822.03
2970.44
2963.48
2956.52
2949.44
2948.10
10
9
8
7
6
5
4
3
2
1
ppm
0.76
4.99
2.00
2.00
0.92
3.01

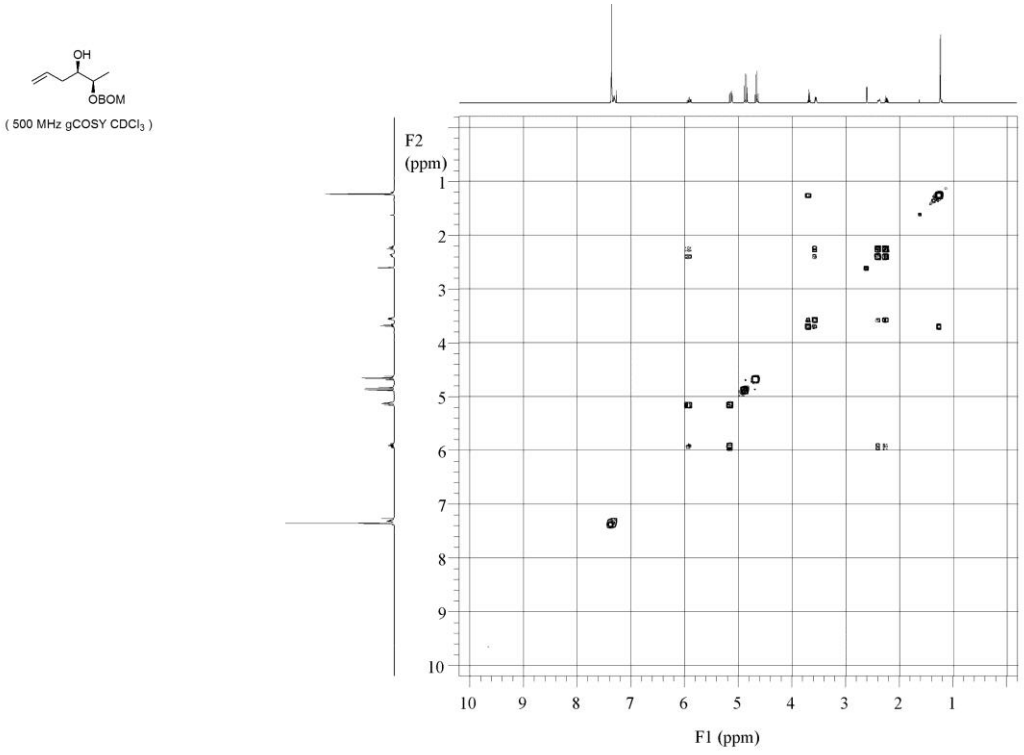

O
H
OBOM
(in CDCl3)
202.704
137.522
128.731
128.115
128.039
94.393
78.396
77.485
77.230
76.979
70.275
15.502
220
200
180
160
140
120
100
80
60
40
20
ppm

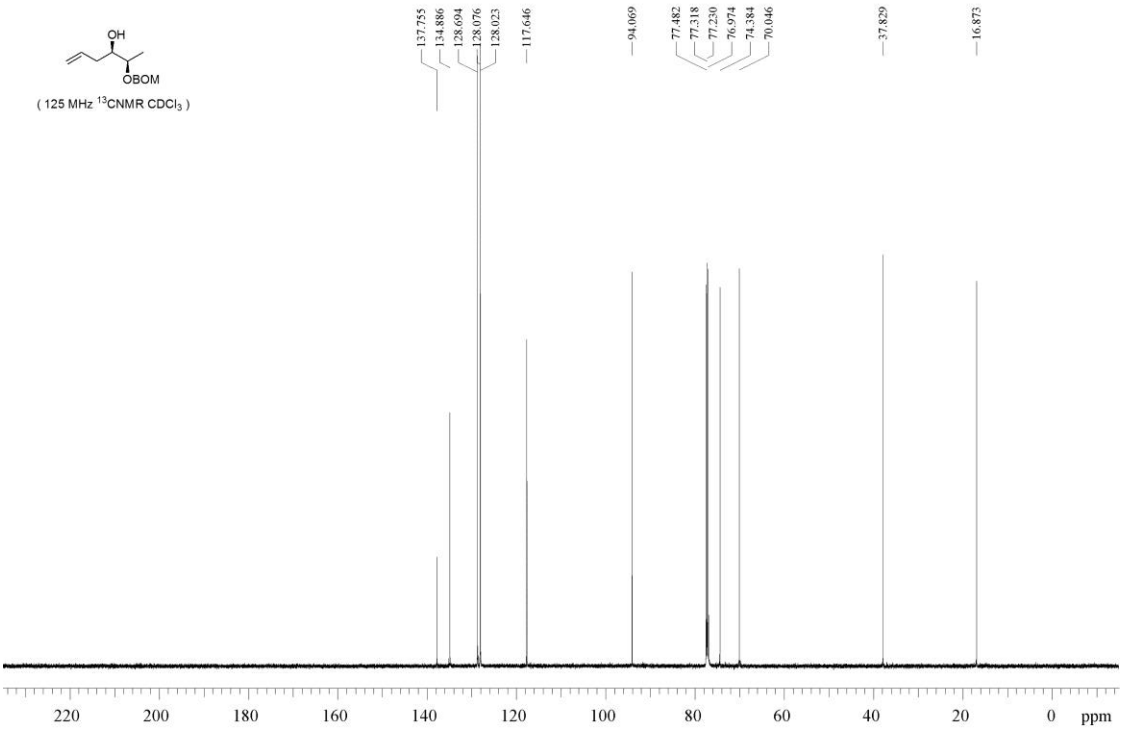

O
H
OBOM
(in CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

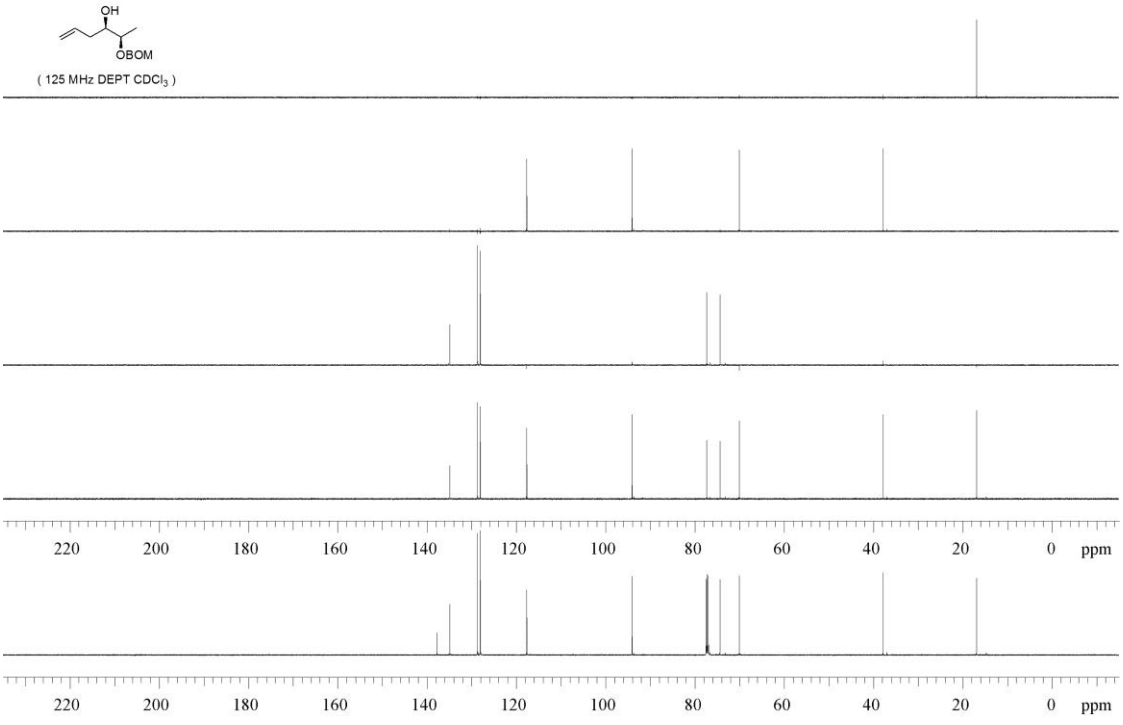

OBOM
(500 MHz, gHMQC, CDCl3)
F2
(ppm)
F1 (ppm)

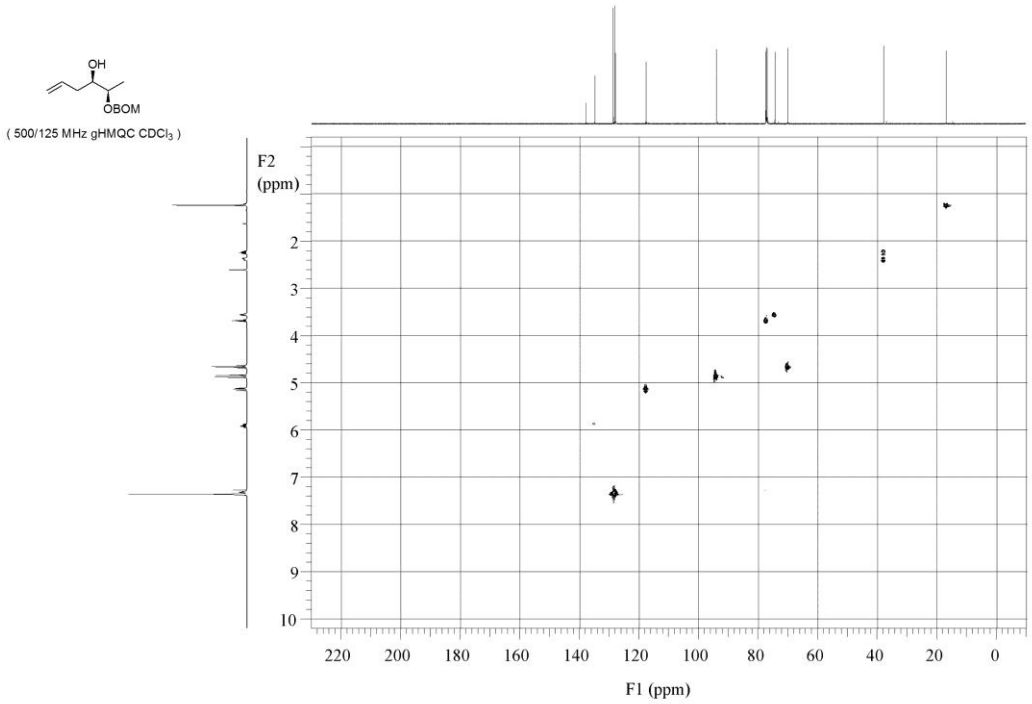

OBOM
(500 MHz, gHMBC, CDCl3)
F2
(ppm)
F1 (ppm)

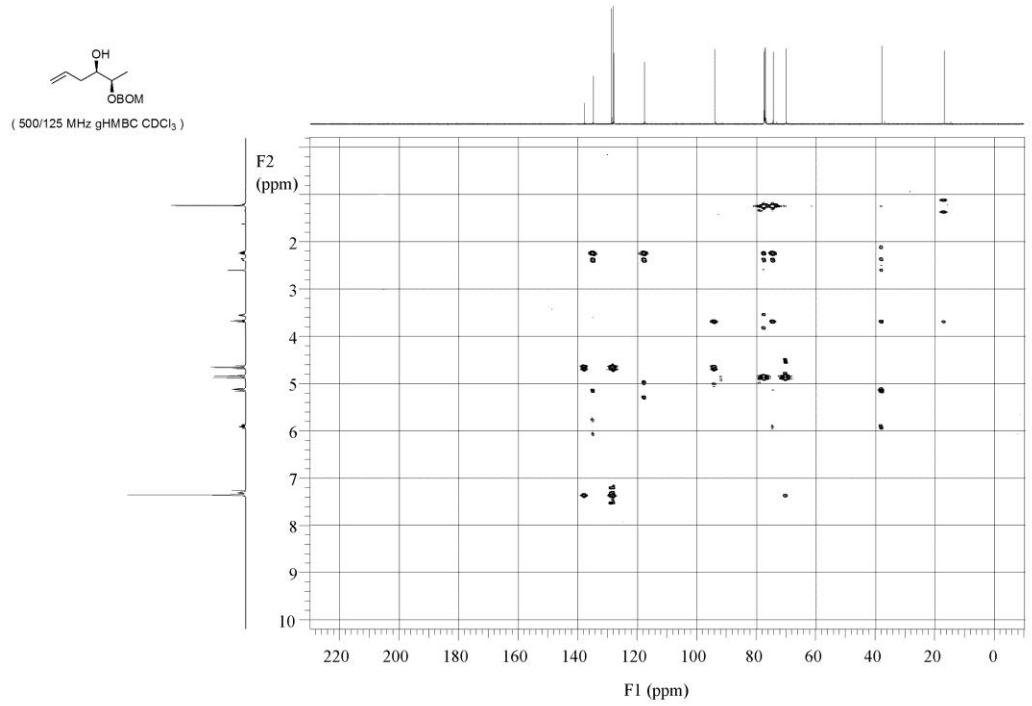

OH
OBOM
(500 MHz ^{1}HNMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
5.06
0.94
1.91
2.04
2.06
0.95
0.92
0.90
0.92
1.01
2.83

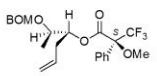

OH
OBOM
(500 MHz gCOSY $CDCl_3$)
F2
(ppm)
F1 (ppm)


OH
OBOM
(125 MHz ^{13}CNMR $CDCl_3$)
137.755
134.886
128.694
128.076
128.023
117.646
94.069
77.482
77.318
77.230
76.974
74.384
70.046
37.829
16.873
220
200
180
160
140
120
100
80
60
40
20
0
ppm

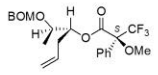

OH
OBOM
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
0
ppm


OH
OBOM
(500/125 MHz gHMQC $CDCl_3$)
F2
(ppm)
F1 (ppm)

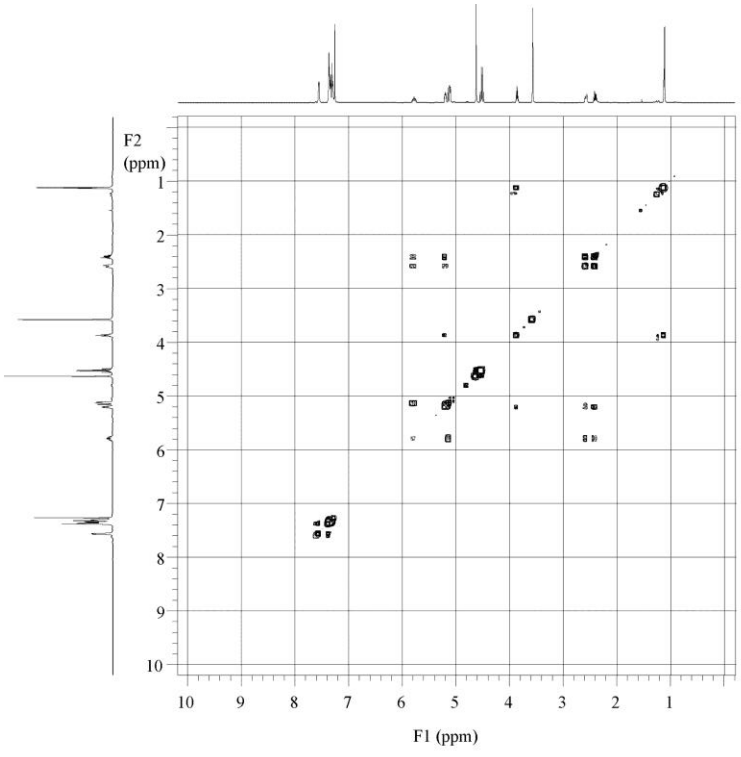

OH
OBOM
(500/125 MHz gHMBC $CDCl_3$)
F2
(ppm)
F1 (ppm)

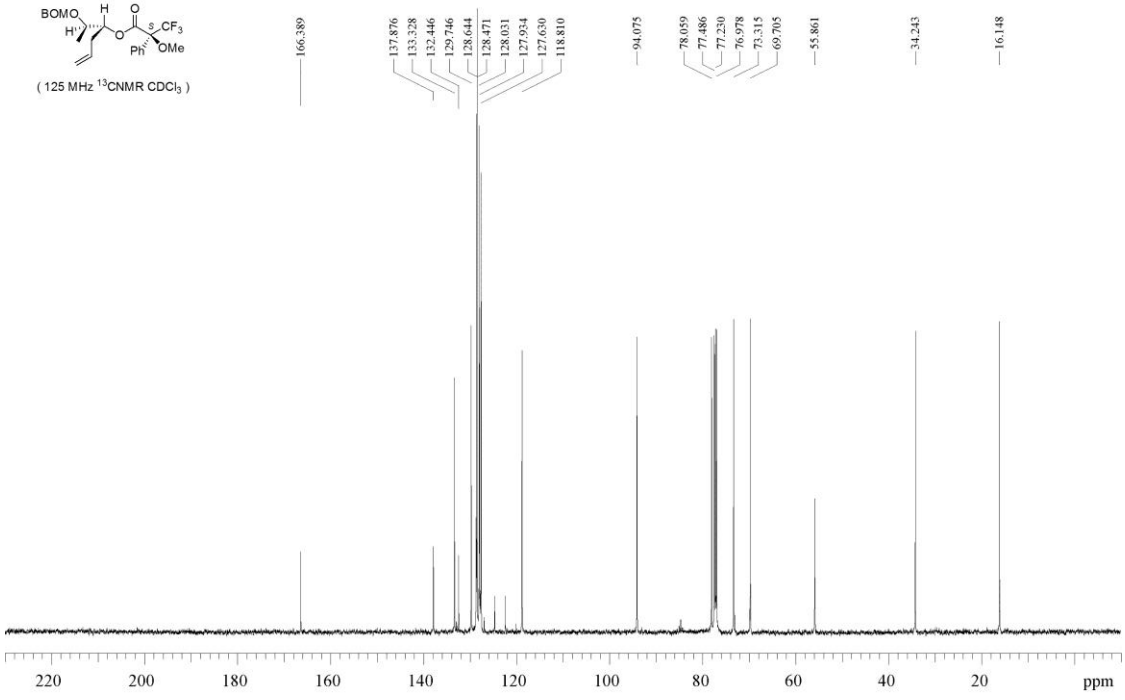


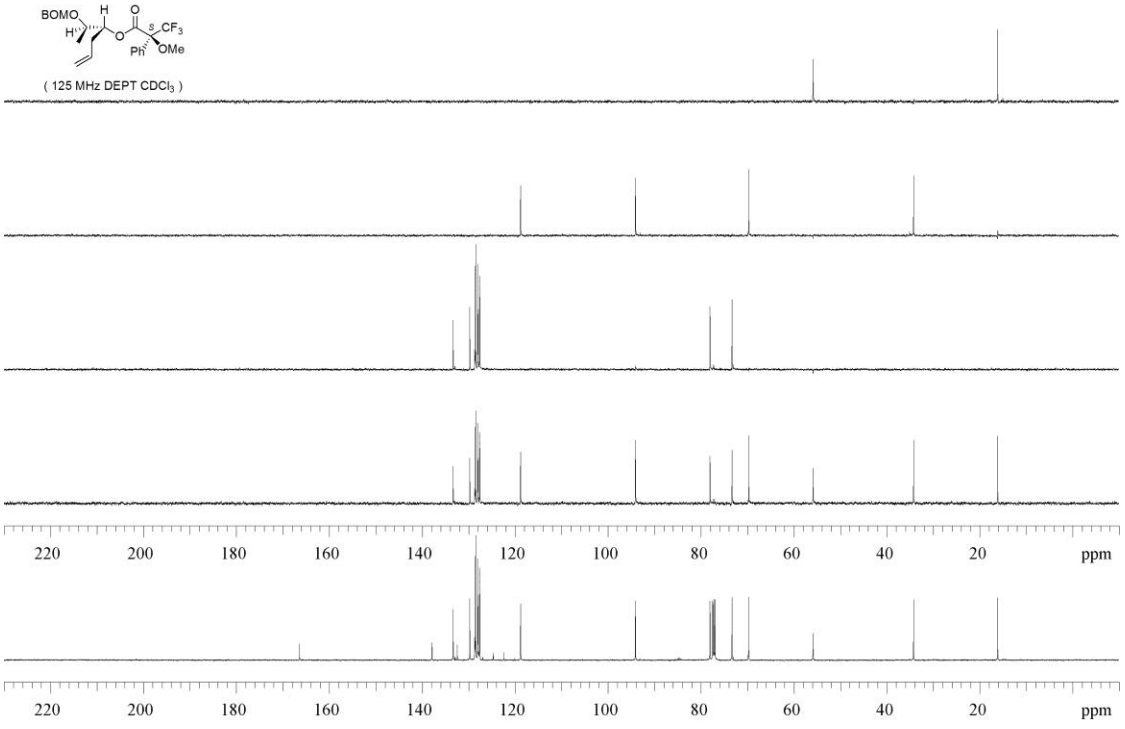
(500 MHz ^{1}HNMR $CDCl_3$)

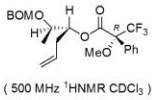


(500 MHz gCOSY $CDCl_3$)

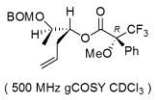



BOMO
H
O
H'
S
CF3
Ph
OMe
(125 MHz 13CNMR CDCl3)
166.389
137.876
133.328
132.446
129.746
128.644
128.471
128.031
127.934
127.630
118.810
94.075
78.059
77.486
77.230
76.978
73.315
69.705
55.861
34.243
16.148
220
200
180
160
140
120
100
80
60
40
20
ppm

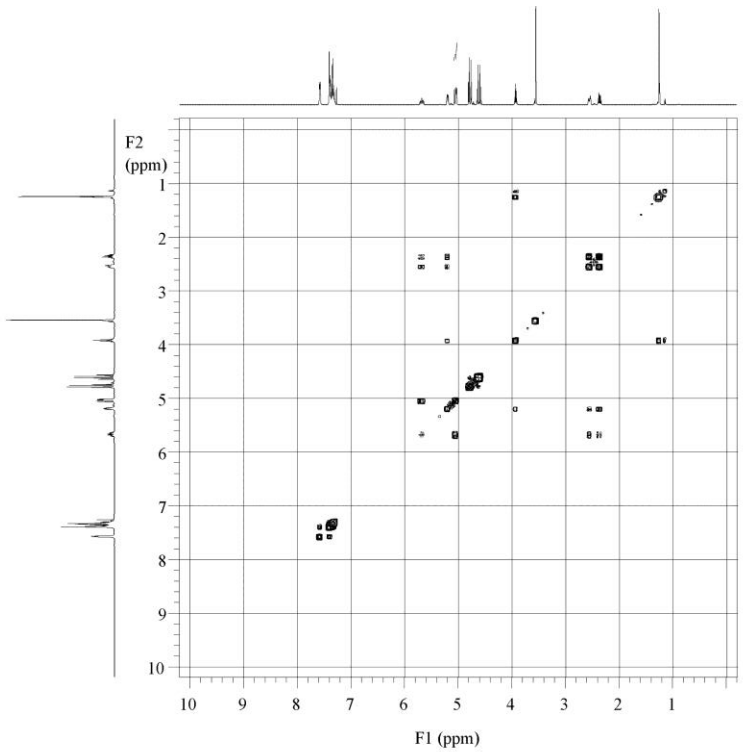

BOMO
H
O
H'
S
CF3
Ph
OMe
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

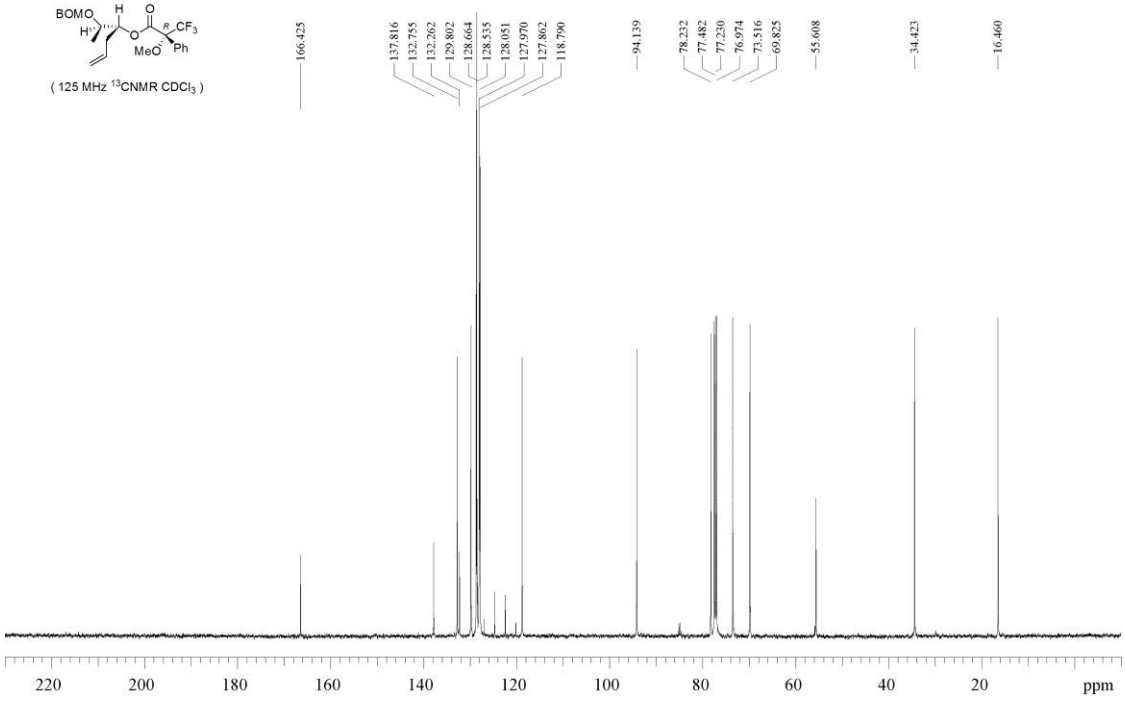


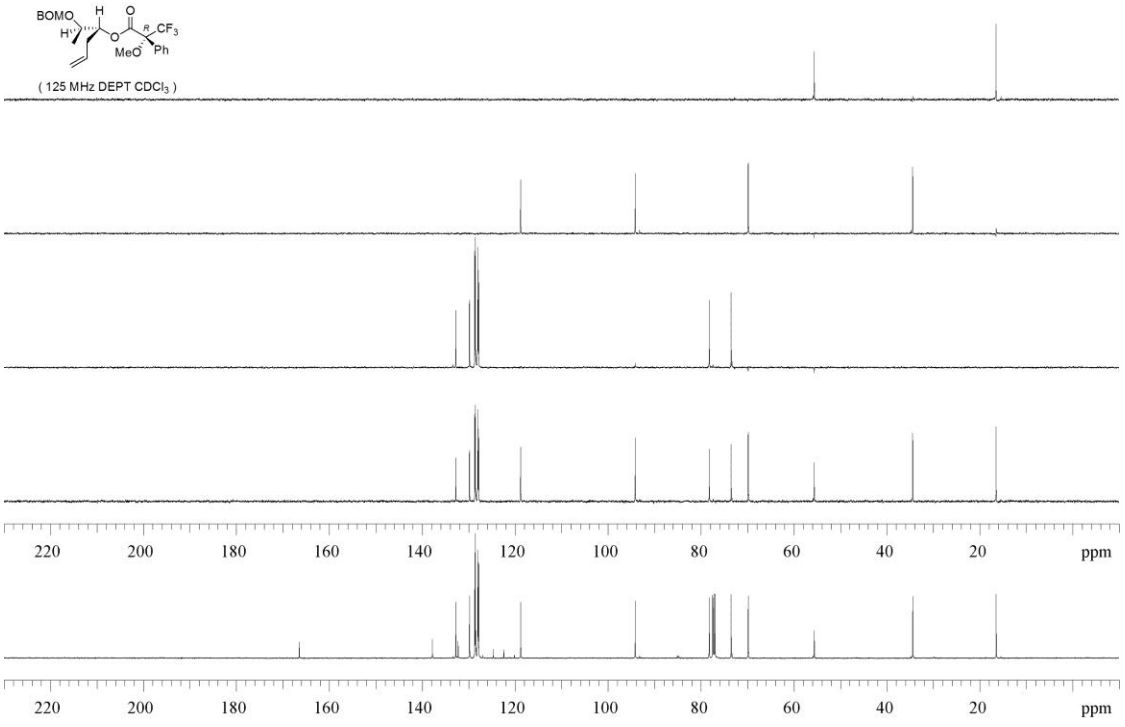
(500 MHz ^{1}HNMR $CDCl_3$)

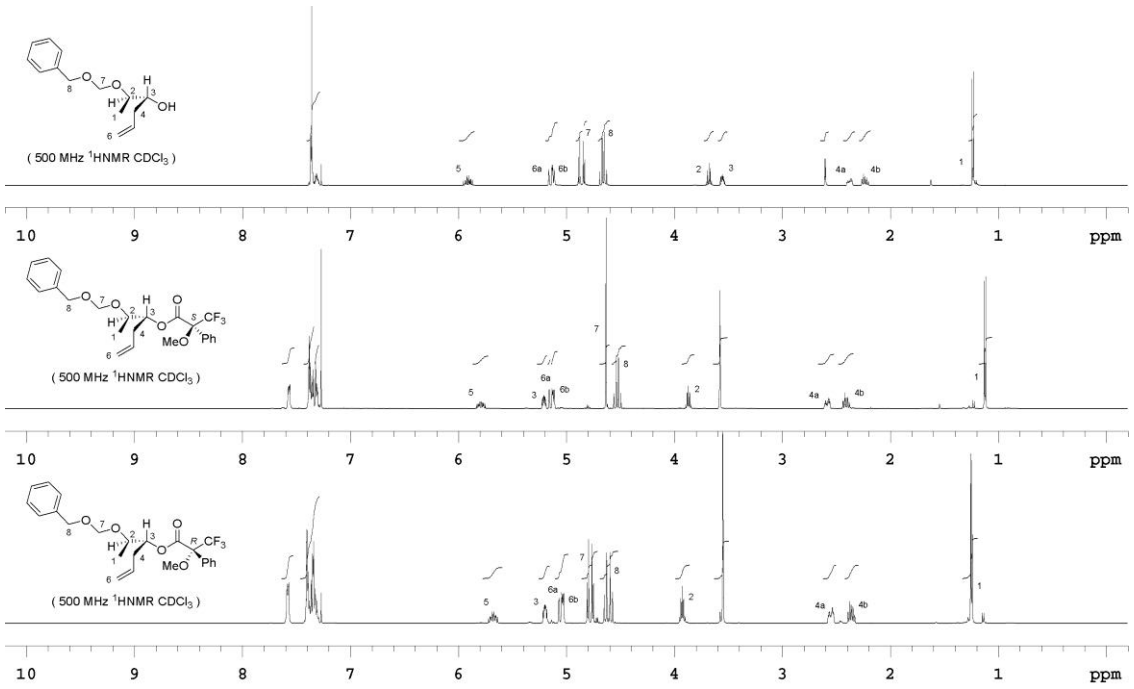


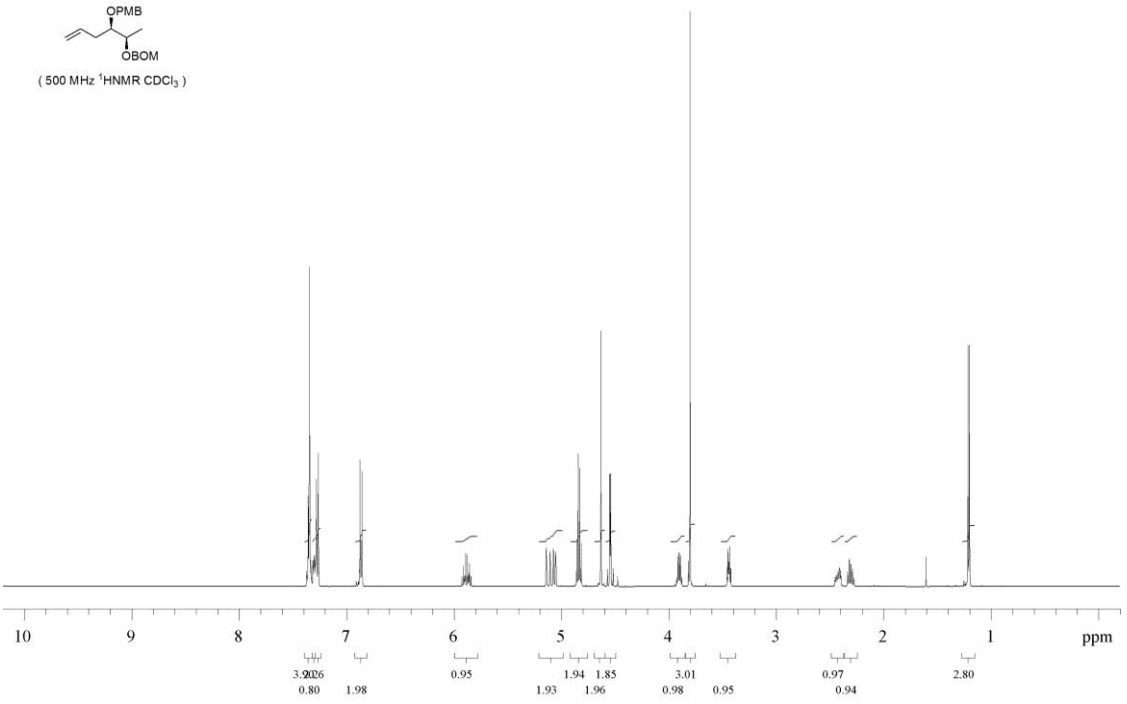
(500 MHz gCOSY $CDCl_3$)

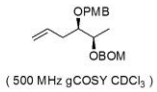



BOMO
H
O
CF3
MeO
Ph
(125 MHz 13CNMR CDCl3)
166.425
137.816
132.755
132.262
129.802
128.664
128.535
128.051
127.970
127.862
118.790
94.139
78.232
77.482
77.230
76.974
73.516
69.825
55.608
34.423
16.460
220
200
180
160
140
120
100
80
60
40
20
ppm

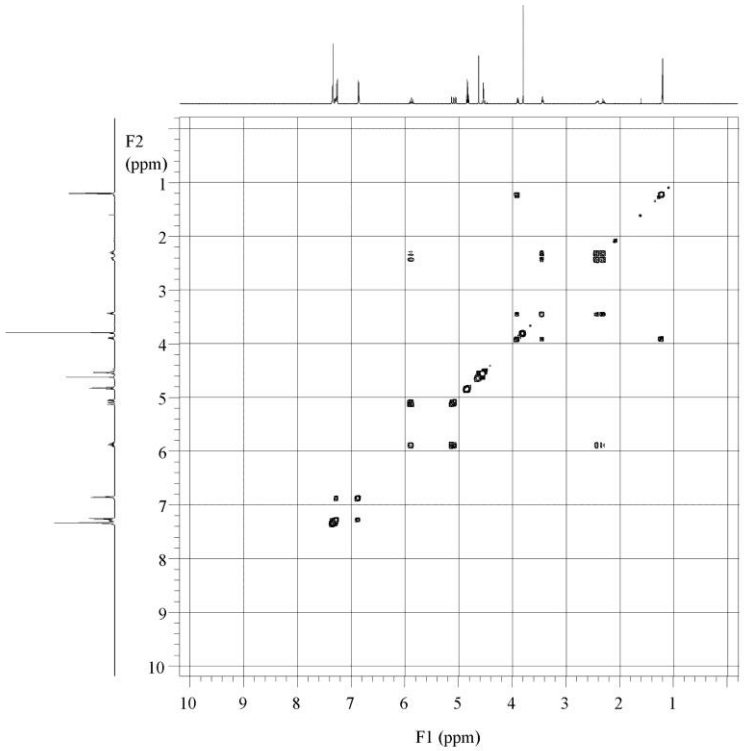

BOMO
H
O
CF3
MeO
Ph
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

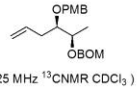

(500 MHz ^{1}HNMR $CDCl_3$)
(500 MHz ^{1}HNMR $CDCl_3$)
(500 MHz ^{1}HNMR $CDCl_3$)
10 9 8 7 6 5 4 3 2 1 ppm


OPMB
OBOM
(500 MHz ^{1}HNMR $CDCl_3$)
10 9 8 7 6 5 4 3 2 1 ppm
3.20 2.26
0.80 1.98
0.95
1.94 1.85
1.93 1.96
3.01
0.98 0.95
0.97
0.94
2.80

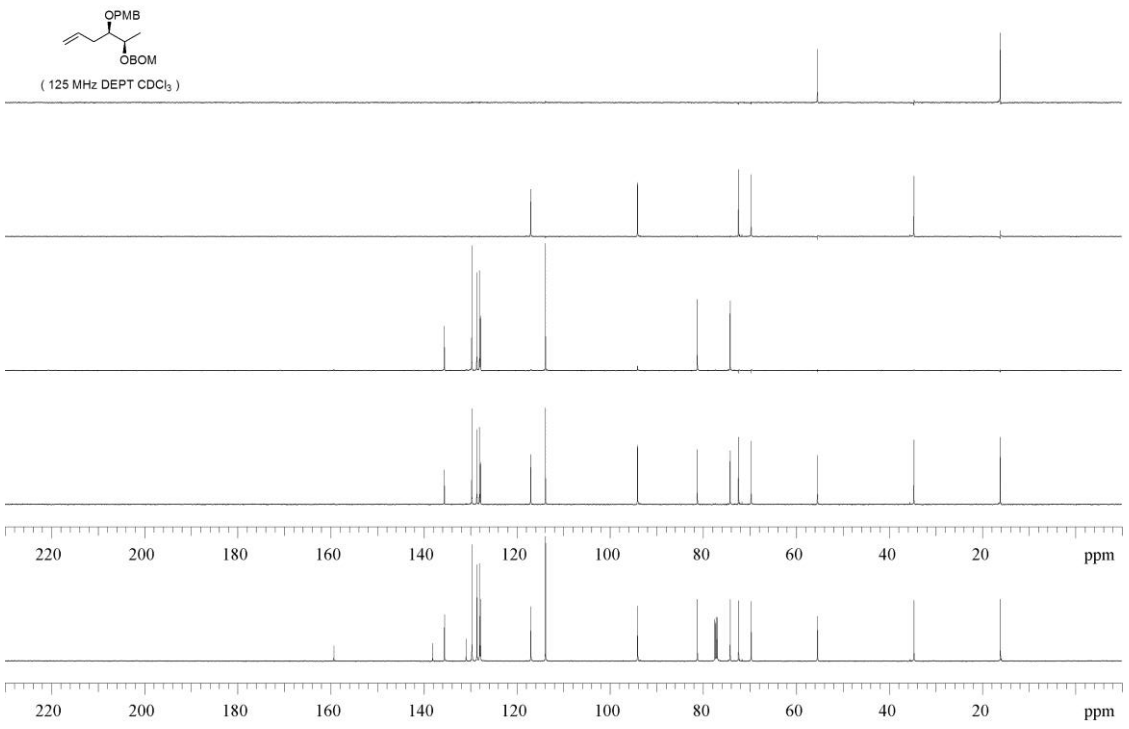


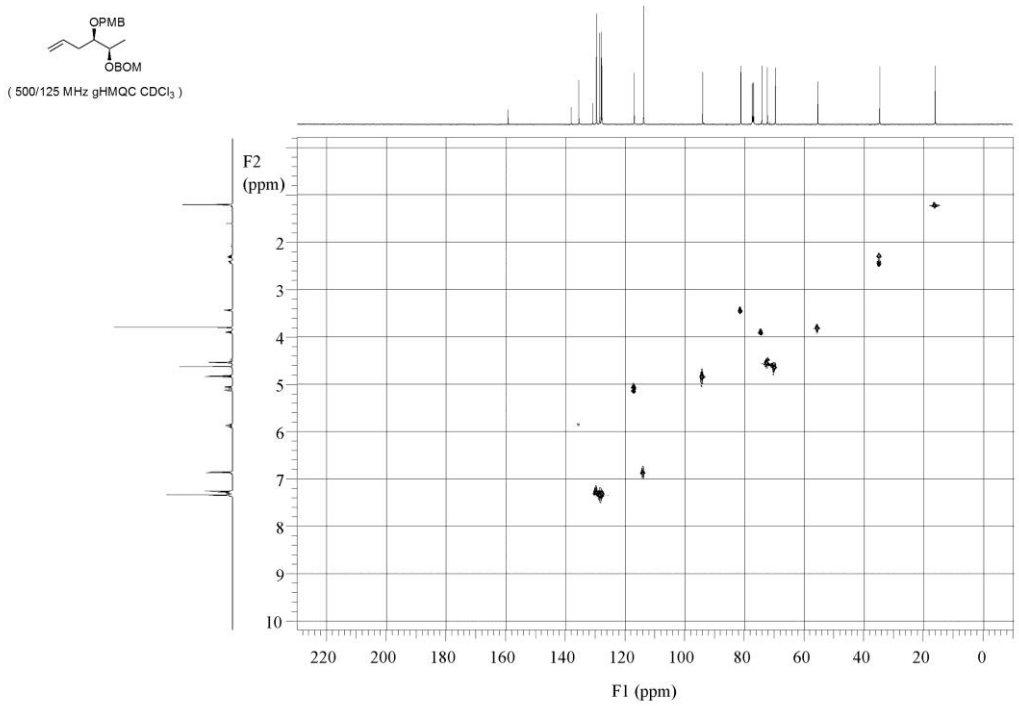
(500 MHz gCOSY $CDCl_3$)

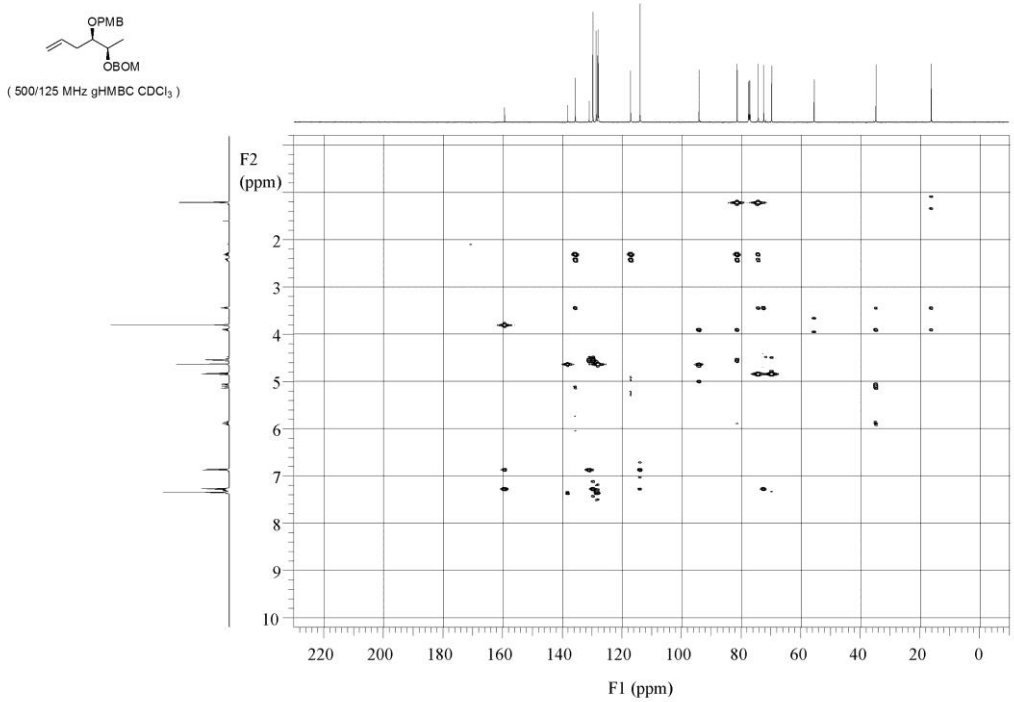


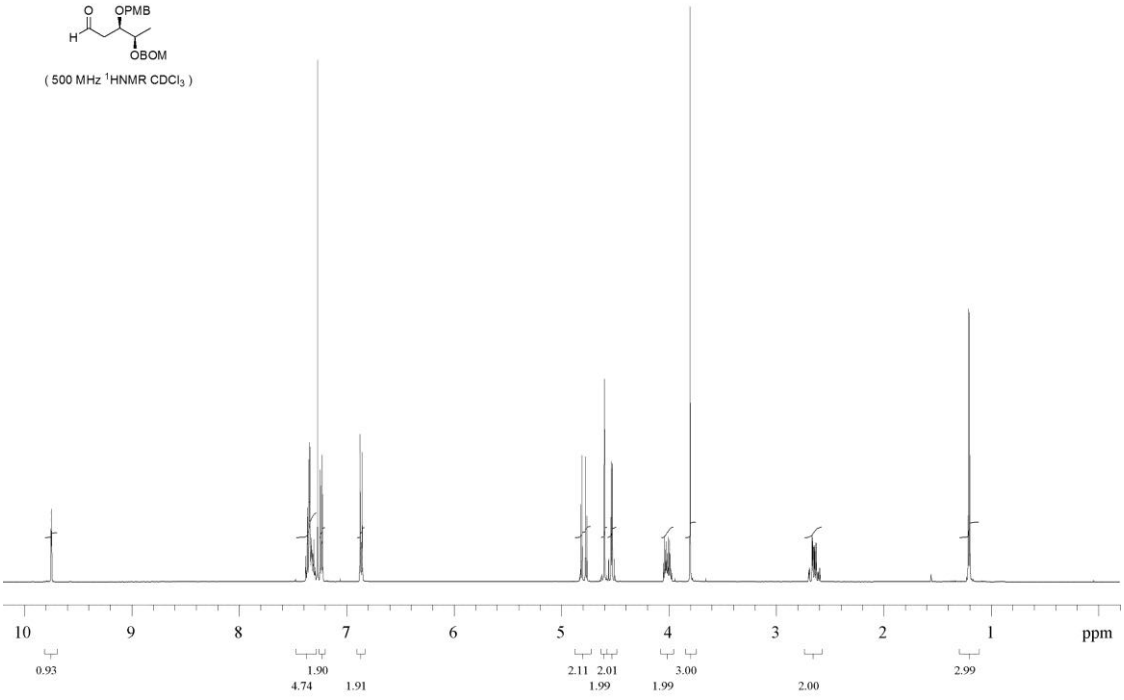


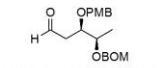
(125 MHz ^{13}CNMR $CDCl_3$)


OPMB
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

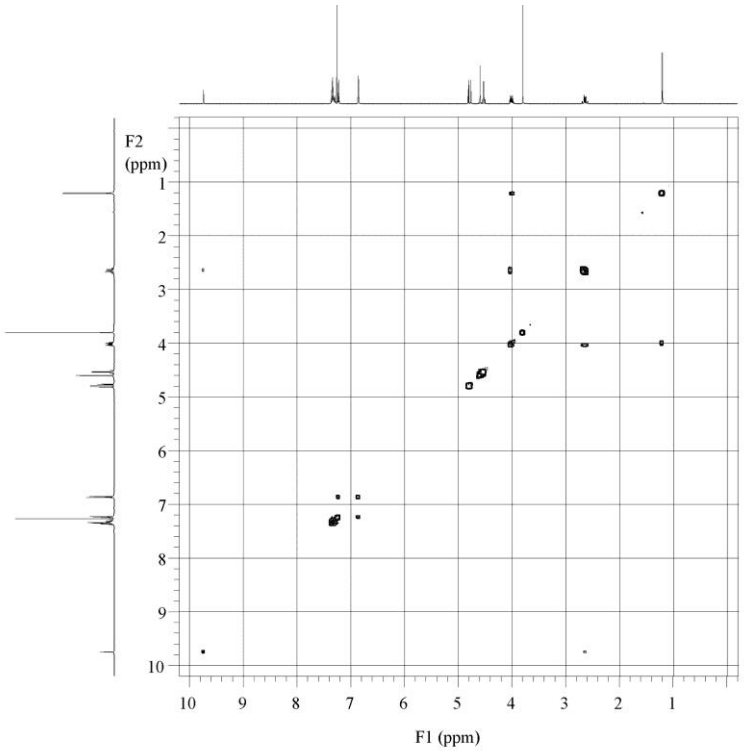

OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)


OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

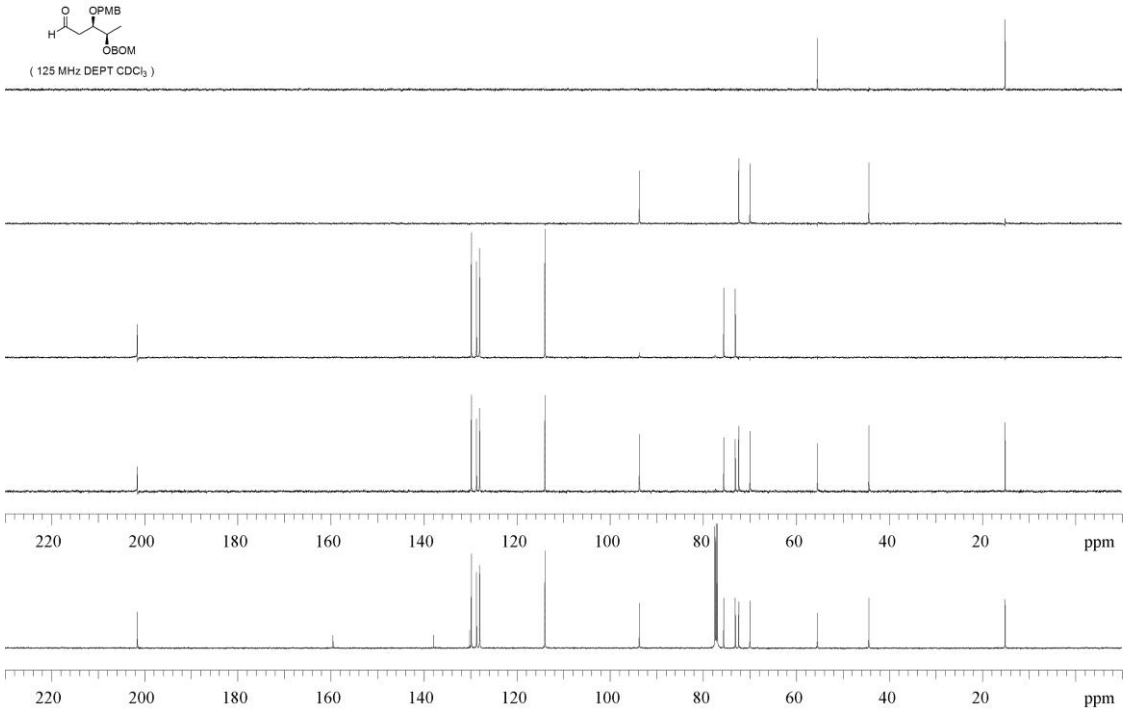

O
OPMB
H
OBOM
(500 MHz 1HNMR CDCl3)
ppm
0.93
1.90
4.74
1.91
2.11
2.01
1.99
1.99
3.00
2.00
2.99

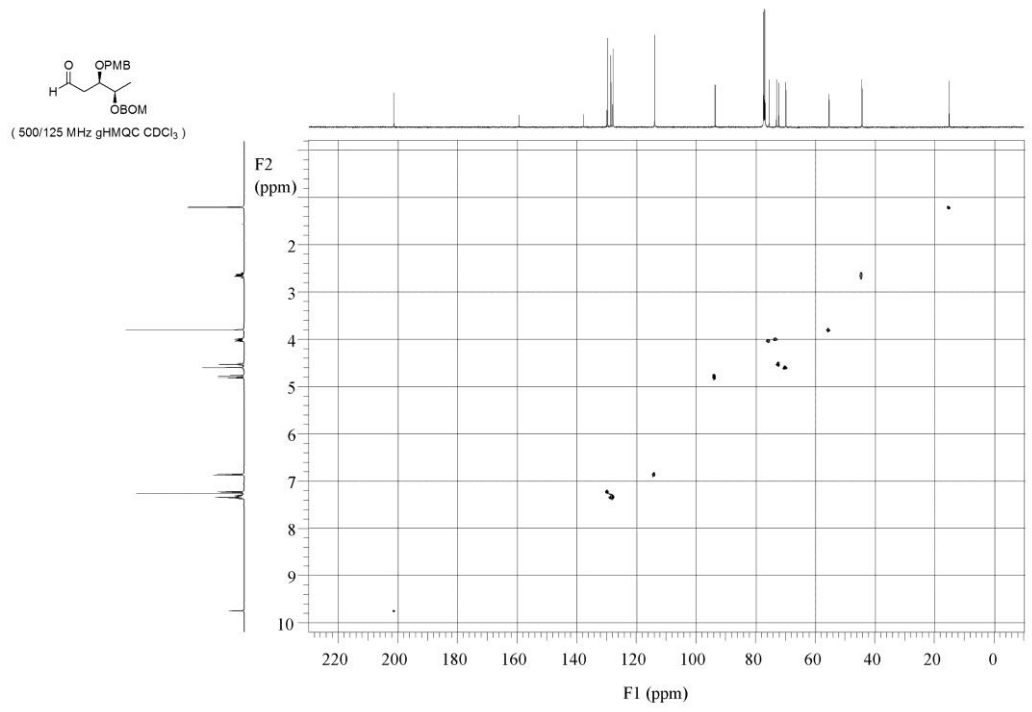


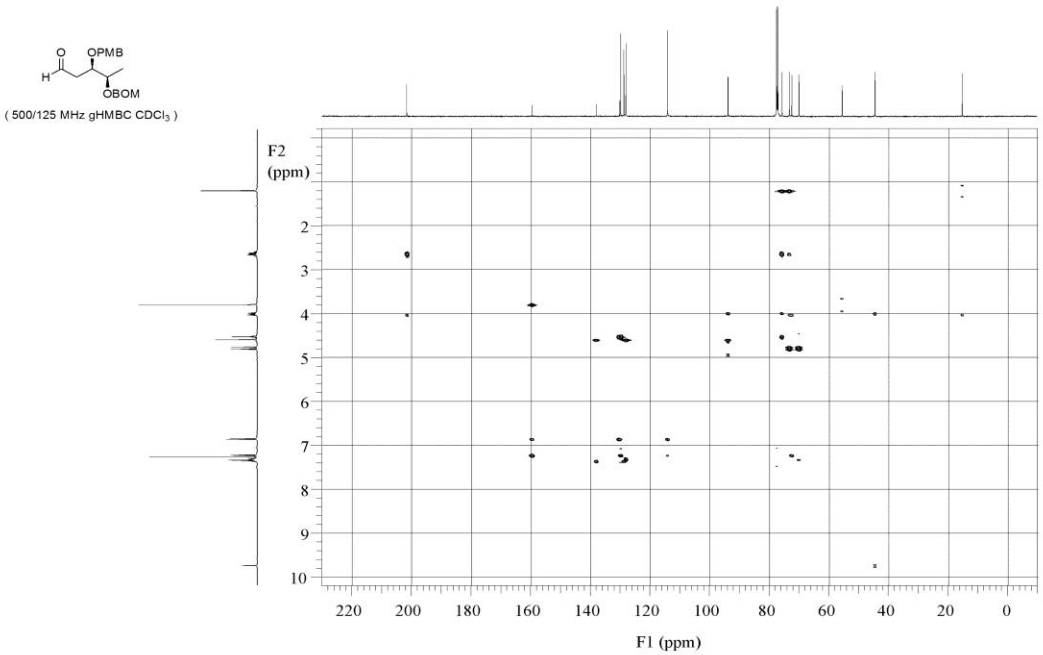
(500 MHz gCOSY $CDCl_3$)

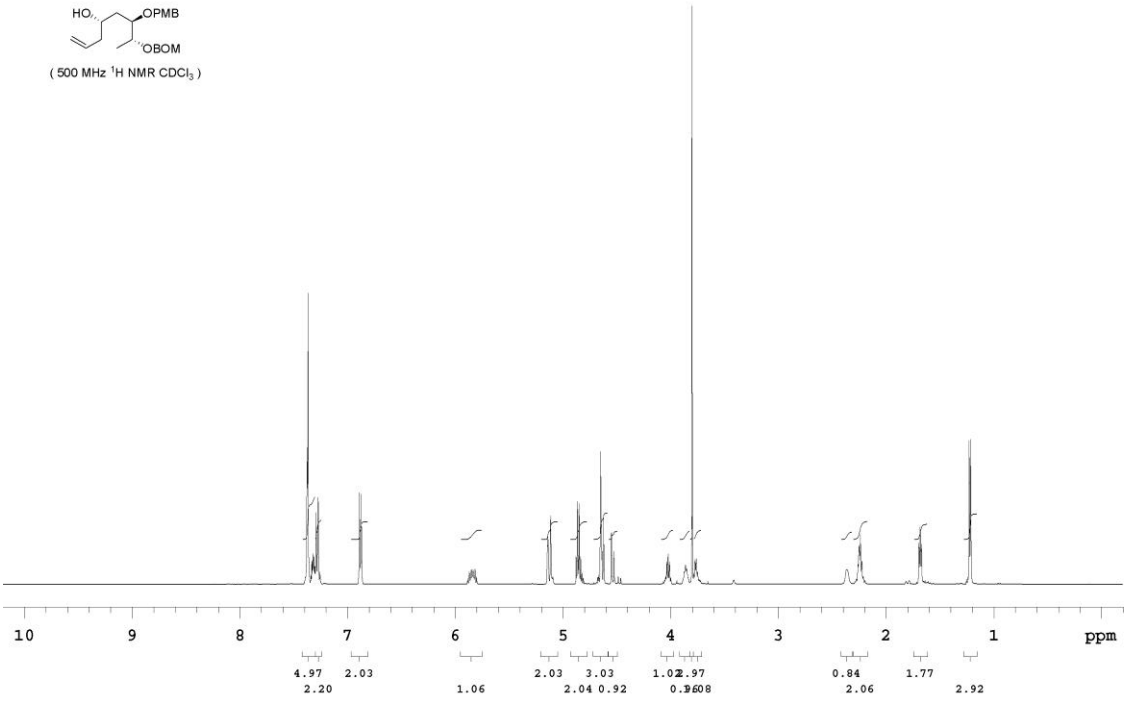


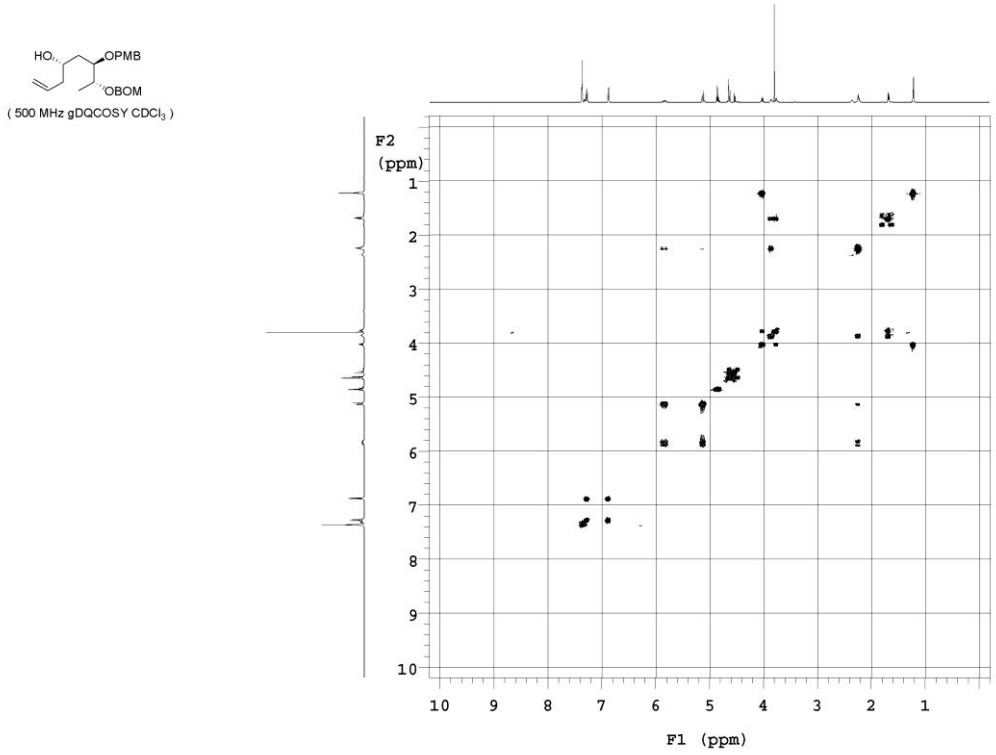
(125 MHz ^{13}CNMR $CDCl_3$)

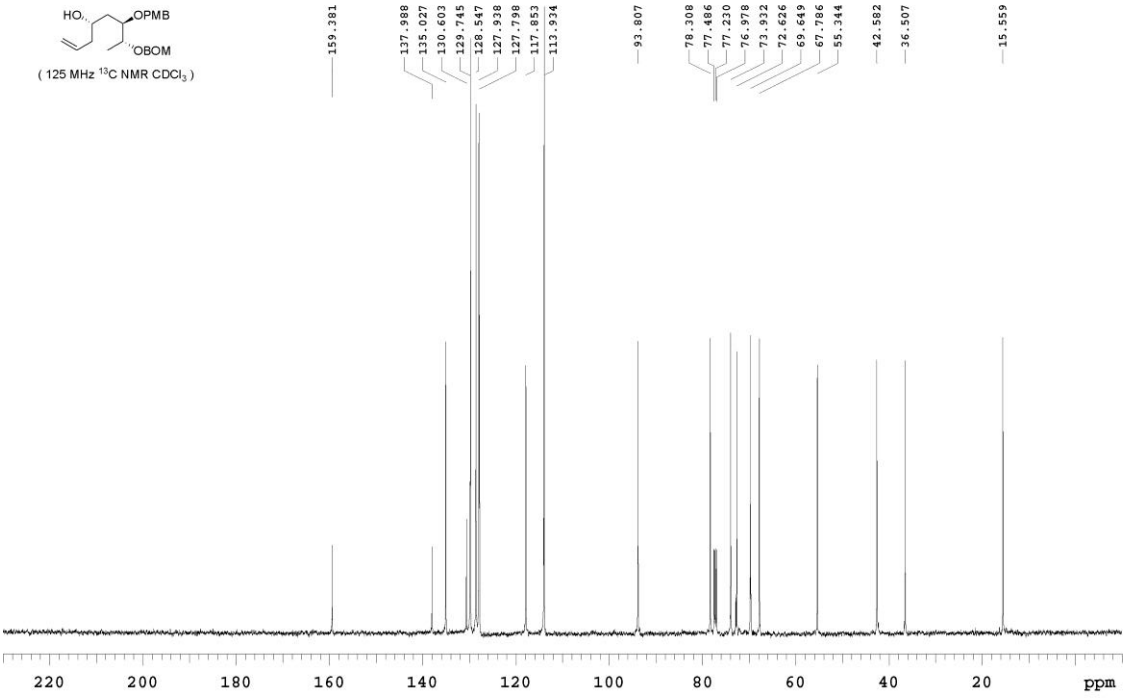

OPMB
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

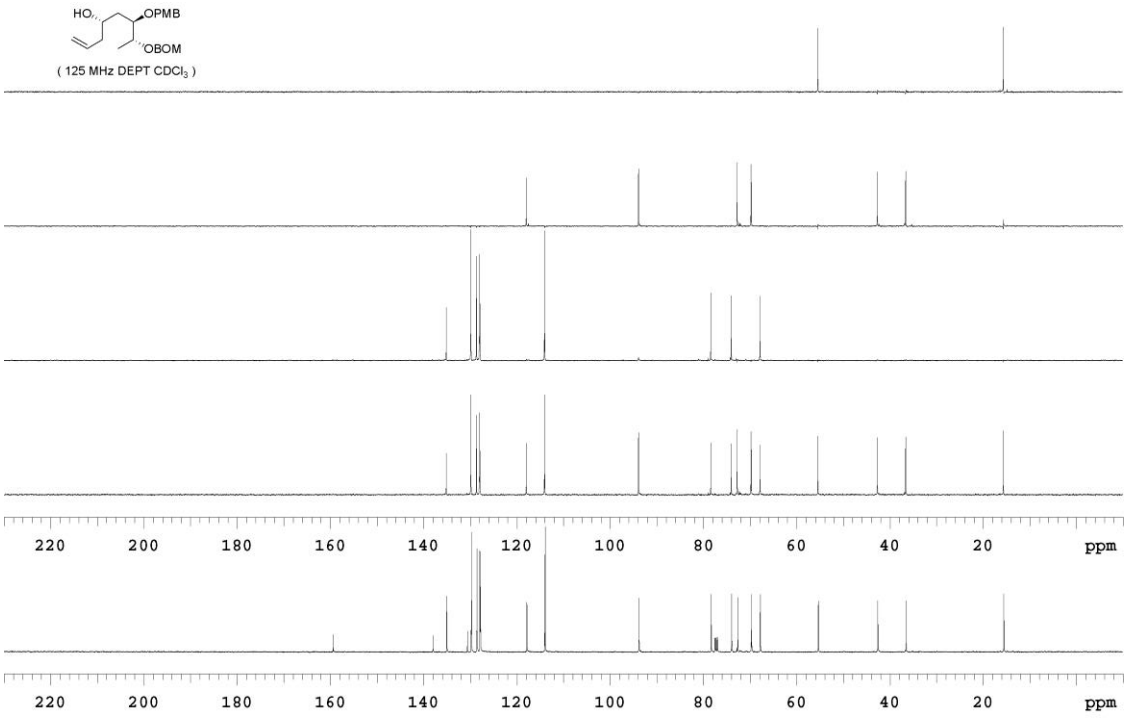

OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

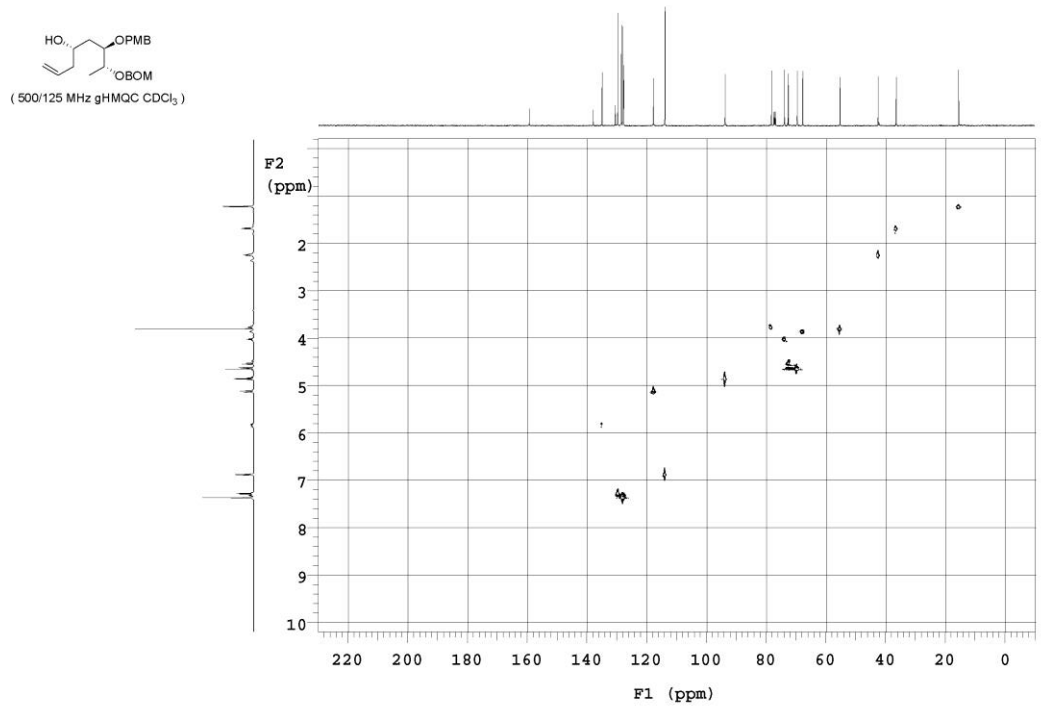

OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

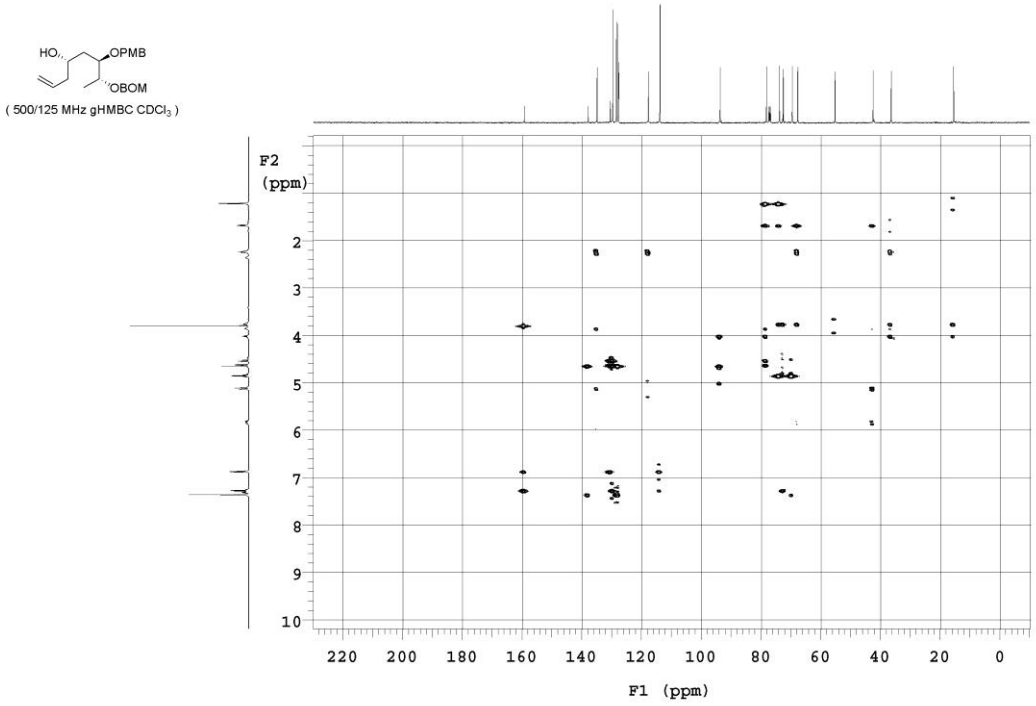

HO
OPMB
OBOM
(500 MHz 1H NMR CDCl3)
ppm
4.97
2.03
2.03
3.03
1.02
2.97
0.84
1.77
2.20
1.06
2.04
0.92
2.06
2.92

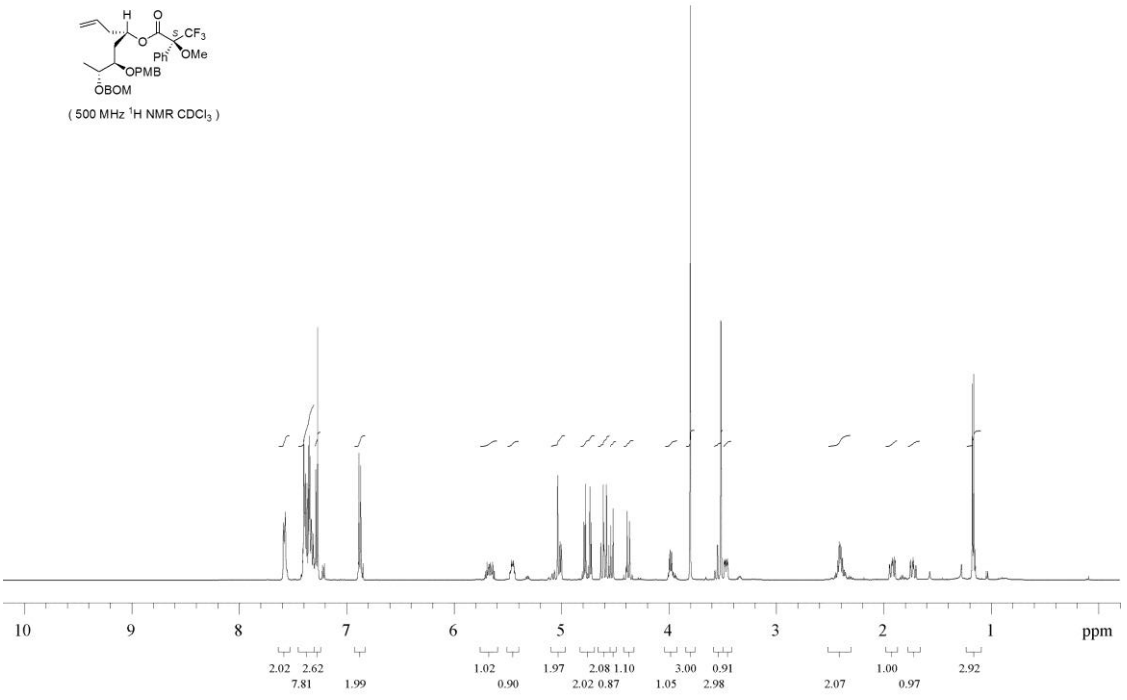

HO
OPMB
OBOM
(500 MHz gDQCOSY CDCl3)
F2 (ppm)
F1 (ppm)

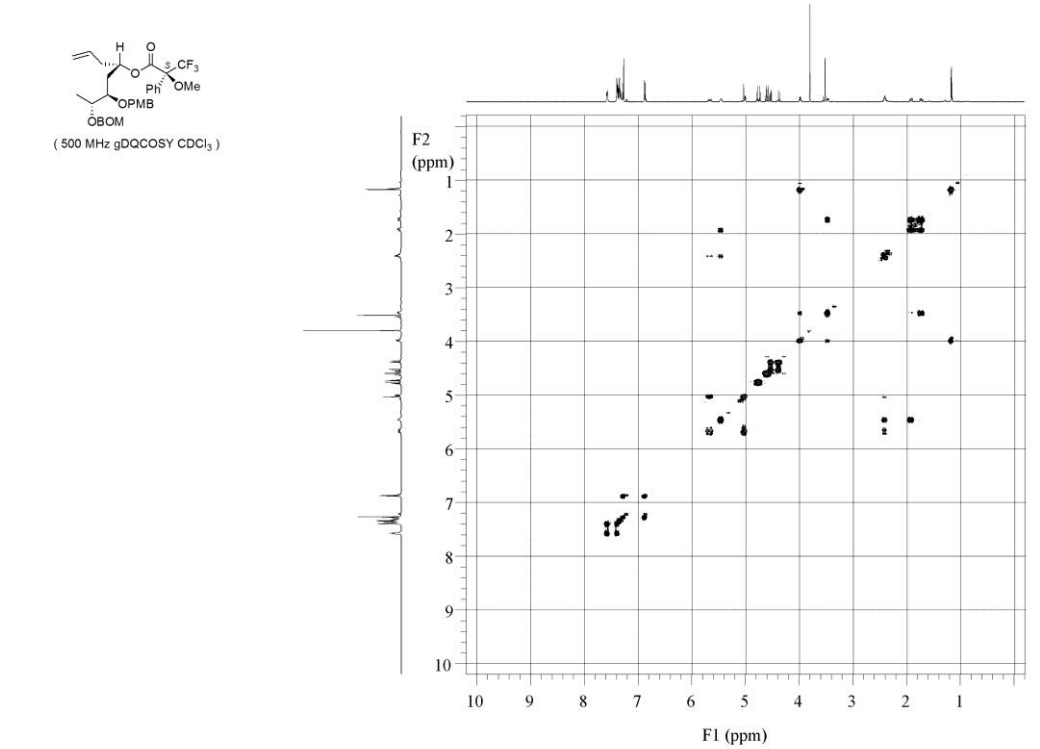

HO
OPMB
OBOM
(125 MHz 13C NMR CDCl3)
159.381
137.988
135.027
130.603
129.745
128.547
127.938
127.798
117.853
113.934
93.807
78.308
77.486
77.230
76.978
73.932
72.626
69.649
67.786
55.344
42.582
36.507
15.559
ppm

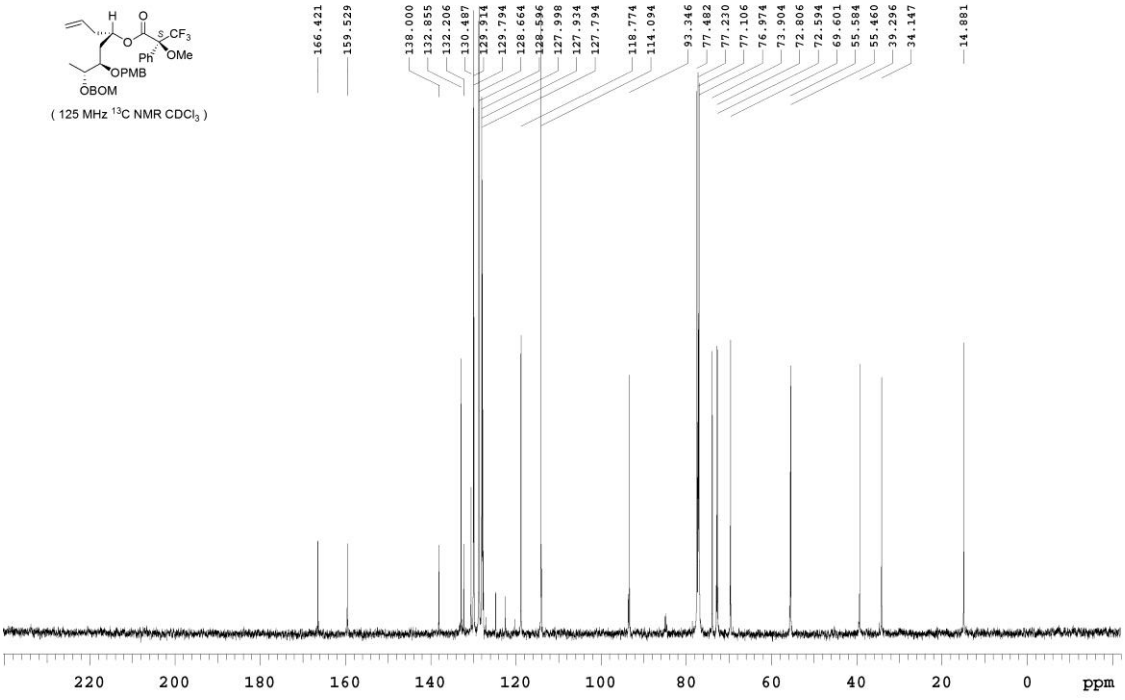

HO
OPMB
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm


HO
OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)


HO
OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2 (ppm)
F1 (ppm)


H
O
CF3
Ph
OMe
OPMB
OBOM
(500 MHz 1H NMR CDCl3)
ppm
2.02 2.62 1.99 1.02 0.90 1.97 2.02 2.08 0.87 1.10 1.05 3.00 2.98 0.91 2.07 1.00 0.97 2.92
7.81


H
O
S
CF3
Ph
OMe
OPMB
OBOM
(500 MHz gDQCOSY CDCl3)
F2
(ppm)
F1 (ppm)


H
O
S
CF3
Ph
OMe
OPMB
OBOM
(125 MHz 13C NMR CDCl3)
166.421
159.529
138.000
132.855
132.206
130.487
129.914
129.794
128.664
128.596
127.998
127.934
127.794
118.774
114.094
93.346
77.482
77.230
77.106
76.974
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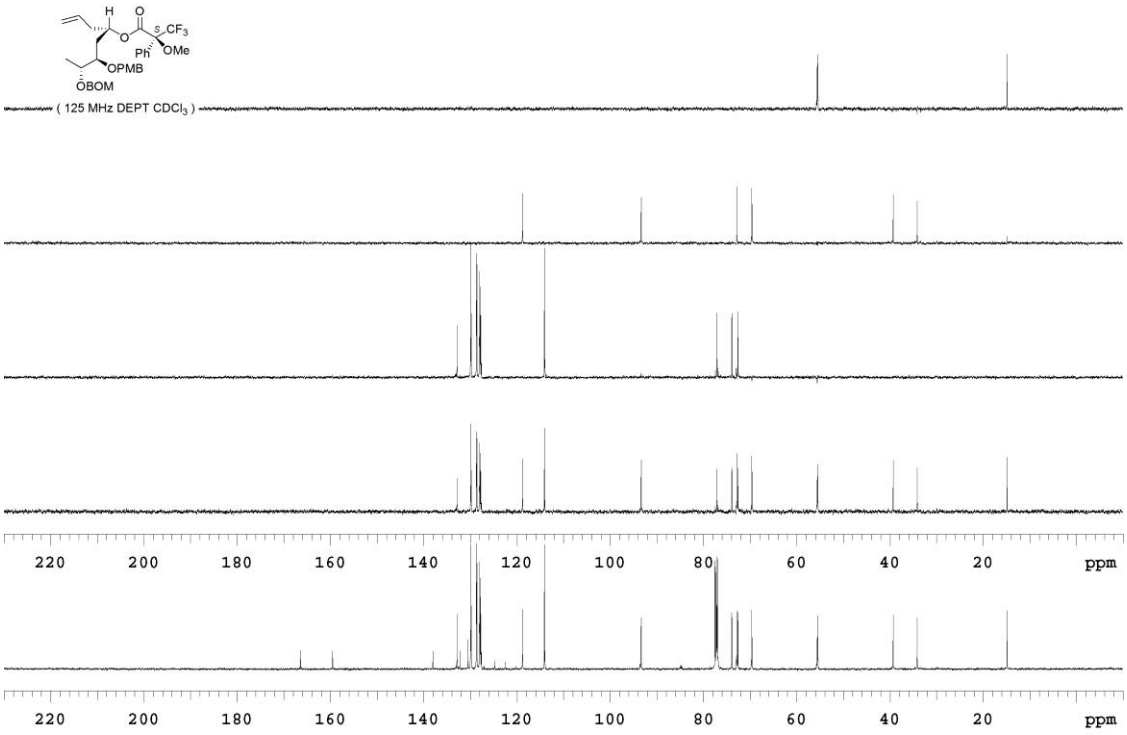
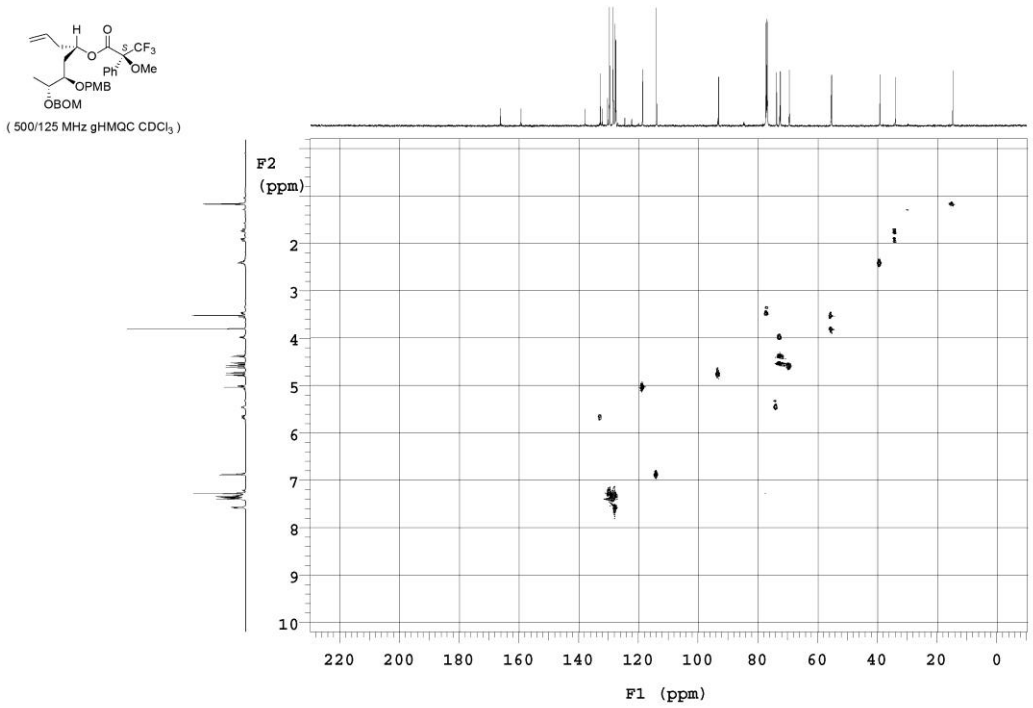
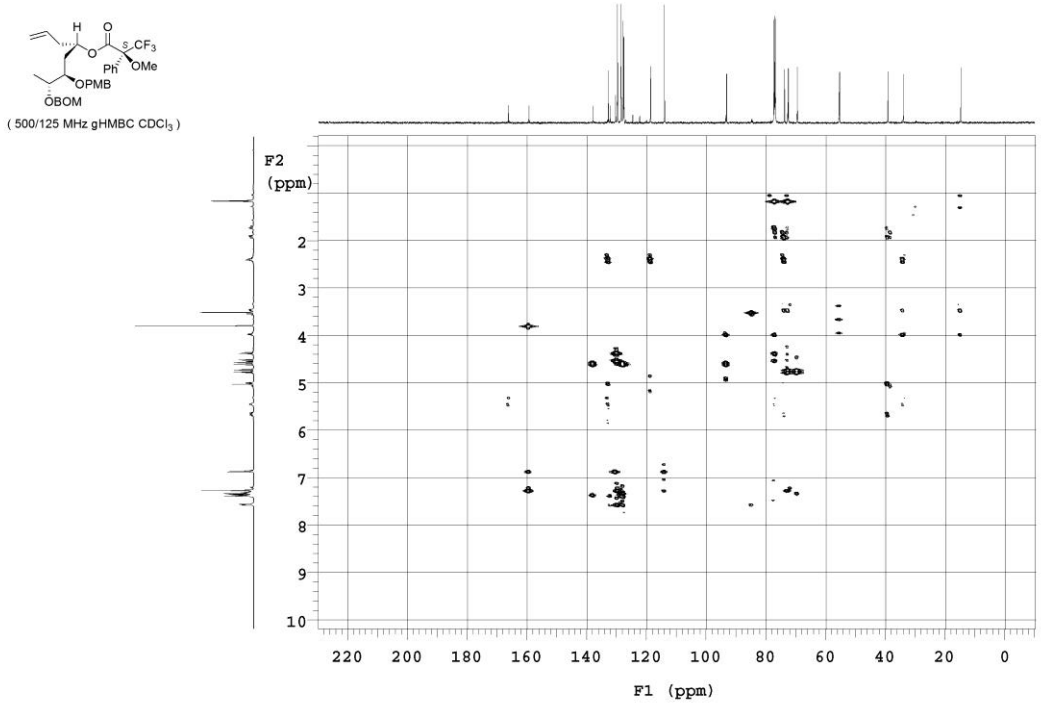
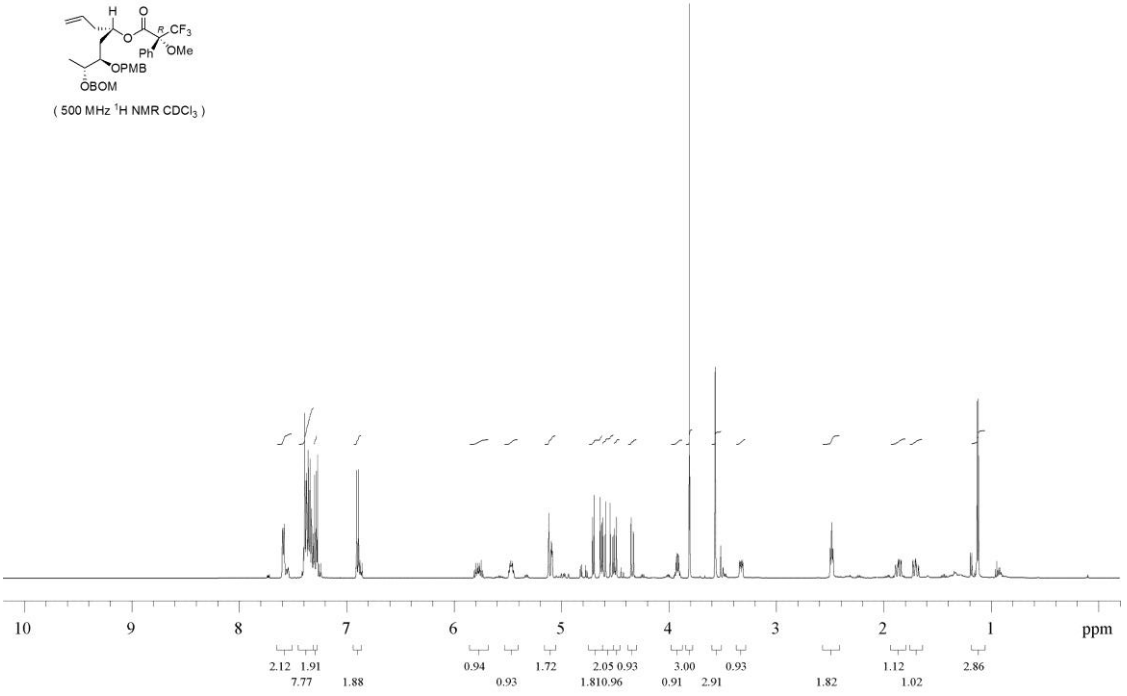
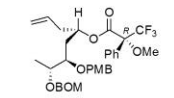
69.601
55.584
55.460
39.296
34.147
14.881
ppm


(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

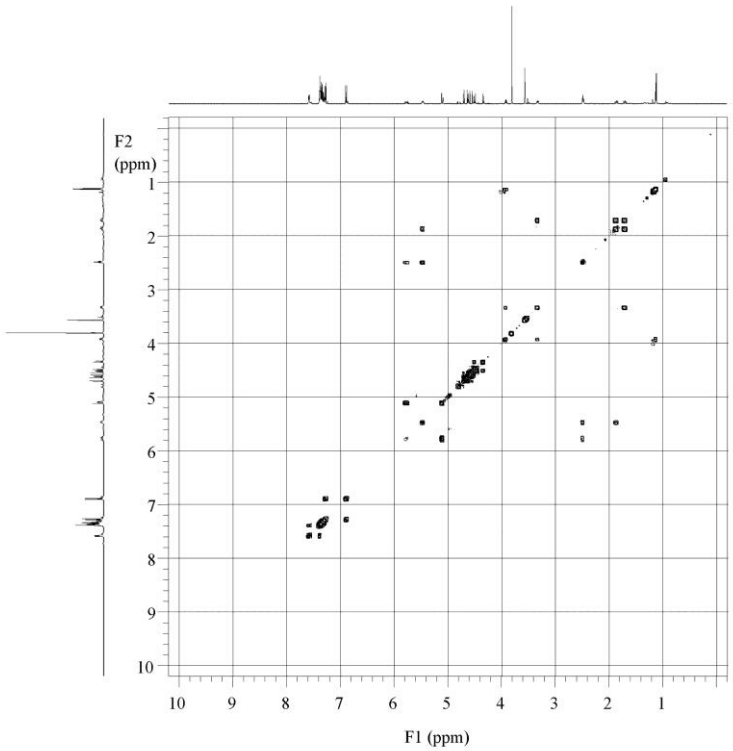

(500/125 MHz gHMQC CDCl3)
F2 (ppm)
F1 (ppm)

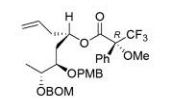

(500/125 MHz gHMBC $CDCl_3$)
F2 (ppm)
F1 (ppm)


(500 MHz ^1H NMR $CDCl_3$)
ppm
2.12 1.91 7.77 1.88 0.94 0.93 1.72 2.05 0.93 1.81 0.96 3.00 0.91 2.91 0.93 1.82 1.12 1.02 2.86

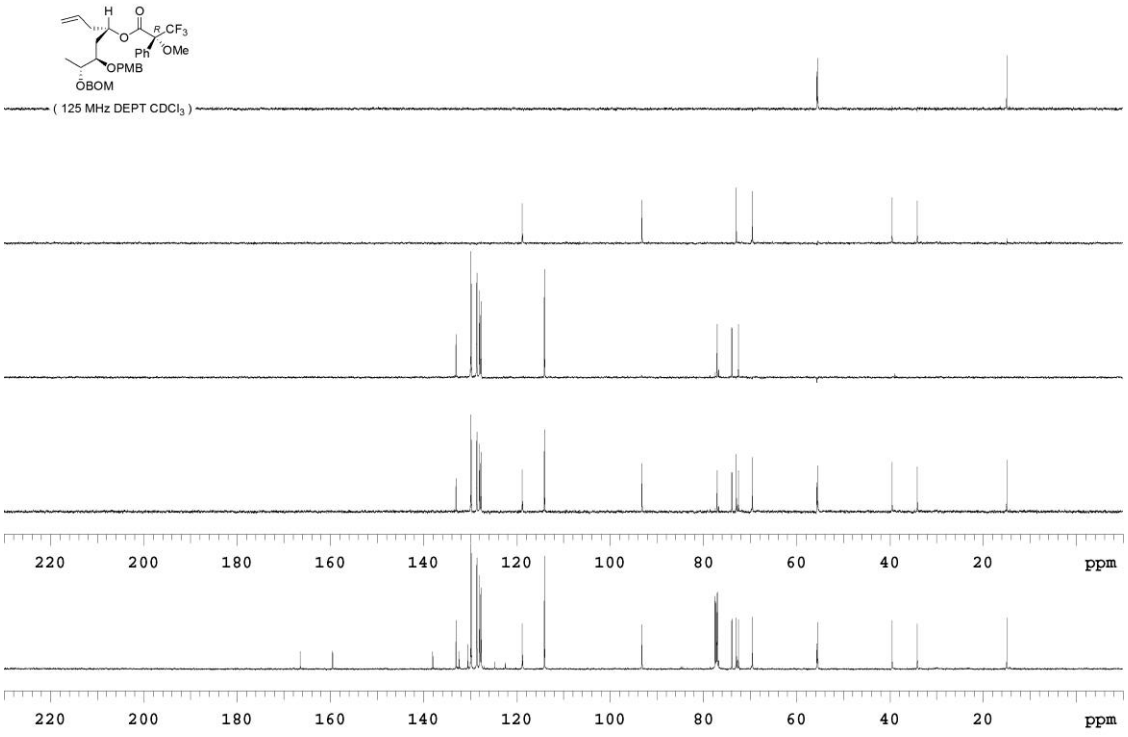


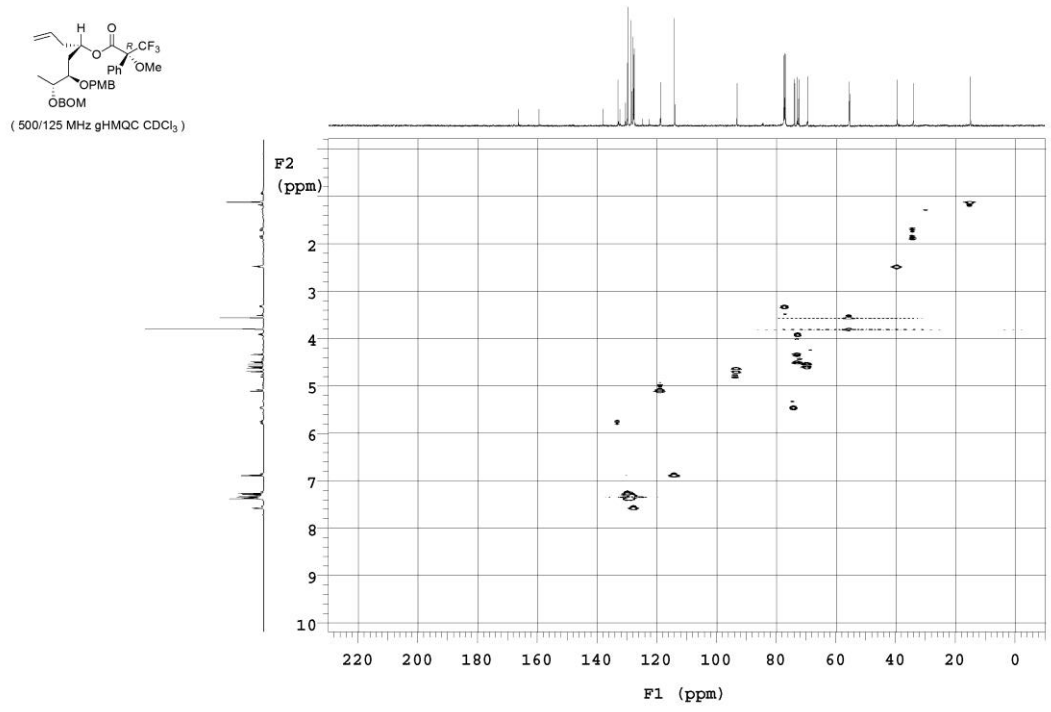
(500 MHz gCOSY $CDCl_3$)

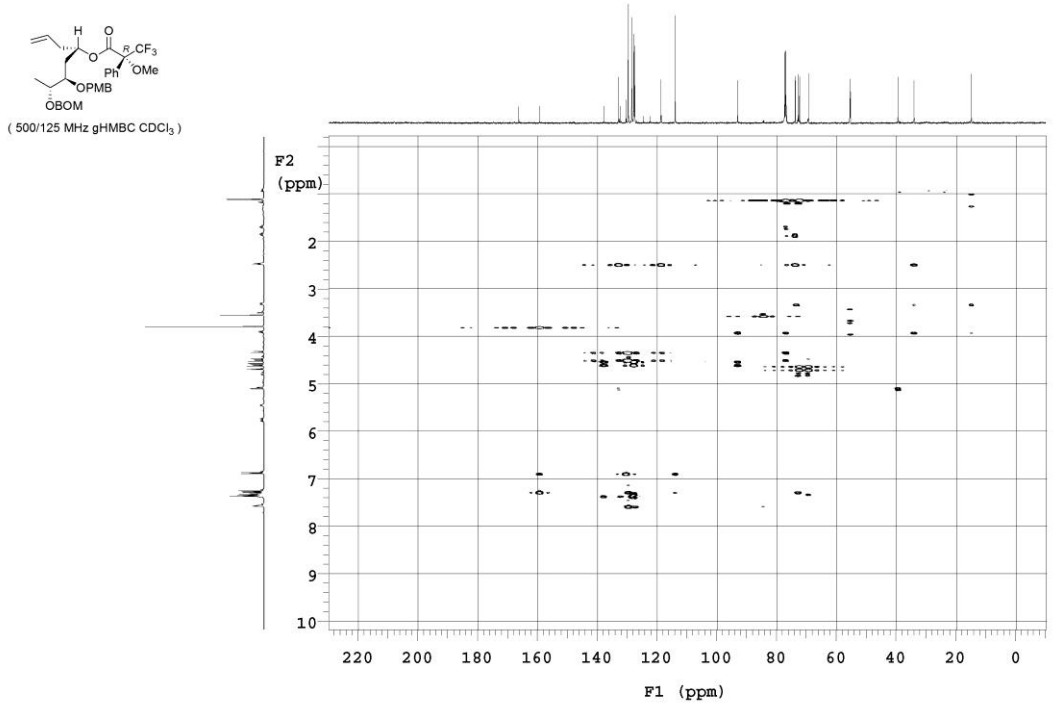


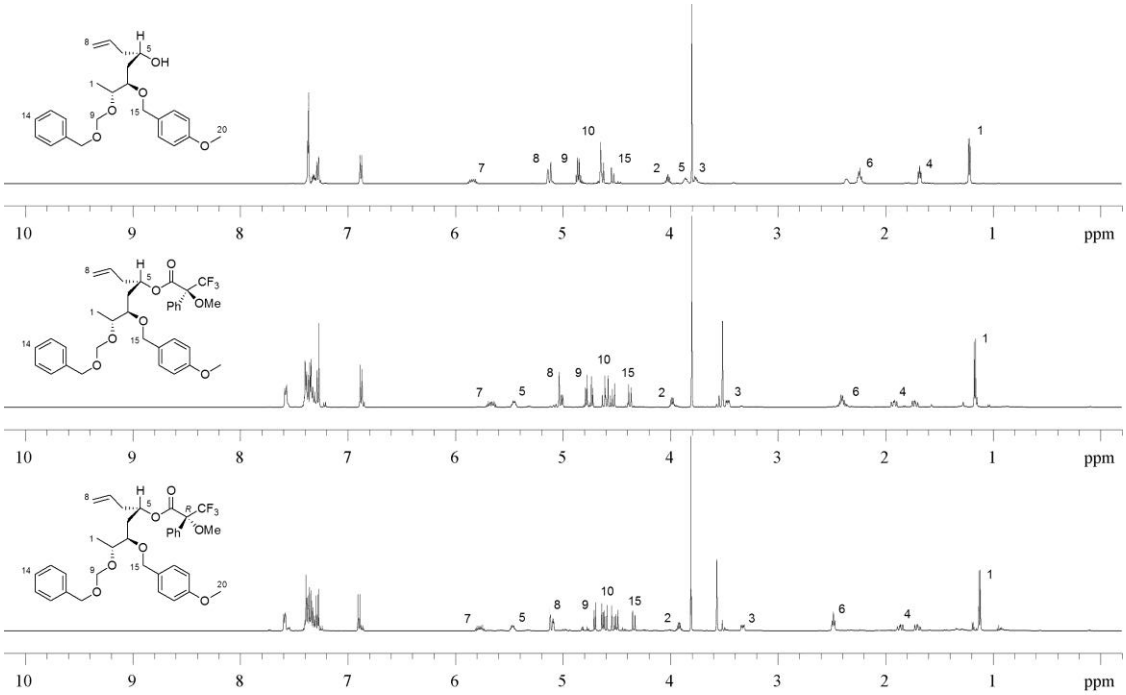


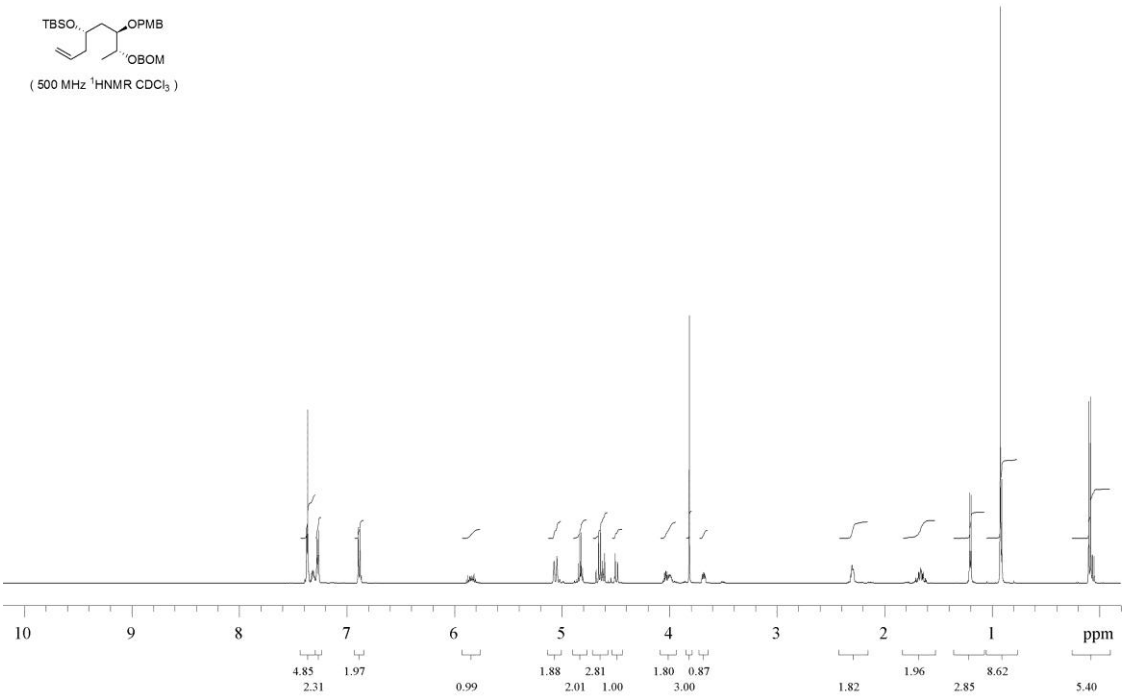
(125 MHz ^{13}C NMR $CDCl_3$)

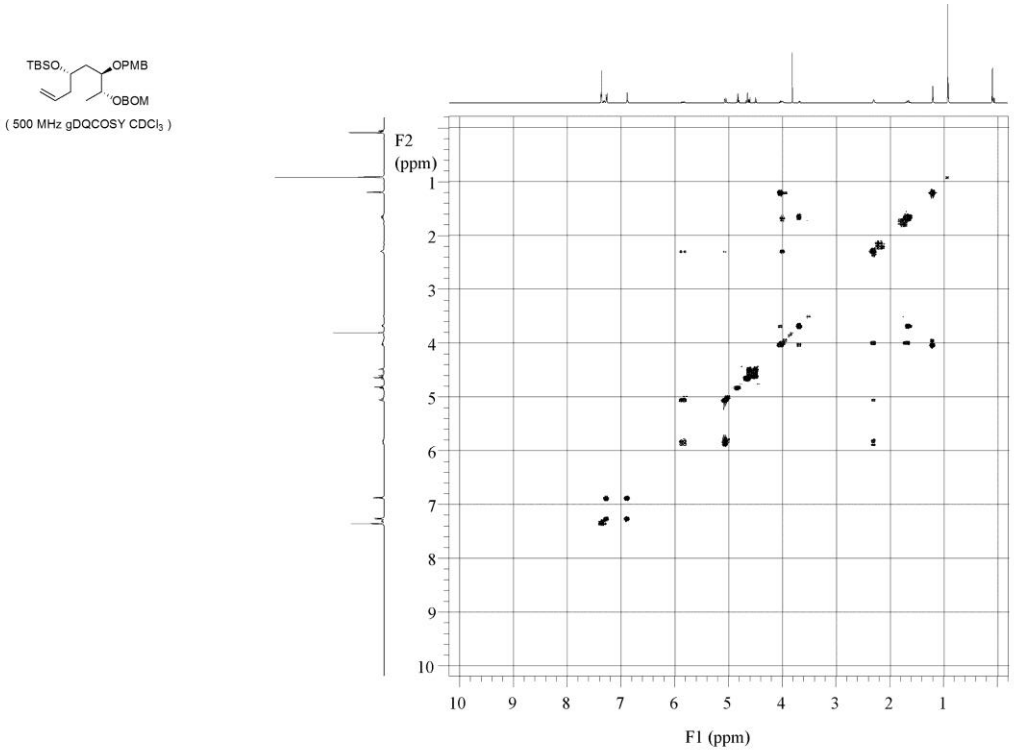

(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

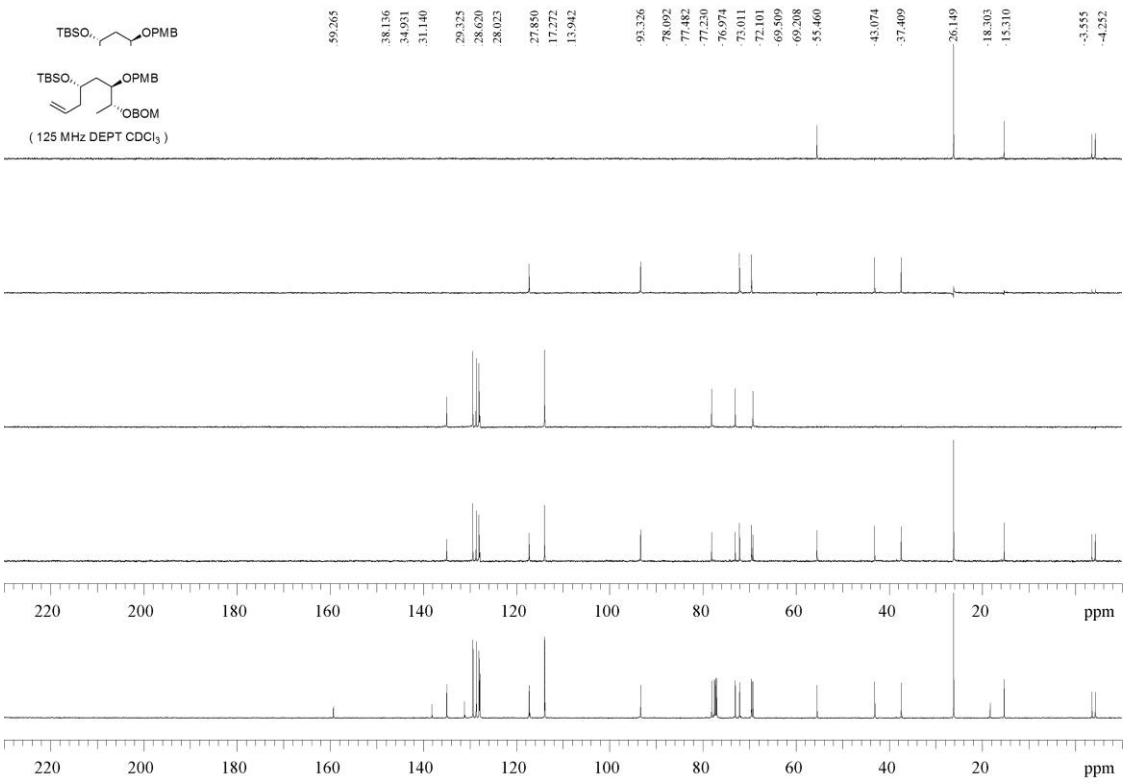

(500/125 MHz gHMQC CDCl3)
F2 (ppm)
F1 (ppm)

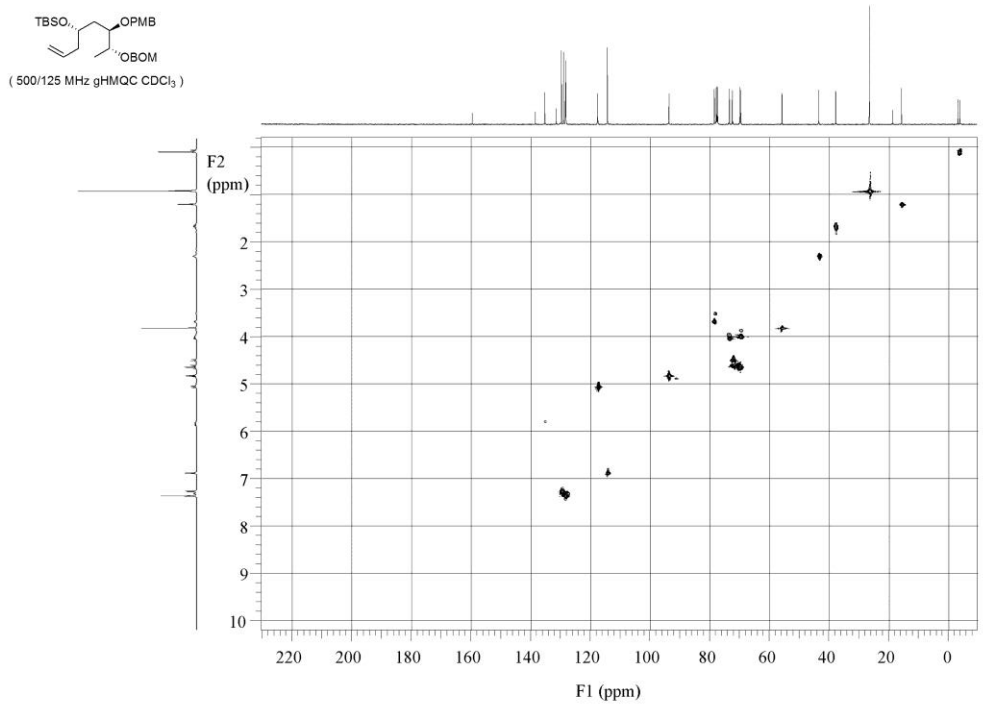

(500/125 MHz gHMBC CDCl3)
F2 (ppm)
F1 (ppm)

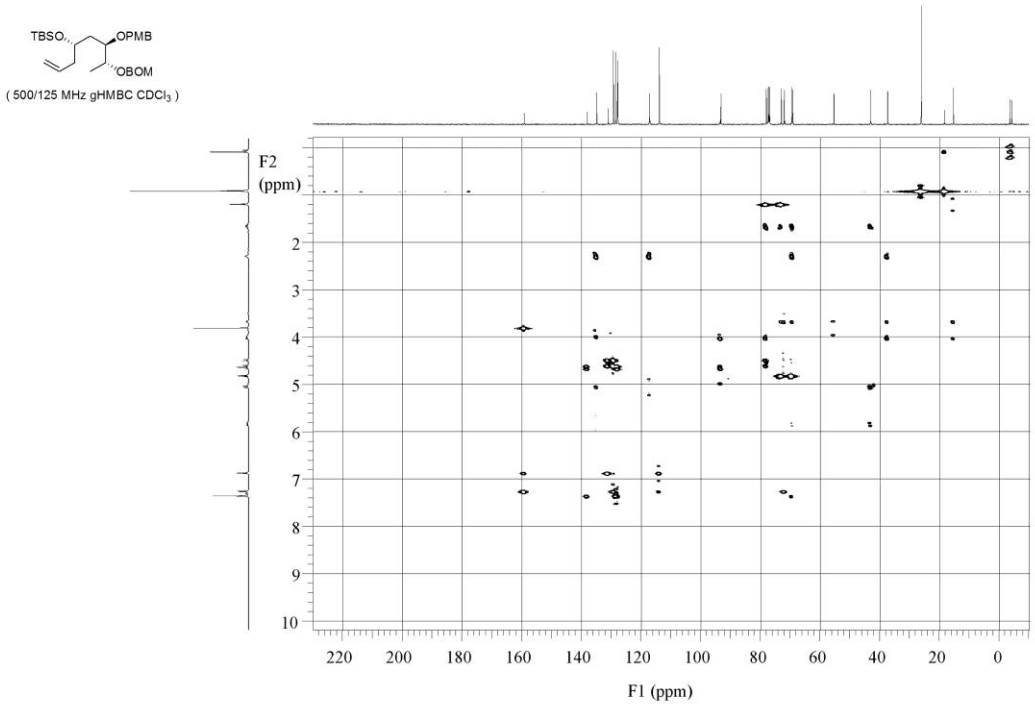

ppm

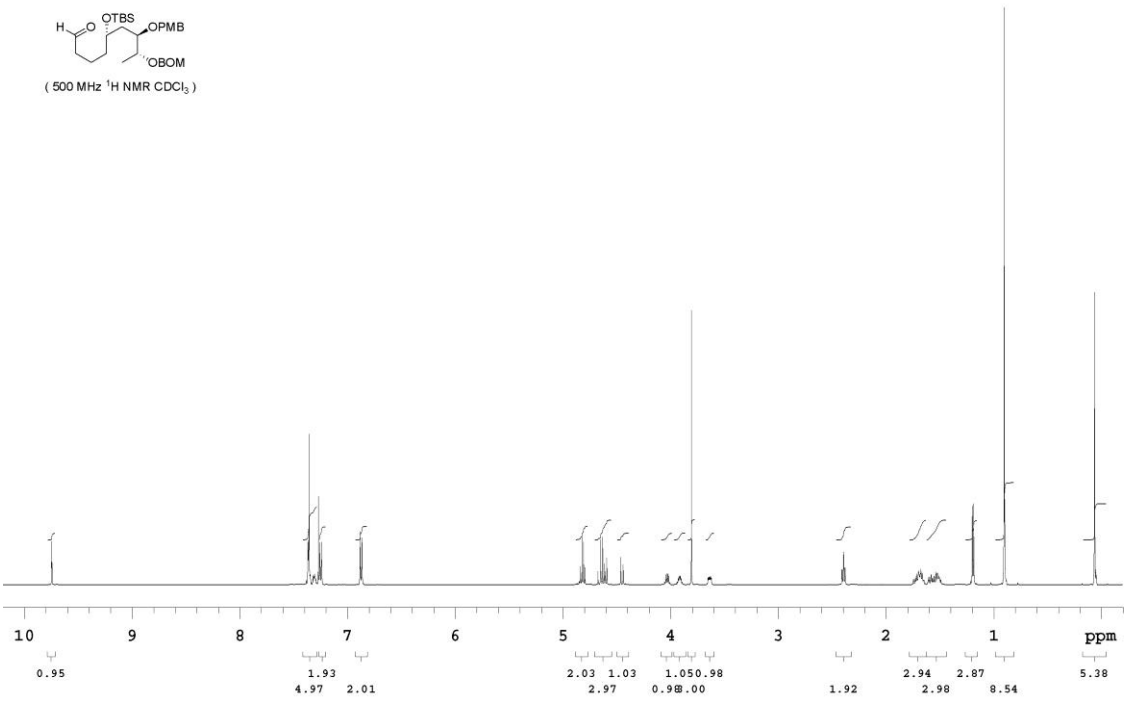

TBSO
OPMB
OBOM
(500 MHz ^{1}HNMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
4.85
1.97
1.88
2.81
1.80
0.87
1.96
8.62
2.31
0.99
2.01
1.00
3.00
1.82
2.85
5.40

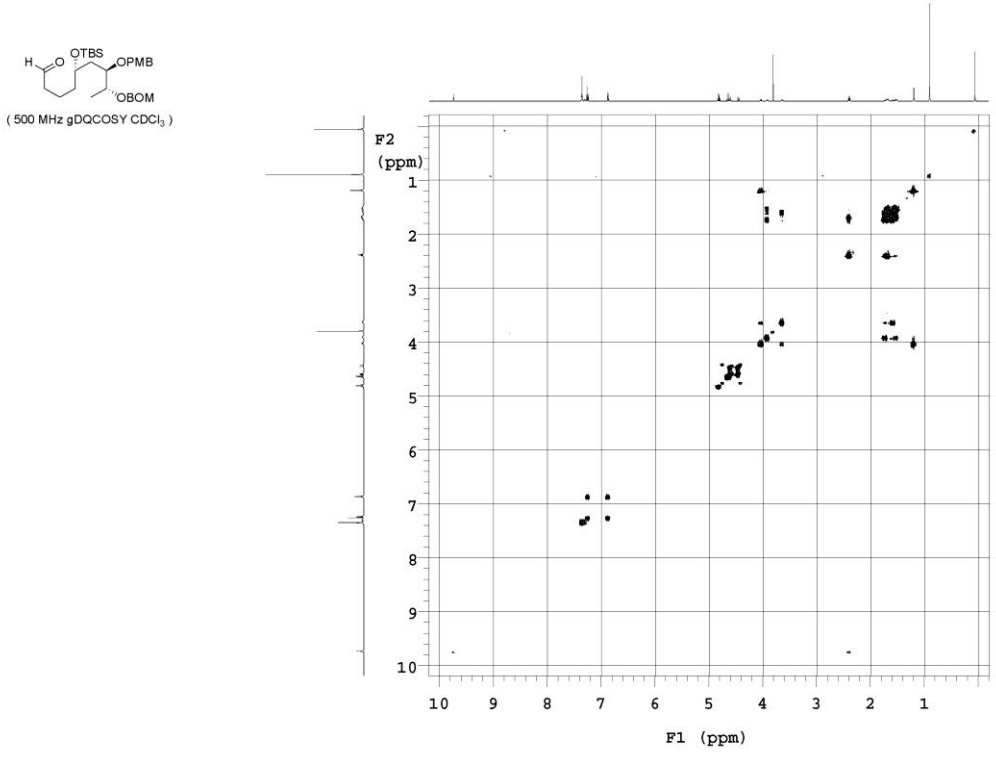

TBSO
OPMB
OBOM
(500 MHz gDQCOSY $CDCl_3$)
F2
(ppm)
F1 (ppm)

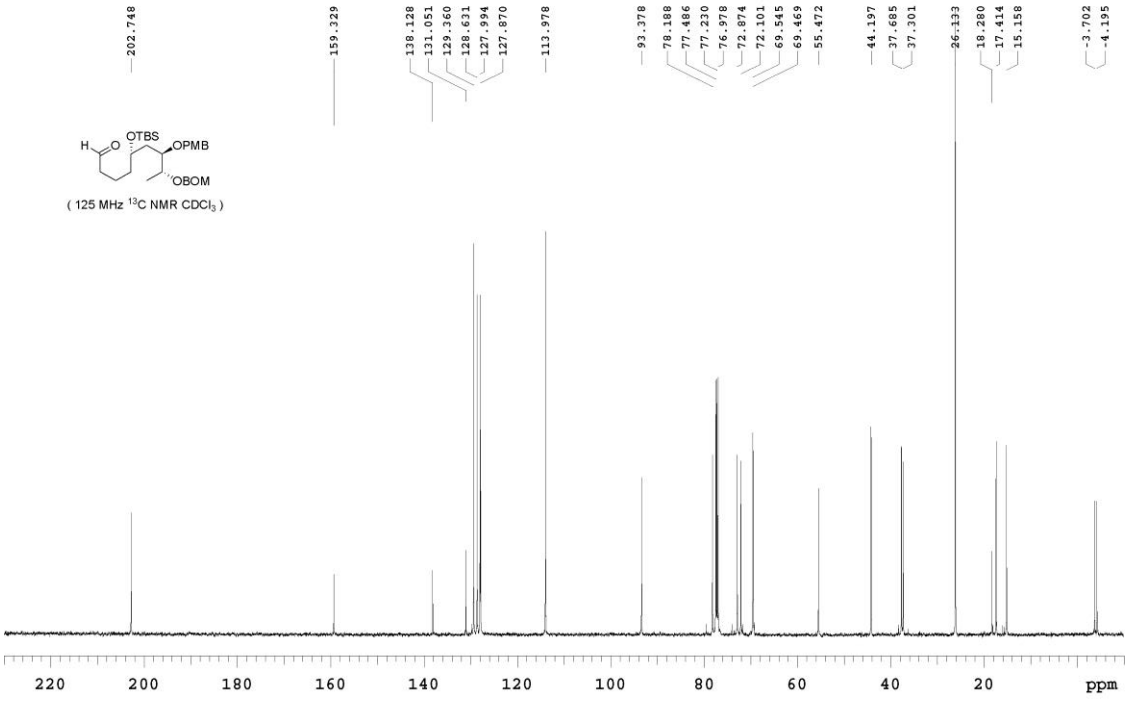

TBSO
OPMB
TBSO
OPMB
OBOM
(125 MHz DEPT CDCl3)
59.265
38.136
34.931
31.140
29.325
28.620
28.023
27.850
17.272
13.942
93.326
78.092
77.482
77.230
76.974
73.011
72.101
69.509
69.208
55.460
43.074
37.409
26.149
18.303
15.310
-3.555
-4.252
220
200
180
160
140
120
100
80
60
40
20
ppm

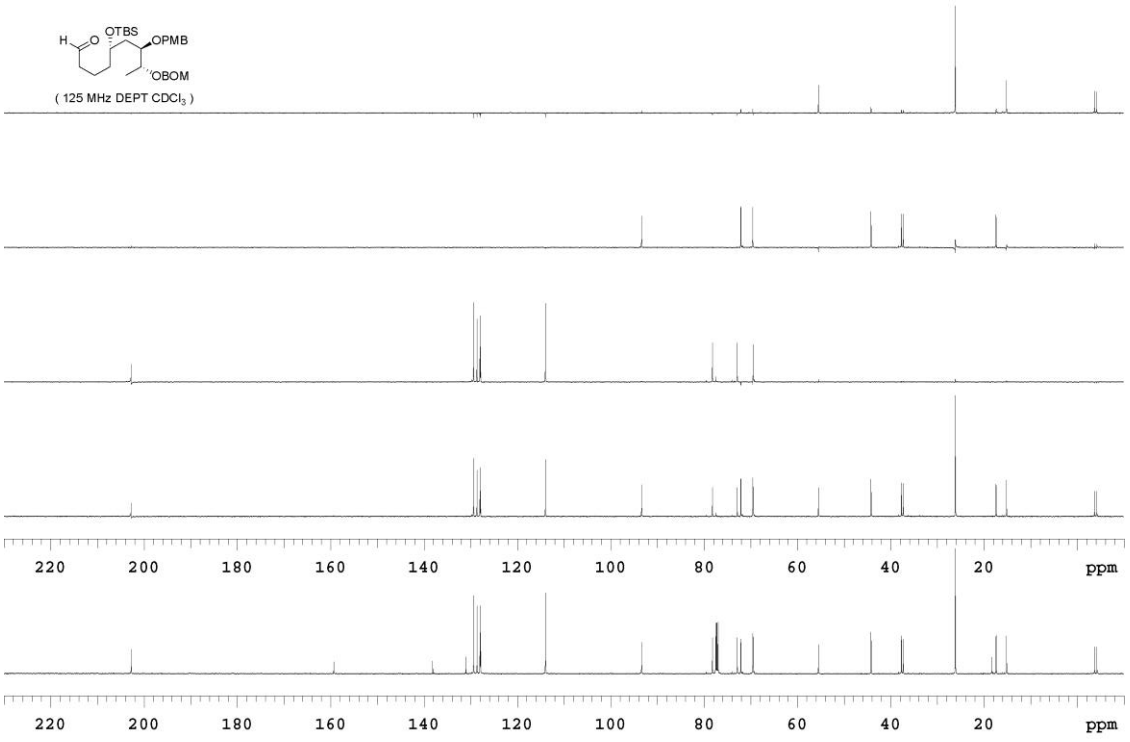

TBSO
OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

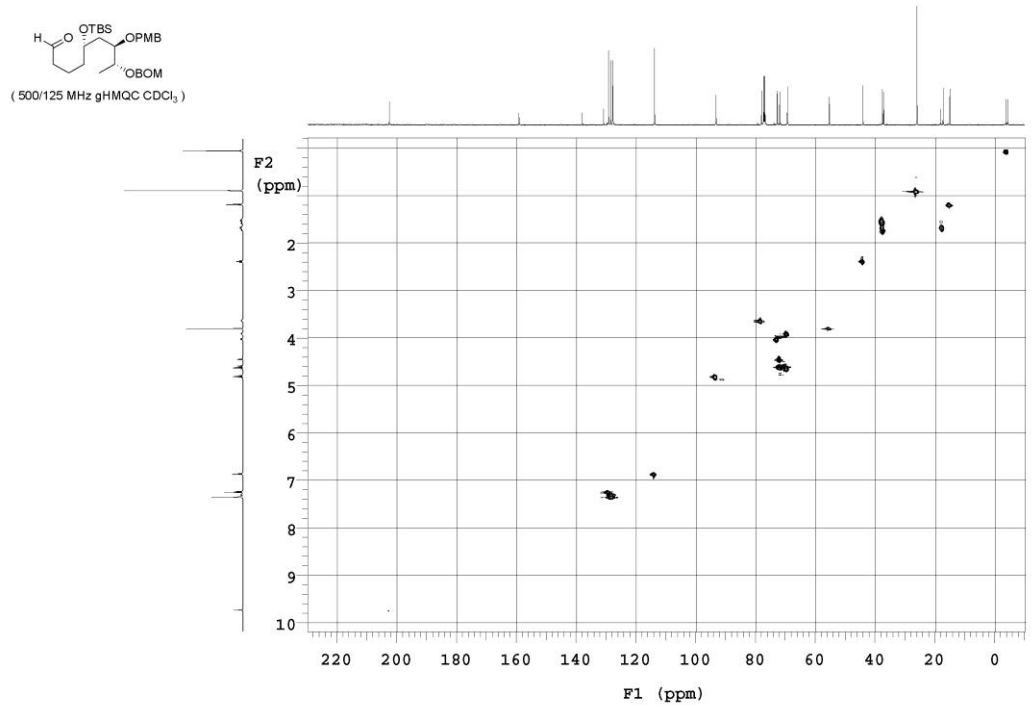

TBSO
OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

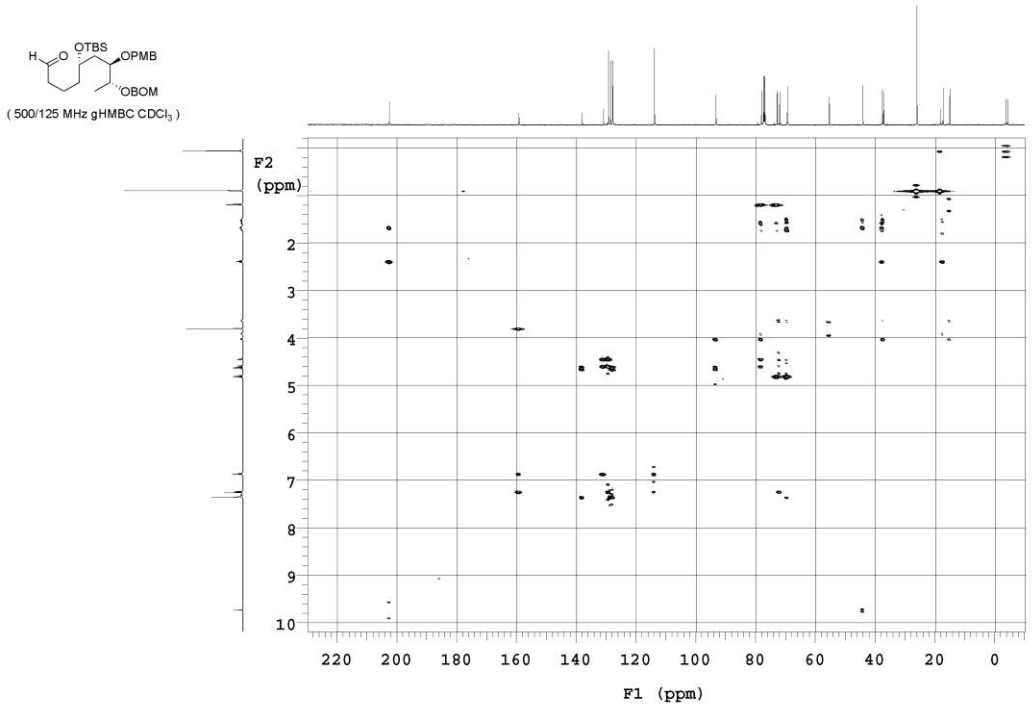

OTBS
OPMB
OBOM
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
0.95
1.93
4.97
2.01
2.03
1.03
2.97
1.05
0.98
8.00
1.92
2.94
2.98
2.87
8.54
5.38

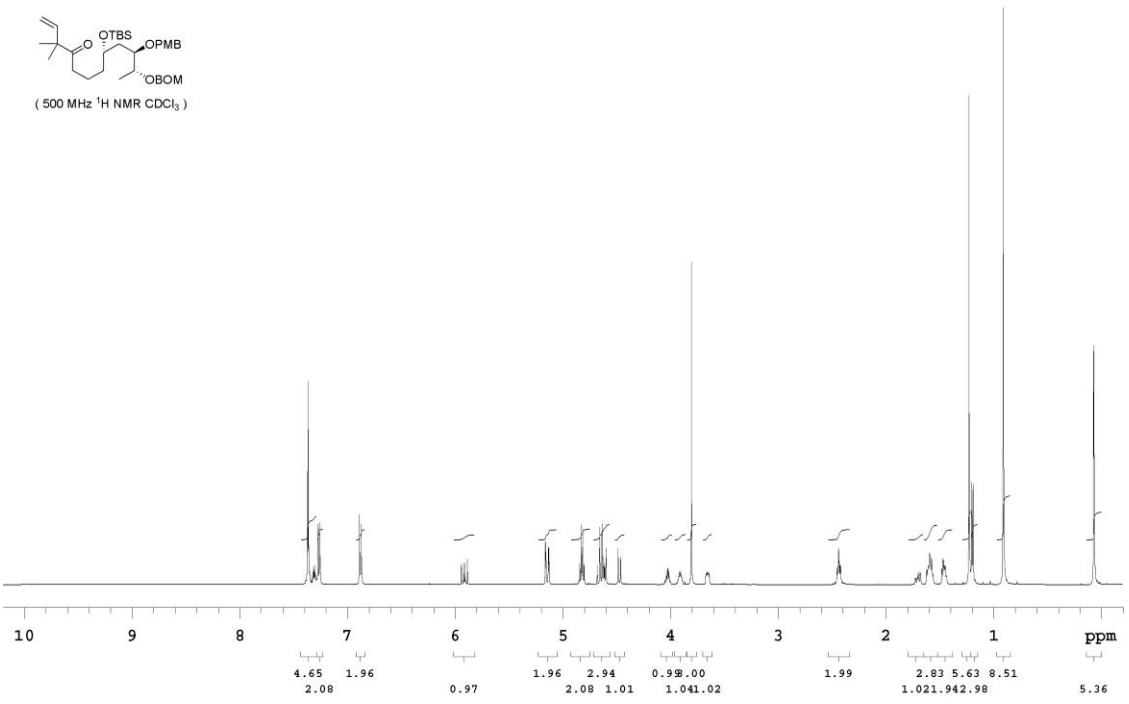

OTBS
OPMB
OBOM
(500 MHz gDQCOSY $CDCl_3$)
F2
(ppm)
F1 (ppm)

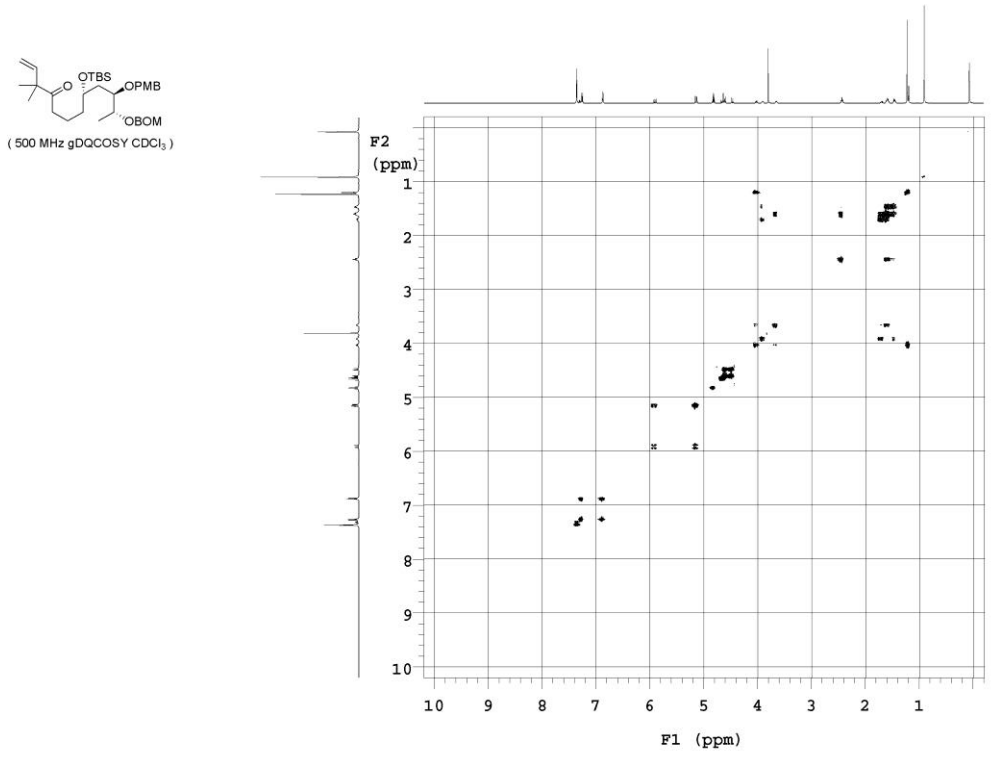

202.748
159.329
138.128
131.051
129.360
128.631
127.994
127.870
113.978
93.378
78.188
77.486
77.230
76.978
72.874
72.101
69.545
69.469
55.472
44.197
37.685
37.301
26.133
18.280
17.414
15.158
-3.702
-4.195
OTBS
OPMB
OBOM
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

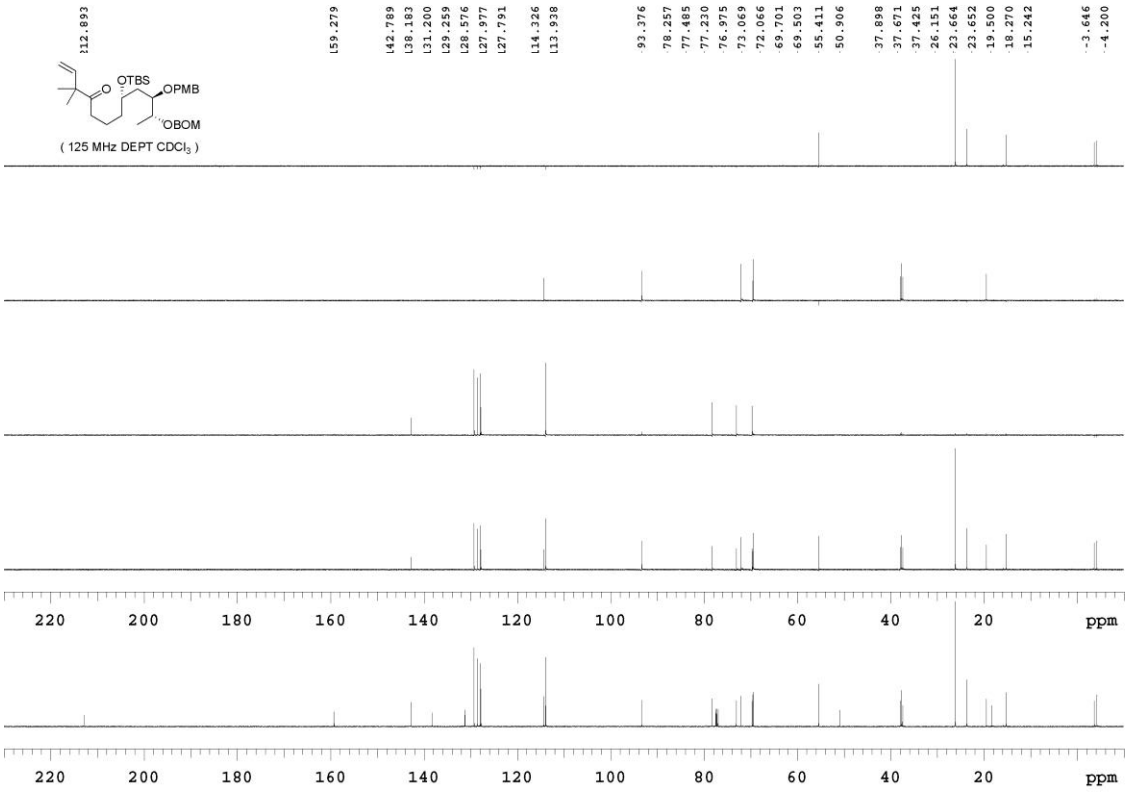

OTBS
OPMB
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

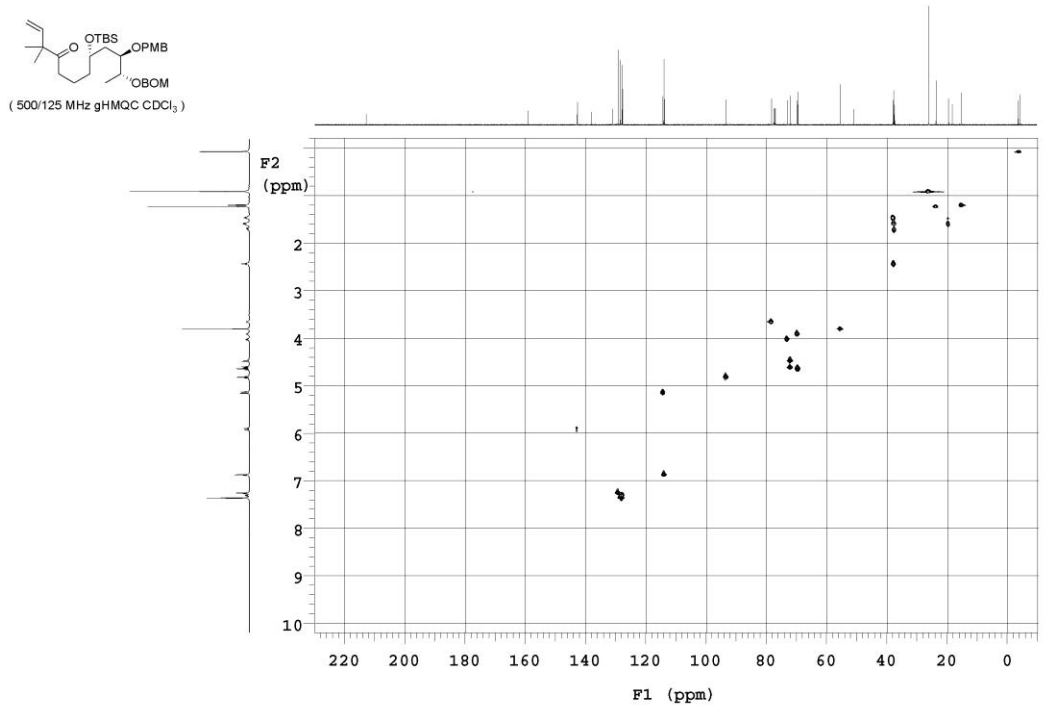

OTBS
OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2 (ppm)
F1 (ppm)

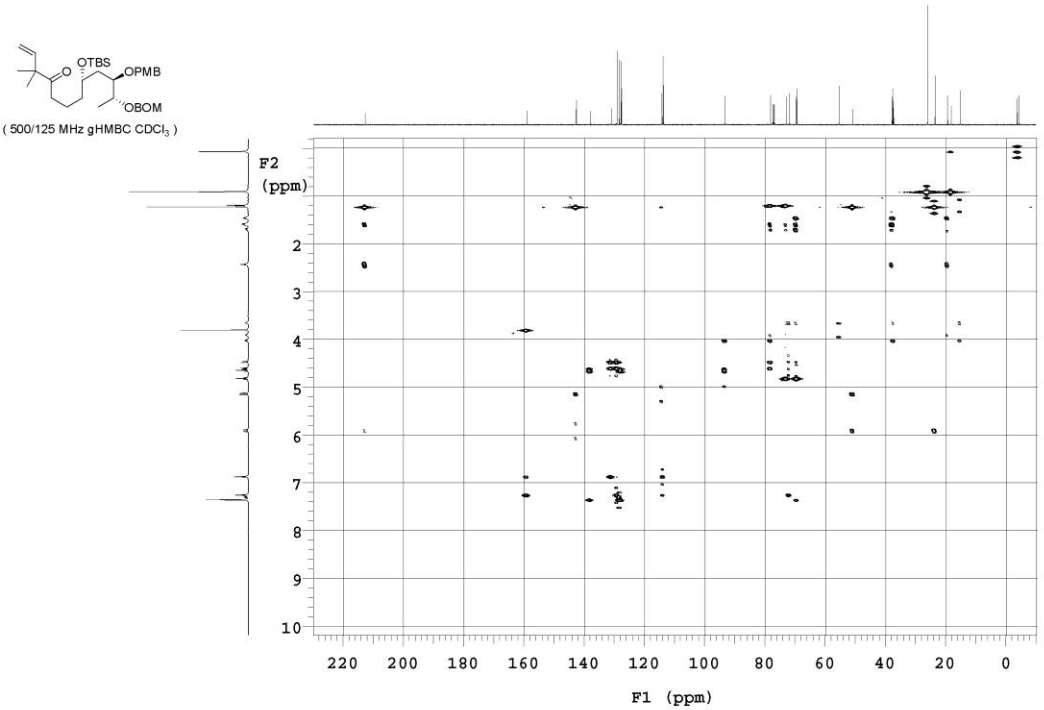

OTBS
OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2 (ppm)
F1 (ppm)

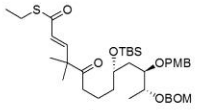

OTBS
OPMB
OBOM
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
4.65 1.96 1.96 2.94 0.95 3.00 1.99 2.83 5.63 8.51
2.08 0.97 2.08 1.01 1.04 1.02 1.02 1.94 2.98 5.36


OTBS
OPMB
OBOM
(500 MHz gDQCOSY $CDCl_3$)
F2 (ppm)
F1 (ppm)
1
2
3
4
5
6
7
8
9
10

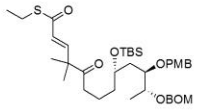

112.893
159.279
142.789
138.183
131.200
129.259
128.576
127.977
127.791
114.326
113.938
93.376
78.257
77.485
77.230
76.975
73.069
72.066
69.701
69.503
55.411
50.906
37.898
37.671
37.425
26.151
23.664
23.652
19.500
18.270
15.242
-3.646
-4.200
OTBS
OPMB
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

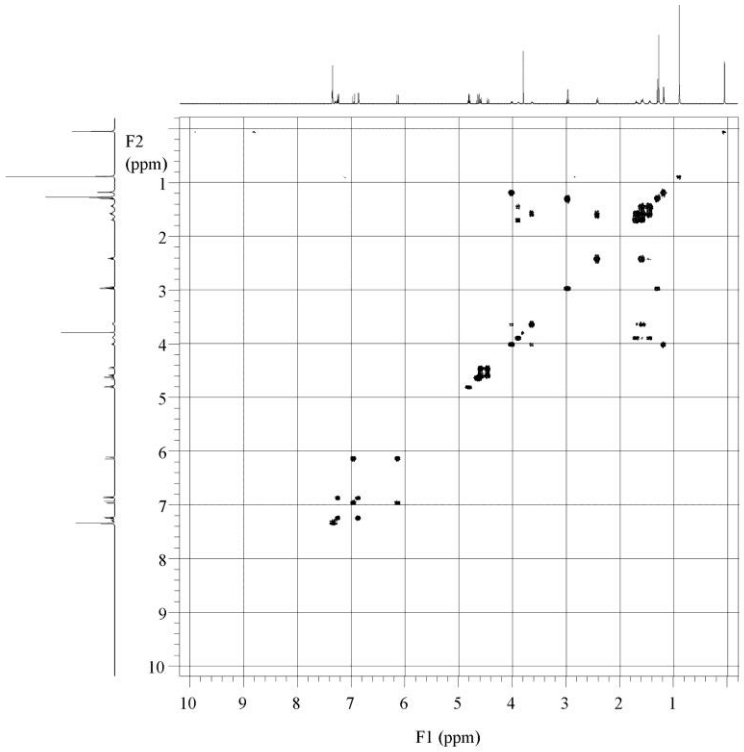

OTBS
OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

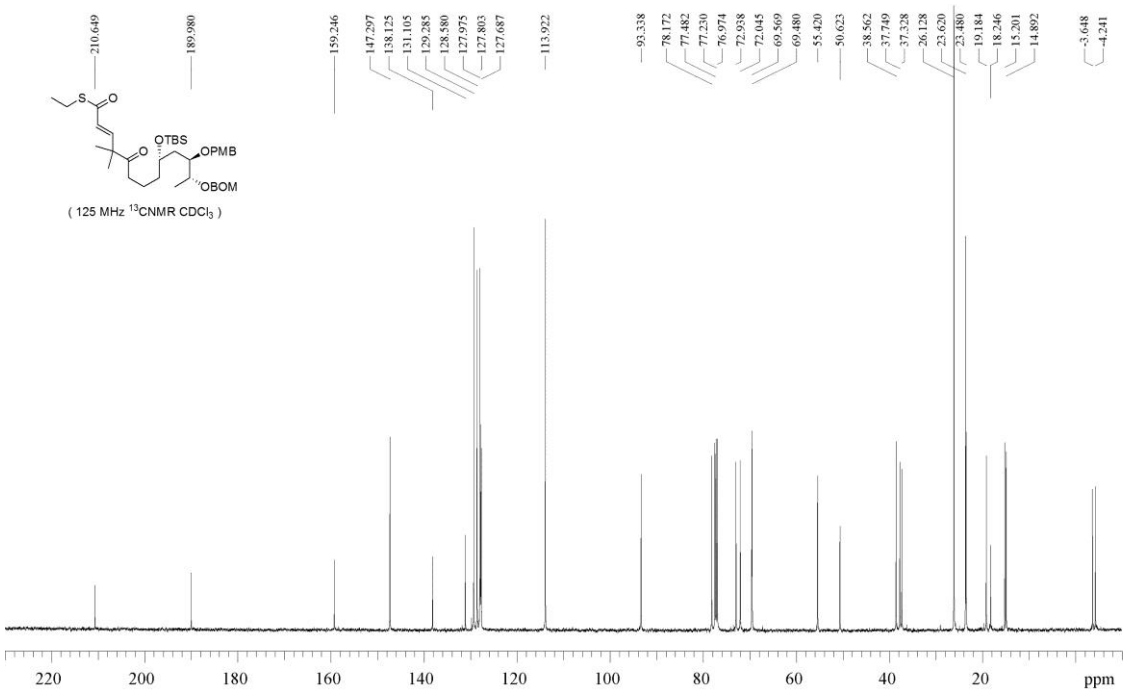


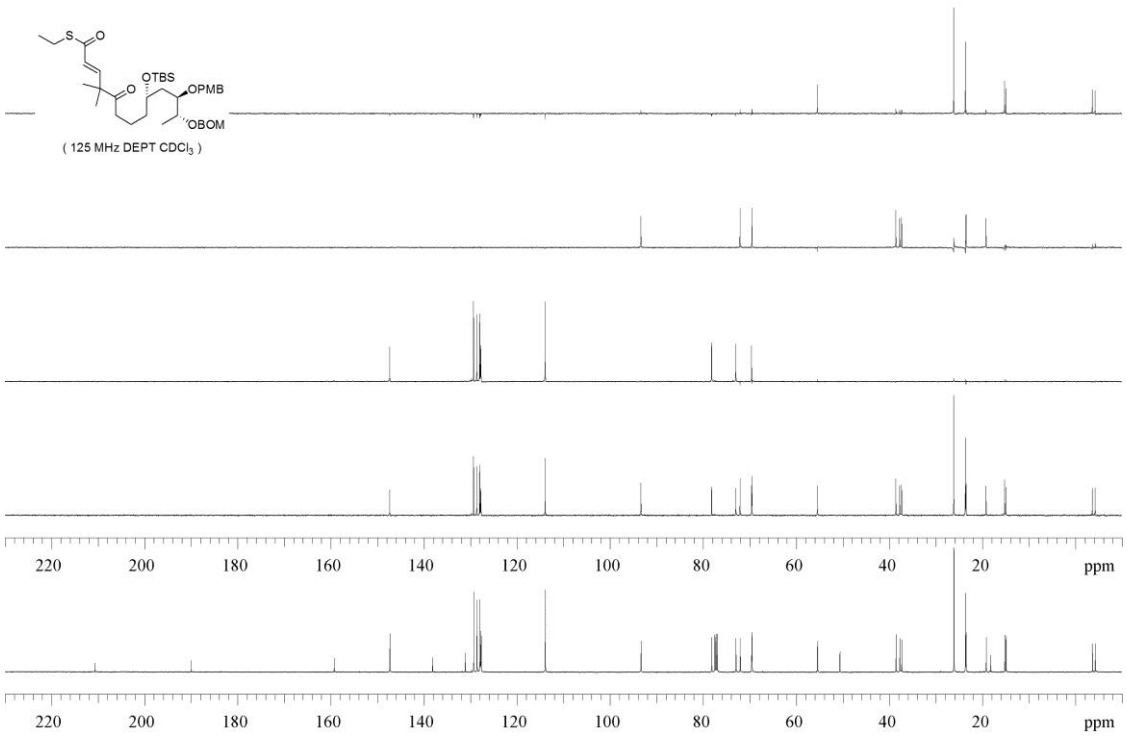
(500 MHz ^{1}HNMR $CDCl_3$)

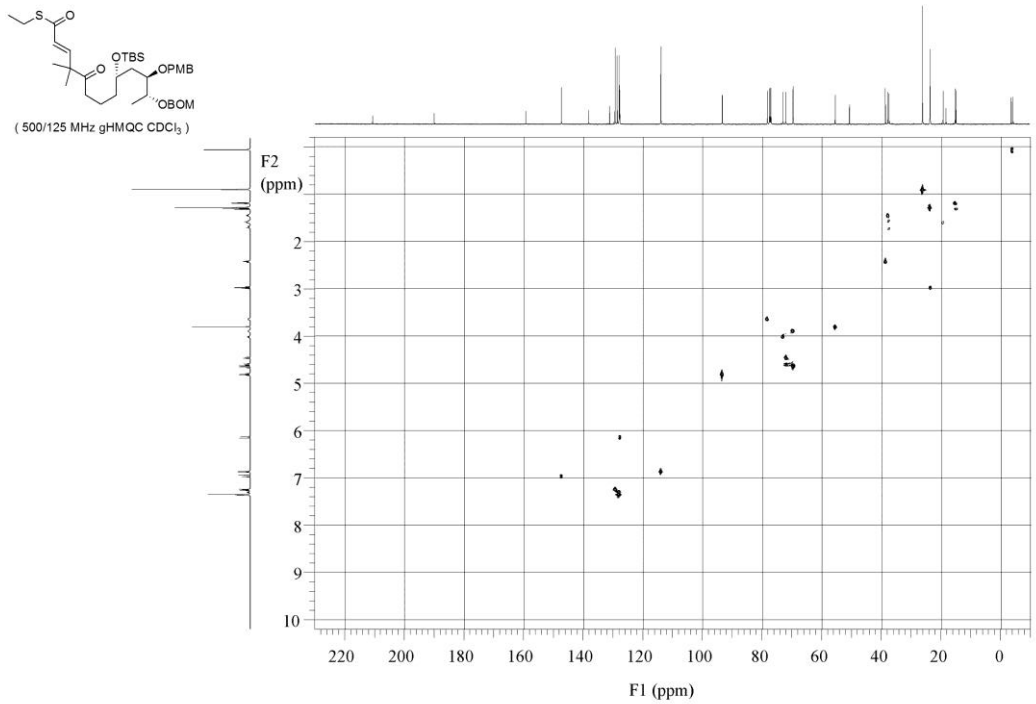


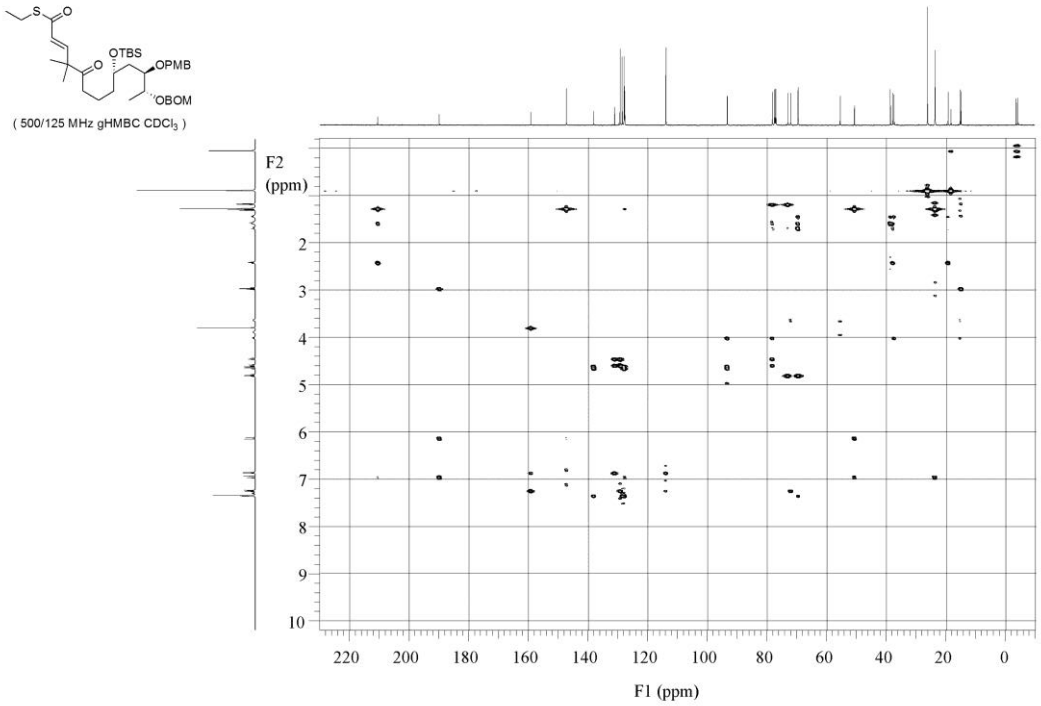
(500 MHz gDQCOSY $CDCl_3$)

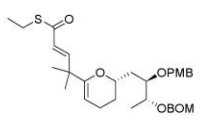



210.649
189.980
159.246
147.297
138.125
131.105
129.285
128.580
127.975
127.803
127.687
113.922
93.338
78.172
77.482
77.230
76.974
72.938
72.045
69.569
69.480
55.420
50.623
38.562
37.749
37.328
26.128
23.620
23.480
19.184
18.246
15.201
14.892
-3.648
-4.241
OTBS
OPMB
OBOM
(125 MHz ^{13}CNMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

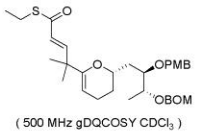

OTBS
OPMB
OBOM
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

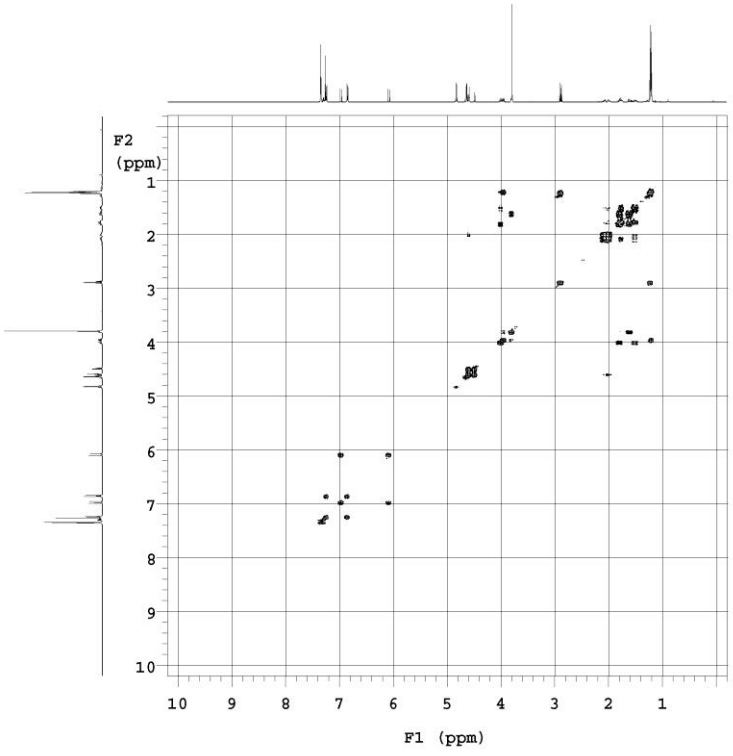

OTBS
OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

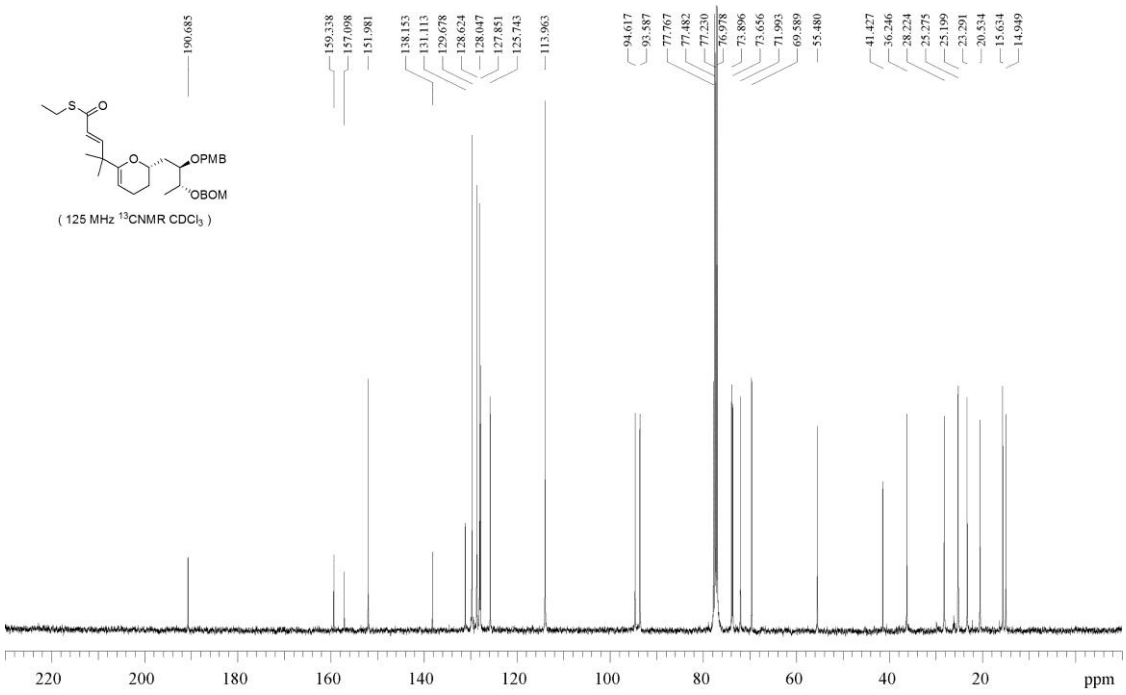


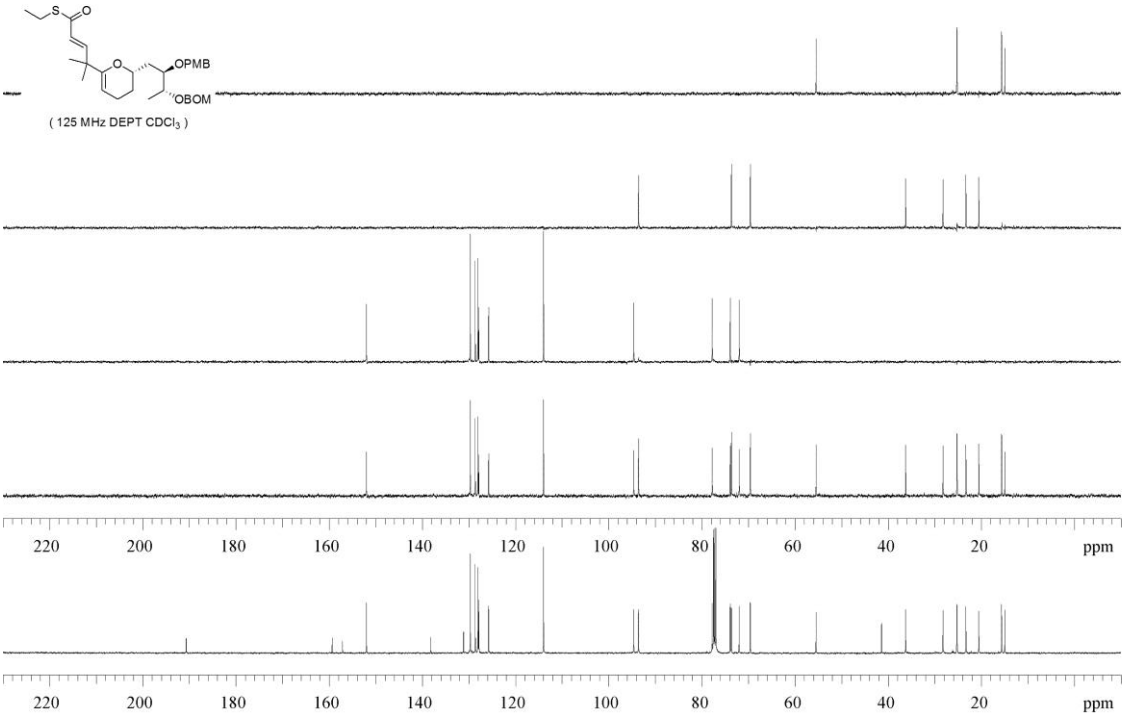
(500 MHz ^{1}HNMR $CDCl_3$)

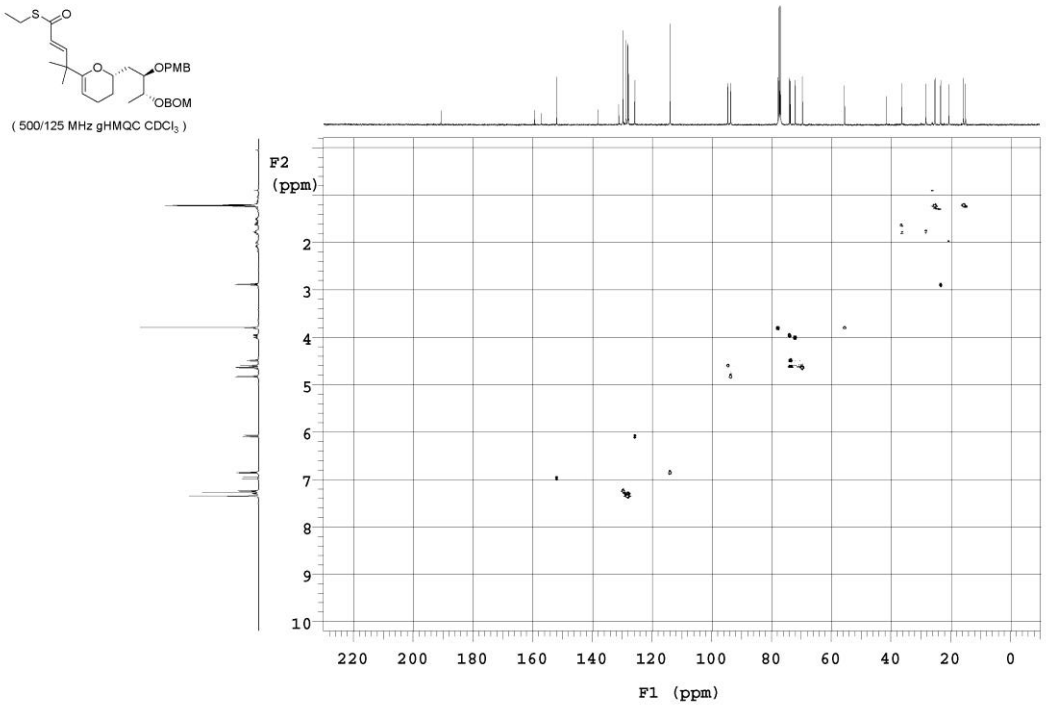


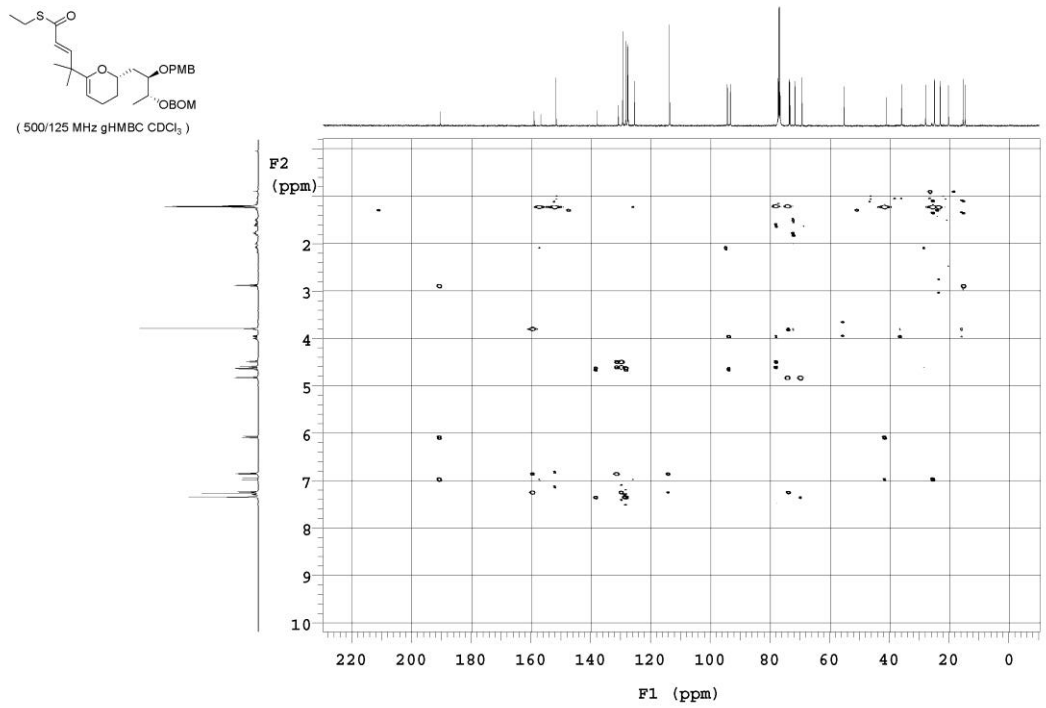
(500 MHz gDQCOSY $CDCl_3$)

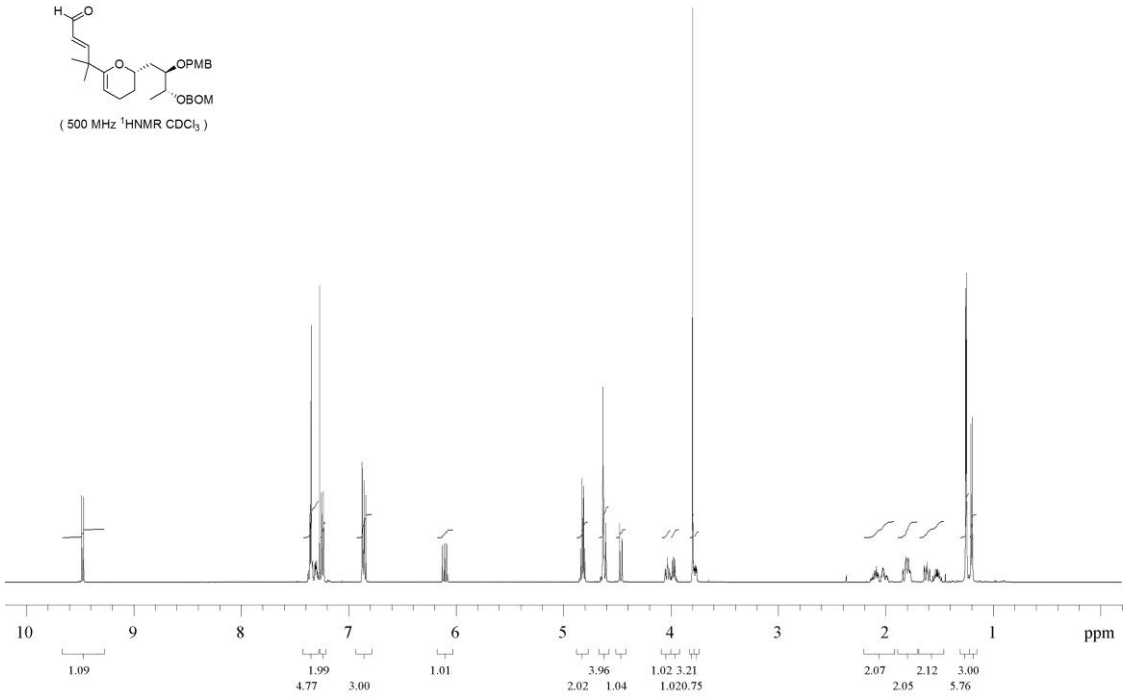


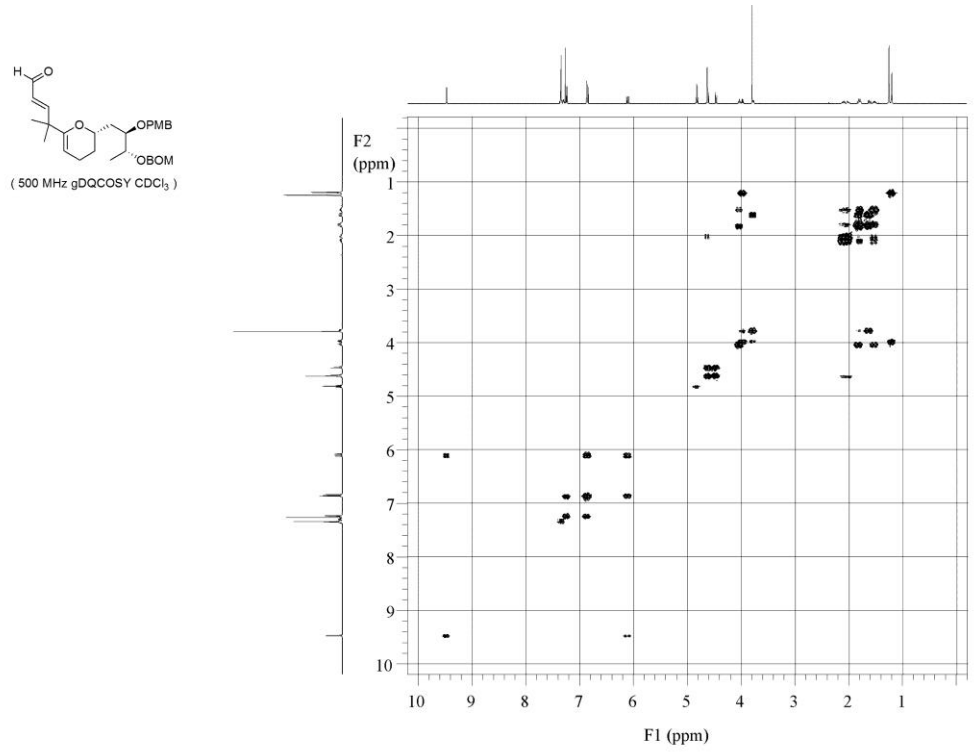

190.685
159.338
157.098
151.981
138.153
131.113
129.678
128.624
128.047
127.851
125.743
113.963
94.617
93.587
77.767
77.482
77.230
76.978
73.896
73.656
71.993
69.589
55.480
41.427
36.246
28.224
25.275
25.199
23.291
20.534
15.634
14.949
OPMB
OBOM
(125 MHz ^{13}CNMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

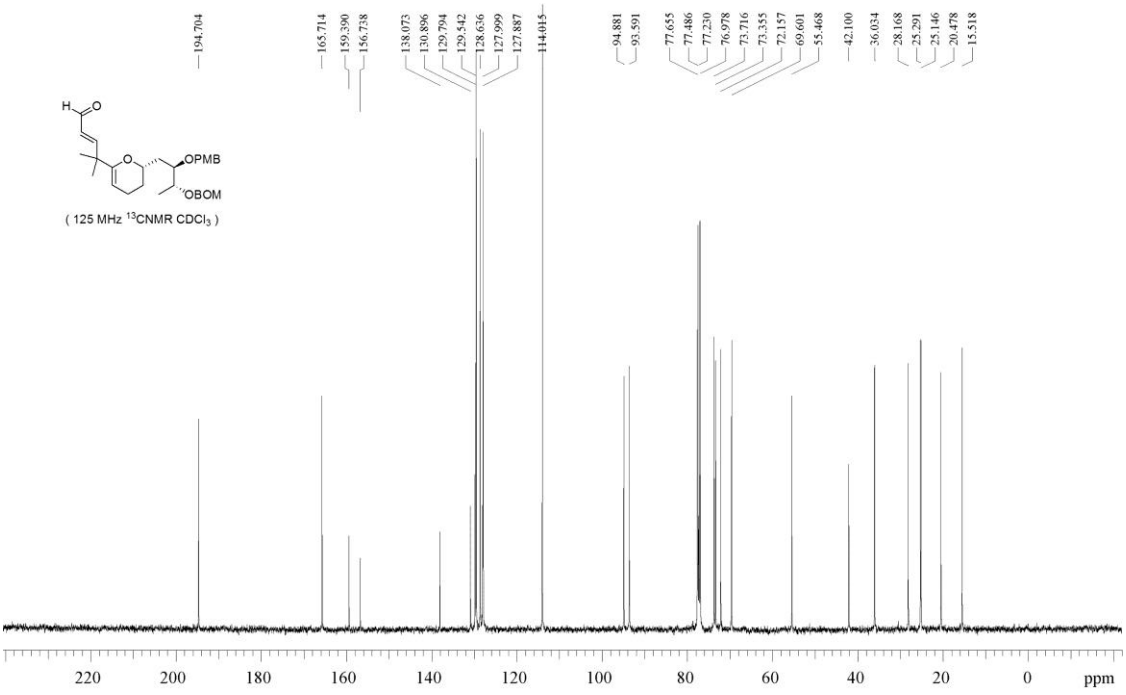

OPMB
OBOM
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

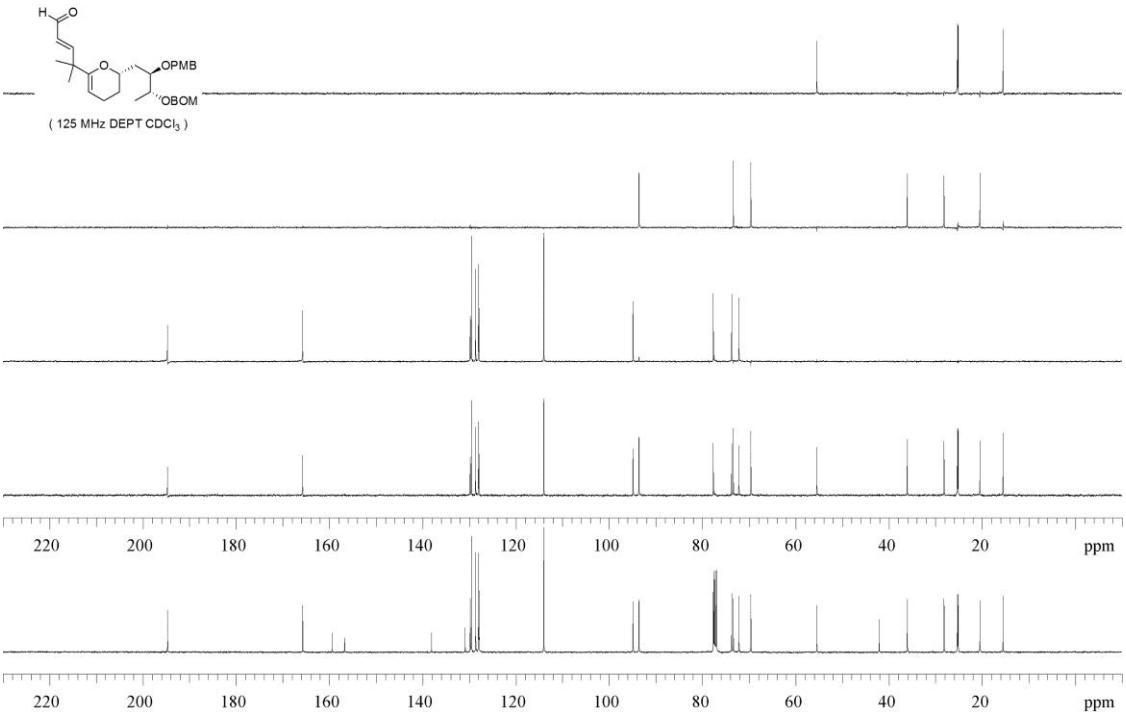

OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

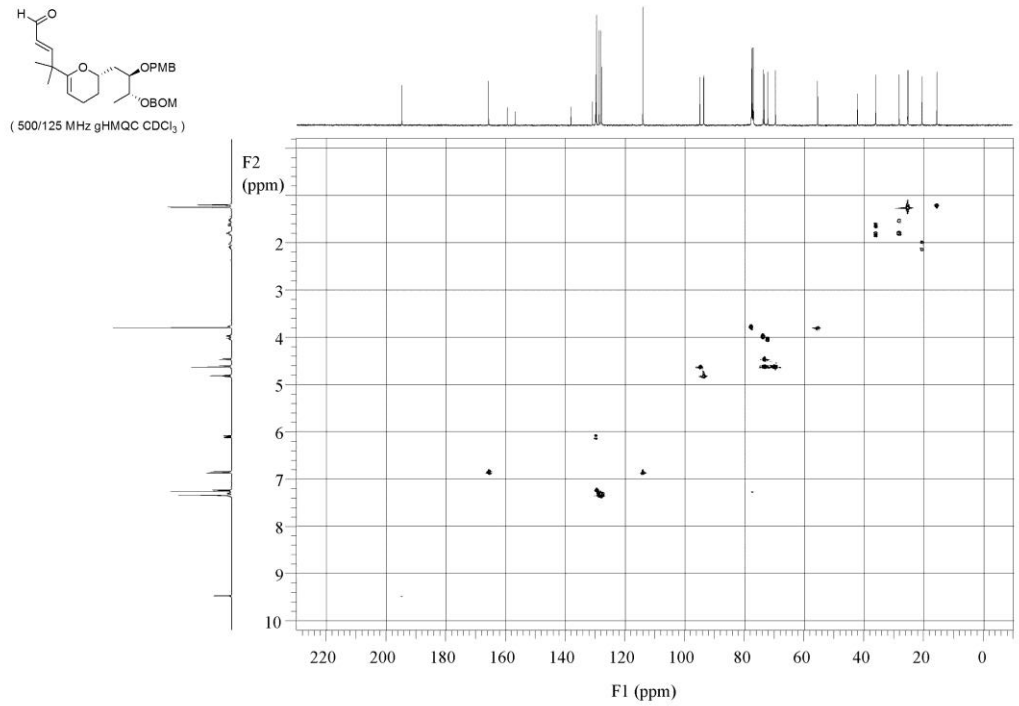

OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

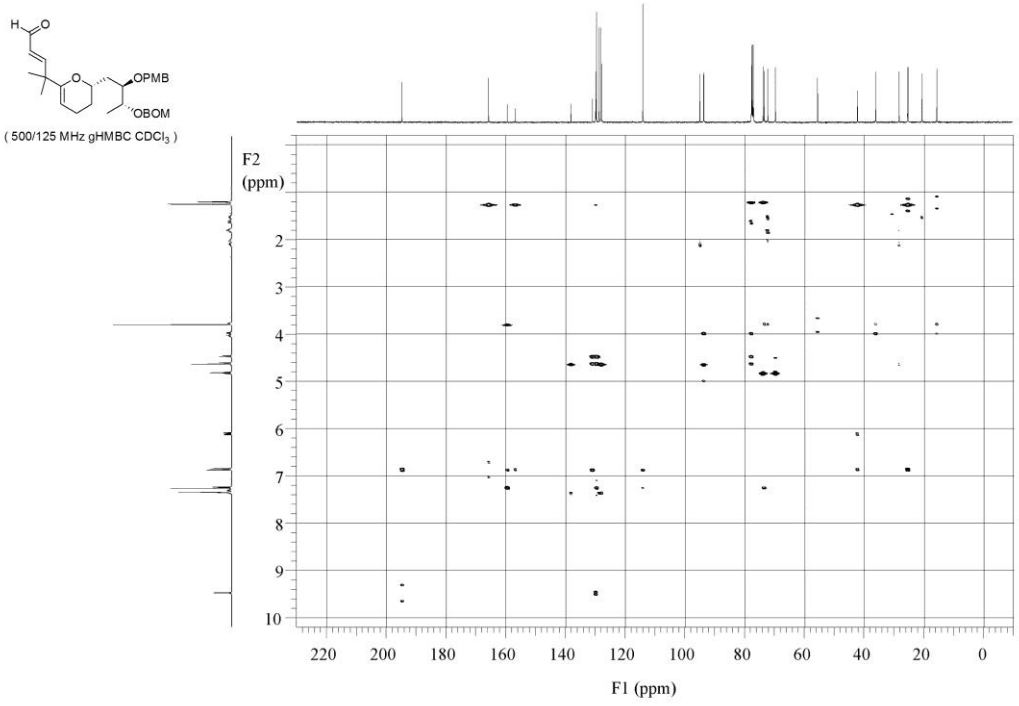

OPMB
OBOM
(500 MHz ^{1}HNMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
1.09
1.99
4.77
3.00
1.01
3.96
2.02
1.04
1.02
3.21
1.02
0.75
2.07
2.05
2.12
3.00
5.76

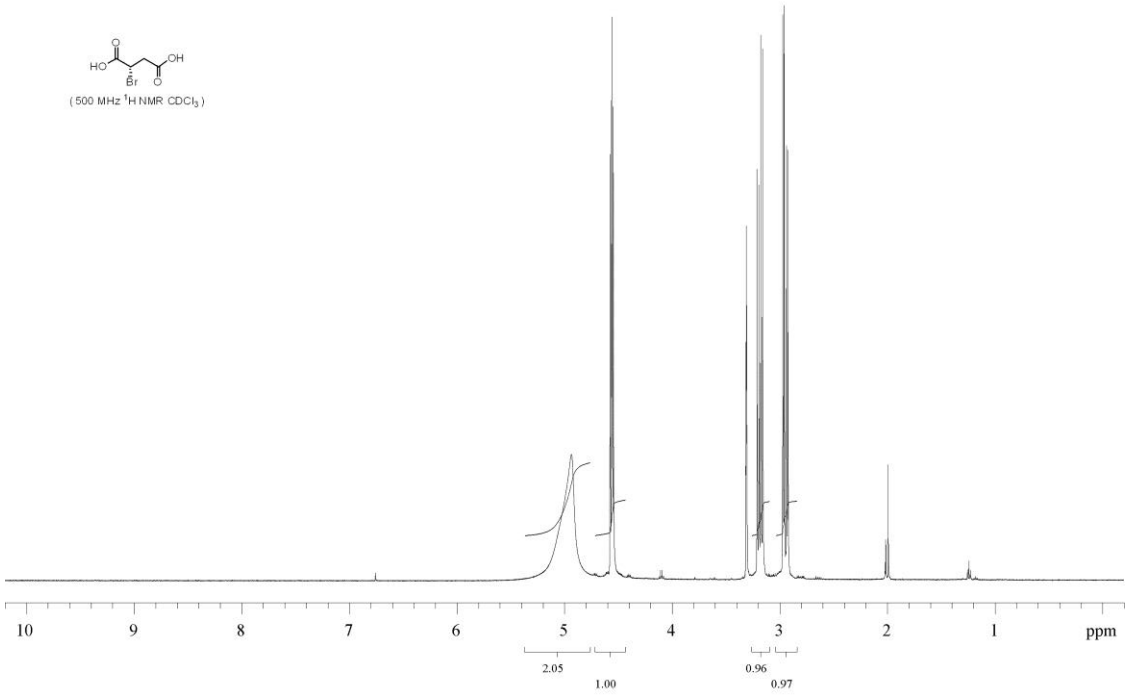

OPMB
OBOM
(500 MHz gDQCOSY $CDCl_3$)
F2
(ppm)
F1 (ppm)

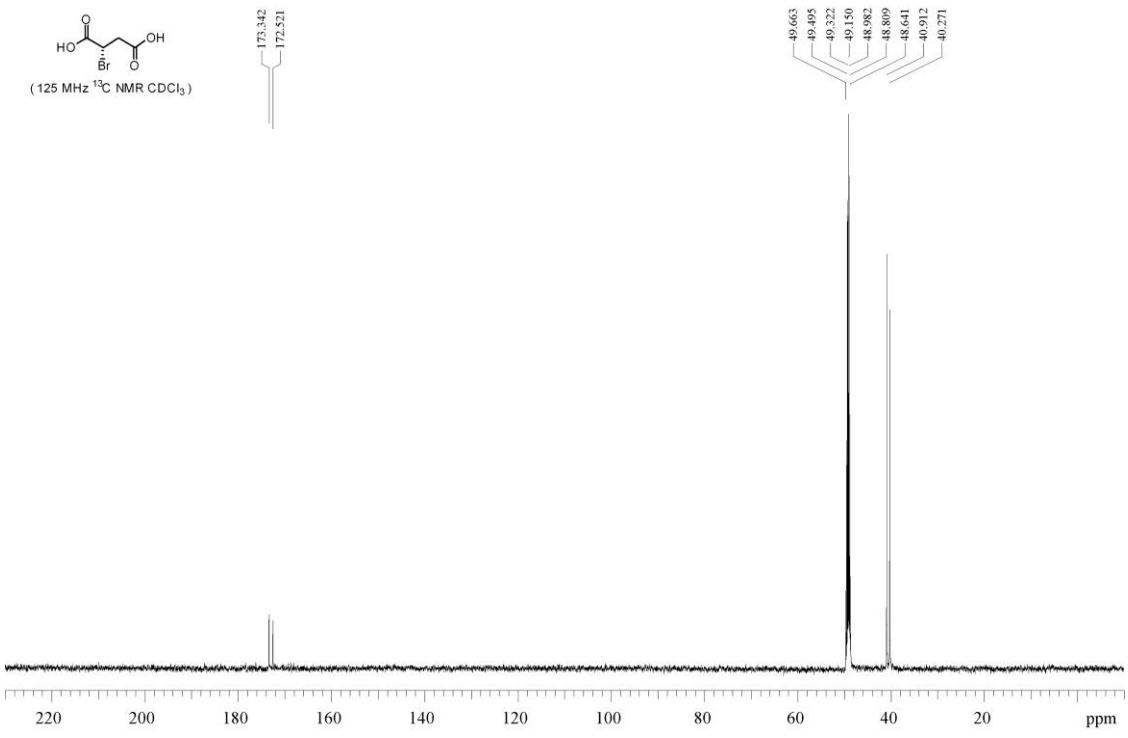

194.704
165.714
159.390
156.738
138.073
130.896
129.794
129.542
128.636
127.999
127.887
114.015
94.881
93.591
77.655
77.486
77.230
76.978
73.716
73.355
72.157
69.601
55.468
42.100
36.034
28.168
25.291
25.146
20.478
15.518
OPMB
OBOM
(125 MHz ^{13}CNMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

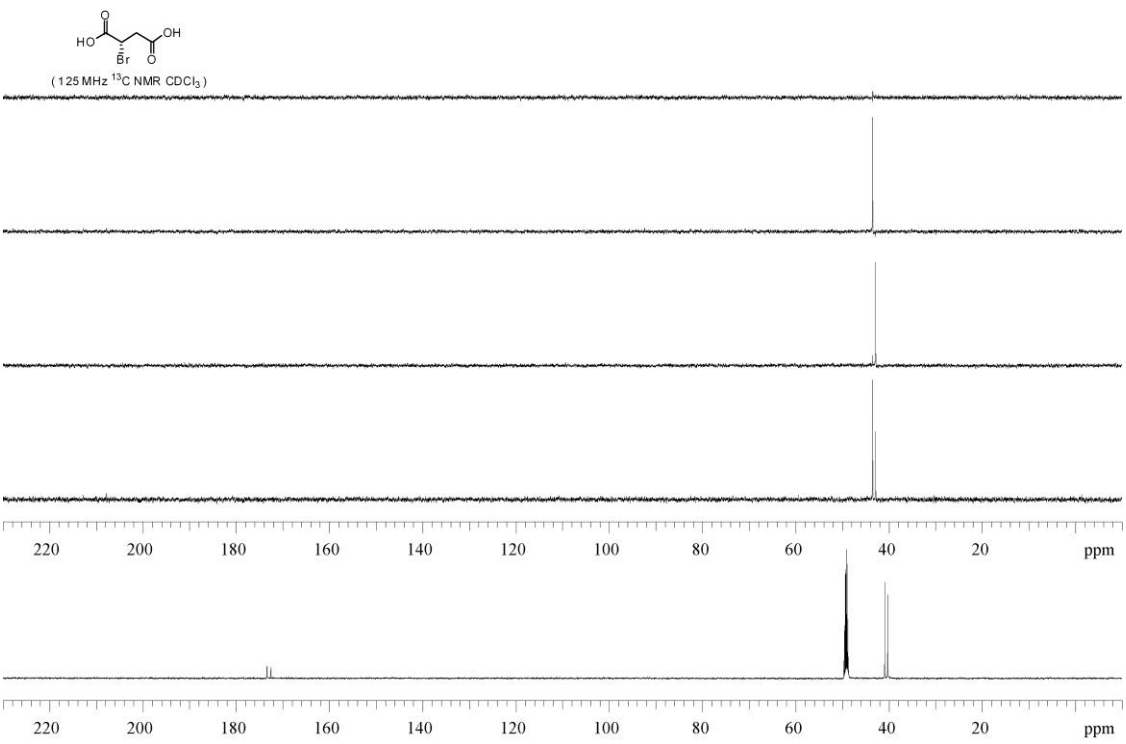

OPMB
OBOM
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

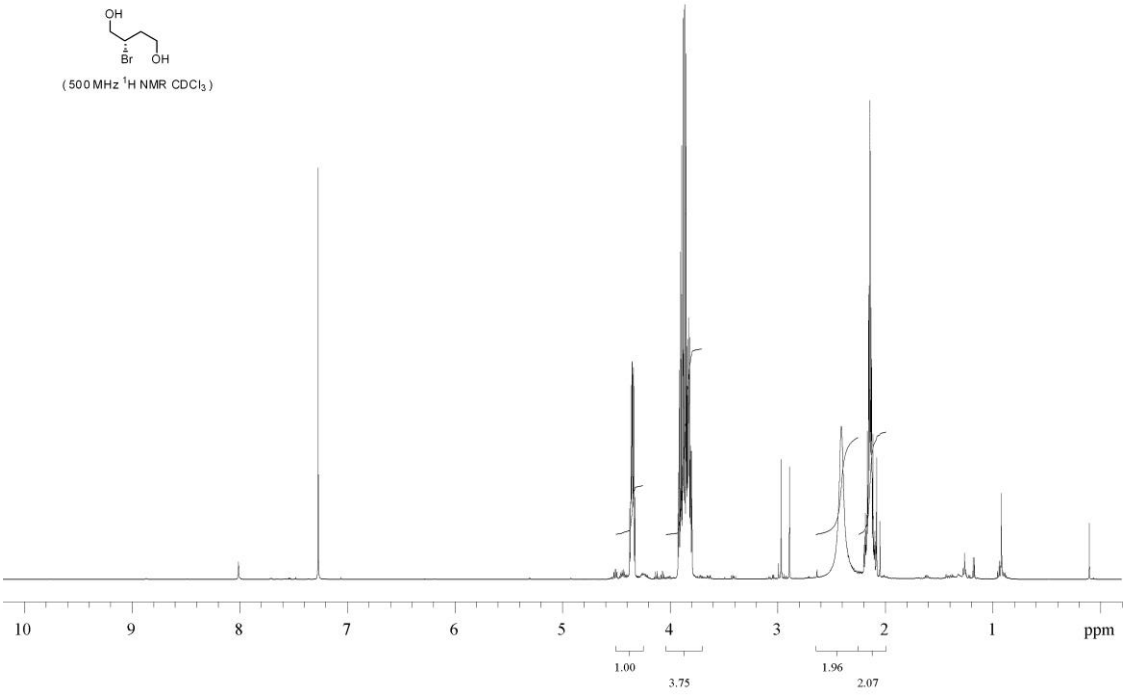

OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

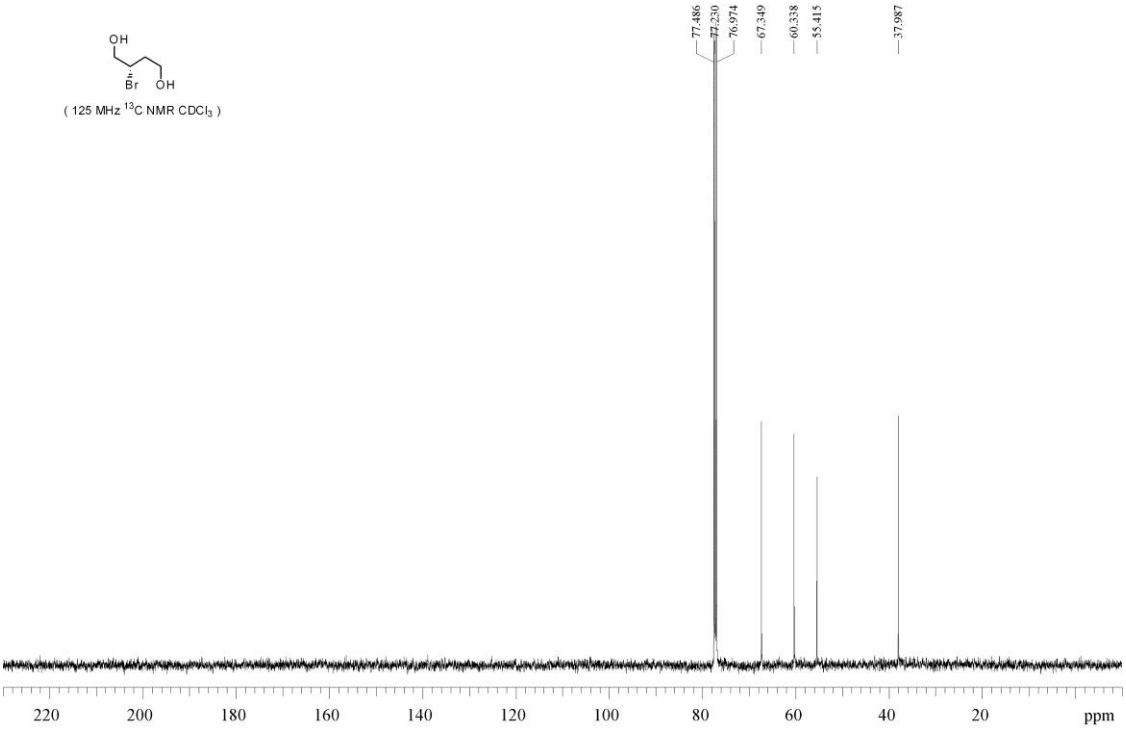

OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

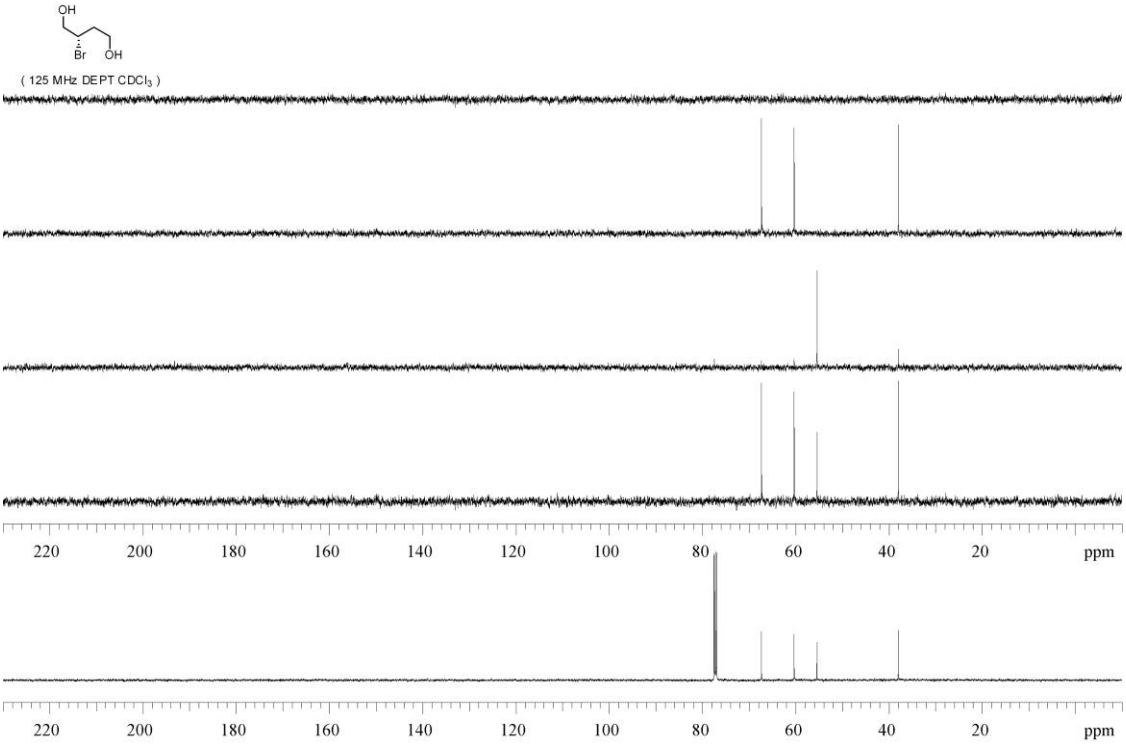

(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
2.05
1.00
0.96
0.97

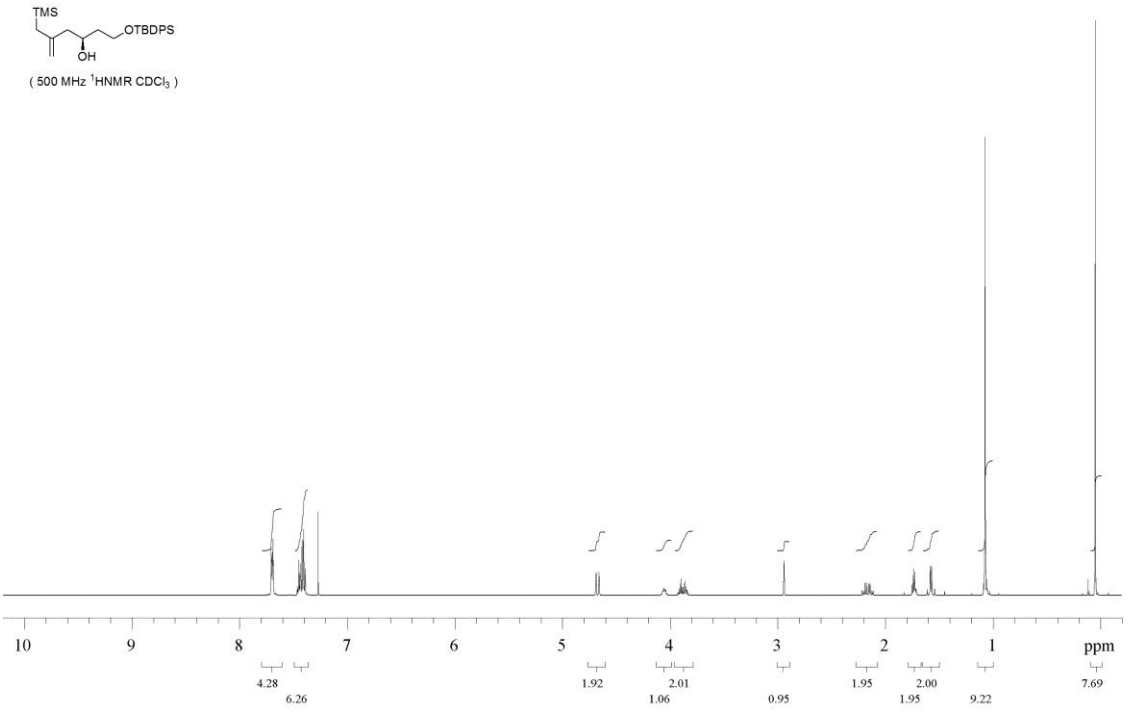

(125 MHz ^{13}C NMR $CDCl_3$)
173.342
172.521
49.663
49.495
49.322
49.150
48.982
48.809
48.641
40.912
40.271
220
200
180
160
140
120
100
80
60
40
20
ppm

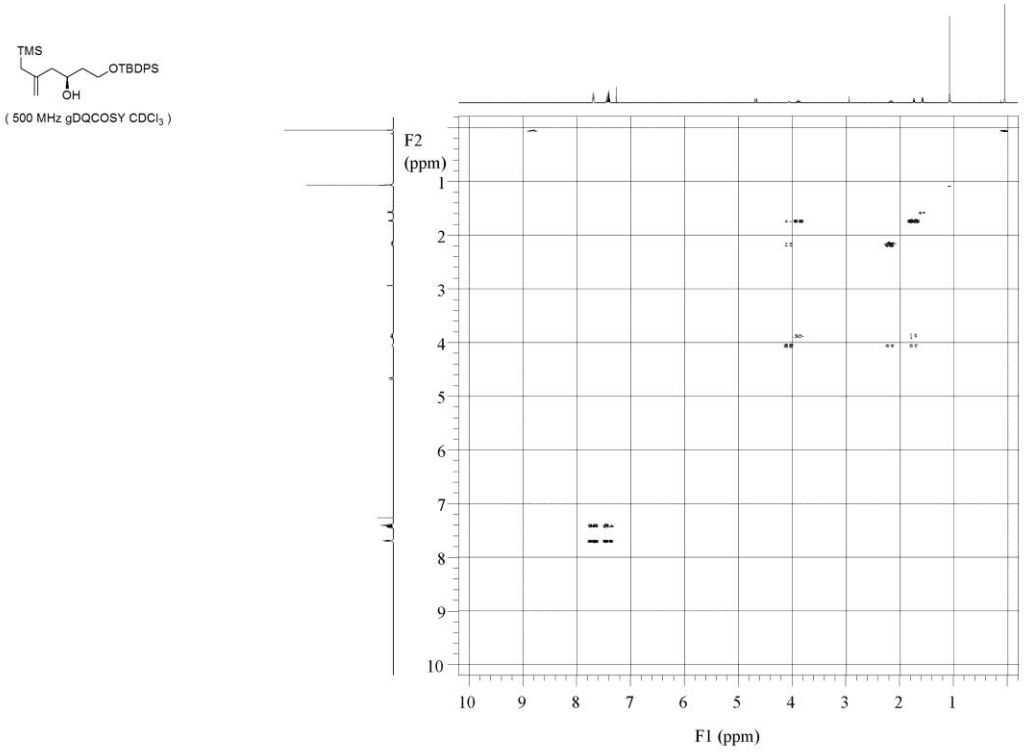

HO
O
OH
Br
O
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

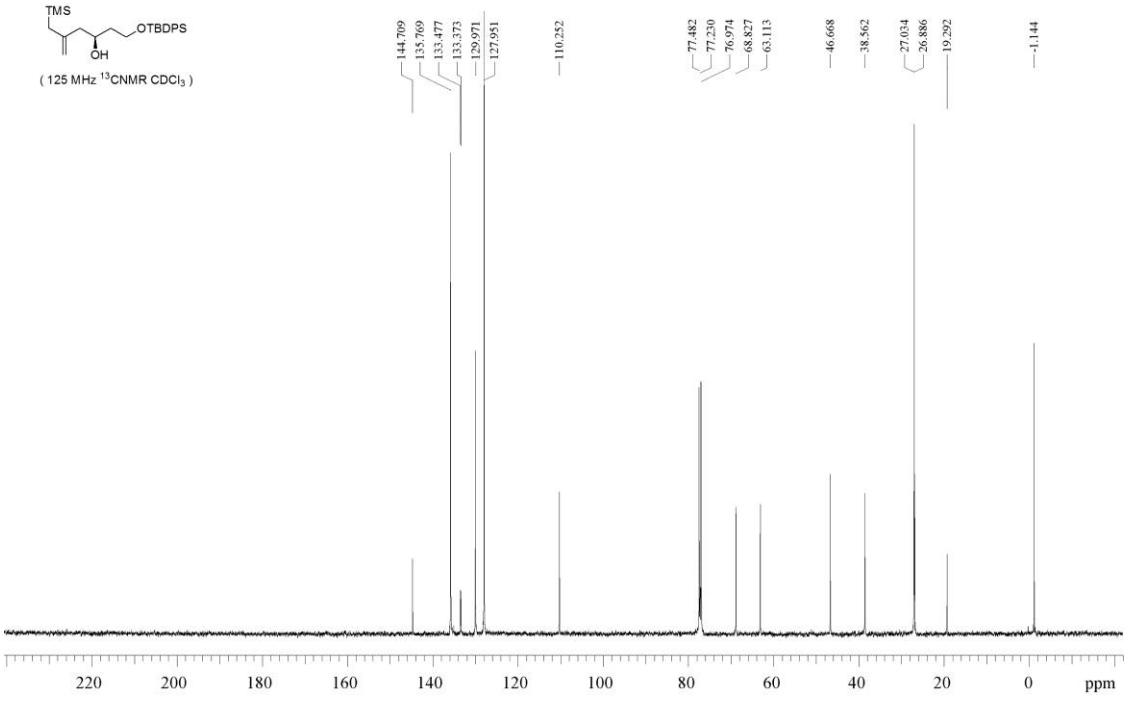

OH
Br
OH
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
1.00
3.75
1.96
2.07

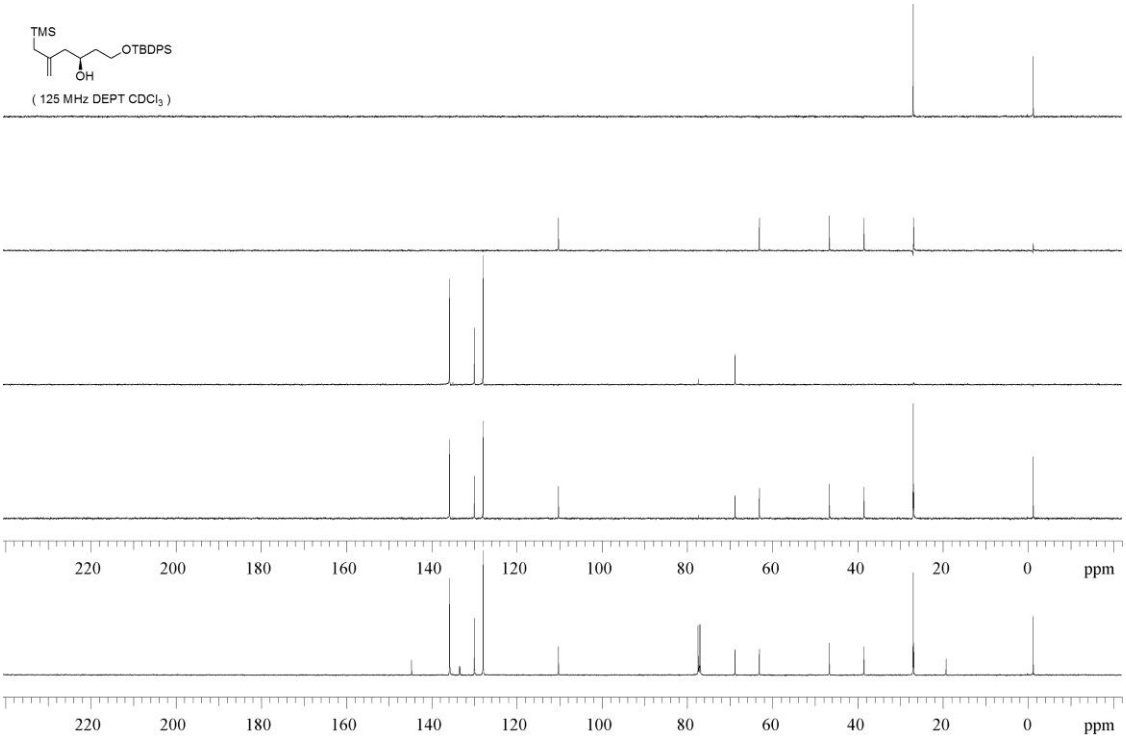

OH
Br
OH
(125 MHz ^{13}C NMR $CDCl_3$)
77.486
77.230
76.974
67.349
60.338
55.415
37.987
220
200
180
160
140
120
100
80
60
40
20
ppm

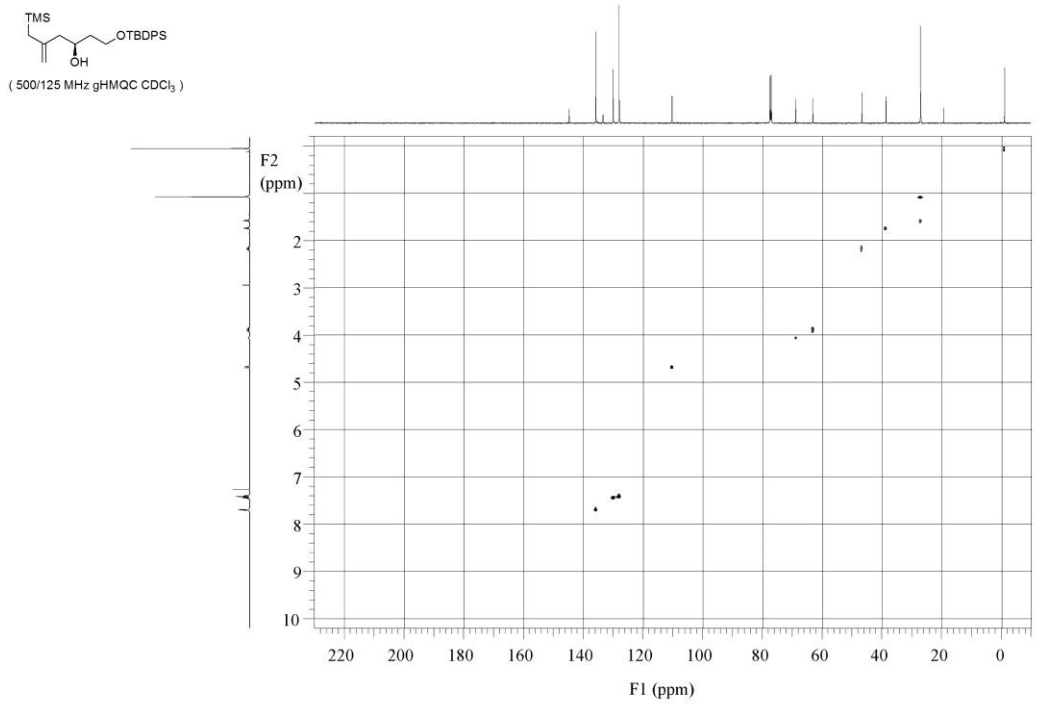

OH
Br
OH
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

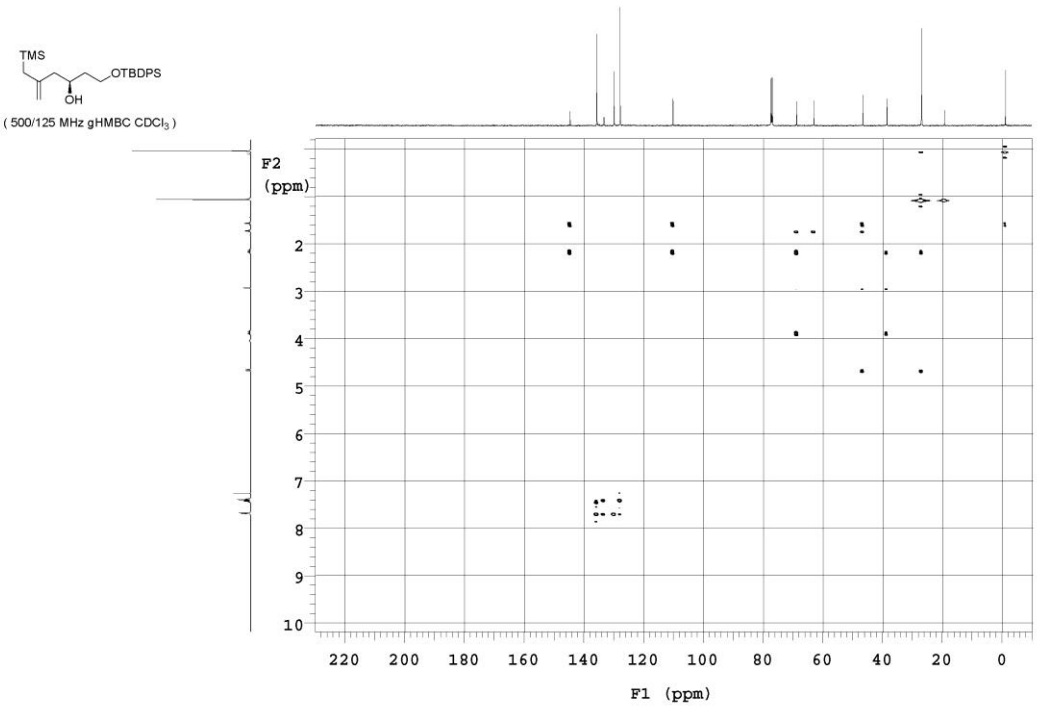

TMS
OTBDPS
OH
(500 MHz ^{1}HNMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
4.28
6.26
1.92
2.01
1.06
0.95
1.95
2.00
1.95
9.22
7.69

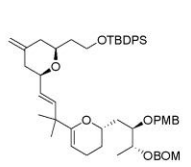

TMS
OTBDPS
OH
(500 MHz gDQCOSY $CDCl_3$)
F2
(ppm)
F1 (ppm)


TMS
OTBDPS
OH
(125 MHz ^{13}CNMR $CDCl_3$)
144.709
135.769
133.477
133.373
129.971
127.951
110.252
77.482
77.230
76.974
68.827
63.113
46.668
38.562
27.034
26.886
19.292
-1.144
220 200 180 160 140 120 100 80 60 40 20 0 ppm

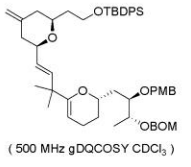

TMS
OTBDPS
OH
(125 MHz DEPT $CDCl_3$)
220 200 180 160 140 120 100 80 60 40 20 0 ppm
220 200 180 160 140 120 100 80 60 40 20 0 ppm


TMS
OTBDPS
OH
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

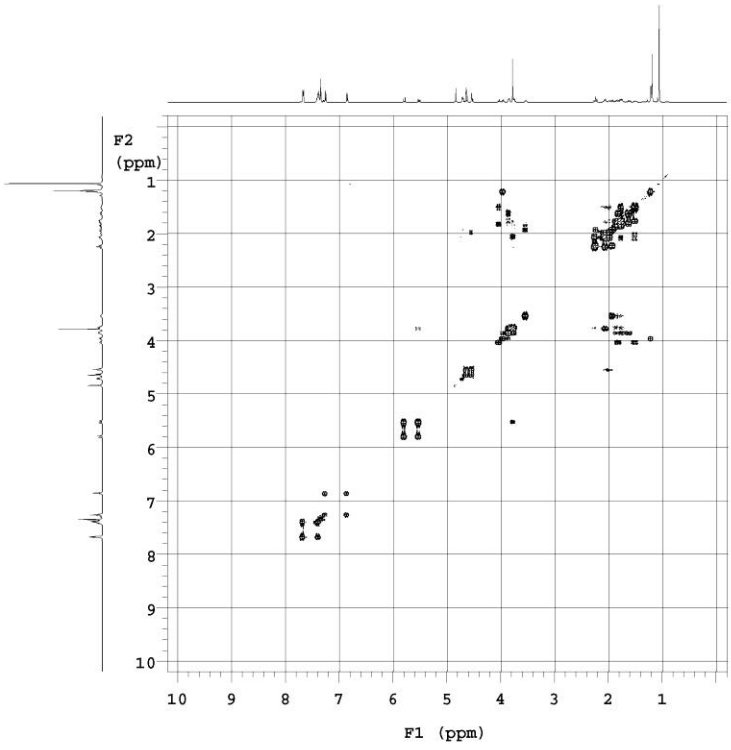

TMS
OTBDPS
OH
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

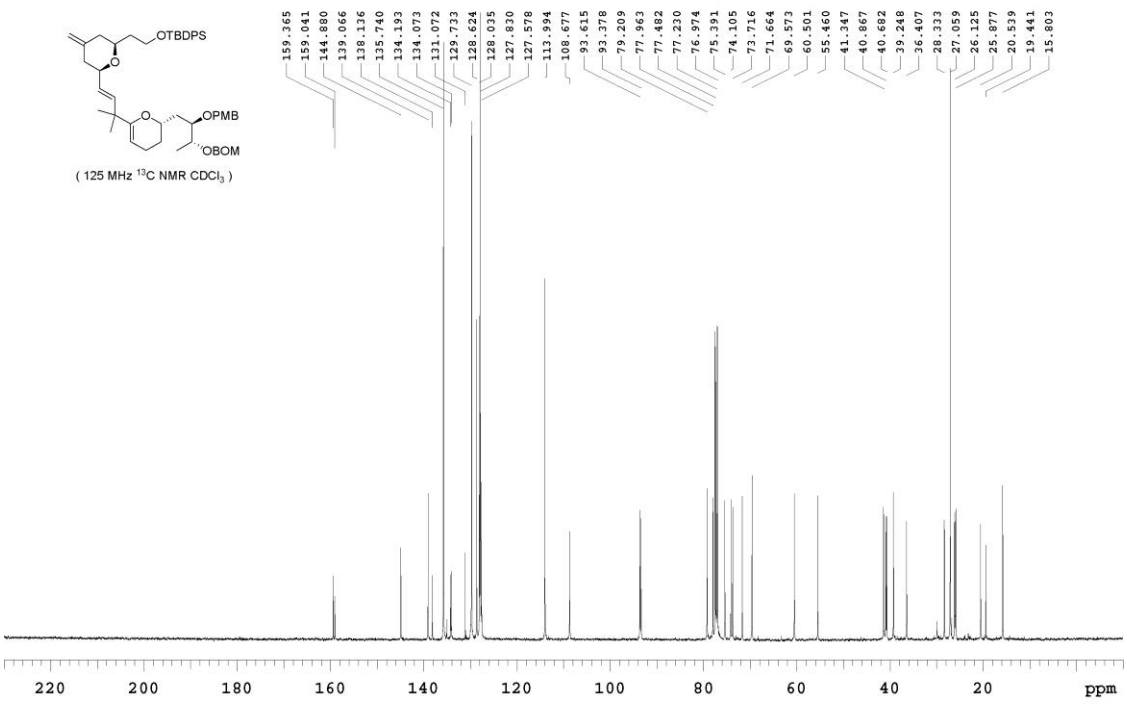


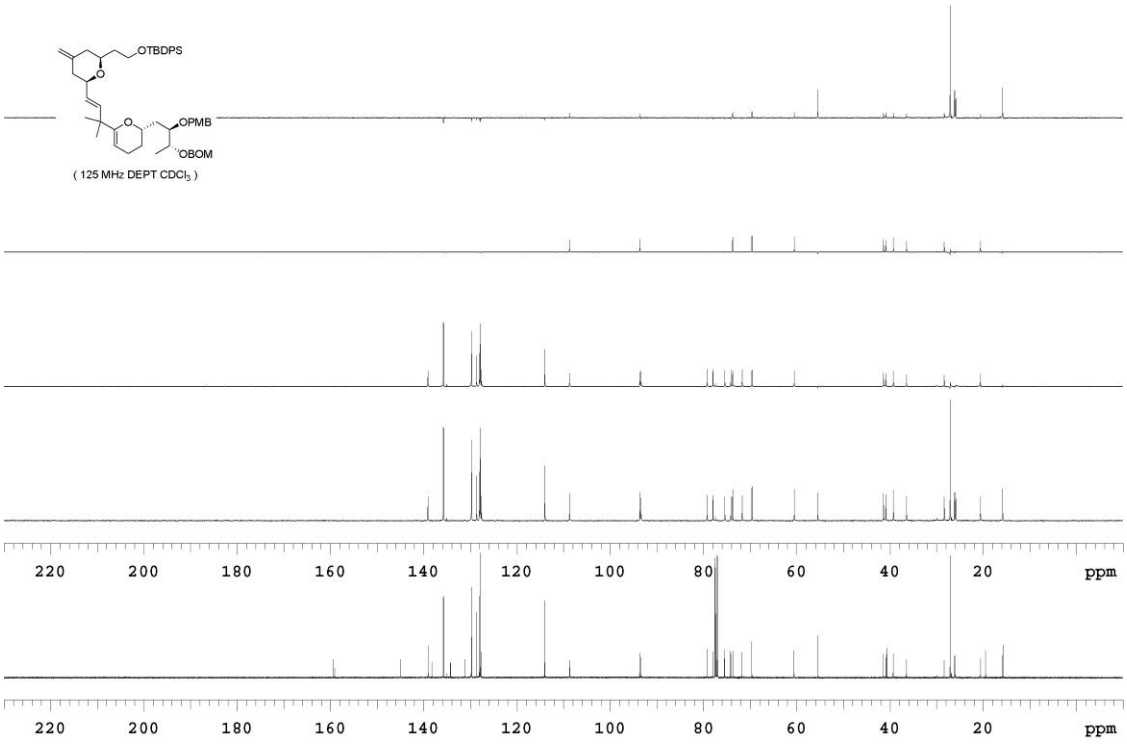
(500 MHz ^{1}H NMR $CDCl_3$)

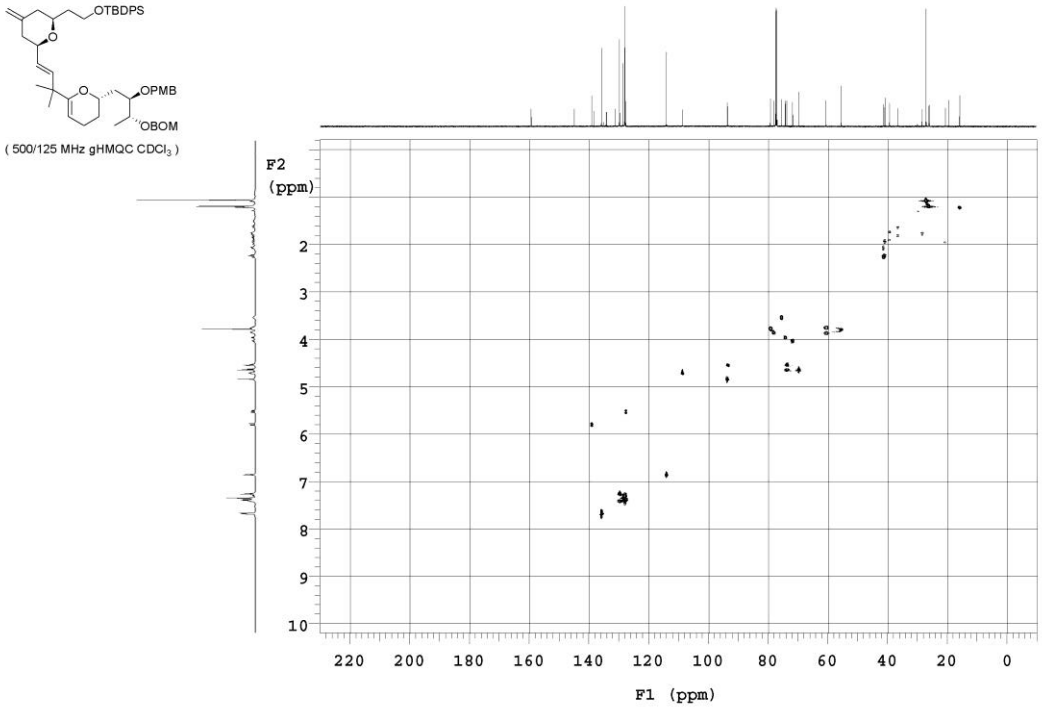


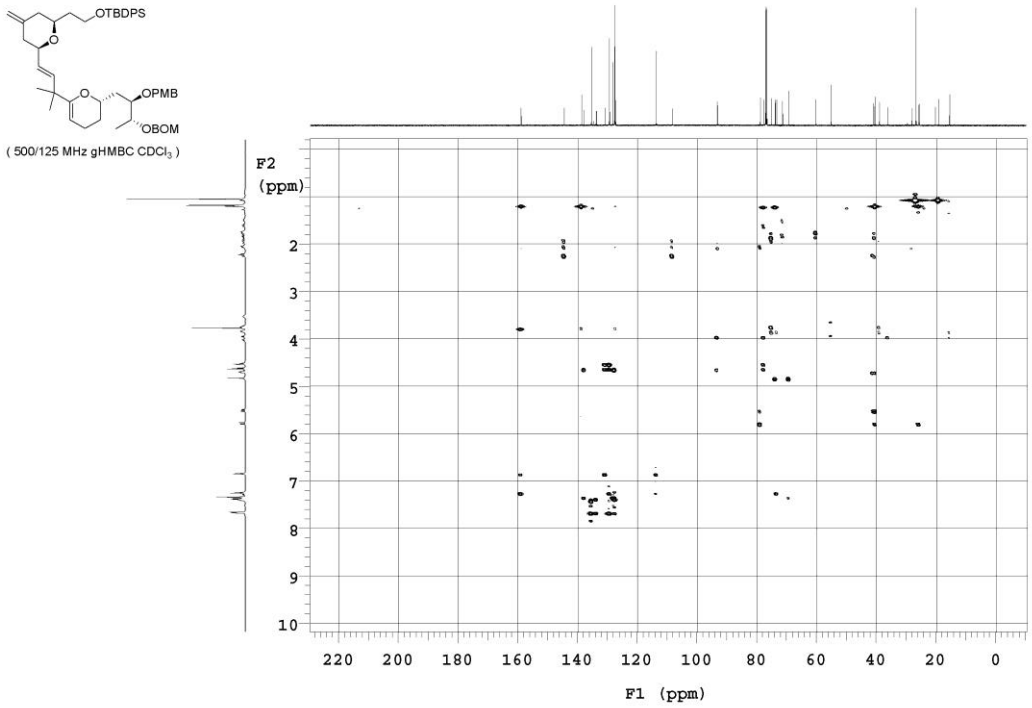
(500 MHz gDQCOSY $CDCl_3$)

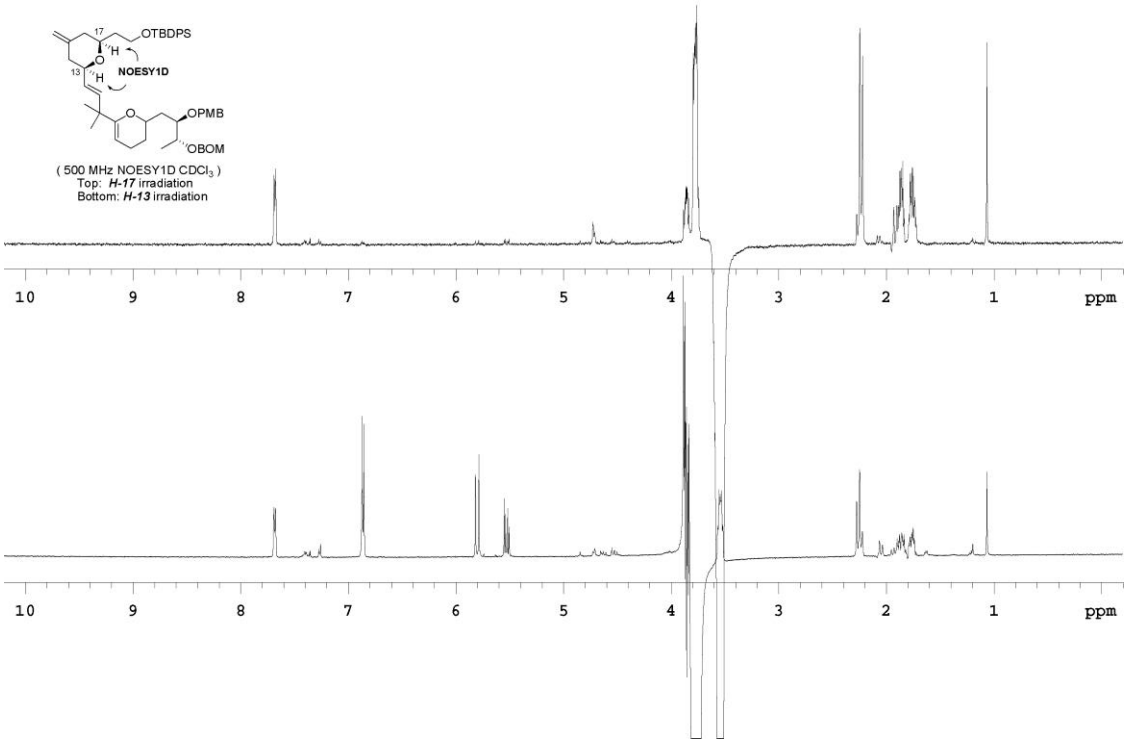


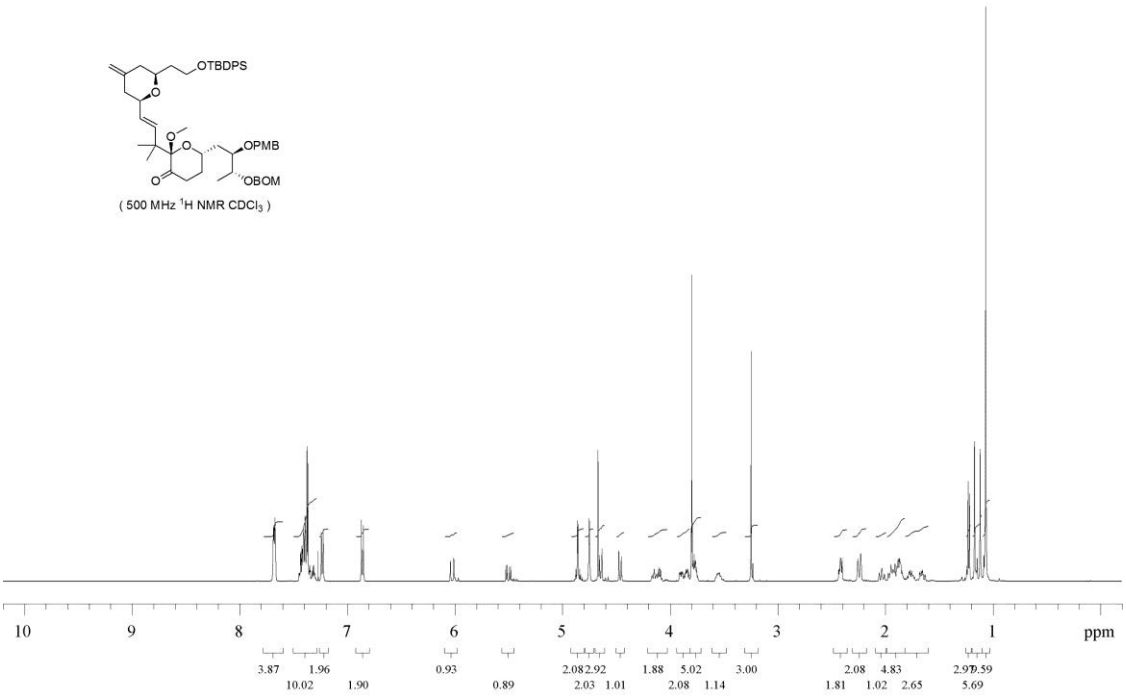

OTBDPS
OPMB
OBOM
(125 MHz ^{13}C NMR $CDCl_3$)
159.365
159.041
144.880
139.066
138.136
135.740
134.193
134.073
131.072
129.733
128.624
128.035
127.830
127.578
113.994
108.677
93.615
93.378
79.209
77.963
77.482
77.230
76.974
75.391
74.105
73.716
71.664
69.573
60.501
55.460
41.347
40.867
40.682
39.248
36.407
28.333
27.059
26.125
25.877
20.539
19.441
15.803
220
200
180
160
140
120
100
80
60
40
20
ppm

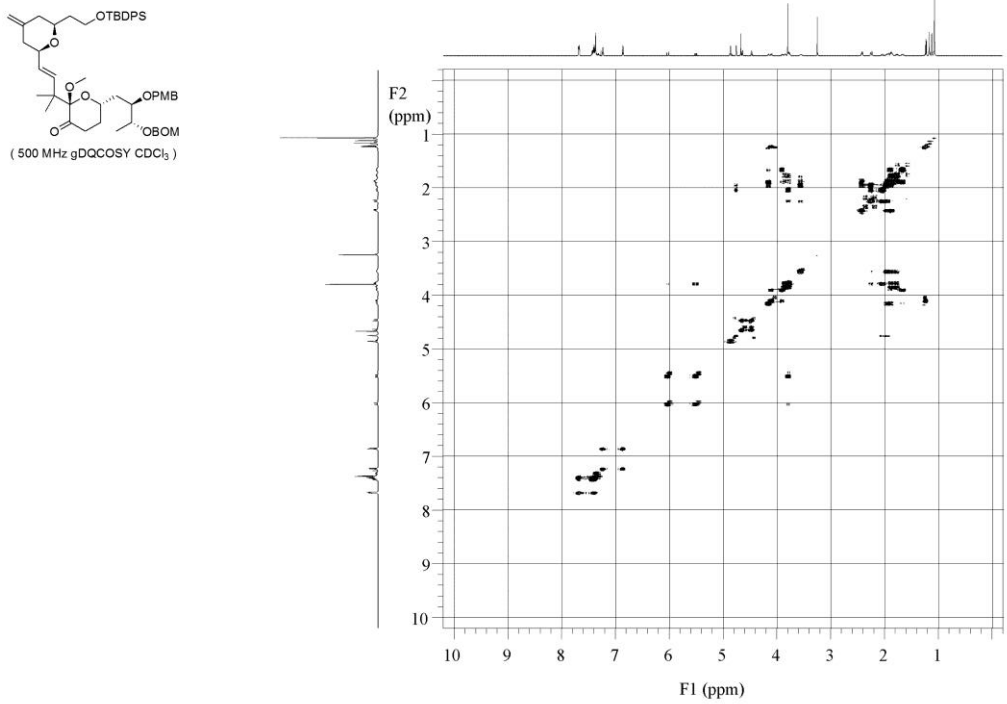

OTBDPS
OPMB
OBOM
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

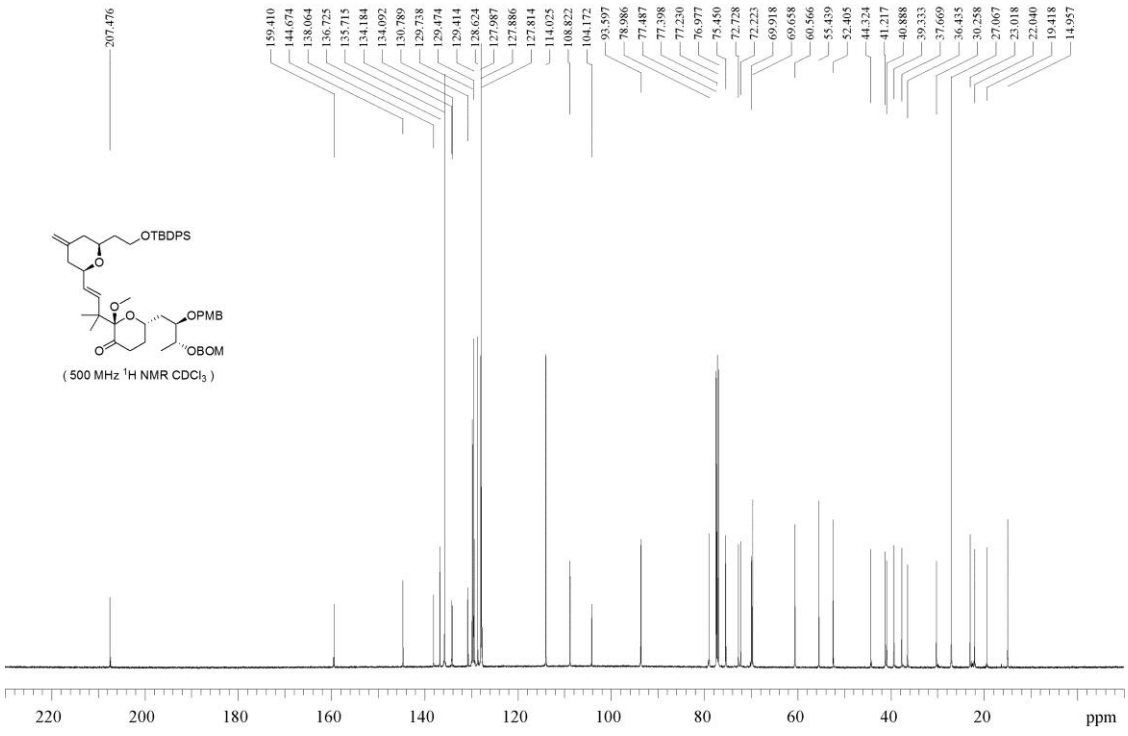

OTBDPS
OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

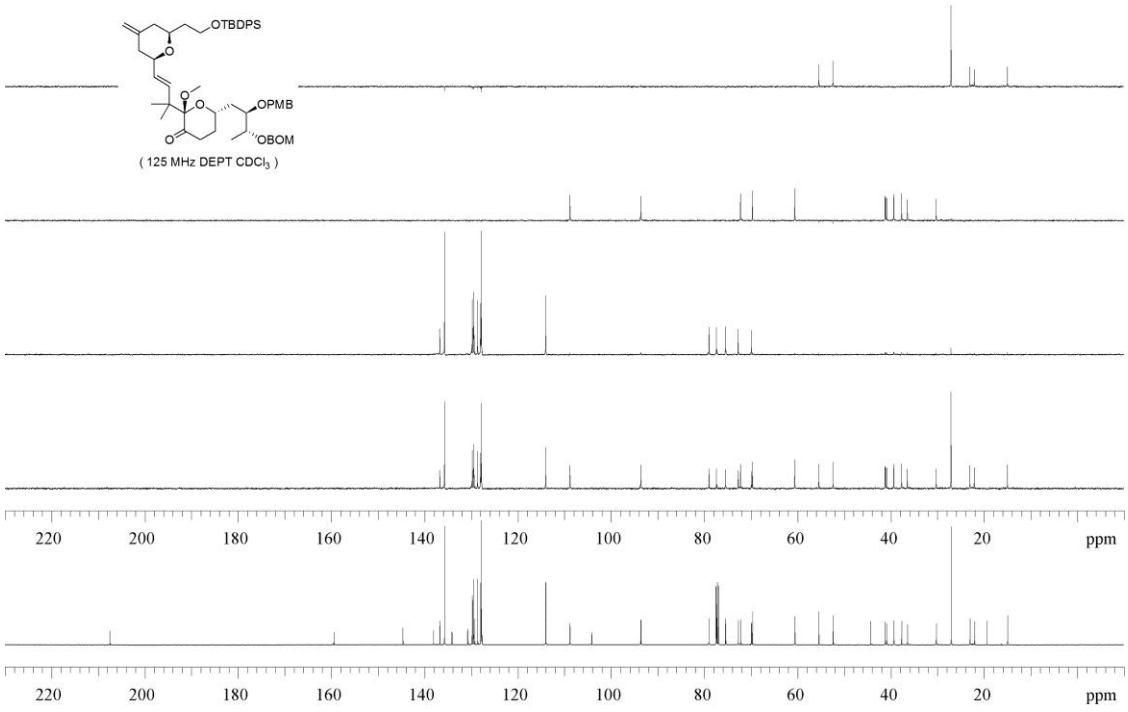

OTBDPS
OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

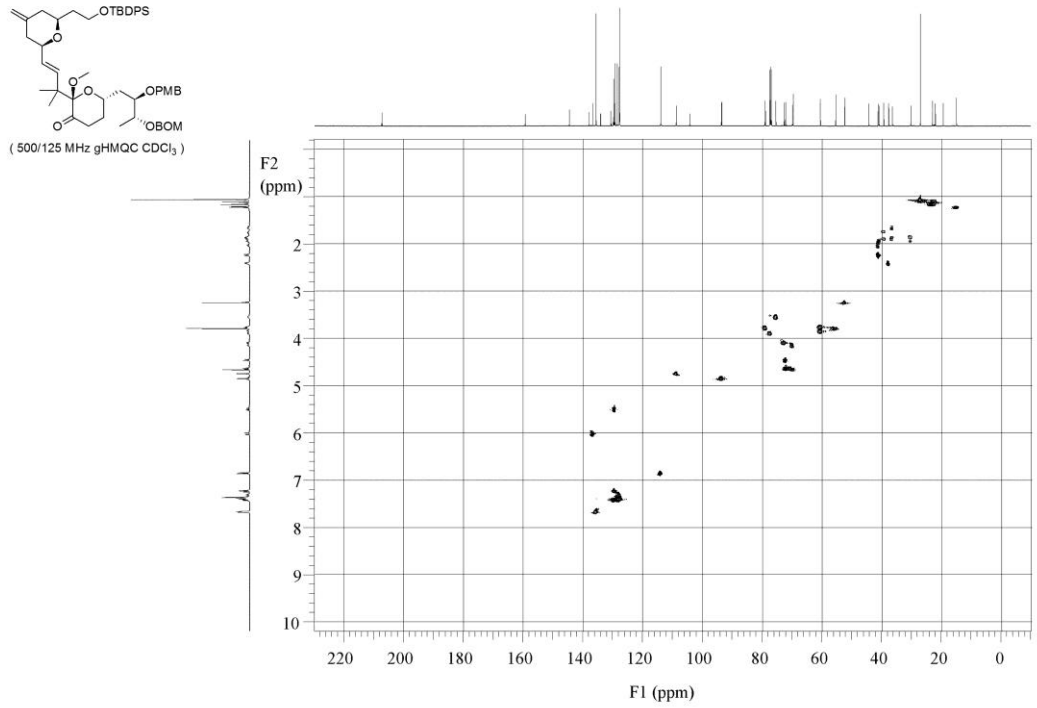

OTBDPS
17
H
O
13
H
NOESY1D
OPMB
OBOM
(500 MHz NOESY1D CDCl3)
Top: H-17 irradiation
Bottom: H-13 irradiation
10
9
8
7
6
5
4
3
2
1
ppm

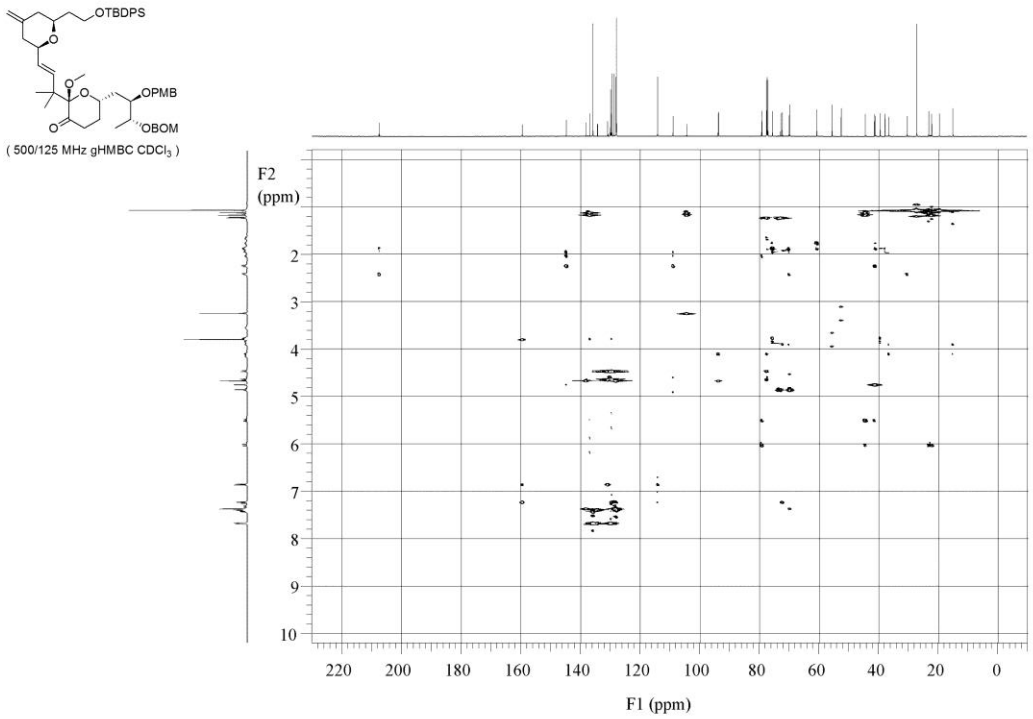

OTBDPS
O
O
O
OPMB
OBOM
O
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm
3.87
1.96
10.02
1.90
0.93
0.89
2.08
2.92
2.03
1.01
1.88
5.02
2.08
1.14
3.00
2.08
4.83
1.81
1.02
2.65
2.97
3.59
5.69

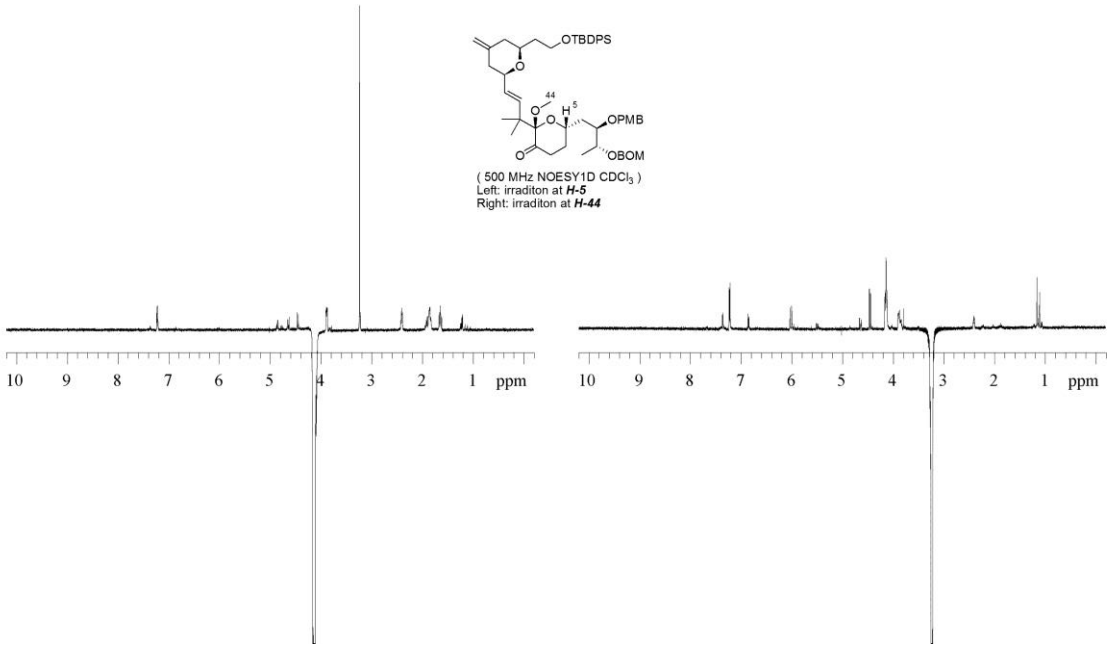

OTBDPS
OPMB
OBOM
(500 MHz gDQCOSY $CDCl_3$)
F2
(ppm)
F1 (ppm)

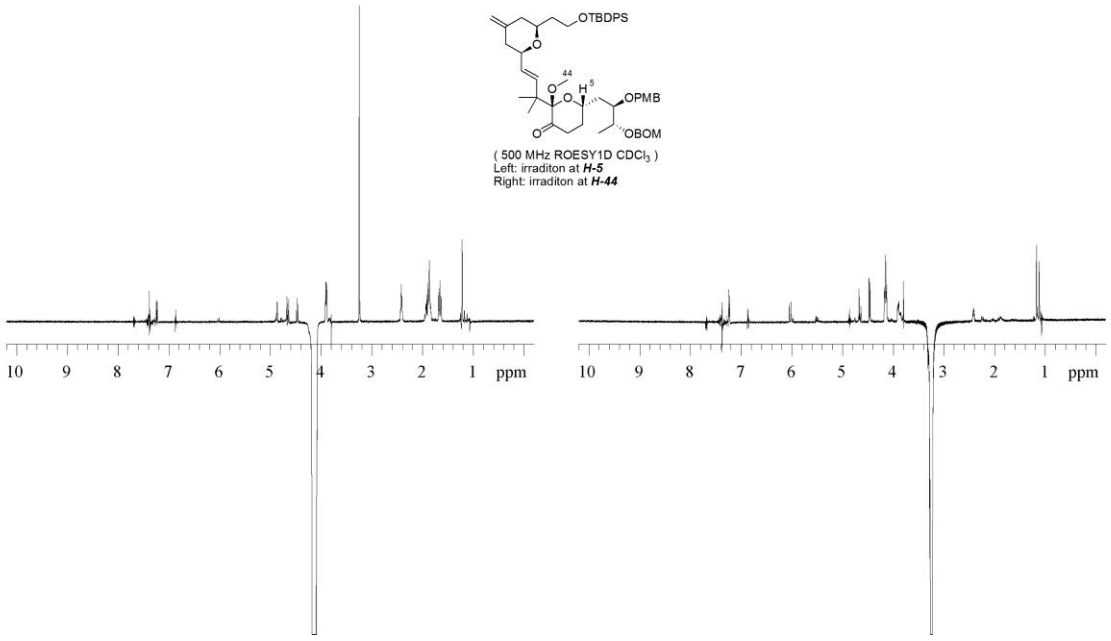

207.476
159.410
144.674
138.064
136.725
135.715
134.184
134.092
130.789
129.738
129.474
129.414
128.624
127.987
127.886
127.814
114.025
108.822
104.172
93.597
78.986
77.487
77.398
77.230
76.977
75.450
72.728
72.223
69.918
69.658
60.566
55.439
52.405
44.324
41.217
40.888
39.333
37.669
36.435
30.258
27.067
23.018
22.040
19.418
14.957
OTBDPS
OPMB
OBOM
(500 MHz ^1H NMR $CDCl_3$)
ppm


OTBDPS
OPMB
OBOM
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

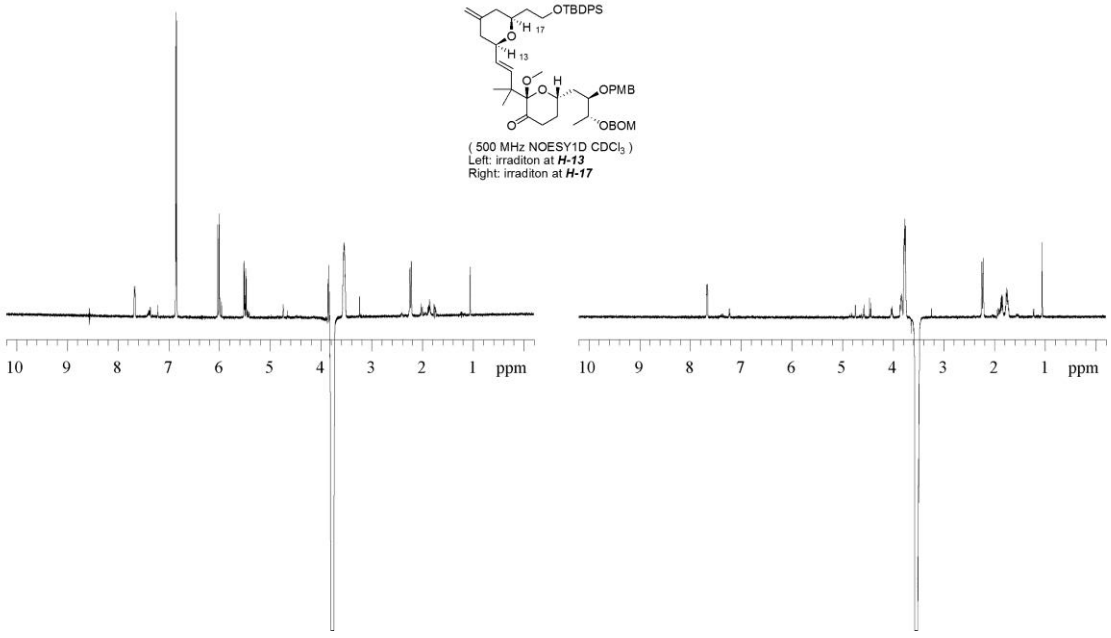

OTBDPS
OPMB
OBOM
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)


OTBDPS
OPMB
OBOM
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

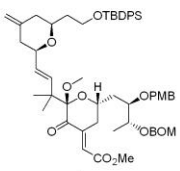

OTBDPS
OPMB
OBOM
(500 MHz NOESY1D CDCl3)
Left: irraditon at H-5
Right: irraditon at H-44
ppm
ppm



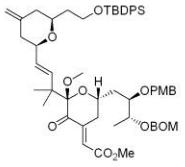
(500 MHz ROESY1D $CDCl_3$)
Left: irraditon at ***H-5***
Right: irraditon at ***H-44***



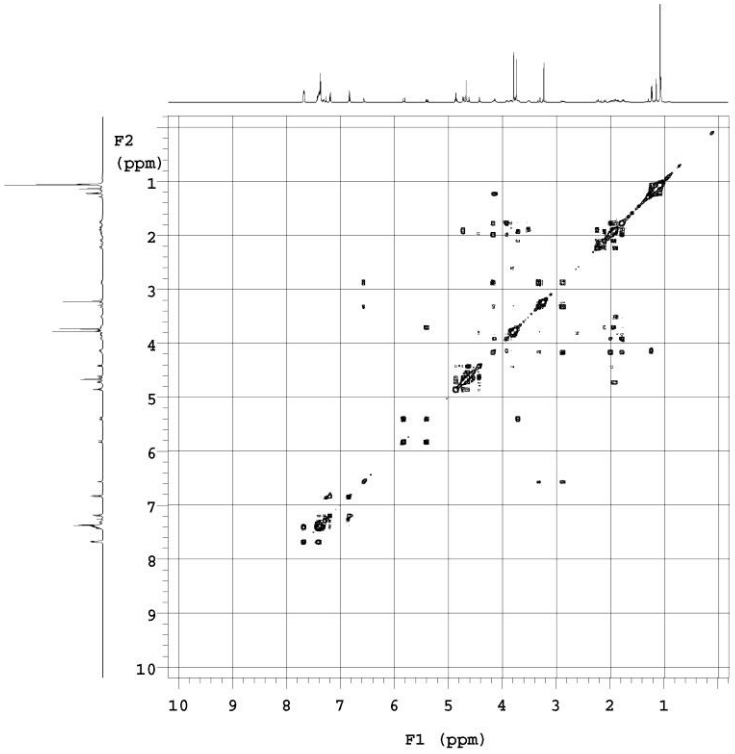
(500 MHz NOESY1D $CDCl_3$)
Left: irraditon at ***H-13***
Right: irraditon at ***H-17***

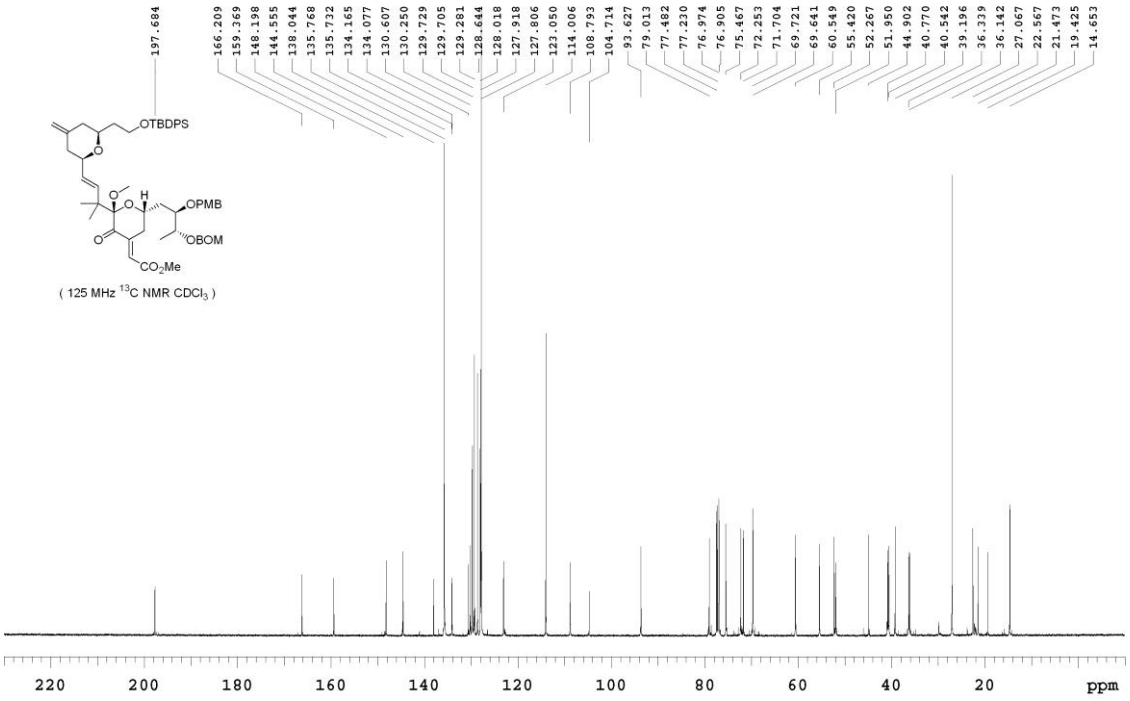


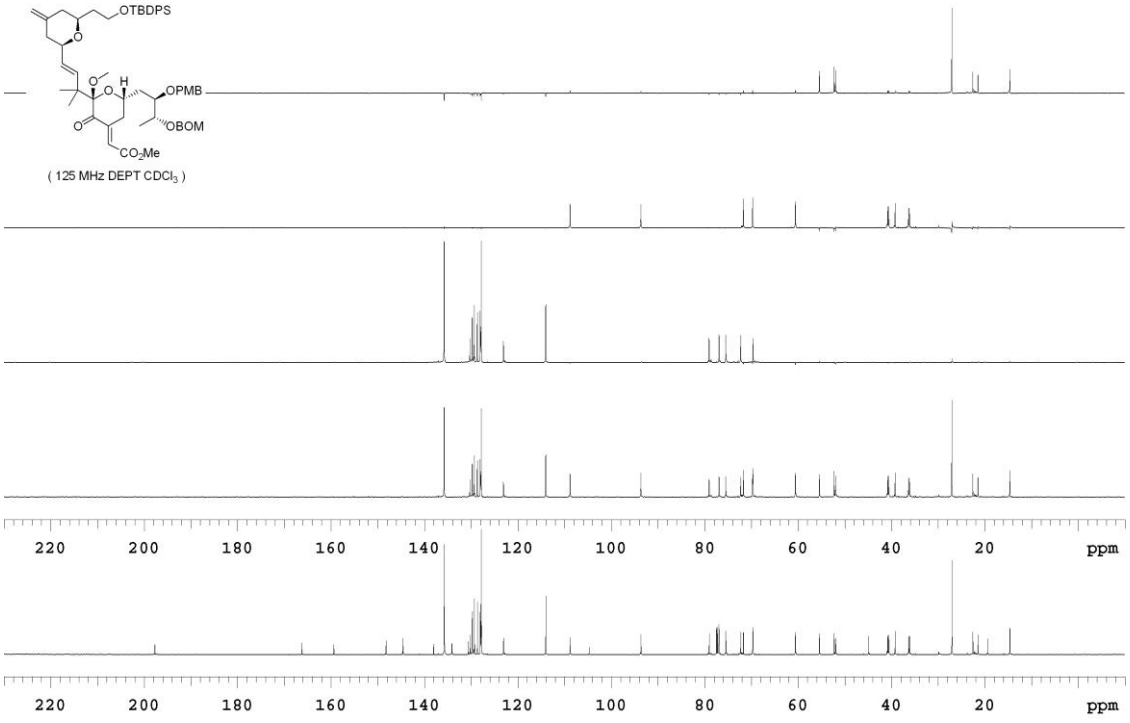
(500 MHz ^{1}H NMR $CDCl_3$)

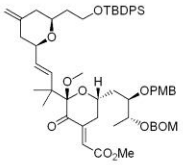


(500 MHz gCOSY $CDCl_3$)

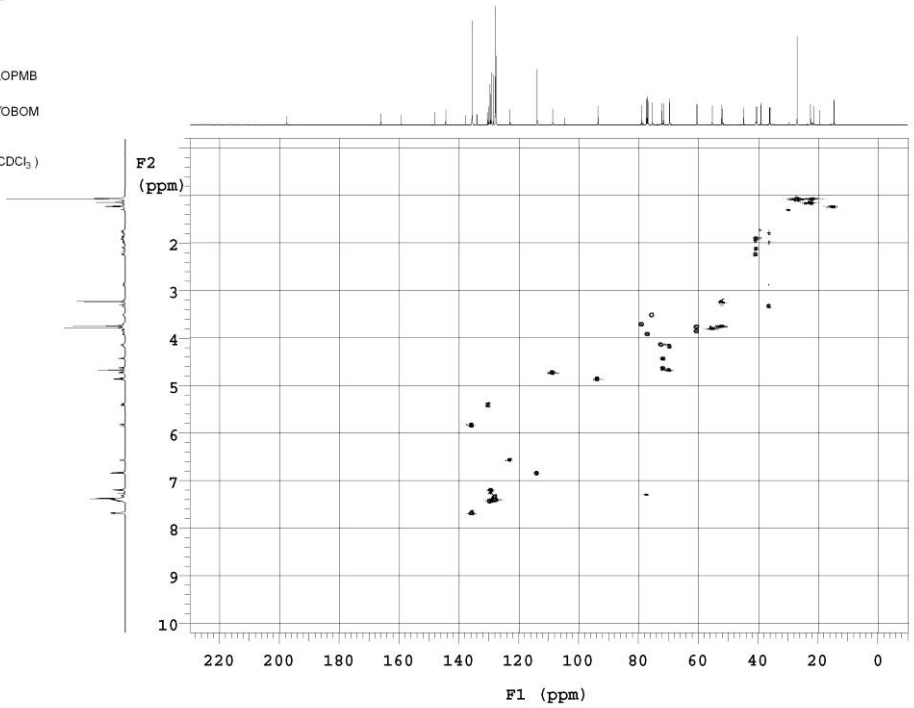


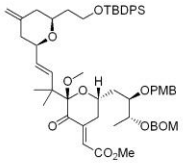

197.684
166.209
159.369
148.198
144.555
138.044
135.768
135.732
134.165
134.077
130.607
130.250
129.729
129.705
129.281
128.644
128.018
127.918
127.806
123.050
114.006
108.793
104.714
93.627
79.013
77.482
77.230
76.974
76.905
75.467
72.253
71.704
69.721
69.641
60.549
55.420
52.267
51.950
44.902
40.770
40.542
39.196
36.339
36.142
27.067
22.567
21.473
19.425
14.653
OTBDPS
OPMB
OBOM
CO2Me
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm


OTBDPS
OPMB
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

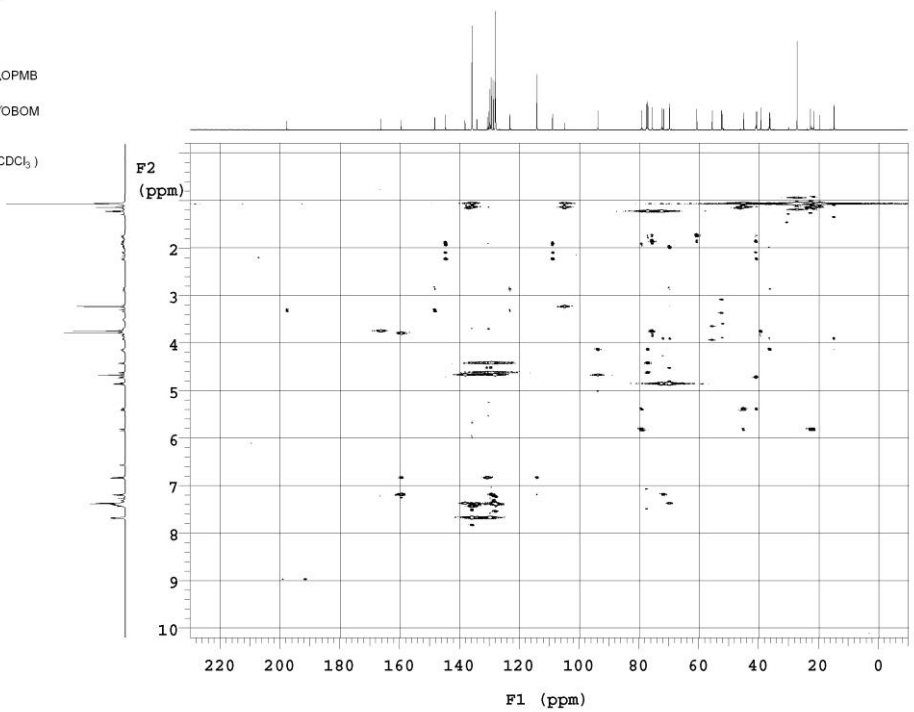


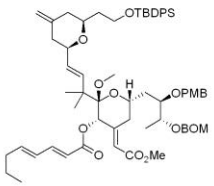
(500/125 MHz gHMQC $CDCl_3$)



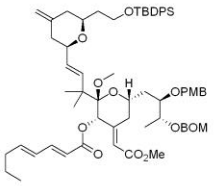


(500/125 MHz gHMBC $CDCl_3$)

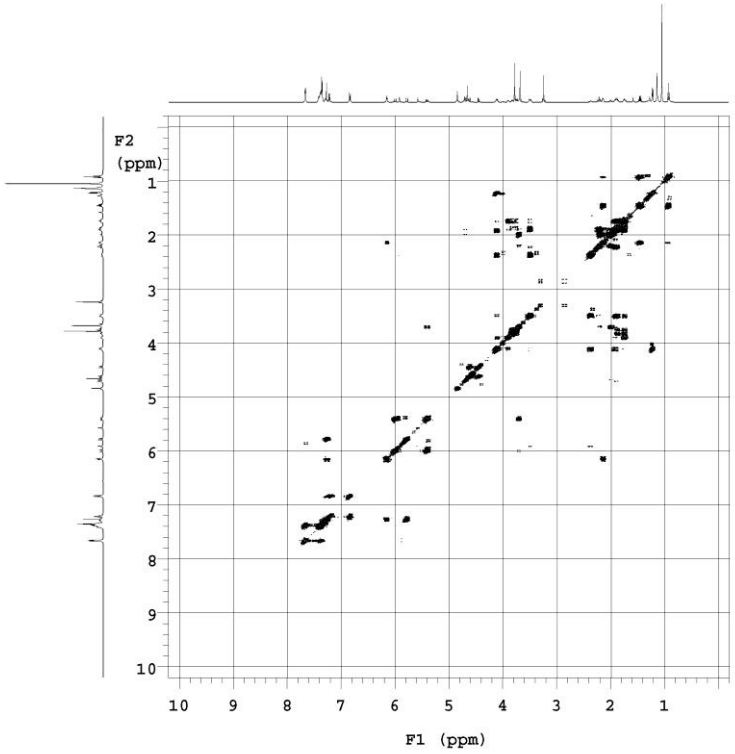


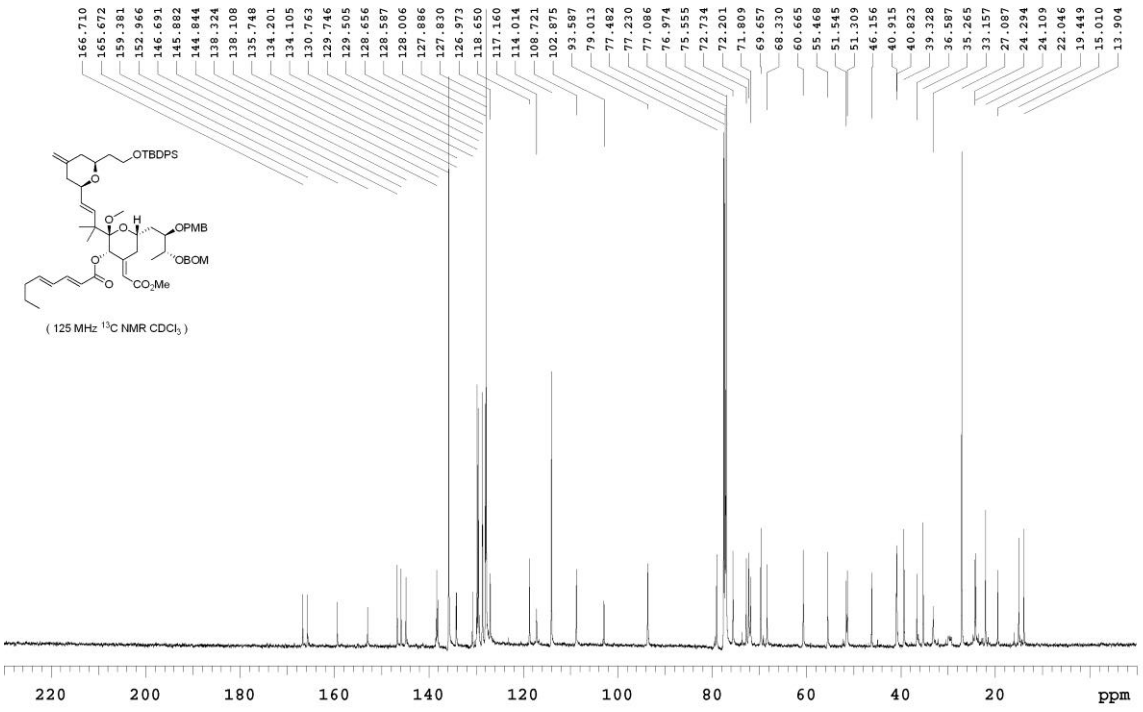


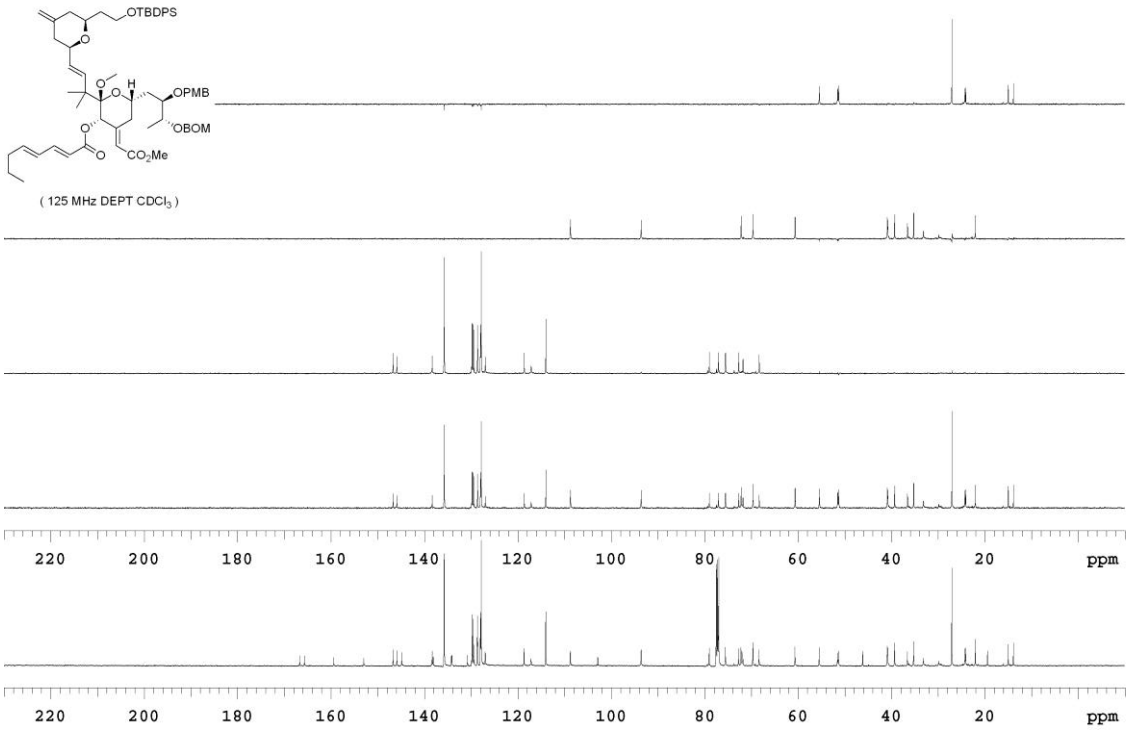
(500 MHz ^{1}H NMR $CDCl_3$)

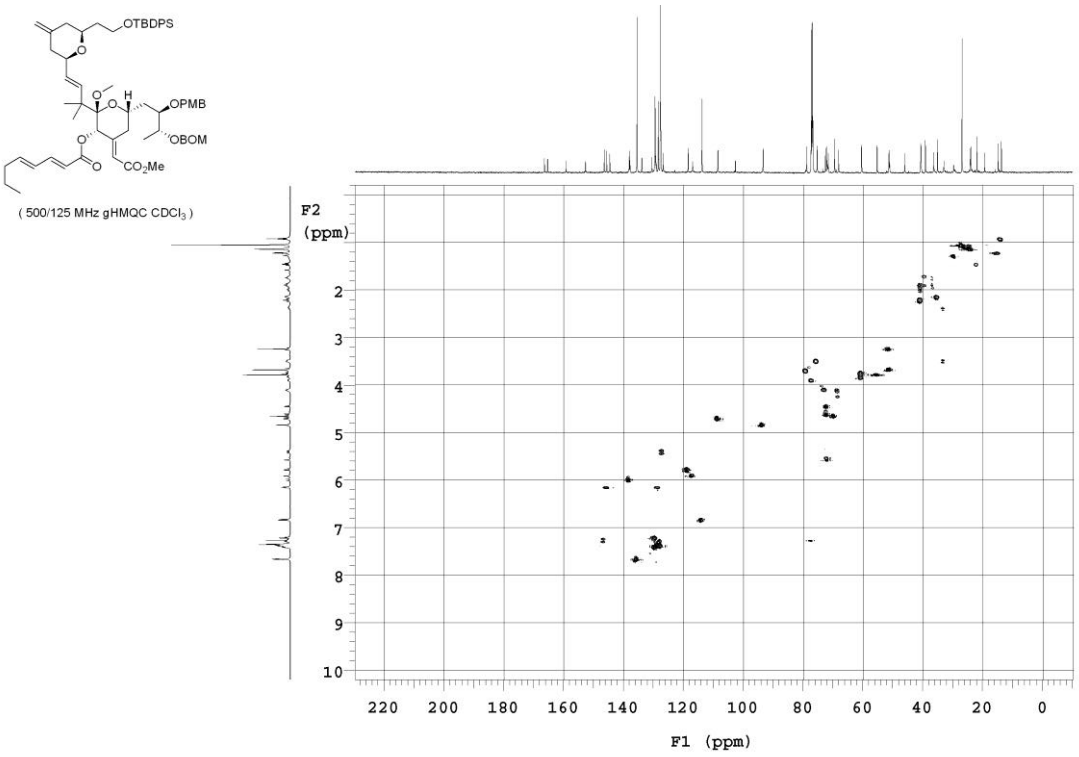


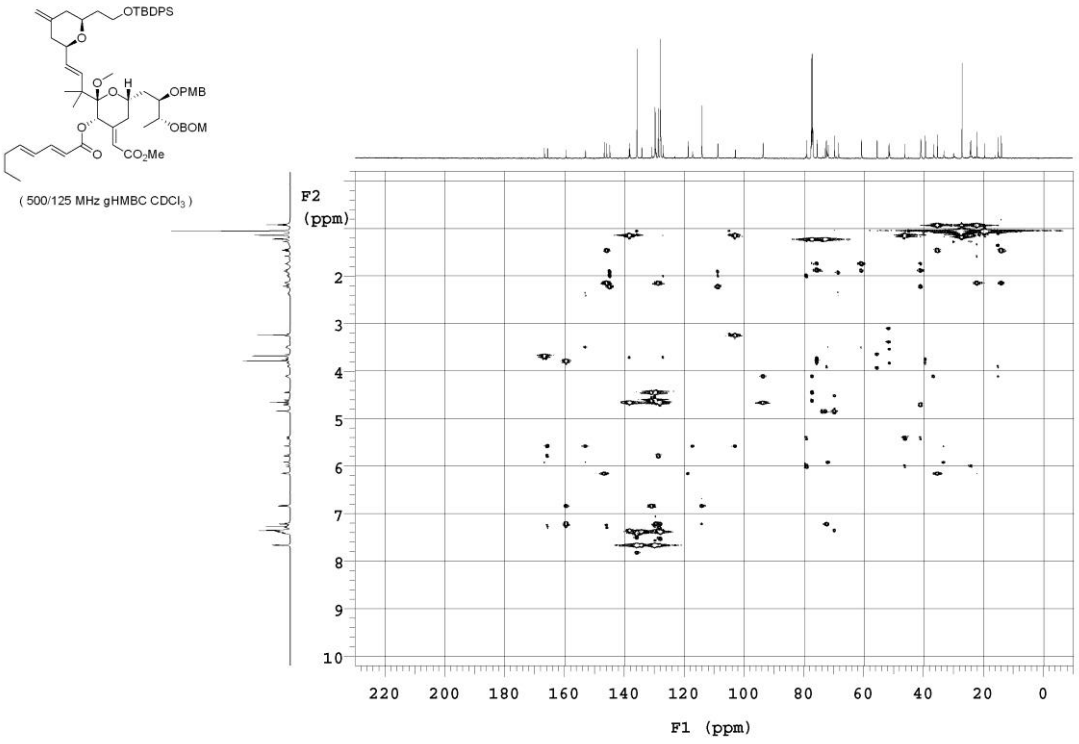
(500 MHz gDQCOSY $CDCl_3$)

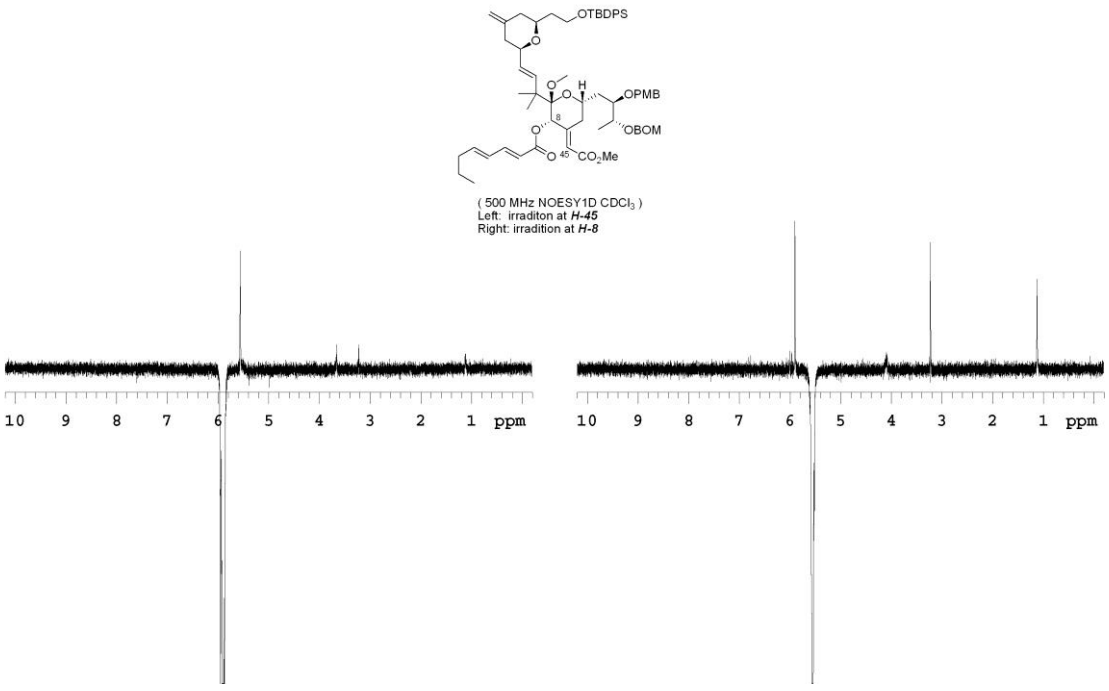


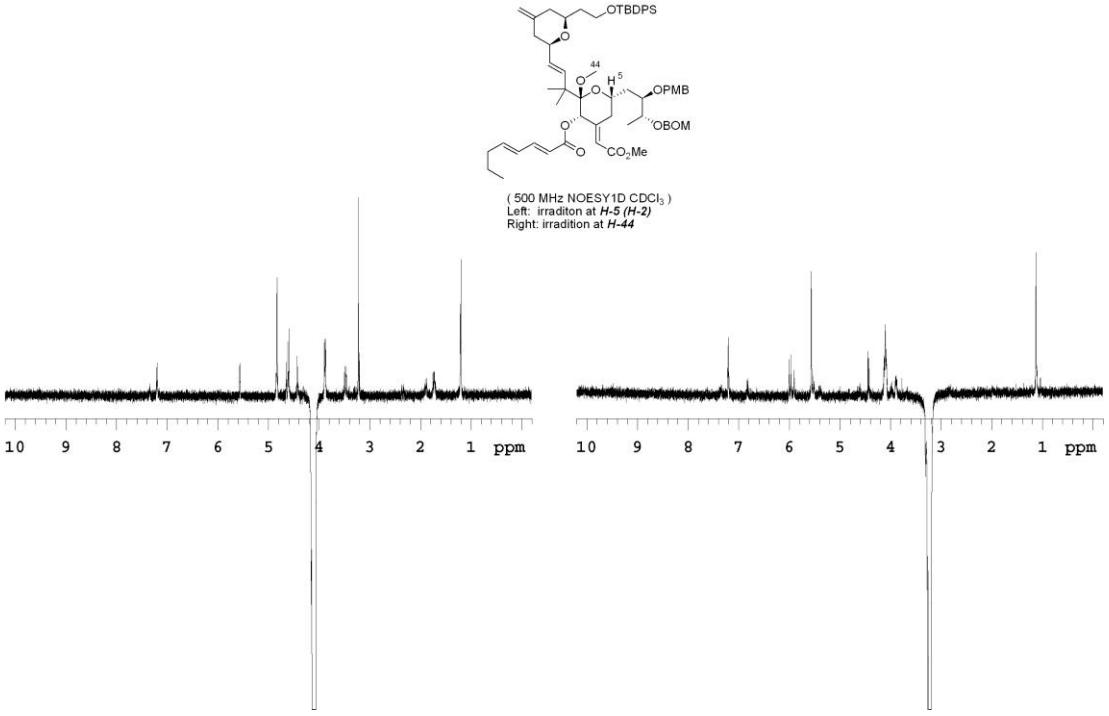

166.710
165.672
159.381
152.966
146.691
145.882
144.844
138.324
138.108
135.748
134.201
134.105
130.763
129.746
129.505
128.656
128.587
128.006
127.886
127.830
126.973
118.650
117.160
114.014
108.721
102.875
93.587
79.013
77.482
77.230
77.086
76.974
75.555
72.734
72.201
71.809
69.657
68.330
60.665
55.468
51.545
51.309
46.156
40.915
40.823
39.328
36.587
35.265
33.157
27.087
24.294
24.109
22.046
19.449
15.010
13.904
OTBDPS
OPMB
OBOM
CO2Me
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

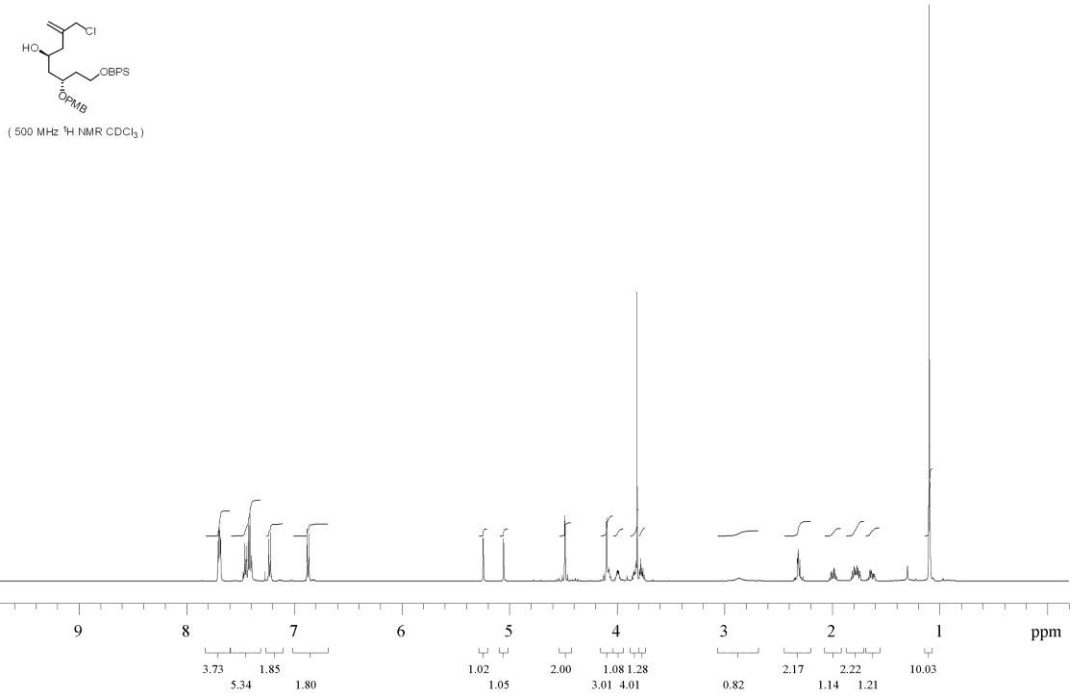

OTBDPS
OPMB
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

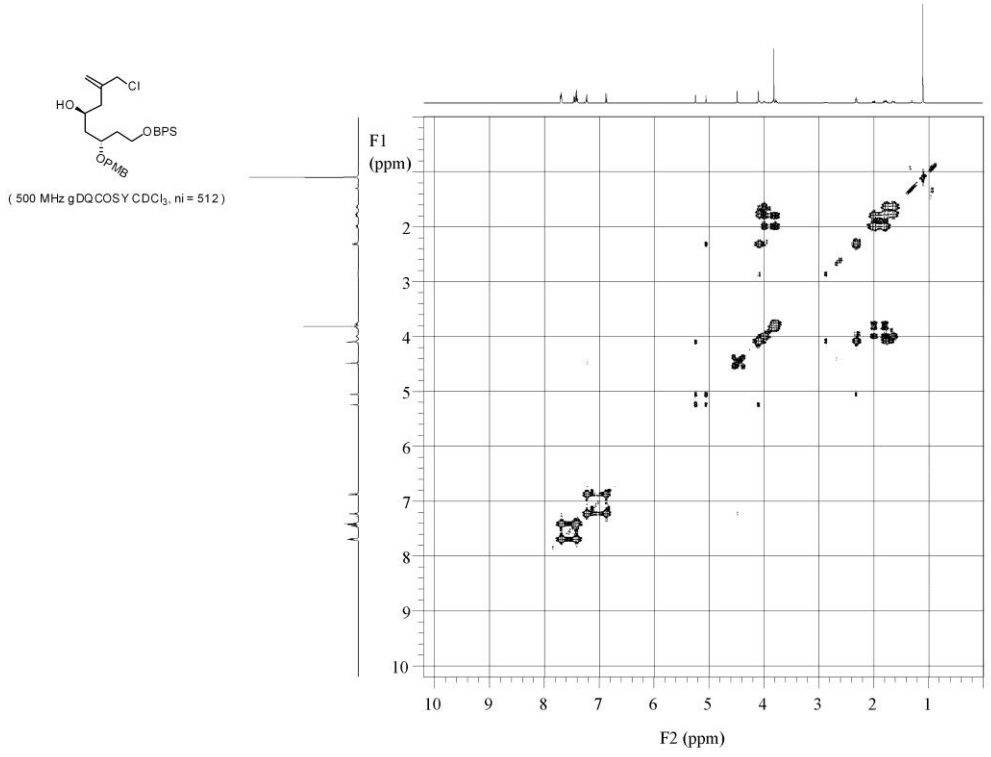

OTBDPS
OPMB
OBOM
CO2Me
(500/125 MHz gHMQC CDCl3)
F2 (ppm)
F1 (ppm)

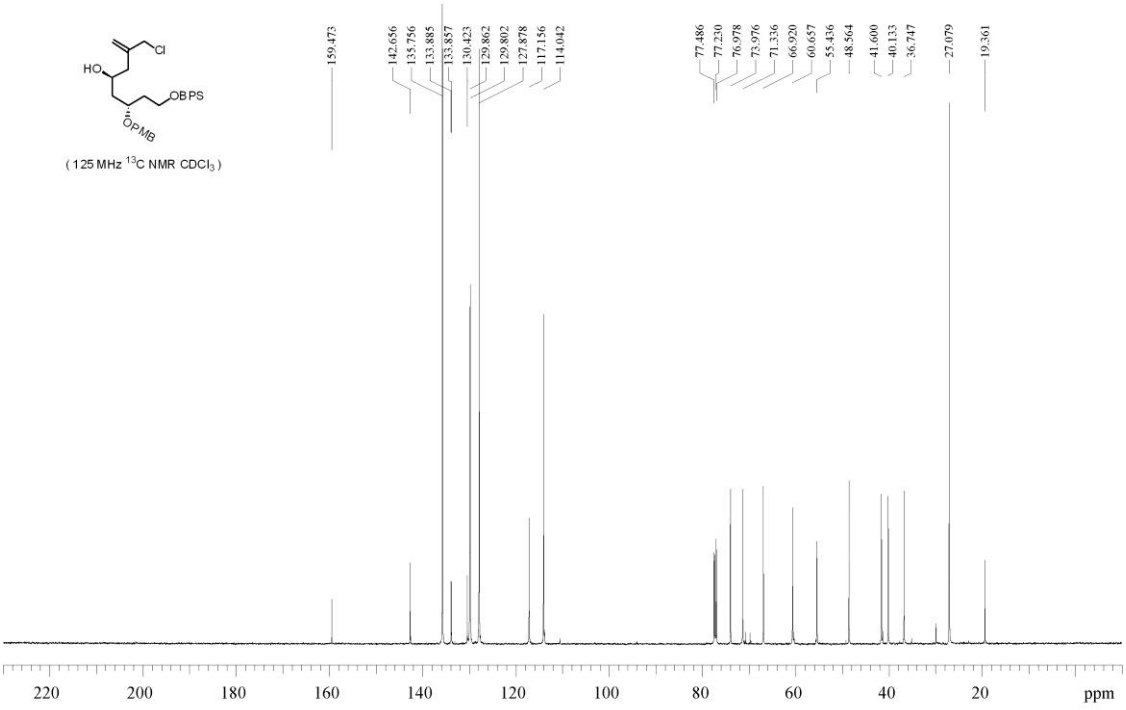

OTBDPS
OPMB
OBOM
CO2Me
(500/125 MHz gHMBC CDCl3)
F2 (ppm)
F1 (ppm)

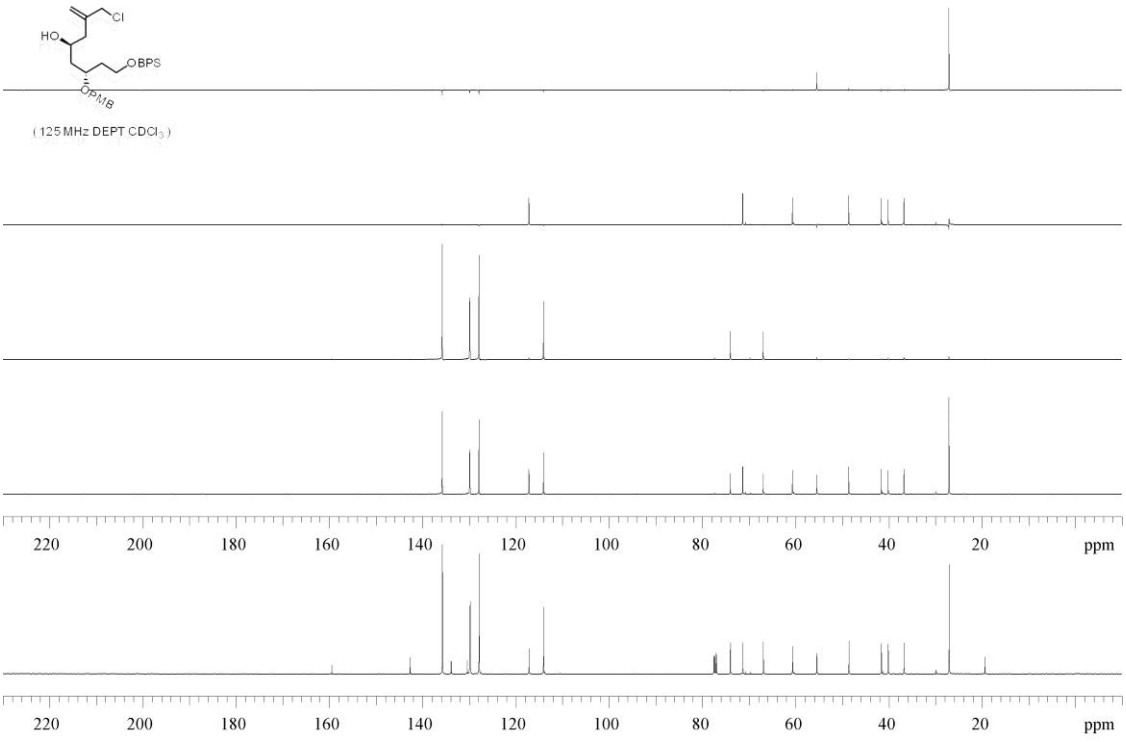

OTBDPS
OPMB
OBOM
CO2Me
(500 MHz NOESY1D CDCl3)
Left: irraditon at H-45
Right: irradition at H-8
10 9 8 7 6 5 4 3 2 1 ppm
10 9 8 7 6 5 4 3 2 1 ppm

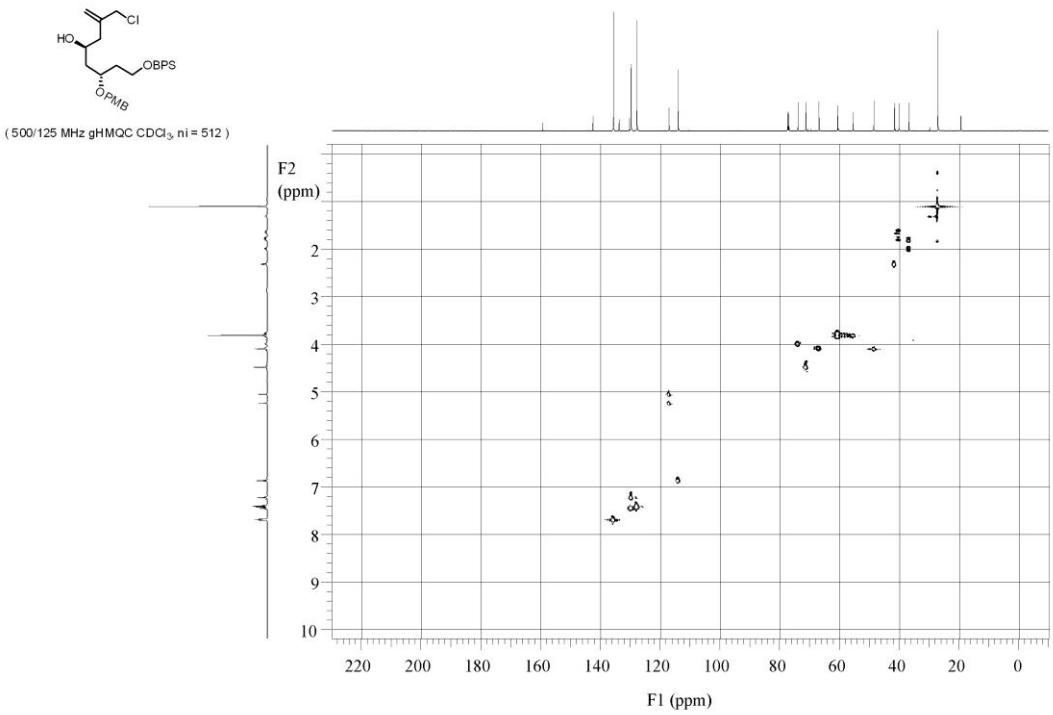

OTBDPS
OPMB
OBOM
CO2Me
(500 MHz NOESY1D CDCl3)
Left: irraditon at H-5 (H-2)
Right: irradition at H-44
10 9 8 7 6 5 4 3 2 1 ppm
10 9 8 7 6 5 4 3 2 1 ppm


Cl
HO
OBPS
OPMB
(500 MHz ^{1}H NMR $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
ppm
3.73
1.85
5.34
1.80
1.02
1.05
2.00
1.08
1.28
3.01
4.01
0.82
2.17
2.22
1.14
1.21
10.03

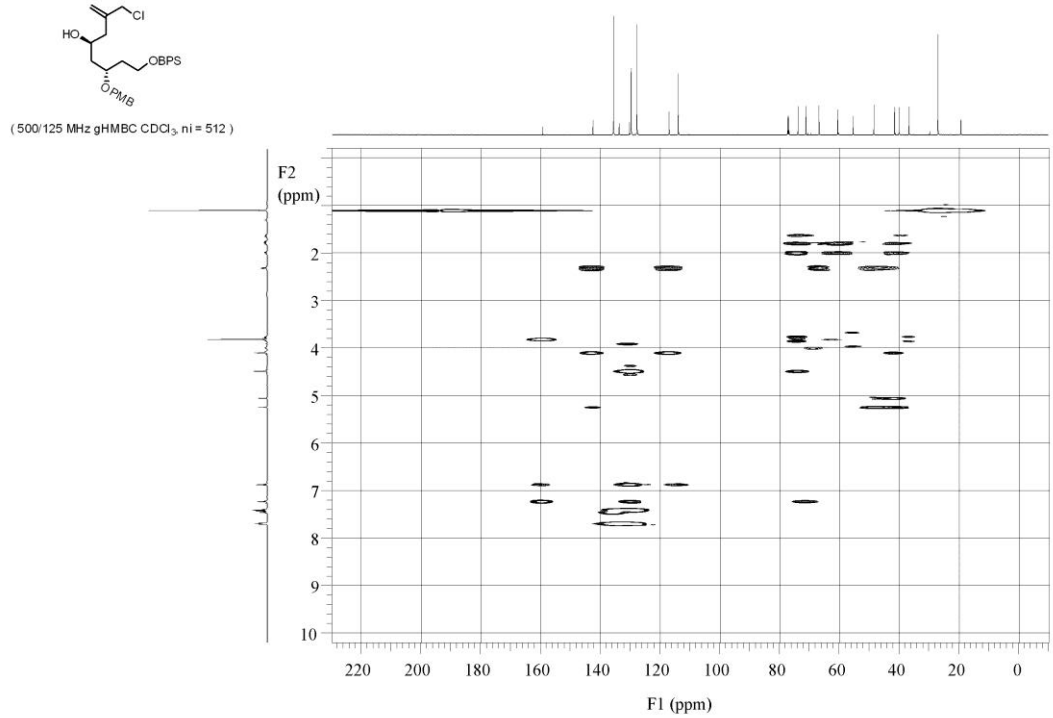

Cl
HO
OBPS
OPMB
(500 MHz gDQCOSY $CDCl_3$, ni = 512)
F1
(ppm)
F2 (ppm)


159.473
142.656
135.756
133.885
133.857
130.423
129.862
129.802
127.878
117.156
114.042
77.486
77.230
76.978
73.976
71.336
66.920
60.657
55.436
48.564
41.600
40.133
36.747
27.079
19.361
Cl
HO
OBPS
OPMB
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

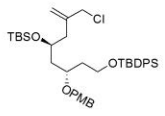

Cl
HO
OBPS
OPMB
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm



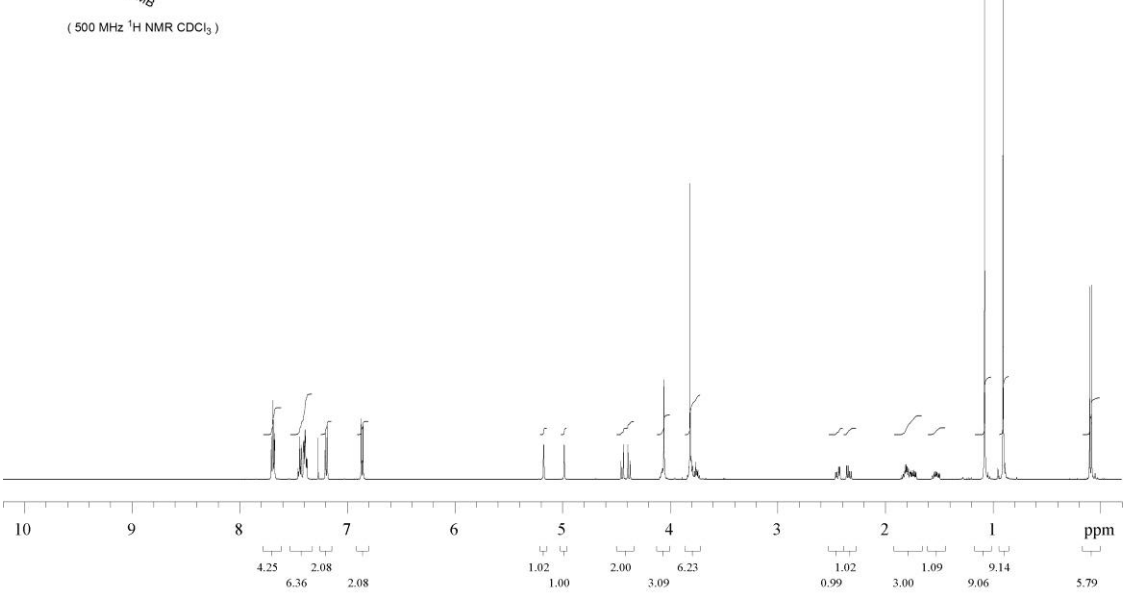
(500/125 MHz gHMQC $CDCl_3$, ni = 512)

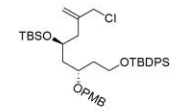


(500/125 MHz gHMBC $CDCl_3$, ni = 512)

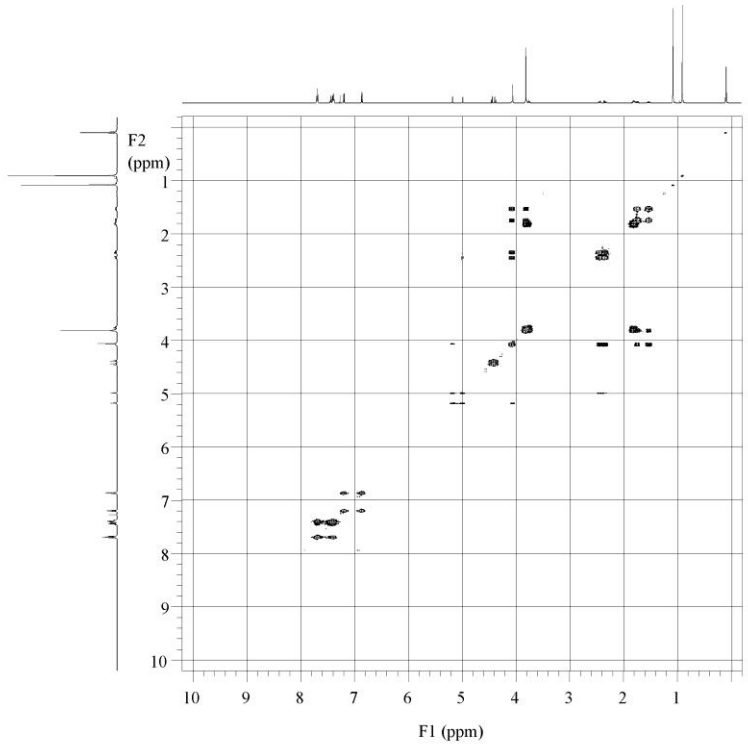


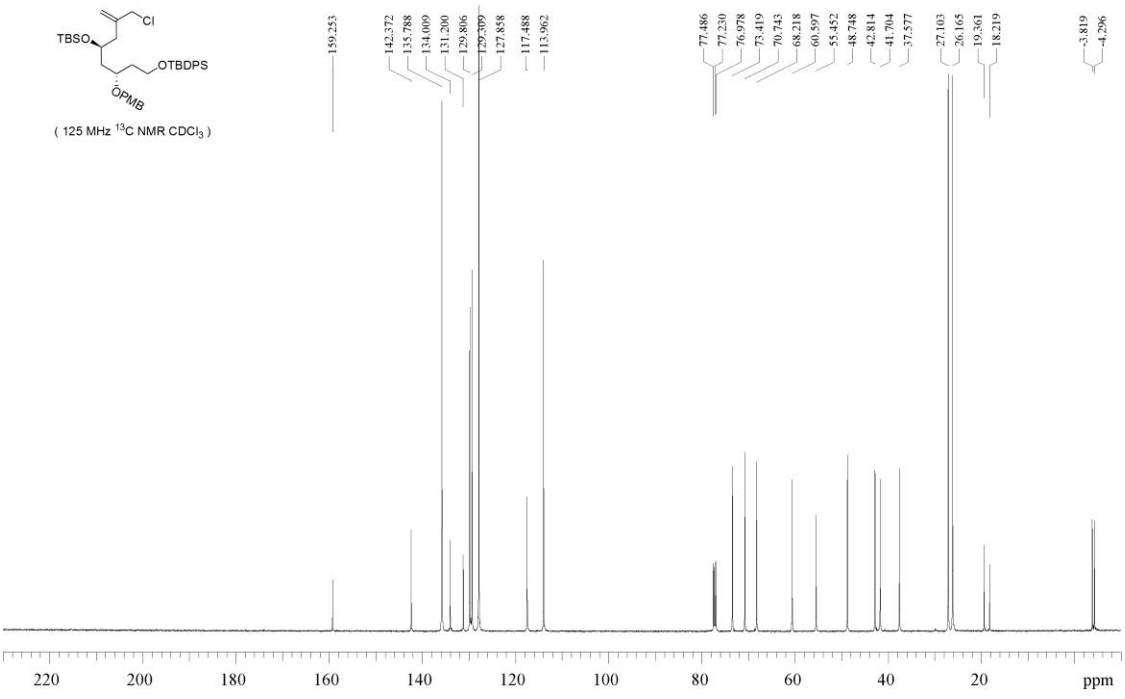
(500 MHz ^{1}H NMR $CDCl_3$)

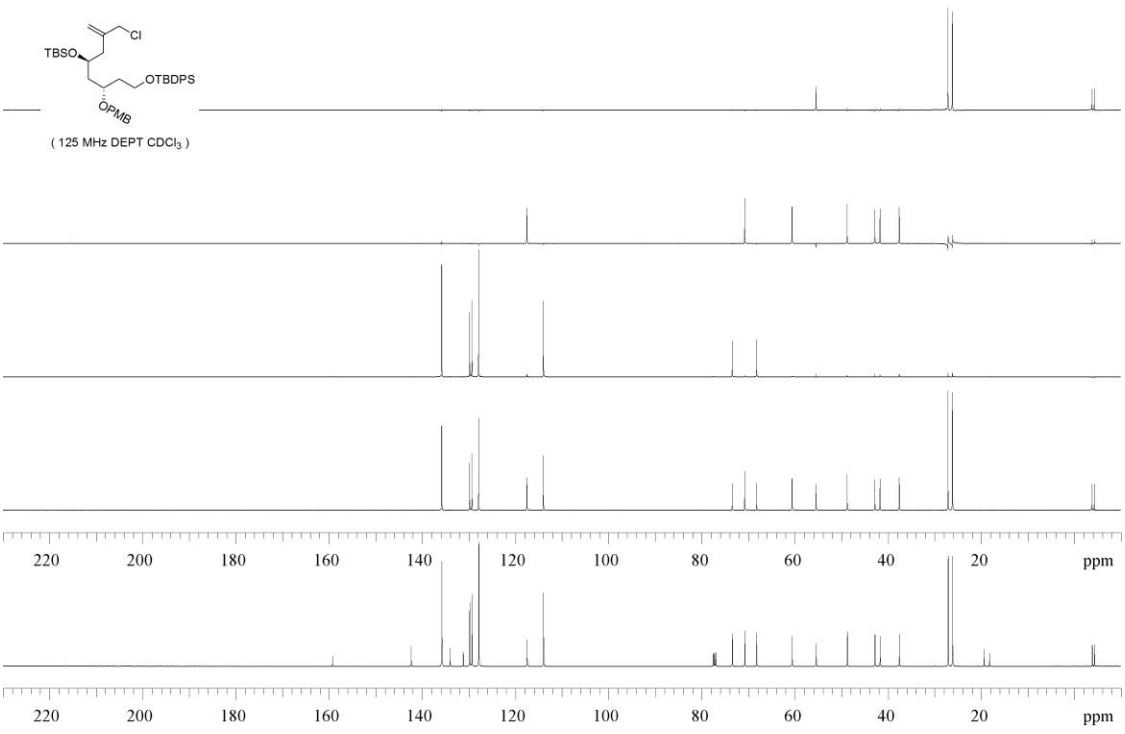


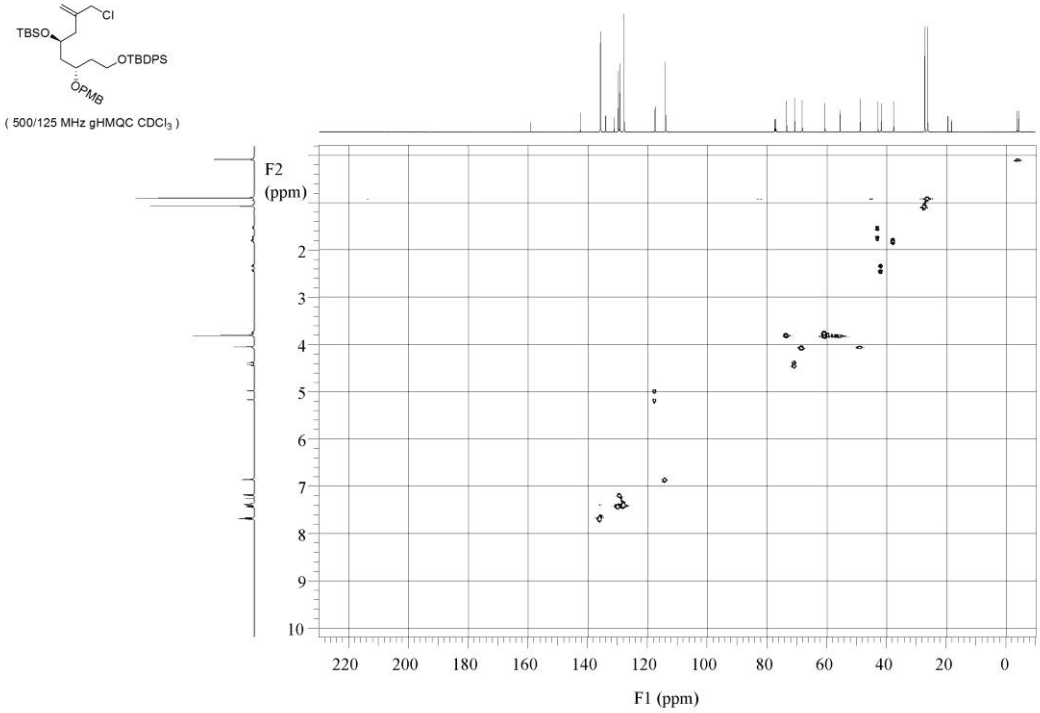


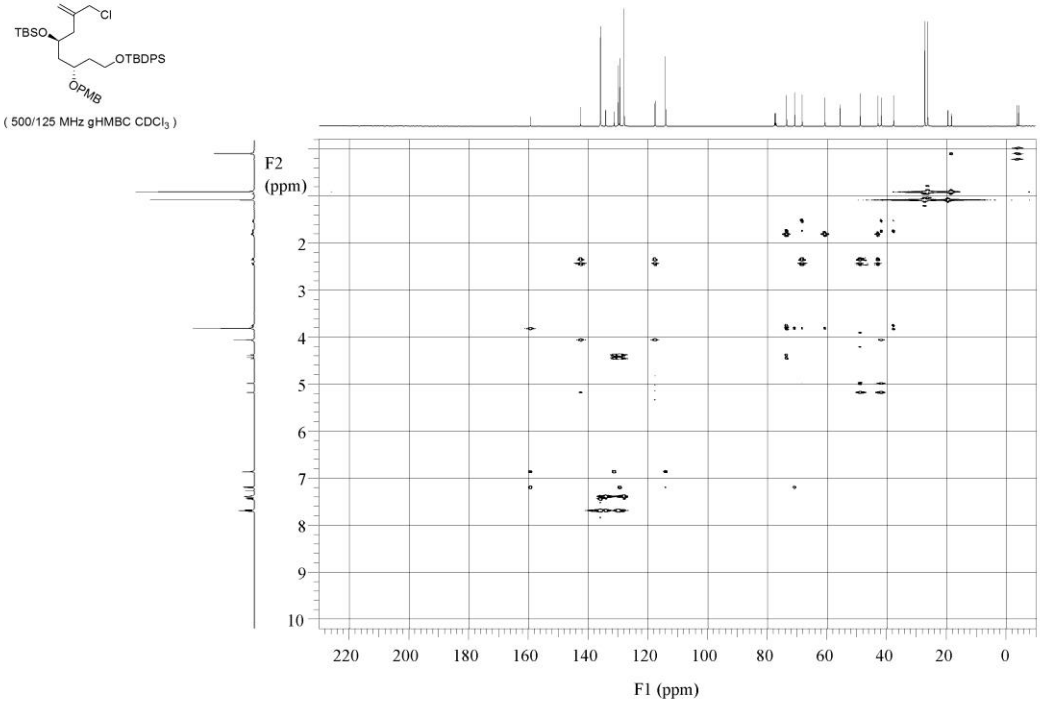
(500 MHz gDQCOSY $CDCl_3$)

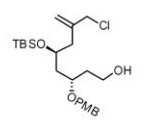



TBSO
Cl
OTBDPS
OPMB
(125 MHz ^{13}C NMR $CDCl_3$)
159.253
142.372
135.788
134.009
131.200
129.806
129.309
127.858
117.488
113.962
77.486
77.230
76.978
73.419
70.743
68.218
60.597
55.452
48.748
42.814
41.704
37.577
27.103
26.165
19.361
18.219
-3.819
-4.296
220
200
180
160
140
120
100
80
60
40
20
ppm

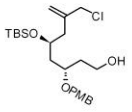

TBSO
Cl
OTBDPS
OPMB
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm


Cl
TBSO
OTBDPS
OPMB
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

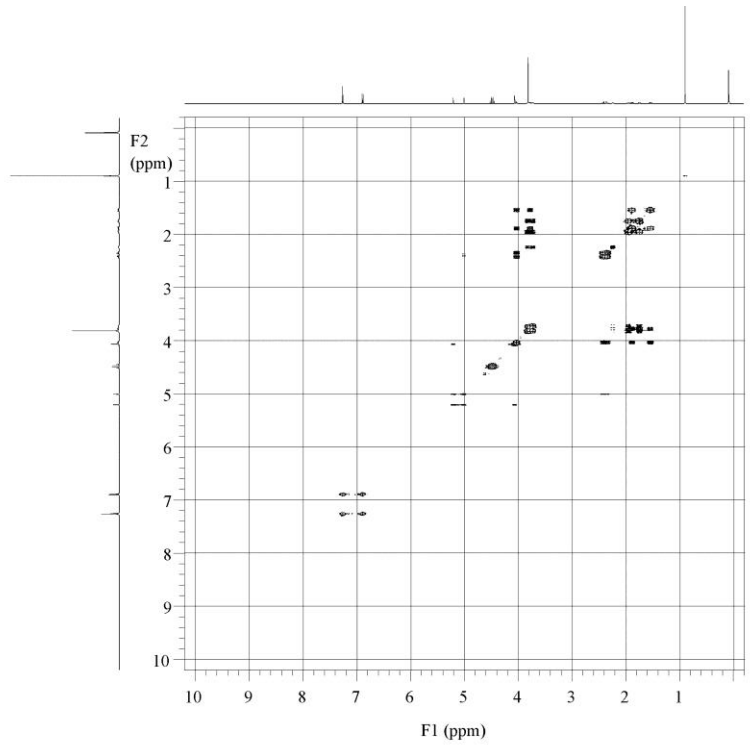

Cl
TBSO
OTBDPS
OPMB
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

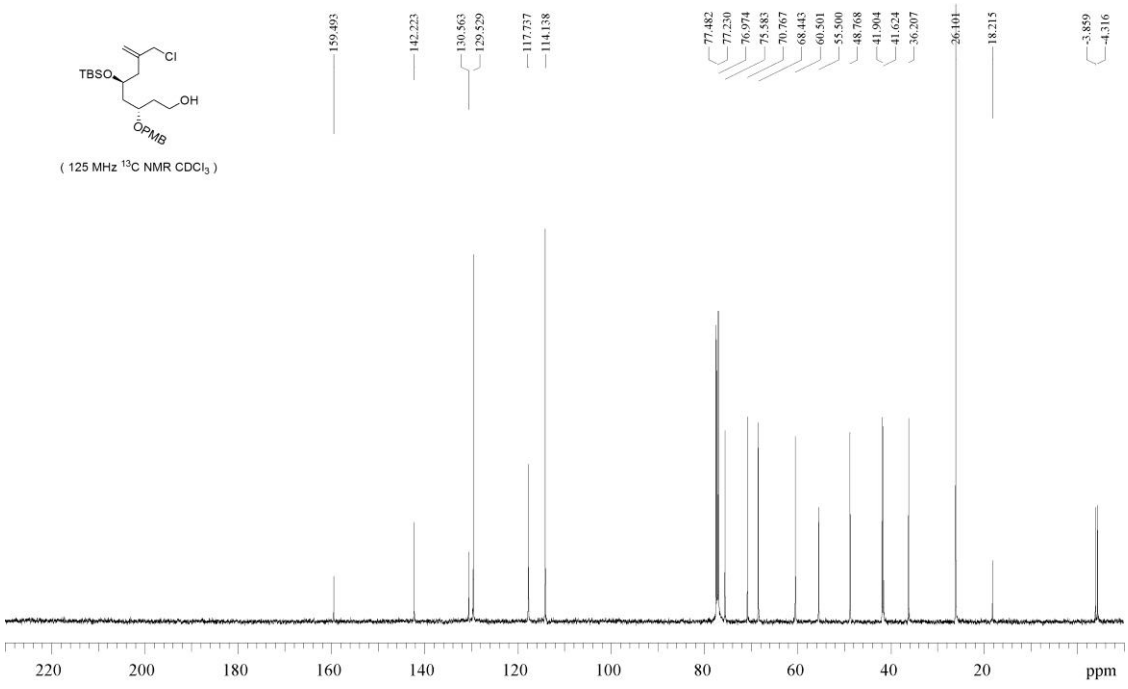


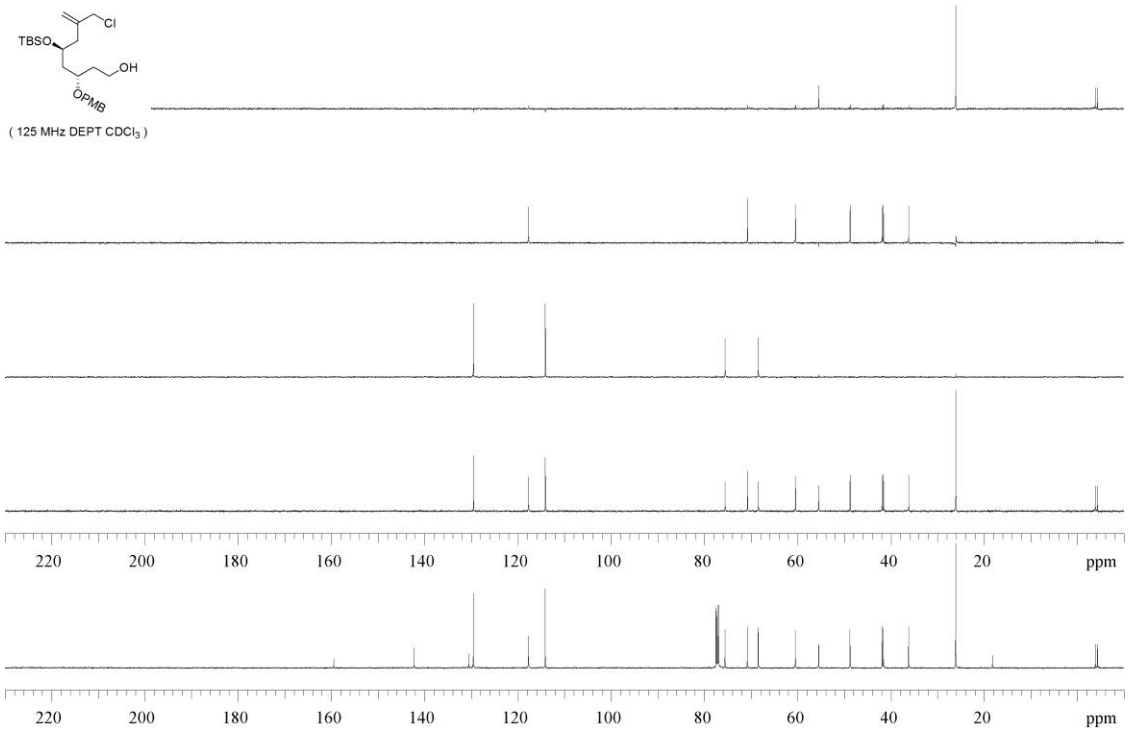
(500 MHz ^{1}H NMR $CDCl_3$)

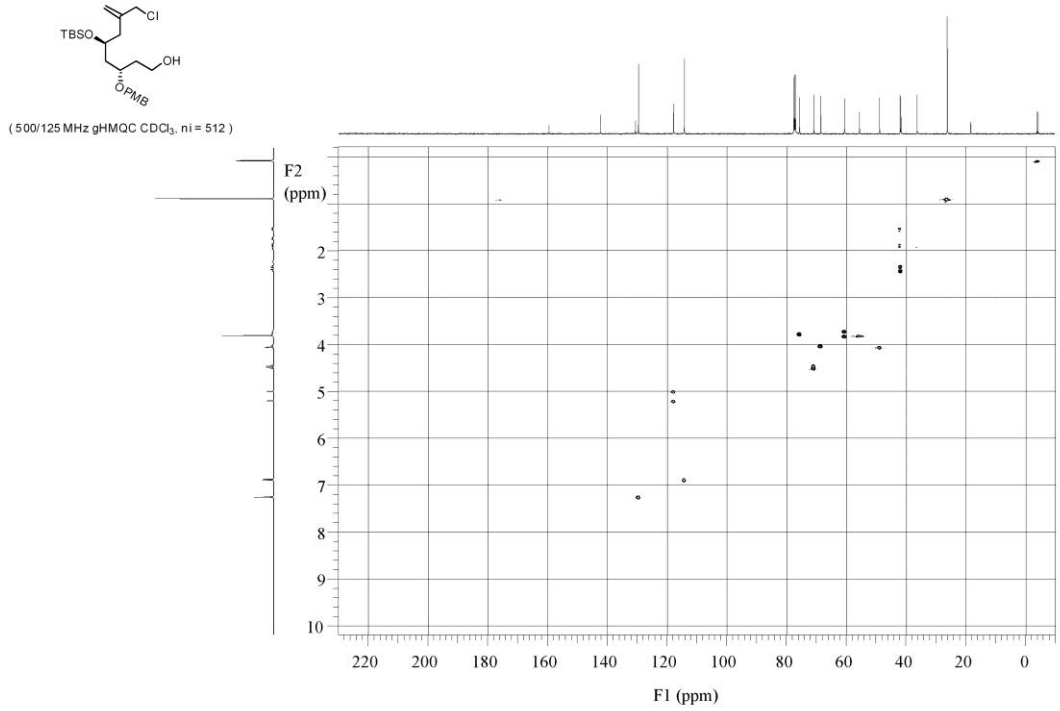


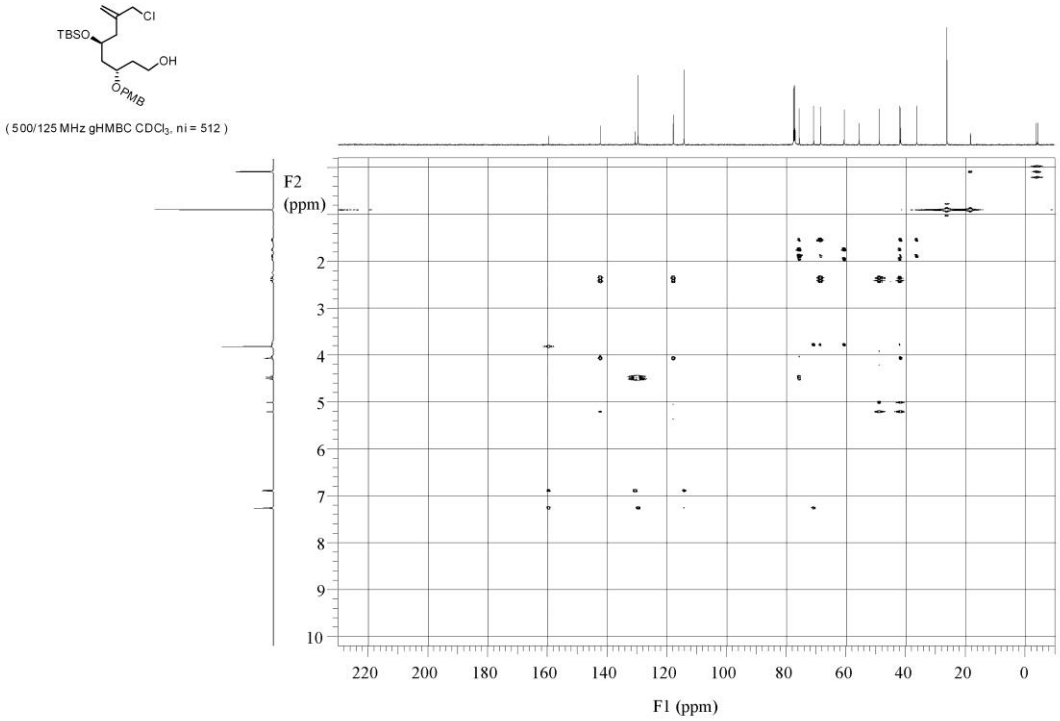
(500 MHz gDQCOSY $CDCl_3$, ni = 512)

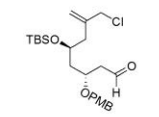



159.493
142.223
130.563
129.529
117.737
114.138
77.482
77.230
76.974
75.583
70.767
68.443
60.501
55.500
48.768
41.904
41.624
36.207
26.101
18.215
-3.859
-4.316
Cl
TBSO
OH
OPMB
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

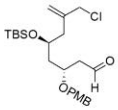

Cl
TBSO
OH
OPMB
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm


Cl
TBSO
OH
OPMB
(500/125 MHz gHMQC CDCl3, ni = 512)
F2
(ppm)
F1 (ppm)

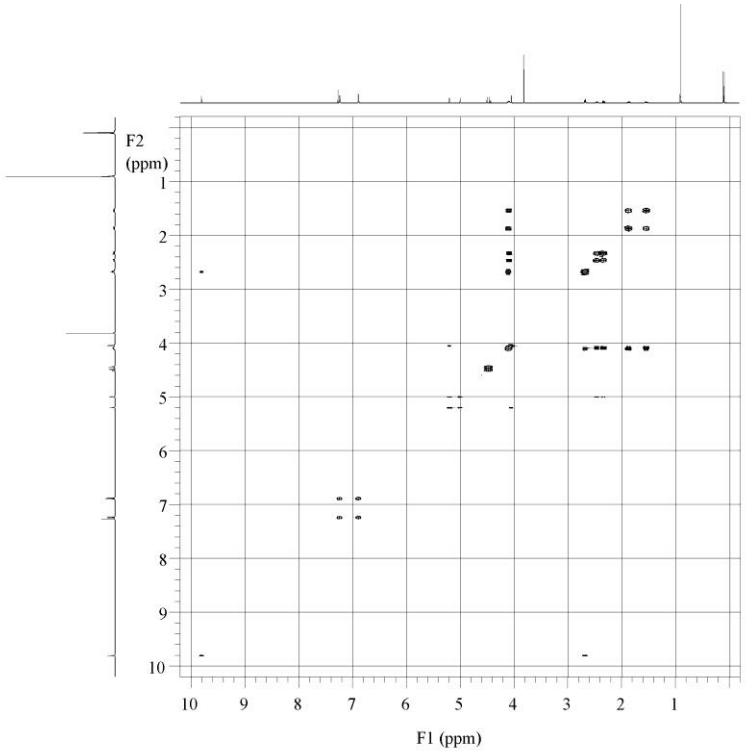

Cl
TBSO
OH
OPMB
(500/125 MHz gHMBC CDCl3, ni = 512)
F2
(ppm)
F1 (ppm)

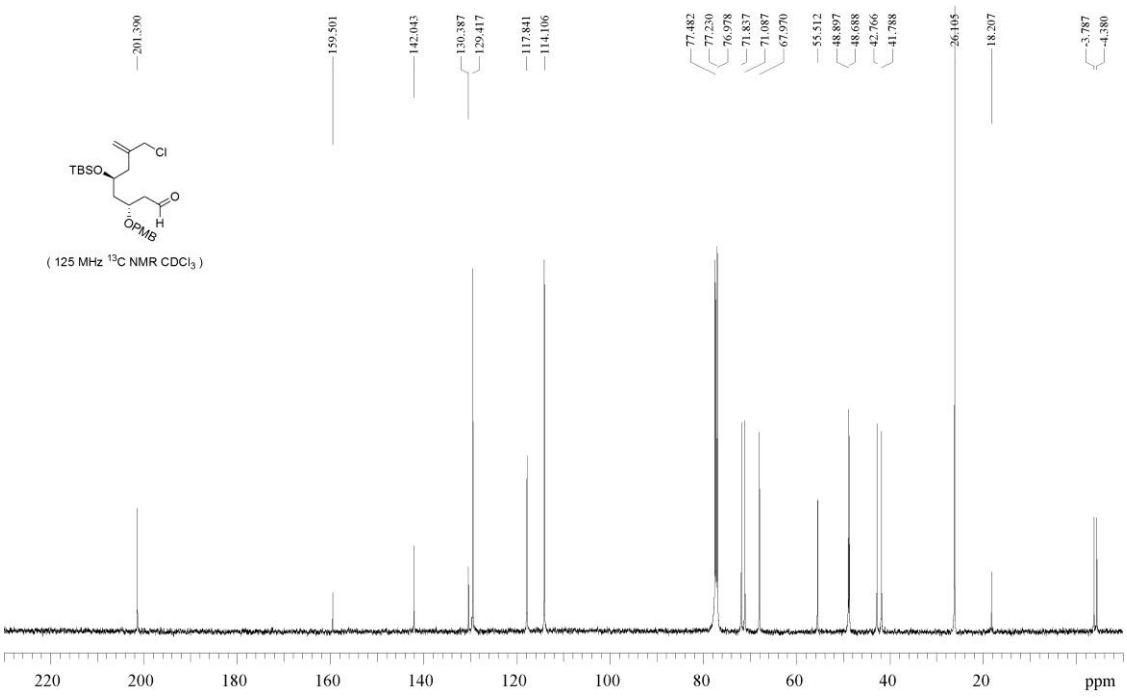


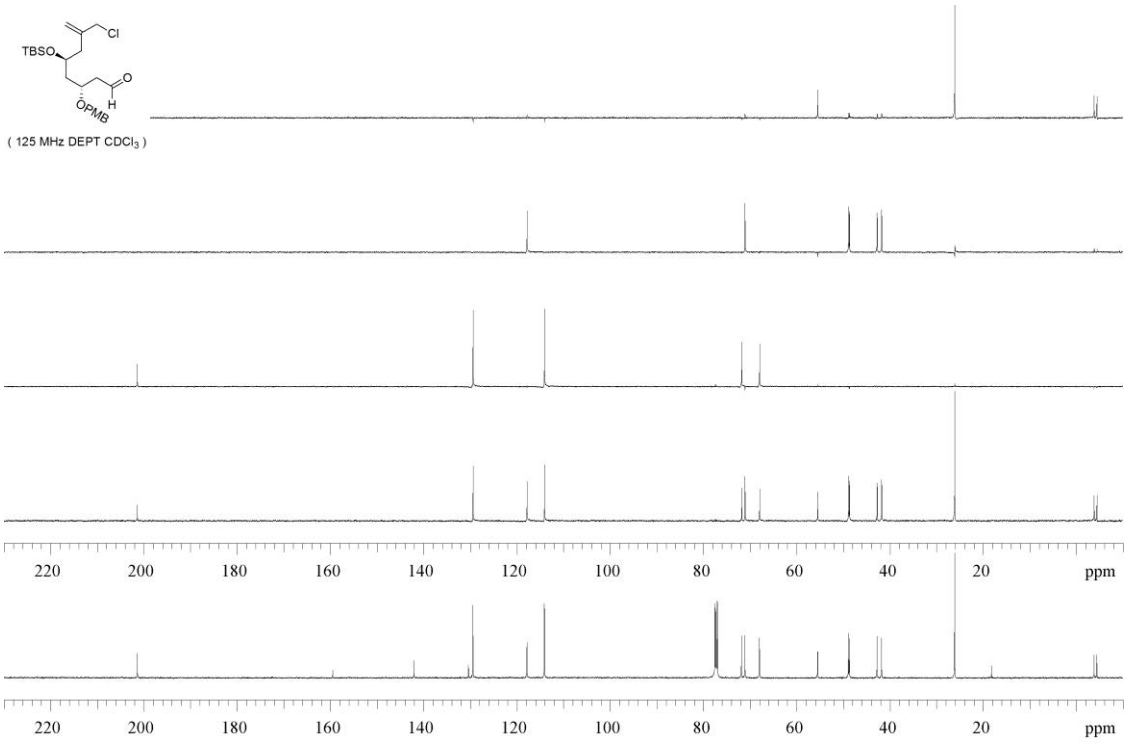
(500 MHz ^{1}H NMR $CDCl_3$)

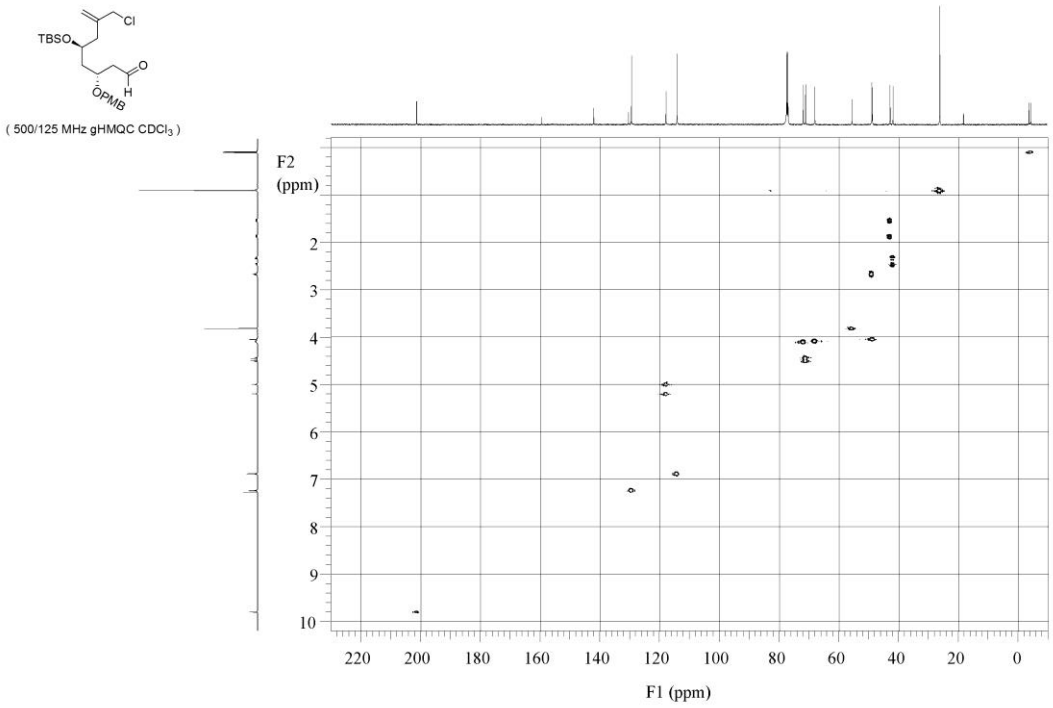


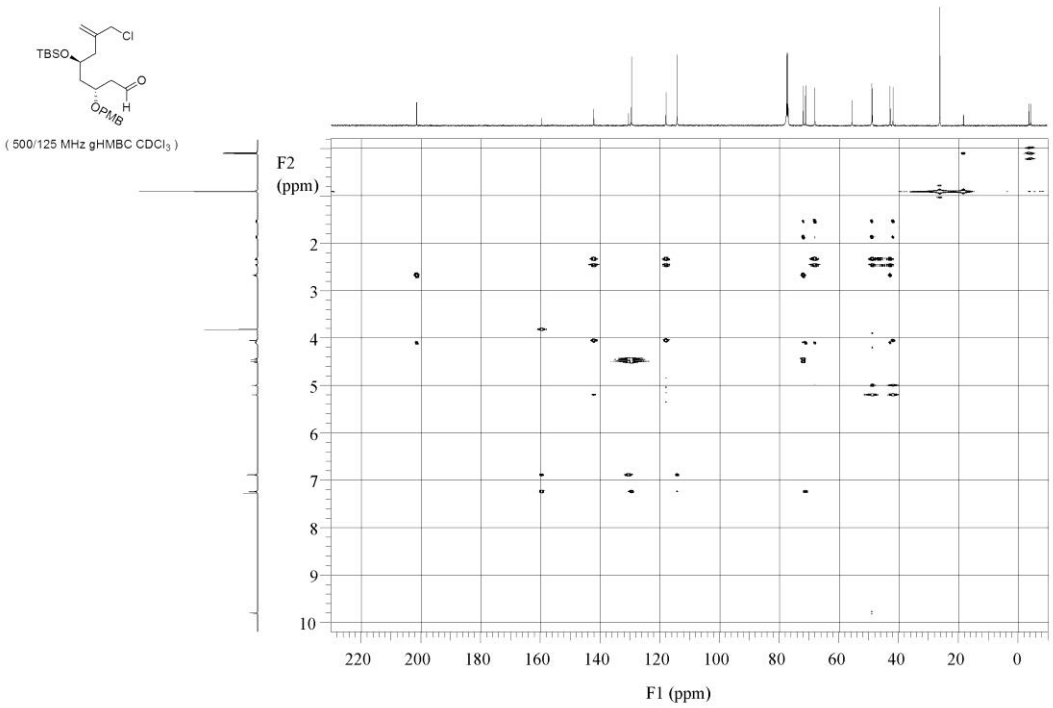
(500 MHz gDQCOSY $CDCl_3$)

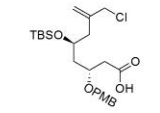



201.390
159.501
142.043
130.387
129.417
117.841
114.106
77.482
77.230
76.978
71.837
71.087
67.970
55.512
48.897
48.688
42.766
41.788
26.105
18.207
-3.787
-4.380
TBSO
Cl
O
H
OPMB
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

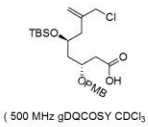

TBSO
Cl
O
H
OPMB
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm


TBSO
Cl
O
H
OPMB
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

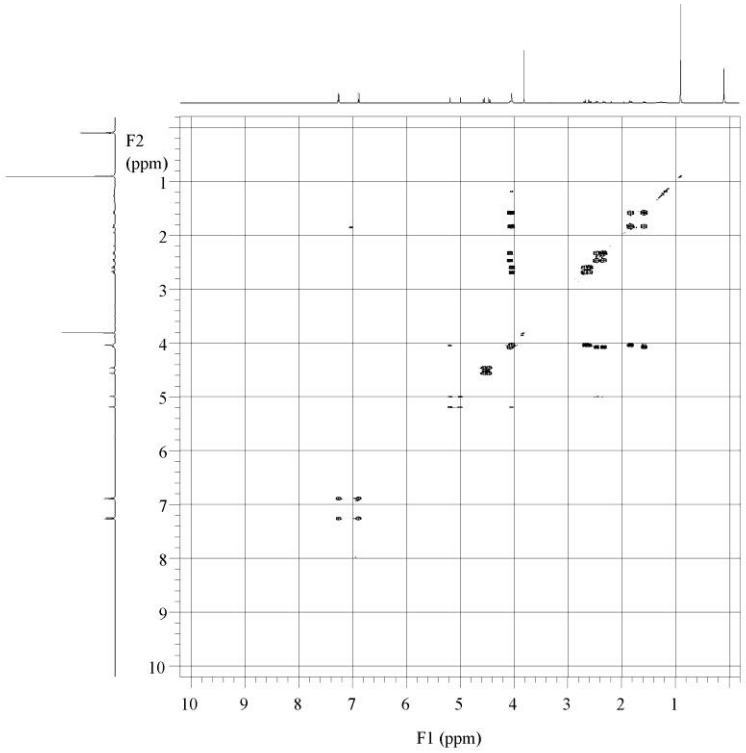

TBSO
Cl
O
H
OPMB
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

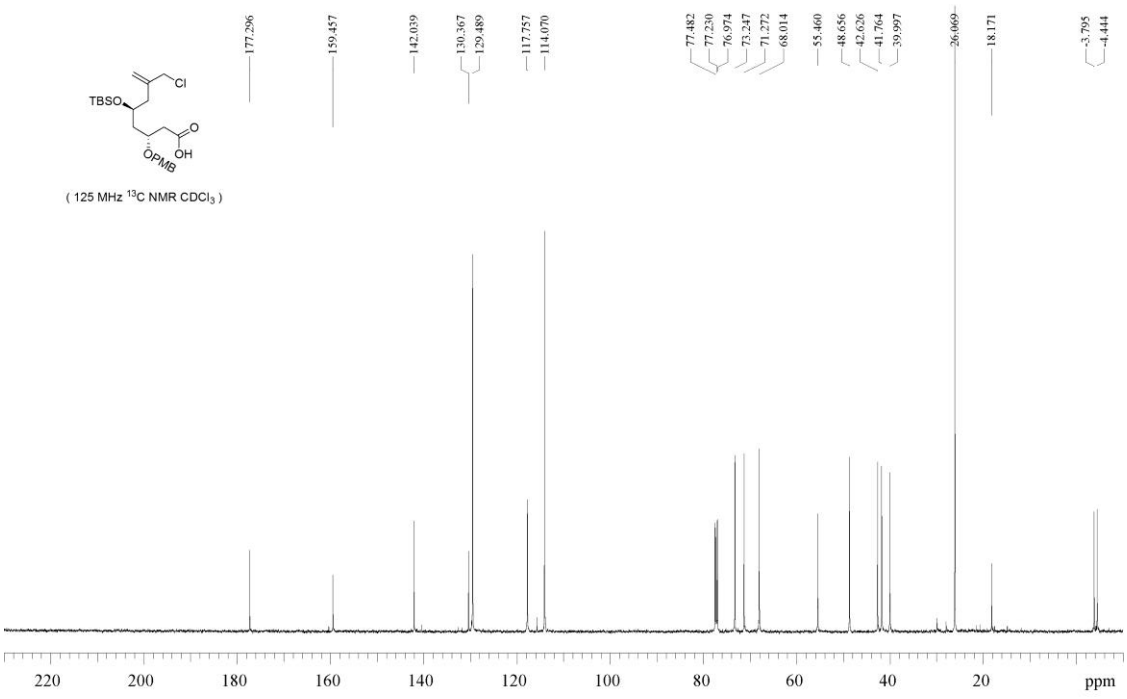


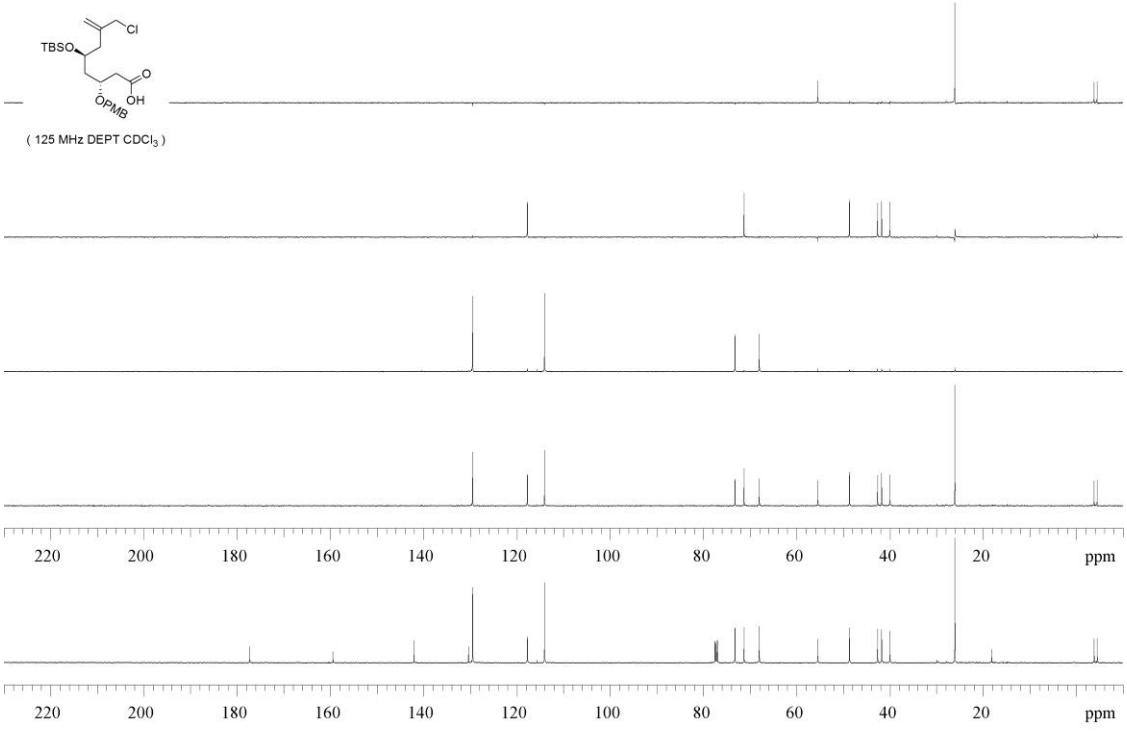
(500 MHz ^{1}H NMR $CDCl_3$)

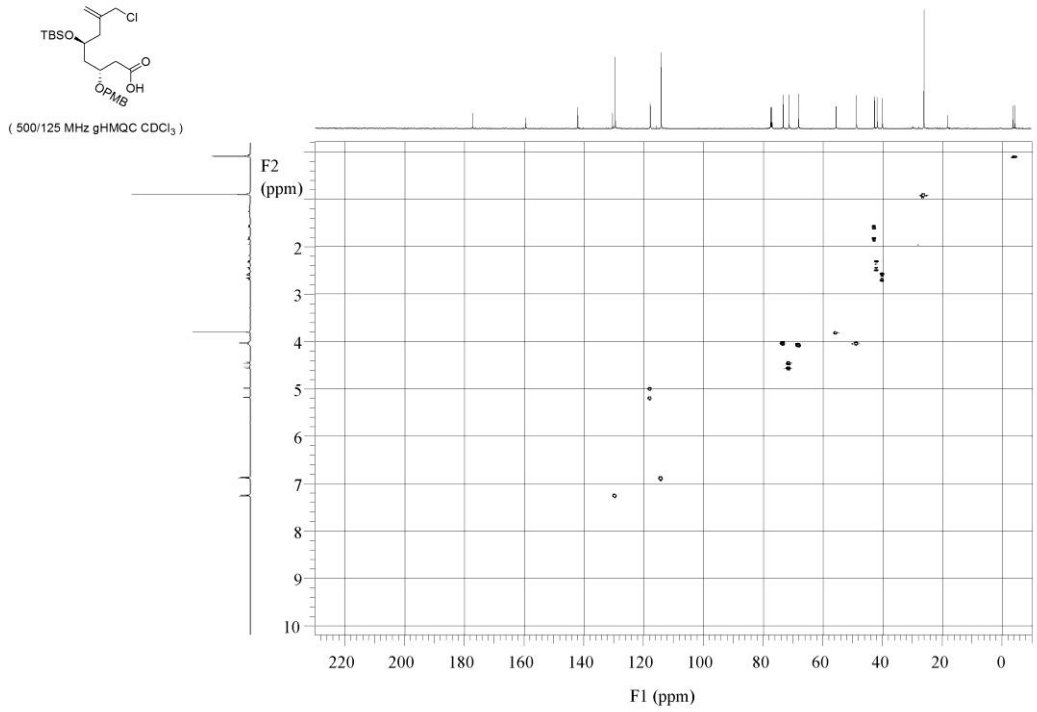


(500 MHz gDQCOSY $CDCl_3$)

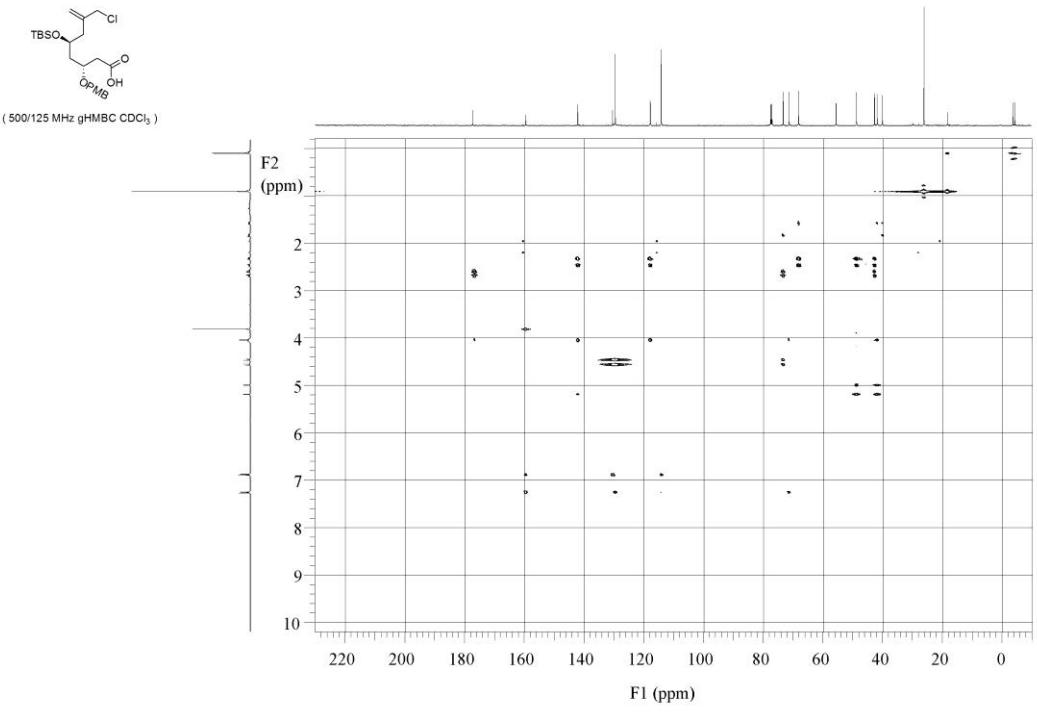



177.296
159.457
142.039
130.367
129.489
117.757
114.070
77.482
77.230
76.974
73.247
71.272
68.014
55.460
48.656
42.626
41.764
39.997
26.069
18.171
-3.795
-4.444
TBSO
Cl
O
OH
OPMB
(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

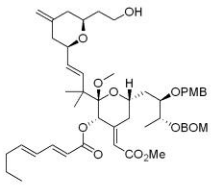

TBSO
Cl
O
OH
OPMB
(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm



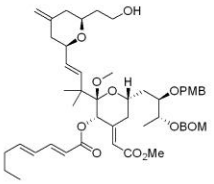
(500/125 MHz gHMQC $CDCl_3$)



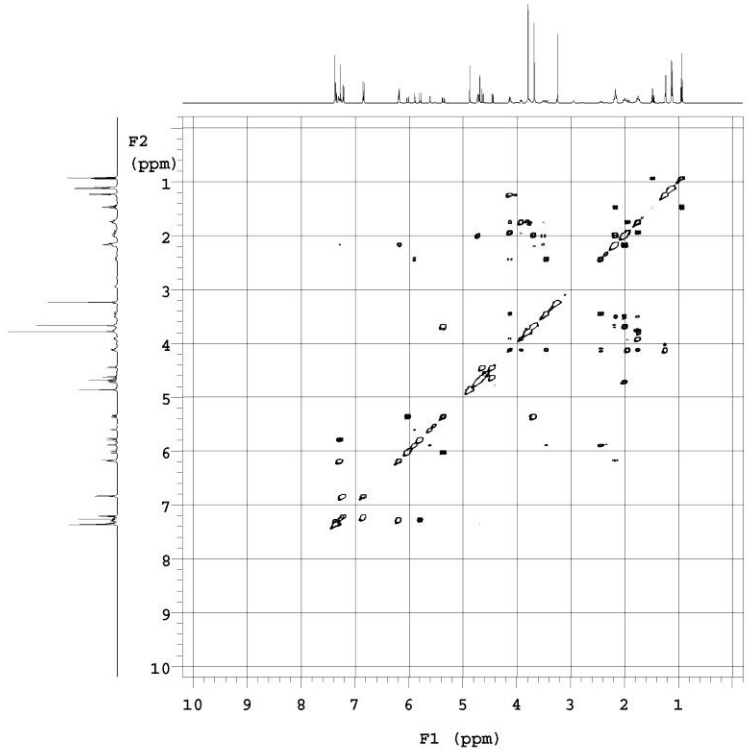
(500/125 MHz gHMBC $CDCl_3$)

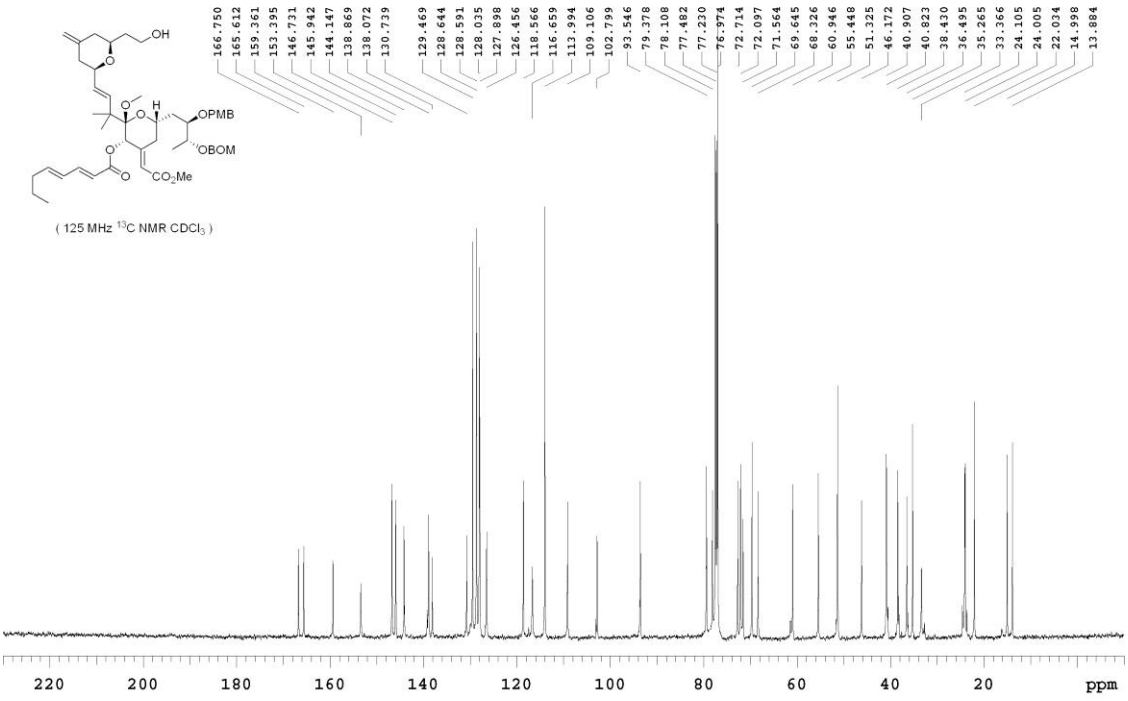


(500 MHz ^{1}H NMR $CDCl_3$)



(500 MHz gCOSY $CDCl_3$)

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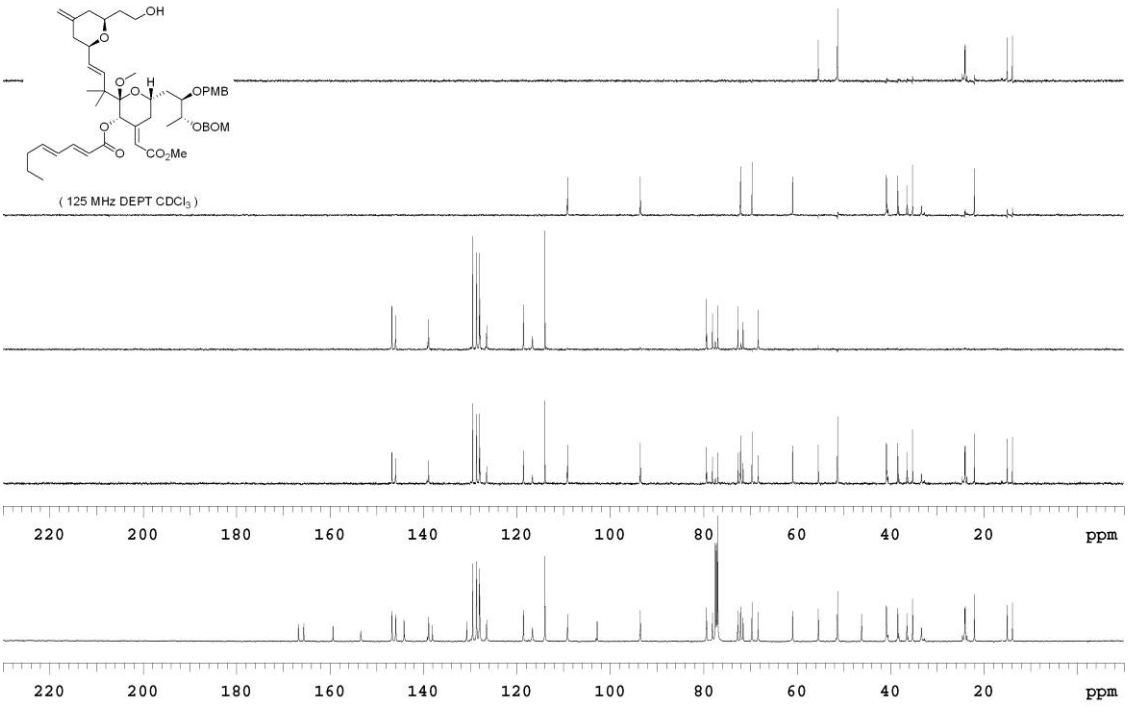
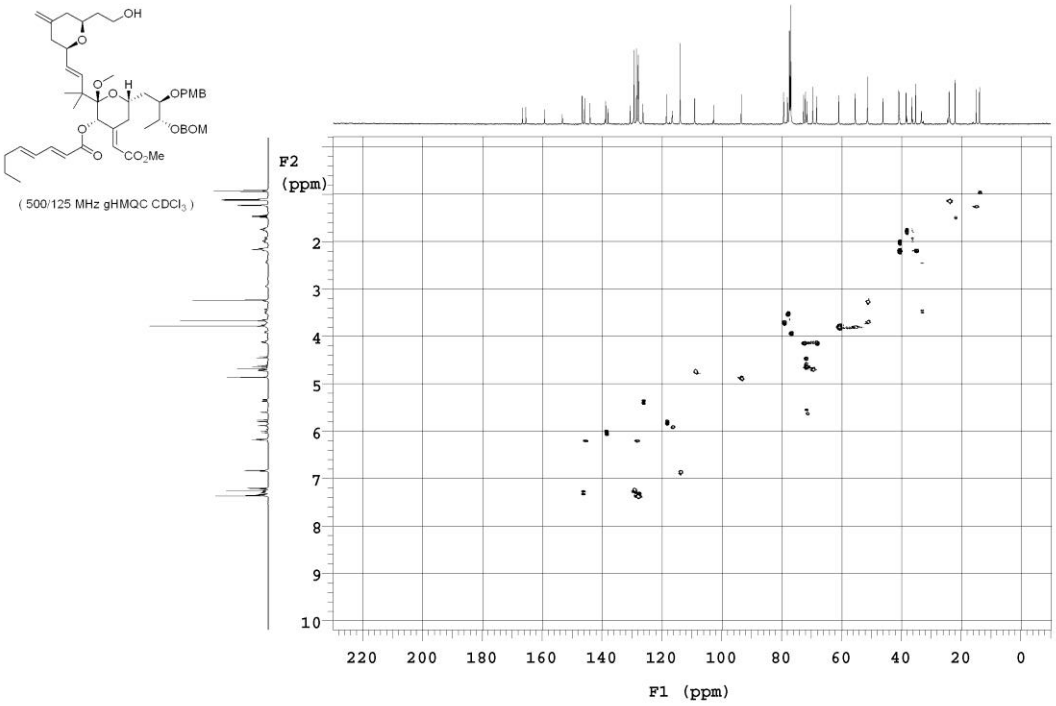
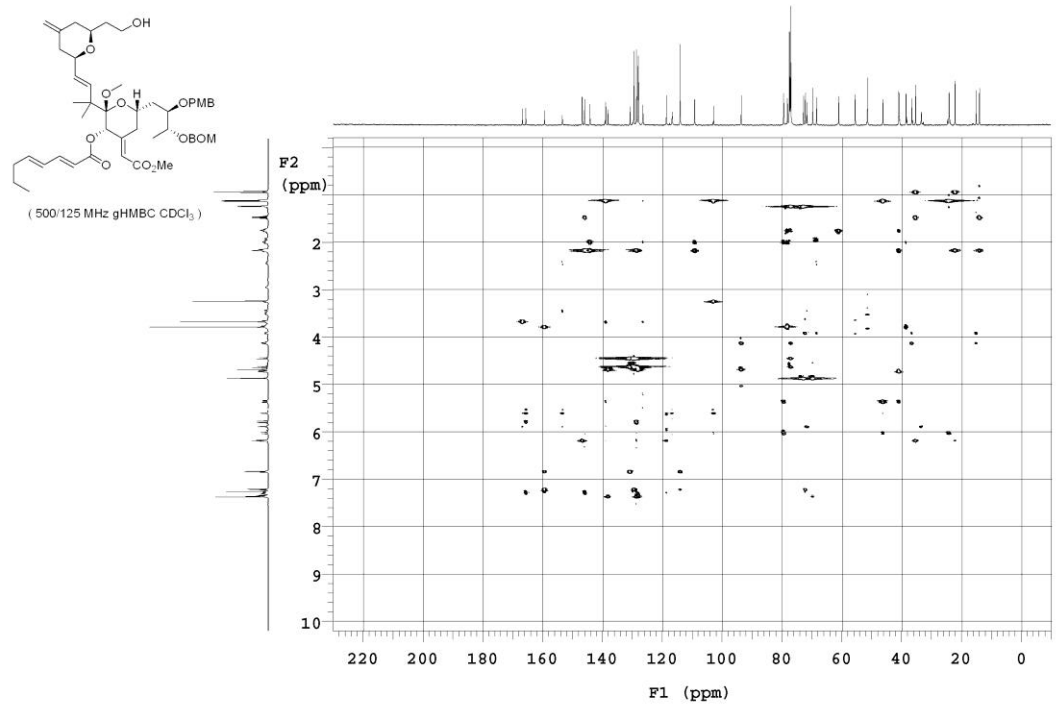
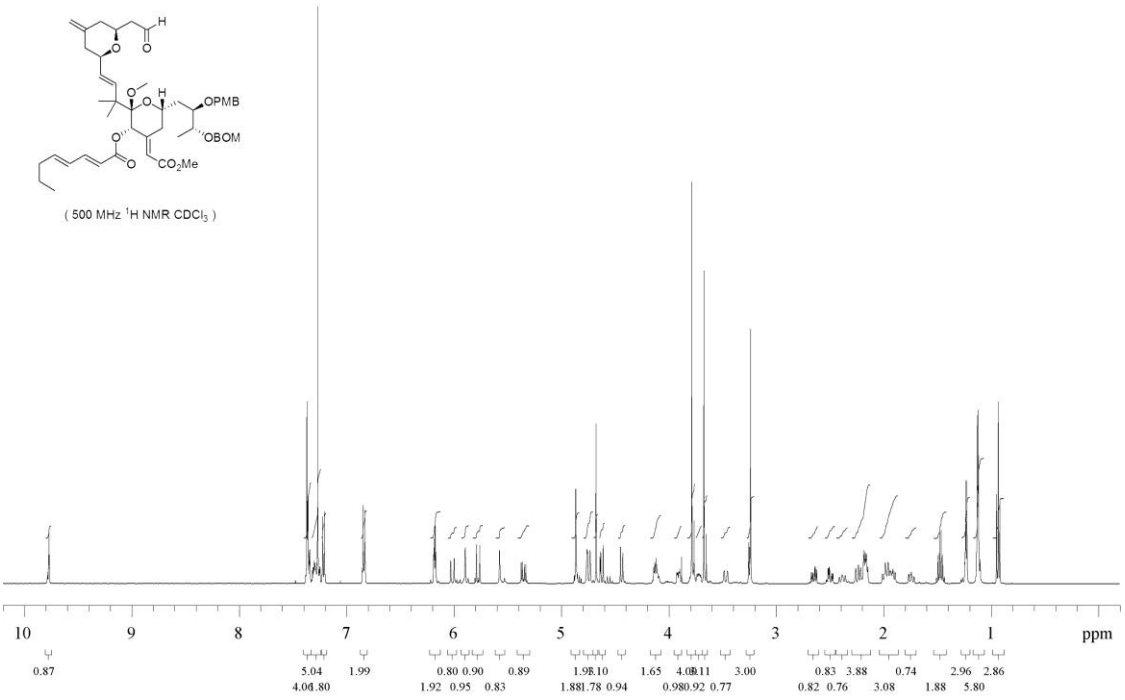
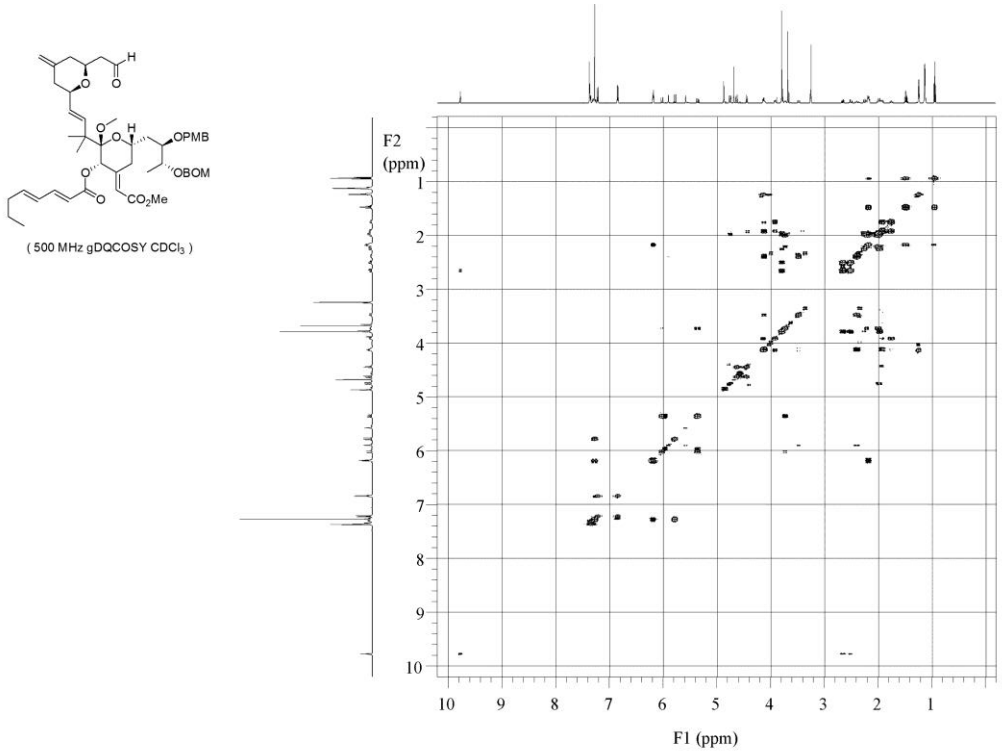
165.612
159.361
153.395
146.731
145.942
144.147
138.869
138.072
130.739
129.469
128.644
128.591
128.035
127.898
126.456
118.566
116.659
113.994
109.106
102.799
93.546
79.378
78.108
77.482
77.230
76.974
72.714
72.097
71.564
69.645
68.326
60.946
55.448
51.325
46.172
40.907
40.823
38.430
36.495
35.265
33.366
24.105
24.005
22.034
14.998
13.884
OH
OPMB
OBOM
CO2Me
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

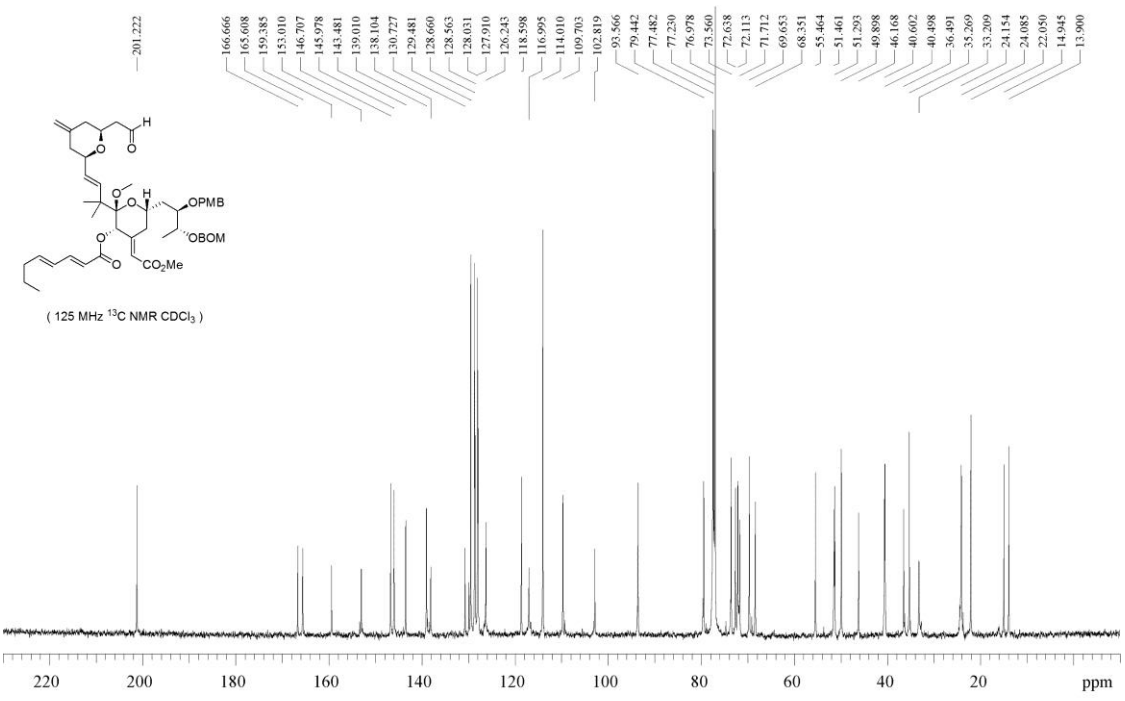

OH
OPMB
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

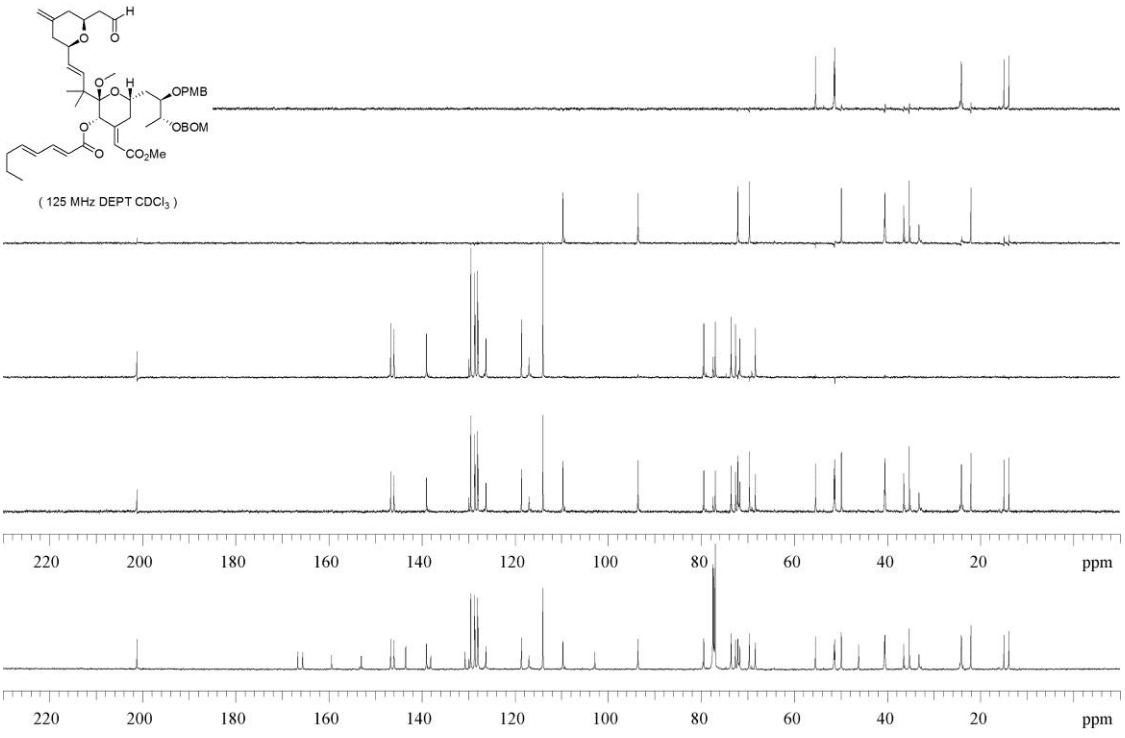

OH
OPMB
OBOM
CO2Me
(500/125 MHz gHMQC CDCl3)
F2 (ppm)
F1 (ppm)

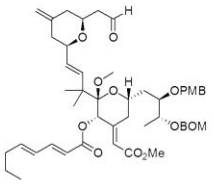

OH
OPMB
OBOM
CO2Me
(500/125 MHz gHMBC CDCl3)
F2 (ppm)
F1 (ppm)


OPMB
OBOM
CO2Me
(500 MHz 1H NMR CDCl3)
10
9
8
7
6
5
4
3
2
1
ppm

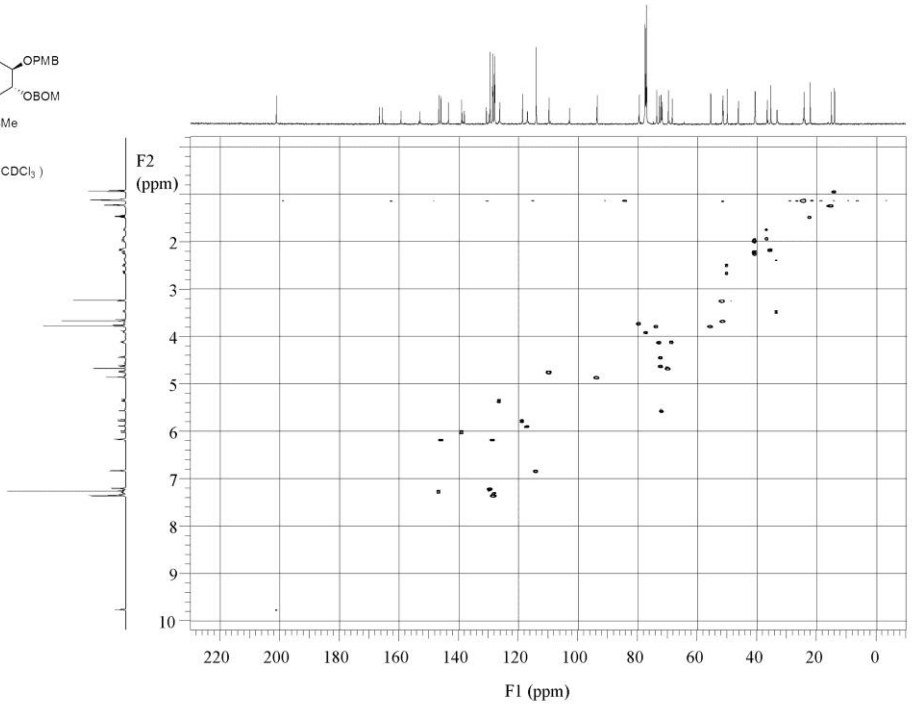

OPMB
OBOM
CO2Me
(500 MHz gDQCOSY CDCl3)
F2
(ppm)
F1 (ppm)

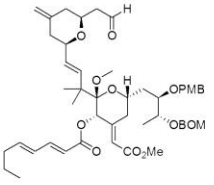

201.222
166.666
165.608
159.385
153.010
146.707
145.978
143.481
139.010
138.104
130.727
129.481
128.660
128.563
128.031
127.910
126.243
118.598
116.995
114.010
109.703
102.819
93.566
79.442
77.482
77.230
76.978
73.560
72.638
72.113
71.712
69.653
68.351
55.464
51.461
51.293
49.898
46.168
40.602
40.498
36.491
35.269
33.209
24.154
24.085
22.050
14.945
13.900
OPMB
OBOM
CO2Me
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm


OPMB
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

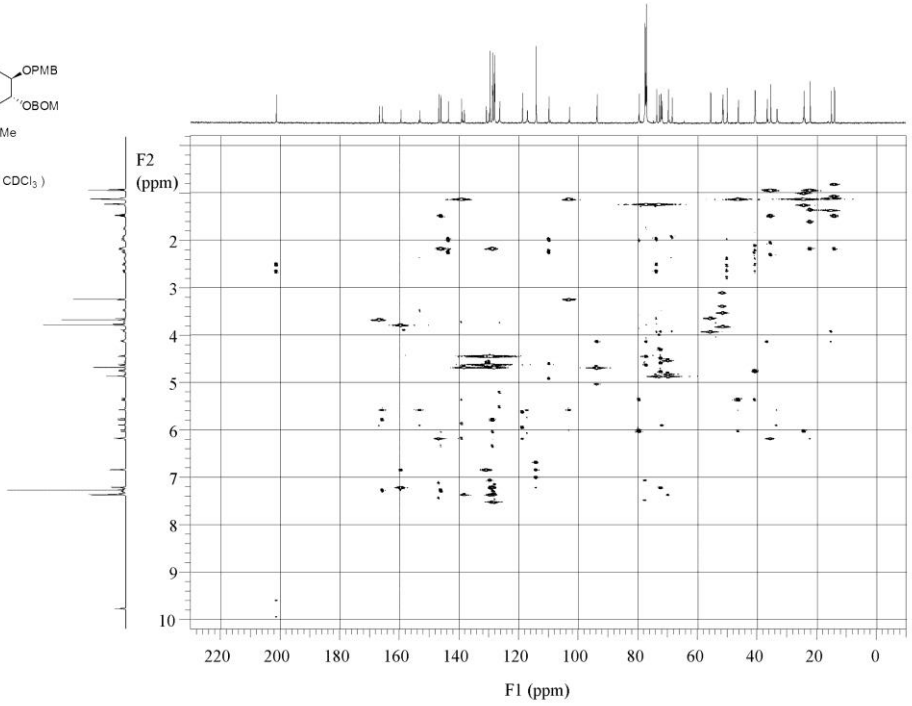


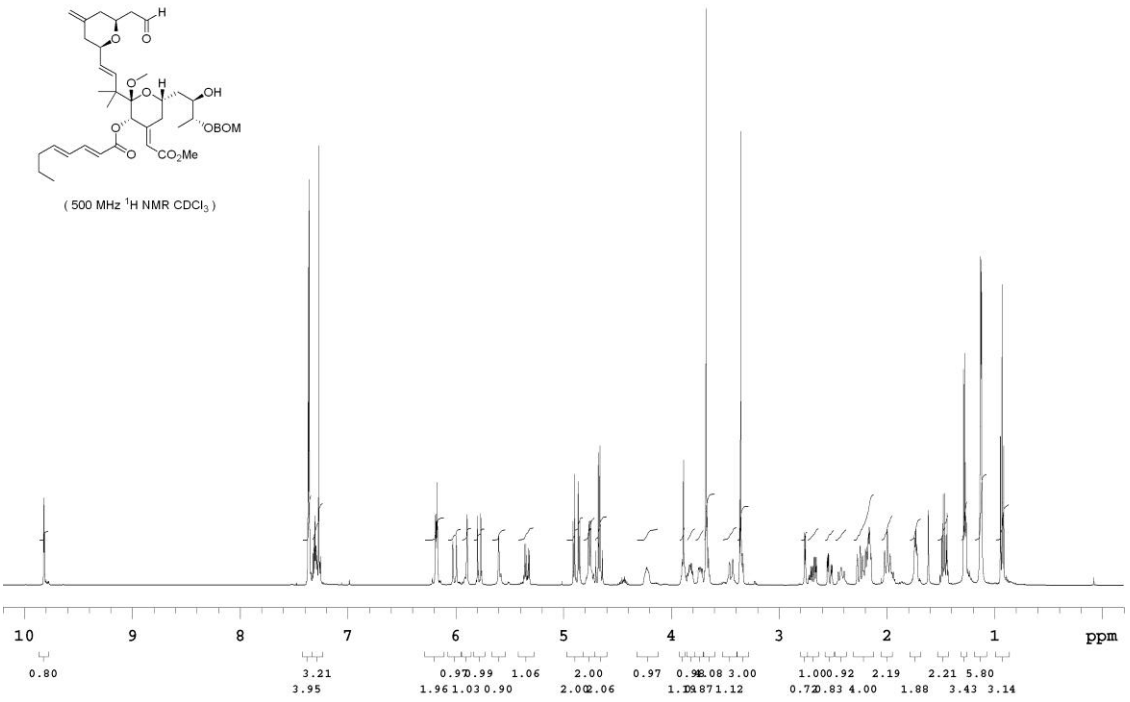
(500/125 MHz HMQC $CDCl_3$)

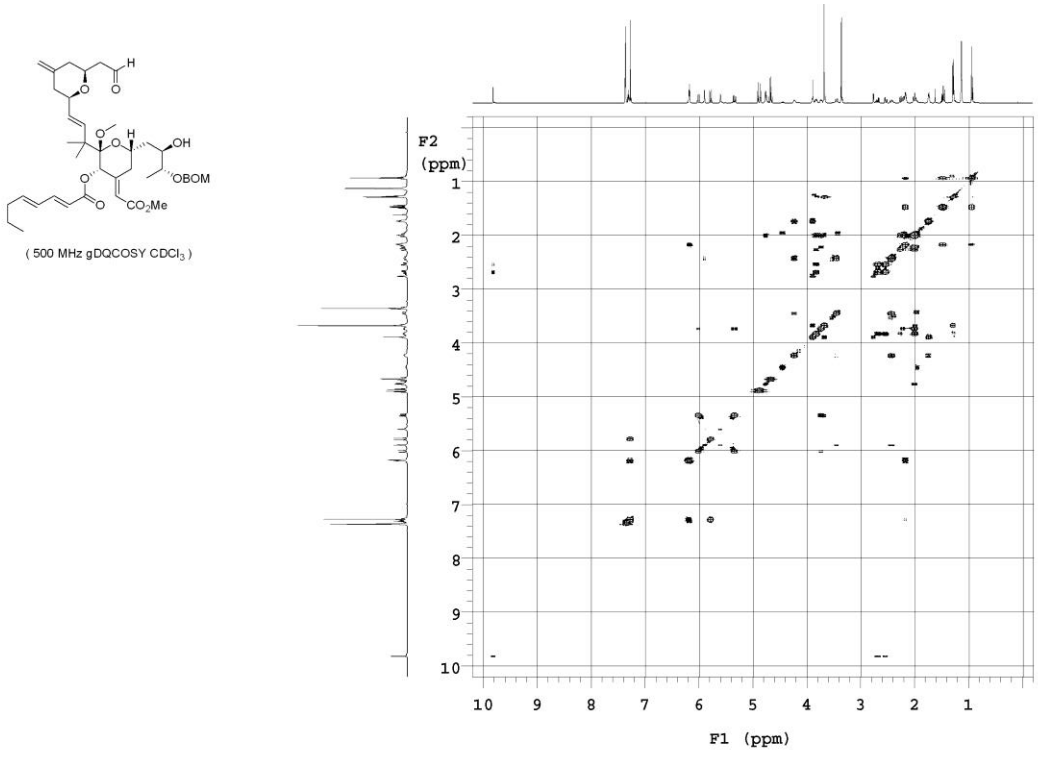


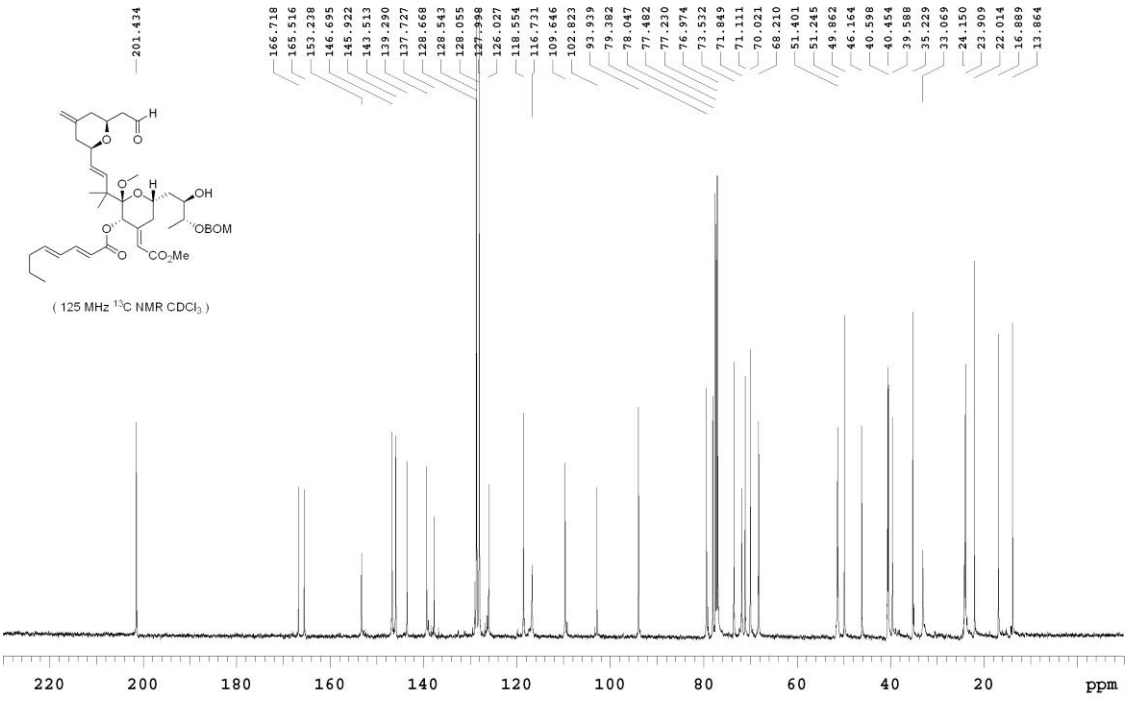


(500/125 MHz gHMBC $CDCl_3$)




(500 MHz ^{1}H NMR $CDCl_3$)
OH
OBOM
CO_2Me
10
9
8
7
6
5
4
3
2
1
ppm


(500 MHz gDQCOSY $CDCl_3$)
OH
OBOM
CO_2Me
F2 (ppm)
F1 (ppm)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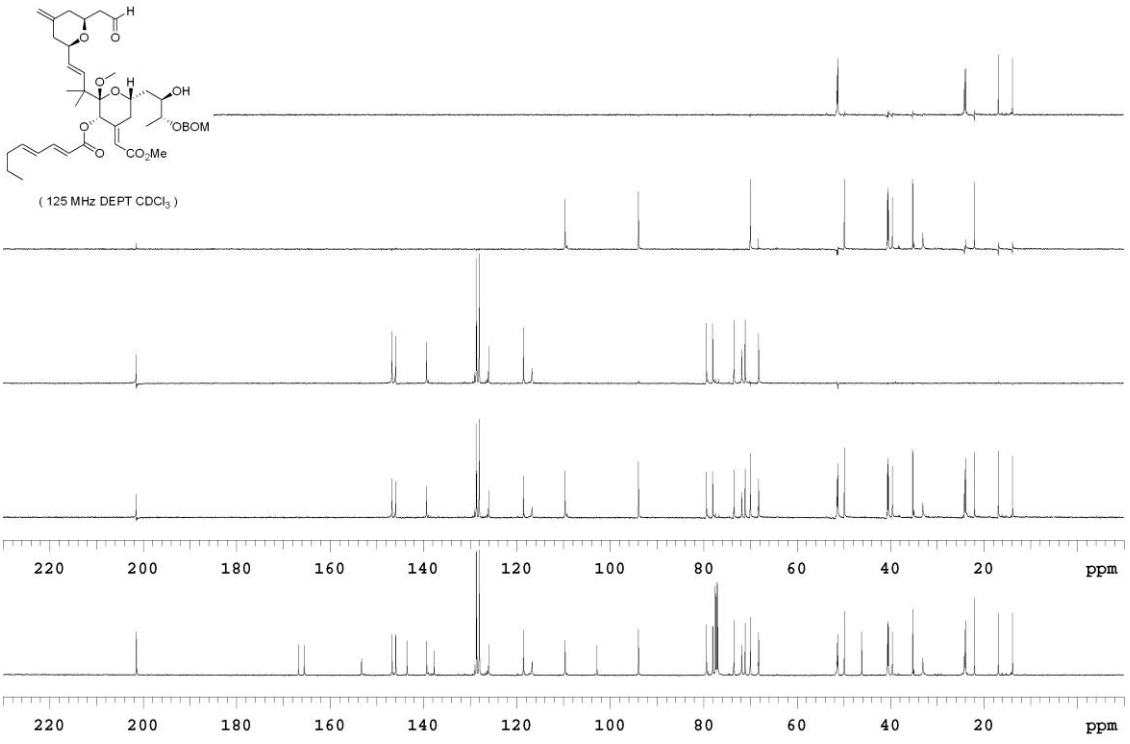
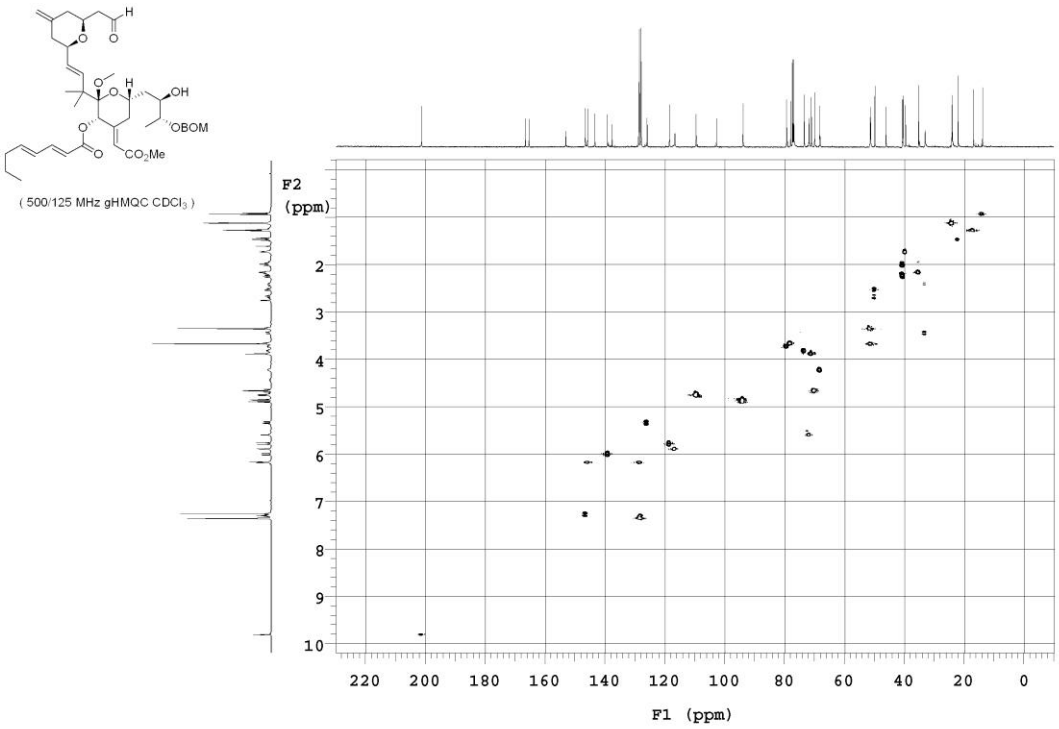
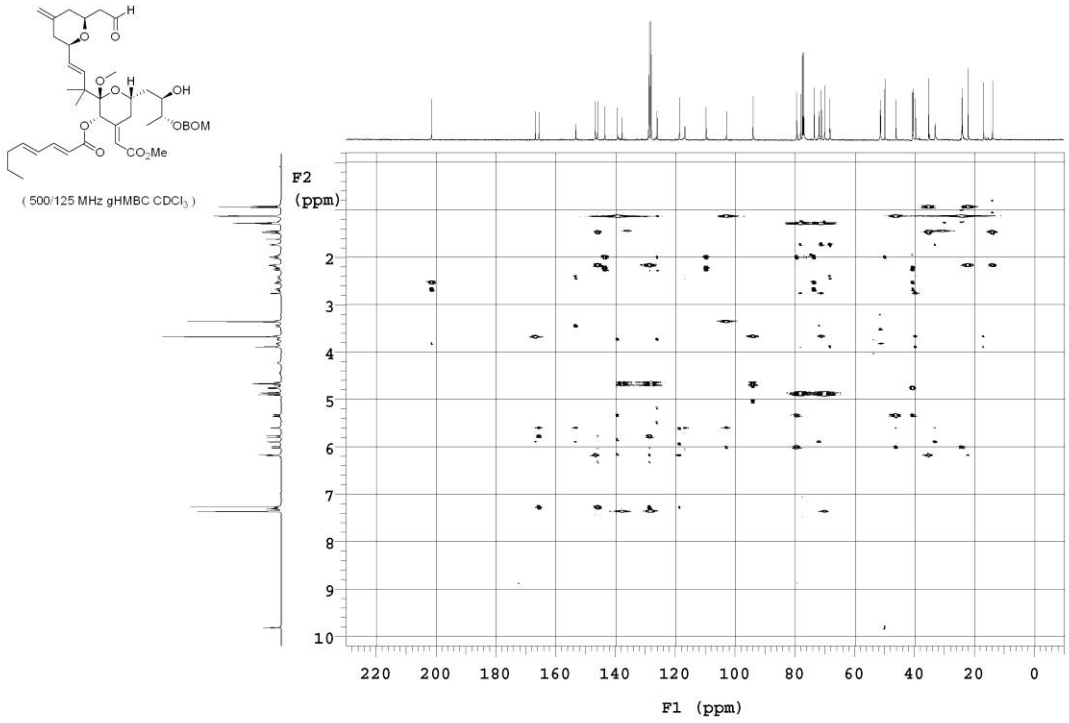
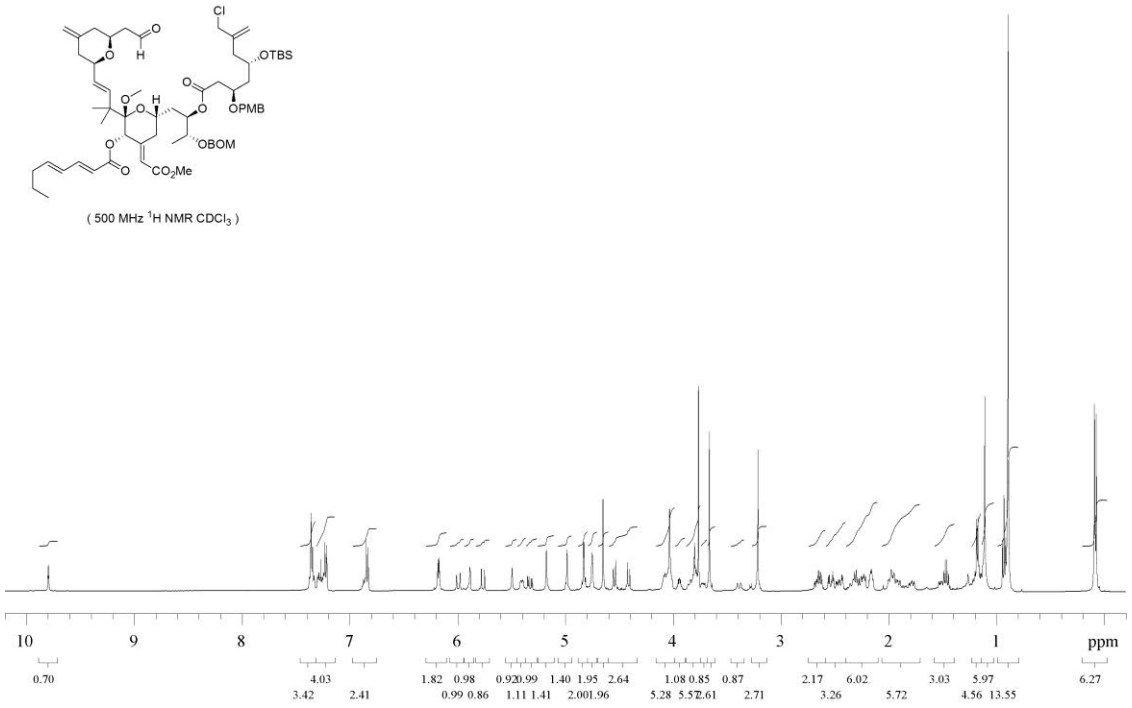
166.718
165.516
153.238
146.695
145.922
143.513
139.290
137.727
128.668
128.543
128.055
127.998
126.027
118.554
116.731
109.646
102.823
93.939
79.382
78.047
77.482
77.230
76.974
73.532
71.849
71.111
70.021
68.210
51.401
51.245
49.862
46.164
40.598
40.454
39.588
35.229
33.069
24.150
23.909
22.014
16.889
13.864
OH
OBOM
CO2Me
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

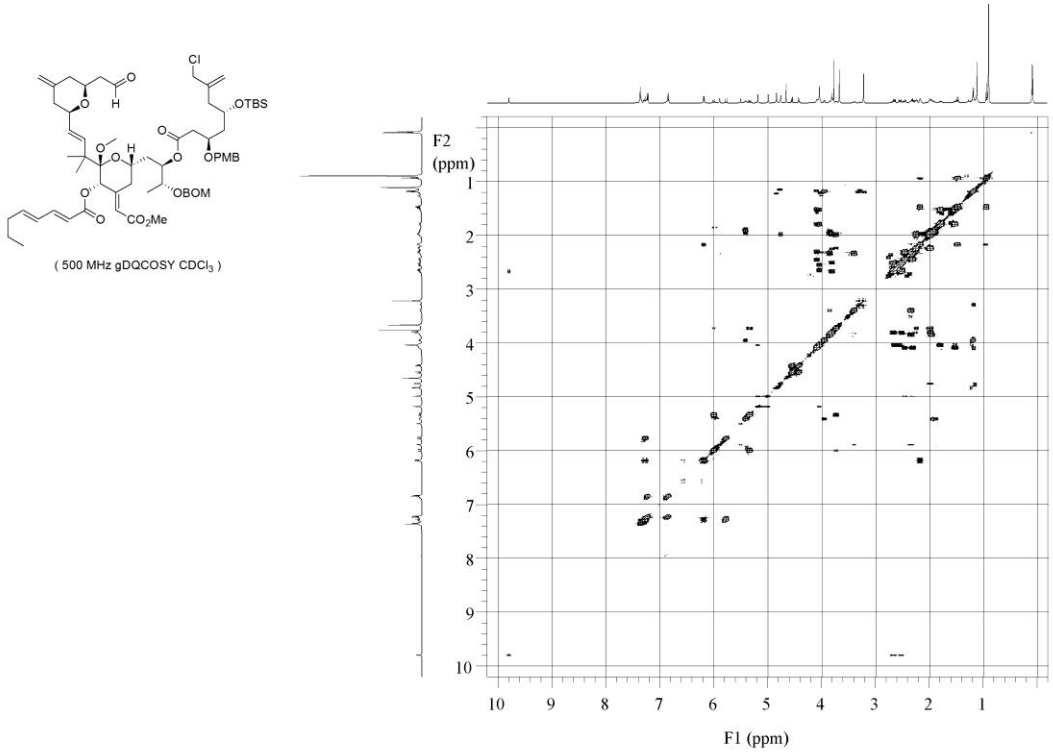

OH
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm


OH
OBOM
CO2Me
(500/125 MHz gHMQC CDCl3)
F2 (ppm)
F1 (ppm)

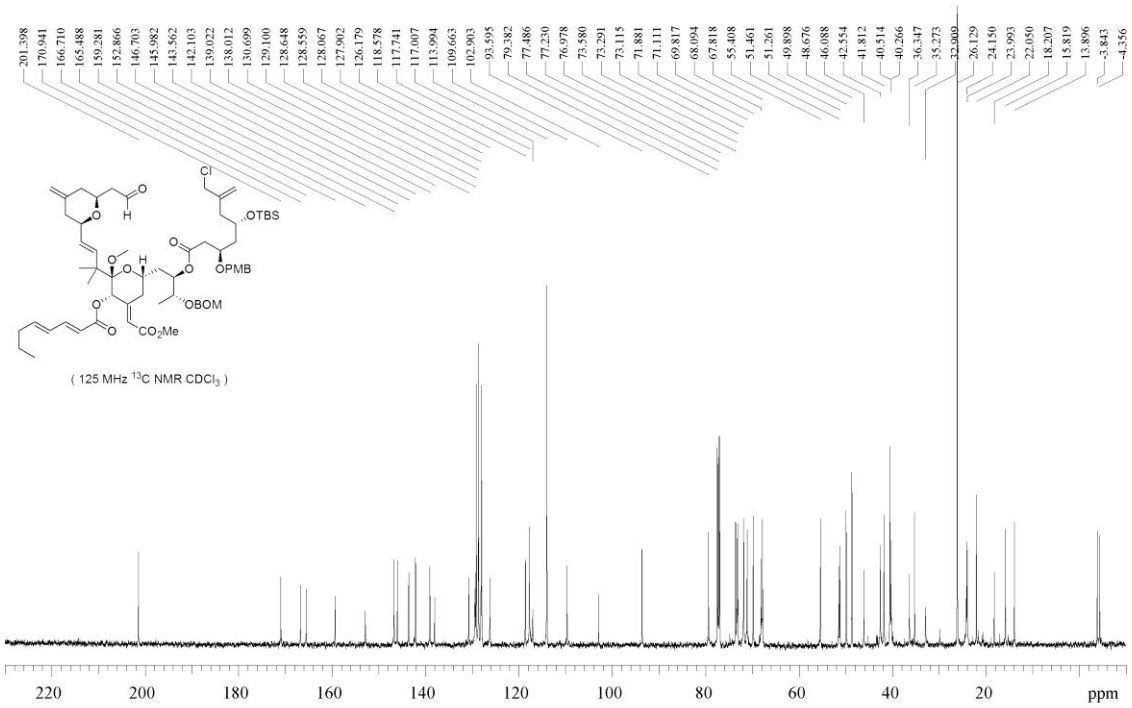

OH
OBOM
CO2Me
(500/125 MHz gHMBC CDCl3)
F2 (ppm)
F1 (ppm)



(500 MHz ^{1}H NMR $CDCl_3$)



(500 MHz gDQCOSY $CDCl_3$)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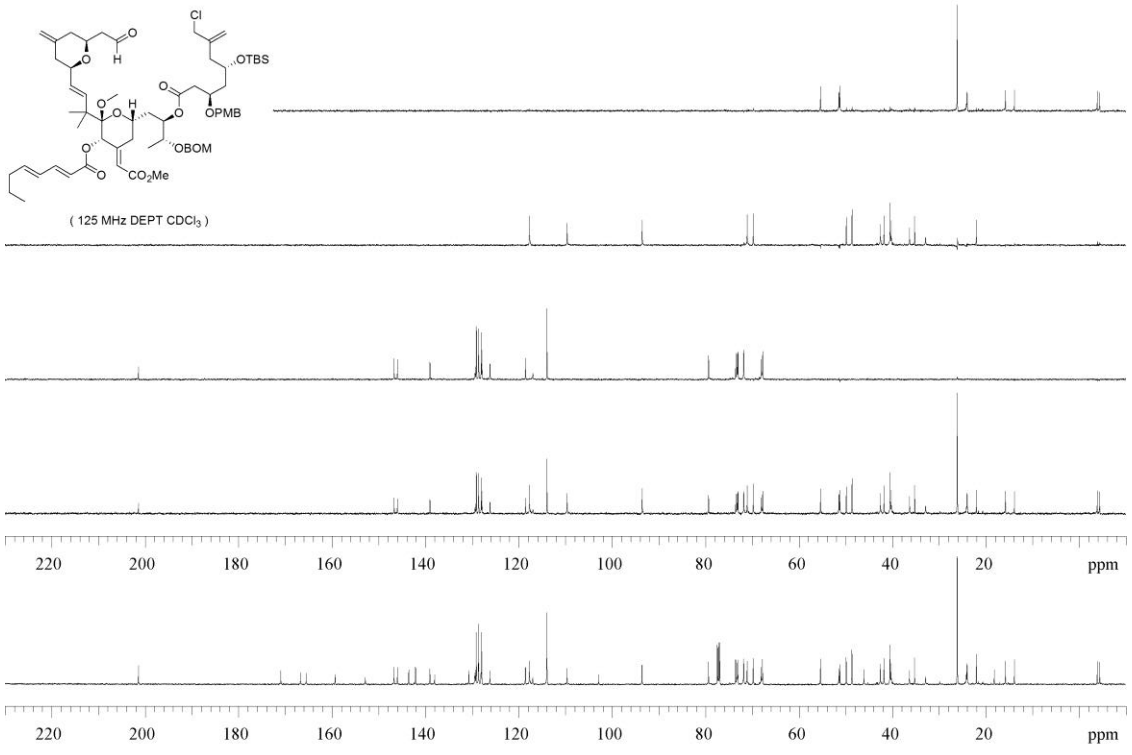
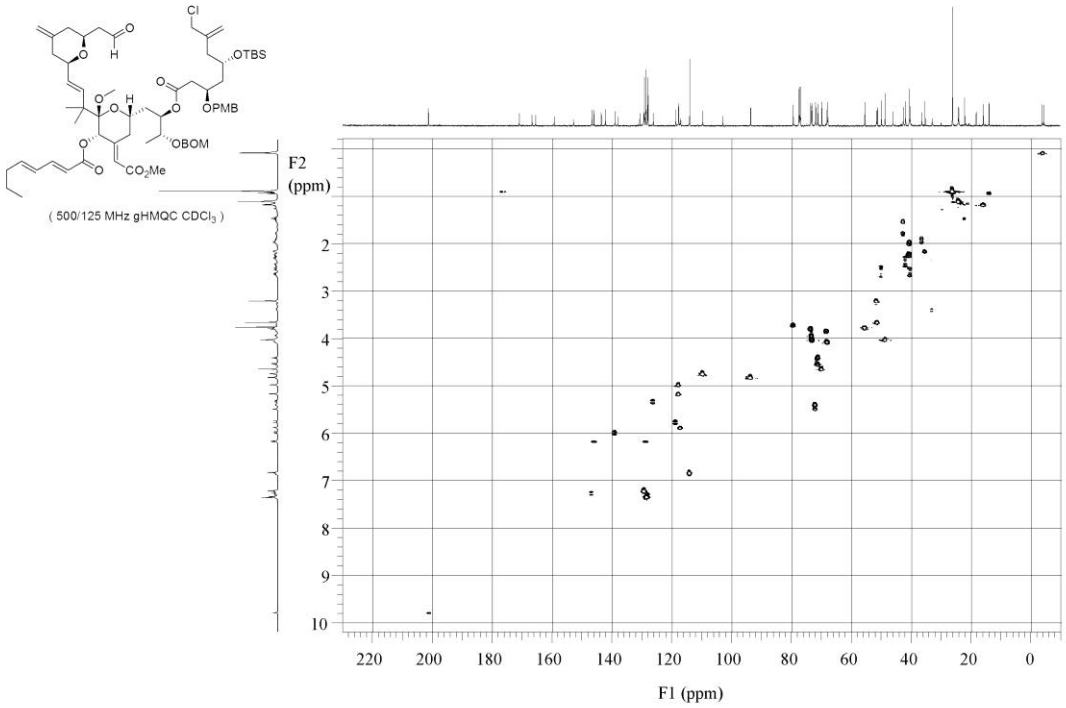
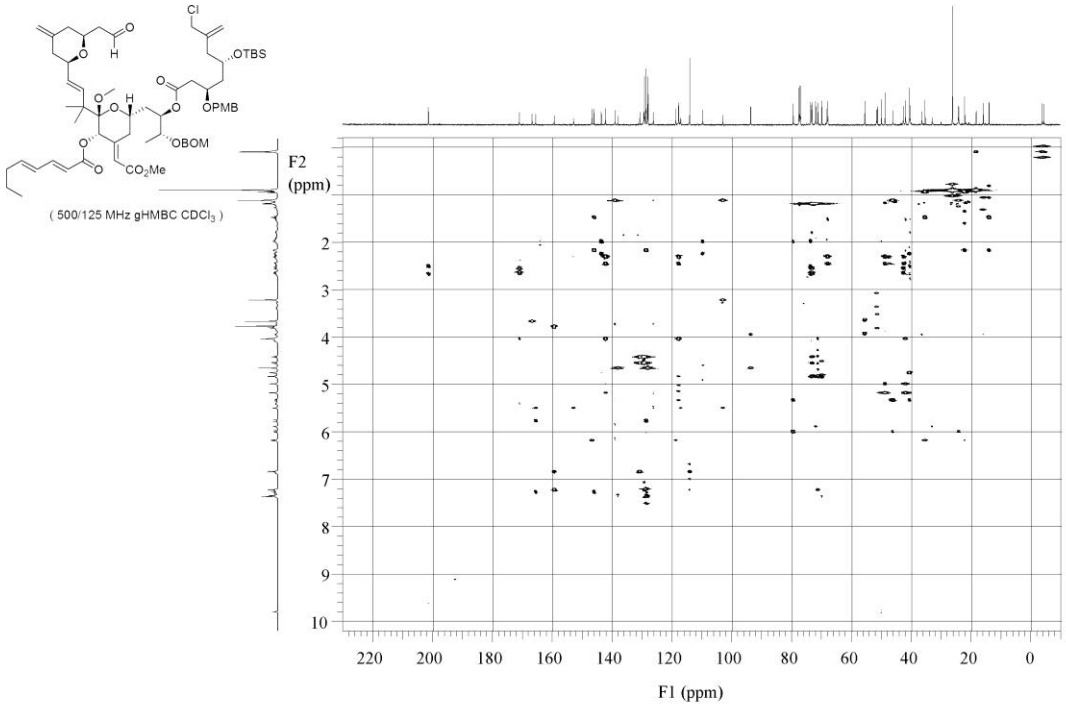
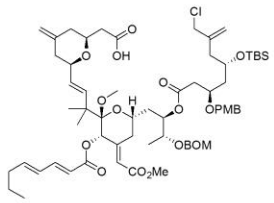
166.710
165.488
159.281
152.866
146.703
145.982
143.562
142.103
139.022
138.012
130.699
129.100
128.648
128.559
128.067
127.902
126.179
118.578
117.741
117.007
113.994
109.663
102.903
93.595
79.382
77.486
77.230
76.978
73.580
73.291
73.115
71.881
71.111
69.817
68.094
67.818
55.408
51.461
51.261
49.898
48.676
46.088
42.554
41.812
40.514
40.266
36.347
35.273
32.909
26.129
24.150
23.993
22.050
18.207
15.819
13.896
-3.843
-4.356
Cl
OTBS
OPMB
OBOM
CO2Me
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

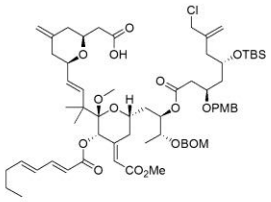

Cl
OTBS
OPMB
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm


Cl
OTBS
OPMB
OBOM
CO2Me
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
F1 (ppm)

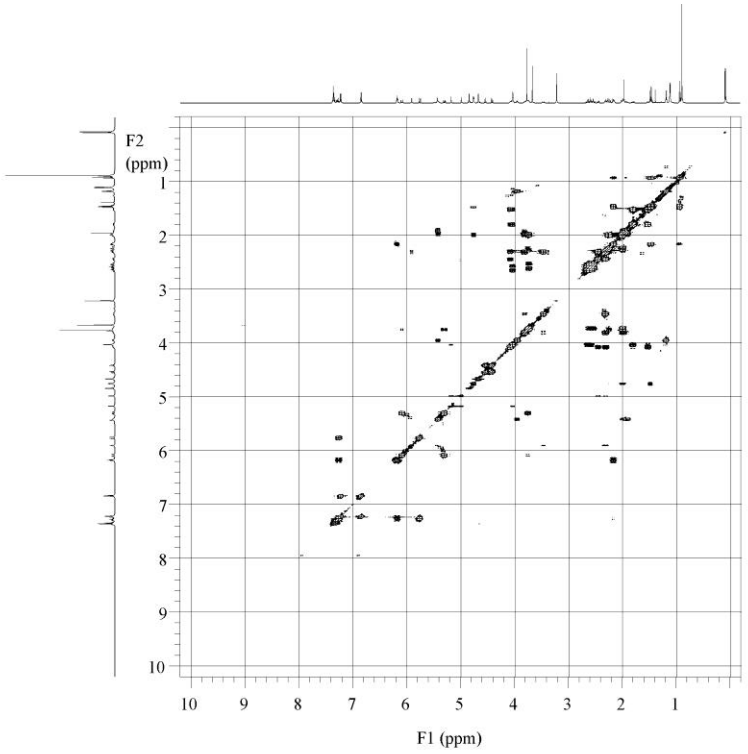

Cl
OTBS
OPMB
OBOM
CO2Me
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
F1 (ppm)

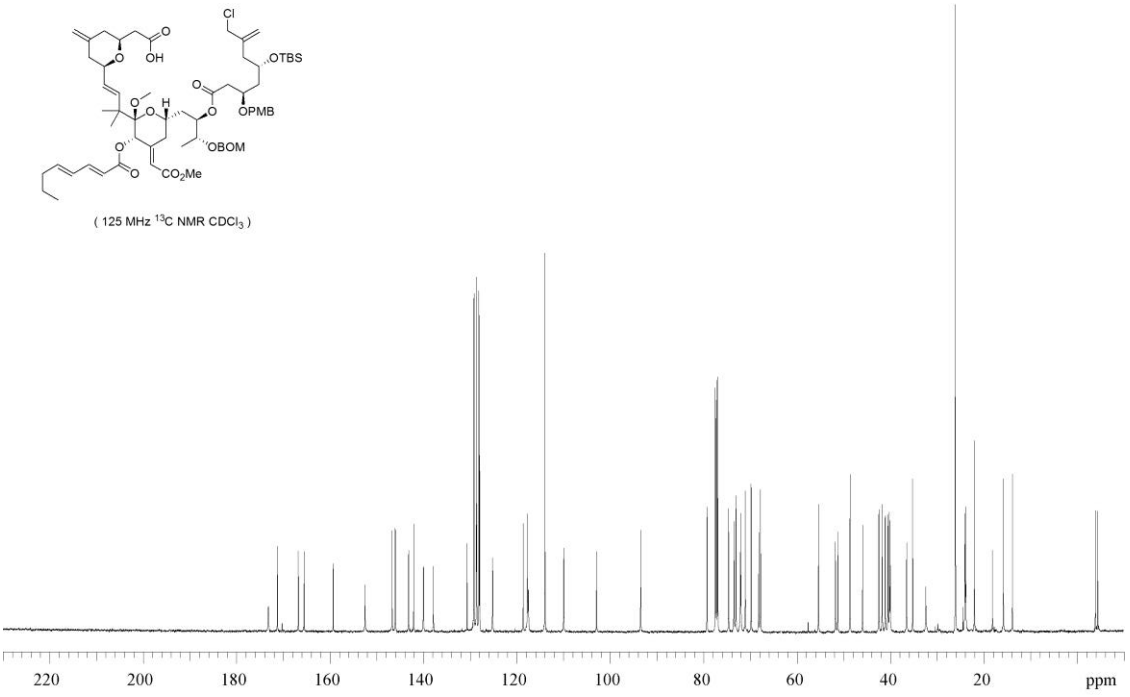


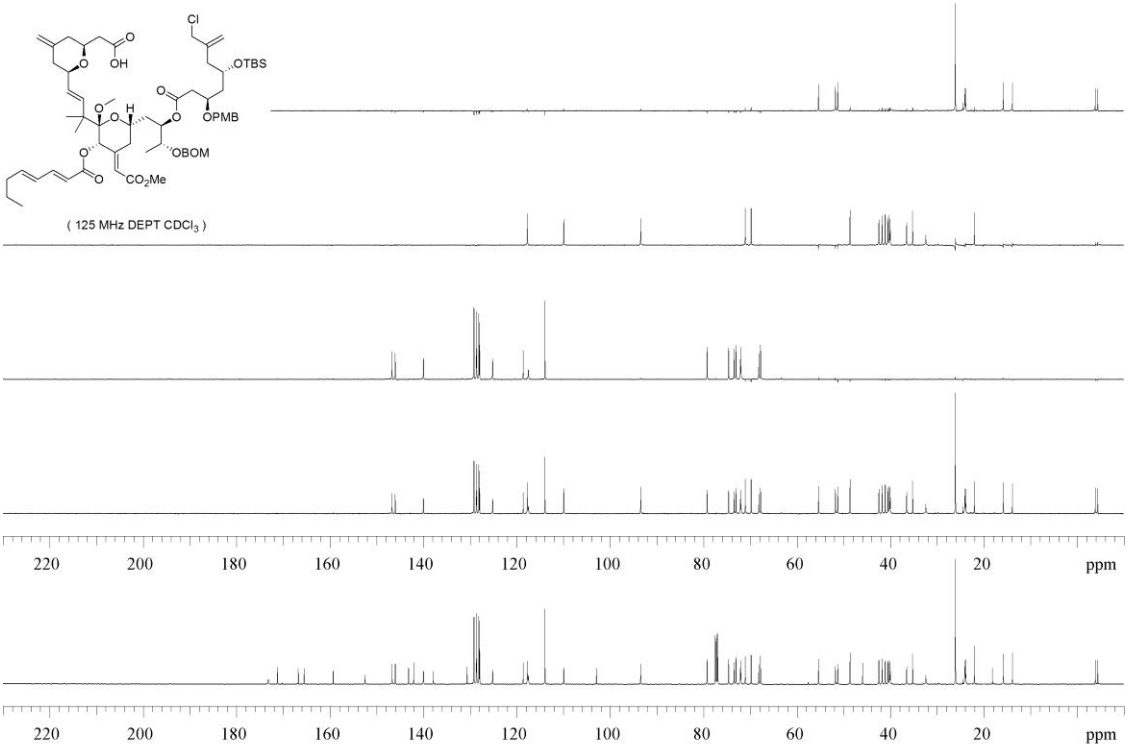
(500 MHz ^{1}H NMR $CDCl_3$)

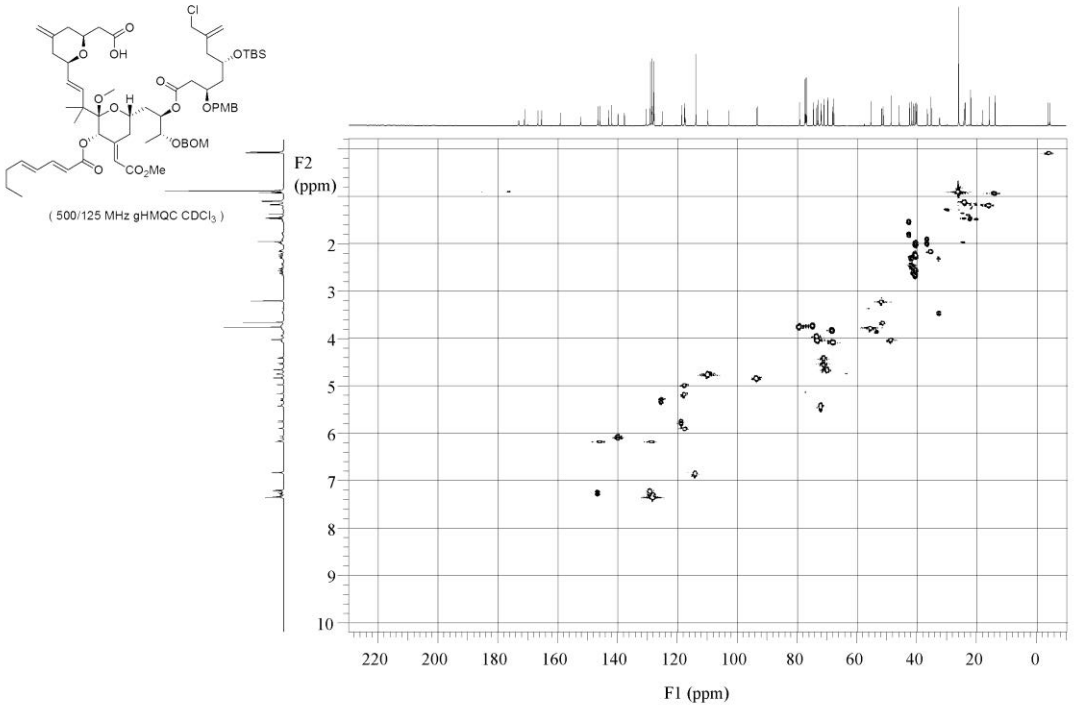


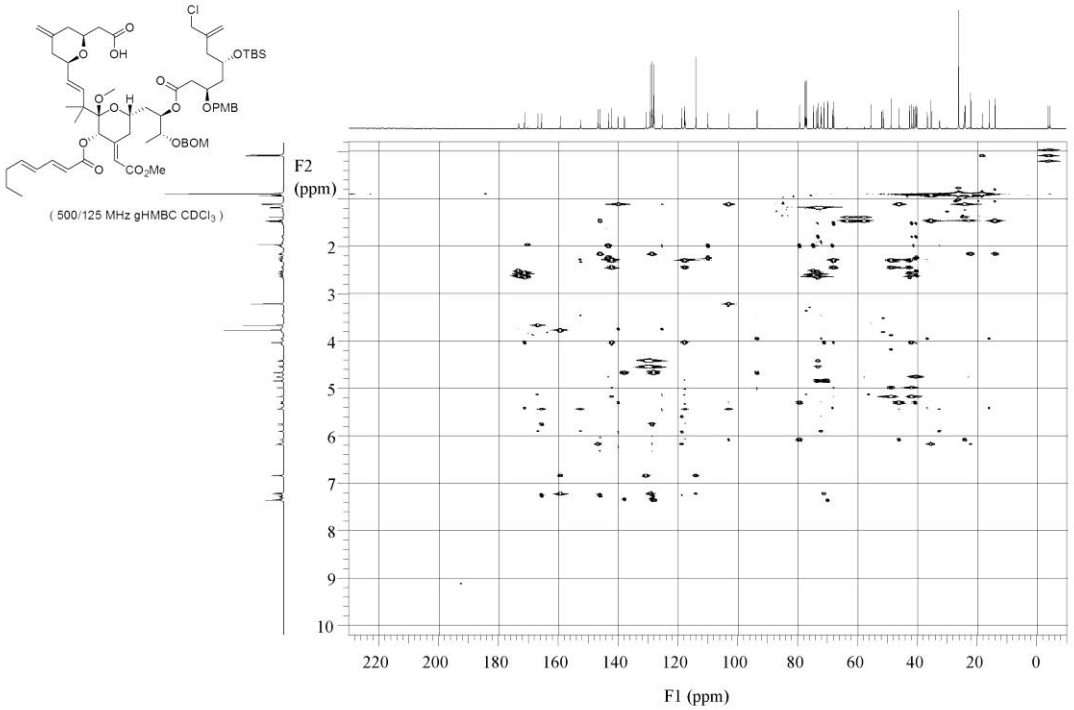
(500 MHz gDQCOSY $CDCl_3$)

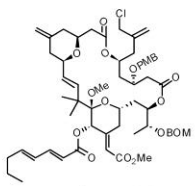



Cl
OTBS
OH
OPMB
OBOM
CO2Me
(125 MHz 13C NMR CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm

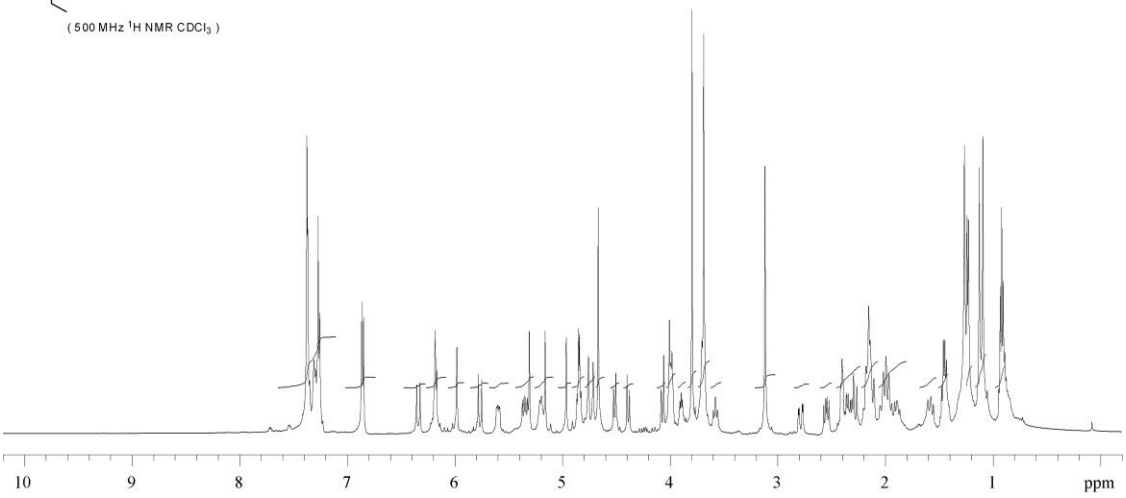

Cl
OTBS
OH
OPMB
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

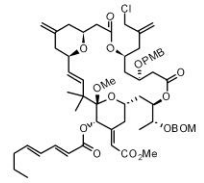

Cl
OTBS
OH
OPMB
OBOM
CO2Me
(500/125 MHz gHMQC CDCl3)
F2
(ppm)
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)


Cl
OTBS
OH
OPMB
OBOM
CO2Me
(500/125 MHz gHMBC CDCl3)
F2
(ppm)
1
2
3
4
5
6
7
8
9
10
220
200
180
160
140
120
100
80
60
40
20
0
F1 (ppm)

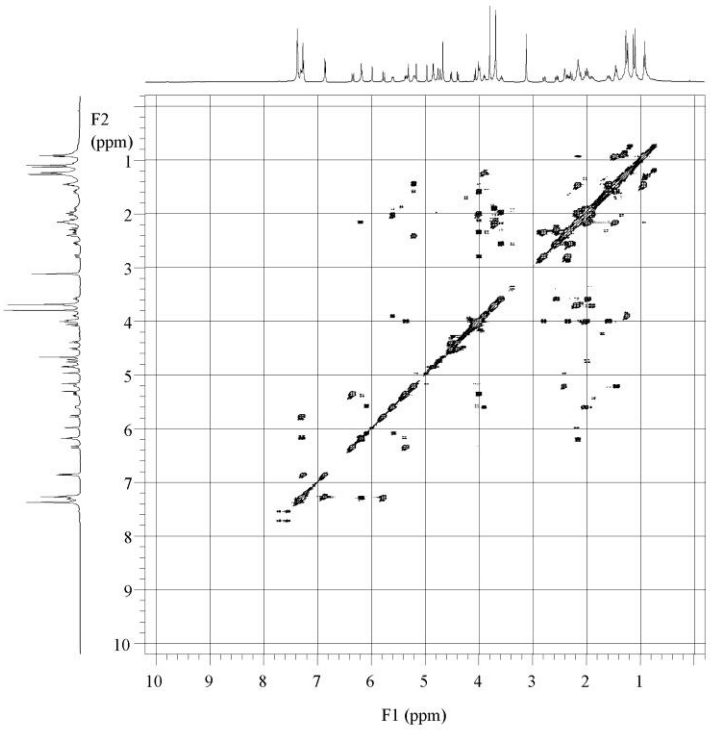


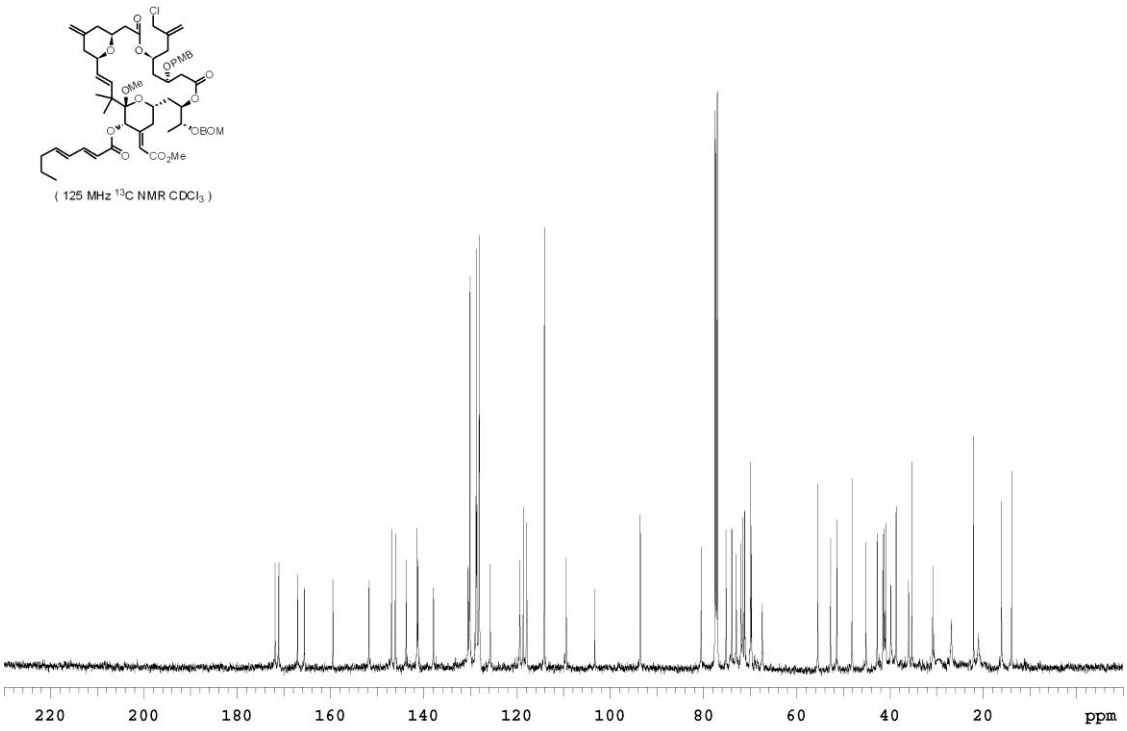
(500 MHz ^{1}H NMR $CDCl_3$)

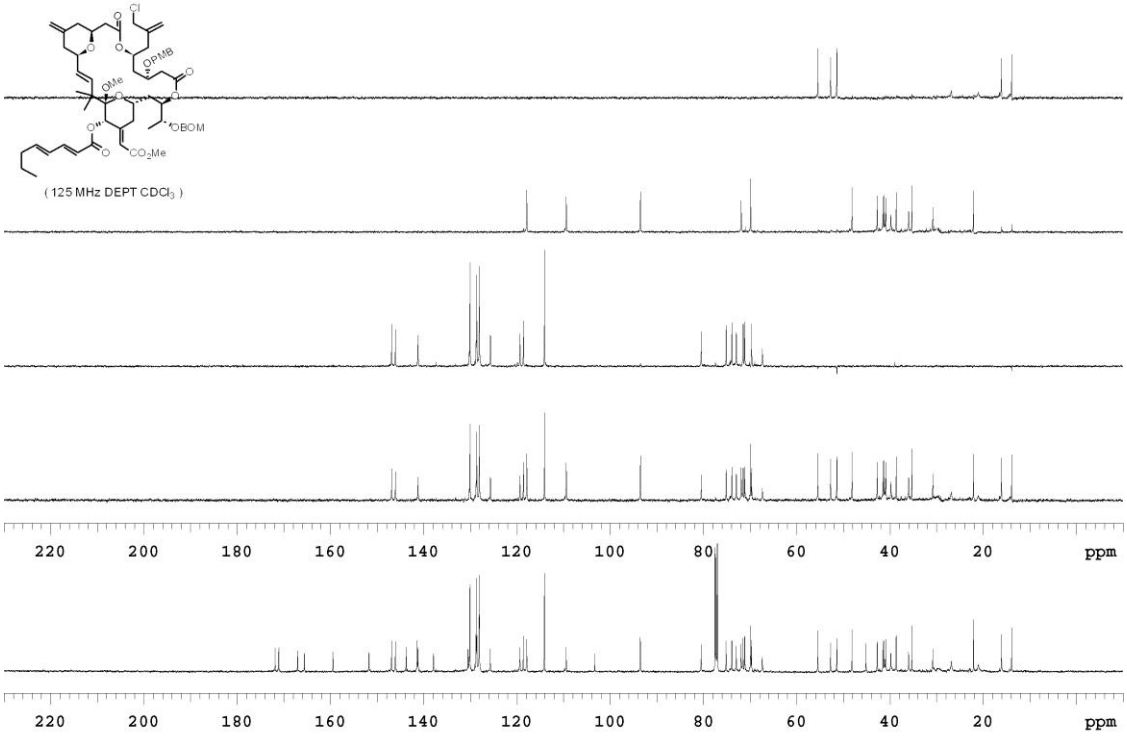


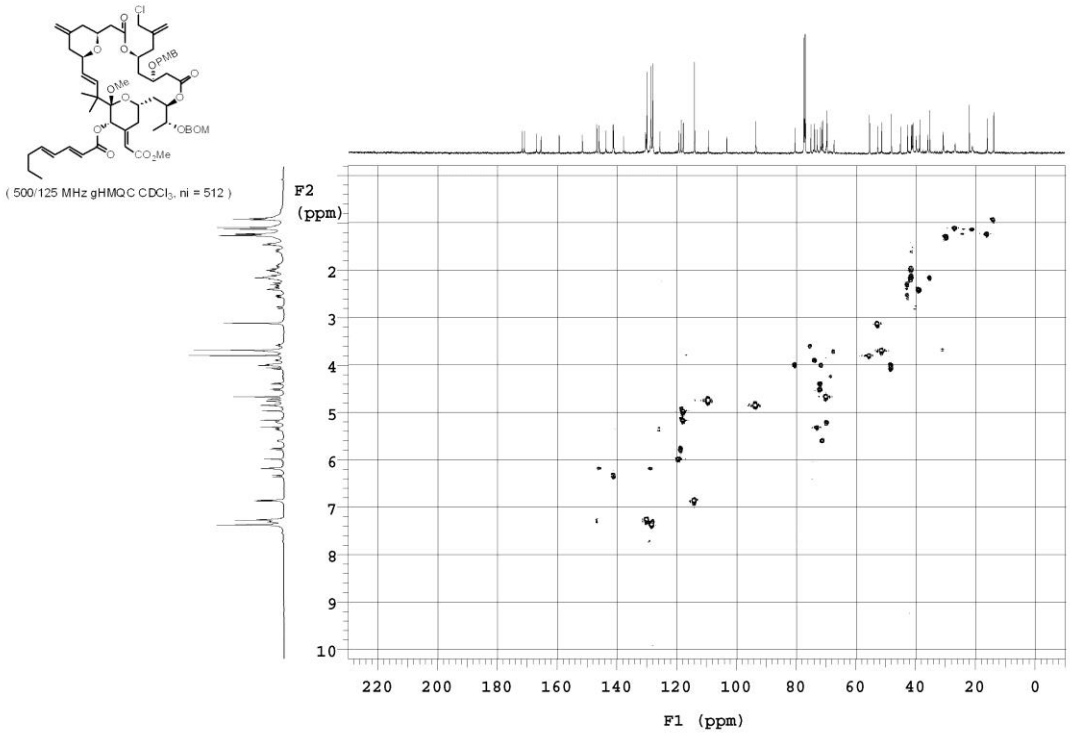


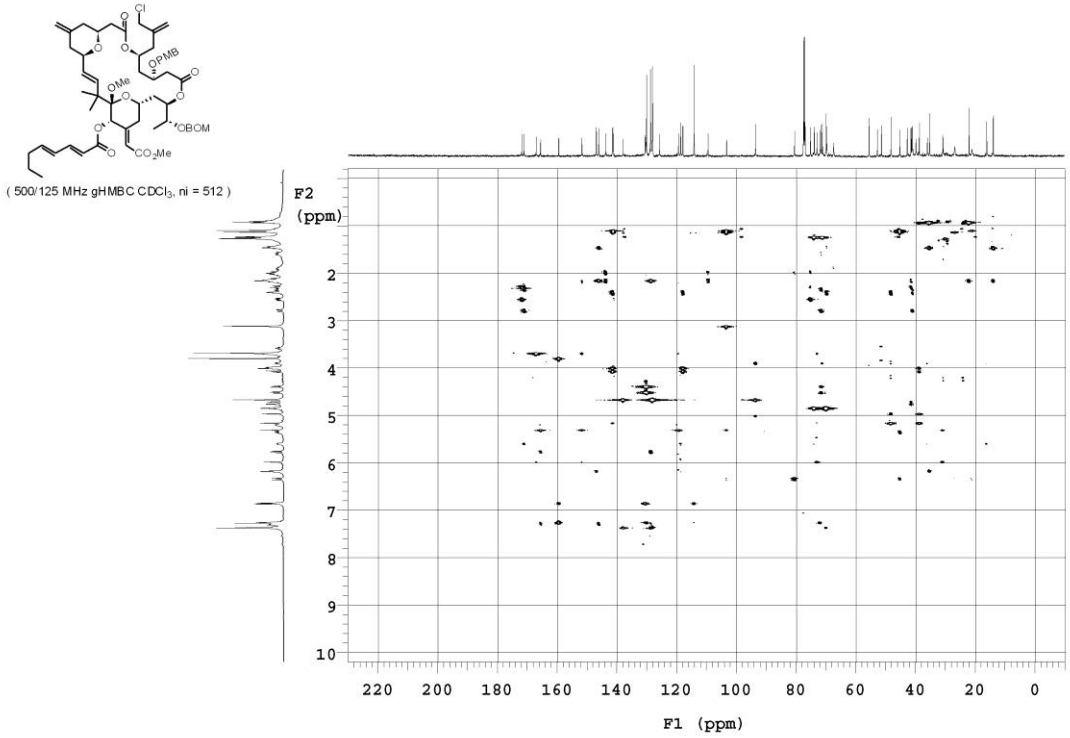
(500 MHz gDQCOSY $CDCl_3$, ni = 512)

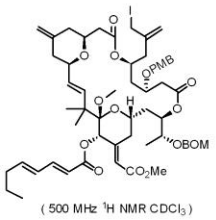



(125 MHz ^{13}C NMR $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm

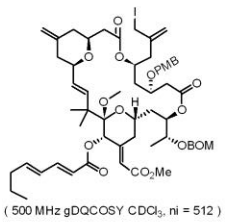

(125 MHz DEPT $CDCl_3$)
220
200
180
160
140
120
100
80
60
40
20
ppm


(500/125 MHz gHMQC CDCl3, ni = 512)
F2 (ppm)
F1 (ppm)

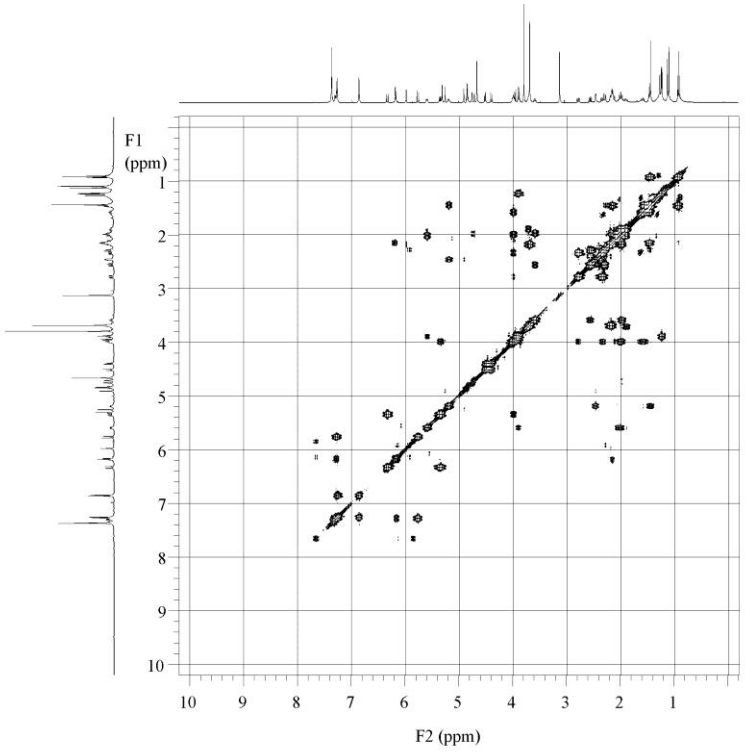

(500/125 MHz gHMBC CDCl3, ni = 512)
F2 (ppm)
F1 (ppm)

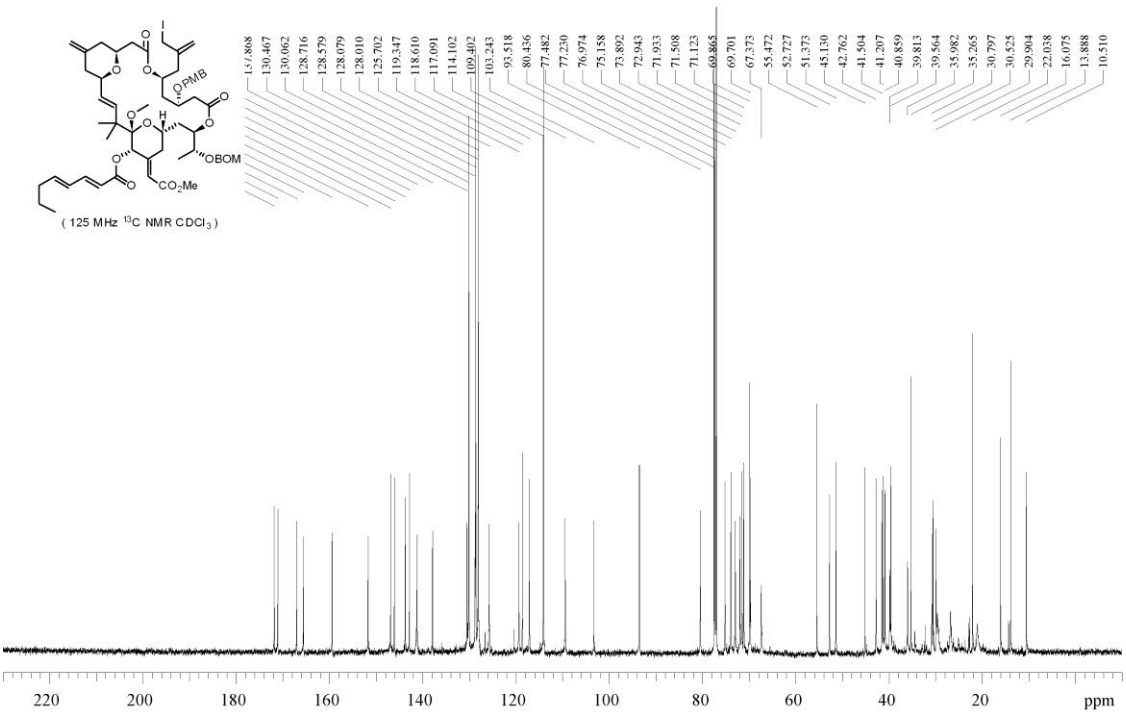


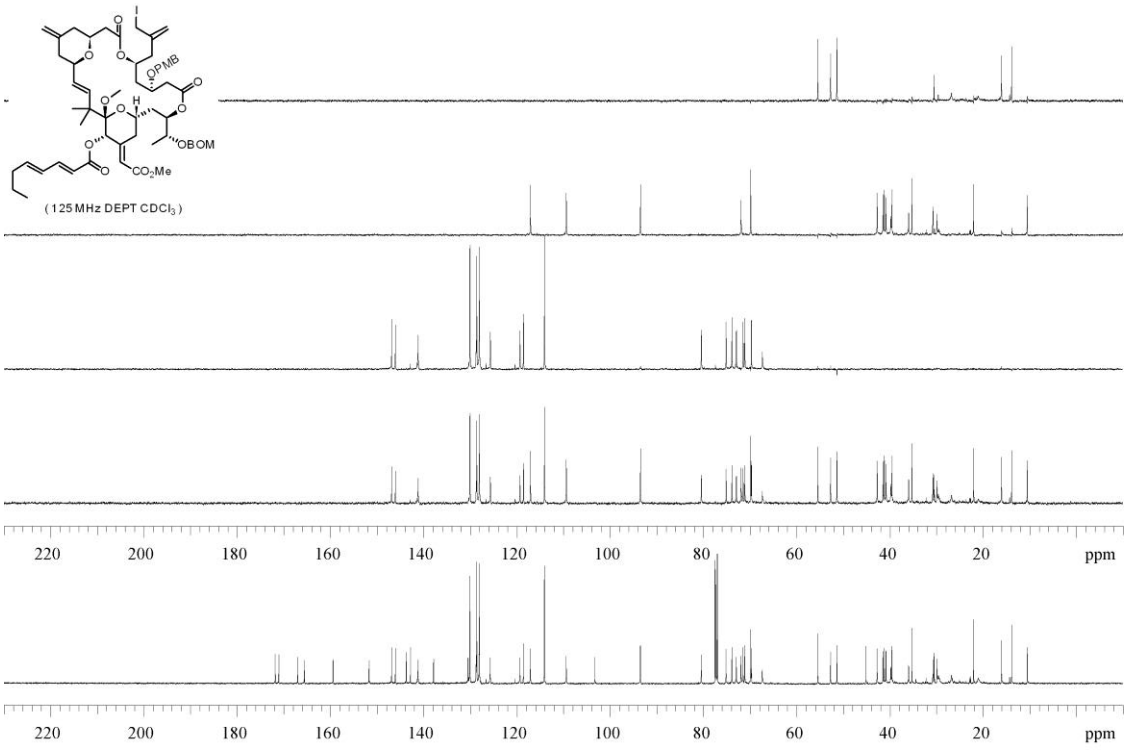
(500 MHz ^{1}H NMR $CDCl_3$)

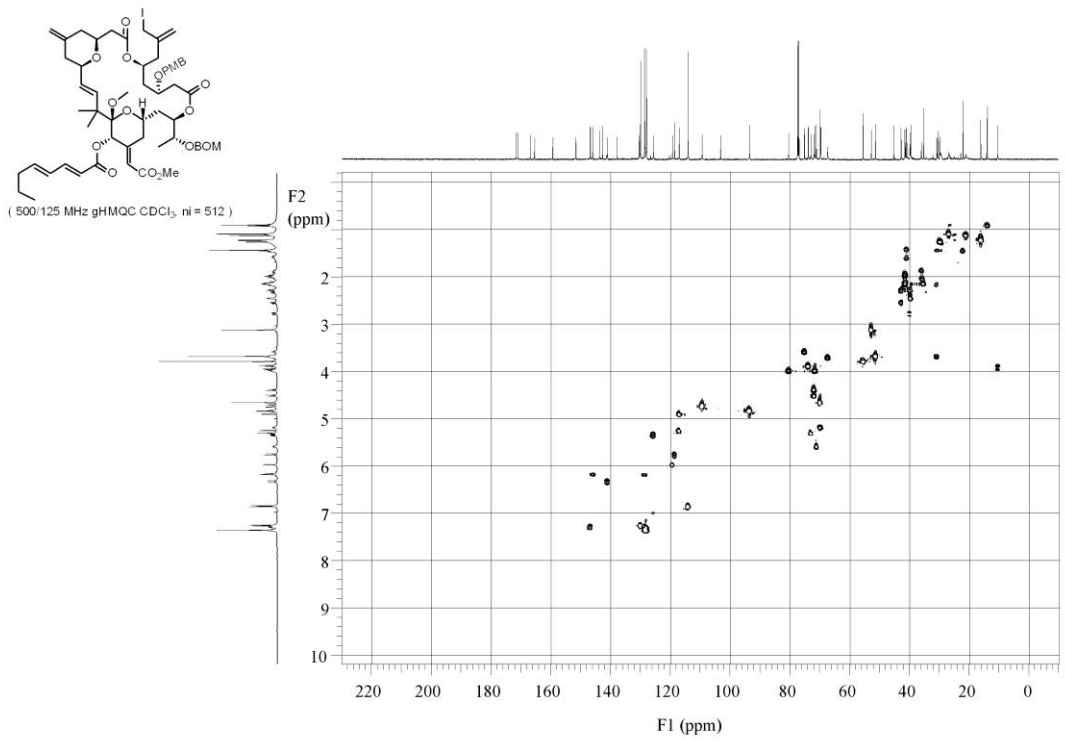


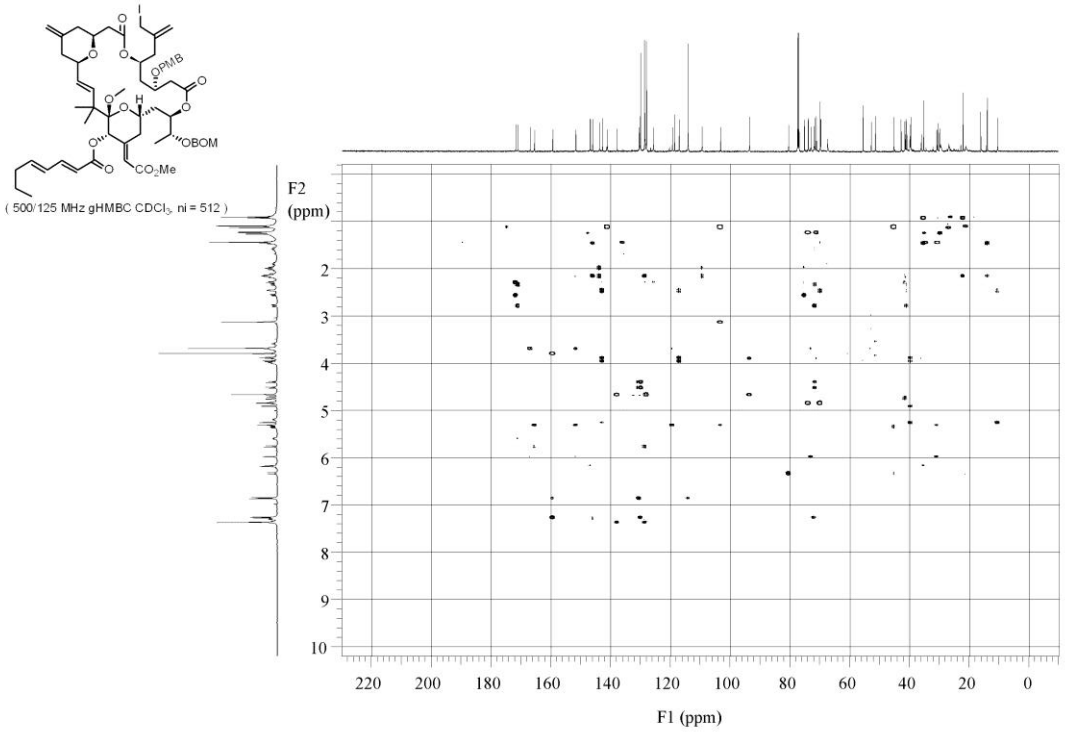
(500 MHz gDQCOSY $CDCl_3$, ni = 512)

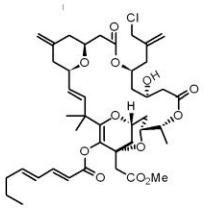



OPMB
OBOM
CO2Me
(125 MHz 13C NMR CDCl3)
167.868
130.467
130.062
128.716
128.579
128.079
128.010
125.702
119.347
118.610
117.091
114.102
109.402
103.243
93.518
80.436
77.482
77.230
76.974
75.158
73.892
72.943
71.933
71.508
71.123
69.865
69.701
67.373
55.472
52.727
51.373
45.130
42.762
41.504
41.207
40.859
39.813
39.564
35.982
35.265
30.797
30.525
29.904
22.058
16.075
13.888
10.510
220
200
180
160
140
120
100
80
60
40
20
ppm

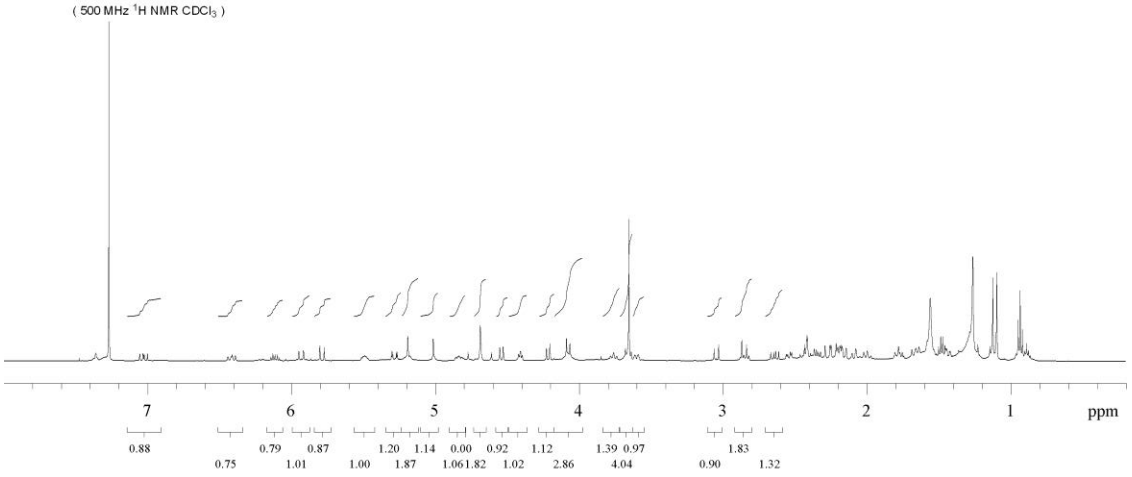

OPMB
OBOM
CO2Me
(125 MHz DEPT CDCl3)
220
200
180
160
140
120
100
80
60
40
20
ppm
220
200
180
160
140
120
100
80
60
40
20
ppm

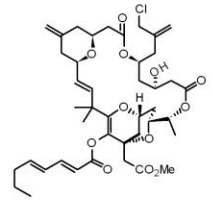

(500/125 MHz gHMQC CDCl3, ni = 512)
F2 (ppm)
F1 (ppm)


(500/125 MHz gHMBC CDCl3, ni = 512)
F2 (ppm)
F1 (ppm)

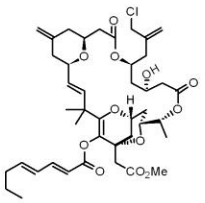


(500 MHz ^{1}H NMR $CDCl_3$)

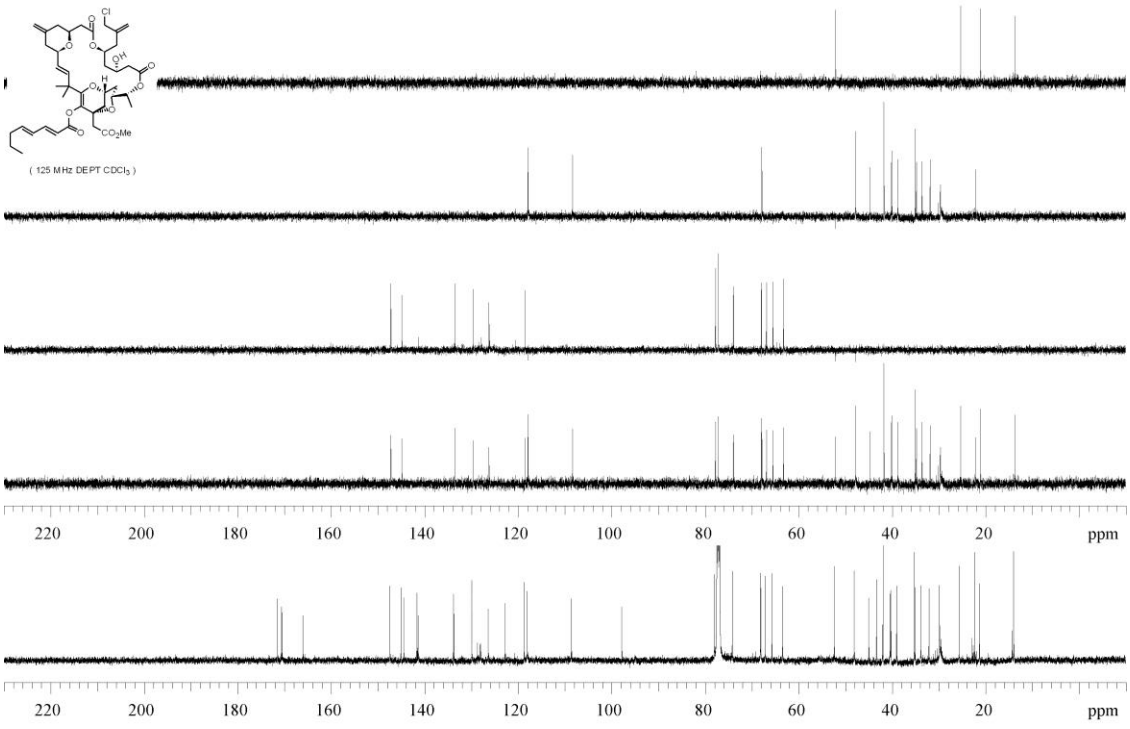




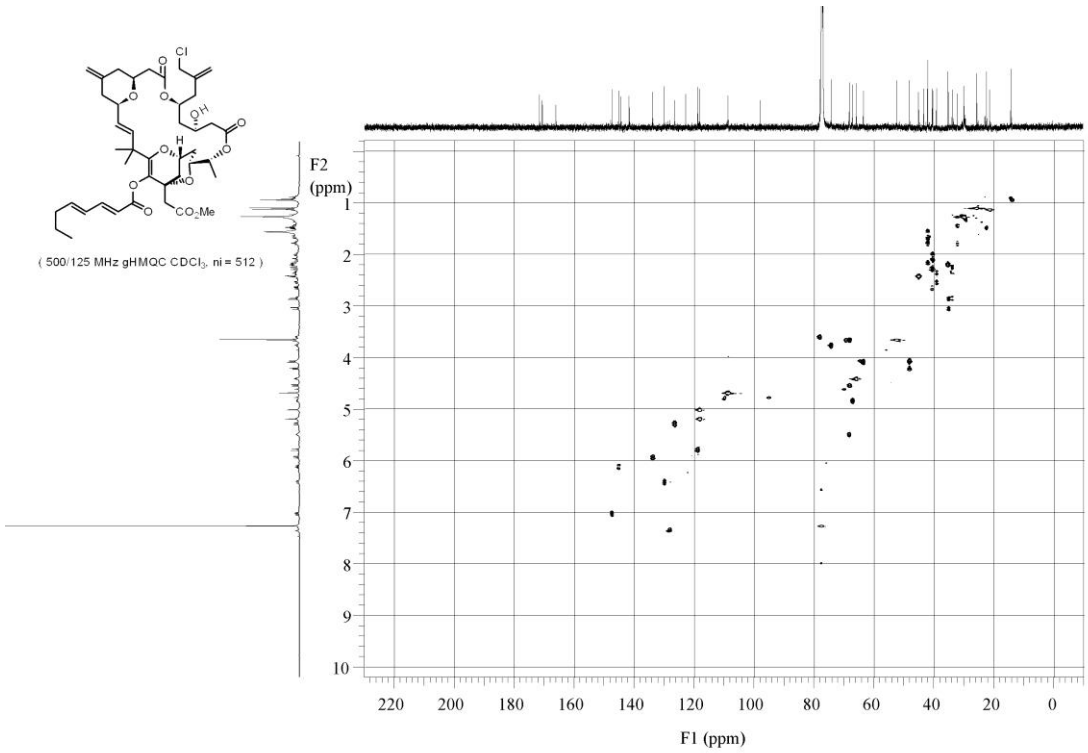
(500 MHz gDQCOSY $CDCl_3$, ni = 512)

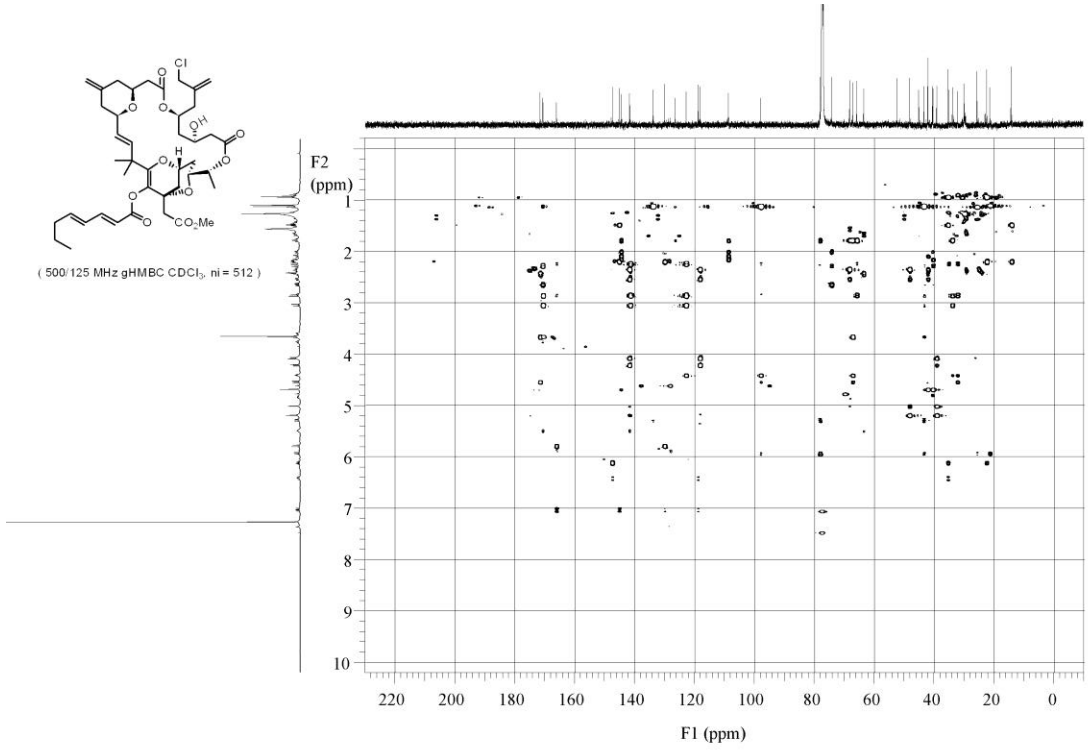


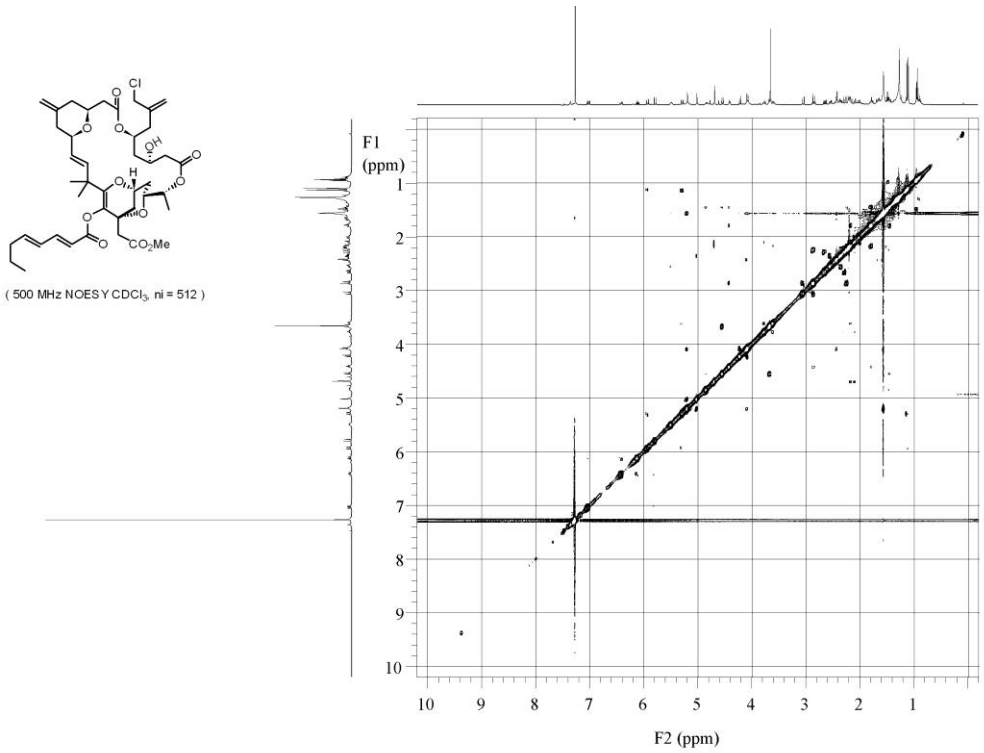
(125 MHz ^{13}C NMR $CDCl_3$)



(125 MHz DEPT $CDCl_3$)


(500/125 MHz gHMQC CDCl3, ni = 512)
F2 (ppm)
F1 (ppm)


(500/125 MHz gHMBC CDCl3, ni = 512)
F2 (ppm)
F1 (ppm)



(500 MHz NOESY $CDCl_3$, ni = 512)