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An Olefin Metathesis-Based Strategy for the Synthesis of New Antitumoral Compounds Inspired by Natural Products

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Doctor en Química
(Mención Internacional)

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D. FRANCISCO SARABIA GARCÍA, CATEDRÁTICO DEL DEPARTAMENTO DE QUÍMICA ORGÁNICA DE LA FACULTAD DE CIENCIAS DE LA UNIVERSIDAD DE MÁLAGA,

CERTIFICA:

Que la memoria adjunta, titulada ''An Olefin Metathesis-Based Strategy for the Synthesis of New Antitumoral Compounds Inspired by Natural Products''**, que para optar al grado de Doctor en Química (Mención Internacional) presenta D. Iván Cheng Sánchez, ha sido realizada bajo mi dirección en los laboratorios del Departamento de Química Orgánica de la Universidad de Málaga.**

Considerando que constituye trabajo de Tesis Doctoral, autorizo su presentación en la Facultad de Ciencias de la Universidad de Málaga.

Y para que así conste, firmo el siguiente certificado, en Málaga a Dieciocho de Octubre de Dos Mil Diecinueve.

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Abstract

This PhD Thesis proposes the discovery and development of new drugs inspired by bioactive natural products, which represent valid platforms for the generation of new chemical entities of pharmaceutical interest. Thus, the combination of structural and functional diversity allows for the identification of new compounds with better biological profiles than the natural counterparts. In order to select suitable synthetic targets, we focused on natural products that are able to offer promising expectations in the biomedicinal field, with new mechanisms of biological action and intriguing molecular structures that could represent the basis of new scaffolds of pharmaceutical interest. In particular, the selected natural products are a microbial polyketide termed (-)-depudecin, and cyclopeptide and cyclodepsipeptide-type compounds from marine origin, the solomonamides A-B and the celebesides A-C. In this PhD Thesis we have established synthetic strategies oriented to the target, but with the possibility of the extension of such strategies to the construction of a molecular diversity through the generation of analogues. For the synthesis of (-)-depudecin, a unique and unexplored histone deacetylase (HDAC) inhibitor with antitumoral detransforming activity, we have established a new total synthesis utilizing an olefin cross-metathesis (CM) reaction as the key step, which was successfully achieved in a convergent and brief manner to provide (-)-depudecin in only 12 steps and 26% overall yield. In addition, the synthetic route was amenable to stereochemical and functional modifications, allowing the preparation of two stereoisomers of (-)-depudecin, the 10-*epi*-depudecin and its enantiomer, as well as homodepudecin and several truncated analogues which were used for a structure-activity relationship (SAR) study in order to identify new leads based on depudecin. In the case of the solomonamides, we have developed a synthetic strategy that comprises two phases: a) a cyclisation phase for the construction of the [15]-membered ring contained in these marine cyclopeptides utilizing an olefin ring-closing metathesis (RCM) as the key reaction; and b) an oxidation phase to give access to the natural products, representing a flexible and diversity-oriented route that would allow for the generation of a variety of analogues via oxidative transformations. In addition, we identified several structurally related solomonamide precursors possessing significant cytotoxicities against various tumor cell lines in the low μM range. In particular, one of these precursors showed potent antiangiogenic effect *in vitro* and *in vivo*, suggesting the potential therapeutic application of solomonamide derivatives as inhibitors of the persistent and deregulated angiogenesis that characterizes cancer and other pathologies. For the last target, the celebesides, [26]-membered cyclodepsipeptides with anti-HIV activity, we envisioned a ring closure process based on a RCM reaction to access their macrocyclic core. We have established a synthetic strategy for the preparation of the peptidic chain contained in these natural products by use of the solid-phase peptide technology, while the synthesis of the polyketide fragment contained in the celebeside A was achieved in a stereoselective manner.

List of Abbreviations

A

Å	angstrom
Ac	acetyl
aq	aqueous

B

BAIB	(diacetoxy)iodobencene
BAE	bovine aortic endothelial
Bn	benzyl
br	broad
Bu	butyl

C

c	concentration for specific rotation measurements
ºC	degree Celsius
^{13}C NMR	carbon nuclear magnetic resonance
CM	cross-metathesis
CTC	2-chlorotrityl chloride
CSA	camphorsulfonic acid

D

δ	NMR chemical shift in parts per million
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutyl aluminium hydride
DIC	*N*,*N*-diisopropylcarbodiimide
DIPEA	diisopropyl ethyl amine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide

E

EDCI	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide·HCl
equiv	equivalent
Et	ethyl

G

g	gram(s)

H

h	hour(s)
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
^{1}H NMR	proton nuclear magnetic resonance
Hz	Hertz
HIV	human immunodeficiency virus

I

IC_{50}	half maximal inhibitory concentration

J

J	coupling constant

L

L	litro
LDA	lithium diisopropylamide

M

m	multiplet
µ	micro
MHz	megahertz
min	minute(s)
mol	mol(s)
mp	melting point
m/z	mass-to-charge ratio

N

N	normal
NMR	nuclear magnetic resonance

P

PCC	pyridinium chlorochromate
pH	hydrogen ion concentration in aqueous solution
ppm	parts per million
pyr	pyridine

Q

q	quartet

R

RCM	ring-closing metathesis
R_f	retention factor
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride

S

s	singlet
SAE	Sharpless asymmetric epoxidation
Super-H	lithium triethylborohydride

T

t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEA	triethyl amine
TEMPO	2,2,6,6-tetramethyl-1-pyperidineiloxy
tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

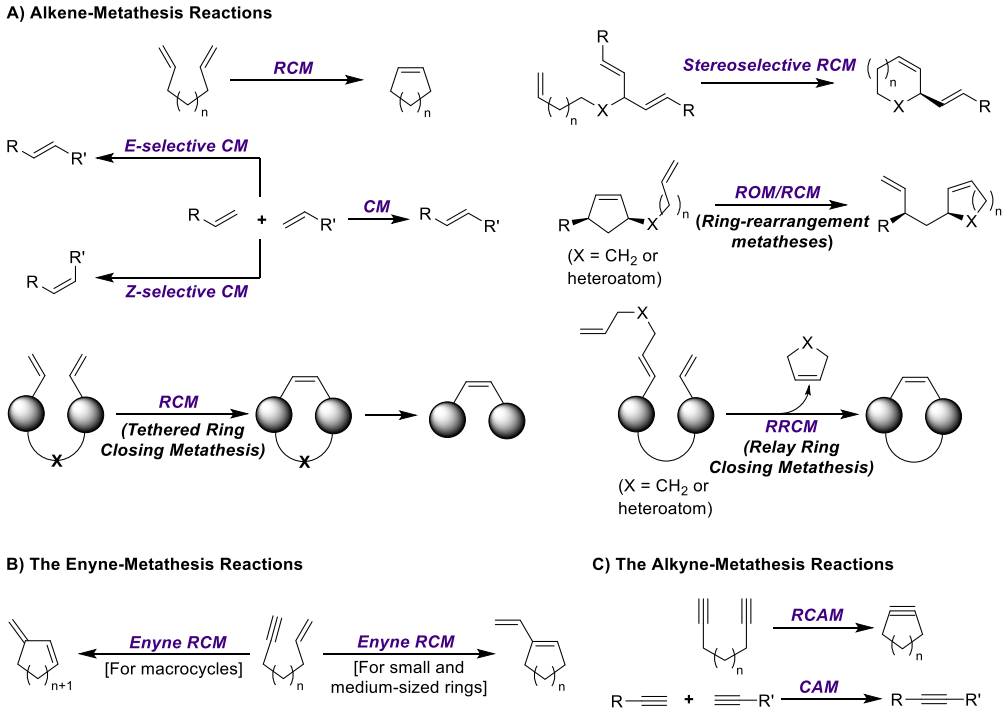
Chapter 1[†]

Introduction

[†] This chapter has been published as a journal article: Cheng-Sánchez, I.; Sarabia, F. *Synthesis* **2018**, *50*, 3749-3786.

1.1. Total Synthesis of Natural Products via Metathesis Reactions

The outstanding and impressive level that organic synthesis has reached in the last few decades, especially in the field of the total synthesis of natural products, can be largely explained by the emergence, design and development of powerful catalysts, which are capable of promoting striking transformations in highly efficient and selective fashions. In fact, the ability of many of them to forge C-C bonds between or within highly functionalized and sensitive compounds has allowed for the preparation of complex frameworks, whose access were previously hampered by the limitations of conventional synthetic methods. Among the myriad of recent catalysts, those developed and designed to promote metathesis reactions have had a profound impact and created a real revolution in the field of total synthesis, by virtue of their ability to promote a stunning number of synthetic transformations, depending on the nature of the starting materials and reaction conditions. Metathesis reactions [1] include the alkene, enyne and alkyne metathesis reactions, together with multiple variants of polyalkenic or polyalkenynic systems as starting precursors involved in cascade processes.[2] Among these, the alkene metathesis reaction (**section A** in **Scheme 1**), in which cyclic olefins or linear alkenes are formed through ring closing metathesis (RCM), cross-metathesis (CM) process, or their different guises (stereoselective, rearrangement, tethered or relay-ring closing metatheses), is the most extensively employed.



Scheme 1. Metathesis Reactions in Organic Synthesis

[1] Metathesis reactions not only include alkene-, enyne- and alkyne-metatheses, but also carbonyl-olefin metathesis, which will not be included in this chapter. For representative reviews about these reactions see: (a) Ravindar, L.; Lekkala, R.; Rakesh, K. P.; Asiri, A. A.; Marwani, H. M.; Quin, H.-L. *Org. Chem. Front.* **2018**, *5*, 1381-1391. (b) Ludwig, J. R.; Schindler, C. S. *Synlett* **2017**, *28*, 1501-1509.

[2] *Handbook of Metathesis*, Vols. 1, 2, 3; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, **2003** (First Edition), **2015** (Second Edition).

Indeed, these transformations occupy a privileged position in modern organic synthesis. Less frequently used but no less important are the enyne and alkyne metatheses (**sections B** and **C** in **Scheme 1**), which have also become valuable synthetic reactions with additional advantages over alkene metatheses. Such is the case of enyne metathesis involved in cascade processes or the case of alkyne metathesis owing to the versatility of the alkyne group by allowing for further transformations, thus considerably expanding the structural diversity of the products that can be formed.

Certainly, behind the success of all these processes are the unique catalysts themselves that enable these transformations. Since the discovery of the first well-defined tungsten carbene catalyst by Katz[3] and the elucidation of the mechanism of alkene metathesis by Chauvin[4] in the 70s, key innovations were the Schrock catalyst **1** in 1990[5] and the discovery of the ruthenium-based catalyst **2** by Grubbs in 1993.[6] These discoveries marked the beginning of an extraordinary and burgeoning race towards more efficient catalysts in terms of activity, stability and functional-group tolerance, represented by the ruthenium species **3**-**14**[7,8,9,10,11,12,13,14,15,16,17,18] (**Figure 1**). These highly efficient catalysts are representative members of three generations of ruthenium complexes, in which the introduction of an *N*-heterocyclic carbene (NHC) ligand (cases of **4**, **6**-**14**) resulted in an increase in the catalytic activity and thermal stability of the catalysts. The catalysts, developed between 1996-2007, gave rise to the rational design of new catalysts to enable both stereoselective and stereoretentive metathesis processes, leading to the molybdenum, tungsten and ruthenium carbene complexes **15**-**27**, among others.[19,20,21,22]

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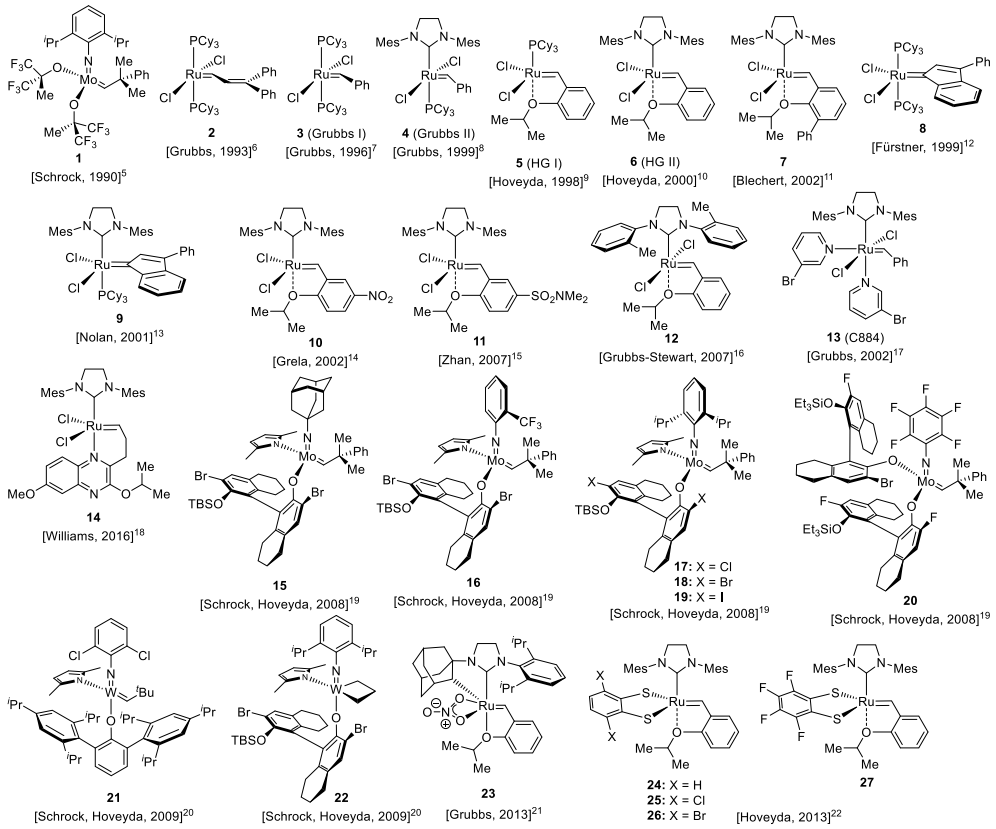

Figure 1. Common Catalysts Used for Alkene and Enyne Metathesis Reactions: Evolution of their Design and Development

Additions to this armory of valuable catalysts, are the water-soluble catalysts in form of PEGylated complexes[23] or ruthenium-based catalysts supported on activated surfaces,[24] which expand even further the scope and applications of the chemistry, particularly in regards to addressing environmental concerns.[25] All these catalysts are appropriate for alkene and enyne-metatheses.[26] Interestingly, for the latter case, the process can be also effected by other transition metal-based catalysts such as those based on Pt, Pd or Ir via a completely different mechanism. A separate case is the alkyne metathesis reaction, which despite the mechanistic similarity with alkene metathesis, requires a different type of catalysts. Indeed, in this case, the variety of catalysts available is not as great as those developed for the alkene metathesis reactions, as will be discussed in more detail later in the alkyne metathesis section. Together with the prominent activity and stability of the aforementioned catalysts, other features that have been improved in the evolution of catalyst design,[27] is the exceptional functional group tolerance that all these catalysts display, which in turn has positioned them as one of the most powerful synthetic tools in the modern organic synthesis. Consequently, total synthesis has

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[26] All these metal carbene complexes are indeed precatalysts or initiators rather than catalysts because these are not recovered unchanged at the end of the process. Being generally accepted the term "catalyst" in the literature, we have opted to use this term along the chapter.
[27] For an excellent review about the evolution of the catalyst design, see: Hoveyda, A. H. *J. Org. Chem.* **2014**, *79*, 4763-4792.

enormously benefitted from the metathesis reactions, as demonstrated by the extensive use of these reactions in their intramolecular and intermolecular versions. In fact, a flurry of contributions in which the metathesis reaction represents either the key step for the successful completion of a synthesis or as a useful and efficient synthetic tool employed along the synthetic course is a growing component of the organic chemistry literature.

Given the relevance and impact of this reaction in the field of organic chemistry, a large number of reviews, books and book chapters have been devoted to all aspects of these reactions. Among all the excellent reviews focused on the applications of metathesis reactions in natural products synthesis,[28] some key contributions by Nicolaou,[29] Pérez-Castells[30] and Prunet[31] in 2005, 2006 and 2011, respectively, are notable. Recently, a review published in 2017 by Vanderwal[32] is noteworthy, wherein the most relevant contributions in the field of the last years were highlighted, but in a very generic form. On the other hand, an excellent book was published dealing with metathesis reactions in the synthesis of natural products, covering all the aspects of these reactions in the field of total synthesis up to 2010.[33] In addition, numerous reviews have been published on very specific items, dealing with a particular type of metathesis reaction or a particular kind of natural products.[34] In light of this publication landscape, the current chapter intends to act as an introduction to this PhD Thesis, in which a metathesis reaction has been used as the key step towards the total syntheses of bioactive natural products. In this context, the current chapter covers the recent advances reported in the field of total synthesis, in which a metathesis reaction has been essential for the completion of the synthesis, for the period 2012-2018, with particular emphasis on recent pioneering contributions, as well as exciting applications in the context of total synthesis, showing the power that this chemistry has to offer and the prospects that it provides for the future.

1.2. Alkene Metathesis in Total Synthesis

1.2.1. Total Syntheses Based on a Ring-Closing Metathesis Reaction

The ring-closing metathesis (RCM) reaction is one of the most employed methodologies to construct cyclic systems, becoming a common synthetic tool in the

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modern organic synthetic laboratory. Indeed, a practically limitless array of carbocyclic or heterocyclic ring systems, including small, medium and large-sized rings, can be constructed utilizing this transformation. In the context of total synthesis, the preparation of small- and medium-sized rings usually plays a complementary role implemented along the synthetic path. However, in the case of macrocyclic systems, the RCM reaction commonly constitutes a crucial step for the completion of the synthesis. For this reason, in this section, we would like to highlight representative examples reported in the last few years in which the RCM reaction was the key step.

As a first series of examples in this category, it is worth mentioning the polyketide-type compounds ripostatins B (**28**)[35] and A (**29**),[36] FD-895 (**30**),[37] cruentaren A (**31**),[38] pikromycin (**32**),[39] zampanolide (**33**),[40] amphidinolide G (**34**),[41] palmerolide A (**35**),[42] ecklonialactone B (**36**),[43] gambieric acid A (**37**),[44] nominal gobienine A (**38**),[45] trienomycins A (**39**) and F (**40**),[46] 13-demethyllyngbyasolide B (**41**),[47] incednam (**42**),[48] sekothrixide (**43**),[49] aspicillin (**44**),[50] macrolide fragment of FD-891 (**45**),[51] carolacton (**46**),[52] cytospolide P (**47**),[53] pectenotoxin (**48**),[54] Sch725674 (**49**),[55] aspergillide B (revised structure, **50**),[56] iriometolide 3a (**51**),[57] paecilomycin B (**52**),[58] fidaxomicin (**53**),[59] exiguolide (**54**),[60] neopeltolide (**55**),[61] methynolide (**56**)[62] and iriomoteolide-2a (**57**)[63] (**Figure 2**).

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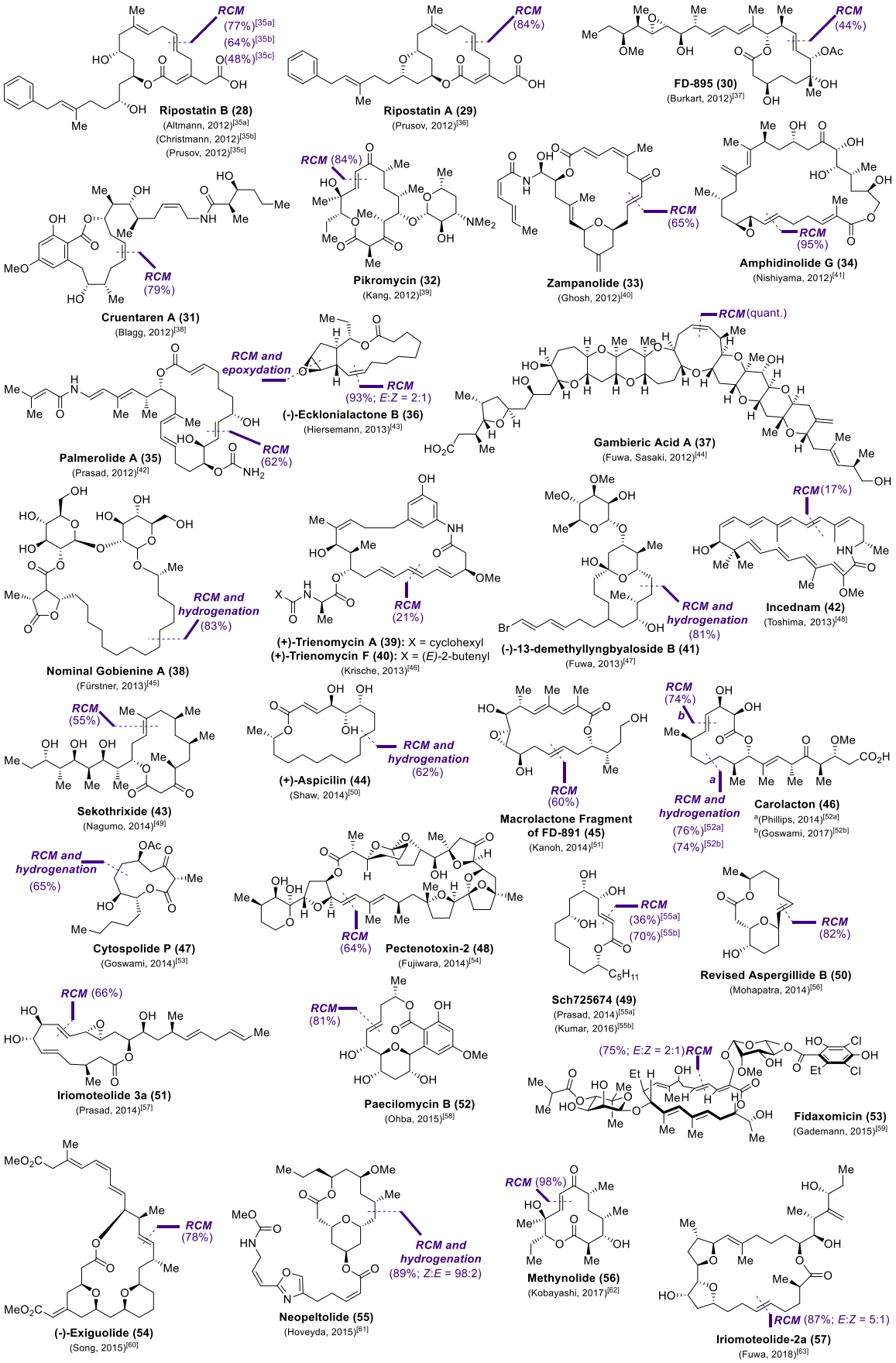

Figure 2. Selected Macrocyclic Polyketides Synthesized via a RCM Reaction (Yields refer only to the RCM reaction)

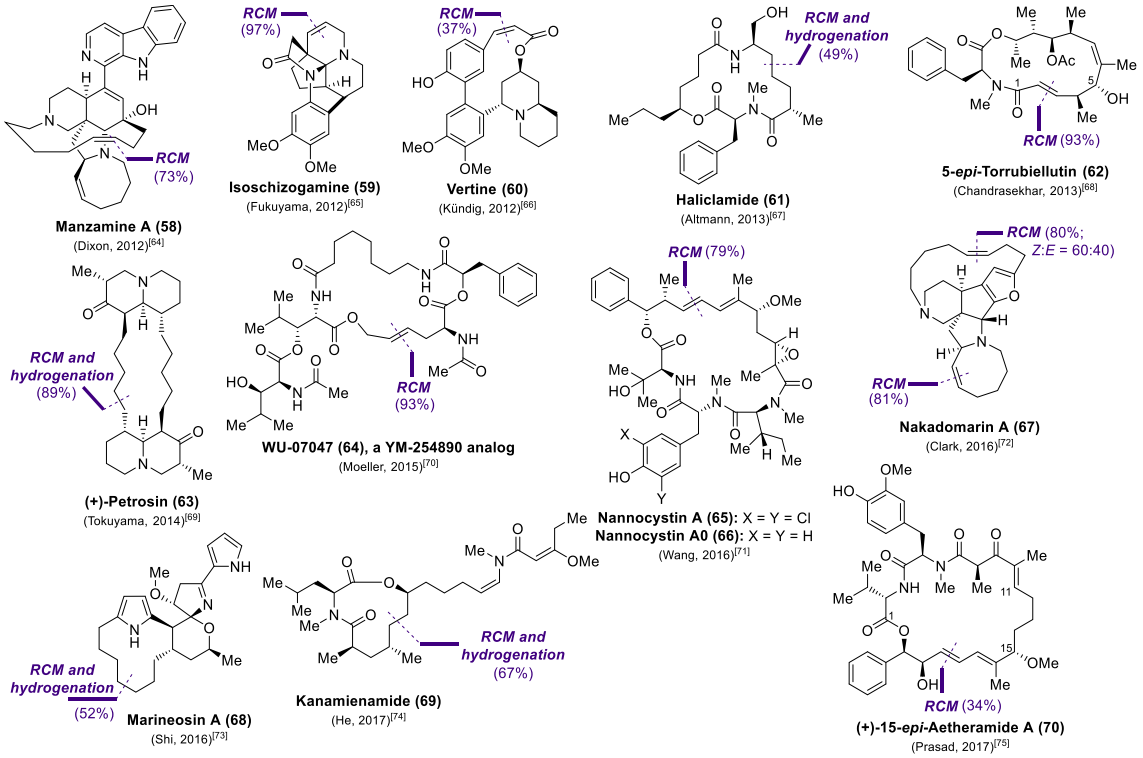

Figure 3. Selected Alkaloids and Cyclodepsipeptides Synthesized via a RCM Reaction (Yields refer only to the RCM reaction)

In addition, the group of alkaloids and cyclodepsipeptides are illustrated with the examples of manzamine A (**58**),[64] isoschizogamine (**59**),[65] vertine (**60**),[66] haliclamide (**61**),[67] 5-*epi*-torrubiellutin (**62**),[68] petrosin (**63**),[69] the YM-254890 analogue **64**,[70] nannocystins A (**65**) and A0 (**66**),[71] nakadomarin A (**67**),[72] marineosin A (**68**),[73] kanamienamide (**69**)[74] and 15-*epi*-aetheramide A (**70**)[75] (**Figure 3**).

Finally, among the total syntheses of terpenes, which employ the RCM reaction, particularly noteworthy are the syntheses of 17-deoxyprovidencin (**71**),[76] uprolide G acetate (**72**),[77] terreumol C (**73**),[78] pavidolide B (**74**)[79] and boscartin F (**75**)[80] (**Figure 4**). As an indication of the effectiveness of the RCM processes, the yields achieved in many cases were reasonable to excellent (44-99% yields), with some exceptions with lower

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[72] Clark, J. S.; Xu, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 4332-4335.
[73] Xu, B.; Li, G.; Li, J.; Shi, Y. *Org. Lett.* **2016**, *18*, 2028-2031.
[74] Reddy, D. P.; Zhang, N.; Yu, Z.; Wang, Z.; He, Y. *J. Org. Chem.* **2017**, *82*, 11262-11268.
[75] Revu, O.; Prasad, K. R. *J. Org. Chem.* **2017**, *82*, 438-460.
[76] Toelle, N.; Weinstabl, H.; Gaich, T.; Mulzer, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3859-3862.
[77] Zhu, L.; Liu, Y.; Ma, R.; Tong, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 627-632.
[78] Frichert, A.; Jones, P. G.; Lindel, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 2916-2919.
[79] Zhang, P.-P.; Yan, Z.-M.; Li, Y.-H.; Gong, J.-X.; Yang, Z. *J. Am. Chem. Soc.* **2017**, *139*, 13989-13992.
[80] Matsuzawa, A.; Shiraiwa, J.; Kasamatsu, A.; Sugita, K. *Org. Lett.* **2018**, *20*, 1031-1033.

yields (17-34%), and in general excellent stereoselectivities, with some exceptions (ecklonialactone, fidaxomycin, iriomoteolide-2a, nakadomarin A), for which the isomeric ratios are indicated.

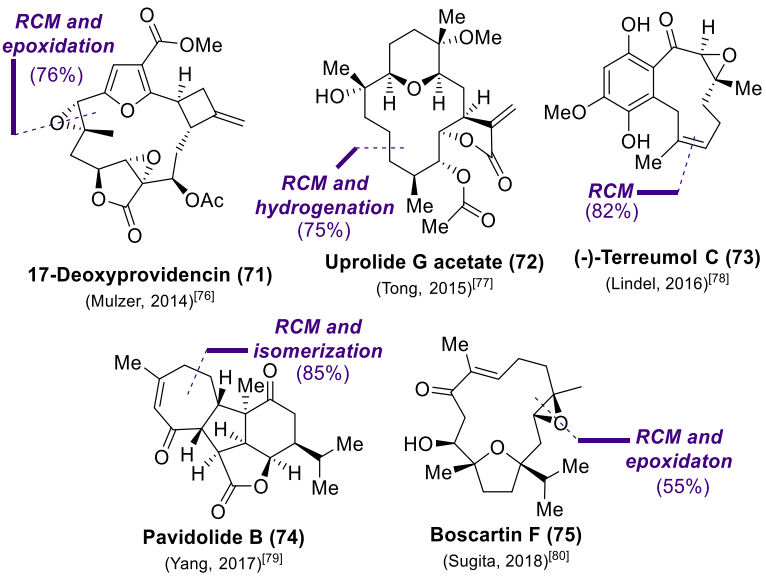
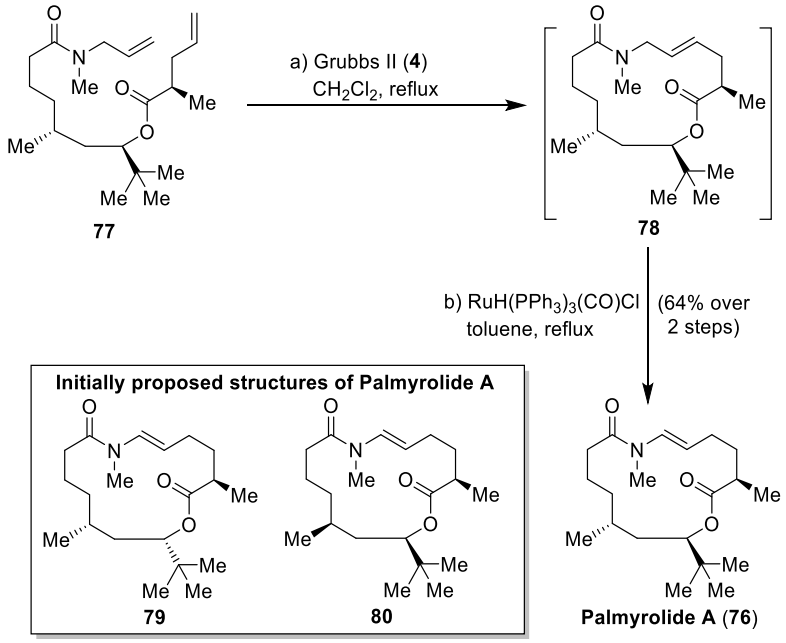


Figure 4. Selected Terpenes Synthesized via a RCM Reaction (Yields refer only to the RCM reaction)

In addition to the previous contributions, we can find in the literature other cases that deserve a more detailed description. A first example is the synthesis by Brimble et al. of palmyrolide A (**76**),[81] a macrolide isolated from *Leptotyngbya cf. sp.* and *Oscillatoria sp.* that displays interesting neuroprotective properties, combined with low cytotoxicity. The synthesis was initially based on a RCM reaction of a starting enamide precursor; however, this RCM attempt failed despite screening of a wide variety of reaction conditions. As a consequence of these disappointing results, the authors considered a sequential RCM/olefin isomerization from the diolefin **77**, with the possibility that the desired isomerization may occur in the presence of the corresponding Grubbs catalyst. However, despite the RCM reaction of diolefin **77** proceeding efficiently when treated with the Grubbs-II catalyst (**4**) to give macrocycle **78**, the isomerization was not observed. This result led the authors to force the isomerization by subsequent treatment of the RCM product with carbonylchlorohydridotris(triphenylphosphine)-ruthenium (II), which then afforded the natural product **76** in a good overall yield. This synthetic study constituted the first reported isomerization of an *N*-allylated tertiary amide in a macrocyclic setting and, furthermore, allowed the revision of the structure of the natural product, which was erroneously assigned to the initial proposed structures **79** and **80** (**Scheme 2**).

[81] (a) Wadsworth, A. D.; Furkert, D. P.; Sperry, J.; Brimble, M. A. *Org. Lett.* **2012**, *14*, 5374-5377. (b) Wadsworth, A. D.; Furkert, D. P.; Brimble, M. A. *J. Org. Chem.* **2014**, *79*, 11179-11193.

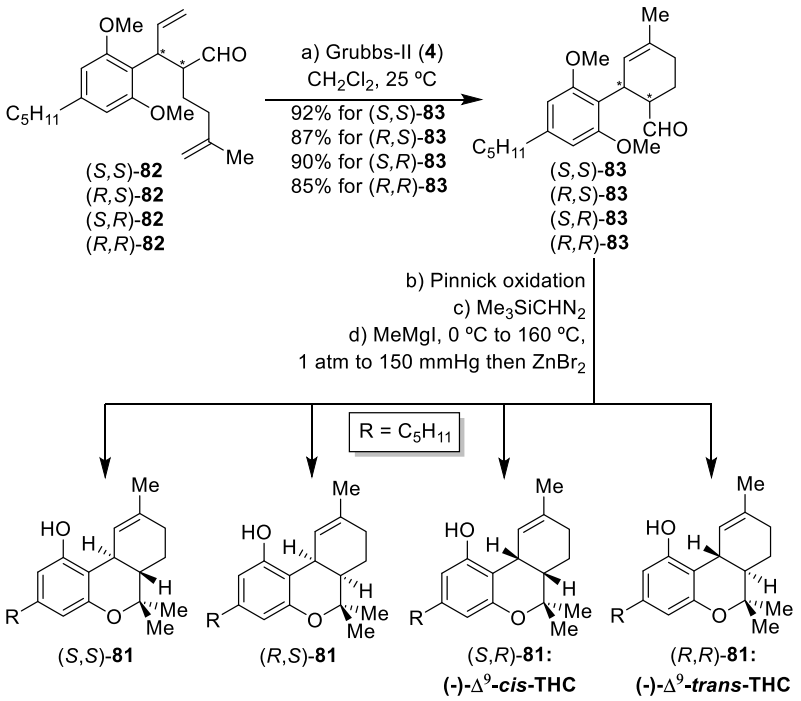


Scheme 2. Total Synthesis of Palmyrolide A (**76**) (Brimble et al. 2012)[81]

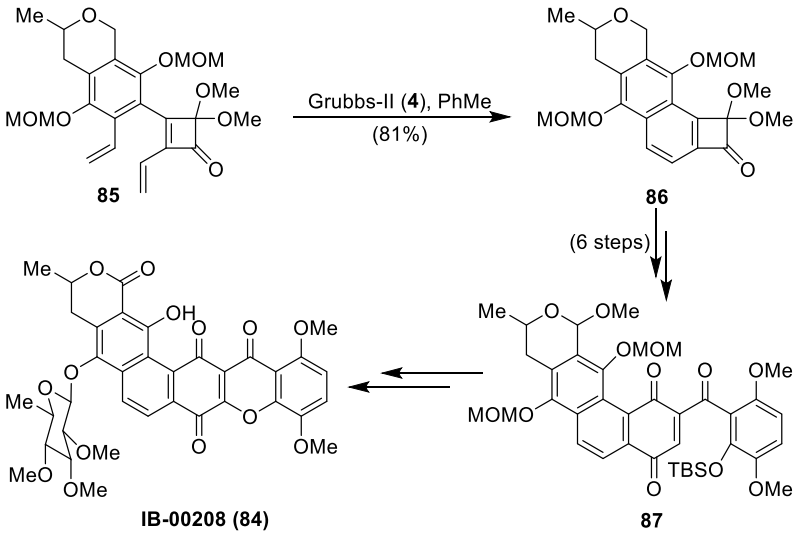
A second relevant example is from Carreira et al., who in a stereodivergent-oriented approach described the synthesis of the four diastereoisomers of Δ^9-tetrahydrocannabinol (**81**) via a RCM reaction from the acyclic precursors **82**.[82] Interestingly, the four stereoisomers of **82** were efficiently prepared by an elegant and novel dual catalytic process based on the use of a set of two chiral catalysts (Ir/(P, olefin) and a secondary amine) for the enantioselective allylation of 5-methyl-5-hexenal. The RCM reaction of each stereoisomer of **82** was achieved under very mild conditions (25 °C) with the Grubbs II catalyst (**4**) to provide the corresponding THC precursors **83** in excellent 85-92% yields, which were transformed into the final products in three additional steps (**Scheme 3**). Previous syntheses of Δ^9-THC (**81**) and related cannabinoid-type compounds have also employed the RCM reaction to construct the cyclohexene ring containing in these intriguing natural products.[83]

The construction of medium-sized rings containing cyclobutanes represents a challenging ring-closing metathesis due to the highly strained character of the resulting bicyclic system. Despite this potential difficulty, the RCM reaction has proven to be highly efficient in many cases. An instructive example of this is demonstrated in the synthesis of the polycyclic xanthone-type antibiotic IB-00208 (**84**), reported by Martin et al.[84] Thus, the synthesis of the key cyclobutenone **86** was successfully achieved via a RCM reaction of precursor **85** when subjected to the Grubbs-II catalyst (**4**). The resulting cyclobutenone was rearranged to the desired xanthone **87** under thermal conditions and represents a general route to construct polycyclic benzoquinones. A few more steps then converted the xanthone **87** into the targeted natural product **84** (**Scheme 4**).

[82] Schafroth, M. A.; Zuccarello, G.; Krautwald, S.; Sarlah, D.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 13898-13901.
[83] (a) Trost, B. M.; Dogra, K. *Org. Lett.* **2007**, *9*, 861-863. (b) Song, Y.; Hwang, S.; Gong, P.; Kim, D.; Kim, S. *Org. Lett.* **2008**, *10*, 269-271.
[84] Yang, J.; Knueppel, D.; Cheng, B.; Mans, D.; Martin, S. F. *Org. Lett.* **2015**, *17*, 114-117.



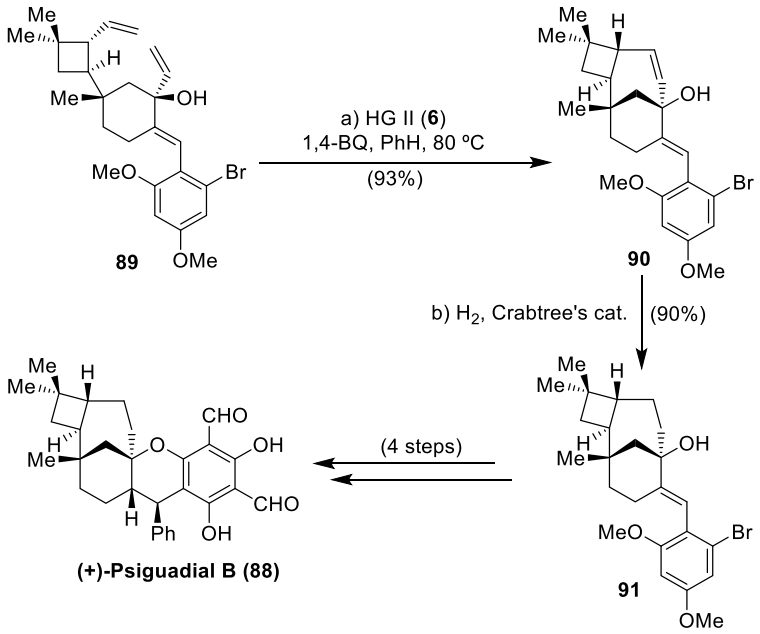
Scheme 3. Total Synthesis of Δ^9-THC ((*R*,*R*)-**81**) and its Stereoisomers (Carreira et al. 2014)[82]



Scheme 4. Total Synthesis of IB-00208 (**84**) (Martin et al. 2015)[84]

As another example of the use of the RCM reaction to fashion cyclobutane-containing polycyclic systems, we highlight the total synthesis of the cytotoxic meroterpenoid psiguadial B (**88**) by Reisman et al.[85] in which the RCM reaction of diolefinic cyclobutane **89**, carried out with the HG II catalyst (**6**) in the presence of 1,4-benzoquinone, afforded in an excellent 93% yield the corresponding tricyclic derivative **90**. After a formidable chemoselective hydrogenation of **90**, which was accomplished in an excellent 90% yield by the action of Crabtree´s catalyst, the resulting product **91** was carried towards the natural product in four additional steps (**Scheme 5**).

[85] Chapman, L. M.; Beck, J. C.; Wu, L.; Reisman, S. E. *J. Am. Chem. Soc.* **2016**, *138*, 9803-9806.



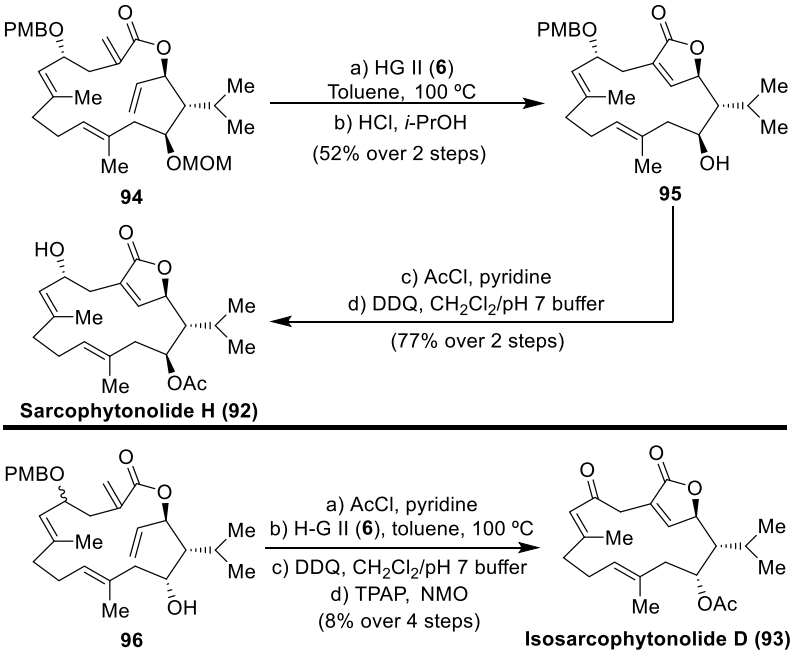
Scheme 5. Total Synthesis of Psiguadial B (**88**) (Reisman et al. 2016)[85]

A stunning example of the power of the RCM reaction can be found in the construction of strained ring systems via a transannular process as applied in the recent synthesis of the cembranolides sarcophytonolide H (**92**) and isosarcophytonolide D (**93**) by Takamura et al.[86] These natural products, isolated from the soft coral of the genus *Sarcophyton*, exhibit potent antifouling activities against the larval settlement of barnacle *Balanus amphirite* with EC_{50} values in the low μg/mL range. In these syntheses, the construction of the butenolide contained in the macrocyclic framework, which is a structural feature of this class of diterpenes, was achieved via a RCM reaction of the corresponding precursors **94** and **96** by treatment with the HG II catalyst (**6**) in toluene at 100 °C. The efficiency of these processes is quite remarkable, given both the steric encumbrance around the ring closure site and the complexity of the system. The completion of the synthesis of both natural products was carried out in three additional steps from the RCM products (**Scheme 6**).

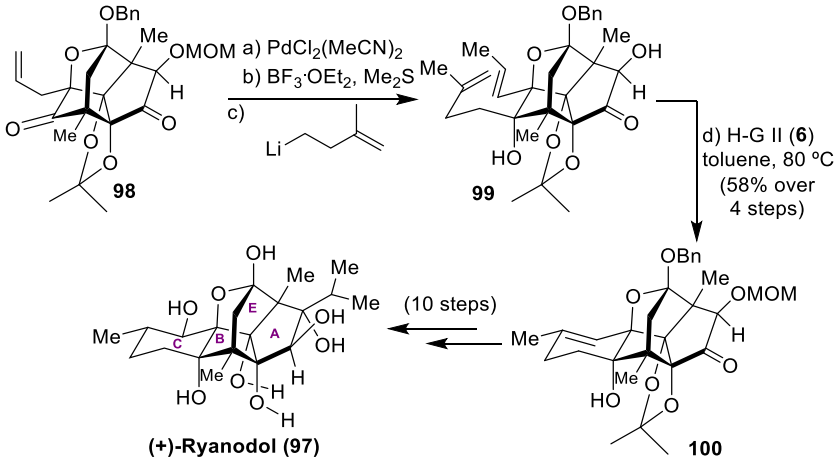
Further evidence for the utility of the RCM reaction in the construction of sterically crowded and highly functionalized ring systems is provided by the recent total synthesis of the highly oxidized diterpenoids ryanodol (**97**) and related diterpenes, natural products that display powerful pharmacological and insecticidal activities via their interactions with the ryanodine receptors.[87] The synthesis of the C-ring of ryanodol was undertaken by Inoue et al. via the RCM reaction of the precursor **99**,[88] prepared from the allylic diketone **98** in three steps, with a 58% yield over four steps, to obtain advanced precursor **100**. Remarkably, once again, the presence of unprotected functionalities was well tolerated under these ruthenium-catalyzed reaction conditions, thus underscoring the

[86] Takamura, H.; Kikuchi, T.; Endo, N.; Fukuda, Y.; Kadota, I. *Org. Lett.* **2016**, *18*, 2110-2113.
[87] Chuang, K. V.; Xu, C.; Reisman, S. E. *Science* **2016**, *353*, 912-915.
[88] (a) Nagatomo, M.; Koshimizu, M.; Masuda, K.; Tabuchi, T.; Urabe, D.; Inoue, M. *J. Am. Chem. Soc.* **2014**, *136*, 5916-5919. (b) Koshimizu, M.; Nagatomo, M.; Inoue, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 2493-2497. (c) Masuda, K.; Koshimizu, M.; Nagatomo, M.; Inoue, M. *Chem. Eur. J.* **2016**, *22*, 230-236.

mildness and efficiency of these reactions in a complex setting. From compound **100**, the completion of the synthesis of ryanodol (**97**) was accomplished in ten additional steps with minimal difficulty (**Scheme 7**).



Scheme 6. Total Synthesis of Sarcophytonolide H (**92**) and Isosarcophytonolide D (**93**) (Takamura et al. 2016)[86]

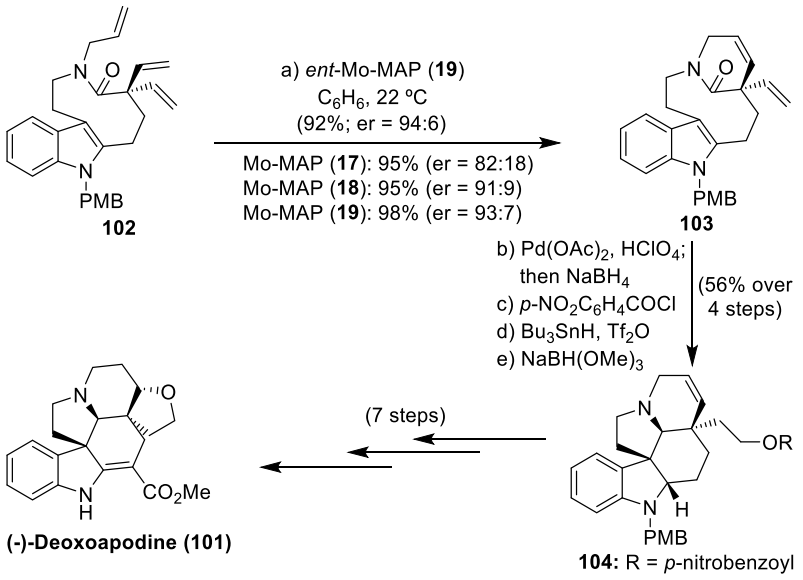


Scheme 7. Total Synthesis of Ryanodol (**97**) (Inoue et al. 2016)[88]

Within the stereoselective RCM processes, the use of chiral catalysts, such as the catalysts **15-22** designed by Hoveyda et al. (see **Figure 1**), allows for the preparation of enantiomerically enriched products.[89] Their applications and level of enantioselective control is nicely illustrated in the synthesis of the alkaloid deoxoapodine (**101**), a member of a family of alkaloids that share the pentacyclic aspidosperma core. This asymmetric synthesis was devised by Movassaghi et al. based on a desymmetrization process of the

[89] For reviews on catalytic enantioselective olefin metathesis see: (a) Ref. 27. (b) Montgomery, T. P.; Johns, A. M.; Grubbs, R. H. *Catalysts* **2017**, *7*, 87 (1-38).

achiral triolefin **102**.[90] Thus, achiral compound **102** was subjected to the catalytic activity of the chiral molybdenum pyrrolide complex **17**, which proved to be efficient in terms of chemical yield and stereoselectivity in the synthesis of quebrachamine,[91] however, in this case, the catalyst offered only moderate enantioselectivity (e.r. = 82:18). This stereochemical outcome was likely influenced by the presence of the amide group in the starting precursor, which could coordinate with the transition metal resulting in a consequent reduction of the catalytic activity. In light of these results, an exploration of other chiral catalysts led to the observation that as the size of the halide substituent on the complex increased, the level of enantioselectivity was improved, with a 93:7 ratio of enantiomers being achieved when the diodo complex **19** was employed. As the natural product possessed the opposite configuration, this result was extended to the enantiomer catalyst *ent*-**19** to obtain the product **103** with the configuration of the natural product in 92% yield and with an enantiomeric ratio of 94:6. With the key product **103** in hand, the synthetic route to the natural product was delineated through the pentacyclic derivative **104**, which was prepared in an efficient manner from **103** according to the steps indicated in **Scheme 8**. From pentacycle **104**, seven additional steps were required for completion of the synthesis of deoxoapodine (**101**) (**Scheme 8**).

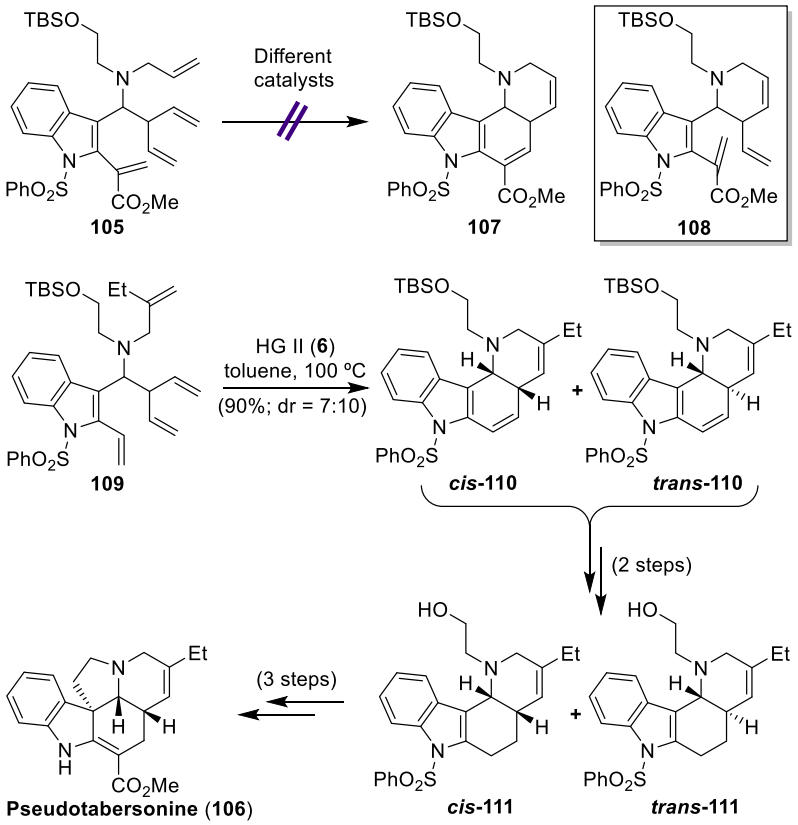


Scheme 8. Total Synthesis of Deoxoapodine (**101**) (Movassaghi et al. 2017)[90]

Despite the excellent functional group tolerance and the low sensitivity to steric hindrances displayed by these catalysts, we can find in the literature numerous examples in which steric factors appear to play a crucial role in unsuccessful ring closure reactions. This is the case for compound **105**, which was devised as a potential precursor for the synthesis of the natural product pseudotabersonine (**106**) by Martin et al.[92] Thus, when **105** was treated with different ruthenium catalysts, including Grubbs-I (**3**), Grubbs-II (**4**), HG II (**6**) or even, the Grubbs-Stewart catalyst (**12**), which is especially reactive towards

[90] Kang, T.; White, K. L.; Mann, T. J.; Hoveyda, A. H.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 13857-13860.
[91] Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943-953.
[92] Cheng, B.; Sunderhaus, J. D.; Martin, S. F. *Tetrahedron* **2015**, *71*, 7323-7331.

sterically hindered olefins, the desired product **107**, resulting from a double RCM process was not observed, instead obtaining the mono-cyclized product **108** in moderate yields, together with degradation products. The authors explored structural modifications of the precursor, by increasing its reactivity by removing the ester group, together with a complete optimization study of the RCM reaction. This extensive study led the authors to define a set of suitable structural requisites and reaction conditions to enable the targeted product. Accordingly, having established **109** as a suitable precursor, when this compound was treated with the HG II (**6**) catalyst in toluene at 100 °C, the desired metathesis product **110** was obtained in a 90% yield albeit as an inseparable mixture of *cis*/*trans* isomers in a 7:10 ratio. After transformation of the diastereomeric mixture **110** into the reduced product **111**, the isomers could be separated, and then, the required *cis* isomer taken forward to completion of the natural product in three more steps (**Scheme 9**).

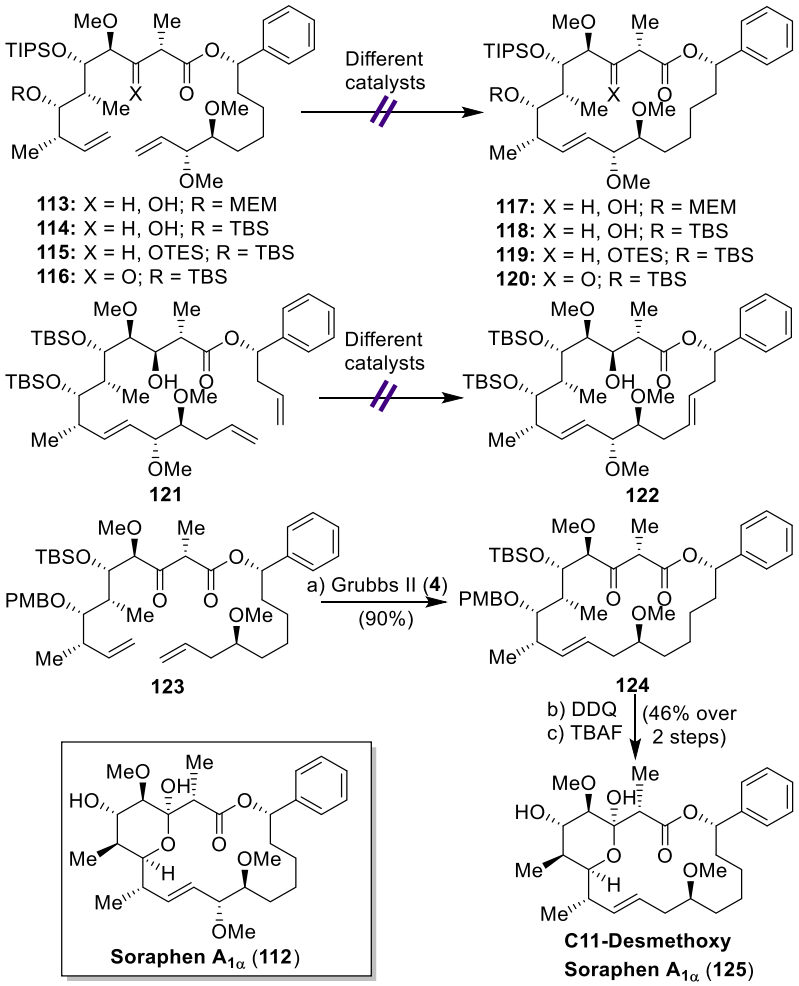


Scheme 9. Total Synthesis of Pseudotabersonine (**106**) (Martin et al. 2015)[92]

A noteworthy case is the natural product soraphen $A_{1\alpha}$ (**112**), whose antimicrobial, antifungus, antidiabetes and anticancer properties has prompted great interest. Preliminary synthetic efforts conducted by Ciufolini et al.,[93] based on a RCM reaction were met with failure for various acyclic precursors (**113-116**). Reasoning that steric factors were responsible for the failed reactions, Kalesse et al.[94] attempted the RCM reactions at less sterically encumbered sites, but the results were similarly unfruitful for precursor **121**. However, the RCM reaction of the desmethoxy precursor **123**, explored

[93] Vincent, G.; Mansfield, D. J.; Vors, J.-P.; Ciufolini, M. A. *Org. Lett.* **2006**, *8*, 2791-2794.
[94] Lu, H.-H.; Hinkelmann, B.; Tautz, T.; Li, J.; Sasse, F.; Franke, R.; Kalesse, M. *Org. Biomol. Chem.* **2015**, *13*, 8029-8036.

by Micalizio et al.,[95] provided in high yield the macrocycle **124** with Grubbs-II catalyst (**4**), proof that steric factors were responsible for the previous failures. From compound **124**, the authors completed the synthesis of the soraphen analogue **125**. (**Scheme 10**).

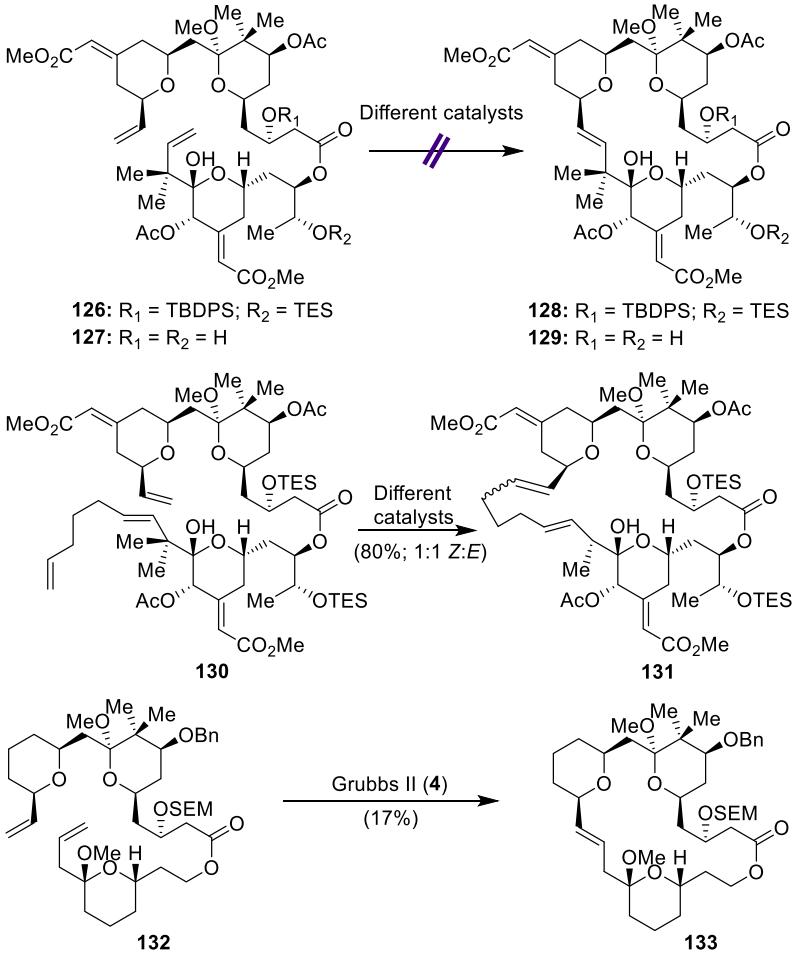


Scheme 10. Synthetic Attempts of Soraphen A1α (**112**) via RCM and Synthesis of the C11-Desmethoxy Analogue **125** (Micalizio et al. 2013)[95]

A paradigmatic example in which the RCM reaction proved to be completely useless was in the synthesis of the bryostatins. The well-known fascinating synthesis of the bryostatins by Trost et al. was preceded by an initial attempt of its total synthesis via a RCM reaction of the diolefins **126** and **127**.[96] However, after extensive screening of different catalysts and conditions, Trost et al. were unable to obtain the corresponding macrocycles **128** and **129**. Furthermore, the implementation of the relay RCM (RRCM) strategy, as we will describe later, did not provide the expected macrocyclic olefin, when the RRCM precursor **130** was subjected to different ruthenium-based catalysts, providing instead the macrocyclic product **131** as a result of the incorporation of the extended olefin onto the final cyclization product. Having ascribed the importance of steric hinderance, imposed by the presence of the gem-dimethyl system at the allylic position, as the reason

[95] Canterbury, D. P.; Scott, K. E. N.; Kubo, O.; Jansen, R.; Cleveland, J. L.; Micalizio, G. C. *ACS Med. Chem. Lett.* **2013**, *4*, 1244-1248.
[96] Trost, B. M.; Yang, H.; Dong, G. *Chem. Eur. J.* **2011**, *17*, 9789-9805.

for these disappointing results, Thomas et al. recently have studied the RCM reaction in model systems of the bryostatins in which the gem-dimethyl group was removed.[97] In their study, the RCM reaction of model compound **132** by exposure to the Grubbs-II catalyst (**4**) furnished the macrocyclic compound **133**, albeit in a poor 17% yield (**Scheme 11**). These results are an indication of the serious hurdles that this class of systems presents for the metathesis reaction.



Scheme 11. Synthetic Studies on Bryostatins via RCM reactions (Trost et al. 2011; and Thomas et al. 2017)[96,97]

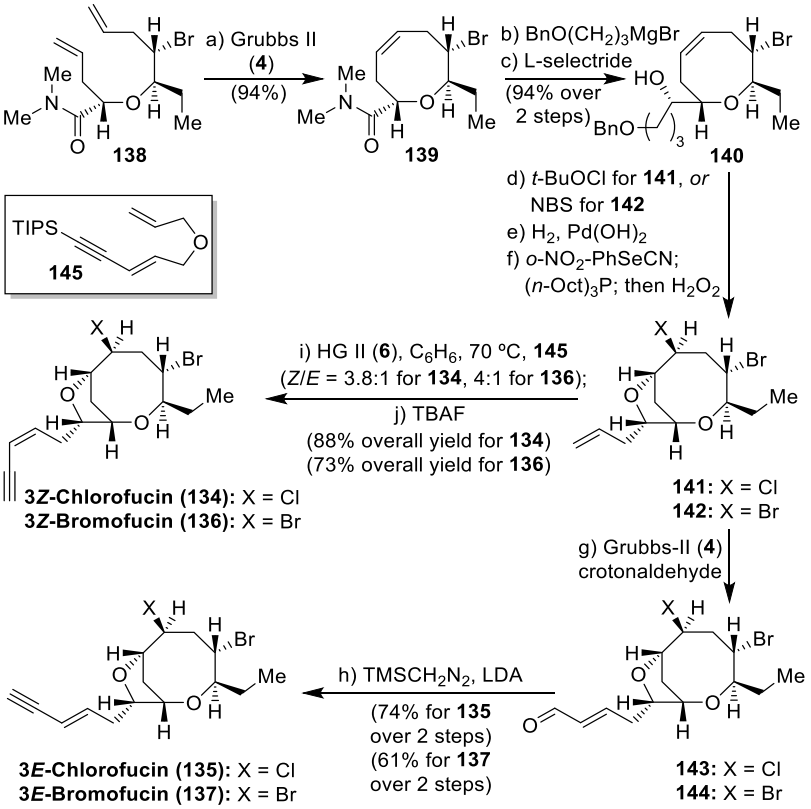
A recent example in which a RCM reaction was combined with a final CM reaction to append the side chain in a stereoselective manner is the synthesis of the halogenated marine metabolites chlorofucins (**134-135**) and bromofucins (**136-137**) by Paton et al.[98] These natural products belong to the family of the bioactive acetogenins isolated from the *Laurencia* red algae that have generated great synthetic interest, particularly in the development of efficient methodologies for the regio- and stereo-controlled construction of the medium-ring oxacycle that characterize these appealing natural products.[99] Furthermore, for the chlorofucins (**134-135**) and bromofucins (**136-**

[97] Dumeunier, R.; Gregson, T.; MacCormick, S.; Omori, H.; Thomas, E. J. *Org. Biomol. Chem.* **2017**, *15*, 2768-2783.
[98] Kim, B.; Sohn, T.-i.; Kim, D.; Paton, R. S. *Chem. Eur. J.* **2018**, *24*, 2634-2642.
[99] Fujiwara, K. *Top. Heterocycl. Chem.* **2006**, *5*, 97-148.

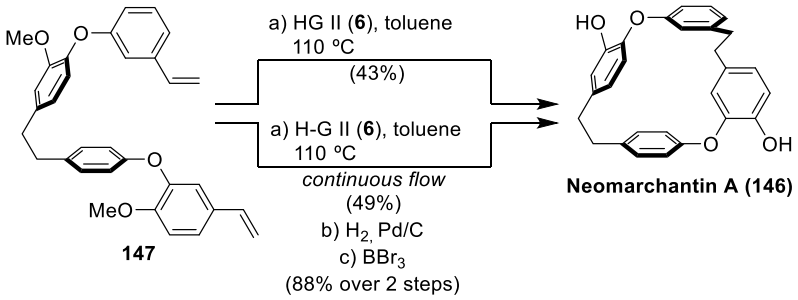
137), their absolute configurations were not established so their asymmetric syntheses could unambiguously confirm their proposed configurations. Thus, the formation of the common oxocene derivative **139** was efficiently undertaken by exposure of the acyclic precursor **138** to the Grubbs II catalyst (**4**). For the incorporation of the halogen with concomitant intramolecular etherification, oxocene **139** was previously transformed into the alcohol **140** in an excellent overall yield and stereoselectivity. With this compound in hand, treatment with *t*-BuOCl or NBS efficiently furnished the corresponding chloro and bromo bicyclic ethers, which were prepared for the key CM reaction by transformation into the terminal olefins **141** and **142**, respectively. For the *E*-selective installation of the enyne moiety, the authors carried out a CM reaction of compounds **141** and **142** with crotonoaldehyde in the presence of the Grubbs-II catalyst (**4**) to yield the corresponding (*E*)-α,β-unsaturated aldehydes, which after a final reaction with lithium TMS-diazomethane delivered the final products **135** and **137** in 74 and 61% overall yields, respectively. For the synthesis of the (*Z*)-isomers, the authors applied the Lee methodology,[100] based on a cross metathesis with enyne **145** in the presence of the HG (II) catalyst (**6**) for the direct delivery of the (*Z*)-isomers of both natural products **134** and **136** in good yields, albeit in modest stereoselectivities in favor of the *Z*-isomer (3.8:1 mixture for **134**; 4:1 for **136**) (**Scheme 12**). Finally, the described stereodivergent strategy to the chlorofucins and bromofucins allowed confirmation of the absolute configurations of these natural products by comparison of the spectroscopic properties and optical rotations of the synthetic compounds with those reported for the natural products.

Metathesis-based methodologies have been used in combination with other innovative technologies in organic synthesis laboratories. Indeed such a case is continuous flow technology, which has been recently implemented in combination with metathesis reactions to enhance their synthetic value.[101] An interesting application of this can be found in the total synthesis of neomarchantin A (**146**), a natural product belonging to the macrocyclic bisbibenzyl family, which has been paid much attention from chemical and biological standpoints due to its intriguing structural and biological features. For example, these compounds exhibit a wide range of biological activities, including antibacterial, antimycotic, antitumoral and antiviral activities. The total synthesis of neomarchantin A (**146**), described by Collins et al.[102] represents the first synthesis of this natural product, which is based on a RCM reaction of the diolefin **147**, to obtain the corresponding macrocyclic derivative in a modest 43% yield when HG II catalyst (**6**) was employed in toluene at 110 °C. Interestingly, when the cyclization reaction was done in continuous flow, the yield of the macrocyclic product could be increased to a 49% yield. Final hydrogenation and methyl ether cleavage afforded the targeted natural product in 88% overall yield (**Scheme 13**).

[100] Hansen, E. C.; Lee, D. *Org. Lett.* **2004**, *6*, 2035-2038.
[101] (a) Monfette, S.; Eyholzer, M.; Roberge, D. M.; Fogg, D. E. *Chem. Eur. J.* **2010**, *16*, 11720-11725. (b) Skowerski, K.; Czarnocki, S. J.; Knapkiewicz, P. *ChemSusChem* **2014**, *7*, 536-542.
[102] Morin, E.; Raymond, M.; Dubart, A.; Collins, S. K. *Org. Lett.* **2017**, *19*, 2889-2892.



Scheme 12. Total Synthesis of Chlorofucins (**134**, **135**) and Bromofucins (**136**, **137**) (Paton, Kim et al. 2018)[98]

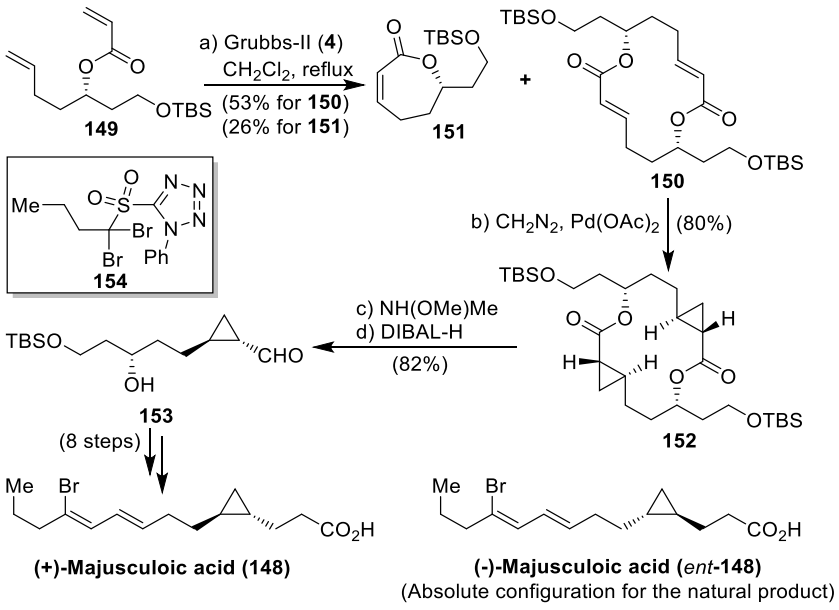


Scheme 13. Total Synthesis of Neomarchantin A (**146**) (Collins et al. 2017)[102]

As a final example for this section, an interesting strategy was delineated for the synthesis of the cyclopropane fattic acid (+)-majusculoic acid (**148**), an interesting secondary metabolite with significant antifungal activity, by Zhang et al.[103] Accordingly, the authors devised a stereoselective cyclopropanation from the C2-symmetric 14-membered dilactone according to previously performed DFT calculations that revealed a preference of the β-faces of both olefins for the attack of the corresponding cyclopropanating reagents. For the synthesis of the required dilactone **150**, the authors envisioned an unusual RCM dimerization from diolefinic monomer **149**. To this aim, after an extensive study in which an array of catalysts, solvents and temperatures were screened, the authors found the Grubbs-II catalyst (**4**) in refluxing dichloromethane as the

[103] Chen, R.; Li, L.; Lin, N.; Zhou, R.; Hua, Y.; Deng, H.; Zhang, Y. *Org. Lett.* **2018**, *20*, 1477-1480.

best condition reactions to obtain the dilactone **150** (53%), accompanied by the monomeric RCM product **151** in a 26% yield. With the dilactone **150** in hand, it was possible to demonstrate the reliability of the theoretical predictions regarding the stereochemical outcome of the cyclopropanation. Indeed, the formation of the biscyclopropane **152** was realized in 80% yield as a single stereoisomer when **150** was treated with diazomethane in the presence of palladium diacetate. The dimerization process was then continued by a dedimerization process by opening of the dilactone **152** with *N*,*O*-dimethylhydroxylamine and reduction of the resulting Weinreb amide to the aldehyde **153**. In a final sequence of eight steps, in which the awkward (*E*,*Z*)-bromodiene system was installed via the new Kocienski-Julia-type reagent **154** developed by the same authors, the synthesis was complete, obtaining a product which matched all the spectroscopic and physical properties with those reported for the natural product, except for the optical rotation, which was the opposite. Therefore, this asymmetric synthesis allowed the confirmation of the absolute configuration for the natural product that corresponded to *ent*-**148**, as initially proposed (**Scheme 14**).



Scheme 14. Total Synthesis of (+)-Majusculoic Acid (**148**) (Zhang et al. 2018)[103]

1.2.2. Total Syntheses Based on a Cross-Metathesis Reaction

In contrast to the RCM reactions, the cross-metathesis (CM) reaction has received less attention in the field of total synthesis, probably due to the inherent difficulties of the intermolecular assembly of two alkenes, in which dimerization processes compete substantially. Despite these difficulties, the appealing features of the metathesis reactions in terms of functional-group tolerance and mild reaction conditions have prompted intense research activity with the goal of minimizing the chemo- and stereoselective issues associated with this modality.

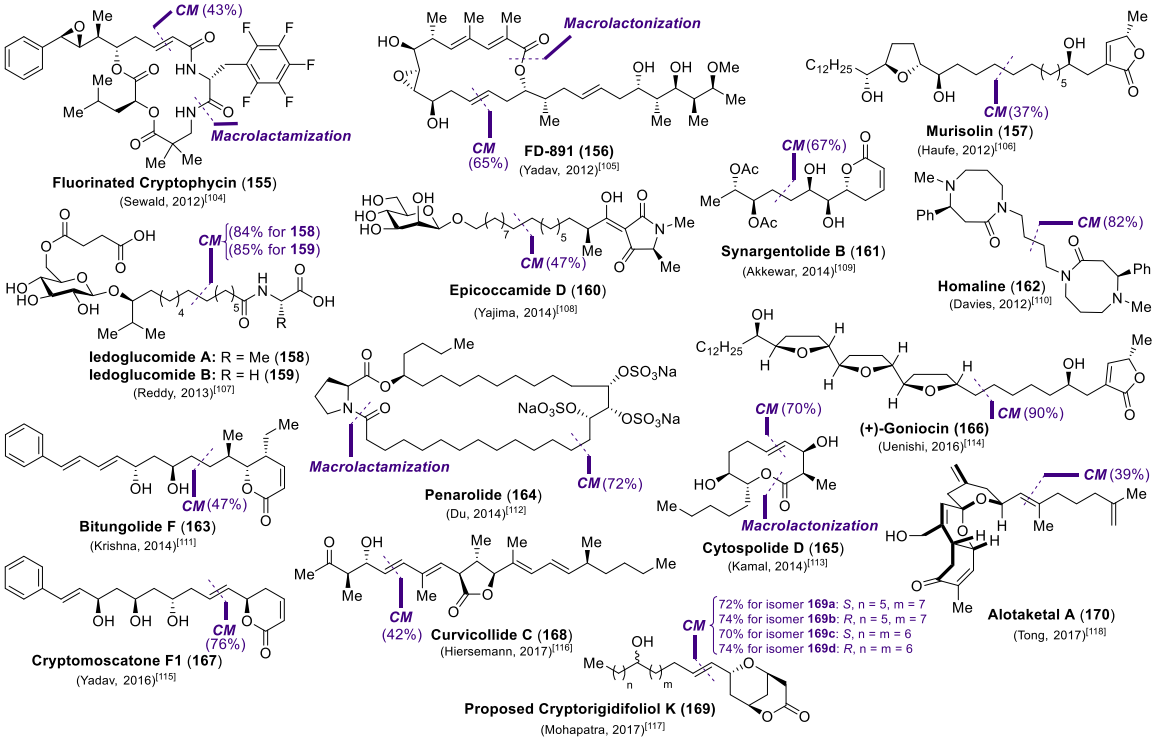
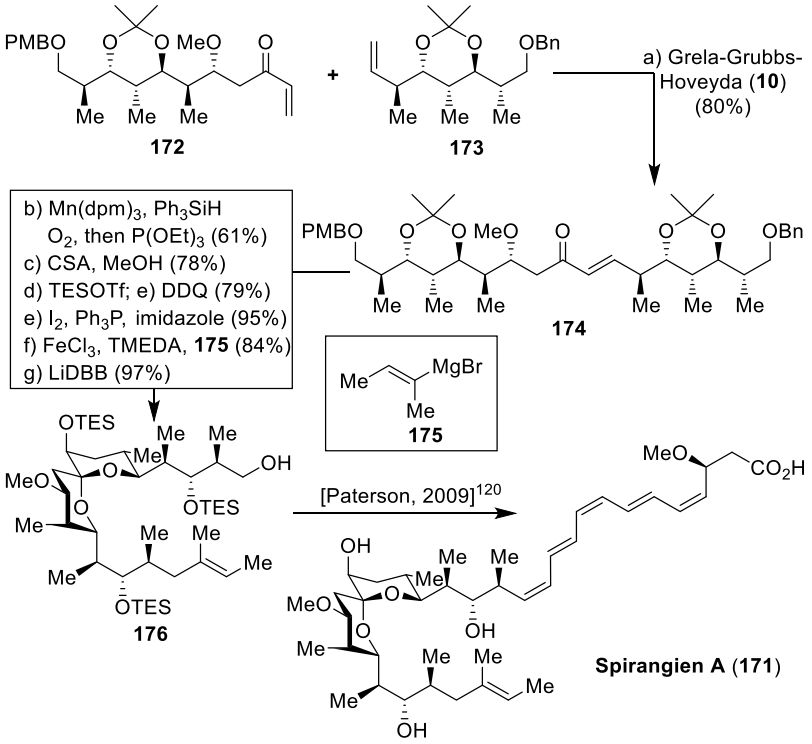


Figure 5. Selected Natural Products Synthesized via a CM Reaction (Yields refer only to the CM reaction)

As a consequence, CM reactions have emerged as a common chain-elongation method to append small side chains or to assemble linear complex molecular frameworks. Concerning the stereoselectivity of the reaction, the thermodynamic control that governs these reactions leads to the preferred formation of the *E*-alkene. Within the field of total synthesis, several interesting syntheses of natural products have been reported in which the CM represented the key step for the coupling of the important fragments of the molecule, thus allowing the completion of the synthesis. Among the most outstanding contributions of the last few years are the total syntheses of the fluorinated cryptophycin **155**,[104] FD-891 (**156**),[105] murisolin (**157**),[106] ledoglucomides A (**158**) and B (**159**),[107] epicoccamide D (**160**),[108] synargentolide B (**161**),[109] homaline (**162**),[110] bitungolide F (**163**),[111] penarolide (**164**),[112] cytospolide D (**165**),[113] goniocin (**166**),[114] cryptomoscatone F1 (**167**),[115] curvicollide C (**168**),[116] proposed structures for cryptorigidifoliol K (**169a-d**),[117] and alotaketal A (**170**)[118] (**Figure 5**).

[104] Weiβ, C.; Bogner, T.; Sammet, B.; Sewald, N. *Beilst. J. Org. Chem.* **2012**, *8*, 2060-2066.
[105] Yadav, J. S.; Das, S. K.; Sabitha, G. *J. Org. Chem.* **2012**, *77*, 11109-11118.
[106] Persich, P.; Kerschbaumer, J.; Helling, S.; Hildmann, B.; Wibbeling, B.; Haufe, G. *Org. Lett.* **2012**, *14*, 5628-5631.
[107] Reddy, C. R.; Jithender, E.; Prasad, K. R. *J. Org. Chem.* **2013**, *78*, 4251-4260.
[108] Yajima, A.; Kawajiri, A.; Mori, A.; Katsuta, R.; Nukada, T. *Tetrahedron Lett.* **2014**, *55*, 4350-4354.
[109] Konda, S.; Bhaskar, K.; Nagarapu, L.; Akkewar, D. M. *Tetrahedron Lett.* **2014**, *55*, 3087-3089.
[110] Davies, S. G.; Lee, J. A.; Roberts, P. M.; Stonehouse, J. P.; Thomson, J. E. *J. Org. Chem.* **2012**, *77*, 7028-7045.
[111] Dayaker, G.; Krishna, P. R. *Helv. Chim. Acta* **2014**, *97*, 868-880.
[112] Gao, Y.; Shan, Q.; Liu, J.; Wang, L.; Du, Y. *Org. Biomol. Chem.* **2014**, *12*, 2071-2079.
[113] Kamal, A.; Balakrishna, M.; Reddy, P. V.; Rahim, A. *Tetrahedron: Asymm.* **2014**, *25*, 148-155.
[114] Suzuki, A.; Sasaki, M.; Nakagishi, T.; Ueda, T.; Hoshiya, N.; Uenishi, J. *Org. Lett.* **2016**, *18*, 2248-2251.
[115] Srinivas, E.; Dutta, P.; Ganganna, B.; Alghamdi, A. A.; Yadav, J. S. *Synthesis* **2016**, *48*, 1561-1567.
[116] Kiedrowski, V. v.; Quentin, F.; Hiersemann, M. *Org. Lett.* **2017**, *19*, 4391-4394.
[117] Reddy, G. S.; Padhi, B.; Bharath, Y.; Mohapatra, D. K. *Org. Lett.* **2017**, *19*, 6506-6509.
[118] Cheng, H.; Zhang, Z.; Yao, H.; Zhang, W.; Yu, J.; Tong, R. *Angew. Chem. Int. Ed.* **2017**, *56*, 9096-9100.

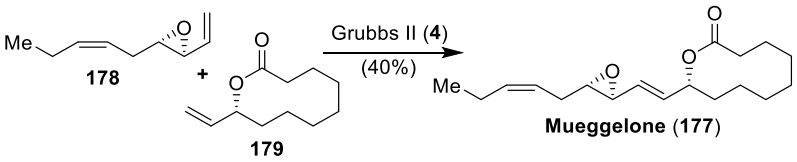
However, there are some specific cases that deserve a more detailed description. As a first example within this category is the formal total synthesis of spirangien A (**171**), a highly potent cytotoxic spiroketal isolated from the prolific myxobacterium *Sorangium cellulosum*. Among the various total syntheses described for this natural product, the one reported by Rizzacasa et al.[119] utilized a CM reaction in the union of the olefins **172** and **173** under the assistance of the Grela-Grubbs-Hoveyda catalyst (**10**). This CM reaction afforded the *E*-enone **174** in an excellent 80% yield, providing a straightforward alternative to the use of a Horner-Wadsworth-Emmons reaction, which requires additional steps for the preparation of the required phosphonate. In this way, the backbone of the spiroketal core found in the natural product was constructed, requiring only six additional steps for the rapid and efficient preparation of the spiroketal precursor **176**. From the advanced spiroketal precursor **176**, the completion of the natural product was reported earlier by Paterson et al. (**Scheme 15**).[120]



Scheme 15. Formal Total Synthesis of Spirangien A (**171**) (Rizzacasa et al. 2013)[119]

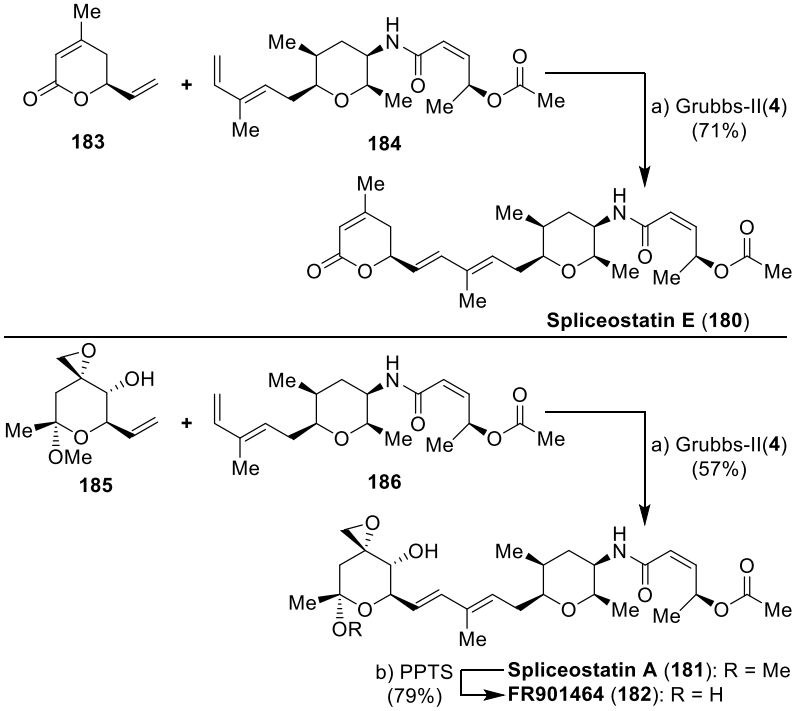
Another case of note is represented by the total synthesis of mueggelone (**177**), an inhibitor of fish embryo larval development. After several total syntheses reported for this interesting natural product, some of which required around 20 steps, Meshram et al.[121] described a convergent total synthesis utilizing only 8 steps in the longest linear sequence, featuring a final CM step in which olefins **178** and **179** were assembled by treatment with the Grubbs II catalyst (**4**) to directly deliver the natural product in a 40% yield (**Scheme 16**).

[119] Gregg, C.; Gunawan, C.; Ng, A. W. Y.; Wimala, S.; Wickremasinghe, S.; Rizzacasa, M. A. *Org. Lett.* **2013**, *15*, 516-519.
[120] Paterson, I.; Findlay, A. D.; Noti, C. *Chem. Asian J.* **2009**, *4*, 594-611.
[121] Kumar, D. A.; Meshram, H. M. *Synth. Commun.* **2013**, *43*, 1145-1154.



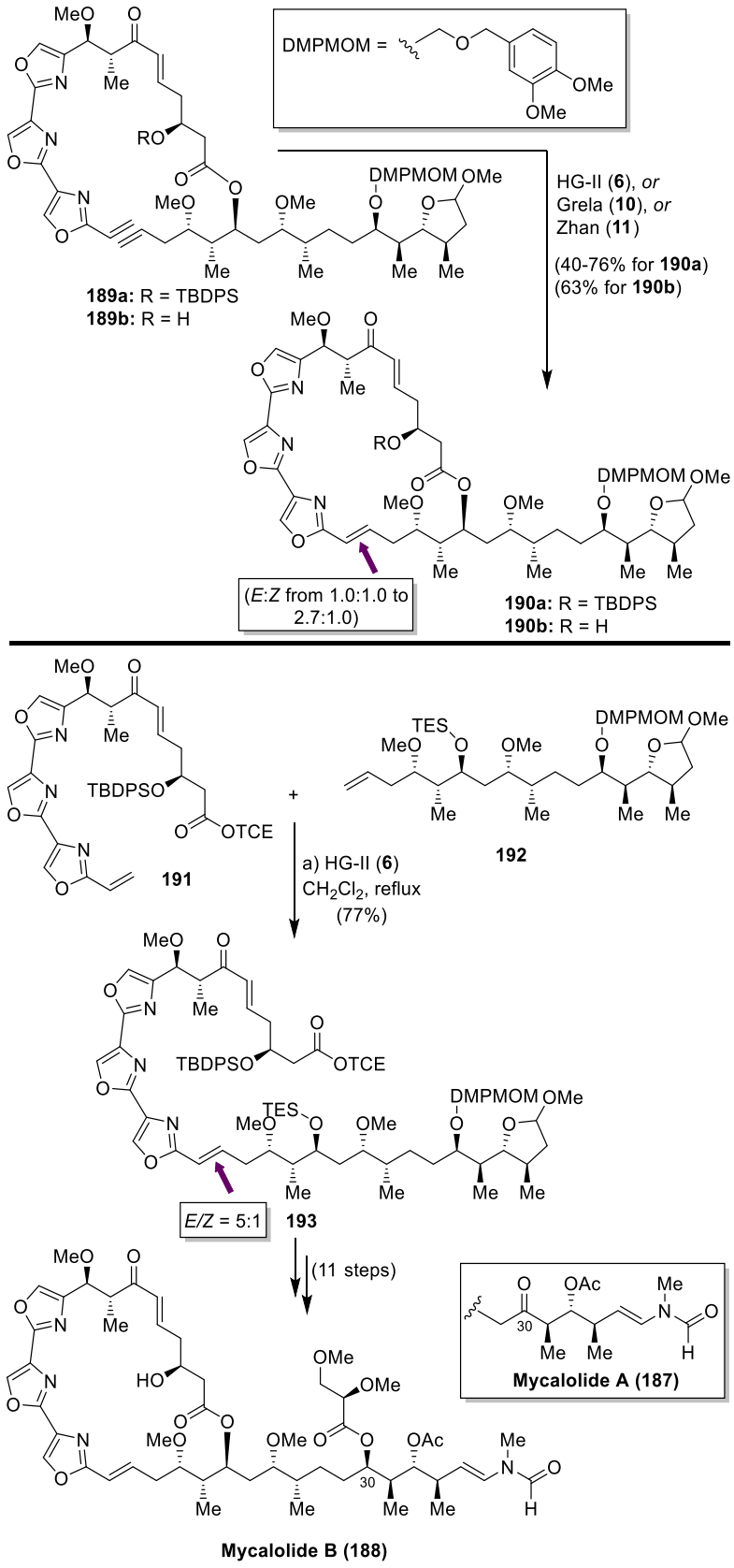
Scheme 16. Total Synthesis of Mueggelone (**177**) (Meshram et al. 2013)[121]

The prominent antitumor activities of spliceostatin E (**180**) and related compounds, such as spliceostatin A (**181**) and FR901464 (**182**), have elicited great interest in their syntheses. Among them, the total syntheses developed by Ghosh et al. is based on a CM reaction,[122] representing a brilliant example of the power and robustness of the methodology. The ability of these natural products to inhibit the cellular splicing process, an essential step for the gene expression, renders them a novel class of anticancer products. In fact, spliceostatin E (**180**) and FR901464 (**182**) exhibit potent anticancer activities in the ranges from 1.5 to 4.1 and from 0.6 to 3.4 nM, respectively, against various human cancer cell lines. The syntheses of both compounds were achieved via a final key CM that efficiently joined fragments **183** and **184** for spliceostatin E (**180**)[122] and **185** and **186** for spliceostatin A (**181**),[123] in 71 and 57% yields, respectively, with both reactions displaying exquisite chemo- and stereo-selectivities. A final acidic treatment of compound **181** afforded the natural product **182** (**Scheme 17**).



Scheme 17. Total Synthesis of Spliceostatins E (**180**) and A (**181**) and FR901464 (**182**) (Ghosh et al. 2013 and 2014)[122,123]

[122] Ghosh, A. K.; Veitschegger, A. M.; Sheri, V. R.; Effenberger, K. A.; Prichard, B. E.; Jurica, M. S. *Org. Lett.* **2014**, *16*, 6200-6203.
[123] (a) Ghosh, A. K.; Chen, Z.-H. *Org. Lett.* **2013**, *15*, 5088-5091. (b) Ghosh, A. K.; Chen, Z.-H.; Effenberger, K. A.; Jurica, M. S. *J. Org. Chem.* **2014**, *79*, 5697-5709.



Scheme 18. Total Synthesis of Mycalolides A (**187**) and B (**188**) (Kigoshi, Kita et al. 2015)[124]

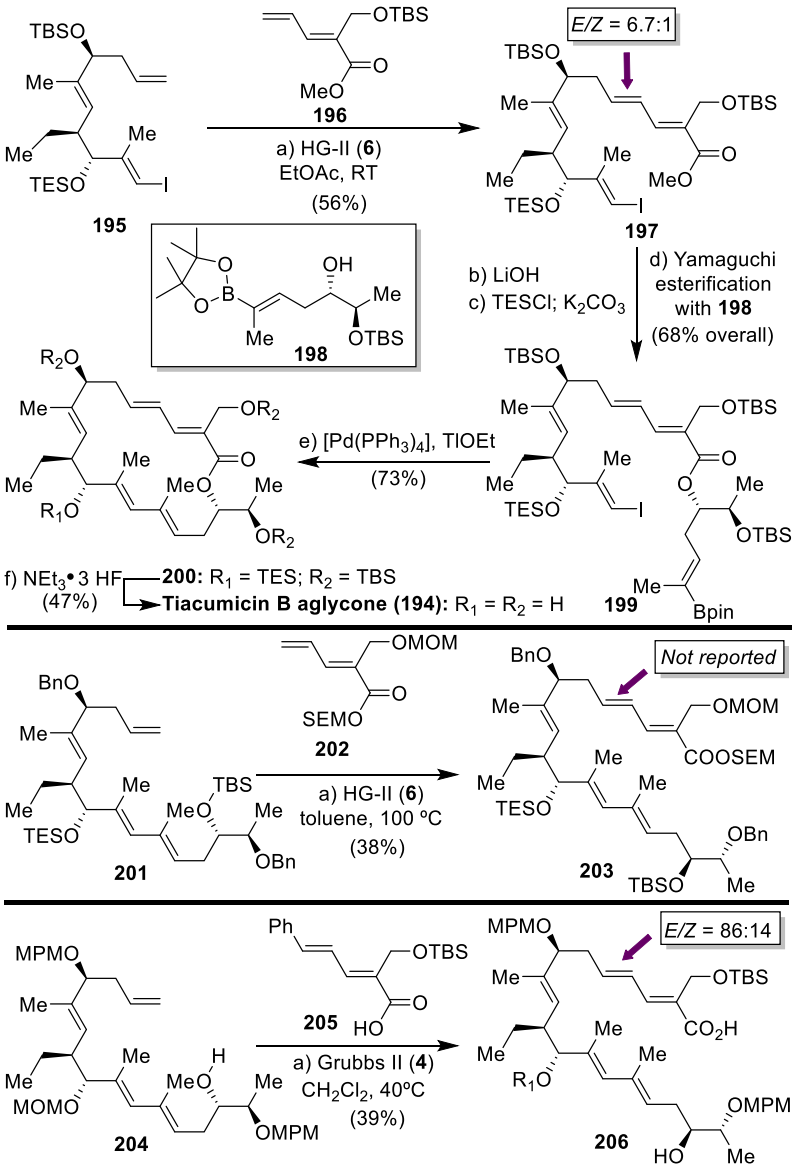
An excellent example that illustrates the advantage that the CM reaction can offer, especially for macrocyclic compounds, over a RCM reaction, are the synthesis of the

natural products mycalolides A (**187**) and B (**188**) by Kigoshi et al.[124] Both compounds, isolated from the marine sponge *Mycale* sp., are members of a family of natural products characterized by the presence of a trisoxazole macrocycle with potent cytotoxic activities as a consequence of actin-depolymerizing activity. A first attempt at the total synthesis was carried out by the authors via a RCM reaction of the diolefins **189a** and **189b**. However, despite this reaction affording the macrocyclic derivatives **190a** and **190b** in reasonably good yields (40-76% depending on the employed catalysts and solvents), the reaction was not stereoselective in both cases, providing a mixture of the *E*:*Z* isomers in the 1:1 to 1.9:1.0 range of ratios. This proportion could be increased to a 2.7:1.0 ratio in favor of the required *E*-olefin when the desilylated derivative **189b** was employed as the starting precursor. As an alternative, the authors attempted a CM/macrolactonization approach which proved to be more efficient. Thus, when a mixture of olefins **191** and **192** was subjected to the catalytic action of the HG-II catalyst (**6**) in refluxing dichloromethane, the olefin **193** was obtained in an impressive 77% yield and in an improved 5:1 mixture of the *E*:*Z* isomers. After the CM step, a Yamaguchi macrolactonization was conducted to prepare the corresponding macrolactone in a remarkable 77% yield, which was finally directed to the natural products mycalolides A (**187**) and B (**188**) in ten additional steps (**Scheme 18**).

The scope of the CM reaction has been expanded to conjugated dienes by Altmann et al.[125] during their synthetic studies directed towards the aglycone of tiacumicin B (**194**), a macrocylic antibiotic with potential application against *Mycobacterium tuberculosis* and whose total synthesis was not reported when the studies were published. Thus, combination of olefin **195** and the conjugated diene **196** in the presence of the HG-II catalyst (**6**) provided a 56% yield of compound **197** as an inseparable mixture of *E*/*Z* isomers in a 6.7:1 ratio. The preparation of ester **199** was followed by a Suzuki macrocyclization, to afford the macrocyclic aglycone derivative of tiacumicin B **200** in a 73% yield. Global desilylation of the macrocyclic derivative **200** was performed with NEt_3•3HF to obtain tiacumicin B aglycone **194**. Soon after this publication, Gademann et al. reported the total synthesis of tiacumicin B, also named fidaxomicin or lipiarmycin A3 (**53**), based on a RCM strategy, as depicted in **Figure 2**.[59] In addition to the Altmann synthetic studies, closely related strategies have been reported by Zhu[126] and, very recently, by Roulland et al.,[127] also using CM reactions. The former achieved the assembly of olefin **201** and diene **202**, while the second carried out the assembly of olefin **204** with diene **205** to yield the corresponding CM products **203** and **206** in 38 and 39% yields, respectively and with stereoselectivities comparable to those obtained by Altmann. However, unlike the studies of Altmann, in these later cases the authors found serious difficulties, mainly with the subsequent removal of the employed protecting groups within the products **203** and **206**, thus forcing them to explore different synthetic

[124] Kita, M.; Oka, H.; Usui, A.; Ishitsuka, T.; Mogi, Y.; Watanabe, H.; Tsunoda, M.; Kigoshi, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 14174-14178.
[125] Glaus, F.; Altmann, K.-H. *Angew. Chem. Int. Ed.* **2015**, *54*, 1937-1940.
[126] Erb, W.; Grassot, J.-M.; Linder, D.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 1929-1932.
[127] Jeanne-Julien, L.; Masson, G.; Astier, E.; Genta-Jouve, G.; Servajean, V.; Beau, J.-M.; Norsikian, S.; Roulland, E. *Org. Lett.* **2017**, *19*, 4006-4009.

strategies in both cases, to overcome these synthetic hurdles and to reach the targeted tiacumicin B aglycone **194** (**Scheme 19**).



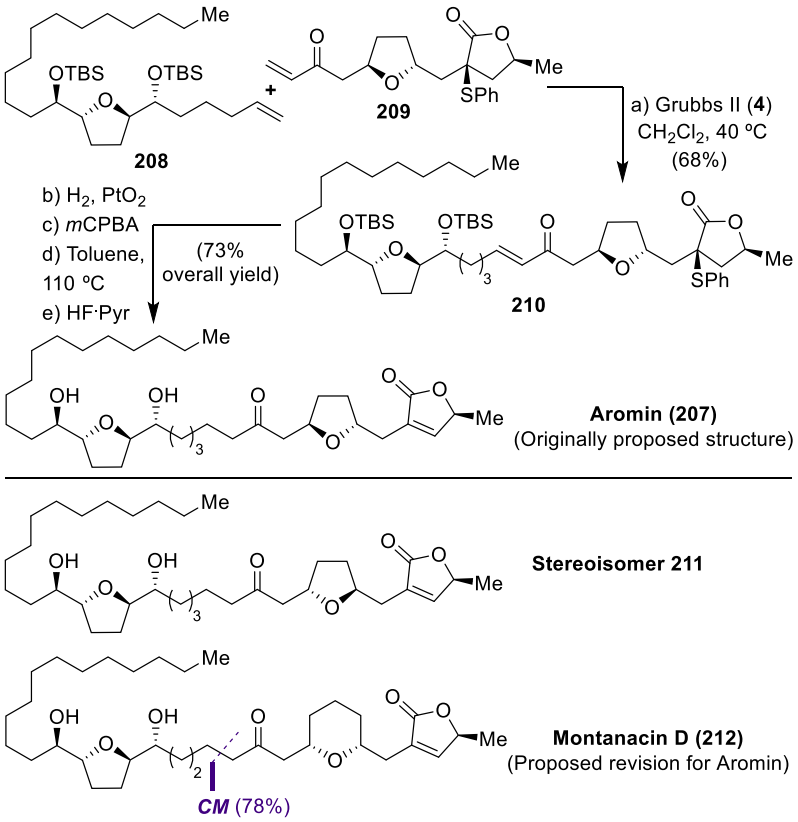
Scheme 19. Total Synthesis of Tiacumicin B aglycone (**194**) by Altmann (2015)[125] and Synthetic Studies by Zhu (2015)[126] and Roulland (2017)[127]

Another relevant contribution of the use of the CM reaction in total synthesis was recently published by Takahashi et al. for the total synthesis of aromin (**207**),[128] a member belonging to the wide family of the *Annonaceous* acetogenins, isolated from the *Annonaceae* plants and which exhibits a broad spectrum of biological activities including anticancer, antibiotic, immunosuppressive, antifeedant and pesticidal activities. Aromin (**207**), isolated together with aromicin in 1996 by McLaughlin, has been recognized as an antitumoral compound with a significant cytotoxicity profile against various tumor cell lines, albeit lower compared to other acetogenins. The synthetic work by Takahashi, based on his previous synthetic work, is interesting for two reasons. On one hand, they

[128] Takahashi, S.; Satoh, D.; Hayashi, M.; Takahashi, K.; Yamaguchi, K.; Nakamura, T.; Koshino, H. *J. Org. Chem.* **2016**, *81*, 11222-11234.

demonstrated the utility of the CM reaction by using the Grubbs 2nd generation catalyst (**4**) to connect a terminal olefin and an enone to construct the corresponding linear *E*-enone. On the other hand, this work also led to the structural revision of aromin (**207**) (**Scheme 20**).

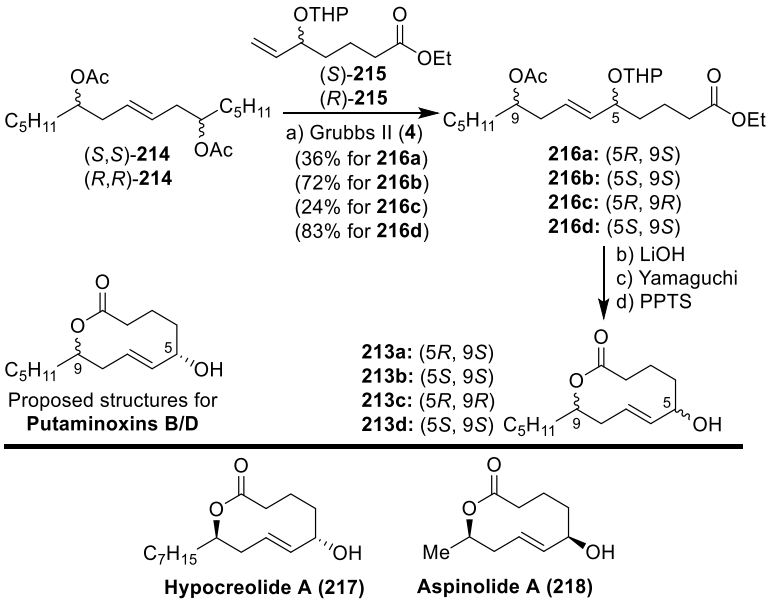
Thus, the assembly of olefin **208** and enone **209** proceeded smoothly when they were exposed to the Grubbs II catalyst (**4**) to provide the *E*-enone **210** in 68% yield and excellent stereoselectivity. With this compound **210** in hand, the authors accomplished the completion of the proposed structure for aromin in four additional steps in a 73% overall yield. Surprisingly, the spectroscopic and physical properties of the synthetic material **207** was notably different from those reported for the natural aromin. According to the detected discrepancies found in the ^{1}H NMR spectra, the authors suggested a structural difference around the central THF ring and, for this reason, they prepared the stereoisomer **211**, according to a similar synthetic sequence as for **207**, but once again, the NMR data were inconsistent with those of the natural product. After an exhaustive comparative analysis of the NMR data of a wide set of acetogenins possessing a 4-hydroxyl group adjacent to the γ-lactone ring, together with a detailed analysis of the MS fragmentations, the authors were led to propose the structure of the natural product montanacin D (**212**), whose synthesis was similarly accomplished by the same authors according to the same CM strategy, for the revised structure for aromin (**Scheme 20**).[129]



Scheme 20. Total Synthesis of Proposed Structure for Aromin (**207**) and its Structural Revision (Takahashi et al. 2016)[128, 129]

[129] Takahashi, S.; Hongo, Y.; Tsukagoshi, Y.; Koshino, H. *Org. Lett.* **2008**, *10*, 4223-4226.

A final example within this section is represented by the interesting synthetic strategy reported by Pietruszka et al. for the synthesis of putaminoxins B/D (**213**), identified as a C-9 epimeric mixture and whose absolute configurations were not yet established.[130] In order to unambiguously establish their absolute configurations, the four possible stereoisomers **213a-d** were prepared by a CM reaction of dimers (*S*,*S*)- and (*R*,*R*)-**214**, previously prepared by a dimerization CM reaction of the corresponding monomers, with olefins (*S*)- and (*R*)-**215**. The choice to use the dimers **214** instead of the corresponding monomeric olefins was justified because better yields were obtained for the desired cross-metathesis products **216** versus CM reactions with the monomers, in which the dimeric products **214** were the main compounds detected. Indeed, when each isomer of **214** was treated with the corresponding (*S*)- and (*R*)-**215**, in the presence of the Grubbs-II catalyst (**4**), the corresponding products **216a-d** were obtained in 36, 72, 24 and 83% yields, respectively. Then, each isomer was subjected to a sequence, that included basic treatment, a Yamaguchi macrolactonization and final THP protecting group removal to provide all the possible stereoisomers of the macrolactone **213** in high yields. With all the isomers in hand, an extensive spectroscopic study, in which the authors compared the NMR data collected from all these compounds with those reported for the natural products, resulted in disappointment. This was due to the inability to correlate the resulting NMR data of the synthetic compounds with those reported for the natural products, thus leading the authors to reconsider the initially proposed structures for putaminoxins B/D. Intriguingly, after a thorough inspection of the NMR data of related nonenolides, they found that the data reported for the natural products hypocreolide A (**217**) and aspinolide A (**218**) matched with those reported for the natural products putaminoxins B/D (**Scheme 21**).



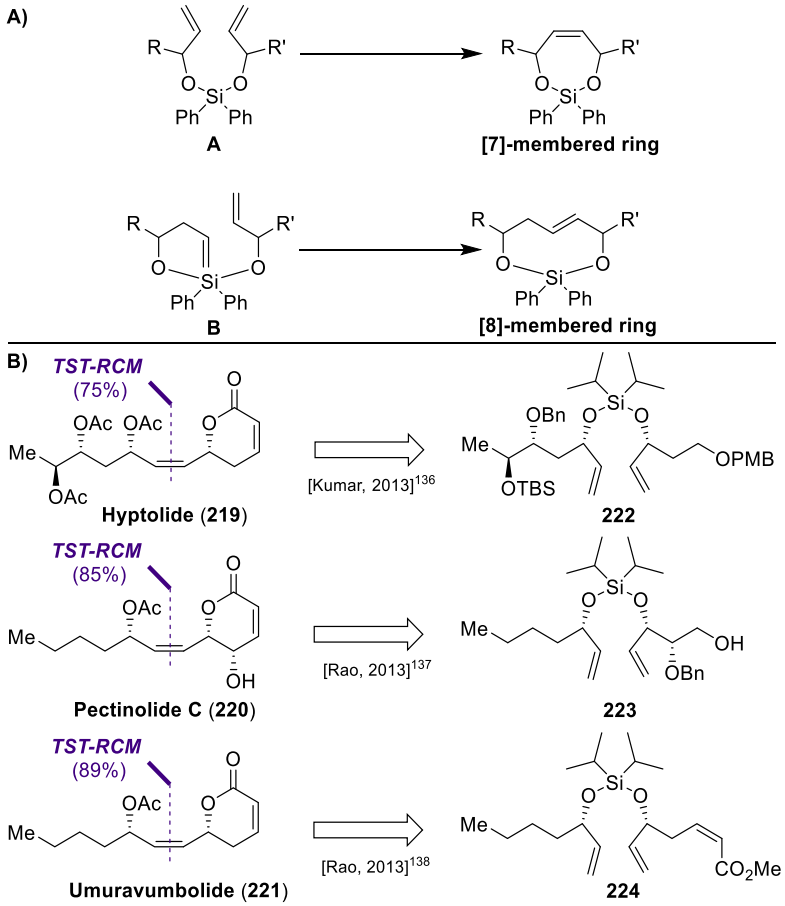
Scheme 21. Total Synthesis and Structural Studies of Putaminoxins B/D (**213**) (Pietruszka et al. 2017)[130]

[130] Bisterfeld, C.; Holec, C.; Böse, D.; Marx, P.; Pietruszka, J. *J. Nat. Prod.* **2017**, *80*, 1563-1574.

1.2.3. Strategies for Selective and Efficient Metathesis Reactions of Alkenes

1.2.3.1. Temporary Tethered Ring-Closing Metathesis

A highly inventive and clever strategy to transform the intermolecular character of the cross-metathesis of alkenes into an intramolecular variant has been explored by means of the development of temporary tethers, through which, the corresponding olefinic partners can be transiently coupled. This strategy not only provides the advantage of the improved efficiency, that is a feature of the RCM versus the CM reaction, but also the possibility of controlling the geometry of the resulting double bond, to favor the *Z*-olefin when a strained ring is temporarily formed. However, this strategy is limited to molecular structures in which a possible linkage of the tether system is present, usually in form of hydroxyl groups at allylic or homoallylic positions. Due to the versatility, stability and ease of cleavage, silicon-based tethers have been the most employed for this strategy. In fact, the temporary silicon-tethered RCM (TST-RCM) was described initially by Grubbs and Fu in 1992.[131] Thus, in order to favor the formation of the *Z*-isomer, a temporary [7]-membered ring is required, for which the silicon tethered is represented by precursor **A**. In case of precursor **B**, whose RCM would deliver a [8]-membered ring, the preference would be the formation of the *E*-isomer (**Scheme 22**, **part A**).



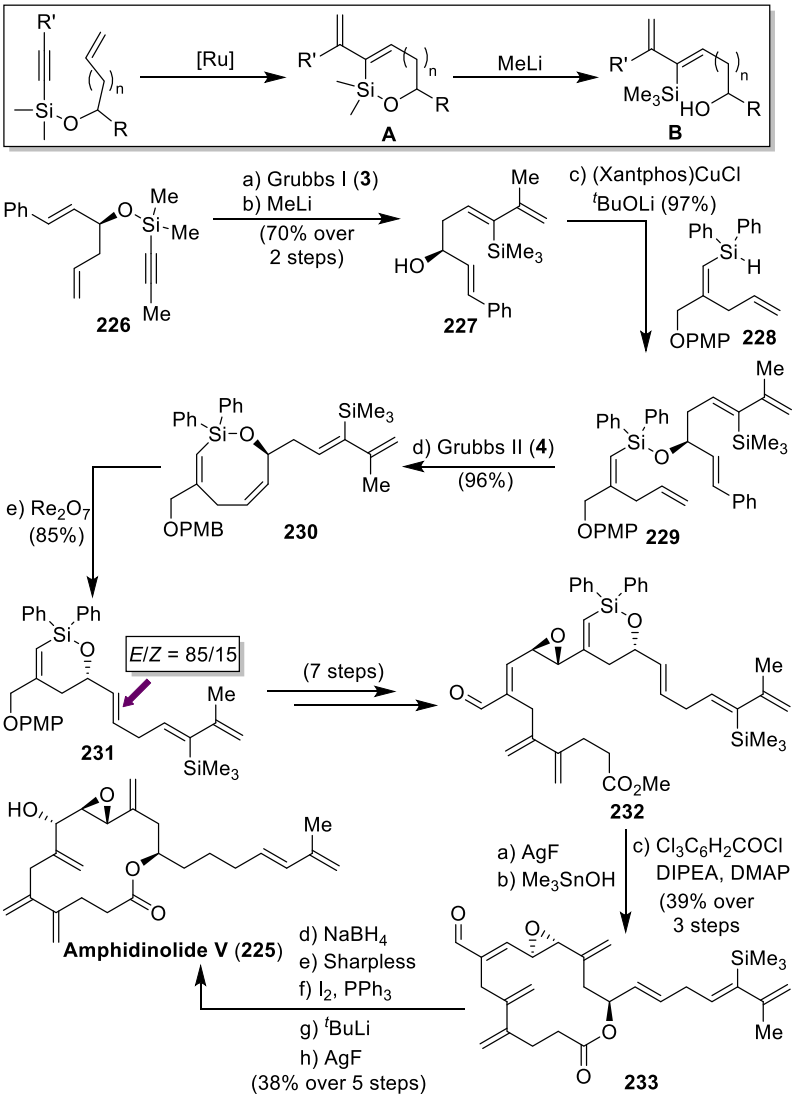
Scheme 22. General Temporary Silicon-tethered RCM (TST-RCM) Reactions and Selected Natural Products Synthesized via this Strategy

[131] Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426-5427.

In 2012, the applications of silicon-tethered RCM in synthesis of natural products was reviewed[132] and, as a consequence, in the present section, we will focus on recent examples published after 2012, together with other cases of tethered RCM reactions based on other tethers and their applications in the total synthesis of natural products. Some relevant contributions to this field are those by Kobayashi,[133] Hoye[134] and Evans,[135] as well as numerous syntheses of natural products belonging to the family of 6-substituted 5,6-dihydro-α-pyrone, such as hyptolide (**219**), [136] pectinolide C (**220**) [137] and umuravumbolide (**221**),[138] all of which have been efficiently achieved according to this strategy from precursors **222**, **223** and **224**, respectively (**Scheme 22**, **part B**).

In addition to silicon-tethered RCM reactions containing a O-Si-O linkage, this strategy has also been utilized with substrates containing an O-Si-C linkage, in which an oxidative or base-induced ring cleavage step is required after the RCM reaction. Prominent amongst these cases is the recent synthesis of the potent cytotoxic natural product amphidinolide V (**225**) by Lee et al., [139] in which the stereo-controlled construction of the existing double bonds was devised utilizing a tethered RCM of silyl ether **229** that provided the RCM product **230** in 96% yield, which was then subjected to an allylic 1,3-transposition mediated by Re_2O_7 to afford siloxane **231** as an 85:15 *E*/*Z* inseparable mixture in a 85% yield. The presence of the trimethylsilyl group in the 1,3-diene subunit was proven to be critical to prevent unwanted side reactions during the metathesis reaction. The RCM precursor **229** was prepared beforehand via an enyne RCM of silyl ether **226** to furnish a cyclic siloxene type **A**, according to the general reaction depicted in **Scheme 23**, which was opened by treatment with methyllithium, to deliver compound type **B**. The resulting alcohol **227** was then coupled with silane **228** via a dehydrogenative reaction, mediated by a catalytic amount of (Xantphos)CuCl and in the presence of lithium tert-butoxide, to afford the targeted precursor **229** in an excellent yield and exquisite control of the double bonds geometry. With compound **231** in hand, the authors proceeded with the connection of the other fragment of the molecule via a cross-aldol condensation to provide aldehyde **232** in seven steps, followed by a Yamaguchi macrolactonization that provided macrocyclic **233**. The completion of the synthesis from this advanced precursor was then executed in five steps, consisting of a Sharpless asymmetric epoxidation from the corresponding allylic alcohol, reductive opening of the resulting diepoxy alcohol and final removal of the trimethylsilyl group (**Scheme 23**).

[132] Cusak, A. *Chem. Eur. J.* **2012**, *18*, 5800-5824.
[133] Matsui, R.; Seto, K.; Fujita, K.; Suzuki, T.; Nakazaki, A.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 10068-10073.
[134] Hoye, T. R.; Jeon, J.; Kopel, L. C.; Ryba, T. D.; Tennakoon, M. A.; Wang, Y. *Angew. Chem. Int. Ed.* **2010**, *49*, 6151-6155.
[135] Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H. R. *J. Am. Chem. Soc.* **2003**, *125*, 14702-14703.
[136] Chowdhury, P. S.; Kumar, P. *Eur. J. Org. Chem.* **2013**, 4586-4593.
[137] Kumar, T. V.; Shankaraiah, G.; Babu, K. S.; Rao, J. M. *Tetrahedron Lett.* **2013**, *54*, 1397-1400.
[138] Kumar, T. V.; Reddy, G. V.; Babu, K. S.; Rao, J. M. *Tetrahedron: Asymm.* **2013**, *24*, 594-598.
[139] Volchkov, I.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 5324-5327.

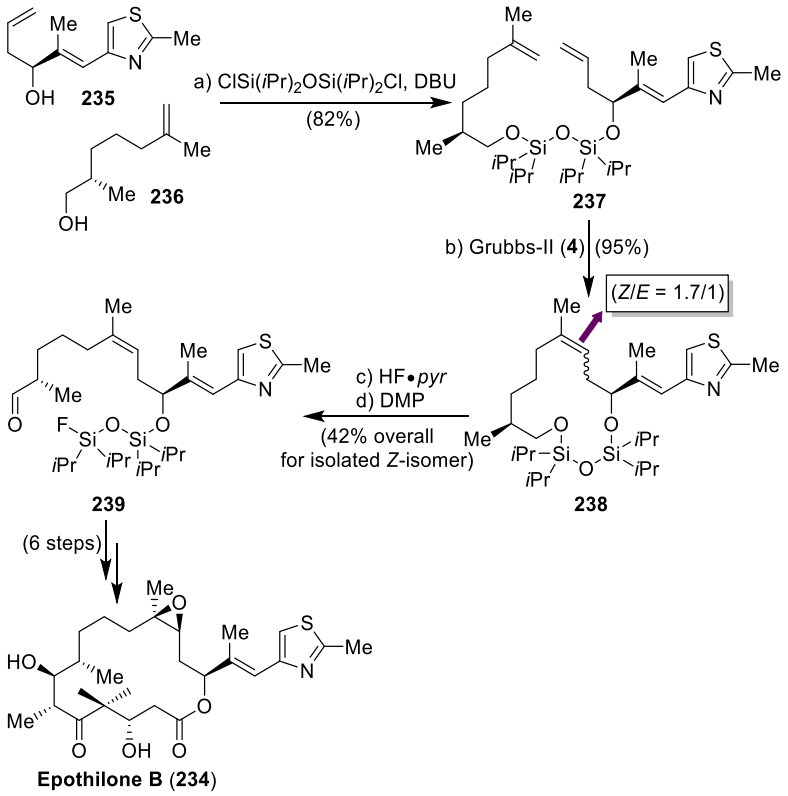


Scheme 23. Total Synthesis of Amphidinolide V (**225**) (Lee et al. 2013)[139]

The use of this strategy for the selective construction of a trisubstituted (*Z*)-olefin is nicely illustrated in the synthesis of the important antimitotic agent epothilone B (**234**), in which the required *Z*-olefin at the C12-C13 bond has been a critical issue, and which different solutions across the vast number of reported synthesis of this natural product have been found.[140] Thus, whereas a conventional RCM of an advanced diolefin precursor was devoid of stereoselectivity, a silicon-tethered RCM reaction initially explored by Mülzer et al. provided the required *Z*-isomer with a remarkable 5:1 selectivity albeit through a long synthetic sequence.[141] In a shorter and rapid approach, Lin et al. explored the RCM reaction through the formation of a bissiloxane-tethered precursor, to secure the double bond geometry.[142] To this aim, the precursor **237**, efficiently prepared by joining segments **235** and **236**, was subjected to the Grubbs-II catalyst (**4**) to yield the corresponding RCM product **238** in nearly quantitative yield (95%) as a 1.7:1 mixture of

[140] (a) Jung, J.-C.; Kache, R.; Vines, K. K.; Zheng, Y.-S.; Bijoy, P.; Valluri, M.; Avery, M. A. *J. Org. Chem.* **2004**, *69*, 9269-9284. (b) Prantz, K.; Mulzer, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5030-5033.
[141] Gaich, T.; Mulzer, J. *Org. Lett.* **2005**, *7*, 1311-1313.
[142] Wang, J.; Sun, B.-F., Cui, K.; Lin, G.-Q. *Org. Lett.* **2012**, *14*, 6354-6357.

Z:*E* isomers, which could be separated after selective cleavage of the silicon-tethered by reaction with HF•pyr. Notably, despite the moderate selectivity of the RCM reaction, the required aldehyde **239** in form of the pure *Z*-isomer was obtained in 40% over three steps, representing the most step-economic synthesis reported thus far. From aldehyde **239**, the completion of the synthesis of epothilone B was accomplished in an efficient manner in 6 steps, with a $TiCl_4$-mediated aldol reaction and a Yamaguchi macrolactonization as the key steps (**Scheme 24**).

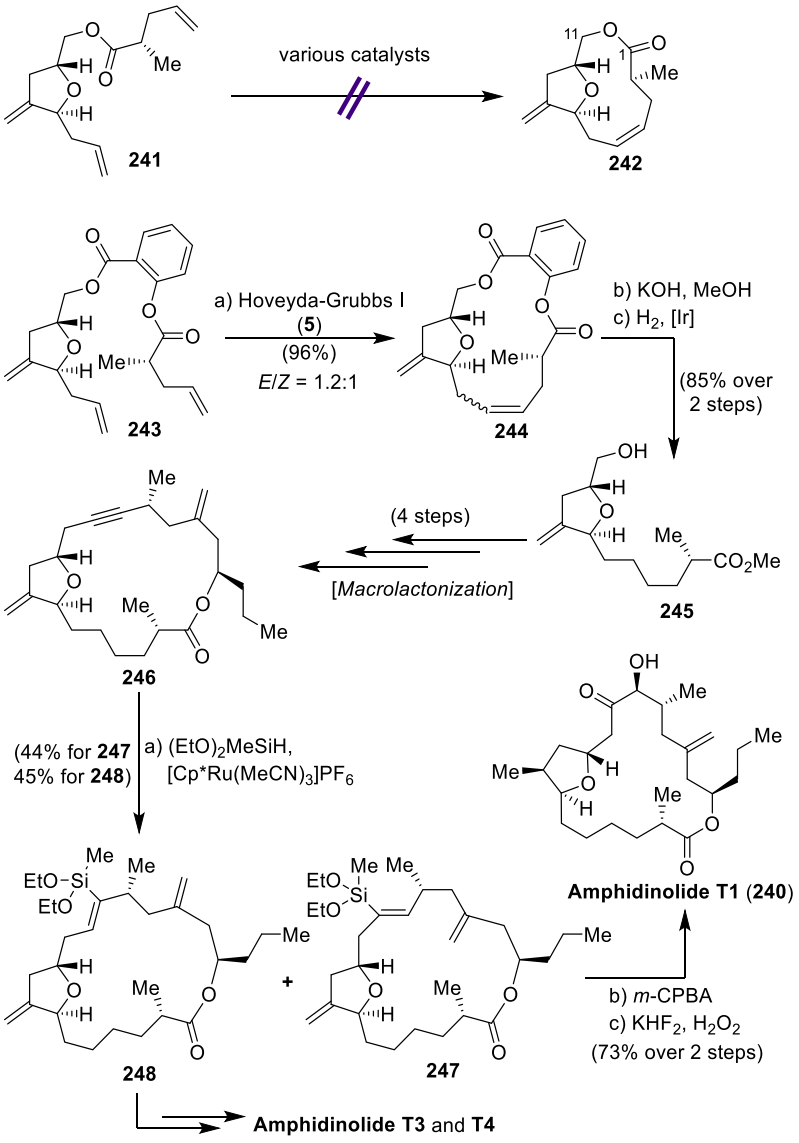


Scheme 24. Total Synthesis of Epothilone B (**234**) (Lin et al. 2017)[142]

The extension of the concept of a temporary tethered RCM to other groups such as esters or acetals would expand the synthetic opportunities that this strategy might offer. One such application is elegantly illustrated with the total syntheses of amphidinolides T1, T3 and T4 by Clark and coworkes.[143] As amphidinolide V, discussed above, the amphidinolides T1, T3 and T4 are also macrolides isolated from marine dinoflagellates with potent cytotoxic activities. Structurally, the so named amphidinolides of the T series are characterized by the presence of a trisubstituted tetrahydrofuran. In the case of amphidinolide T1 (**240**), the synthesis of the C1-C11 fragment was initially attempted by utilization of a CM reaction to connect the corresponding olefins, but all attempts were thwarted to obtain the desired CM product. The implementation of a tethered RCM strategy to prepare this fragment was then attempted via a temporary ester, for which diolefin ester **241** was prepared, but again, the reaction was found to be unsuccessful, instead obtaining the RCM product **242**. In light of these discouraging results, the use of

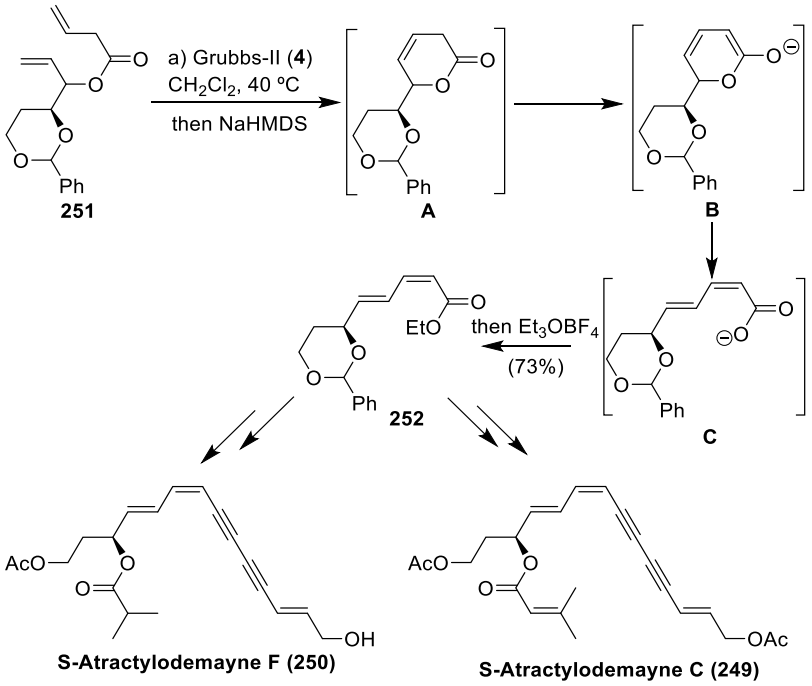
[143] Clark, J. S.; Romiti, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 10072-10075.

a salicylate spacer as an alternative ester-tether RCM was explored; indeed the treatment of **243** with the Hoveyda-Grubbs I catalyst (**5**) afforded an isomeric mixture (*E*/*Z* = 1.2:1) of the lactone **244** in an impressive 96% yield. The removal of the spacer group was carried out by base treatment, followed by a chemoselective hydrogenation to complete the western fragment of the natural product in form of the product **245**. The coupling of this fragment with the eastern fragment provided access to the corresponding seco acid, which was subjected to a Yamaguchi macrolactonization to provide **246**, representing the macrocyclic core of the amphidinolides T. The completion of the synthesis of this natural product was achieved with the hydrosilylation of the alkyne present in **246** using the ruthenium catalyst $[CpRu(MeCN)_3]PF_6$ that afforded a 1:1 mixture of isomeric *Z*-vinylsilanes **247** and **248**, which could be separated by chromatography. Whereas, **252** was transformed into amphidinolide T1 (**240**) via epoxidation of the vinylsilane, followed by a Fleming-Tamao oxidation, the product **248** provided amphidinolides T3 and T4 under the same synthetic sequence (**Scheme 25**).



Scheme 25. Total Synthesis of Amphidinolides T (Clark et al. 2013)[143]

The ester-tethered RCM was similarly used in the synthesis of polyacetylene-type metabolites, such as the atractylodemaynes C (**249**) and F (**250**) by Schmidt et al.[144] as a way of controlling the geometry of the depicted double bonds. According to a tandem RCM/base-induced eliminative ring opening, carried out in one pot, the authors were able to construct a *E*,*Z*-diene derivative, found in these natural products. Thus, when compound **251** was treated with the Grubbs-II catalyst (**4**), followed by NaHMDS and Meerwein´s salt, compound **252** was obtained in a 73% overall yield through intermediates **A**, **B** and **C**. Starting from the resulting ester **252**, the installation of the enediyne moiety of the atractylodemaynes C and F was achieved without issues via alkynyl homologation and a Sonogashira coupling (**Scheme 26**).

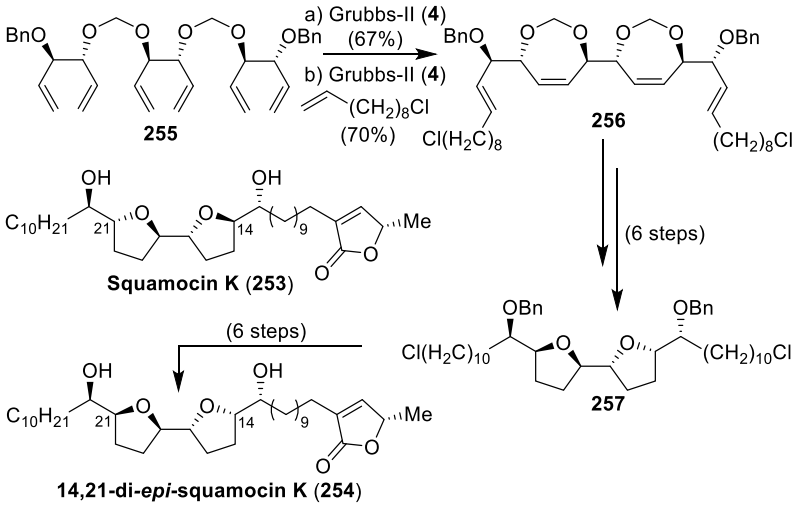


Scheme 26. Total Synthesis of S-Atractylodemaynes C (**249**) and F (**250**) (Schmidt et al. 2017)[144]

As an alternative to the silicon tethered RCM reaction, the use of acetals to connect both olefinic partners has also been developed and recently applied in the synthesis of a stereoisomer of squamocin K (**253**), the 14,21-di-*epi* isomer **254** by Hou et al.[145] Squamocin K, as other *Annonaceous* acetogenins, displays a wide range of biological activities, such as antitumor, antiparasitic, pesticidal, antimicrobial and immunosuppressive activities, by virtue of its inhibition of mitochondrial complex I. In this synthetic proposal, precursor **255**, readily prepared from a C2 symmetric diene diol, was treated with the Grubbs-II catalyst (**4**) to obtain the resulting RCM product, as a result of a multiple RCM process. In a second step, the assembly of the resulting polyene and 10-chloro-1-decene was induced by treatment again with the Grubbs-II catalyst (**4**) to deliver the complete framework of this class of natural products in form of compound **256**. Finally, the completion of the synthesis of this stereoisomer of squamocin K was

[144] Schmidt, B.; Audörsch, S. *J. Org. Chem.* **2017**, *82*, 1743-1760.
[145] Liu, C.-W.; Yeh, T.-C.; Chen, C.-H.; Yu, C.-C.; Chen, C.-S.; Hou, D.-R.; Guh, J.-H. *Tetrahedron* **2013**, *69*, 2971-2976.

achieved in 12 additional steps, including the formation of the required tetrahydrofurane rings, via previous activation of the resulting hydroxyl groups as mesyl derivatives and subsequent intramolecular displacements to afford **257**, and the final introduction of the unsaturated lactone (**Scheme 27**).



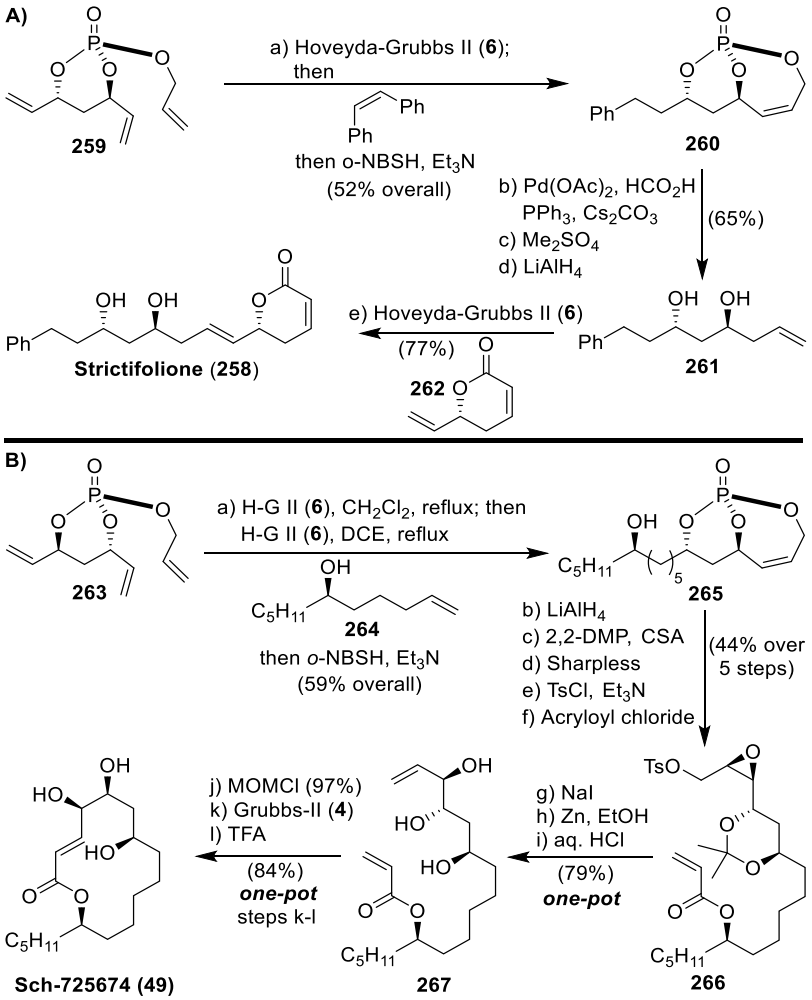
Scheme 27. Total Synthesis of 14,21-di-*epi*-squamocin K (**254**) (Hou et al. 2013)[145]

A unique tether for a RCM reaction was employed by Hanson in the synthesis of strictifolione (**258**),[146] a natural product isolated from the stem bark of *Cryptocaria stritifolia* with antifungal activities. In their synthesis, the authors used a phosphate-tether that allowed in one pot, a sequential RCM, CM and a chemoselective hydrogenation process, followed by a one-pot, sequential reductive allylic transposition/tether removal and final CM. To this end, olefinic phosphate **259** was treated with the HG II catalyst (**6**) and then, after solvent evaporation, addition of *cis*-stilbene in DCE and heating at 60 °C for 2 h. The subsequent chemoselective diimide reduction provided phosphate **260** in 52% overall yield. The following one-pot protocol was initiated with the reaction of **260** with $Pd(OAc)_2$ in the presence of formic acid, cesium carbonate and PPh_3 to produce a reductive allylic transposition, followed by addition of methyl sulfate and treatment of $LiAlH_4$ to furnish diol **261** in 65% overall yield. A final CM reaction with vinyl lactone **262** in the presence of the HG II catalyst (**6**) provided the natural product strictifolione **258** in a 77% yield (**Scheme 28**, **part A**).

In a similar strategy, the same authors described the synthesis of the antifungal macrolide Sch-725674 (**49**),[147] wherein the phosphate **263** was treated in a similar one-pot RCM/CM/chemoselective hydrogenation sequence as described for **259**, with the use of alkene **264** to obtain compound **265** in a 59% yield. The removal of the phosphate tether was accomplished by treatment with $LiAlH_4$ and, then, after a sequence of transformations, including selective protection of the 1,3 diol system as an acetal, a Sharpless asymmetric epoxidation of the resulting allylic alcohol, a selective tosylation

[146] Jayasinghe, S.; Venukadasula, P. K. M.; Hanson, P. R. *Org. Lett.* **2014**, *16*, 122-125.
[147] Bodugam, M.; Javed, S.; Ganguly, A.; Torres, J.; Hanson, P. R. *Org. Lett.* **2016**, *18*, 516-519.

of the primary alcohol and introduction of the acryloyl unit, provided compound **266**. This compound was set up for a reductive opening process, which was carried out in one pot by sequential treatment with NaI, Zn and acidic work-up, to deliver diolefin **267**. In contrast to a direct RCM reaction of diolefinic triol **267**, carried out by Prasad et al. (See **Figure 2**), that afforded the natural product in a modest 36%, Hanson et al. found that prior protection of compound **267** as the MOM derivative resulted in a more efficient RCM process to provide the final product **49** in 84% yield after removal of the protecting groups with TFA (**Scheme 28**, **part B**).



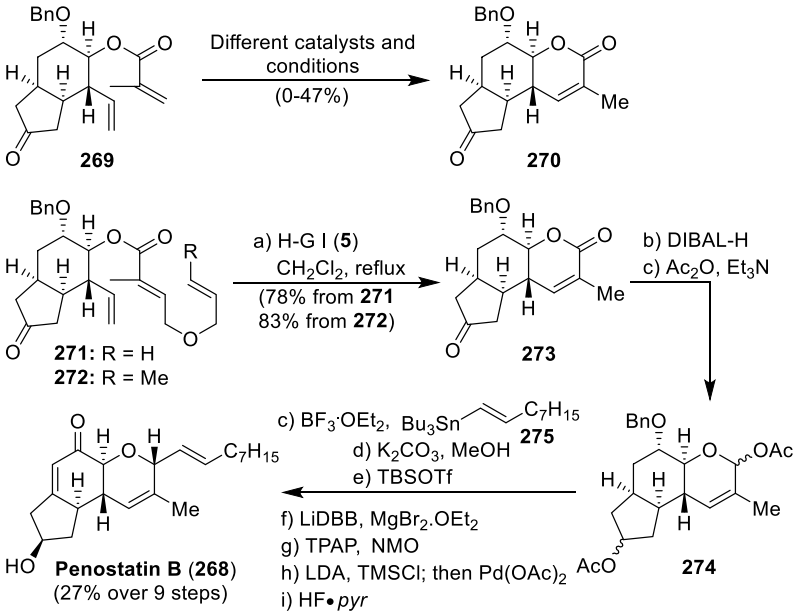
Scheme 28. Total Synthesis of Strictifolione (**258**) and Sch-725674 (**49**) (Hanson et al. 2014, 2016)[146,147]

1.2.3.2. Relay Ring-Closing Metathesis

Since the pioneering work of the Hoye group on the relay ring-closing metathesis (RRCM) concept in 2004,[148] and the first application in total synthesis by the Porco group in the same year,[149] many syntheses have benefited enormously from this strategy as a method to surmount the instances in which the RCM reactions proved ineffective or

[148] Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210-10211.
[149] Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A. Jr. *Angew. Chem. Int. Ed.* **2004**, *43*, 3601-3605.

sluggish, mainly due to steric factors, as well as electronic factors.[150] A representative example to illustrate the implementation of this strategy and its dramatic effect can be found in the recent synthesis of the cytotoxic natural product penostatin B (**268**) by the Shishido group. [151] Having devised a RCM strategy for the preparation of the dihydropyran system contained in the natural product, the examination of this reaction with the acyclic precursor **269** by using various catalysts and different reaction conditions provided the desired unsaturated δ-lactone **270** in a modest 46% yield, as the best case, when the HG-I catalyst (**5**) was employed. In an effort to improve upon this yield, the authors made use of the relay RCM strategy, for which precursors **271** and **272** were prepared. The treatment of these compounds with the same catalyst provided the RCM product **273** in improved 78 and 83% yields from **271** and **272**, respectively, demonstrating the synthetic value of this strategy. With compound **273** in hand, the introduction of the alkenyl appendage was successfully achieved from acetyl pyranoside **274**, via vinyl stannane **275** in a high stereoselective manner. Finally, the manipulation towards the final product was undertaken in six additional steps (**Scheme 29**).

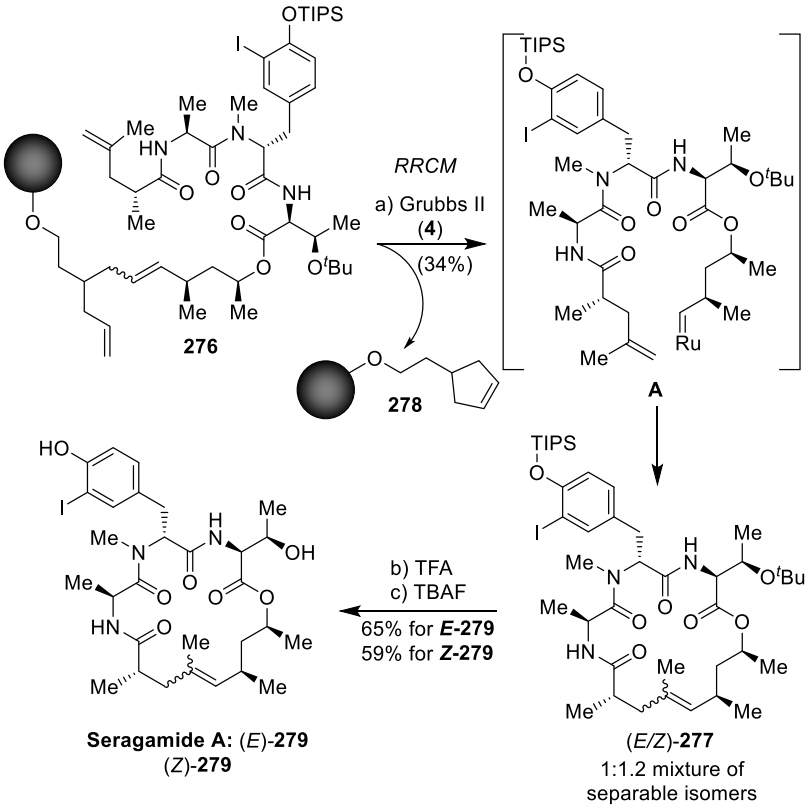


Scheme 29. Total Synthesis of Penostatin B (**268**) (Shishido et al. 2012)[151]

In the development of an enabled and flexible strategy for the synthesis of the cyclodepsipeptidic-like natural products related to the jasplakinolide/geodiamolide family, Waldmann et al. designed a divergent solid phase synthesis for this class of compounds based on a unique RRCM strategy on solid phase to construct the macrocyclic core, directing the catalyst´s action to the required break point.[152] With the preparation of a PS resin for the linkage of the peptidic chain, which carried a diene unit, the acyclic precursor loaded onto the resin (resin **276**) was synthesized in an efficient manner. The

[150] For a review on RRCM, see: Wallace, D. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 1912-1915.
[151] Fujioka, K.; Yokoe, H.; Yoshida, M.; Shishido, K. *Org. Lett.* **2012**, *14*, 244-247.
[152] Arndt, H.-D.; Rizzo, S.; Nöcker, C.; Wakchaure, V. N.; Milroy, L.-G.; Bieker, V.; Calderon, A.; Tran, T. T. N.; Brand, S.; Dehmelt, L.; Waldmann, H. *Chem. Eur. J.* **2015**, *21*, 5311-5316.

subsequent reaction with the Grubbs-II catalyst (**4**) delivered the protected cyclodepsipeptide **277** in 34% yield as a 1:1.2 mixture of a separable *E*/*Z* isomers, through the formation of the carbene intermediate **A** with the concomitant release of resin **278**. The removal of the protecting groups of each pure isomer afforded natural product seragamide A (**279**) and its *Z*-isomer. In a similar fashion, a collection of jaspamide analogues was generated for biological studies as antitumor agents (**Scheme 30**).

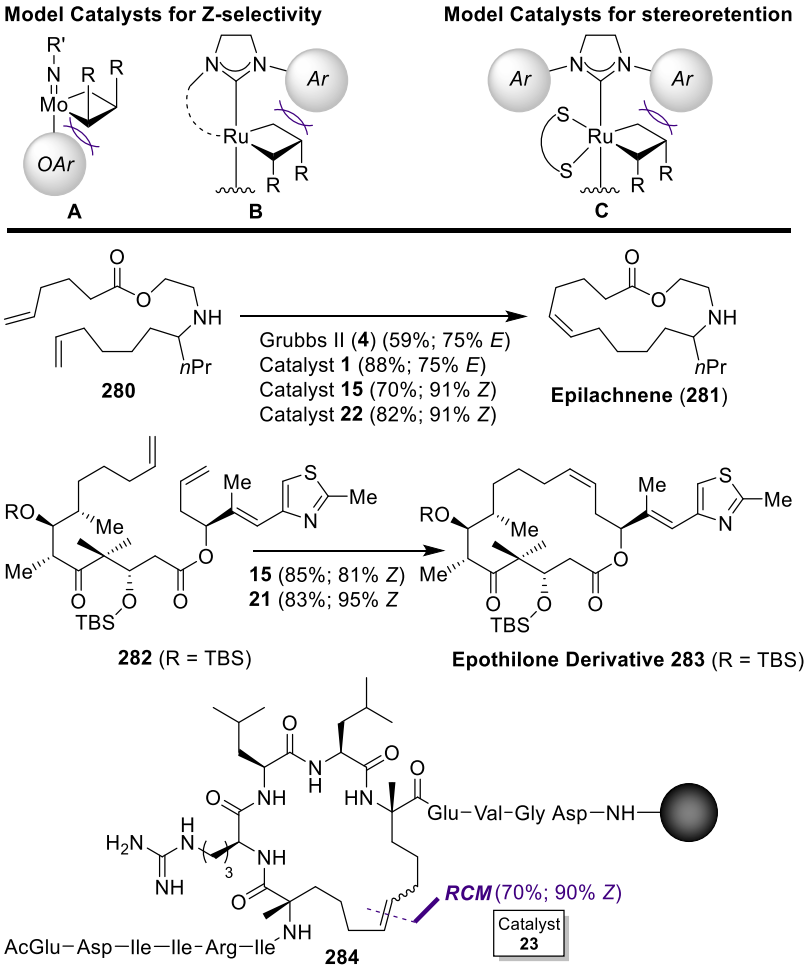


Scheme 30. Total Synthesis of Seragamide A (*E*-**279**) and Related Cyclodepsipeptides (Waldmann et al. 2015)[152]

1.2.3.3. Stereoselective Alkene Metathesis

The reversible nature of olefin metathesis represents a practically insurmountable barrier to access to the often energetically less favored *Z*-olefin. As a consequence, the design and development of catalysts capable of providing high *Z* selectivity, either in RCM as in CM reactions, represents an important challenge. To this aim, initial efforts by Schrock, Hoveyda et al. have been focused largely on the modification of the ancillary ligands bound to the metal center and have led to the identification of the first *Z*-selective catalysts based on molybdenum and tungsten (catalysts **15**-**22** in **Figure 1**).[153] In this family of catalysts, the introduction of a bulky aryloxy moiety forces the substituents on the generated metallacyclobutane intermediate (**A**) (**Scheme 31**) all *syn* to yield the *Z*-olefin in a kinetically controlled process.

[153] Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Chem. Eur. J.* **2013**, *19*, 2726-2740.

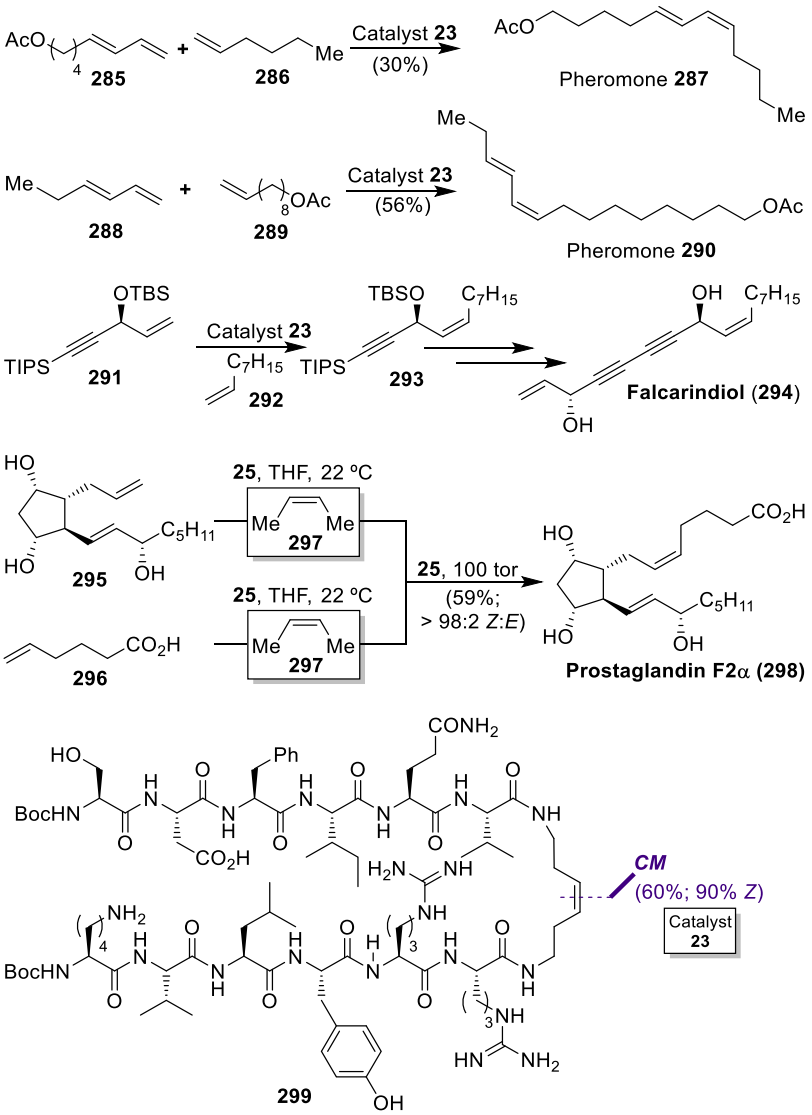


Scheme 31. Applications of Z-Selective RCM Reactions in Total Synthesis

On the other hand, the advent of ruthenium-based catalysts (for example catalyst **23** in **Figure 1**), in which bulky aryl groups are introduced on the *N*-heterocyclic carbene, by Grubbs et al. allowed similar access to a Z-selective process through intermediates type **B**.[154] The *E*-isomers, despite their formation being generically favored in these reactions for thermodynamic reasons, there are numerous cases in which the small energy difference between the *E* and the *Z* isomers, results in a mixture of both geometric isomers. In view of this situation, the development of catalysts that promote kinetically *E*-selective processes represents a new challenge. In response to this requirement, Grubbs et al. have described the first catalysts capable of generating *E*-olefins starting from *E*-olefins as the reactants.[155] This new generation of catalysts is termed stereoretentive olefin metathesis catalysts, which feature the presence of a cyclic catecholthiolate unit (catalysts **24-27** in **Figure 1**)[22,156] and proceed through intermediates type **C**. To this arsenal of valuable and useful catalysts developed in the last few years one must also add

[154] Herbert, M. B.; Suslick, B. A.; Liu, P.; Zou, L.; Dornan, P. K.; Houk, K. N.; Grubbs, R. H. *Organometallics* **2015**, *34*, 2858-2869.
[155] (a) Johns, A. M.; Ahmed, T. S.; Jackson, B. W.; Grubbs, R. H.; Pederson, R. L. *Org. Lett.* **2016**, *18*, 772-775. (b) Ahmed, T. S.; Grubbs, R. H. *J. Am. Chem. Soc.* **2017**, *139*, 1532-1537.
[156] (a) Montgomery, T. P.; Ahmed, T. S.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 11024-11036. (b) Montgomery, T. P.; Grandner, J. M.; Houk, K. N.; Grubbs, R. H. *Organometallics* **2015**, *36*, 3940-3953.

chiral catalysts, with which it is possible to perform asymmetric olefin metathesis,[157] as described in **Scheme 8**. A detailed description of the design and development of these new selective catalysts, as well as their applications in synthesis of natural products, has been widely covered in various reviews.[158] Nevertheless, we would like to summarize in this section relevant examples of selective RCM and CM reactions as representative applications that prove the synthetic validity and potential of these new generation of catalysts. Thus, in **Scheme 31** are summarized examples of *Z*-selective RCM reactions[156,159] and in **Scheme 33** cases of *Z*-selective CM reactions[160] in the field of the total synthesis.



Scheme 32. Applications of Z-Selective CM Reactions in Total Synthesis

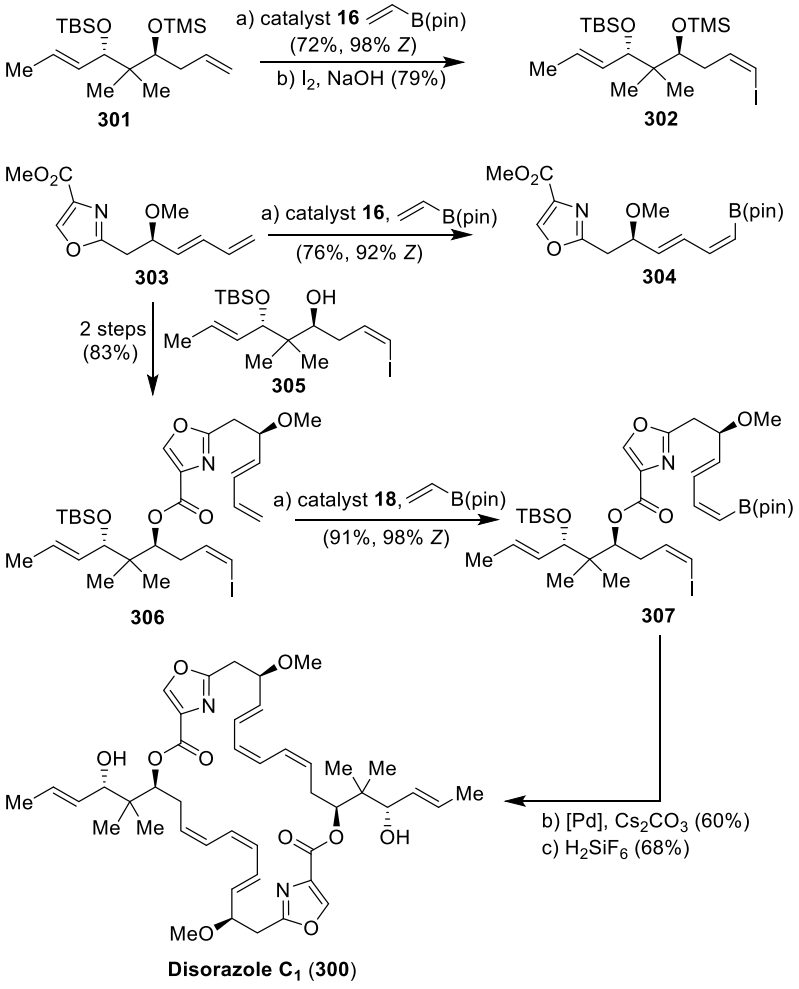
[157] (a) Hartung, J.; Dornan, P. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2014**, *136*, 13029-13037. (b) Yu, M.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 215-220.

[158] (a) Herbert, M. B.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 5018-5024. (b) Werrel, S.; Walker, J. C. L.; Donohoe, T. J. *Tetrahedron Lett.* **2015**, *56*, 5261-5268.

[159] Mangold, S. L.; Grubbs, R. H. *Chem. Sci.* **2015**, *6*, 4561-4569.

[160] (a) Mangold, S. L.; O´Leary, D. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2014**, *136*, 12469-12478. (b) Dornan, P. K.; Wickens, Z. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 7134-7138. (c) Luo, S.-X.; Cannon, J. S.; Taylor, B. L. H.; Engle, K. M.; Houk, K. N.; Grubbs, R. H. *J. Am. Chem. Soc.* **2016**, *138*, 14039-14046. (d) Dornan, P. K.; Lee, D.; Grubbs, R. H. *J. Am. Chem. Soc.* **2016**, *138*, 6372-6375. (e) de Léséleuc, M.; Godin, E.; Parisien-Collette, S.; Lévesque, A.; Collins, S. K. *J. Org. Chem.* **2016**, *81*, 6750-6756. (f) Xu, C.; Shen, X.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 10919-10928.

Particularly relevant is the synthesis of prostaglandin F2α (**298**) according to the recent strategy developed by Hoveyda et al.[163f] based on the original and brilliant concept of methylene capping. This strategy was designed to broaden the scope of the *Z*-selective cross-metathesis protocols, which is inefficient with olefins containing allylic or homoallylic alcohols, aryl groups, aldehydes or carboxylic acid susbtituents. Having identified *Z*-butene (**297**) as a suitable capping agent, respective treatments of trihydroxy olefin **295** and unsaturated carboxylic acid **296** with alkene **297** and the Ru dithiolate catalyst **25**, followed by mixing and treatment with additional catalyst **25** under reduced pressure, afforded prostaglandin F2α (**298**) in 59% yield and >98:2 selectivity in favor of the desired *Z*-olefin (**Scheme 32**). The use of this capping agent avoids the formation of the unstable methylidene species in favor of a more stable substituted carbene, allowing the use of substrates without resorting to protecting groups. This elegant strategy was similarly used for the synthesis of *Z*-macrocyclic alkenes.



Scheme 33. Total Synthesis of Disorazole C1 (**300**) (Hoveyda et al. 2014)[161]

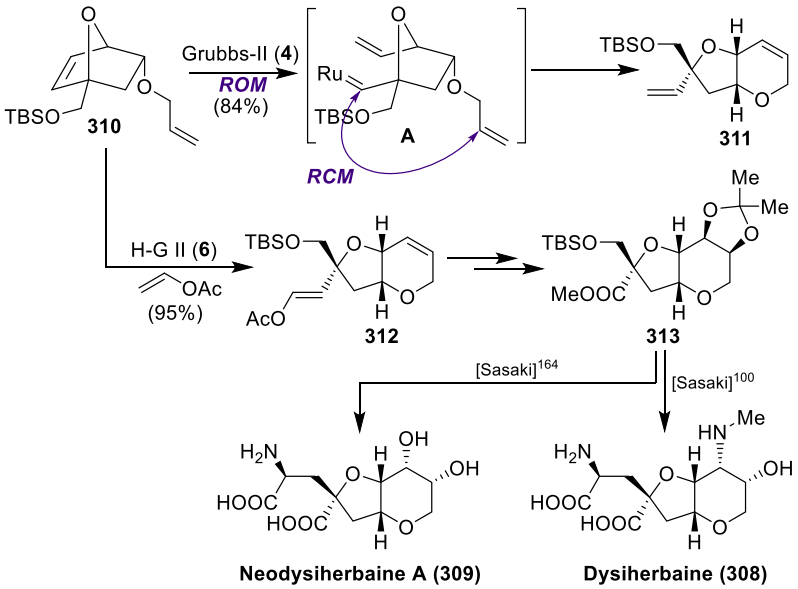
An outstanding application of these selective catalysts in the synthesis of complex natural products is the synthesis of disorazole C1 (**300**),[161] a secondary metabolite that displays excellent anticancer and antifungal profiles, described by Hoveyda et al. The presence of the (*Z*,*Z*,*E*)-1,3,5-triene unit demands an exquisite level of geometric control for a stereoselective synthesis of this fragment. In an initial approach, the authors prepared the *Z*-vinyl iodide **302** and the *E*,*Z*-diene **304** in excellent yields and complete stereoselectivity by using the catalyst **16** from the terminal olefins **301** and **303**, respectively. However, after coupling of both fragments via a Suzuki reaction, the subsequent dimerization process failed to form the resulting coupling product. Therefore, the authors decided to assemble the acid derived from ester **303** and vinyl iodide **305** and the resulting ester **306** transformed into the *Z*-boronic ester **307**, mediated by the catalyst **18**. With this compound in hand, the authors conducted the dimerization process in a carefully optimized reaction, where the choice of palladium catalyst, base and solvent was critical to obtaining a good yield (60%) of the resulting [30]-membered ring protected disorazole C1. Final desilylation provided the coveted natural product **300** (**Scheme 33**).

1.2.3.4. Alkene Metathesis in Tandem Reactions

The design of suitable multifunctional molecules that enable the triggering of a cascade of events, including a sequential alkene metathesis process or a combination of an alkene metathesis with other types of reactions in a well-defined order would provide a formidable increase in structural complexity in a single operation. As a consequence, we can find in the literature a large number of total syntheses and synthetic approaches in which alkene metathesis processes in cascade sequences, by combination of ROM/RCM or RCM/CM reactions, have been applied.[162] An initial interesting synthetic application of these processes in total synthesis is found in the formal total syntheses of dysiherbaine (**308**) and neodysiherbaine A (**309**) by Lee et al.[163] through an elegant ROM/RCM tandem process from bicyclic compound **310**, which was prepared in enantiomerically pure form through a stereoselective Diels-Alder reaction, followed by resolution of the racemic mixture. This compound **310** underwent an initial ROM process, that delivered a ruthenium intermediate **A**, followed by a RCM reaction when subjected to the Grubbs-II catalyst (**4**), to yield bicyclic derivative **311**, which represents the core skeleton of dysiherbaine and related compounds with the correct relative stereochemistry. The need to selectively oxidize the cyclic olefin in the presence of the terminal alkene found in compound **311** forced the authors to increase the difference of reactivities between the olefins by the preparation of the enol acetate **312**, prepared in the same way as **311**, but in the presence of vinyl acetate and using Hoveyda-Grubbs II catalyst (**6**) for a final CM with vinyl acetate. In this way, compound **312** was obtained in an excellent 95% yield, generating a very well differentiated electronic environment between both

[161] Speed, A. W. H.; Mann, T. J.; O´Brien, R. V.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 16136-16139.
[162] For a recent review about the use of metathesis cascade reactions in synthesis of natural products, see: Han, J.-C.; Li, C.-C. *Synlett* **2015**, *26*, 1289-1304.
[163] Lee, H.-Y.; Lee, S.-S.; Kim, H. S.; Lee, K. M. *Eur. J. Org. Chem.* **2012**, 4192-4199.

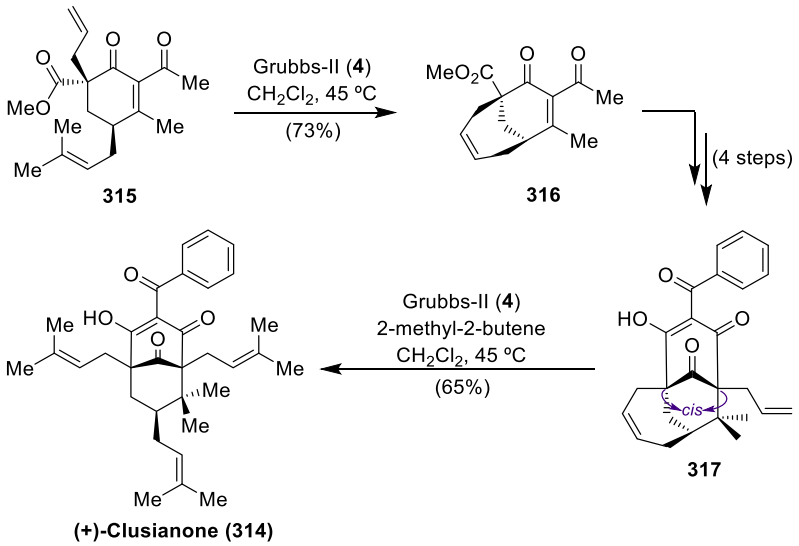
alkenes for further selective functionalization. In fact, the authors succeeded in the preparation of advanced precursor **313** via transformation of the enol acetate into a temporary alcohol, followed by dihydroxylation of the cyclic olefin, protection of the resulting diol as an acetal, oxidation of the primary alcohol to the acid and esterification. The resulting product **313** was utilized by Sasaki et al.[164] in their total syntheses of the natural products dysiherbaine (**308**) and neodysiherbaine A (**309**), thus representing the formal synthesis of both natural products (**Scheme 34**).



Scheme 34. Formal Total Synthesis of Dysiherbaine (**308**) and Neodysiherbaine A (**309**) (Lee et al. 2012)[163]

Particularly interesting are the syntheses of clusianone (**314**) and clavilactone A (**318**) which utilize combinations of cascade processes of metathesis reactions. In the case of clusianone (**314**), a natural product isolated from *C. congestiflora* with antiviral activity against HIV and Epstein-Barr virus, its synthesis was envisaged by Plietker et al.[165] from tricyclic derivative **317**, prepared from bicyclic compound **316** via an allylation/intramolecular Claisen-condensation-benzoylation sequence. Thus, when **317** was treated with the Grubbs-II catalyst (**4**) in the presence of isoamylene, the natural product clusianone (**314**) was obtained in a 65% yield as the result of a tandem ROM/CM process. The preparation of the bicycle[4.3.1]undecenone derivative **316** via a RCM reaction from **315**, was conceived by the authors as a way of controlling the stereochemical outcome in favor of the desired *cis*-relative configuration of the final product due to the conformationally restricted environment imposed by the bicyclic system. The subsequent ROM reaction, followed by a CM reaction, in the presence of 2-methyl-2-butene, allowed the unmasking of the prenylated side chains present in the final product (**Scheme 35**).

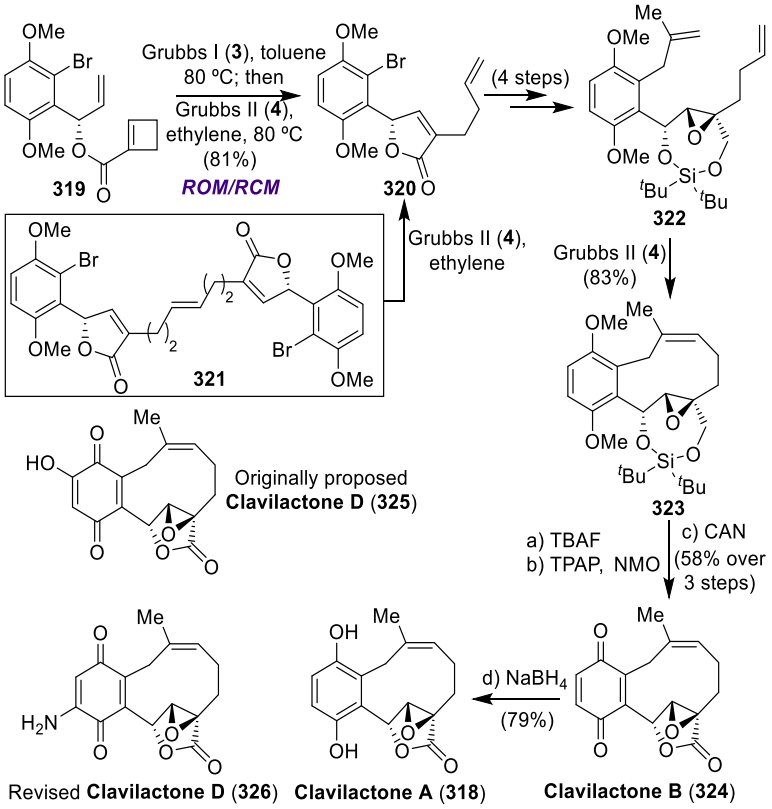
[164] Shoji, M.; Akiyama, N.; Tsubone, K.; Lash, L. L.; Sanders, J. M.; Swanson, G. T.; Sakai, R.; Shimamoto, K.; Oikawa, M.; Sasaki, M. *J. Org. Chem.* **2006**, *71*, 4227-4231.
[165] Horeischi, F.; Guttroff, C.; Plietker, B. *Chem. Commun.* **2015**, *51*, 2259-2261.



Scheme 35. Total Synthesis of Clusianone (**314**) (Plietker et al. 2015)[165]

The same strategy was employed by these authors in the synthesis of guttiferone A.[166] For the clavilactones, a family of natural products structurally characterized by a rigid 10-membered macrocycle fused to a hydroquinone and to an α,β-epoxy-γ-lactone, the cyclobutenecarboxylate **319** was devised by Takao et al. as an appropiate precursor to promote a tandem ROM/RCM reaction mediated by a ruthenium-based catalyst.[167] In fact, when **319** was treated with the Grubbs-I catalyst (**3**), the desired ROM/RCM product **320** was obtained, but in only 28% yield, due to the formation of the dimer **321** in 15% yield, together with recovered starting material in 47% yield. In an attempt to improve upon this modest result, the authors found that exposure of dimer **321** to the Grubbs-II catalyst (**4**) in ethylene atmosphere produced the desired product **320** in good yields. In practice, this tandem process was accomplished in one pot by sequential treatment of **319** with the Grubbs-I catalyst (**3**) in the presence of 2,6-dichloro-1,4-benzoquinone, followed by the treatment with the Grubbs-II catalyst (**4**) in atmospheric ethylene at 80 °C to provide the final product **320** in 81% overall yield. The formation of the oxirane ring was carried out in a highly chemo- and stereoselective fashion by reaction of *m*-CPBA with the cyclic olefinic bis-silylether derivative, obtained from **320** by reduction and bis-silylation of the resulting diol. The resulting epoxide **322** was then reacted with the Grubbs-II catalyst (**4**) to obtain the macrocyclic derivative **323** in a notable 83% yield. The completion of the synthesis of clavilactone A (**318**) was efficiently accomplished in four additional steps, mainly functional groups interconversions, through quinone **324** that corresponds to clavilactone B. In a similar synthetic sequence, the same authors prepared the originally proposed structure of clavilactone D (**325**),[168] which led to its structural revision, identifying **326** as the correct structure (**Scheme 36**).

[166] Horeischi, F.; Biber, N.; Plietker, B. *J. Am. Chem. Soc.* **2014**, *136*, 4026-4030.
[167] Takao, K.-i.; Nanamiya, R.; Fukushima, Y.; Namba, A.; Yoshida, K.; Tadano, K.-i. *Org. Lett.* **2013**, *15*, 5582-5585.
[168] (a) Takao, K.-i.; Nemoto, R.; Mori, K.; Namba, A.; Yoshida, K.; Ogura, A. *Chem. Eur. J.* **2017**, *23*, 3828-3831. (b) Takao, K.-i.; Mori, K.; Kasuga, K.; Nanamiya, R.; Namba, A.; Fukushima, Y.; Nemoto, R.; Mogi, T.; Yasui, H.; Ogura, A.; Yoshida, K.; Tadano, K.-i. *J. Org. Chem.* **2018**, *83*, 7060-7075.



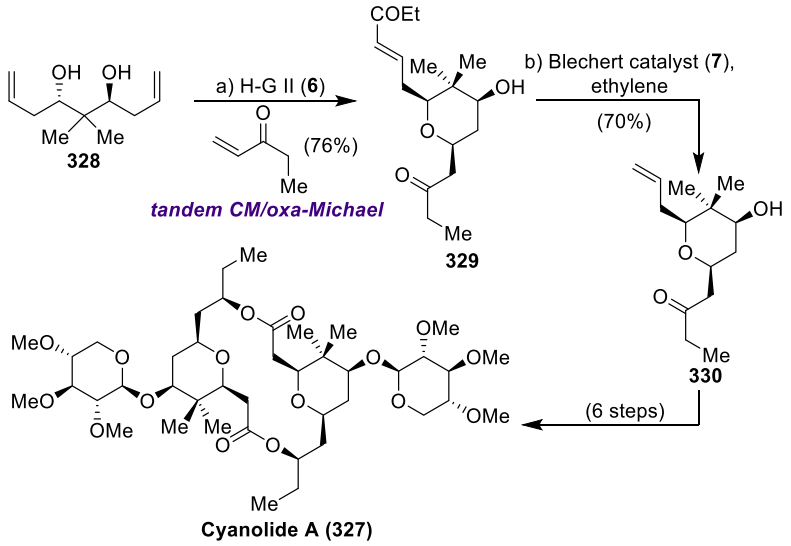
Scheme 36. Total Synthesis of Clavilactones A (**318**), B (**324**) and D (**326**) (Takao et al. 2013 and 2018)[167,168]

A cascade process that involves an alkene metathesis with other types of reactions has also been explored. As such, an application is the tandem CM/oxa-Michael cyclization employed by Krische et al. in the synthesis of the C2-symmetric natural product cyanolide A (**327**),[169] a potent molluscicidal agent against the water snail *Biomphalaria glabrata*, which actually is a vector of the human parasitic disease schistosomiasis. Thus, when diol **328** was treated with the Hoveyda-Grubbs II catalyst (**6**), in the presence of vinylethyl ketone, the compound **329** was obtained in 76% yield as a 10:1 mixture of diastereoisomers. This pyrane derivative is the result of an initial double CM reaction, followed by an oxa-Michael cyclization. In a second CM round, compound **329** was treated with the Blechert catalyst (**7**) in an ethylene atmosphere to yield olefin **330** in 70% yield. A few more steps from **330** completed a concise total synthesis of cyanolide A (**327**) (**Scheme 37**).

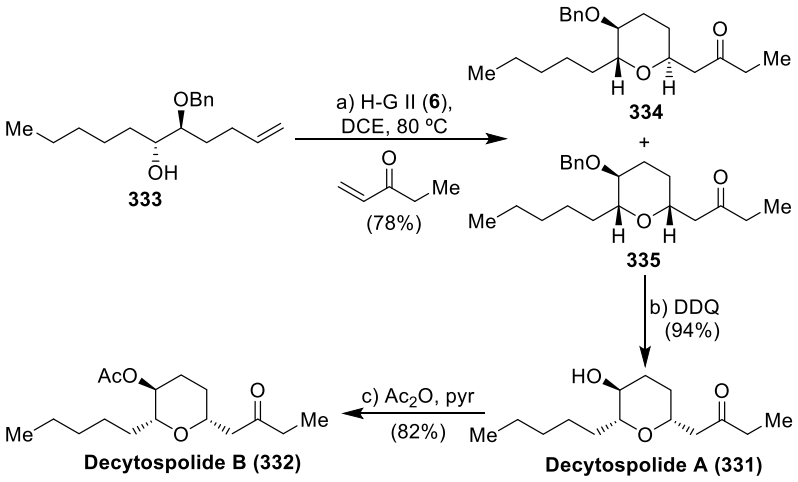
Another such application is the synthesis of the tetrahydropyrane containing natural products decytospolides A (**331**) and B (**332**) by Kommu et al.[170] which was rapidly achieved when the hydroxyl olefin **333** was subjected to treatment of the Hoveyda-Grubbs II catalyst (**6**) in the presence of ethylvinyl ketone to provide the pyranes **334** and **335** in a 78% combined yield and as a 9:1 mixture of stereoisomers, in favor of

[169] Waldeck, A. R.; Krische, M. J. *Angew. Chem. Int. Ed.* **2013**, *52*, 4470-4473.
[170] Kammari, B. R.; Bejjanki, N. K.; Kommu, N. *Tetrahedron: Asymm.* **2015**, *26*, 296-303.

the desired 2,6-*cis*-pyrane **335**. Removal of the benzyl group of **335** afforded decytospolide A (**331**), whose acetylation provided decytospolide B (**332**) (**Scheme 38**).



Scheme 37. Total Synthesis of Cyanolide A (**327**) (Krische et al. 2013)[169]

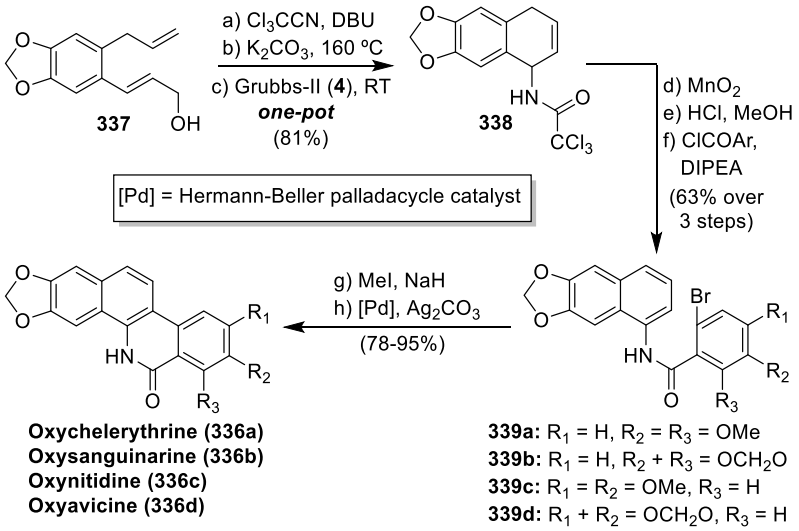


Scheme 38. Total Synthesis of Decytospolides A (**331**) and B (**332**) (Kommu et al. 2015)[170]

An interesting approach towards the synthesis of isoquinoline-type alkaloids, such as oxychelerythrine (**336a**), oxysanguinarine (**336b**), oxynitidine (**336c**) and oxyvicine (**336d**) has been described by Sutherland et al. [171] based on a tandem Overman rearrangement/RCM for rapid access to amino-substituted 1,4-dihydronaphtalene scaffolds, which represent key precursors for the synthesis of the benzo[*c*]phenanthridine system found in these natural products. The one-pot Overman rearrangement/RCM was efficiently achieved after extensive optimization, finding that when **337** was converted into the corresponding trichloroacetimidate, heated to 160 °C in the presence of potassium carbonate and then submitted to the action of the Grubbs-II catalyst (**4**) at room

[171] Calder, E. D. D.; McGonagle, F. I.; Harkiss, A. H.; McGonagle, G. A.; Sutherland, A. *J. Org. Chem.* **2014**, *79*, 7633-7648.

temperature, the corresponding 1,4-dihydronaphtahlene **338** was obtained in 81% yield. From this privileged compound, the authors completed the syntheses of the alkaloids **336a-d** after aromatization of **338**, followed by coupling with the corresponding 2-bromobenzoic acid derivatives and an intramolecular biaryl Heck coupling reaction in a very high efficient manner. In the final Heck coupling (step h of the sequence), Sutherland et al. employed the more stable Hermann-Beller palladacycle catalyst, given the very high temperature (160 °C) required for the intramolecular coupling of their precursors **339a-d** (**Scheme 39**). A related tandem Overman rearrangement and ring-closing enyne metathesis, followed by a Diels-Alder reaction was utilized by the same authors in the synthesis of amino-substituted indanes and tetralins.[172]



Scheme 39. Total Synthesis of Oxybenzo[*c*]phenanthridine Alkaloids **336a-d** (Sutherland et al. 2014)[171]

1.3. Enyne Metathesis in Total Synthesis

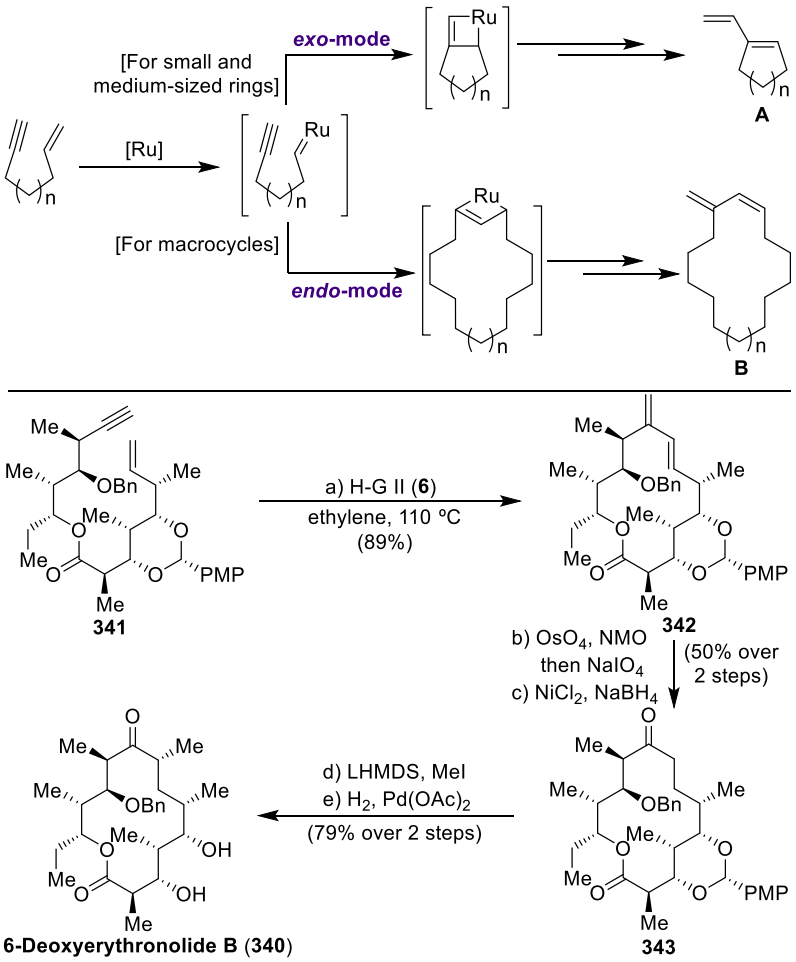
As in previous sections, in this section we will focus on recent contributions recorded in the last few years (2012-present), taking into account that the ring-closing enyne metathesis (RCEYM) reaction has been similarly covered in numerous reviews.[173]

1.3.1. Total Syntheses Based on a Ring-Closing Enyne Metathesis Reaction

The synthetic value of an intramolecular metathesis reaction of an enyne (RCEYM) is due to the versatility that is offered by the resulting cyclic dienes, which can be utilized in subsequent transformations, such as cycloaddition reactions. On the other hand, in contrast to other metathesis processes, the enyne metathesis can be promoted by other metal catalysts, such as Pt^{2+}, Pt^{4+} or Ir, or even Lewis acids, by a different mechanism but with the same result. Interestingly, in contrast to the alkene RCM, for the

[172] Grafton, M. W.; Farrugia, L. J.; Sutherland, A. *J. Org. Chem.* **2013**, *78*, 7199-7207.
[173] Selected reviews of enyne metathesis in synthesis of natural products: (a) Mori, M. *Materials* **2010**, *3*, 2087-2140. (b) Mori, M. *Adv. Synth. Catal.* **2007**, *349*, 121-135. (c) Dragutan, I.; Dragutan, V.; Demonceau, A.; Delaude, L. *Curr. Org. Chem.* **2013**, *17*, 2678-2720.

enyne RCM, the mode of the ring closure can be different depending on the size of the cyclic system.[174] Thus, whereas in small and medium-sized rings, the cyclization pathway goes through an *exo*-mode that delivers the product type **A**, in a macrocylization process, the ring closure can go through an *endo*-pathway, owing to the increased flexibility of the large ring system, that should afford the product type **B**.



Scheme 40. Different Pathways of the Ring-Closing Enyne Metathesis and Total Synthesis of 6-Deoxyerythronolide B (**340**) (Krische et al. 2014)[175]

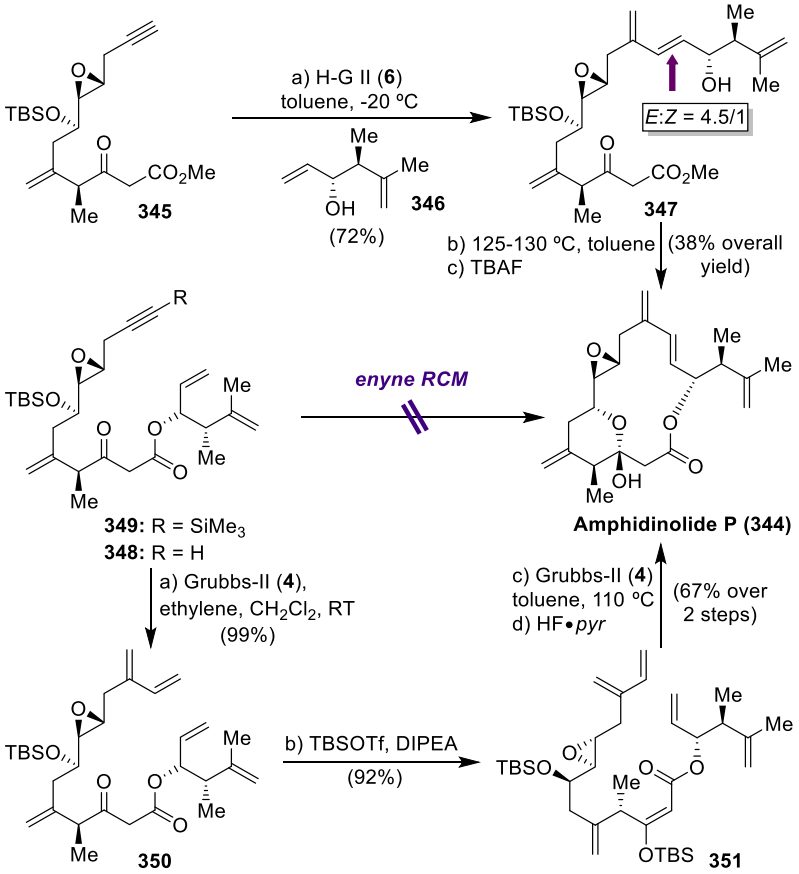
A clear example of the formation of this class of type **B** compounds is the synthesis of 6-deoxyerythronolide B (**340**) by Krische et al.,[175] who prepared macrocyclic **342** in 89% yield when the enyne **341** was treated with the HG-II catalyst (**6**) in an atmosphere of ethylene at 110 °C, with no detection of regioisomers. With the formation of the 14-membered macrocycle, the completion of the synthesis of the deoxyerythronolide B (**340**) was delineated through a synthetic sequence that included selective oxidation of the exocyclic double bond, reduction of the resulting enone through a Ni-catalyzed conjugate reduction, stereoselective methylation of the resulting ketone **343** and final removal of the protective groups via catalytic hydrogenation (**Scheme 40**). Given the usual involvement of the enyne RCM products in subsequent transformations

[174] A general review about enyne metathesis: Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317-1382.
[175] Gao, X.; Woo, S. W.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 4223-4226.

of the resulting diene in a tandem process, the majority of cases found in the literature correspond to this category and will be discussed later in section 1.3.3.

1.3.2. Total Syntheses Based on an Enyne Cross Metathesis Reaction

Several problems are associated with the selectivity of an intermolecular enyne metathesis, for example alkene-alkene and alkyne-alkyne metathesis processes can compete with the alkene-alkyne coupling, as well as the possible formation of geometric *E*/*Z* mixtures. Indeed, these problems are the likely reasons for the limited use of this modality of metathesis versus the intramolecular variant. Due to the scarcity of examples in which an enyne cross-metathesis is employed in the realm of total synthesis, it is worth emphasizing those where the reaction has been successfully applied. Such a case is the synthesis of amphidinolide P (**344**) by Diver,[176] in which an enyne cross-metathesis allowed access to the main backbone of the natural product.



Scheme 41. Total Synthesis of Amphidinolide P (**344**) (Diver et al. 2015)[176]

In practice, alkyne **345** and alkene **346** were coupled by treatment with the HG-II catalyst (**6**) at low temperature (-20 °C) to give diene **347** in 72% yield and as a 4.5:1 *E*/*Z* mixture of geometric isomers. The completion of the synthesis was achieved according to the Williams protocol[177] to obtain pure amphidinolide P (**344**) in 38% overall yield. Surprisingly, when the authors attempted the synthesis of this natural product via an

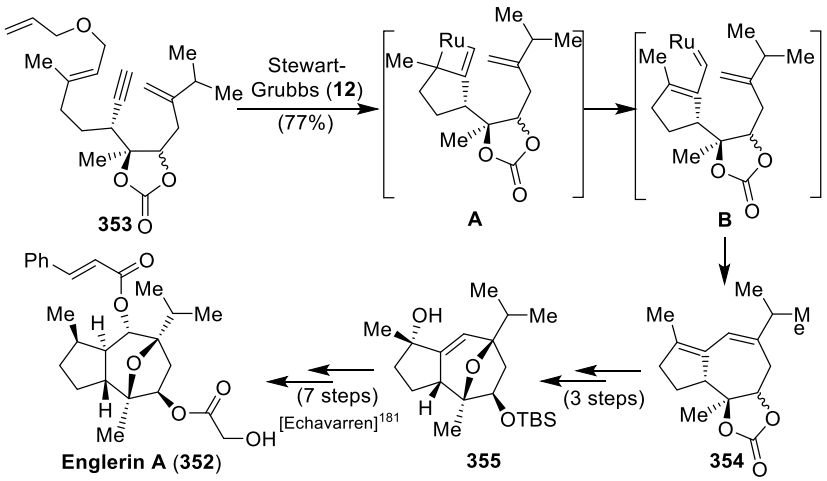
[176] Jecs, E.; Diver, S. T. *Org. Lett.* **2015**, *17*, 3510-3513.
[177] Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945-948.

enyne RCM, they failed to obtain any ring closure product, either from **348** or from the more stable TMS derivative **349**. However, when **348** was subjected to the Grubbs-II catalyst (**4**) in an ethylene atmosphere, they could obtain, in almost quantitative yield, the 1,3-diene **350**, which was envisioned as a suitable precursor for a final RCM step. In this case, the authors observed that the RCM reaction of its corresponding silyl enol ether, compound **351**, with the Grubbs-II catalyst (**4**) proceeded in a better yield, compared with the direct RCM reaction of the diene **350**, likely due to the introduction of additional rigidity in the system that would favor the connection of the involved alkenes. The RCM product, obtained as a mixture of the corresponding silyl enol ether and ketone, was transformed into amphidinolide P (**344**) by reaction with HF•pyr in 67% yield over two steps (**Scheme 41**). This contribution joins the synthesis by Lee based on a RCM approach.[178]

1.3.3. Enyne Metathesis in Tandem Reactions

Among the different variants of the metathesis reactions that employ enynes as starting precursors, those that involve the enyne metathesis as part of a cascade process have been the most exploited, due to their great potential for the generation of complex polycyclic systems in a single step. Given the synthetic consequences of such processes, enyne metathesis in cascade processes has occupied a strategic position in the synthesis of natural products containing complex polycyclic systems and the topic of several comprehensive reviews.[179] One finds two well-differentiated types of tandem processes involving enyne metathesis: a) Multiple intramolecular metathesis reactions in a programmed polyenyne system. In this case, the polyenyne precursor is properly designed to trigger a highly orchestrated cascade that ensures the right regiochemical outcome, once the initial metal carbene is formed in the right position; and b) a tandem process consisting of an initial enyne ring-closing metathesis, followed by a second reaction, usually a cycloaddition reaction, of the resulting diene. In the first case, we find a relevant example in the formal synthesis of englerin A (**352**) by Parker et al.[180] (**Scheme 42**).

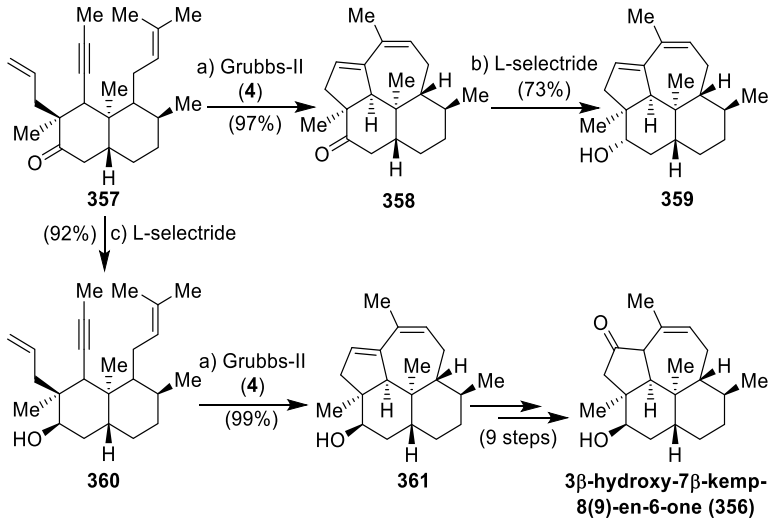
[178] Hwang, M.-h.; Han, S.-J.; Lee, D.-H. *Org. Lett.* **2013**, *15*, 3318-3321.
[179] (a) Li, J.; Lee, D. *Eur. J. Org. Chem.* **2011**, 4269-4287. (b) Kotha, S.; Meshram, M.; Tiwari, A. *Chem. Soc. Rev.* **2009**, *38*, 2065-2092. (c) Kaliappan, K. P. *Lett. Org. Chem.* **2005**, *2*, 678-686.
[180] Lee, J.; Parker, K. A. *Org. Lett.* **2012**, *14*, 2682-2685.



Scheme 42. Total Synthesis of Englerin A (**352**) (Parker et al. 2014)[180]

The intriguing structure of this natural product, in conjunction with its striking pharmaceutical properties, has prompted intense research activity directed towards its total synthesis, as well as the generation of analogues for medicinal chemistry studies. Among the seminal and elegant contributions developed for the synthesis of this natural product, the one by Parker was based on a ene-yne-ene metathesis cyclization in a tandem process. In order to secure the initiation process in the right direction, the authors developed a relay metathesis cascade from precursor **353**, in form of a diastereoisomeric mixture, which was readily available from geraniol in seven steps. Thus, when compound **353** was treated with the Stewart-Grubbs catalyst (**12**), the expected tricyclic derivative **354** was obtained in a 77% combined yield of both stereoisomers, which could be separated by chromatographic methods. The power of this tandem metathesis reaction is reflected by the fact that only the guaiadiene system was generated in a strict order of events through ruthenium carbenes species **A** and **B** due to the triggering effect exerted by the terminal allyl ether. The formation of the oxygen bridge present in the natural product was then accomplished by means of an oxymercuration and subsequent demercuration process that afforded the advanced intermediate **355**. The transformation of this compound into englerin A (**352**) has already been described by Echavarren in seven steps (**Scheme 42**).[181]

[181] Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519.



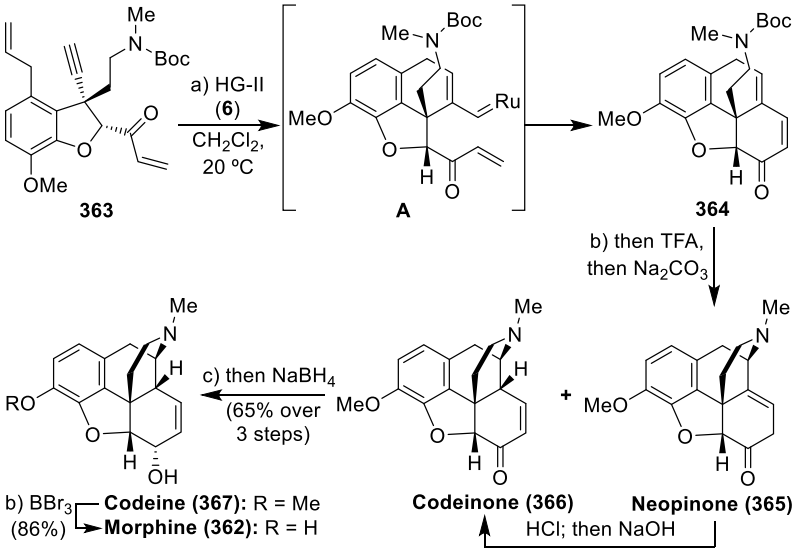
Scheme 43. Total Synthesis of Kempenone **356** (Metz et al. 2017)[183]

Another representative and unique example is the synthesis of the complex tetracyclic diterpenes belonging to the kempene family, such as the kempenone **356**, which was isolated from the defense secretion of higher termites *Nasutitermes octopolis*. In contrast to the long multistep approaches reported by Paquette and Deslongchamps for the construction of the tetracyclic core of these terpenes,[182] Metz et al. reported the preparation of this polycyclic system in one step and in excellent yield from the dienyne **357**, prepared from the Wieland-Miescher ketone in 20 steps.[183] Thus, exposure of **357** to the Grubbs-II catalyst (**4**) afforded the tetracyclic derivative **358** in an astonishing 97% yield. Whereas the reduction of the resulting tetracyclic ketone **358** with L-selectride provided the alcohol **359** with the opposite stereochemistry of the natural product, reduction of the bicyclic ketone precursor **357** provided the correct diastereoisomer **360** under the same reduction conditions. In a similar way as **357**, dienyne **360** was subjected to the treatment of the Grubbs-II catalyst (**4**) to obtain the tetracyclic alcohol **361** in almost quantitative yield (99%). From this compound, the synthesis of the kempenone **356** was achieved in 9 additional steps (**Scheme 43**).

Yet another instructive example for this section is the elegant synthesis of (±)-morphine (**372**) by Smith et al.,[184] in which the intricate pentacyclic system contained in this fascinating natural product was generated utilizing a cascade ene-yne-ene ring closing metathesis of the highly functionalized benzofuran **363**, prepared in just six steps from commercially available starting materials. In the crucial metathesis event, the catalytic action of the HG-II catalyst (**6**) smoothly promoted a sequential cascade of events, initiated with an enyne-RCM reaction, that generated the ruthenium alkylidene intermediate **A**, and continued with a final RCM reaction to produce tetracyclic compound **364**. Despite this product being isolated in an impressive 94% yield, the authors decided to continue with the synthetic sequence without isolation of the resulting

[182] (a) Paquette, L. A.; Sauer, D. R.; Cleary, D. G.; Kinsella, M. A.; Blackwell, C. M.; Anderson, L. G. *J. Am. Chem. Soc.* **1992**, *114*, 7375-7387. (b) Caussanel, F.; Wang, K.; Ramachandran, S. A.; Deslongchamps, P. *J. Org. Chem.* **2006**, *71*, 7370-7377.
[183] Wang, Y.; Jäger, A.; Gruner, M.; Lübken, T.; Metz, P. *Angew. Chem. Int. Ed.* **2017**, *56*, 15861-15865.
[184] Chu, S.; Münster, N.; Balan, T.; Smith, M. D. *Angew. Chem. Int. Ed.* **2016**, *55*, 14306-14309.

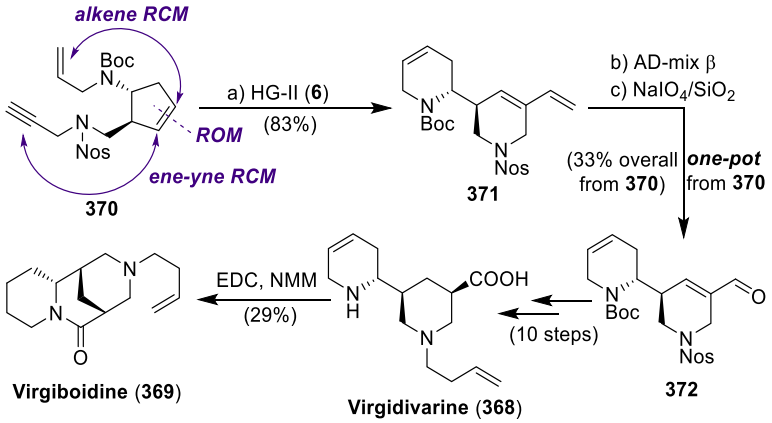
tetracycle **364**. The compound was then subjected to a 1,6-addition reaction by treatment with TFA and then sodium carbonate. As a result, a 10:1 mixture of compounds corresponding to neopinone (**365**) and codeinone (**366**) was obtained. The treatment of this mixture with HCl, followed by a NaOH work-up, allowed for the isomerization of neopinone (**365**) to codeinone (**366**). The reduction of **366** with sodium borohydride afforded codeine (**367**) as a single diastereoisomer and in 65% overall yield from **363**. Finally, demethylation of codeine with boron tribromide yielded racemic morphine (**362**) in 86% yield (**Scheme 44**).



Scheme 44. Total Synthesis of (±)-morphine (**362**) (Smith et al. 2016)[185]

An interesting example of the synthetic application of domino metathesis in the field of the alkaloid-type natural products is the recent syntheses of virgidivarine (**368**) and virgiboidine (**369**), which are piperidine and piperidino-quinolizidine alkaloids isolated from the leaves of African leguminosae *Virgilia divaricata* and *Virgilia oroboides* and whose biological activities have not been studied. Blechert et al.[185] planned the construction of the common dipiperidine core of these natural products via a ene-ene-yne ring-rearrangement metathesis (RRM) from the dienic system represented by compound **370**, foreseeing an initial ROM process of the cyclopentene unit, followed by a double alkene RCM-enyne RCM process of the resulting ROM intermediate. Thus, when precursor **370**, prepared from *cis*-cyclopent-2-en-1,4-diol via enzymatic desymmetrization, was exposed to the HG-II catalyst (**6**) under ethylene atmosphere, compound **371** was obtained in a remarkable 83% yield, according to the expected mechanistic course delineated by the authors. Combined with the tandem metathesis reactions, the resulting metathesis product was transformed into the aldehyde **372** by an oxidative treatment, in a 33% overall yield in one pot. From this aldehyde, both alkaloids were prepared, requiring 10 steps to synthesize virgidivarine (**368**), followed by the synthesis of virgiboidine (**369**), after a final lactamization reaction of **368** with EDC (**Scheme 45**).

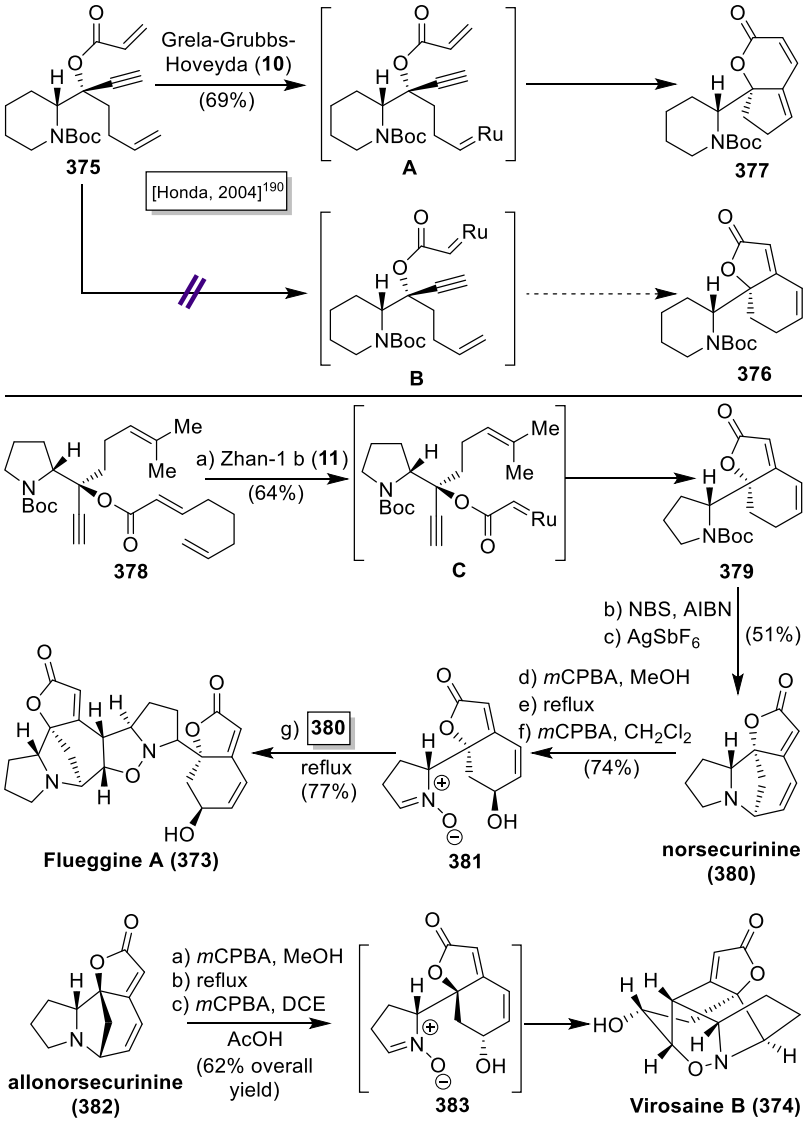
[185] Kress, S.; Weckesser, J.; Schulz, S. R.; Blechert, S. *Eur. J. Org. Chem.* **2013**, 1346-1355.



Scheme 45. Total Synthesis of Virgidivarine (**368**) and Virgiboidine (**369**) (Blechert et al. 2013)[185]

With regards to recent examples, special attention is deserved for the synthesis of the anticancer alkaloids flueggine A (**373**) and virosine B (**374**) by the Li group.[186] These compounds, belonging to the securinega family, possess unique structural features and interesting biological properties that cover a wide range of activities. The synthesis of these compounds was based on an elegant RRCM of a dienyne system for the controlled construction of the core structure represented by norsecurinine (**380**). Thus, their syntheses were envisioned to proceed via a 1,3-dipolar cycloaddition between norsecurinine (**380**) and nitrone **381**, which would be prepared from norsecurinine **380** by oxidative treatment with *m*-CPBA (**Scheme 46**).

[186] Wei, H.; Qiao, C.; Liu, G.; Yang, Z.; Li, C.-c. *Angew. Chem. Int. Ed.* **2013**, *52*, 620-624.



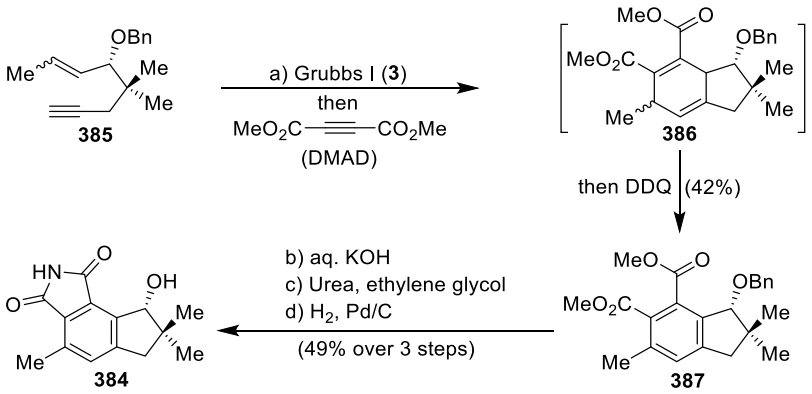
Scheme 46. Total Synthesis of Flueggine A (**373**) and Virosaine B (**374**) (Li, Yang et al. 2013)[186]

In a similar strategy towards the related alkaloid securinine, Honda et al.[187] attempted its synthesis through a tandem RCM of the dienyne **375**. However, when this precursor was reacted with different ruthenium catalysts, such as the Grela-Grubbs-Hoveyda (**10**), the desired γ-lactone **376** was not detected, obtaining instead the δ-lactone **377** in 69% yield. The preference of the catalyst to react with the butenyl group rather than the acrylate moiety, through intermediate **A**, could explain the outcome of this reaction. In an attempt to favor the formation of the required ruthenium complex at the less reactive alkene, Li et al. proposed the trienyne **378** as a suitable precursor to promote the preferential formation of intermediate **C** through the initiation of the reaction at the less sterically encumbered terminal olefin. In fact, when compound **378** was subjected to the action of the Zhan-1 b catalyst (**11**), among others, compound **379** was obtained in a reproducible and acceptable 64% yield. The completion of the synthesis of norsecurinine was undertaken in 3 additional steps, allylic bromation, Boc deprotection and a

[187] Honda, T.; Namiki, H.; Kaneda, K.; Mizutani, H. *Org. Lett.* **2004**, *6*, 87-89.

nucleophilic cyclization under basic conditions. After some additional experimentation, the authors found out that this transformation could be achieved in only one step by exposure of the resulting bromide to the acid $AgSbF_6$ in an improved 85% yield. Finally, the preparation of the nitrone **381** from norsecurinine (**380**), according to the Magnus protocol,[188] was followed by a cycloaddition reaction with **380** to obtain natural product flueggine A (**373**) in a 77% yield. In a related approach, they also prepared virosaine B (**374**) by an intramolecular cycloaddition of nitrone **383**, prepared from the isomer allonorsecurinine **382** in three steps (**Scheme 46**).

In the second group of the cascade reactions involving enyne-RCM processes, we wish to highlight those that combine the metathesis reaction with a Diels-Alder cycloaddition of the resulting diene as a way for the construction of a bicyclic system in a rapid and efficient fashion. Within this category of tandem reactions, the synthesis of the norsesquiterpene-type alkaloids, such as the anticancer alkaloid **384**, which were isolated from the culture of mushroom-forming fungus *Flammulina velutipes*, was accomplished using a tandem enyne-RCM/Diels-Alder/aromatization sequence in one-pot by Reddy et al.[189] Thus, the treatment of the acyclic precursor **385** with the Grubbs-I catalyst (**3**) in toluene at 50 °C was followed by a Diels-Alder reaction with dimethyl acetylene-dicarboxylate (DMAD) and then, treatment with DDQ of the resulting Diels-Alder adduct **386**, which was not isolated, to provide the final compound **387** in a moderate 42% overall yield. The elaboration of this product towards the final alkaloid **384** was accomplished without issues in three additional steps with a 49% overall yield (**Scheme 47**).



Scheme 47. Total Synthesis of the Norsesquiterpene Alkaloid **384** (Reddy et al. 2014)[189]

1.4. Alkyne Metathesis in Total Synthesis

1.4.1. Total Syntheses Based on a Ring-Closing Alkyne Metathesis Reaction

The wide range of reactivities that alkynes possess, compared with alkenes, imparts the alkyne metathesis as a very powerful tool with a broader field of synthetic

[188] Magnus, P.; Rodríguez-López, J.; Mulholland, K.; Matthews, I. *Tetrahedron* **1993**, *49*, 8059-8072.
[189] Kashinath, K.; Jadhav, P. D.; Reddy, D. S. *Org. Biomol. Chem.* **2014**, *12*, 4098-4103.

opportunities. Thus, some advantages of alkynes over alkenes include the stereo-controlled partial reduction of the triple bond, which allows stereoselective access to the *E* or the *Z*-alkene, and its excellent reactivity against electrophilic metals such as Ag, Pt or Hg, which allows for further functionalization. On the other hand, the catalysts required for the alkyne metathesis reactions are completely different. From the first Mortreux system developed in 1974,[190] the evolution towards more efficient, stable and functional group tolerant catalysts, developed firstly by Schrock (catalyst **388**)[191] and later by Fürstner (catalysts **389**)[192] (**Figure 6**), has propelled the alkyne metathesis reaction to become an excellent synthetic tool for the generation of macrocyclic structures as applied to the synthesis of natural products and bioactive compounds.

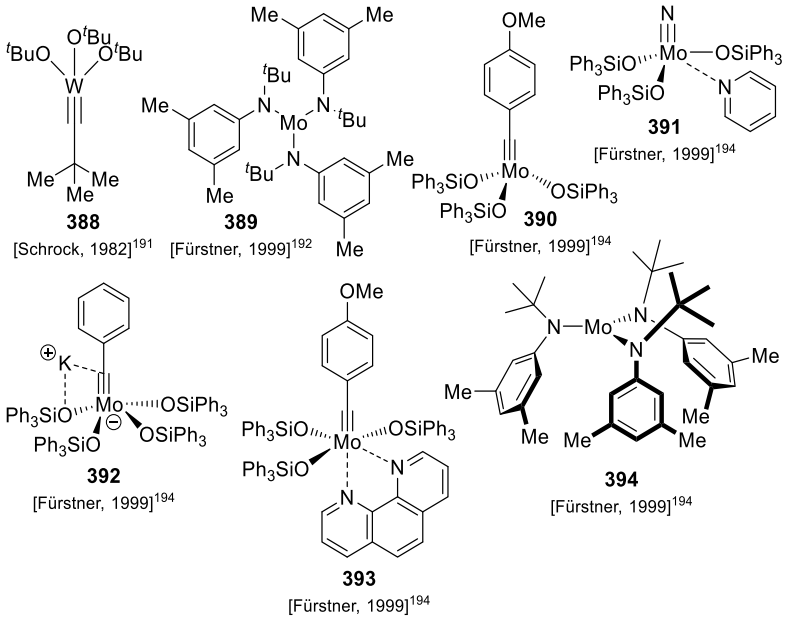


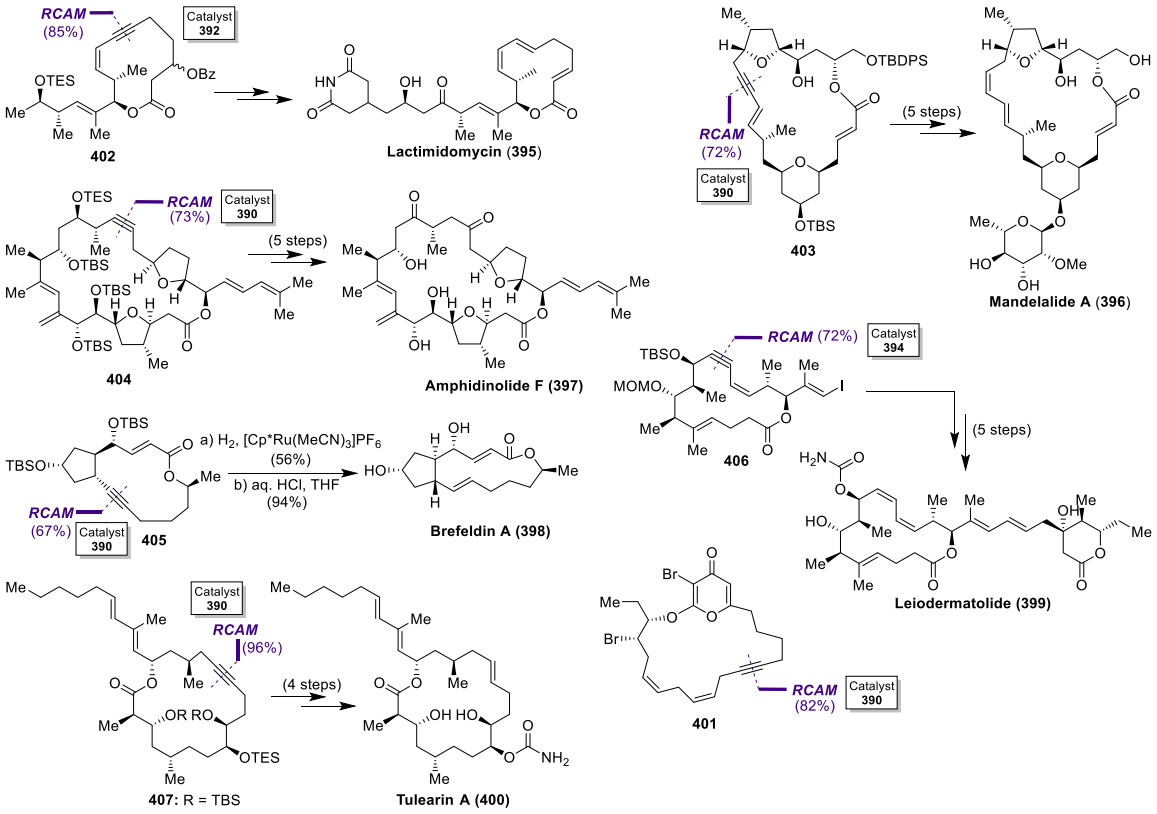
Figure 6. Common Catalysts Used for Alkyne Metathesis Reactions

Since the first example of an alkyne ring-closing metathesis in 1999 by Fürstner,[193] we can find in the literature many applications of this type of reaction in the preparation of complex macrocyclic natural products, some of the which has been linked to the development of even more efficient and stable catalysts in the last years (catalysts **390**-**394**).[194] As for the catalysts used in alkene metathesis, the catalysts for alkyne metathesis are precatalysts, which are activated to form the active species responsible for catalytic action. In fact, precatalysts **389** or **394** are activated by reaction with CH_2Cl_2 to form in situ the corresponding monochloro derivatives, which are the catalytically active species.[195] One of the main architects of the responsible for the spectacular irruption of this reaction in modern organic synthesis has been Fürstner, who not only by his seminal contributions in total synthesis but also in his work on the development of new catalysts

[190] Mortreux, A.; Blanchard, M. *J. Chem. Soc. Chem. Commun.* **1974**, 786-787.
[191] Schrock, R. R.; Clark, D. N.; Sancho, J.; Wengrovius, J. H.; Rocklage, S. M.; Pedersen, S. F. *Organometallics* **1982**, *1*, 1645-1651.
[192] Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **1999**, *121*, 9453-9454.
[193] Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108-11113.
[194] (a) Schaubach, S.; Gebauer, K.; Ungeheuer, F.; Hoffmeister, L.; Ilg, M. K.; Wirtz, C.; Fürstner, A. *Chem. Eur. J.* **2016**, *22*, 8494-8507 and references therein. (b) Wu, X.; Tamm, M. *Beilstein J. Org. Chem.* **2011**, *7*, 82-93.
[195] Fürstner, A.; Mathes, C.; Lehmann, C. W. *Chem. Eur. J.* **2001**, *7*, 5299-5317.

has reached spectacular progress and promoted the field. During his prolific and impressive research career, many reviews have been reported about this reaction covering the main contributions of the Fürstner group as well as of other groups.[196] The last contributions reported in the period 2015-2017 however have not been covered and thus will be reviewed in this section.

Thus, selected examples are illustrated in **Scheme 48**, in which the natural products lactimidomycin (**395**),[197] mandelalide A (**396**),[198] amphidinolide F (**397**),[199] brefeldin A (**398**),[200] leidodermatolide (**399**),[201] tulearin A (**400**)[202] or brominated 4-pyrone-type natural products[203] (for example **401**) were efficiently synthesized from their corresponding acyclic dialkynes and that provided the corresponding alkyne macrocycles (**402**-**407**) in good to excellent yields.

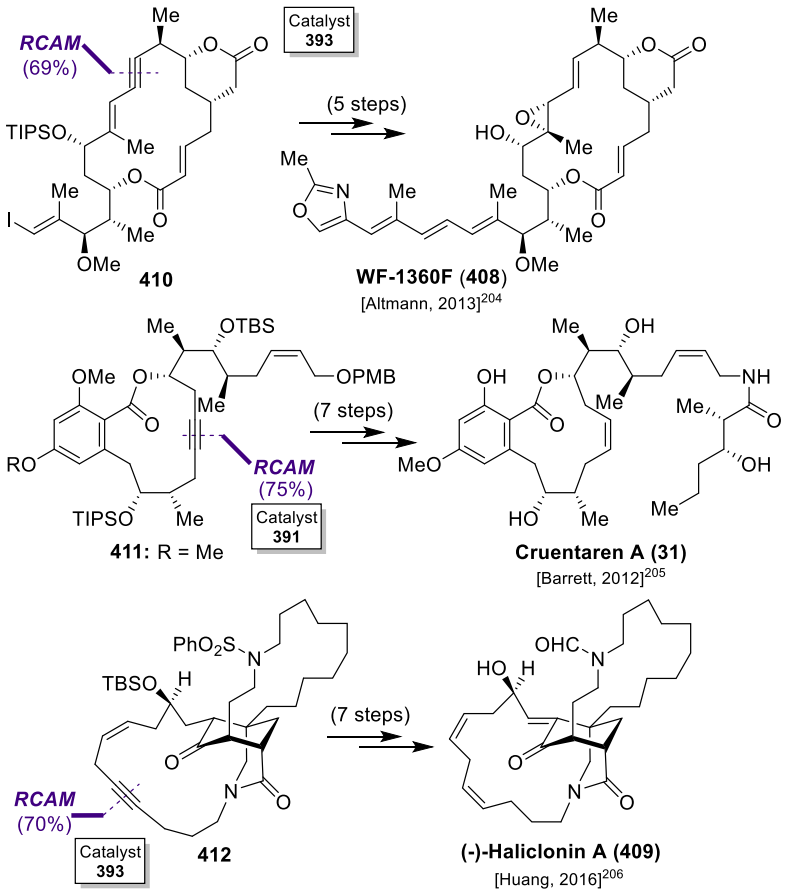


Scheme 48. Selected Natural Products synthesized via a RCAM reaction by the Fürstner Group (period 2013-present)

[196] Selected reviews on alkyne metathesis: (a) Fürstner, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 8587-8598. (b) Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 2794-2819. (c) Zhang, W.; Moore, J. S. *Adv. Synth. Catal.* **2007**, *349*, 93-120. (d) Fürstner, A.; Davies, P. W. *Chem. Commun.* **2005**, 2307-2320.
[197] Micoine, K.; Persich, P.; Llaveria, J.; Lam, M.-H.; Maderna, A.; Loganzo, F.; Fürstner, A. *Chem. Eur. J.* **2013**, *19*, 7370-7383.
[198] (a) Willwacher, J.; Fürstner, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 4217-4221. (b) Willwacher, J.; Heggen, B.; Wirtz, C.; Thiel, W.; Fürstner, A. *Chem. Eur. J.* **2015**, *21*, 10416-10430.
[199] (a) Valot, G.; Regens, C. S.; O´Malley, D. P.; Godineau, E.; Takikawa, H.; Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9534-9538. (b) Valot, G.; Mailhol, D.; Regens, C. S.; O´Malley, D. P.; Godineau, E.; Takikawa, H.; Phillipps, P.; Fürstner, A. *Chem. Eur. J.* **2015**, *21*, 2398-2408.
[200] Fuchs, M.; Fürstner, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 3978-3982.
[201] Mailhol, D.; Willwacher, J.; Kausch-Busies, N.; Rubitski, E. E.; Sobol, Z.; Schuler, M.; Lam, M.-H.; Musto, S.; Loganzo, F.; Maderna, A.; Fürstner, A. *J. Am. Chem. Soc.* **2014**, *136*, 15719-15729.
[202] Lehr, K.; Schulthoff, S.; Ueda, Y.; Mariz, R.; Leseurre, L.; Gabor, B.; Fürstner, A. *Chem. Eur. J.* **2015**, *21*, 219-227.
[203] Hoffmeister, L.; Fukuda, T.; Pototschnig, G.; Fürstner, A. *Chem. Eur. J.* **2015**, *21*, 4529-4533.

In the depicted representative cases, the alkynes were reduced to the corresponding *E*-alkenes (cases of natural products **395**, **398** and **400**), *Z*-alkenes (cases of **396** and **399**) or even, not transformed such as the cases of the 4-pyrone **401**. For the particular case of amphidinolide F (**397**), the alkyne was subjected to a hydration reaction to obtain a ketone under platinum catalysis. Similarly relevant are the syntheses of WF-1360F (**408**),[204] cruentaren A (**31**)[205] and haliclonin A (**409**),[206] reported by the Altmann, Barrett and the Huang research groups, respectively, in which after the alkyne macrocycle formation via a RCAM reaction, the resulting macrocyclic alkynes (**410**-**412**) were reduced to the *E*-olefin for the case of **410** or to the *Z*-olefins by means of a Lindlar catalyst-mediated hydrogenation for **411** and **412** (**Scheme 49**).

More intriguing and challenging are the cases in which introduction of a methyl group into the alkyne is required to be transformed into a methyl-branched alkene in a regio- and stereo-controlled manner. Such cases can be found in the synthesis of the natural products 5,6-dihydrocineromycin B (**413**), disciformycins B (**414**) and nannocystin Ax (**415**) by the Fürstner group.



Scheme 49. Selected Natural Products synthesized via a RCAM reaction by other Research Groups (period 2013-present)

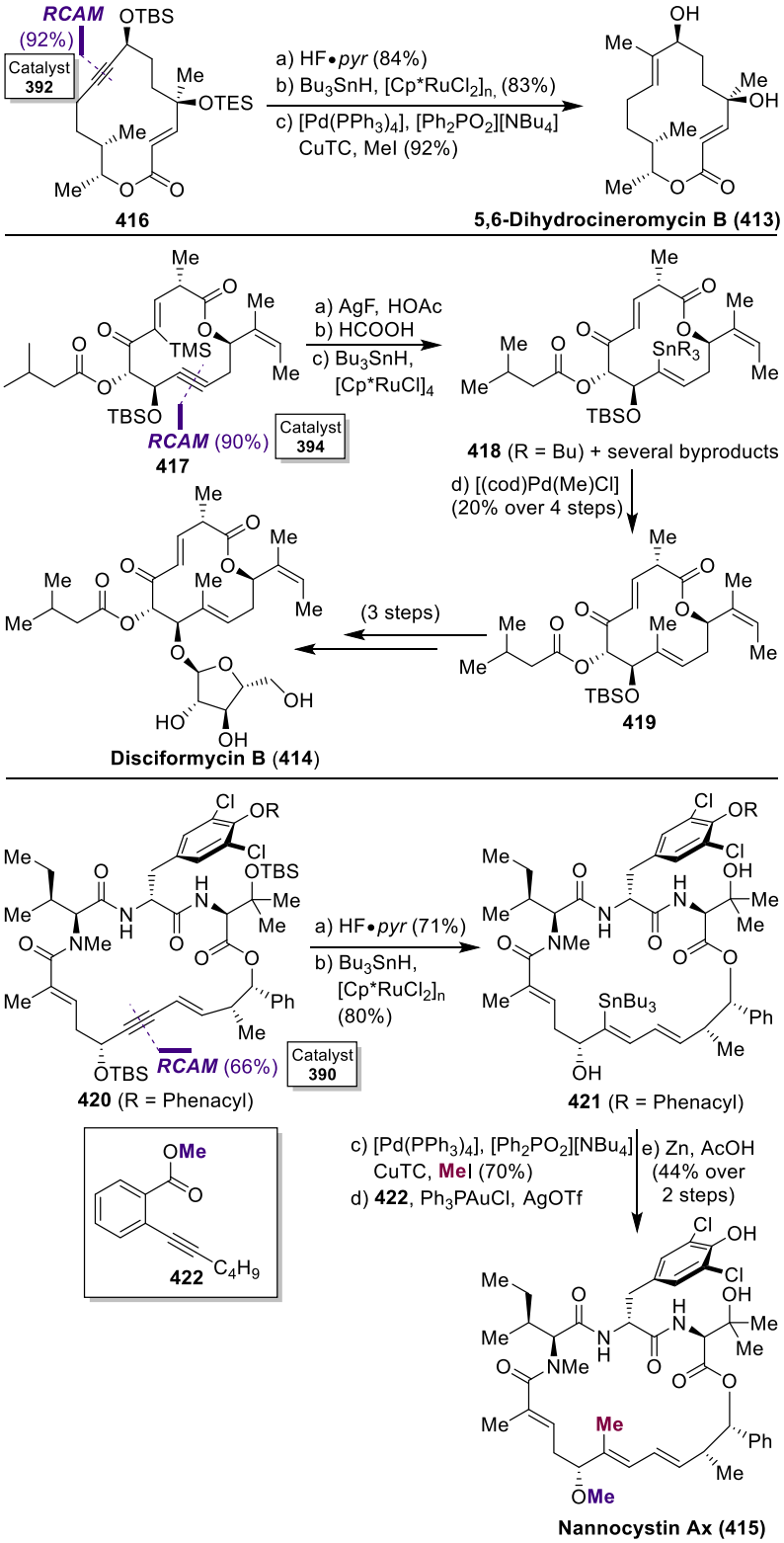
[204] Neuhaus, C. M.; Liniger, M.; Stieger, M.; Altmann, K.-H. *Angew. Chem. Int. Ed.* **2013**, *52*, 5866-5870.
[205] Fouché, M.; Rooney, L.; Barrett, A. G. M. *J. Org. Chem.* **2012**, *77*, 3060-3070.
[206] Guo, L.-D.; Huang, X.-Z.; Luo, S.-P.; Cao, W.-S.; Ruan, Y.-P.; Ye, J.-L.; Huang, P.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 4064-4068.

To this aim, the recent methodology developed by the same group, based on the ruthenium-catalyzed *trans*-hydrostannation of alkynes, was envisioned as a solution to this synthetic problem given the excellent levels of regioselectivity exhibited by this reaction when applied to unprotected propargyl alcohol derivatives. Thus, for the case of 5,6-dihydrocineromycin B (**413**),[207] when alkyne **416**, obtained from the corresponding acyclic dialkyne by reaction with the molybdenum alkylidyne complex **392**, was desilylated by reaction with HF, the resulting propargyl alcohol was treated with Bu_3SnH in the presence of the ruthenium catalyst $[Cp^*RuCl_2]_n$. As a result, the corresponding *a*-alkenylstannane was obtained as a single isomer. Having introduced the stannyl group, a Stille reaction was carried out by exposure to copper thiophene-2-carboxylate (CuTC), $[Ph_2PO_2][NBu_4]$ and $[Pd(PPh_3)_4]$ in the presence of methyl iodide to afford the final natural product (**413**) in excellent yield. It is important to highlight the importance of the order of addition and stoichiometry of the reactants in this reaction to avoid undesired protodestannation processes. In a similar situation, the macrocyclic alkyne **417**,[208] obtained in excellent yield from its corresponding dialkyne precursor by reaction with precatalyst **394**, required the installation of the methyl group for the synthesis of disciformycins A and B, interesting macrolides-type antibiotics with considerable activity against resistant Gram-positive bacteria (**Scheme 50**).

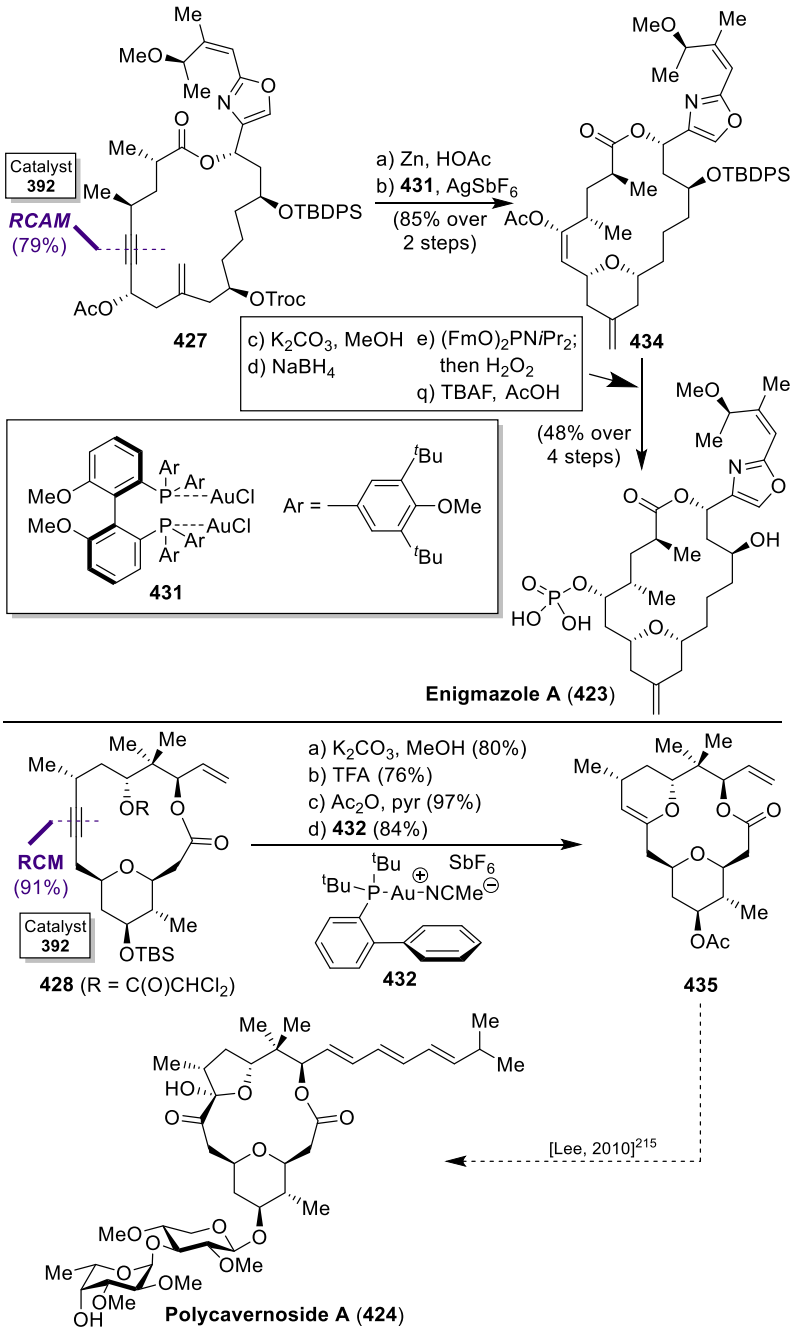
As the previous case, the transformation of compound **417** into its hydroxyl derivative was followed by a rapid *trans*-hydrostannation reaction. In contrast to the previous case, as to other numerous examples carried out by the Fürstner group, on this occasion a 3:1 mixture of stannyl regioisomers, in favor of **418**, was obtained, likely due to the competing interactions of the hydroxyl group, via hydrogen bonding, with the ruthenium catalyst and with the neighboring ester carbonyl group. In addition to this lack of regioselectivity, the observation that the stannyl derivative was quite sensitive forced the authors to continue with the crude product mixture to the following step, which consisted of a methylation reaction. Once again, this reaction proved to be sluggish, as a mixture of products was obtained under conventional conditions. In light of these unsatisfactory results, the authors decided to use stoichiometric amounts of the methyl donor [(cod)Pd(Cl)Me] to obtain the desired product **419** in a 20% overall yield after four steps from **417**. Final glycosidation and global deprotection provided the elusive disciformycin B (**415**) in the first instance, and then disciformycin A after an isomerization reaction. Similarly challenging proved to be the synthesis of nannocystin Ax (**415**),[209] a cytotoxic cyclodepsipeptide isolated from myxobacteria. After a successful alkyne RCM reaction that provided macrocyclic alkyne **420** in a 66% yield by the action of catalyst **390**, the OH-directed hydrostannation was achieved by sequential desilylaton and treatment with Bu_3SnH, in the presence of catalytic amounts of $[Cp^*RuCl_2]_n$, to obtain the corresponding stannane **421** as a single regio- and stereo-isomer. The methylation was then achieved according to previous conditions to provide the desired methyl derivative in a reasonable good yield (70%). The methylation of the hydroxyl

[207] Rummelt, S. M.; Preindl, J.; Sommer, H.; Fürstner, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 6241-6245.
[208] Kwon, Y.; Schulthoff, S.; Dao, Q. M.; Wirtz, C.; Fürstner, A. *Chem. Eur. J.* **2018**, *24*, 109-114.
[209] Meng, Z.; Souillart, L.; Monks, B.; Huwyler, N.; Herrmann, J.; Müller, R.; Fürstner, A. *J. Org. Chem.* **2018**, *83*, 6977-6994.

group proved to be similarly challenging, finding, after extensive experimentation, that the methyl ester **422** provided a proper source of electrophilic methyl by its in situ generation in a gold-catalyzed cyclization. Final reductive cleavage of the phenacyl group furnished the targeted natural product **415** (**Scheme 50**).



Scheme 50. Selected Natural Products synthesized via a RCAM/Hydrostannation reactions by the Fürstner Group

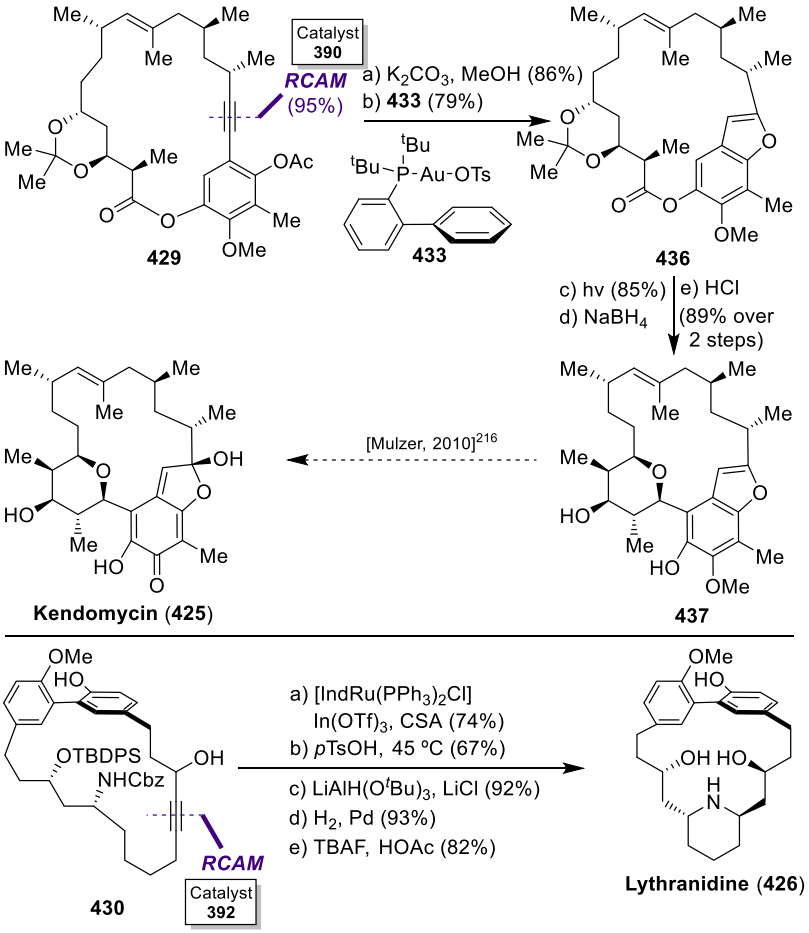


Scheme 51. Selected Natural Products synthesized via a RCAM/Gold Catalysis by the Fürstner Group (I)

Beyond the transformation of the alkyne into an alkene or even a methyl-substituted alkene, as discussed before, the reactivity of the alkyne functional group allows the construction of a heterocyclic ring, providing extraordinary opportunities to access more complex structural systems compared to the alkene chemistry. These post-metathetic transformations have been similarly explored by Fürstner et al. in the synthesis of a plethora of natural products. In this set of new synthetic opportunities, the recent syntheses of enigmazole A (**423**),[210] polycavernoside A (**424**),[211] kendomycin (**425**)[212]

[210] Ahlers, A.; de Haro, T.; Gabor, B.; Fürstner, A. *Angew. Chem. Int. Ed.* **2016**, *55*, 1406-1411.
[211] Brewitz, L.; Llaveria, J.; Yada, A.; Fürstner, A. *Chem. Eur. J.* **2013**, *19*, 4532-4537.
[212] Hoffmeister, L.; Persich, P.; Fürstner, A. *Chem. Eur. J.* **2014**, *20*, 4396-4402.

and lytharanidine (**426**)[213] represent excellent examples of this synthetic potential. In all these cases, the macrocyclic alkynes (**427**-**430**) were synthesized from their corresponding acyclic dialkynes. From these alkynes, in the cases of enigmazole A, polycavernoside A and kendomycin, a trasannular pyrane (for enigmazole A) and a furan ring (for polycavernoside A and kendomycin) were constructed by activation of the alkyne with gold-based catalysts (**431**-**433**)[214] to provide compounds **434**-**436**. In the cases of polycavernoside A and kendomycin, the syntheses were formal, having been described by Lee[215] and Mulzer[216] from advanced precursors **435** and **437**, respectively. On the other hand, for the synthesis of lytharanidine, formation of a piperidine ring was required, which was achieved by a sequence of redox isomerization, followed by transannular aza-Michael addition from macrocyclic alkyne **430** (**Schemes 51** and **52**).

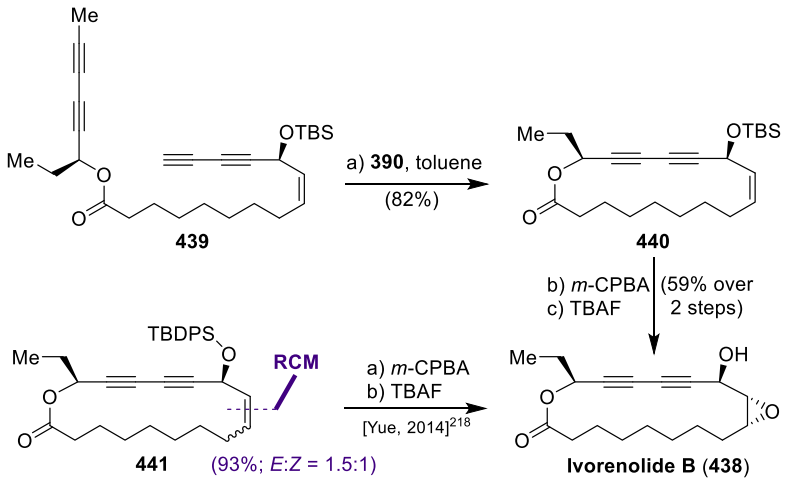


Scheme 52. Selected Natural Products synthesized via a RCAM/Gold Catalysis by the Fürstner Group (II)

An intriguing last case is the synthesis of ivorenolide B (**438**) by the Fürstner group based upon a macrocyclization of a diterminal diyne to prepare the 1,3-diyne system found in this unprecedented natural product.[217] Ivorenolide B belongs to a family

[213] Gebauer, K.; Fürstner, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 6393-6396.
[214] Fürstner, A. *Acc. Chem. Res.* **2014**, *47*, 925-938.
[215] Woo, S. K.; Lee, A. *J. Am. Chem. Soc.* **2010**, *132*, 4564-4565.
[216] Magauer, T.; Martin, H. J.; Mülzer, J. *Chem. Eur. J.* **2010**, *16*, 507-519.
[217] Ungeheuer, F.; Fürstner, A. *Chem. Eur. J.* **2015**, *21*, 11387-11392.

of macrolides isolated from the stem bark of *Khaya ivorensis*, which has been reported to inhibit concanavalin A-induced T-cell and lipopolysaccharide-induced B cell proliferations. This noteworthy biological activity confers it a clinical application as an immunosuppressive agent comparable to cyclosporine A. The synthesis of Fürstner et al. was delineated according to a RCAM reaction of the diterminal acyclic dyine **439**, which by treatment with catalyst **390** furnished in a remarkable 82% yield the desired [17]-membered ring **440** with the embedded 1,3-diyne unit and no detection of side products derived from ring contraction or oligomerization processes. The subsequent epoxidation, performed in a regio- and stereoselective manners with *m*-CPBA, followed by silyl ether deprotection provided the targeted ivorenolide B (**438**) (**Scheme 53**). This synthesis improved notably with the contribution by Yue et al.,[218] which, based on a RCM reaction, provided the macrocyclic lactone **441** as a 1.5:1 mixture with the *E*-olefin as the major isomer. Despite this stereochemical problem, Yue´s synthesis allowed confirmation of the absolute configuration of the natural product (**Scheme 53**).



Scheme 53. Total Synthesis of Ivorenolide B (**438**) (Fürstner et al. 2015)[217]

1.4.2. Other Types of Alkyne Metathesis Reactions

To conclude this chapter, it is necessary to mention that, as in alkene metathesis reactions, we can find also examples of the use of the alkyne cross-metathesis[219] or tethered RCAM reactions.[220] Despite the power and scope that the alkyne metathesis demonstrates, utilization of these alkyne metathesis variants in the context of total synthesis is not well represented, with most examples being found mainly in polymerization reactions.[221] Nevertheless, given the potential and efficiency of the methodology, there is no doubt that the trend will be an increase in the use of this chemistry in the construction of natural products.

[218] Wang, Y.; Liu, Q.-F.; Xue, J.-J.; Zhou, Y.; Yu, H.-C.; Yang, S.-P.; Zhang, B.; Zuo, J.-P.; Li, Y.; Yue, J.-M. *Org. Lett.* **2014**, *16*, 2062-2065.
[219] For a recent representative example see: Ralston, K. J.; Ramstadius, H. C.; Brewster, R. C.; Niblock, H. S.; Hulme, A. S. *Angew. Chem. Int. Ed.* **2015**, *54*, 7086-7090.
[220] For a recent representative example see: Guy, A.; Oger, C.; Heppekausen, J.; Signorini, C.; De Felice, C.; Fürstner, A.; Durand, T.; Galano, J.-M. *Chem. Eur. J.* **2014**, *20*, 6374-6380.
[221] Zhang, W.; Moore, J. S. *Macromolecules* **2004**, *37*, 3973-3975 and references therein.

1.5. Summary

As amply demonstrated in the literature, metathesis reactions are recognized as one of the most important and powerful reactions in the last decades rendering their main inventors the Nobel Prize in 2005. The synthetic value and great potential of these reactions have been driven by the tremendous progress witnessed in the last years regarding the design and development of efficient and stable catalysts based on metallocarbenes. As a consequence, these reactions enjoy broad scope, generality and a great deal of flexibility for structural diversity. Furthermore, as proof of these features is their extensive utilization in the field of organic synthesis, with particular impact in the total synthesis of natural products. These reactions in their different modalities (alkene, enyne and alkyne-metathesis reactions), versions (intra- and inter-molecular reactions), and strategies (tethered-, relay-, stereoselective metathesis, among others) have become a standard tool in the modern organic synthesis laboratory, being determinant in the completion of a wide array of natural products. In the current chapter we have demonstrated the increasing value and flurry of synthetic opportunities that these reactions provide.

Chapter 2

Aims

The current PhD Thesis proposes the discovery and development of new drugs inspired by bioactive natural products which represent valid platforms for the generation of new chemical entities of pharmaceutical interest. Thus, the combination of structural and functional diversity allows for the identification of new compounds with better biological profiles than the natural counterparts. In order to select suitable synthetic targets, we focused on natural products that are able to offer promising expectations in the biomedicinal field, with new mechanisms of biological action and intriguing molecular structures that could represent the basis of new scaffolds of pharmaceutical interest. In particular, the selected natural products are a microbial polyketide termed (-)-depudecin, and cyclopeptide and cyclodepsipeptide-type compounds from marine origin, the solomonamides A-B and the celebesides A-C. The scarcity of these natural products and the difficult accessibility from their natural sources have hampered further studies towards their biological and chemical profile. Despite the scarcity of the material, the preliminary biological evaluations of these natural products revealed very interesting biological properties. The intriguing preliminary biological profiles of the selected compounds, the requirement to have more material for further biological studies and to gain insight into their mechanisms of action and to confirm their novel and unprecedented molecular structures justify a research plan that could generate new knowledges from the chemical and biological standpoints. From the synthetic perspective, the selected natural products share an olefin metathesis reaction as the key step of their syntheses, which will be showed in detail in their respective chapters.

Thus, the following specific objectives were established for this PhD Thesis:

Objective 1. The establishment of flexible and convergent synthetic strategies towards the total synthesis of the selected natural products.
Objective 2. The implementation of the previously established synthetic routes to the generation of analogues of the selected natural products.
Objective 3. The biological evaluation of the synthetic natural products and analogues.

Chapter 3[†]

Depudecin Campaign

[†] Part of this chapter has been published as the following journal papers: (a) García-Ruiz, C.; Cheng-Sánchez, I.; Sarabia, F. *Org. Lett.* **2015**, *17*, 5558-5561. (b) Cheng-Sánchez, I.; García-Ruiz, C.; Guerrero-Vásquez, G. A.; Sarabia, F. *J. Org. Chem.* **2017**, *82*, 4744-4757.

3.1. Isolation, Structure and Biology of Depudecin

The disclosure and recognition of the crucial role of histone deacetylases (HDAC) and histone acetyl transferases (HAT) in the regulation of gene expression, which occurs through a tight control of the acetylation state of histones, has generated significant interest in their utility as new promising targets for cancer therapies.[222] Thus, whereas the acetylated histones lead to a local expansion of chromatin, increasing the accessibility of regulatory proteins to DNA, the action of HDACs produces positively-charged histones that increase their affinities with DNA and, thereby, block the transcription of anti-tumor genes.[223] HDACs are the enzymes responsible for the removal of the acetyl group from lysine residues of histones and other proteins; and are comprised of 18 isoforms grouped into four different classes (I-IV).[224] The inhibition of these enzymes in the context of a neoplastic epigenome, in which they are overexpressed and play important roles in promoting cancer progression,[225] leads to the restoration of a normal epigenetic state and induces the expression of tumor-suppresive genes.[226] Consequently, inhibitors of HDAC (HDACi) have attracted considerable attention from the scientific community as novel potential anticancer agents.[227] An indication of this interest is the flurry of activity directed towards the design and synthesis of inhibitors, which have been classified into five categories according to their modes of action.[228] As a consequence of this intense activity, three of them (vorinostat, belinostat and romidespin) have been recently approved by the FDA for clinical anticancer therapies, whereas a remarkable number of other HDACi have undergone clinical trials for the treatment of a variety of hematological malignancies and solid tumors.[229] The fact that other proteins, including transcription factors, DNA repair enzymes, signal transduction and inflammation mediators, among others, are also substrates of HDACs, further demonstrates their involvement in a wide variety of biological processes, including cell cycle and mitosis, DNA damage repair, cellular stress responses, protein degradation, cytokine signalling, immunity, inflammation, angiogenesis, apoptosis and cell invasion.[230] In fact, HDACs are involved not only in cancer, but also in other pathologies such as neurological diseases, immune disorders[231] and infections.[232] On the other hand, the general lack of isoform selectivity

[222] (a) Norton, V. G.; Imai, B. S.; Yau, P.; Bradbury, E. M. *Cell* **1989**, *57*, 449–457. (b) Turner, B. M. *Cell* **2002**, *111*, 285–291. (c) Huang, L. *J. Cell Physiol.* **2006**, *209*, 611–716. (d) Minucci, S.; Pelicci, P. G. *Nat. Rev. Cancer* **2006**, *6*, 38–51. (e) Jenuwein, T.; Allis, C. D. *Science* **2001**, *293*, 1074–1080.
[223] Brandl, A.; Heinzel, T.; Krämer, O. H. *Biol. Cell* **2009**, *101*, 193–205.
[224] Gregoretti, I. V.; Lee, Y. M.; Goodson, H. V. *J. Mol. Biol.* **2004**, *338*, 17-31.
[225] (a) Muller, B. M.; Jana, L.; Kasajima, A.; Lehmann, A.; Prinzler, J.; Budczies, J.; Winzer, K. J.; Dietel, M.; Weichert, W.; Denkert, C. *BMC Cancer* **2013**, *13*, 215. (b) Wilson, A. J.; Byun, D. S.; Popova, N.; Murray, L. B.; L'Italien, K.; Sowa, Y.; Arango, D.; Velcich, A.; Augenlicht, L. H.; Mariadason, J. M. *J. Biol. Chem.* **2006**, *281*, 13548–13558.
[226] Taunton, J.; Hassig, C. A.; Schreiber, S. L. *Science* **1996**, *272*, 408–411.
[227] (a) Newkirk, T. L.; Bowers, A. A.; Williams, R. M. *Nat. Prod. Rep.* **2009**, *26*, 1293–1320. (b) Miller, T. A.; Witter, D. J.; Belvedere, S. *J. Med. Chem.* **2003**, *46*, 5097–5116. (c) Meinke, P. T.; Liberator, P. *Curr. Med. Chem.* **2001**, *8*, 211–235. (d) Monneret, C. *Eur. J. Med. Chem.* **2005**, *40*, 1–13.
[228] (a) Iakshmi, A.; Madhusudhan, T.; Kumar, D. P.; Padmavathy, J.; Saravanan, D.; Kumar, Ch. P. *Int. J. Pharm. Sci. Rev. Res.* **2011**, *10*, 38-44. (b) Carafa, V.; Nebbioso, A.; Altucci, L. *Rec. Patents Anti-Cancer Drug Discov.* **2011**, *6*, 131–145.
[229] (a) West, A. C.; Johnstone, R. W. *J. Clin. Invest.* **2014**, *124*, 30-39. (b) Ververis, K.; Hiong, A.; Karagiannis, T. C.; Licciardi, P. V. *Biol. Targets Ther.* **2013**, *7*, 47-60. (c) Ma, X.; Ezzeldin, H. H.; Diasio, R. B. *Drugs* **2009**, *69*, 1911-1934. (d) New, M.; Olzscha, H.; La Thangue, N. B. *Mol. Oncol.* **2012**, *6*, 637–656.
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[231] (a) Falkenberg, K. J.; Johnstone, R. W. *Nat. Rev. Drug Discov.* **2014**, *13*, 673-691. (b) Kazantsev, A. G.; Thompson, L. M. *Nat. Rev. Drug Discov.* **2008**, *7*, 854-868.
[232] (a) Ouaissi, M.; Ouaissi, A. *J. Biomed. Biotechnol.* **2006**, *2006*, 13474-13483. (b) Rotili, D.; Simonetti, G.; Savarino, A.; Palamara, A. T.; Migliaccio, A. R.; Mai, A. *Curr. Top. Med. Chem.* **2009**, *9*, 272-291.

exhibited by current inhibitors towards the HDAC family,[233,234] which are involved in a plethora of biological functions, explains the diverse biological effects that they may produce,[235] thus reducing their therapeutic window by promoting undesirable side effects and toxicity.

In this context, (-)-depudecin (**442**), isolated from the culture broths of the fungus *Alternaria brassicicola* in 1992 [236] and later, from the weed pathogen *Nimbya scirpicola*,[237] has been identified as a selective inhibitor of histone deacetylases I and II with an IC_{50} in the low μM range, according to biological studies carried out by Schreiber et al.[238] In contrast to representative HDACi, such as **443**-**447** (**Figure 7, A**), depudecin represents a unique inhibitor of these enzymes by virtue of its molecular structure, featuring the presence of two oxirane rings separated by a *trans* double bond.

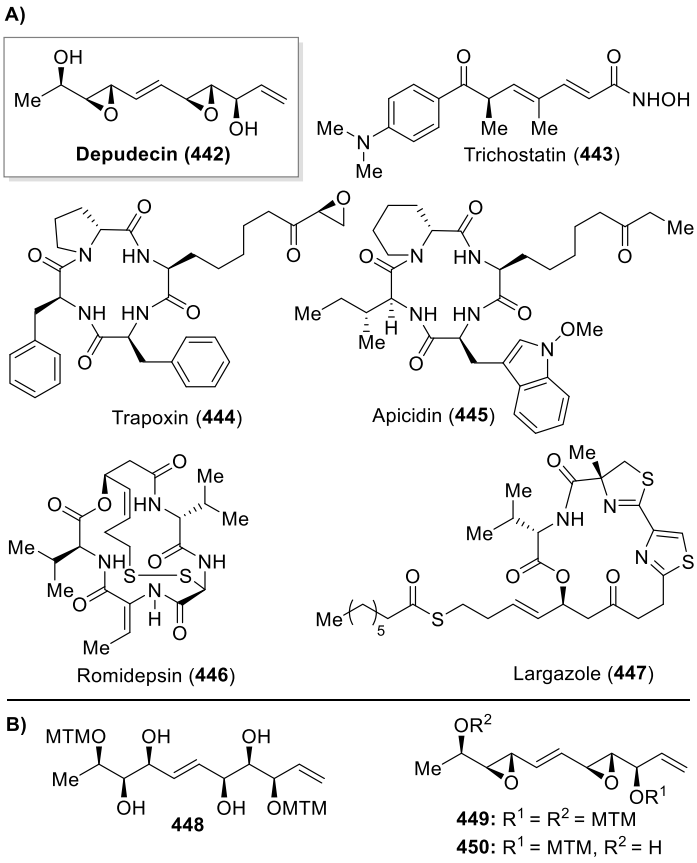

Figure 7. Molecular Structures of (-)-Depudecin (**442**) and Other HDAC Inhibitors (A) and Synthetic Intermediates Prepared by Schreiber et al. (B).

[233] (a) Balasubramanian, S.; Verner, E.; Buggy, J. J. *Cancer Lett.* **2009**, *280*, 211-221. (b) Wang, Y.; Stowe, R. L.; Pinello, C. E.; Tian, G.; Madoux, F.; Li, D.; Zhao, L. Y.; Li, J.-L.; Wang, Y.; Wang, Y.; Ma, H.; Hodder, P.; Roush, W. R.; Liao, D. *Chem. Biol.* **2015**, *22*, 273-284. (c) Bradner, J. E.; West, N.; Grachan, M. L.; Greenberg, E. F.; Haggarty, S. J.; Warnow, T.; Mazitschek, R. *Nat. Chem. Biol.* **2010**, *6*, 238-243. (d) Thaler, F.; Mercurio, C. *ChemMedChem* **2014**, *9*, 523-536.

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[235] (a) Manal, M.; Chandrasekar, M. J. N.; Priya, J. G.; Nanjan, M. J. *Bioorg. Chem.* **2016**, *67*, 18-42. (b) Marks, P. A. *Biochim. Biophys. Acta* **2010**, *1799*, 717-725. (c) Bolden, J. E.; Peart, M. J.; Johnstone, R. W. *Nat. Rev. Drug Discov.* **2006**, *5*, 769-784.

[236] Matsumoto, M.; Matsutani, S.; Sugita, K.; Yoshida, H.; Hayashi, F.; Terui, Y.; Nakai, H.; Uotani, N.; Kawamura, Y.; Matsumoto, K.; Shoji, J.; Yoshida, T. *J. Antibiot.* **1992**, *45*, 879–885.

[237] Tanaka, M.; Ohra, J.; Tsujino, Y.; Sawaji, Y.; Fujimori, T. *Biosci. Biotech. Biochem.* **1994**, *58*, 565–566.

[238] Kwon, H. J.; Owa, T.; Hassig, C. A.; Shimada, J.; Schreiber, S. L. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 3356–3361.

Originally discovered as part of a biological screen directed towards the identification of antitumour agents with detransforming activity,[239] depudecin was identified as a bioactive metabolite capable of reverting the transformed morphology of tumor cells NIH3T3, doubly transfected with v-*ras* and v-*src* oncogenes.[240] The ability of depudecin to regulate the cytoskeletal architecture of tumoral cells is due to the restoration of the actin stress fiber.

This biological activity elicited a great biomedical and biological interest[241] by virtue of its potential as an antitumor agent and as a molecular probe[242] for the investigation of signalling pathways that regulate the actin stress fiber, as well as for further understanding the biological roles of HDACs. Depudecin induced not only morphological changes but also cell cycle arrest and cellular differentiation, which could be attributed to its inhibition against HDAC[243] as mentioned above. It is likely that its inhibitory action against HDAC is a result of the presence of biologically reactive oxirane rings that could block the active site of the enzymes through the irreversible formation of a covalent bond between the nucleophlic residues within the active site and the oxirane rings.[244] In fact, Schreiber demonstrated that the epoxy and hydroxyl groups of depudecin were essential for the biological activity, as the synthetic analogue **450** showed very weak activity, and **448** and **449** were completely inactive against transformed NIH3T3 cells (**Figure 7, B**).[245] Furthermore, depudecin also exhibited remarkable anti-angiogenesis activity that endowed it with potent anti-proliferative activity against HUVEC.[246] Finally, in addition to its antitumor properties, depudecin was also identified as a potent anti-protozoal agent against *Neospora caninum*, without any side effects for the host cell.[247]

3.2. Chemistry of Depudecin

Despite the intriguing biological activities of depudecin and its unique molecular structure, it is rather surprising that only one total synthesis has been reported so far, by the group of Schreiber in 1995 (**Scheme 54**).[24] Although this synthesis was a long linear synthesis, it was able to provide enough amounts of synthetic (-)-depudecin for further biological studies. As depicted in **Scheme 54**, the synthesis was based on an asymmetric methodology that used a one-pot procedure for the stereoselective conversion of *syn*-vicinal diols **448** into *trans*-epoxides **449**, proceeding in 23 steps with an overall yield of 0.7% from (-)-diethyl D-tartrate (**451**). This synthesis also required the previously

[239] Itazaki, H.; Nagashima, K.; Sugita, K.; Yoshida, H.; Kawamura, Y.; Yasuda, Y.; Matsumoto, K.; Ishii, K.; Uotani, N.; Nakal, H.; Terui, A.; Yoshimatsu, S.; Ikenishi, Y.; Nakagawa, Y. *J. Antibiot.* **1990**, *43*, 1524–1532.
[240] Sugita, K.; Yoshida, H.; Matsumoto, M.; Matsutani, S. *Biochem. Biophys. Res. Commun.* **1992**, *182*, 379–387.
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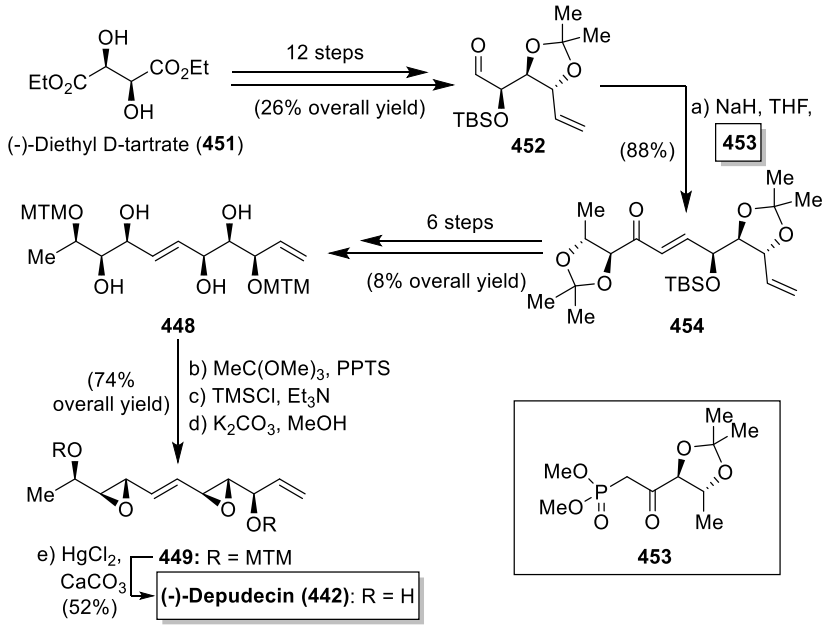
[242] (a) Salisbury, C. M.; Cravatt, B. F. *J. Am. Chem. Soc.* **2008**, *130*, 2184-2194. (b) Wang, C.; Schroeder, F. A.; Wey, H.-Y.; Borra, R.; Wagner, F. F.; Reis, S.; Kim, S. W.; Holson, E. B.; Haggarty, S. J.; Hooker, J. M. *J. Med. Chem.* **2014**, *57*, 7999-8009.
[243] (a) Montero-Melendez, T.; Dalli, J.; Perretti, M. *Cell Death Different.* **2013**, *20*, 567-575. (b) Raynal, N. J.-M.; Si, J.; Taby, R. F.; Gharibyan, V.; Ahmed, S.; Jelinek, J.; Estécio, M. R. H.; Issa, J.-P. J. *Cancer Res.* **2012**, *72*, 1170-1181.
[244] A possible similar irreversible inhibition has been demonstrated for the potent HDAC inhibitors trapoxins: Taunton, J.; Collins, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10412-10422.
[245] Shimada, J.; Kwon, H. J.; Sawamura, M.; Schreiber, S. L. *Chem. Biol.* **1995**, *2*, 517–525.
[246] Oikawa, T.; Onozawa, C.; Inose, M.; Sasai, M. *Biol. Pharm. Bull.* **1995**, *18*, 1305–1307.
[247] Kwon, H. J.; Kim, J.-H.; Kim, M.; Lee, J.-K.; Hwang, W.-S.; Kim, D.-Y. *Veter. Parasitol.* **2003**, *112*, 269-276.

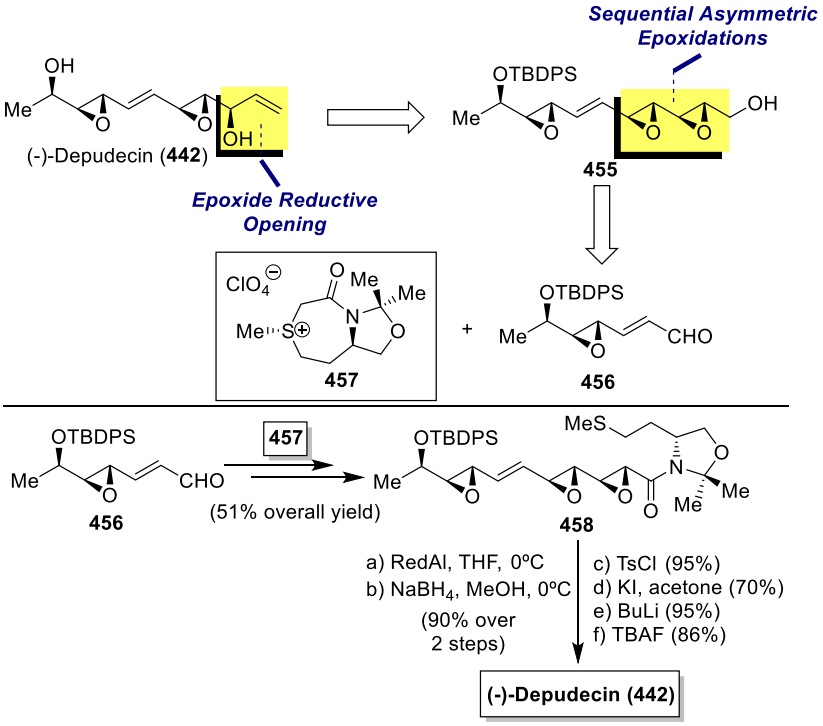
preparation of the phosphonate **453** in order to obtain the linear chain with the *trans* double bond contained in the natural depudecin, through a Wittig-Horner reaction with aldehyde **452** (**Scheme 54**).



Scheme 54. Total Synthesis of (-)-Depudecin (Schreiber et al. 1995)[245]

Prompted by its striking biological properties and enticing structure, we decided to initiate a research program directed towards the synthesis of natural depudecin and analogues. Our initial synthetic plan was based on a linear synthetic strategy, whose retrosynthetic analysis is depicted in **Scheme 55**, and was recently culminated with the total synthesis of (-)-depudecin.[248] Accordingly, we envisioned triepoxy alcohol **455** as a direct precursor of depudecin via an epoxide reductive elimination process. For the preparation of **455**, we devised the use of a new class of chiral sulfonium salts (**457** and *ent*-**457**), developed in our laboratories,[249,250] for the stereoselective construction of the oxirane rings contained in the natural product. Thus, we prepared triepoxy amide **458** in a remarkable 51% overall yield over 6 steps and with complete stereoselectivity from α,β-unsaturated aldehyde **456**, involving a sequential formation of a diepoxide system mediated by sulfonium salt **457**. From this highly valuable tri-epoxide amide, the completion of the synthesis of depudecin was achieved without problems through triepoxy alcohol **455** proceeding in 17 steps and 19% overall yield from (+)-methyl D-lactate (**462**) (**Scheme 55**).

[248] García-Ruiz, C.; Cheng-Sánchez, I.; Sarabia, F. *Org. Lett.* **2015**, *17*, 5558-5561.
[249] (a) Sarabia, F.; Chammaa, S.; García-Castro, M.; Martín-Gálvez, F. *Chem. Commun.* **2009**, 5763-5765. (b) Sarabia, F.; Vivar-García, C.; García-Castro, M.; Martín-Ortiz, J. *J. Org. Chem.* **2011**, *76*, 3139-3150. (c) Sarabia, F.; Vivar-García, C.; García-Castro, M.; García-Ruiz, C.; Martín-Gálvez, F.; Sánchez-Ruiz, A.; Chammaa, S. *Chem. Eur. J.* **2012**, *18*, 15190–15201.
[250] Synthetic applications of sulfonium salts **457** and *ent*-**457**: (a) Sarabia, F.; Martín-Gálvez, F.; Chammaa, S.; Martín-Ortiz, L.; Sánchez-Ruiz, A. *J. Org. Chem.* **2010**, *75*, 5526–5532. (b) Sarabia, F.; Chammaa, S.; García-Ruiz, C. *J. Org. Chem.* **2011**, *76*, 2132–2144. (c) Martín-Gálvez, F.; García-Ruiz, C.; Sánchez-Ruiz, A.; Valeriote, F. A.; Sarabia, F. *ChemMedChem* **2013**, *8*, 819–831. (d) Sarabia, F.; Martín-Gálvez, F.; García-Ruiz, C.; Sánchez-Ruiz, A.; Vivar-García, C. *J. Org. Chem.* **2013**, *78*, 5239-5253. (e) Sarabia, F.; Vivar-García, C.; García-Ruiz, C.; Sánchez-Ruiz, A.; Pino-González, M. S.; García-Castro, M.; Chammaa, S. *Eur. J. Org. Chem.* **2014**, 3847–3867. (f) García-Ruiz, C.; Cheng-Sánchez, I.; Sarabia, F. *Synthesis* **2016**, *48*, 1655-1662.



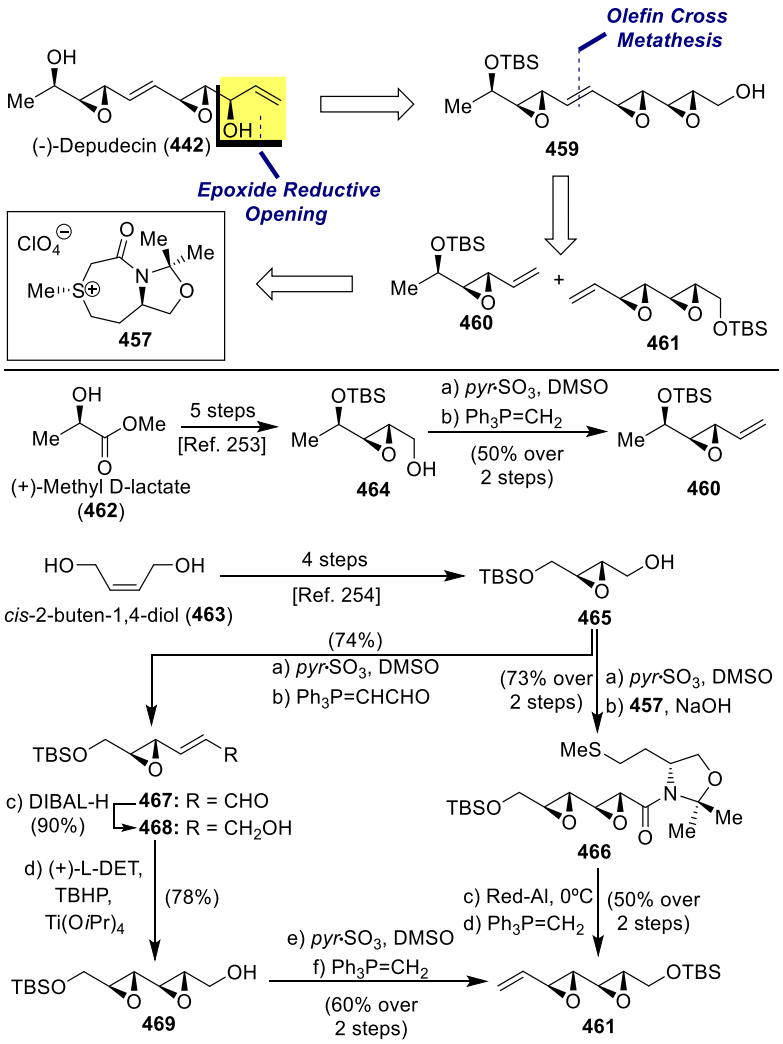
Scheme 55. Total Synthesis of (-)-Depudecin: The Linear Approach (Sarabia et al. 2015)[248]

In order to develop an improved and expeditious access to natural depudecin, as well as to access additional analogues for further biological screenings, we decided to explore a synthetic alternative based on a olefin cross-metathesis strategy as a shorter and more convergent approach.

3.3. Total Synthesis of (-)-Depudecin based on an Olefin Cross-Metathesis Approach

For the new synthesis of depudecin, we conceived of a convergent approach wherein an olefin cross-metathesis reaction would serve as the key step to join the terminal olefins **460** and **461**. Thus, according to the retrosynthetic analysis depicted in **Scheme 56**, (-)-depudecin (**442**) could be obtained again from a triepoxy alcohol (**459** in this case) via an epoxide reductive elimination process[251] in the synthetic direction. This triepoxy alcohol **459**, in turn, could be delivered from a key olefin cross-metathesis of compounds **460** and **461**. The preparation of these metathesis precursors was envisioned to be readily feasible from the commercially available (+)-methyl-D-lactate (**462**) and *cis*-2-buten-1,4-diol (**463**), respectively. The synthesis of the required precursors proceeded as shown in **Scheme 56**.

[251] Nicolaou, K. C.; Duggan, M. E.; Ladduwahetty, T. *Tetrahedron Lett.* **1984**, *25*, 2069-2072.



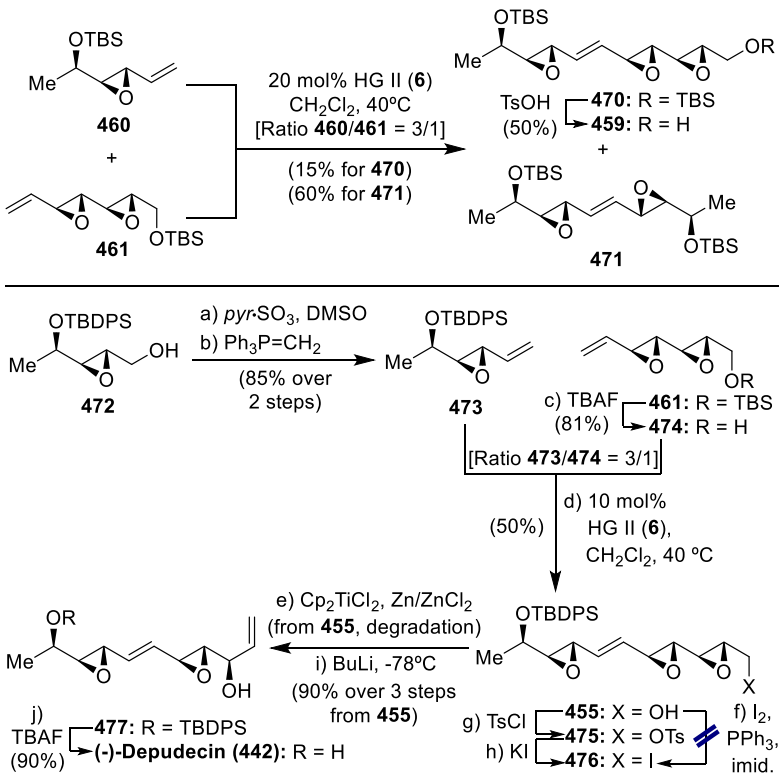
Scheme 56. The Convergent Approach to (-)-Depudecin via Olefin Cross-Metathesis: Synthesis of the Precursors

Thus, we begun with the synthesis of **460** starting from **462**, which was transformed into epoxy alcohol **464** via a Sharpless asymmetric epoxidation (SAE),[252] from the corresponding allylic alcohol.[253] From epoxy alcohol **464**, the synthesis continued by a two step sequence, involving oxidation and Wittig reaction, to obtain **460** in a 50% overall yield. For the other key fragment **461**, we planned to start from the known epoxy alcohol **465**,[254] obtained from *cis*-2-buten-1,4-diol (**463**) in 4 steps. From **465**, the construction of the second oxirane ring was achieved via the sulfonium salt **457** by reacting the aldehyde derived from a Parikh-Doering oxidation of **465**,[255] to obtain diepoxy amide **466** in a remarkable 73% over two steps and complete stereoselectivity.[250f] Subsequent reduction of **466** with Red-Al, followed by a Wittig reaction, afforded alkene **461** in 50% yield over 2 steps. Alternatively, diepoxy olefin **461** was also obtained via a Sharpless asymmetric epoxidation (SAE) of allylic alcohol **468**, resulting from the reduction of the α,β-unsaturated aldehyde **467**, to provide diepoxy alcohol **469**, which

[252] Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.
[253] Stivala, C. E.; Zakarian, A. *Org. Lett.* **2009**, *11*, 839-842.
[254] (a) Bhunia, N.; Das, B. *Synthesis* **2015**, *47*, 1499-1509. (b) Eppley, A. W.; Totah, N. I. Tetrahedron **1997**, *53*, 16545-16552.
[255] Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

was transformed into the olefin **461** in 60% yield over two steps (**Scheme 56**). Comparatively, the overall yields for both synthetic routes are similar (36.5 and 31%, respectively), with the advantage of the sulfonium salt route being shorter than the SAE path.

With both key fragments in hand, we investigated the viability of the cross-metathesis reaction. For the assembly of both epoxy olefin units, a cross-metathesis of alkenes under the influence of the Hoveyda-Grubbs 2nd generation catalyst (**6**) (see **Figure 1** in **Chapter 1**) was initially attempted.[256] The result was the cross-metathesis product **470**, however in a very low yield (15%), and with the homodimerization compound **471**, as the major product (60%). Various reaction conditions and stochiometries of the involved alkenes were evaluated, including second cycles of metathesis, but these failed to improve the yield of the desired product in all cases. Despite the yield of this reaction being variable and generally modest, we were able to access **459** by a selective deprotection step of the primary alcohol, which was accomplished in the presence of TsOH, resulting in the key triepoxy alcohol **459**, in a 50% yield (**Scheme 57**).



Scheme 57. The Convergent Approach to (-)-Depudecin via Olefin Cross-Metathesis: Completion

Despite these discouraging results, we decided to press forward with the synthetic strategy by exploring the cross-metathesis from different precursors. To this aim, we reasoned that the placement of a more bulky protected group on the hydroxyl group of the lactate fragment could reduce the dimerization process thus favoring the cross-

[256] For related olefin cross-metathesis reactions involving epoxy olefins see: (a) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831-4832. (b) McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, *4*, 593-595.

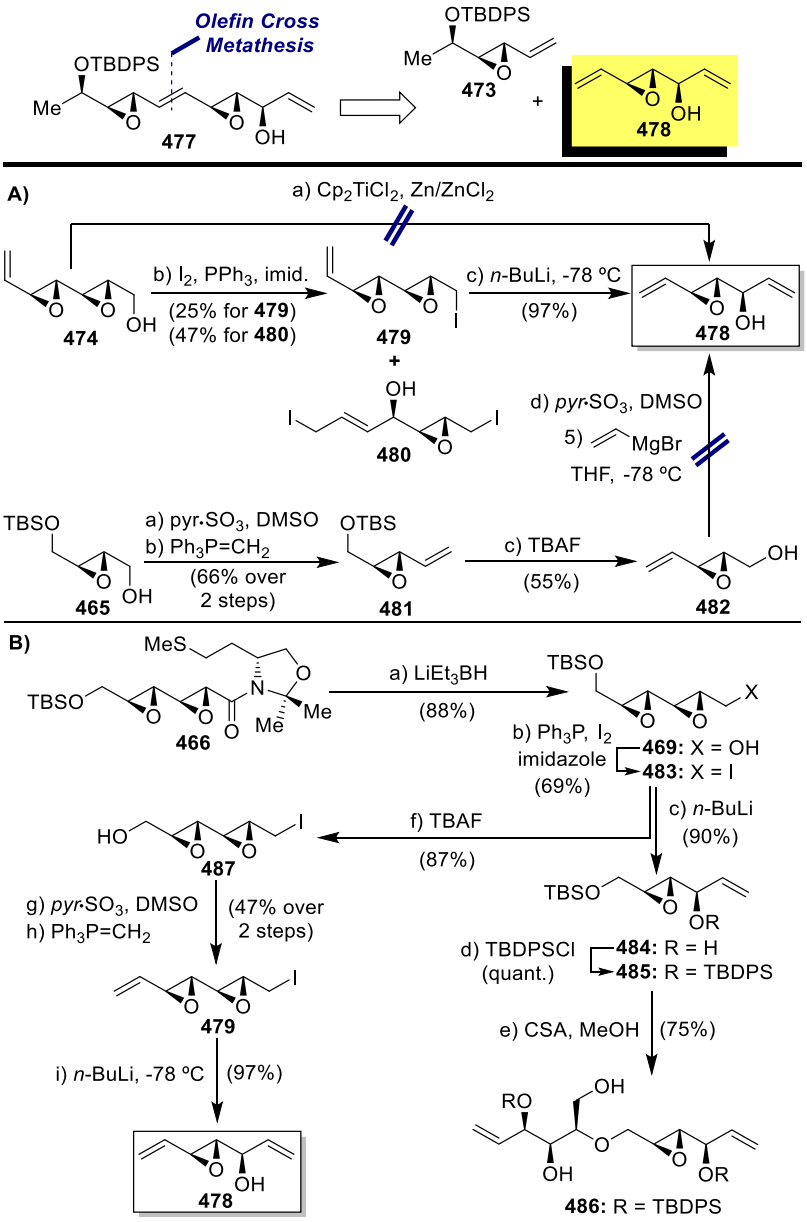
metathesis reaction. Therefore, we considered a second attempt with the TBDPS derivative **473**, prepared in the same way as for **460** from the known epoxy alcohol **472**.[248] On the other hand, we decided to use the unprotected diepoxy olefin **474**, as the other metathesis precursor, with the purpose of obtaining a product more closer to depudecin, and without the requirement of additional selective deprotection steps.

To our delight, the crucial cross-metathesis reaction between precursors **473** and **474**, in the presence of HG-II (**6**) catalyst in refluxing dichloromethane, proceeded smoothly to afford the coveted cross-metathesis product **455** in a reasonable and reproducible 50% yield, exclusively as the *E*-isomer, with no detection of the corresponding dimer of **473** (**Scheme 57**). With compound **455** in hand, we proceeded to completion of the synthesis of (-)-depudecin. To this end, we initially attempted a straightforward synthesis of depudecin derivative **477** from triepoxy alcohol **455** through a titanocene-assisted epoxide reductive opening.[257] In this event, triepoxy alcohol **455** was subjected to the combined action of Cp_2TiCl_2/Zn. Unfortunately, the result of this reaction was a complex mixture of decomposition products, with none of the desired protected depudecin **477** detected. Similarly discouraging was the attempt of preparing iodide **476** directly from **455** by treatment with iodine/Ph_3P in the presence of imidazole, which also resulted in a complex mixture of degradation products. Given these unsuccessful results in our attempt to shorten the number of steps for the completion of the synthesis of depudecin, we returned to our synthetic sequence employed in our first total synthesis. Fortunately, we were able to improve the yields of the subsequent transformations after optimization of the reaction conditions. Thus, the alcohol **455** was converted into the corresponding alcohol **477**, through tosylation and subsequent displacement of the intermediate tosylate **475** with NaI, to obtain iodide **476**, which was then subjected to treatment with BuLi and no further purification. As a result, the resulting alcohol **477** was obtained in a 90% overall yield over three steps from **455**. The final deprotection step provided natural depudecin (**442**), similarly in an improved yield (90% versus 86% in our first total synthesis) (**Scheme 57**). The physical and spectroscopic properties of synthetic **442** were in accordance to those reported for the natural compound.[15,23]

In light of these encouraging results, we devised the possibility of a direct cross-metathesis reaction between olefin **473** and diolefin **478** that would furnish the direct precursor **477** in a single step (**Scheme 58**). It is important to consider that this metathesis reaction is prone to give a mixture of different products, due to the presence of two terminal olefins in **478**. However, a possible coordination involving the allylic alcohol and the catalyst could arrest the catalytic cycle at this terminal olefin to favor the metathesis in the desired direction.[258] To this end, we proceeded with the synthesis of compound **478**, whose synthesis was more difficult than initially expected, despite its

[257] Yadav, J. S.; Shekharam, T.; Gadgil, V. R. *J. Chem. Soc. Chem. Commun.* **1990**, 843-844.
[258] Despite a coordination between the allylic alcohol and the catalyst has been proposed to justify the failure of the cross-metathesis reaction (see Gurjar, M. K.; Yakambram, P. *Tetrahedron Lett.* **2001**, *42*, 3633-3636), there is some controversy at this respect because other authors have reported the opposite effect for this type of systems. In this case, see: Maishal, T. K.; Sinha-Mahapatra, D. K.; Paranjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43*, 2263-2267.

small size. Initially, we attempted the direct reductive opening of diepoxy alcohol **474**, again by the action of a titanocene reducing agent. As in the case for compound **455**, the reaction was completely unsuccessful.

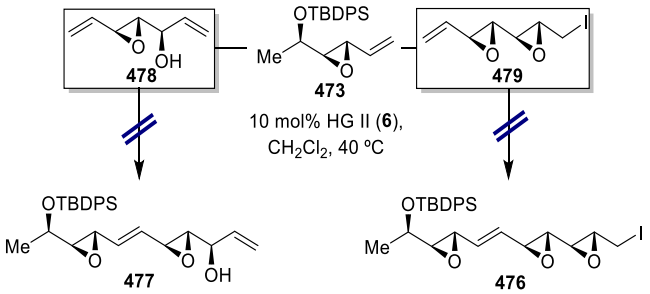


Scheme 58. A Direct Cross-Metathesis Approach to (-)-Depudecin: Synthesis of Precursor **478**

Thus, we proceeded with the preparation of iodide **479** by direct iodination of **474** to obtain **479** albeit in a poor yield (25%), due to the formation of the diiodide **480** in a 47% yield, as the main product. Despite this disappointing yield, iodide **479** was subjected to the action of BuLi to provide the targeted diolefin **478**, in almost quantitative yield. Given the poor yield of the iodination step, we attempted the synthesis of this compound via a tosylate derivative. However, the result was similarly disappointing due to competing ring opening reactions of the oxirane with the halides present in the reaction mixture, during both the tosylation, as well as during the nucleophilic iodination step. The

low yielding conversion of diepoxy alcohol **474** to the target **478**, through iodide **479**, prompted us to investigate various other synthetic alternatives. Thus, in a second attempt, we prepared epoxy alcohol **482**[259] from **465**, in order to construct the hydroxy allylic system via a vinyl magnesium bromide addition to the resulting aldehyde. However, after oxidation of **482**, the reaction with the Grignad reagent failed to deliver the desired product (**Scheme 58, part A**).

In a third alternative route, we chose to test the approach involving early stage installation of the allylic alcohol system, in order to construct at a later time, the terminal olefin adjacent to the epoxide. Thus, starting from **469**, which was readily obtained from diepoxy amide **466**, compound **484** was efficiently synthesized and then elaborated for the introduction of the other terminal olefin. In particular, after protection of **484** as a TBDPS ether, the selective deprotection of the primary alcohol of the resulting *bis*-silyl ether **485** afforded, unfortunately, compound **486** as a result of the opening of the resulting epoxy alcohol by another epoxy alcohol molecule. Finally, in a fourth attempt, from iodide **483**, we decided to prepare olefin **479** prior to the reductive opening process. Thus, desilylation of iodide **483** was followed by an oxidation step of the resulting alcohol **487**, followed by a Wittig reaction, to afford **479** in a modest 47% overall yield. From iodide **479**, the synthesis of **478** proceeded in a similar manner as described above (**Scheme 58, part B**). With the diolefin **478** in hand, the cross-metathesis reaction was attempted under the same conditions as previously described for the synthesis of **455**. To our dismay, the reaction was completely unsuccessful, with the formation of a complex mixture of compounds and no detection of any cross-metathesis product, such as the desired **477**. In a modified attempt to obtain additional direct precursor of depudecin, we tried the cross-metathesis of olefins **473** and **479**. Unfortunately, the result was similarly disappointing with no detection of the desired product **476** (**Scheme 59**).

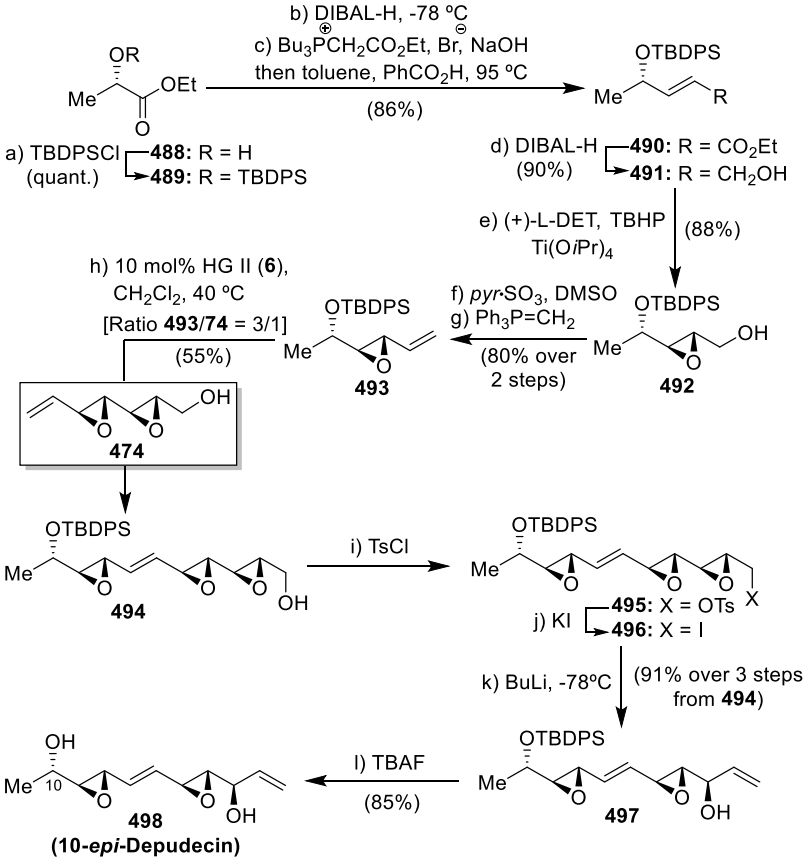


Scheme 59. Attempts of the Direct Cross-Metathesis Approach

[259] Epoxy alcohol **482** has been described in the literature, being prepared by other methodology: Al-Rawi, S.; Hinderlich, S.; Reutter, W.; Giannis, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 4366-4370.

3.4. Synthesis of Stereoisomeric Analogues of (-)-Depudecin and Homodepudecin

Due to the previous unsatisfactory results, the direct approach to depudecin was abandoned in favor of the route described in **Scheme 57**. Having secured a cross-metathesis strategy for this natural product, we decided to pursue depudecin analogues utilizing this methodology. Since the oxirane rings appears to be essential and required for the biological activity of depudecin, we decided to retain these functional groups within the designed analogues, considering therefore depudecin stereoisomers as the most interesting and promising compounds from a biological standpoint. In this sense, we considered as prime candidates the 10-*epi* analogue of depudecin, compound **498**, and the enantiomer, (+)-depudecin (*ent*-**442**), which would be obtained from the readily available (-)-ethyl L-lactate (**488**) as a common starting material



Scheme 60. Total Synthesis of 10-*epi*-depudecin (**498**)

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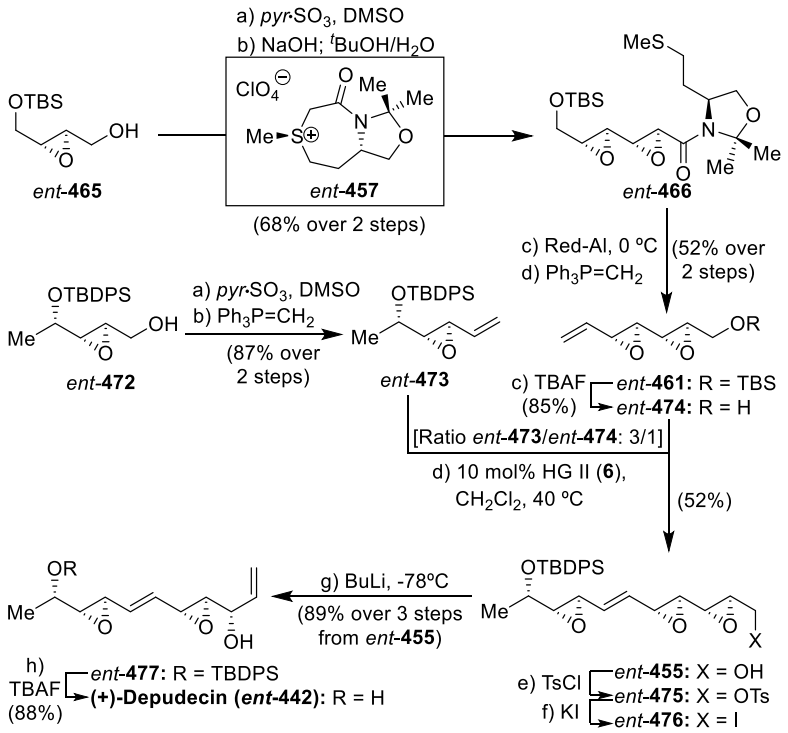
In the case of the 10-*epi* analogue of depudecin, the synthesis of the precursor **493** was carried out from (-)-ethyl L-lactate (**488**) in an efficient and stereoselective manners (54% yield over 7 steps) via a tandem Wittig-Martin[260]/SAE, according to the sequence depicted in **Scheme 60**.[261] Then, following on our previously developed strategy to

[260] Harcken, C.; Martin, S. F. *Org. Lett.* **2001**, *3*, 3591-3593.
[261] The synthesis of allylic alcohol **491** has been described in the literature according to a slightly modified protocol: Crimmins, M. T.; Jacobs, D. L. *Org. Lett.* **2009**, *11*, 2695–2698.

depudecin, we subjected **493** to a cross-metathesis reaction with **474** to afford product **494** in a reasonable 55% yield. From **494**, the completion of depudecin analogue **498** followed the same synthetic sequence as for (-)-depudecin (**442**) through compounds **495**-**497** and in similar yields (**Scheme 60**).

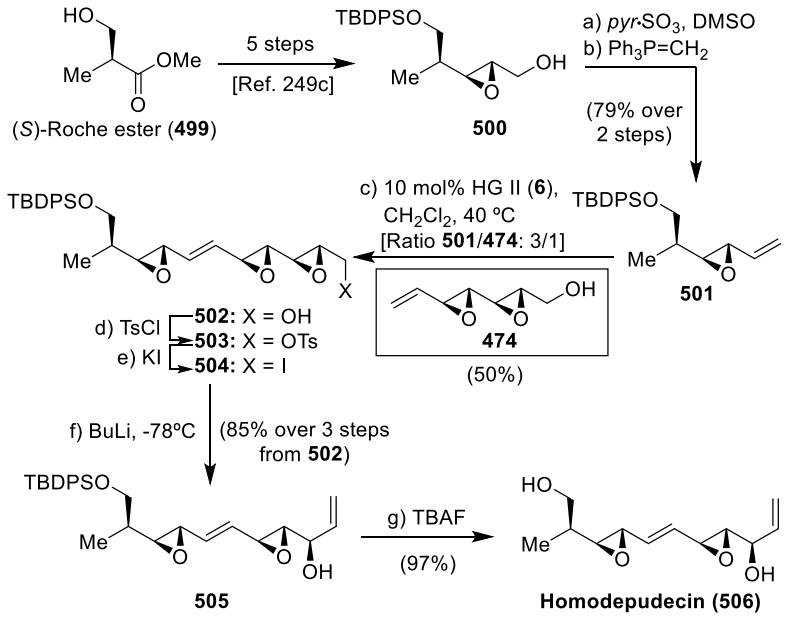
Finally, for the synthesis of the enantiomer of depudecin, the compounds *ent*-**473** and *ent*-**474** were prepared without any difficulty via Sharpless asymmetric epoxidation for *ent*-**473**, from the corresponding allylic alcohol **491**, through epoxy alcohol *ent*-**472**,[262] and via chiral sulfonium salt *ent*-**457** for *ent*-**474**. Both olefinic precursors were then joined via a cross-metathesis reaction to afford *ent*-**455** in a 52% yield, which was taken on to (+)-depudecin (*ent*-**442**) as described above for the natural product (**Scheme 61**).



Scheme 61. Synthesis of (+)-depudecin (***ent*-442**)

In addition, we extended this methodology to the synthesis of homodepudecin **506**, a new structural analogue of (-)-depudecin (**Scheme 62**). Its synthesis started from epoxy alcohol **500**, previously obtained from (*S*)-Roche ester (**499**) in 5 steps,[249c] which was transformed into epoxy alkene **501** in 79% over 2 steps. The olefinic precursor **501** was subjected to a cross-metathesis reaction with diepoxy alkene **474** to afford **502** in 50% yield. The completion of the synthesis of homodepudecin **506** from **502** was achieved through the same synthetic sequence described above for (-)-depudecin (**442**).

[262] Epoxy alcohol *ent*-**472** was prepared via Sharpless asymmetric epoxidation from **491** in similar yield and stereoselectivity as described by us for the synthesis of **472** reported in reference 248.



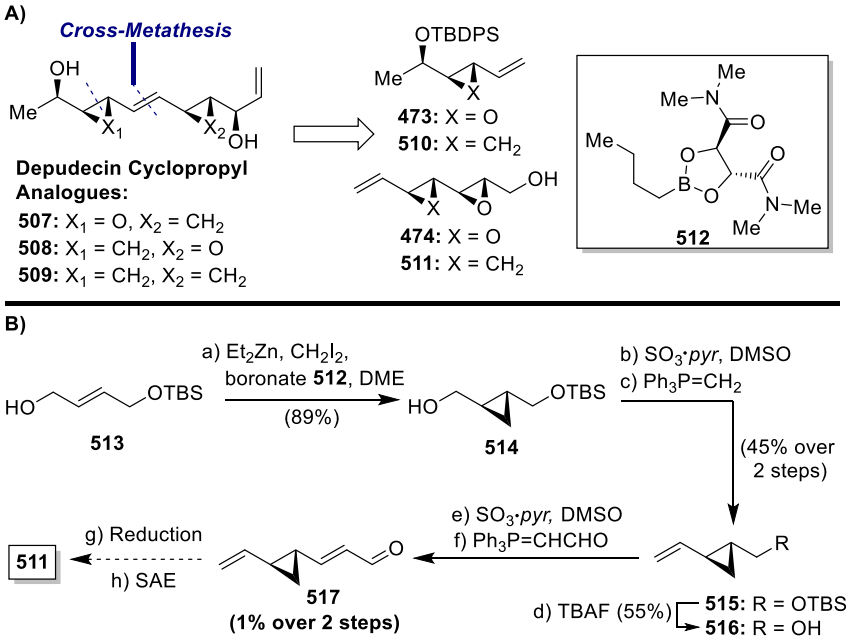
Scheme 62. Synthesis of Homodepudecin (**506**)

3.5. Synthesis of Cyclopropyl and Truncated Analogues of Depudecin

Once we achieved the total syntheses of (-)-depudecin and its stereoisomeric analogues, (+)-depudecin and the epimer at C10 position, as well as homodepudecin, we focused on the extension of the previous synthetic strategy, based on the olefin cross-metathesis reaction, for the generation of cyclopropyl depudecin analogues. The substitution of the oxirane rings by cyclopropyl rings could allow us to prove if the epoxides are essential upon the biological activity in an analogue that keeps the same spatial conformation that the natural product. In addition, we will be able to complete a structure-activity relationship (SAR) study in order to identify new leads based on depudecin.[263] With this objective in mind, we envisioned the synthesis of the cyclopropyl depudecin analogues **507-509** as shown in **Scheme 63**, **part A**, via an olefin cross-metathesis reaction of precursors **473**/**510** and **474**/**511**. The installation of the cyclopropyl rings was planned through a Charette enantioselective cyclopropanation[264] mediated by the chiral dioxaborolane **512**. Thus, we started with the preparation of the required cross-metathesis precursors. For the consecution of compound **511**, allylic alcohol **513** was treated with Et_2Zn, CH_2I_2 and borolane **512** (Charette's reaction conditions) to obtain **514** in high yield (89%). Subsequent Parikh-Doering oxidation of the alcohol **514**, followed by a Wittig reaction and TBS deprotection provided alkene **516** in moderate yields. Thus, alcohol **516** was transformed into the corresponding aldehyde, which was subjected to a subsequent Wittig reaction to yield α,β-unsaturated aldehyde **517** in a disappointing 1% yield over two steps. This unforeseen difficulty found working

[263] For a review about the benefits of the cyclopropyl moiety in preclinical/clinical drugs see: Talele, T. T. *J. Med. Chem*. **2016**, *59*, 8712–8756.
[264] For a review of cyclopropanation strategies see: Ebner, C.; Carreira, E. M. *Chem. Rev*. **2017**, *117*, 11651–11679.

with these substrates was probably due to their highly volatile character that could explain the low yield obtained in the synthetic sequence (**Scheme 63**, **part B**).

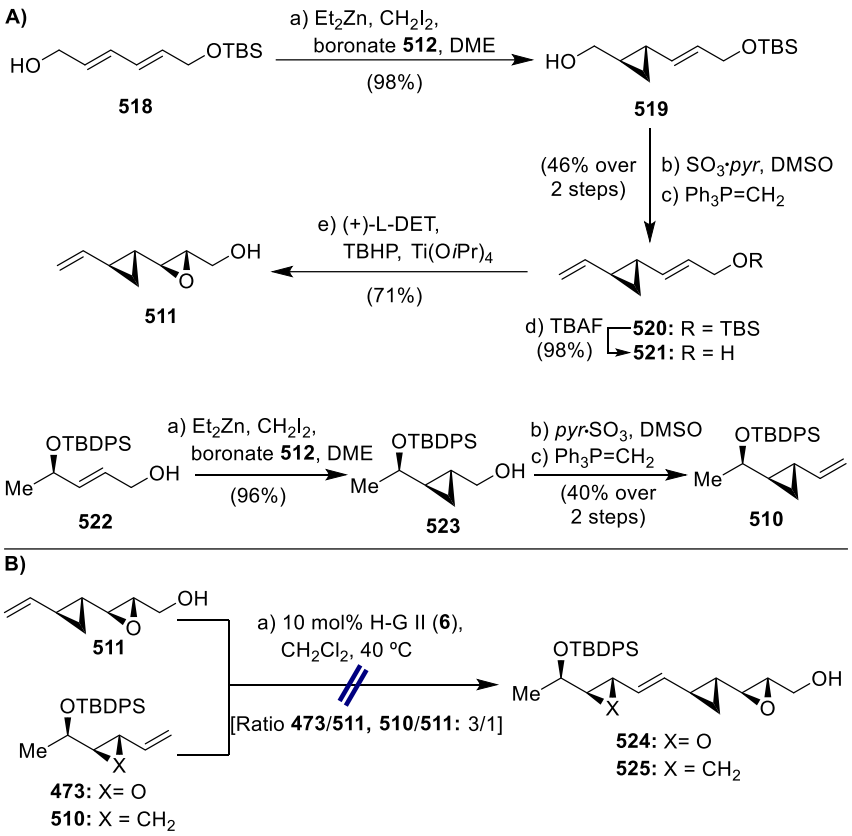


Scheme 63. Retrosynthetic Analysis of Cyclopropyl Depudecin Analogues (A) and Attempts towards the Synthesis of Precursor **511** (B)

With the aim to obtain the cross-metathesis precursor **511** in an efficient manner, we decided to avoid the preparation of the problematic aldehyde **517.** With this purpose, we started the synthesis from the known α,β,γ,δ-unsaturated alcohol **518**,[265] which was subjected to a Charette cyclopropanation to yield cyclopropyl derivative **519** in an excellent 98% yield. Then, a two-steps sequence, involving an oxidation and a Wittig reaction, provided **520**, which was treated with TBAF to obtain allylic alcohol **521**. To our delight, a final Sharpless asymmetric epoxidation of **521** provided metathesis precursor **511** in a 71% yield. In parallel to these synthetic works, we carried out the preparation of the required second metathesis precursor, compound **510**, from allylic alcohol **522** via a Charette cyclopropanation under the same reactions conditions showed above, followed by the introduction of the alkene moiety through an oxidation/Wittig reaction sequence without difficulty (**Scheme 64**, **part A**). For the assembly of cyclopropyl olefin units **511** and **510**, a cross-metathesis of alkenes under the influence of the HG-II (**6**) catalyst in refluxing dichloromethane was attempted. However, despite the use of the same reactions conditions employed in the synthesis of (-)-depudecin and related analogues showed above, in this case the reaction met with failure, without detection of the expected metathesis product **525**, instead starting material together with degradation products were obtained. Additional attempts that included more forcing conditions (toluene, 100 ºC) and other catalysts (Grubbs 1st and 2nd generations, Hoveyda-Grubbs 1st generation) were thwarted, with similar results than before. These disappointing results pointed out that the cyclopropyl rings may play a key role in the

[265] Dias, L. C.; de Luca, Jr. E. C. *J. Org. Chem*. **2017**, *82*, 3019–3045.

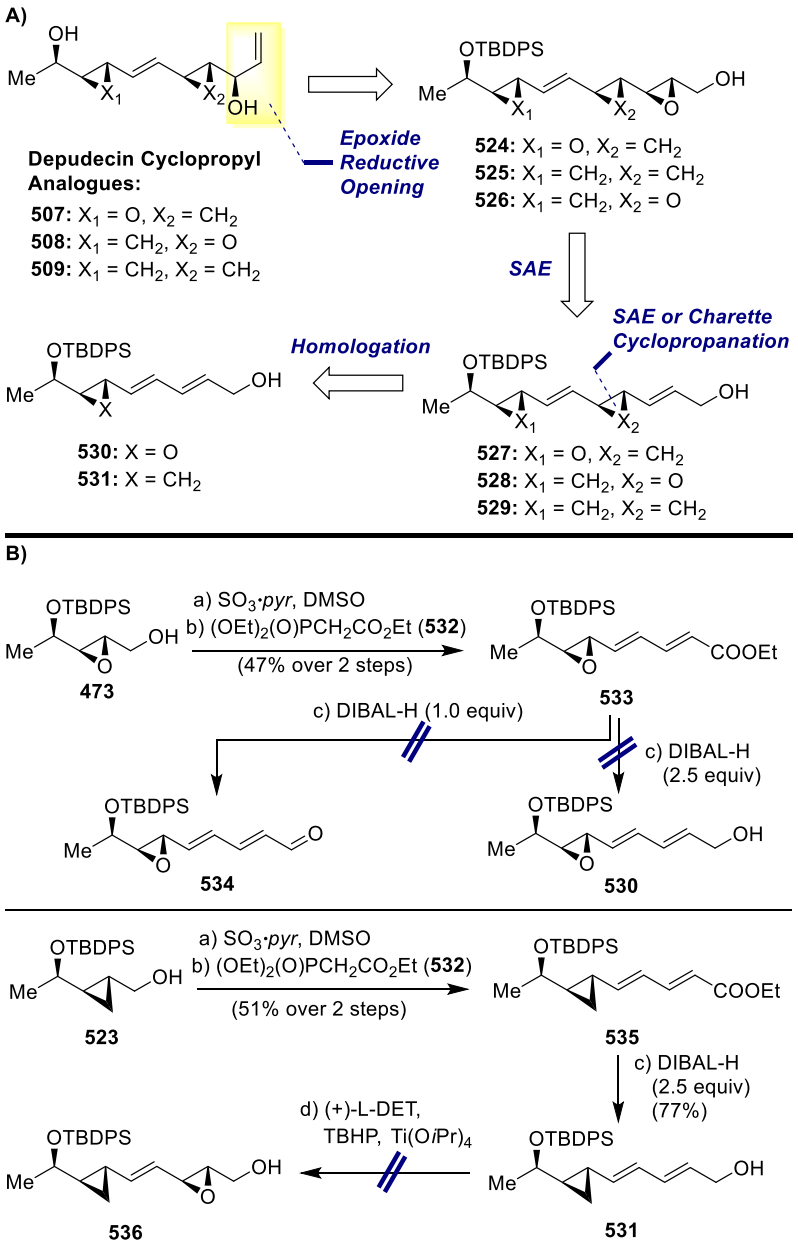
outcome of this reaction. In a last attempt, we carried out the cross-metathesis reaction of compounds **511** and **473** under the same reaction conditions for related cases. Unfortunately, the result of this reaction was similar as the previous case, with no detection of the desired compound **524** (**Scheme 64**, **part B**).



Scheme 64. Towards the Synthesis of Cyclopropyl Depudecin Analogues via Cross-Metathesis Reaction: Synthesis of Precursors **510** and **511** (A) and Attempts of the Cross-Metathesis Reaction (B)

Due to the failure of the cross-metathesis reaction, we decided to use a linear strategy in order to access these cyclopropyl analogues. This new synthetic plan was based on the retrosynthetic analysis depicted in **Scheme 65**, **Part A**. Thus, the key precursors **524-526** could be achieved via Sharpless asymmetric epoxidation (SAE) from the allylic alcohols **527-529**. In turn, **527-529** could be obtained through a SAE or Charette cyclopropanation from α,β,γ,δ-unsaturated alcohol **530** or **531** followed by a subsequent homologation reaction. With this synthetic plan in mind, we started with the synthesis of α,β,γ,δ-unsaturated ester **533** from epoxy alcohol **473** through a two-steps sequence involving a Parikh-Doering oxidation followed by a Wittig reaction yielding **533** in 47% over two steps. The next seemingly simple reduction of this ester however proved more problematic than expected. For example, treatment of **533** with DIBAL-H provided a complex mixture of degradation products, with no detection of the expected alcohol **530**. Others attempts of reduction, for example the use of 1.0 equiv of DIBAL-H to obtain the corresponding aldehyde **534** met in failure with similar results as the previous case. We surmised that the reason of the failure of this reduction was due to the

epoxide opening as a side reaction.[266] This hypothesis was confirmed when we carried out the reduction of the α,β,γ,δ-unsaturated ester **535**, under the same reaction conditions than for **533**, yielding in this case the desired alcohol **531** in 77% yield. Unfortunately, on this occasion, the subsequent Sharpless asymmetric epoxidation (SAE) of **531** did not yield the expected epoxy alcohol **536**, instead a complex mixture of degradation products were obtained. Several attempts of this reaction confirmed the difficulties of such SAE (**Scheme 65**, **Part B**).



Scheme 65. Towards the Synthesis of Cyclopropyl Depudecin Analogues via Linear Strategy: Retrosynthetic Analysis (A) and Attemps of Synthesis of **530** and **531** (B)

[266] For epoxide opening competing with ester reduction in a similar structural system see: Takamura, H.; Wada, H.; Lu, N.; Kadota, I. *Org. Lett*. **2011**, *13*, 3644–3647.

The failures of the cross-metathesis reaction in the convergent strategy as well as the reduction and SAE reactions in the linear strategy towards the cyclopropyl depudecin analogues forced us to abandon the preparation of these analogues in favour of truncated depudecin analogues. The design of these new analogues was based on structural modifications which would allow us to complete a preliminary structure-activity relationship (SAR) study for depudecin. With this aim, we decided to prepare truncated analogues which could retain or modify the hydroxyl groups, the oxirane rings and/or the olefins contained in the natural depudecin in order to test the effect of these functional groups upon the biological activity. Futhermore, the stereochemistry of the designed analogues could be modified or retained. The proposed truncated depudecin analogues **537**-**544** are shown in **Figure 8**.

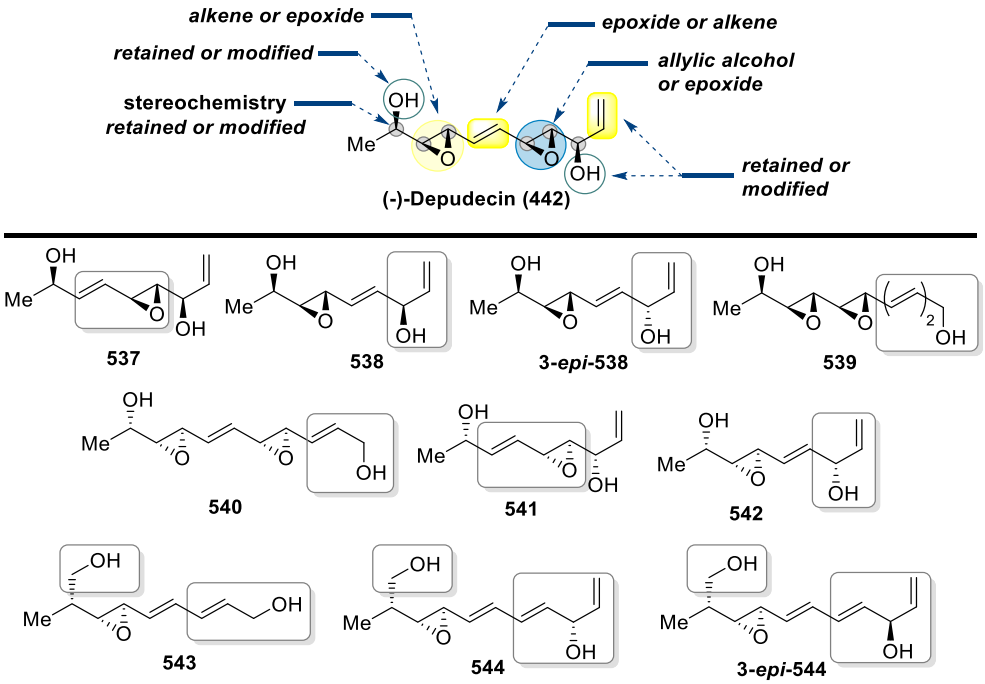
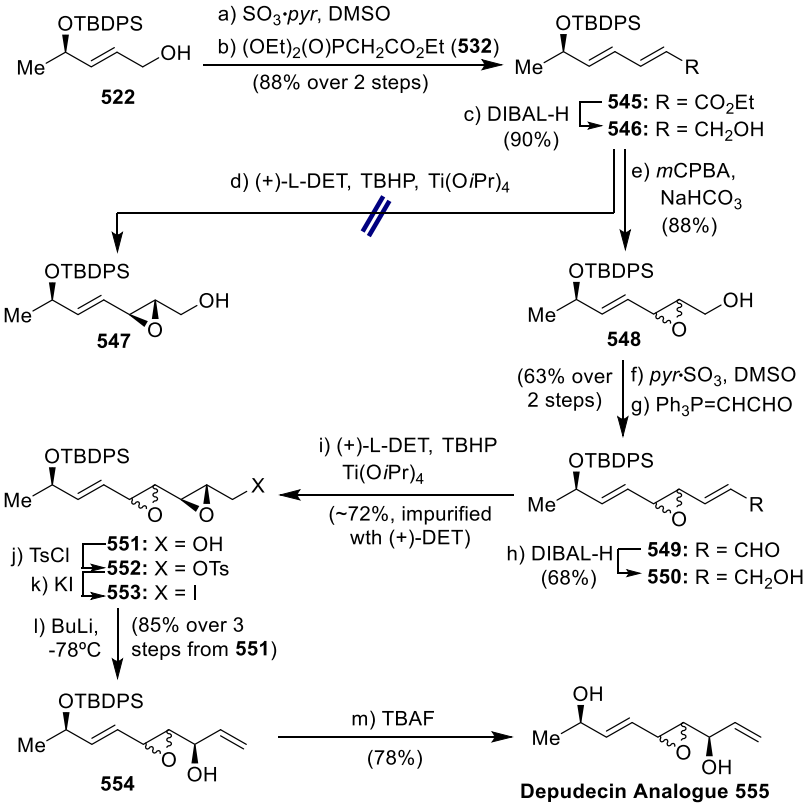


Figure 8. Proposed Truncated Depudecin Analogues

With this purpose, for the synthesis of analogue **537** we started from α,β-unsaturated ester **545** obtained from allylic alcohol **522** in two steps, which was transformed into α,β,γ,δ-unsaturated alcohol **546** by use of DIBAL-H in a 90% yield. However, the next Sharpless asymmetric epoxidation (SAE) of **546** did not provided the corresponding epoxy alcohol **547**. The result of this SAE was similarly than for previously shown allylic alcohol **531**, instead a complex mixture of degradation products were obtained. In order to avoid this problematic SAE, we decided to carry out the epoxidation reaction by use of *m*-CPBA, obtaining epoxy alcohol **548** in a 88% yield as a 1:1 inseparable mixture of diastereoisomers. Then, **548** was transformed into α,β-unsaturated aldehyde **549** in a 63% yield over two steps and was followed by DIBAL-H reduction of **549** to provide allylic alcohol **550** in a 68% yield. In this case, the SAE provided diepoxy alcohol **551** (~72%, impurified with (+)-DET after column chromatography) which was undertaken under a similar three-steps sequence as in

previous cases (tosyl protection/iodation/reductive elimination) to obtain allylic alcohol **554** in a 85% overall yield. To complete the synthesis, a final TBDPS deprotection step by treatment of **554** with TBAF afforded depudecin analogue **555** as a inseparable mixture of isomers (ratio 1:1). Despite this stereochemical outcome, this mixture of isomers could be of interest for the planned SAR study (**Scheme 66**).

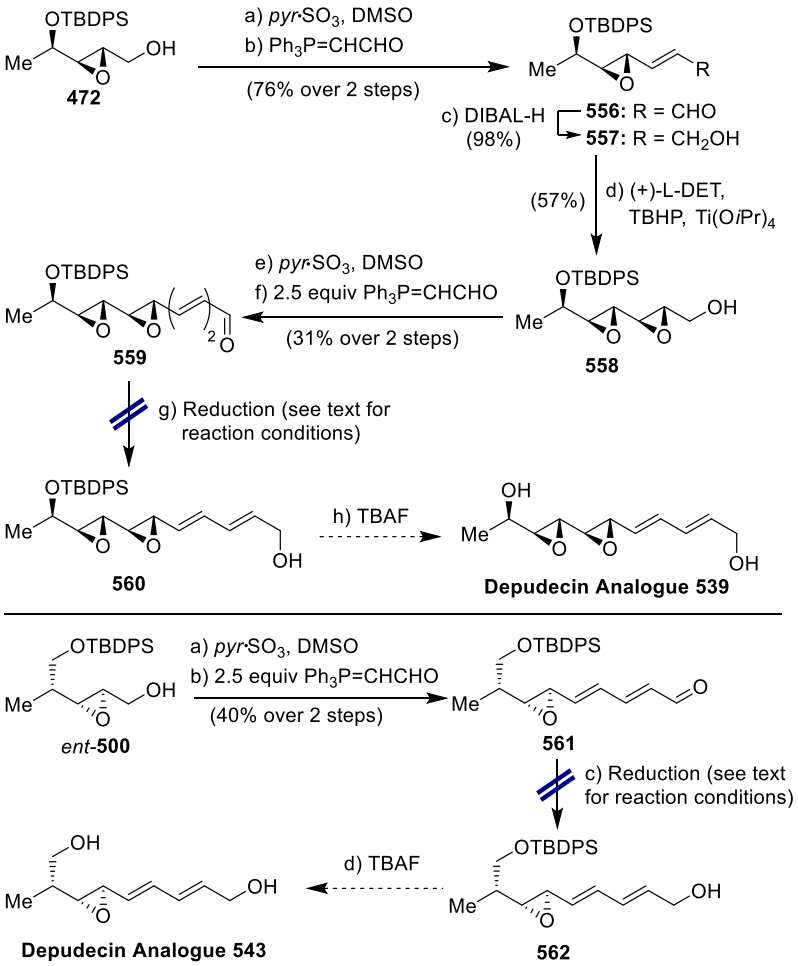


Scheme 66. Towards the Synthesis of Truncated Depudecin Analogues: Synthesis of Analogue **555**

The synthetic efforts towards analogue **539** started from epoxy alcohol **472** which was transformed into diepoxy alcohol **558** in four steps and good yields, as shown in steps a)-d) in **Scheme 67**. Then, diepoxy alcohol **558** was oxidized to the corresponding aldehyde and was followed by treatment with excess of Ph_3P=CHCHO to afford the α,β,γ,δ-unsaturated aldehyde **559** in a modest 31% yield over two steps. Once again, as in the previous case for the reduction of α,β,γ,δ-unsaturated ester **533**, the next seemingly simple reduction of aldehyde **559** was found to be very problematic. Thus, a first attempt of reduction of **559** with DIBAL-H afforded a complex mixture of degradation products, with no detection of alcohol **560**. We surmised that the reason of the failure of this reduction was due to the competition of the 1,2- and 1,4-hydride additions. Others attempts of reduction, for example the selective 1,2-reduction under Luche's conditions[267] or even the selective reduction by the action of 9-BBN[268] met in failure with similar results as the previous case. Indeed, the same problem was found in the the preparation of depudecin analogue **543** during the reduction of the α,β,γ,δ-unsaturated aldehyde **561**

[267] Luche, J. L. *J. Am. Chem. Soc*. **1978**, *100*, 2226-2227.
[268] Krishnamurthy, S.; Brown, H. C. *J. Org. Chem*. **1977**, *42*,1197-1201.

in order to obtain alcohol **562** (**Scheme 67**). Similarly disappointing were the synthetic attempts towards analogues **538**, 3-*epi*-**538**, **542**, **544** and 3-*epi*-**544**, for which the last TBDPS deprotection step did not afford the expected products, instead a complex mixture of unidentified degradation products were obtained in all cases (**Scheme 68**).

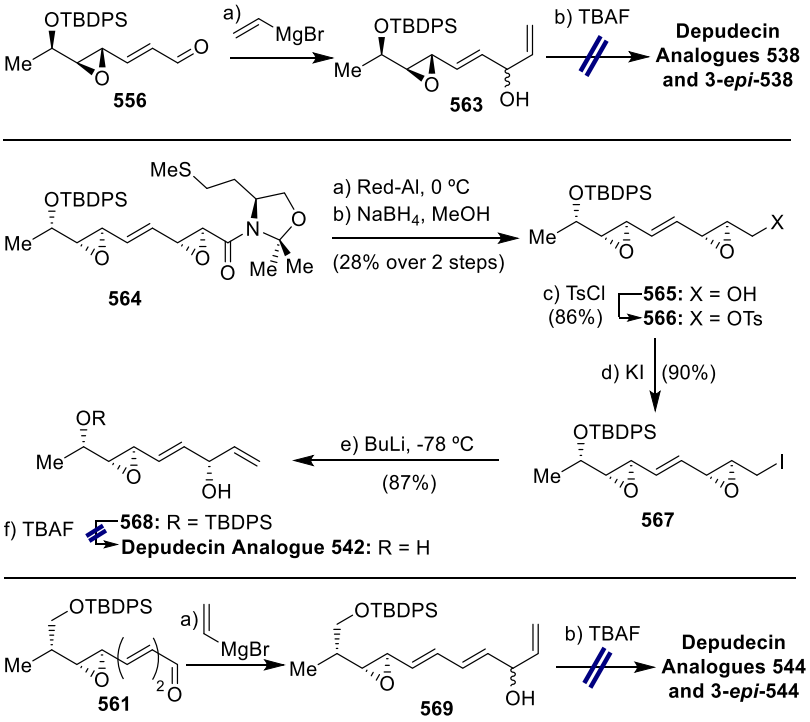


Scheme 67. Towards the Synthesis of Truncated Depudecin Analogues: Attempts towards the Synthesis of Analogues **539** and **543**

In light of these discouraging results, we focused our efforts in the synthesis of the last two remaining proposed truncated depudecin analogues, compounds **540** and **541** (**Scheme 69**). For this purpose, we decided to take advantage of the chemistry of sulfonium salts in order to avoid the problems that appeared in the reduction reactions of α,β,γ,δ-unsaturated esters or aldehydes as well as in the SAE of α,β,γ,δ-unsaturated alcohols, that proved more problematic than expected. Thus, we started from epoxy amide **564**[269] which was subjected to a two-steps sequence, involving a Red-Al reduction followed by a Wittig-Martin reaction, to yield α,β-unsaturated ester **570** in 28% yield over two steps. Subsequent reduction of **570** by treatment with DIBAL-H afforded allylic alcohol **571**, albeit in a poor yield (22%). To complete the synthesis, TBDPS group in

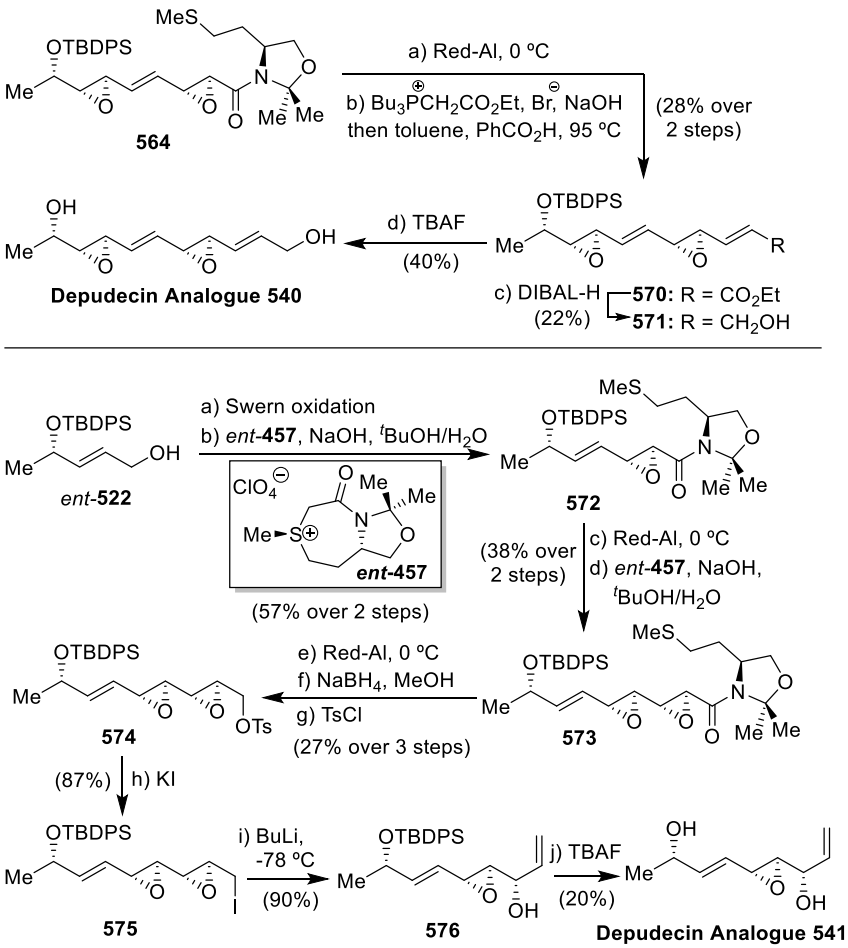
[269] Epoxy amide **564** was prepared in exactly the same manner as its enantiomer reported in reference 248.

571 was removed by use of TBAF to obtain depudecin analogue **540** in a 40% yield (**Scheme 69**).



Scheme 68. Towards the Synthesis of Truncated Depudecin Analogues: Attempts towards the Synthesis of Analogues **538**, 3-*epi*-**538**, **542**, **544** and 3-*epi*-**544**

For the consecution of depudecin analogue **541**, we started from allylic alcohol *ent*-**522**, which was subjected to a Swern oxidation to obtain the corresponding aldehyde. The crude obtained aldehyde was then reacted with the sulfonium salt *ent*-**457** to obtain epoxy amide **572** in 57% over two steps. Epoxy amide **572** was treated with Red-Al and the resulting epoxy aldehyde reacted with sulfonium salt *ent*-**457** to obtain diepoxy amide **573** in a 38% over two steps. Then, treatment of diepoxy amide **573** with Red-Al followed by $NaBH_4$ afforded the corresponding diepoxy alcohol which was then tosylated to obtain **574** in 27% over three steps from **573**. Subsequent iodide displacement of the tosyl group in **574** was followed by a reductive epoxide opening process by the action of BuLi to provide **576** in 90% yield. Finally, a deprotection step of the TBDPS group in **576** afforded depudecin analogue **541** in 20% yield (**Scheme 69**).



Scheme 69. Towards the Synthesis of Truncated Depudecin Analogues: Synthesis of Analogues **540** and **541**

3.6. Biological Evaluation of (-)-Depudecin and Analogues

At this stage of the work, where we were able to complete the synthesis of natural depudecin as well as various analogues, we decided to stop the synthetic work and explore the biological activities of the synthesized compounds. In collaboration with the group of Prof. Ana R. Quesada from the Molecular Biology and Biochemistry Department of Málaga University, we carried out preliminary biological evaluations based on the measure of the antitumoral properties of the selected compounds against a panel of various tumor cell lines. The selected compounds for this study were the (-)-depudecin (**442**), its enantiomer, (+)-depudecin (*ent*-**442**), the 10-*epi*-depudecin (**498**) and the truncated analogues **540**, **541** and **555** (**Figure 9**). In a preliminary evaluation, we examined the cytotoxicity activity of such compounds using four different cancer cell lines (HL-60, MDA-MB-231, HT-1080 and U87MG), as well as a primary culture of non transformed bovine aorta endothelial (BAEC) cells to test antiangiogenic effect[270] (**Table 1**).

[270] Cárdenas, C; Quesada, A. R.; Medina, M. A. *Cell. Mol. Life Sci.* **2006**, *63*, 3083–3089.

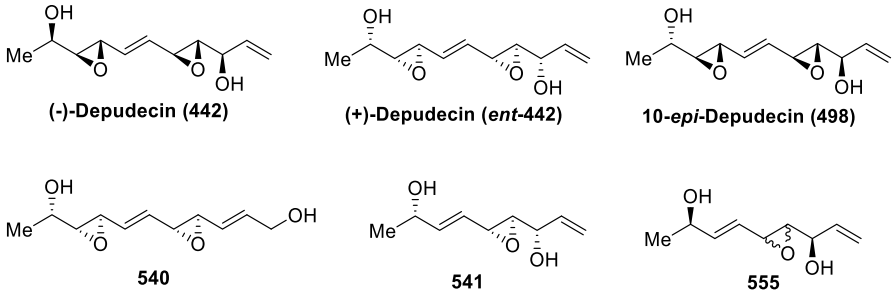


Figure 9. Synthesized (-)-Depudecin and Analogues Submitted to Biological Evaluation

Table 1. *In vitro* Antitumor Activities of Depudecin and Analogues against Various Tumor Cell Lines and BAEC (IC_{50}, μM)[a]

Compound	BAEC[b]	HL60[c]	MDA-MB-231[d]	HT-1080[e]	U87MG[f]
(-)-depudecin (442)	24,1 ± 3,5	28,7 ± 6,4	45 ± 11,8	44,9 ± 3,9	85,6 ± 0.6
(+)-depudecin (*ent*-442)	> 100	78,6 ± 6,7	> 100	> 100	> 100
10-*epi*-depudecin (498)	37,5 ± 7,5	31,1 ± 1,7	53,8 ± 6,3	43,3 ± 3,1	> 100
540	52,1 ± 5,0	46,8 ± 6,2	61,1 ± 3,2	50,5 ± 0,7	84,6 ± 6,9
541	38,0 ± 7,5	34,3 ± 9,6	55,6 ± 1,4	42,63 ± 2,9	> 100
555	> 100	39,8 ± 6,7	> 100	> 100	> 100

[a] *In vitro* cytotoxicities were determined according to the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide dye reduction assay. The IC_{50} values were obtained from semilogarithmic dose-response plots as the concentration of compound yielding a 50% of cell survival. [b] BAEC: Non transformed bovine aortic endothelial cells. [c] HL60: Human promyelocytic leukemia. [d] MDA-MB-231: Human breast adenocarcinoma. [e] HT1080: Human fibrosarcoma. [f] U87MG: Gioblastoma.

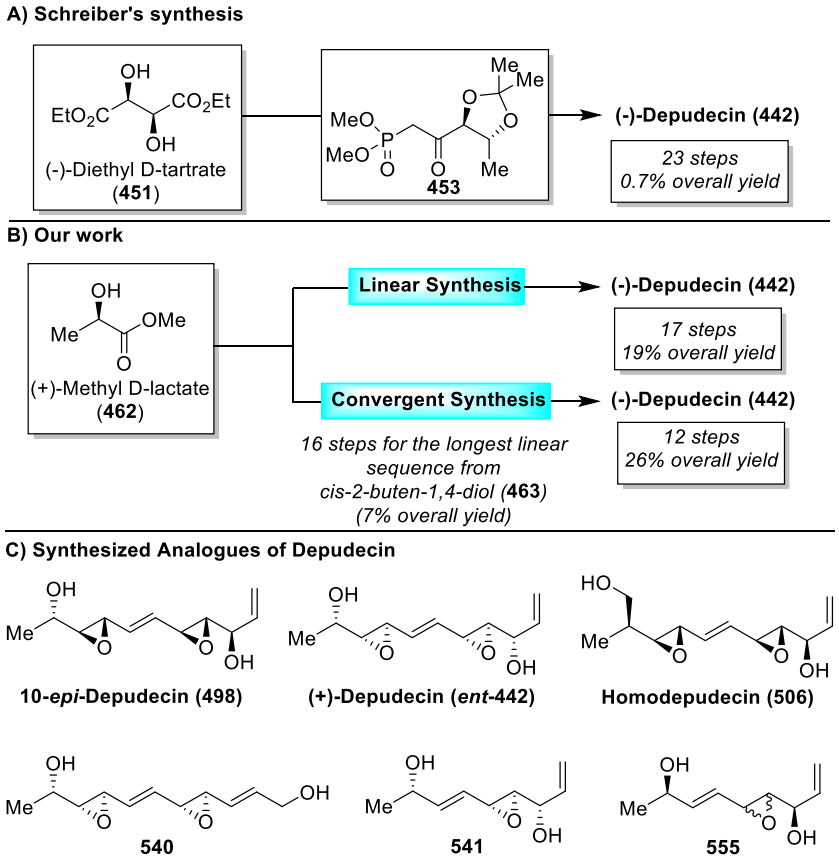
The results of these biological evaluations clearly revealed that (-)-depudecin (**442**) displayed the best biological values for the series in the moderate μM range against all the tumoral cell lines. In addition, (-)-depudecin (**442**) was also cytotoxic against the endothelial cells line (BAEC), which may indicate a putative antiangiogenic effect of this compound.[270] The analogues 10-*epi*-depudecin (**498**), **540** and **541** showed a close IC_{50} value compared with (-)-depudecin. In contrast, the enantiomer of depudecin (*ent*-**442**) and analogue **555** were practically devoid of antitumor activity, except for the HL-60 cell line in the case of **540**, but moderately.

From these results it is important to highlight the importance of the stereochemistry upon the biological activity, as concluded when biological activities of (+)-depudecin (*ent*-**442**) and (-)-depudecin (**442**) are compared. However, by considering the activities of other analogues, especially compounds **540** and **541**, it is difficult to conclude that the stereochemistry is the only determinant for the observed biological activities due to the antitumor activities are not significantly different except for (+)-depudecin and compound **555**. We could conclude safely that the C-10 stereochemistry of (-)-depudecin is not important by comparing the activity with that of compound **498**. On the other hand, the similar IC_{50} values of analogue **541** compared with (-)-depudecin (**442**) in almost all the cancer cell lines tested, including BAEC, clearly shows that the simultaneous presence of the two epoxide groups is not essential upon the biological activity, due to the removal of a epoxide group in analogue **541** did not cause the loss of

the antitumoral activity. Finally, when (+)-depudecin (*ent*-**442**) is compared with analogue **540**, we can concluded that the terminal allylic system is not key upon the biological activity since the isomer **540** showed best values of inhibition for all the cancer cell lines tested.

3.7. Summary

In conclusion, we have established a new synthesis of (-)-depudecin (**442**), which greatly improves upon our previous linear synthesis. Comparatively, whereas the first total synthesis, reported by Schreiber, required 23 linear steps from (-)-diethyl D-tartrate (**451**), with an overall yield of 0.7%, our first linear synthesis from (+)-methyl D-lactate (**462**) was achieved in 17 steps in a 19% overall yield (**Scheme 70**). As continuation of our previous work, we have developed a second generation synthetic route to depudecin utilizing an olefin cross-metathesis reaction as the key step, which was successfully achieved in a convergent manner to provide (-)-depudecin (**442**) in only 12 steps and 26% overall yield from **462**. In addition, the synthetic route was amenable to stereochemical and functional modifications, allowing the preparation of two stereoisomers of (-)-depudecin, the 10-*epi*-depudecin (**498**) and its enantiomer (*ent*-**442**), as well as homodepudecin (**506**), which represent unique analogues that will further assist us to evaluate the influence of the stereochemistry and functional modifications upon biological activity.



Scheme 70. Summary of the Syntheses of Depudecin and Analogues

Futhermore, we have complemented the set of analogues with the preparation of truncated analogues **540**, **541** and **555**. The synthesized products (-)-depudecin, (+)-depudecin, 10-*epi*-depudecin and the truncated analogues were biologically evaluated against several tumor cell lines, including endothelial cells and the results led us to complete a preliminary structure-activity relationship (SAR) study for this intriguing natural product concluding that: a) the C-10 stereochemistry of the product is not essential upon the biological activity; b) the presence of at least one of the epoxide groups is key upon the biological activity, but it is not necessary the simultaneous presence of both epoxides; and c) the terminal allylic alcohol system is not essential, and it can be substitued by its isomer (**Figure 10**).

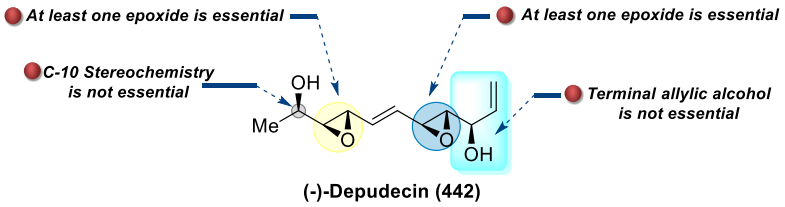


Figure 10. Preliminary Structure-Activity Relationship (SAR) study of Depudecin

Chapter 4[†]

Solomonamide Campaign

[†] Part of this chapter has been published as the following journal papers: (a) Cheng-Sánchez, I.; García-Ruiz, C.; Sarabia, F. *Tetrahedron Lett.* **2016**, *57*, 3392-3395. (b) Cheng-Sánchez, I.; Carrillo, P.; Sánchez-Ruiz, A.; Martínez-Poveda, B.; Quesada, A. R.; Medina, M. A.; López-Romero, J.; Sarabia, F. *J. Org. Chem.* **2018**, *83*, 5365-5383. (c) Carillo, P.; Martínez-Poveda, B.; Cheng-Sánchez, I.; Guerra, J.; Tobia, C.; López-Romero, J. M.; Sarabia, F.; Medina, M. A.; Quesada, A. R. *Mar. Drugs* **2019**,*17*, 228 (1-18).

4.1. Isolation, Structure and Biology of the Solomonamides

The discovery of new natural products offers significant opportunities for the identification and development of new leads and scaffolds in medicinal chemistry, as well as a great deal of fascination for organic chemists by virtue of their structural diversity and challenging molecular frameworks that many of them exhibit.[271] In particular, the marine world represents a uniquely rich source of new bioactive metabolites with unprecedented structures, fascinating biological profiles and valuable therapeutic potential[272]. The increasing interest for compounds of marine origin in biomedical and pharmaceutical research derives from the potential clinical applications exhibited by them, according to their antitumoral, antiinflammatory, antiangiogenic and/or antimicrobial properties reported.[273]

Marine organisms and more specific sponges, which are considered the largest remaining source of undiscovered natural products, produce a variety of unique chemical classes with wide biological profiles due to the conditions that differ significantly from terrestrial environments, which include aggressive, exigent and competitive surroundings that lead to the production of potent active molecules.[274] Among the myriad of sources for marine natural products, particularly prolific is the marine sponge *Theonella swinhoei*, which has proven to be an impressive source of secondary metabolites,[275] providing at least nine different classes of natural products. In addition to the very well-known and important polyketide swinholide, discovered 30 years ago,[276] the Theonella genus is notable for providing a wide range of bioactive peptidic-type natural products, including acyclic peptides (polytheonamides and koshikamides), cyclic peptides (kombamide, orbiculamide, barangamide, cupolamide, perthamides, etc..), large-ring bicyclic peptides such as the theonellamides, depsipeptides (koshikamides, papuamides, nagahamide or theopapuamide) and glycopeptides.[277] As further proof of the value of the genus Theonella as an outstanding and bountiful source of new peptides, Zampella et al. recently isolated two new cyclopeptides termed the solomonamides A (**577**) and B (**578**), from a Solomon islands collection. These cyclopeptides possessed unique molecular structures and potent *in vivo* anti-inflammatory activities.[278] An exhaustive spectroscopic analysis of both compounds facilitated the elucidation of their intricate cyclic structures, revealing

[271] (a) Samuelsson, G.; Lars, B. *Drugs of Natural Origin*; Swedish Pharmaceutical Press: Stockholm, **2017**, 7th edition. (b) Nicolaou, K. C.; Chen, J. S.; Dalby, S. M. *Bioorg. Med. Chem.* **2009**, *17*, 2290–2303. (c) Grabley, S.; Thiericke, R. *Drug Discovery from Nature*; Springer-Verlag: Berlin, **2000**.

[272] (a) Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, M. R. *Nat. Prod. Rep.* **2017**, *34*, 235–294 and references therein.

[273] (a) Ercolano, G., De Cicco, P., Ianaro, A. *Mar. Drugs* **2019**, *17*, 31 (1-31). (b) Zhang, H., Dong, M., Chen, J., Wang, H., Tenney, K., Crews, P. *Mar. Drugs* **2017**, *15*, 351 (1-29). (c) Martínez-Poveda, B., Quesada, A.R., Medina, M.Á. *Mar. Drugs* 2017, *15*, 325 (1-13). (d) Calcabrini, C.; Catanzaro, E.; Bishayee, A.; Turrini, E.; Fimognari, C. *Mar. Drugs.* **2017**, *15*, 310 (1-34). (e) Ruocco ,N., Costantini, S., Palumbo, F., Costantini, M. *Mar Drugs* 2017, *15*, 173 (1-16). (f) Máximo, P., Ferreira, L.M., Branco, P., Lima, P., Lourenço, A. *Mar. Drugs* 2016, *14*, 139 (1-71). (g) García-Vilas, J.A., Martínez-Poveda, B., Quesada, A.R., Medina, M.Á. *Mar. Drugs* 2016, 14, 1 (1-12).

[274] Gogineni, V.; Hamann, M. T.; *Biochim. Biophys. Acta* **2018**, 1862, 81–196.

[275] Wegerski, C. J.; Hammond, J.; Tenney, K.; Matainaho, T.; Crews, P. *J. Nat. Prod.* **2007**, *70*, 89–94.

[276] Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1985**, *26*, 511–514.

[277] Festa, C.; De Marino, S.; Sepe, V.; Monti, M. C.; Luciano, P.; D'Auria, M. V.; Débitus, C.; Bucci, M.; Vellecco, V.; Zampella, A. *Tetrahedron* **2009**, *65*, 10424–10429 and references therein.

[278] Festa, C.; De Marino, S.; Sepe, V.; D'Auria, M. V.; Bifulco, G.; Débitus, C.; Bucci, M.; Vellecco, V.; Zampella, A. *Org. Lett.* **2011**, *13*, 1532-1535.

the presence of three conventional amino acids (D-Ala, Gly and L-Ser) and an unprecedented 4-amino(2'-amino-4'-hydroxyphenyl)-3,5-dihydroxy-2-methyl-6-oxohexanoic acid (ADMOA) and the corresponding 5-deoxy derivative (AHMOA) for solomonamides A and B, respectively. The absolute configurations were tentatively established by a combination of spectroscopic and theoretical methods, which resulted in the proposal of the depicted absolute configurations as the most likely (**Figure 11**). Not surprisingly, these interesting and novel cyclopeptides were found to possess interesting biological properties. Solomonamide A (**577**) displayed potent anti-inflammatory activity *in vivo*, causing a significant 60% reduction of inflammation at a very low dose (100 μg/Kg). Unfortunately, the extreme scarcity of the solomonamides has precluded a thorough biological evaluation. In fact, the anti-inflammatory activity of solomonamide B (**578**) was not evaluated due to limited amounts. In this regard, the chemical synthesis of these intriguing natural products could represent the solution for this 'problem of supply'.[279]

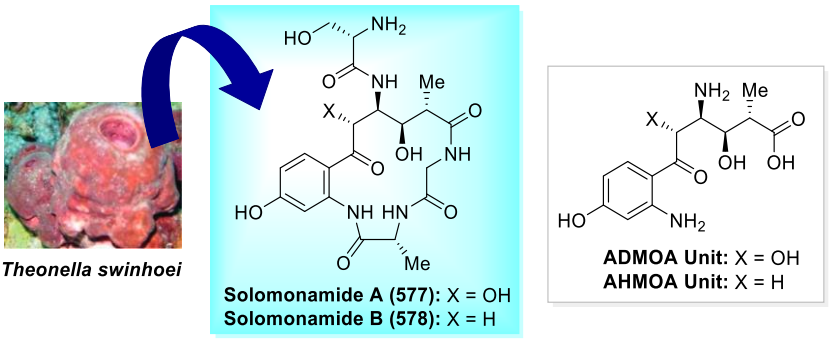


Figure 11. Initially Proposed Molecular Structures of Solomonamides A and B

4.2. Chemistry of the Solomonamides

The extreme scarcity of the isolated solomonamides from the natural sources is a drawback for further pharmacological assays. This difficulty to access large amounts of these compounds from their natural sources makes quite difficult to gain insight into their biological profiles and mechanism of action and justifies the chemical synthesis of these natural products. Thus, the chemical synthesis of these unexplored cyclopeptides could represent a solution to provide enough amounts of material to carry out extensive biological studies and confirm their initially proposed structures. As a consequence, by the time we initiated this research project, the solomonamides had been elicited interest with the publication of some synthetic approaches,[280] including the synthesis of a deoxy analogue of solomonamide B.[281] In parallel with the development of our research work, two new synthetic approaches were published,[282] culminating with the total synthesis of

[279] For a review about the termed 'problem of supply' that has hampered the development of natural-products derived drugs see: Newman, D.J. *Pharmacol. Ther.* **2016**, *162*, 1–9.
[280] (a) Kashinath, K.; Vasudevan, N.; Reddy, D. S. *Org. Lett.* **2012**, *14*, 6222–6225. (b) Kavitha, N.; Kumar, V. P.; Chandrasekhar, S. *Tetrahedron Lett.* **2013**, *54*, 2128–2130. (c) Reddy, D. S.; Kormirishetty, K.; Natrajan, V. WO Patent 2014083578 A1, Nov 27, **2013**.
[281] Vasudevan, N.; Kashinath, K.; Reddy, D. S. *Org. Lett.* **2014**, *16*, 6148–6151.
[282] (a) Kashinath, K.; Dhara, S.; Reddy, D. S. *Org. Lett.* **2015**, *17*, 2090–2093. (b) Kavitha, N.; Chandrasekhar, S. *Org. Biomol. Chem.* **2015**, *13*, 6242–6248.

solomonamide B (**578**),[283] and later solomonamide A (**577**),[284] by the Reddy group. Very recently, the same group has reported the preparation of some stereoisomers of solomonamide macrocycles, by changing the stereochemical pattern of the non-peptide fragment AHMOA.[285] More importantly, the total syntheses of solomonamides A and B led to the revision of the initially proposed structures for **577** and **578**, with the correction of the configurations at C-3 and at C-4 positions to the (3*S*, 4*S*)-isomer (compound **580**) instead of the proposed (3*R*, 4*R*) for solomonamide B (**578**) and the correction of the configuration at C-3, C-4 and C-5 to the (3*S*, 4*S*, 5*S*)-isomer (compound **579**) instead of the proposed (3*R*, 4*R*, 5*R*) for solomonamide A (**577**) (**Figure 12**).

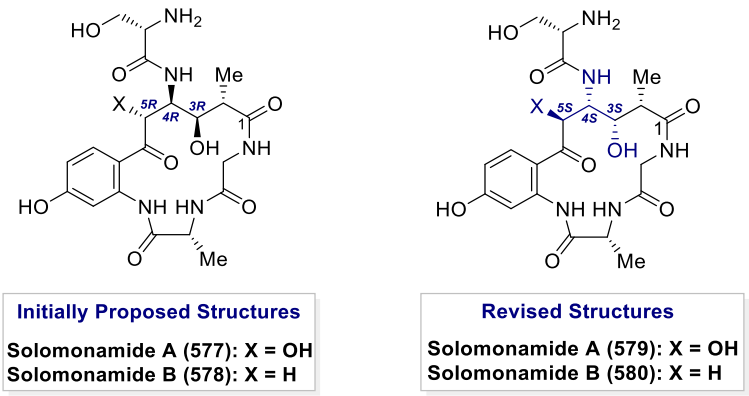
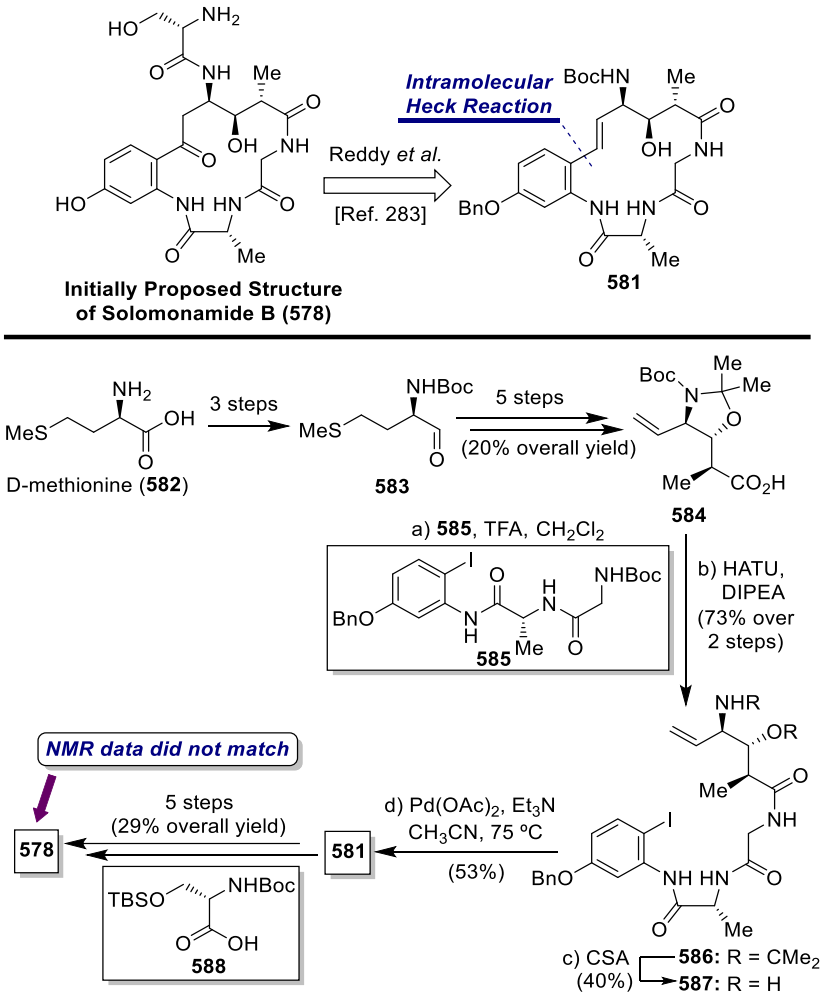


Figure 12. Revised Structures of Solomonamides A and B (Reddy et al. 2016 and 2018)[283, 284]

From the retrosynthetic point of view, the total syntheses of solomonamides accomplished by Reddy et al. were based on a key intramolecular Heck reaction to obtain the macrocyclic core of the solomonamides, represented by compound **581** in **Scheme 71**. Thus, the synthesis started from D-methionine aldehyde **583**, previously prepared from D-methionine **582**, which was transformed into acid **584** in 5 steps, involving a Brown's crotylation as the key reaction to generate the required *syn*-1,2-amino alcohol system. Then, acid **584** was coupled with the amine derived from peptide **585** to obtain iodo derivative **586** in a 73% yield over two steps, followed by the acetal deprotection to afford **587** in a modest 40% yield. The key intramolecular Heck reaction was then carried out by the action of $Pd(OAc)_2$ in presence of triethylamine in a high diluted acetonitrile solution at 75 ºC to obtain compound **581** in a 53% yield. From macrocyclic **581**, the synthesis of **578** was achieved in five additional steps in a 29% overall yield, involving a Boc deprotection, a peptide coupling with serine derivative **588**, a key regioselective Wacker oxidation to install the ketone group and a final removal of protecting groups by hydrogenolysis and TFA (**Scheme 71**).

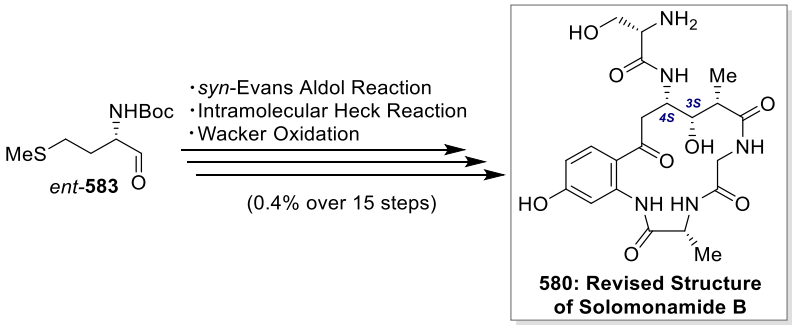
[283] Kashinath, K.; Jachak, G. R.; Athawale, P. R.; Marelli, U. K.; Gonnade, R. G.; Reddy, D. S. *Org. Lett.* **2016**, *18*, 3178–3181.
[284] Jachak, G.; Athawale, P. R.; Agarwal, H.; Barthwal, M. K.; Lauro, G.; Bifulco, G.; Reddy, D. S. *Org. Biomol. Chem*. **2018**, *16*, 9138–9142.
[285] Jachak, G. R.; Athawale, P. R.; Choudhury, R.; Kashinath, K.; Reddy, D. S. *Chem. Asian J.* **2019**, *just accepted*. DOI: 10.1002/asia.201901075



Scheme 71. Total Synthesis of the Initially Proposed Structure of Solomonamide B (**578**) via Intramolecular Heck Reaction (Reddy et al. 2016)[283]

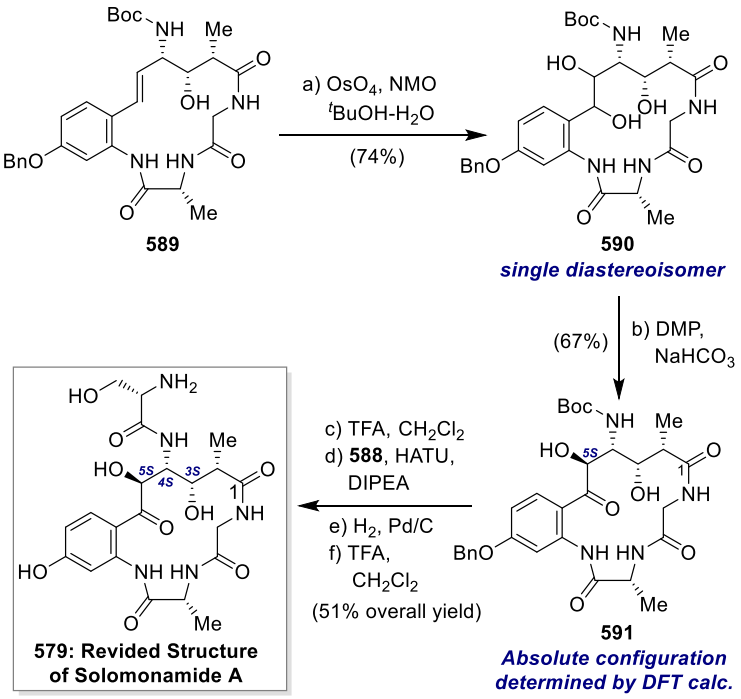
From the retrosynthetic point of view, the total syntheses of solomonamides accomplished by Reddy et al. were based on a key intramolecular Heck reaction to obtain the macrocyclic core of the solomonamides, represented by compound **581** in **Scheme 71**. Thus, the synthesis started from D-methionine aldehyde **583**, previously prepared from D-methionine **582**, which was transformed into acid **584** in 5 steps, involving a Brown's crotylation as the key reaction to generate the required *syn*-1,2-amino alcohol system. Then, acid **584** was coupled with the amine derived from peptide **585** to obtain iodo derivative **586** in a 73% yield over two steps, followed by the acetal deprotection to afford **587** in a modest 40% yield. The key intramolecular Heck reaction was then carried out by the action of $Pd(OAc)_2$ in presence of triethylamine in a high diluted acetonitrile solution at 75 ºC to obtain compound **581** in a 53% yield. From macrocyclic **581**, the synthesis of **578** was achieved in five additional steps in a 29% overall yield, involving a Boc deprotection, a peptide coupling with serine derivative **588**, a key regioselective Wacker oxidation to install the ketone group and a final removal of protecting groups by hydrogenolysis and TFA (**Scheme 71**). However, the spectroscopic data for synthetic solomonamide B did not match with those reported for the natural compound by Zampella

et al.[278] Considering that the relative and absolute configurations of the three stereocenters contained in the polyketide fragment were established through computational methods, Reddy et al. planned to achieve the synthesis of the (3*S*, 4*S*)-isomer instead of the initially proposed (3*R*, 4*R*)-isomer. With this purpose, the authors started from the enantiomer of aldehyde *ent*-**583** which was subjected to a Evans aldol reaction to construct the *syn*-1,2-amino alcohol system which contains the (3*S*, 4*S*)-stereochemistry upon the ADMOA fragment. Then, the same synthetic sequence described above was implemented to complete the synthesis of targeted compound **580** in a 0.4% over 15 steps from aldehyde *ent*-**583**. In this case, the spectroscopic data of synthetic **580** matched with those reported for the natural solomonamide B, therefore confirming the revised structure of solomonamide B (**Scheme 72**).



Scheme 72. Total Synthesis of Revised Structure of Solomonamide B (**580**) via Intramolecular Heck Reaction (Reddy et al. 2016)[283]

As the structure of solomonamide B was derived from solomonamide A, the structure of solomonamide A also needed revision. Due to solomonamide A was biogenetically derived from solomonamide B, the three stereocenters (2*S*, 3*S* and 4*S*) present in solomonamide B should be contained in solomonamide A, thus leaving one stereocenter at the C5 position of the ADMOA fragment whose absolute stereochemistry needed to be fixed, initially established as 5*R*. With this aim, the authors carried out the synthesis of the (3*S*, 4*S*, 5*S*)-isomer instead of the initially proposed (3*R*, 4*R*, 5*R*)-configuration. Thus, macrocyclic compound **589**, previously obtained through the synthesis of the revised solomonamide B was subjected to an Upjohn dihydroxylation to obtain triol **590** in a 74% yield as a single diastereoisomer. The reason for which this last reaction proceeded in a stereoselective manner could be explained by the rigid conformation of the macrocycle through intramolecular H-bonding. Subsequent selective bencylic oxidation by the use of Dess-Martin periodinane (DMP) afforded the α-hydroxy ketone **591** in a 67% yield. From this ketone **591**, compound **579** was obtained in four additional steps, and its spectroscopic data were matching with those reported for the natural solomonamide A. With the aim to confirm the absolute C5-configuration generated during the Upjohn dihydroxylation, the authors employed a QM/NMR approach based on comparison of the experimental ^{13}C NMR chemical shift data and the predicted values calculated at the density functional theory (DFT) level for all the possible theoretical diastereoisomers, concluding the assignment of the C5-configuration as 5*S* (**Scheme 73**).



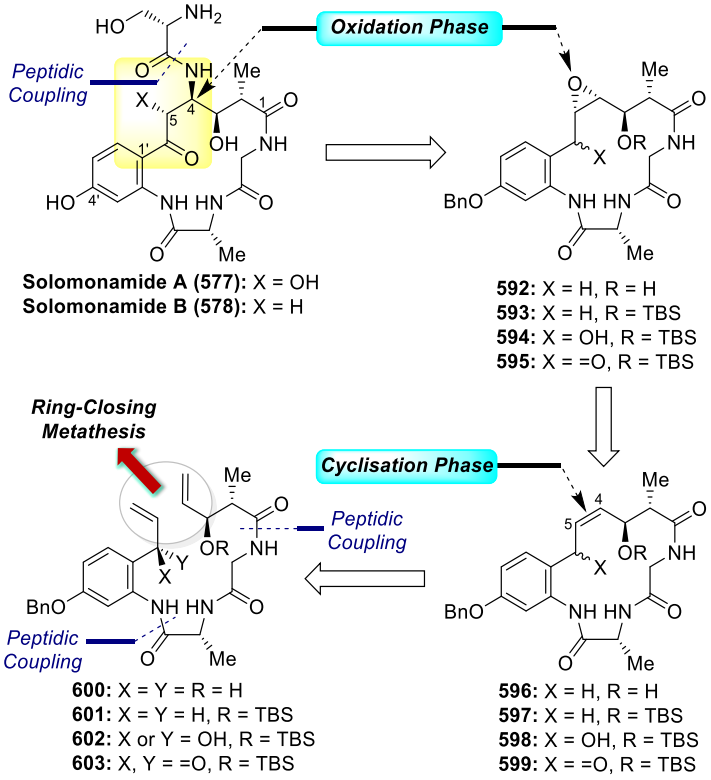
Scheme 73. Total Synthesis of the Revised Structure of the Solomonamide A (**579**) (Reddy et al. 2018)[284]

4.3. An Olefin Metathesis Approach towards the Solomonamides

Our ongoing interest in the discovery and development of new potential leads based on cyclopeptidic- and cyclodepsipeptidaic-type compounds,[286, 250b] prompted us to initiate a research program directed toward the total synthesis of this novel and unexplored class of cyclopeptides. With the aim of establishing a flexible and divergent synthetic strategy capable of providing not only the natural products, but also provide an entry into a plethora of analogues for biological studies, we sought to explore the ring-closing metathesis (RCM) reaction as the key step for construction of the macrocycle. This cyclisation step would be followed by an oxidation phase, which would incorporate the functional groups needed to reach the final oxidation stage found in the natural products. From a strategic perspective, we considered that the construction of the macrocyclic core at the 4,5-bond would be capable of providing rapid access not only to the final products, but also to analogues from late stage intermediates, allowing for the facile entry into numerous scaffolds. Furthermore, it is worthy to note that this synthetic strategy utilizes simple starting materials, avoiding the construction of the complex ADMOA residue, which can be constructed in the later stages of the synthesis through an epoxidation of the olefins **596**-**599**, followed by an oxirane-ring opening process to introduce the amine group. Accordingly, as detailed in **Scheme 74**, our delineated strategy in retrosynthetic terms begins with the straightforward amide disconnection of the L-

[286] (a) Sarabia, F.; Chammaa, S.; Sánchez-Ruiz, A.; Martín-Ortiz, L.; López-Herrera, F. J. *Curr. Med. Chem.* **2004**, *11*, 1309–1332. (b) Sarabia, F.; Chammaa, S. *J. Org. Chem.* **2005**, *70*, 7846–7857. (c) Sarabia, F.; Chammaa, S.; García-Castro, M. *J. Org. Chem.* **2005**, *70*, 7858–7865. (d) Goh, S.; Hohmeier, A.; Stone, T. C.; Offord, V.; Sarabia, F.; García-Ruiz, C.; Good, L. *Appl. Environ. Microbiol.* **2015**, *81*, 5650–5659.

serine residue, followed by the removal of the functional groups, which would be introduced by means of oxidative manipulations (oxidation phase) of the resulting metathesis products. In this way, the synthetic strategy would render the corresponding macrocyclic alkenes represented by the *cis*-$\Delta^{4,5}$ derivatives **596-599**, which would possess or not various functionalities at the benzylic position. All these macrocyclic compounds, in turn, could be obtained from the corresponding acyclic precursors **600-603** via a ring-closing metathesis process (**Scheme 74**). In addition, during the execution of this synthetic work, Reddy et al. published the total synthesis of solomonamide B,[283] based on an intramolecular Heck reaction as described above in **Scheme 71**, and led to the revision of the initially proposed structure for **578**. As the present synthetic studies were initiated prior to the Reddy publication, we targeted the initially proposed structures for the solomonamides.

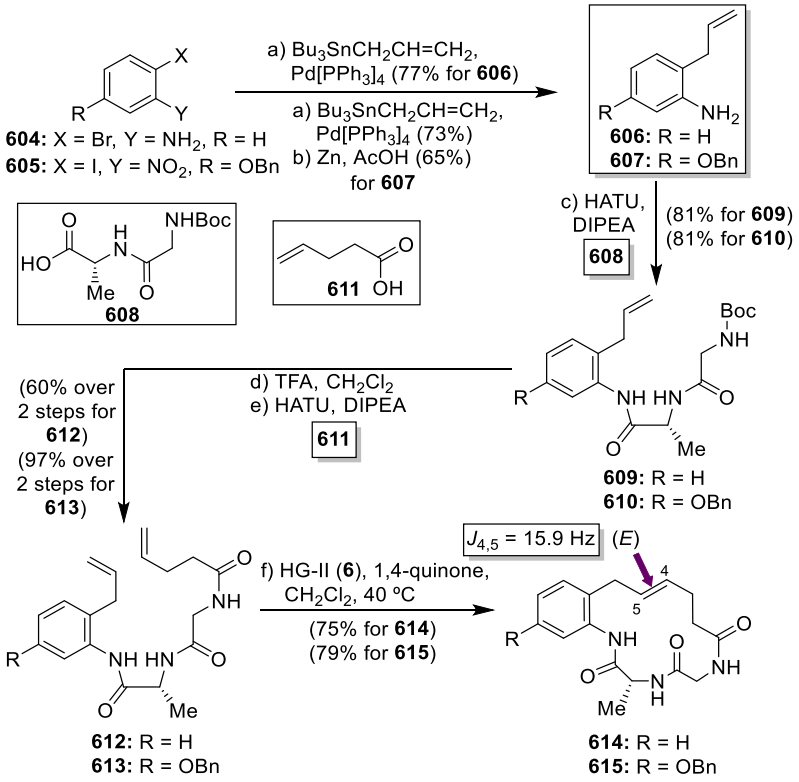


Scheme 74. Retrosynthetic Analysis for the Solomonamides

4.3.1. Ring-Closing Metathesis at the C4-C5 Bond

Encouraged by the appealing features of this synthetic strategy, as mentioned above, we initiated the synthetic route. Our initial forays toward the solomonamide structures were conducted to demonstrate the viability of the olefin metathesis approach, based on the disconnection of the 4,5-positions bond, using the model compounds **614** and **615** (**Scheme 75**). To this end, the readily accessible dipeptides **612** and **613** were

prepared from 2-bromo aniline **604** and the iodonitrobenzene derivative **605**,[287] respectively, according to the synthetic sequence depicted in **Scheme 75**, entailing a Stille reaction for compound **606**, and a sequential Stille reaction/reduction, for compound **607**. Couplings of the resulting anilines **606** and **607** with dipeptide **608**[283] furnished the corresponding dipeptides **609** and **610**, which, after Boc deprotection, were coupled with commercial acid **611** to yield the targeted ring-closing metathesis precursors **612** and **613**. Thus, **612** and **613** were treated with 10 mol% of Hoveyda-Grubbs 2nd generation (HG-II) catalyst in refluxing dichloromethane in the presence of *p*-benzoquinone[288] to obtain the expected macrocycles **614** and **615** in excellent 75 and 79% yields, respectively, as the sole products of the reaction. The newly formed double bonds ($\Delta^{4,5}$) of **614** and **615** were determined in both cases to be exclusively in the *E*-configuration, as evidenced by a coupling constant *J* of 15.9 Hz (**Scheme 75**).

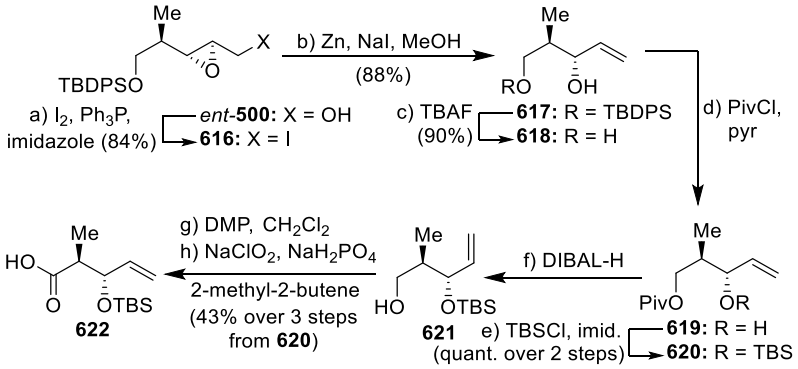


Scheme 75. Towards the Total Synthesis of Solomonamides: RCM of Model Compounds **614** and **615**

Despite this stereochemical outcome, and with the possibility in mind that the structural pattern of the acyclic precursor could influence the double bond geometry and switch in favour to the desired *Z*-isomer,[289] we proceeded to extend this reaction to the desired system. To this aim, olefinic acid **622** was previously prepared from the described epoxy alcohol *ent*-**500**,[249c] according to the methodology reported in the literature for

[287] Jin-Gim, H.; Li, H.; Lee, E.; Ryu, J.-H.; Jeon, R. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 513–517.
[288] Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.
[289] For representative examples of the influence of the structural pattern in the stereochemistry of the ring-closing metathesis, see: (a) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960–7973. (b) Vassilikogiannakis, G.; Margaros, I.; Tofi, M. *Org. Lett.* **2004**, *6*, 205–208. (c) Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G.; Mathison, C. J. N. *J. Am. Chem. Soc.* **2005**, *127*, 8872–8888.

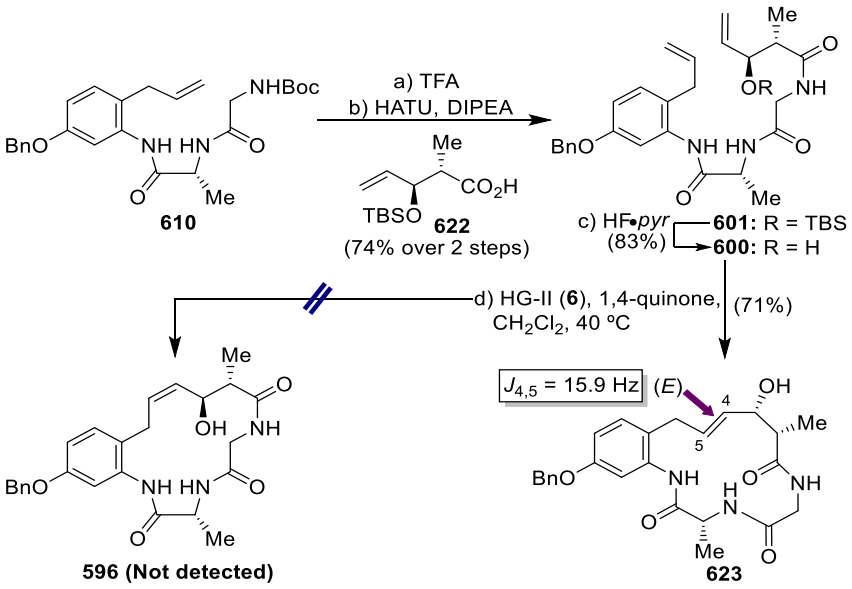
related compounds.[290] Thus, after the transformation of *ent*-**500** into the iodide **616**, a reductive opening process was accomplished by treatment with Zn/NaI to obtain allylic alcohol **617**. After treatment of **617** with TBAF, all attempts to directly oxidize the primary alcohol to the corresponding acid of the resulting diol **618** met with no success. These disappointing results forced us to manipulate the primary and secondary hydroxyl groups of **618**, via selective protection and deprotection steps, to obtain alcohol **621** without difficulty. Olefinic alcohol **621** was then oxidized in two steps, Dess-Martin periodinane (DMP) oxidation followed by final treatment of the aldehyde with sodium chlorite under Pinnick conditions to furnish acid **622** in good overall yield (**Scheme 76**).



Scheme 76. Synthesis of the Olefinic Acid **622**

The assembly of compounds **610** and **622** was achieved in a similar manner as described before for **612**, providing **601** in a 74% overall yield. Upon exposure of **601** to HG-II catalyst, the expected macrocycle **597** was not obtained, instead recovering starting material, together with a significant degree of decomposition. Attributing steric factors to this failed cyclisation, the silyl protecting group was removed by treatment of **601** with HF•pyr to give allylic alcohol **600**. Various reports in the literature, describing metathesis reactions involving allylic alcohols, indicate that these structural systems may favour the closing process,[291] although other studies point out that these systems result in detrimental effects for the metathesis reaction.[292] Nonetheless, when allylic alcohol **600** was treated with the HG-II catalyst in dichloromethane at 40 ºC in the presence of *p*-benzoquinone, the *E*-olefin **623** was obtained exclusively in a gratifying 71% yield, with no formation of the required *Z*-isomer **596**, as revealed by the ^{1}H NMR spectra of the crude reaction mixture (**Scheme 77**).

[290] Reddy, S. V.; Kumar, K. P.; Ramakrishna, K. V. S.; Sharma, G. V. M. *Tetrahedron Lett.* **2015**, *56*, 2018-2022.
[291] (a) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123–1125. (b) Maishal, T. K.; Sinha-Mahapatra, D. K.; Paranjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43*, 2263–2267. (c) Imahori, T.; Ojima, H.; Tateyama, H.; Mihara, Y.; Takahata, H. *Tetrahedron Lett.* **2008**, *49*, 265–268. (d) Imahori, T.; Ojima, H.; Yoshimura, Y.; Takahata, H. *Chem. Eur. J.* **2008**, *14*, 10762–10771.
[292] (a) Cheng-Sánchez, I.; García-Ruiz, C.; Guerrero-Vásquez, G. A.; Sarabia, F. *J. Org. Chem.* **2017**, *82*, 4744–4757. (b) Paquette, L. A.; Efremov, I. *J. Am. Chem. Soc.* **2001**, *123*, 4492–4501. (c) Gurjar, M. K.; Yakambram, P. *Tetrahedron Lett.* **2001**, *42*, 3633–3636.

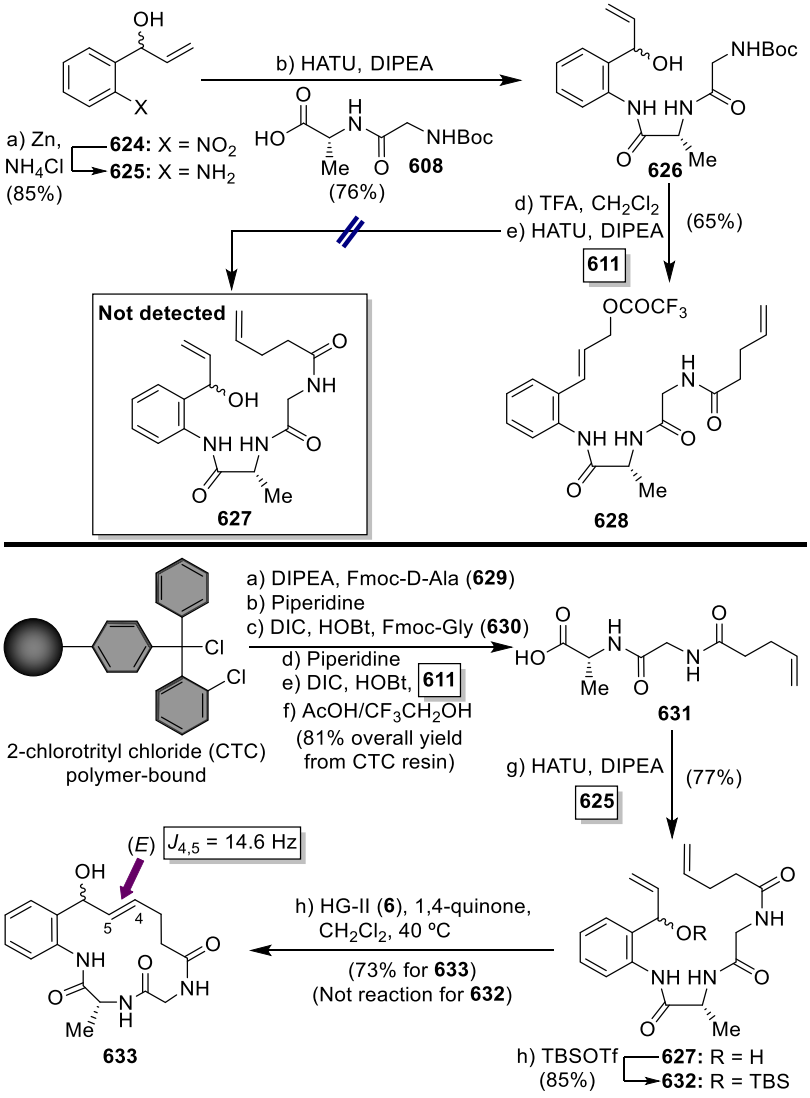


Scheme 77. Towards the Total Synthesis of Solomonamides: Synthesis of Macrocycle **623**

In parallel to these preliminary works, we accomplished related synthetic studies extended to more functionalised precursors that would provide for a shortened path towards the completion of the synthesis of these natural substances. In this direction, we pursued the preparation of the macrocycles **598** and **599** (See **Scheme 74**) as potential advanced precursors. In order to rapidly inspect the validity of this approach, we initially worked with a model system represented by the deoxy aromatic derivatives. Thus, the readily accessible allylic alcohol **624**[293] was transformed into the aniline **625** by treatment with Zn/NH_4Cl. Following the delineated synthesis for previous compounds, **625** was coupled with dipeptide **608** to yield the coupled product **626** as a 1:1 mixture of diastereoisomers. The assembly of **626** with acid **611** was preceded by Boc deprotection under conventional acidic conditions, followed by amide coupling assisted by HATU. Disappointingly, the expected coupling product **627** was not detected, instead the derivative **628** was obtained as a result of a cationic rearrangement of the labile allylic alcohol **626**, which probably occurred during the Boc deprotection step under the acidic conditions used (**Scheme 78**). Different attempts for removal the Boc group under mild acidic (TMSCl, TMSOTf, $Sn(OTf)_2$, $TiCl_4$, $SnCl_4$), neutral (I_2, TBAF, H_2O at reflux) or basic conditions (Na_2CO_3, K_3PO_4, NaO^tBu)[294] resulted similarly unfruitful with the formation of rearranged byproducts, recovery of starting material or degradation, respectively. As a consequence of these results, we considered a direct coupling between aniline **625** and the peptidic fragment **631**, which was efficiently prepared by utilising solid phase peptide synthesis (SPPS) as described in **Scheme 78**. Thus, the coupling of aniline **625** and acid **631** provided the desired diolefinic precursor **627** in a 77% yield. Finally, the ring-closing metathesis of **627** under the same conditions as in previous cases,

[293] Carrión, M. D.; Chayah, M.; Entrena, A.; López, A.; Gallo, M. A.; Acuña-Castroviejo, D.; Camacho, M. E. *Bioorg. Med. Chem.* **2013**, *21*, 4132–4142.
[294] For a comprehensive revision of different methods of Boc cleavage see: (a) Dandepally, S. R.; Williams, A. L. *Tetrahedron Lett.* **2009**, *50*, 1071-1074. (b) Kumar, G. P.; Rambabu, D.; Rao, M. V. B.; Pal, M. *J. Chem.* **2013**, *2013*, 916960; *Chem. Abstr.* **2013**, *160*, 723475.

afforded the macrocyclic derivative **633** in a 73% yield as the *E*-isomer, supported by the $J_{4,5}$ coupling constant (14.6 Hz), and as a 1:1 mixture of diastereoisomers (**Scheme 78**). Interestingly, the protected precursor **632**, prepared by silylation of **627** with TBSOTf, did not provide the corresponding macrocylic derivative when it was treated with the HG-II catalyst under the same conditions used for **627**, indicating that steric factors may be responsible for the failed ring closure.



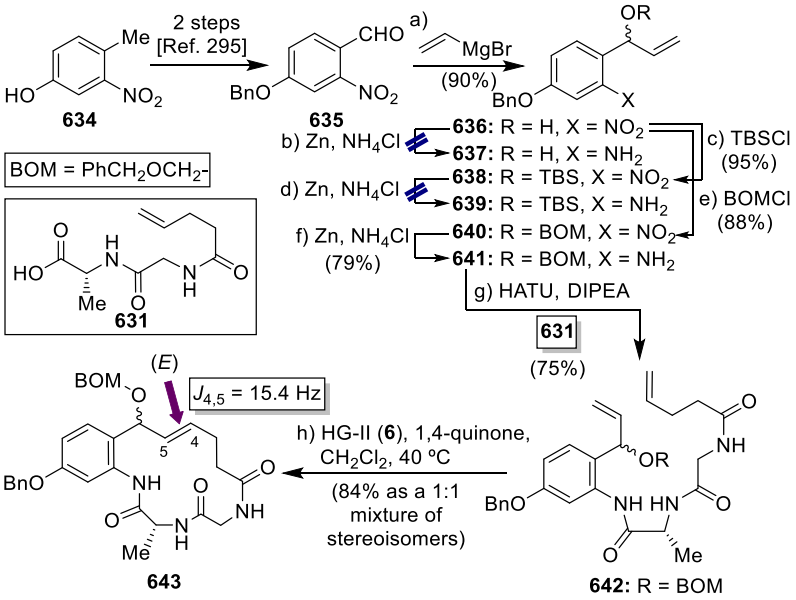
Scheme 78. Towards the Total Synthesis of the Solomonamides via Diolefin **627**

The extension of this synthetic scheme to the aromatic system contained in the natural products was initiated with the aldehyde **635** prepared from commercially available **634**.[295] Subsequent treatment of aldehyde **635** with magnesium vinylbromide provided allylic alcohol **636**, which required the reduction of the nitro group to the corresponding amine to give **637**. This seemingly simple operation however proved more problematic than expected. For example, treatment of **636** with Zn/NH_4Cl did not provide

[295] Hengartner, U.; Batcho, A. D.; Blount, J. F.; Leimgruber, W.; Larscheid, M. E.; Scott, J. W. *J. Org. Chem.* **1979**, *44*, 3748–3752.

the expected aniline **637**, instead a complex mixture of unidentifiable degradation products were obtained. We surmised that the benzyloxy group installed in the aromatic ring was playing a crucial role in the reactivity of the benzylic alcohol, making it especially sensitive even under the weak acidic conditions of the reduction reaction. To circumvent this rather disappointing outcome, we decided to protect the hydroxyl group as the silyl ether **638**. However, the Zn-mediated reduction of the nitro group did not provide the expected aniline **639**, instead the result again was the formation of a complex mixture of degradation products.

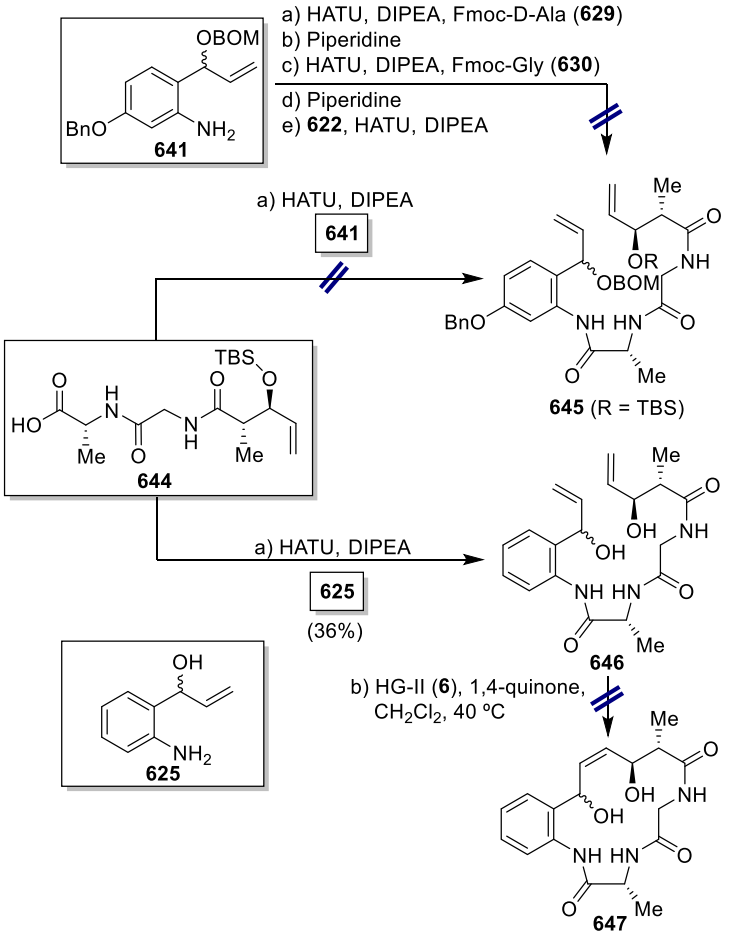
Other reduction methods, including $LiAlH_4$ or Ni-Raney, were attempted but they also were unsucessful. Finally, the more robust BOM ($PhCH_2OCH_2$-) protecting group proved to be the solution for this problematic reduction, as the BOM derivative **640** provided the expected aniline **641** when treated with Zn/NH_4Cl in a reasonable and reproducible 79% yield. The linkage of aniline **641** and dipeptide **631** was then performed as described above for **627** to obtain compound **642**, which was subjected to the ring-closing metathesis to provide macrocycle **643** in an excellent 84% yield as a 1:1 mixture of diastereoisomers and the *E*-olefin as the only detectable double bond isomer. It is intriguing that this ring-closing metathesis process proceeded in such good yield, despite the presence of a protecting group at the hydroxyl group of the diolefinic precursor (**Scheme 79**).



Scheme 79. Towards the Total Synthesis of the Solomonamides via Diolefin **642**

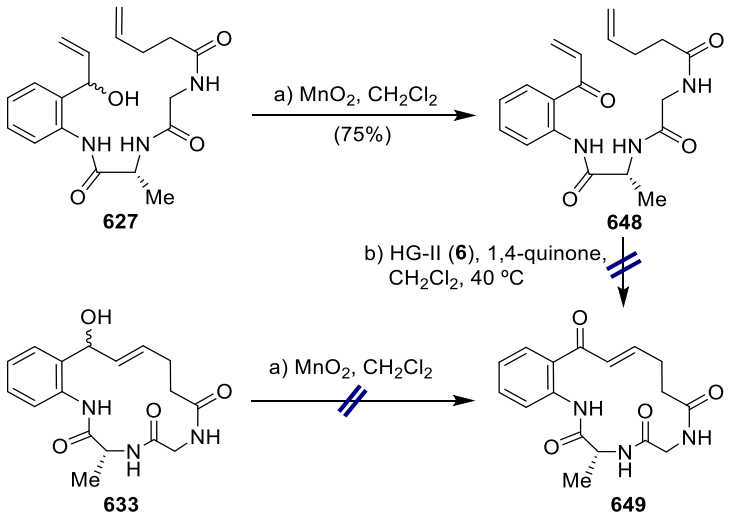
The implementation of this synthetic scheme onto the more functionalised system found in the natural products was then confronted by the assembly of acid **644**, prepared by SPPS (See Experimental Part in **Chapter 7**) and **641** under conventional conditions employed in this work (HATU/DIPEA). However, no desired product **645** was obtained despite attempts with an array of coupling reagents such as BOP, PyBOP, DIC/HOBt or DIC/HOAt. Reasoning that steric hindrances around the acid **644** could explain this failure, we attempted the synthesis of the advanced precursor **645** by sequential couplings

of aniline **641** with the amino acid derivatives **629** and **630** and the less sterically encumbered acid **622**. Unfortunately, the last coupling with acid **622** did not provide the expected product **645**, instead a complex mixture of HATU derivatives was obtained from the starting acid. Intrigued by these failed reactions, we turned our attention to the simple aniline **625**, in which the hydroxyl group at C6 position was free, in order to determine the reasons of the serious hurdles found during this synthetic course. To this end, aniline **625** and acid **644** were coupled by treatment with HATU/DIPEA and the corresponding coupling product **646** was obtained, albeit in a low 36% yield, with the unexpected cleavage of the silyl protecting group. Several attempts of this reaction revealed its lack of reproducibility, confirming the difficulties of such a coupling. Although obtained in low yield, compound **646** was in hand and we were in position to investigate the ring-closing metathesis reaction for this more complex system. The reaction, undertaken under similar conditions as in previous cases, did not give the expected macrocycle **647**, thus demonstrating the unsuitability of these substrates in the construction of the macrocylic core of the solomonamides via RCM. The reason for failure is most likely due to the sensitivity of the reaction to steric factors arising from the presence of substituents at both allylic and benzylic positions (**Scheme 80**).



Scheme 80. Exploration of the RCM in More Complex Systems

In yet another attempt to access the macrocyclic solomonamide precursors functionalised at the benzylic position, we considered the incorporation of a ketone at this position, since this is the functional group present in the natural products. In addition, the generation of the α,β-unsaturated ketone system, after the macrocyclisation process, would allow for the rapid and facile access to an epoxide via oxidation of the double bond. Notably, we were skeptical about the success of the metathesis reaction in such a system, represented by compound **648**, given that the olefin is unactivated as it is conjugated (α,β-unsaturated phenylketone). Despite this concern, we opted to experimentally verify the chemical reactivity of **648** under the action of the Hoveyda-Grubbs and related catalysts. To this aim, we prepared ketone **648** by oxidation of the alcohol **627** with MnO_2 and then, subjected to the catalytic action of the Hoveyda-Grubbs 2nd generation, keeping in mind the difficulty of this reaction due to the inactivated nature of the double bond of the α,β-unsaturated ketone system. Indeed, this reaction did not provide any desired product, even when the reaction was forced using drastic conditions (ex. toluene at 60 ºC and 100 ºC), instead providing recovered starting material in all cases. In another attempt to obtain cyclic ketone **649**, cyclic alcohol **633** was treated with MnO_2 but the result was similarly unsuccessful, with only starting material recovered and no detection of the coveted ketone **649** (**Scheme 81**).

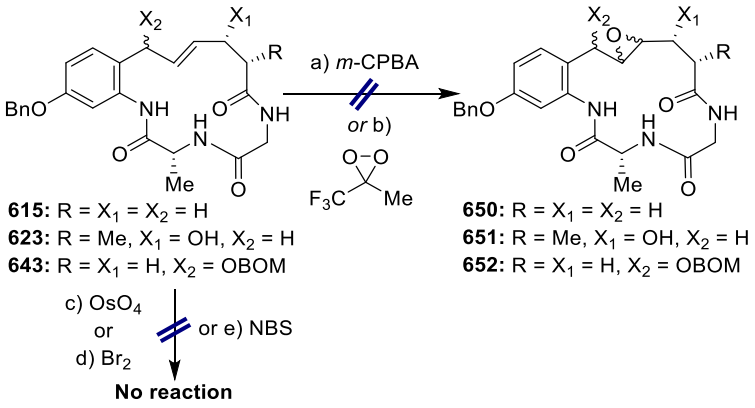


Scheme 81. Exploration of the RCM of the Diolefinic Ketone **648**

Although a *Z*-geometry for the $\Delta^{4,5}$ double bond was proposed to provide access to the *syn*-1,2-difunctionalized system present at these positions in the natural products, the fact that we obtained instead the *E*-olefinic macrocycles in all cases represented an additional difficulty in this study to obtain the final targets. Nonetheless, this synthetic strategy was not discarded at this point, as synthetic methods are available to provide the required *syn* isomer from a *trans* double bond.[296] Consequently, we decided to continue

[296] (a) Martín-Ortiz, L.; Chammaa, S.; Pino-González, M. S.; Sánchez-Ruiz, A.; García-Castro, M.; Assiego, C.; Sarabia, F. *Tetrahedron Lett.* **2004**, *45*, 9069–9072. (b) Miyashita, M.; Mizutani, T.; Tadano, G.; Iwata, Y.; Miyazawa, M.; Tanino, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 5094–5097. (c) Yu, X.-Q.; Yoshimura, F.; Ito, F.; Sasaki, M.; Hirai, A.; Tanino, K.; Miyashita, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 750–754.

with the present synthetic approach and the next step was to evaluate the feasibility of such compounds to provide more oxidized derivatives through an oxidation phase that would give access to the final products. In this sense, we studied the oxidation of compounds **615**, **623** and **643** as representative macrocyclic precursors of the solomonamides. Thus, when **615** or **623** were subjected to the oxidative action of *m*-CPBA, we found, to our dismay, that these reactions did not yield the expected epoxides **650** or **651**. Instead, starting materials were recovered in both cases. In light of these discouraging results, we attempted the epoxidation utilizing the dioxirane derived from trifluoromethylketone,[297] however the result was similarly frustrating, with no formation of any desired oxidation products. Other oxidative reactions were screened, such as a dihydroxylation reaction mediated by OsO_4, and electrophilic additions, mediated by the actions of bromine or NBS, but these did not provide favorable results, not detecting formation of any of the possible oxidation products. The poor solubility observed for these cyclic compounds in common organic solvents could explain the lack of reactivity found for them towards the oxidative reagents. However, the more soluble derivative **643** also proved to be unreactive when it was subjected to the epoxidation reagents (*m*-CPBA and dioxirane species), resulting in the recovery of starting material and no detection of epoxide **652** (**Scheme 82**).



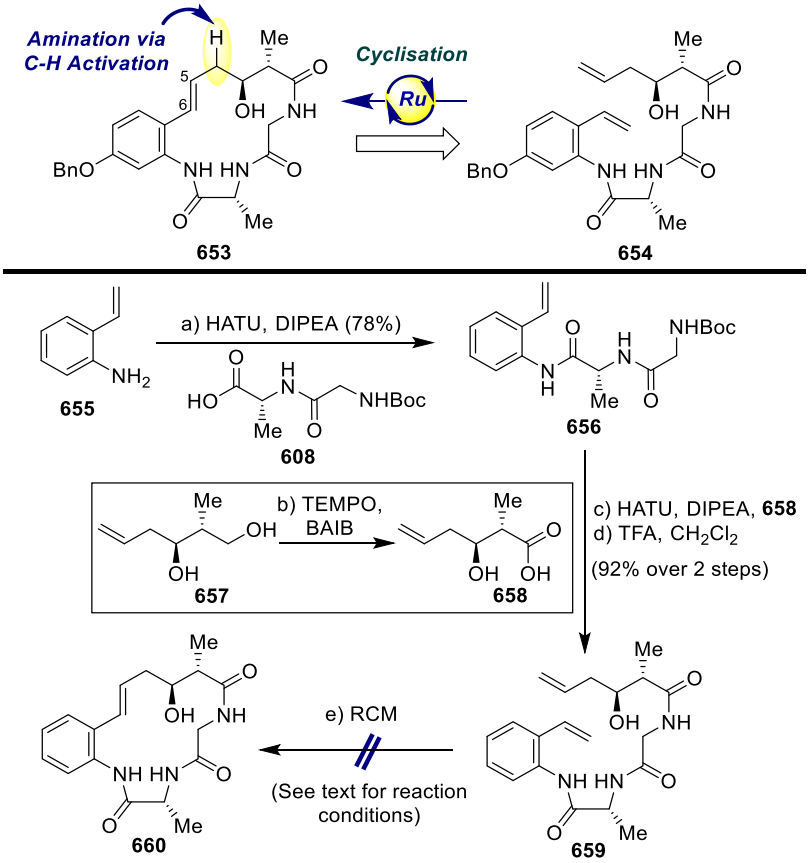
Scheme 82. Attempts of Oxidation of the RCM Products

Theoretical studies were carried out in order to justify the lack of reactivity exerted by these macrocyclic compounds. Thus, initial results from DFT calculations carried out in solution showed that the HOMO orbital of the molecules is centered around the intracyclic phenyl ring with a low electronic density around the alkene moiety.[298] This result suggests that the main reactive point for the oxidant should not be the alkene, as it could be expected, but the aromatic ring. At this stage, no further work was required to recognize that oxidation of the previous solomonamide precursors was extremely hard to accomplish. Therefore, a new approach was considered.

[297] Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887–3889.
[298] DFT calculations were carried out using Gaussian 09 at the B3LYP/6-31G' level of theory using the SMD solvation methodology, choosing acetonitrile as solvent.

4.3.2. Ring-Closing Metathesis at the C5-C6 Bond

Given the results obtained during the synthetic studies towards the solomonamides utilizing the macrocyclic construction at the C4-C5 bond, we turned our attention to the construction of the macrocyclic core of the solomonamides at the C5-C6 bond. In relation to the synthetic strategy explored in the previous section, the removal of the functional groups, which should be accessible during an oxidation phase, would lead to the relatively simple precursor **653**. Whereas the styryl double bond could be transformed into a ketone or an α-hydroxy ketone via Wacker or dihydroxylation oxidations for solomonamides A and B, respectively, the introduction of the required amine group at the C4 position was initially planned via a C-H activation.



Scheme 83. Second Approach to the Solomonamides via RCM: The C5-C6 Disconnection

The syntheses of the key precursor **653** would be performed by a RCM of the acyclic derivative **654**, whose synthesis would be achieved by simple peptidic-like assemblies between the corresponding amine and olefinic acid. As in the previous synthetic exploration, we preferred to initiate this study with the model compound **659** to test the viability of the new synthetic proposal. The preparation of this RCM precursor was successfully achieved from the simple aniline **655**[299] by sequential couplings with dipeptide **608** and hydroxy acid **658**, obtained from the known diol **657**[300] by selective

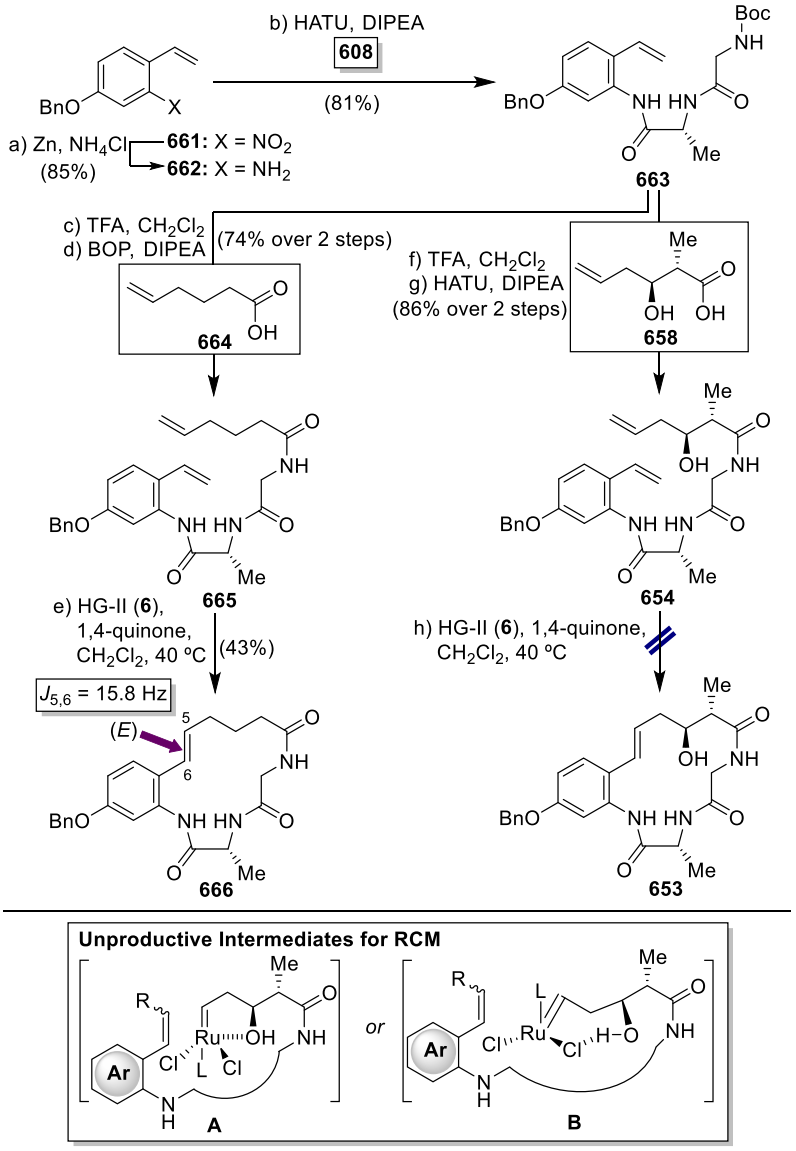
[299] Aoyama, A.; Endo-Umeda, K.; Kishida, K.; Ohgane, K.; Noguchi-Yachide, T.; Aoyama, H.; Ishikawa, M.; Miyachi, H.; Makishima, M.; Hashimoto, Y. *J. Med. Chem.* **2012**, *55*, 7360–7377.
[300] Wagner, H.; Harms, K.; Koert, U.; Meder, S.; Boheim, G. *Angew. Chem. Int. Ed.* **1996**, *35*, 2643-2646.

oxidation with TEMPO/BAIB. With compound **659** in hand, we proceeded with the olefin metathesis reaction by use of the HG-II catalyst in refluxing dichloromethane. However, it was with much disappointment, that this reaction failed to afford any macrocyclic product, leading instead to decomposition and/or polymerization, together with the recovery of some starting material (~12%). Additional attempts that included more forcing conditions (toluene at 65ºC or 100 ºC) and other catalysts (Grubbs 1st and 2nd generations, Hoveyda-Grubbs 1st generation) were thwarted, with no detection of the desired macrocyclic product **660** (**Scheme 83**).

Despite these discouraging results, we decided to press forward with the synthetic strategy by exploring the ring closing metathesis in the real system represented by the product **654**. We reasoned that in the case of the metathesis precursor **654**, the electronic effect of the benzyloxy group at the *para* position with respect to the styryl double bond could exert a favourable effect in terms of reactivity for the unreactive olefin. In order to confirm this hypothesis, we prepared the styryl derivative **663** from compound **661** in a very good overall yield. We then proceeded to test the construction of the macrocyclic ring of the solomonamide model system **666**. To this end, compound **663** was coupled with commercial acid **664** to obtain the acyclic precursor **665** in a 74% yield. Having prepared compound **665**, we were primed to test our hypothesis regarding the favourable electronic donating effect of the benzyloxy group on the ring-closing metathesis reaction. Indeed, we were gratified to discover that cyclic compound **666** was obtained in a 43% yield and, exclusively, as the *E*-isomer, when the acyclic precursor **665** was exposed to the HG-II catalyst in refluxing dichloromethane in the presence of 1,4-benzoquinone (**Scheme 84**).

In light of this encouraging result, the ring-closing metathesis was extended to the advanced intermediate **654**, which was efficiently prepared from the Boc derivative **663** and acid **658** in 86% overall yield, according to the previously described fragment coupling protocol. To our dismay, treatment of **654** with the HG-II catalyst, under the same conditions previously employed in earlier cases, did not provide the coveted solomonamide precursor **653**, providing instead degradation products and recovered starting material. A possible explanation for the failure of the metathesis reaction is the formation of either the five-membered ring intermediate **A**,[301] by chelation of the ruthenium carbenoid with the hydroxyl group, or the seven-membered ring chelate intermediate **B**,[302] in which sequestration of the ruthenium carbenoid species occurred through a hydrogen bond of the hydroxyl group with the chlorine atom, which could explain the inactivation of the catalyst for the RCM (**Scheme 84**).

[301] Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E. *Org. Lett.* **2001**, *3*, 2209–2212.
[302] Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378–8379.

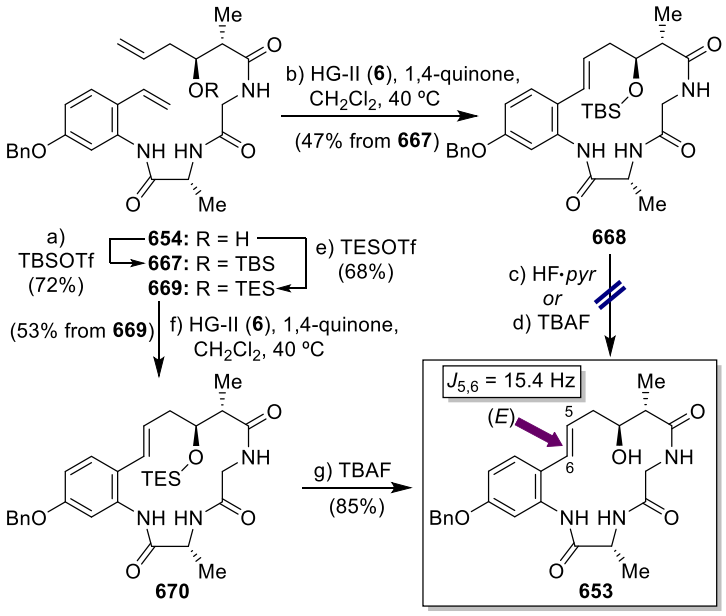


Scheme 84. RCM of the Acyclic Precursors **654** and **665**

As support for this mechanistic hypothesis,[303] we decided to protect the hydroxyl group to avoid the formation of the proposed unproductive intermediates. Therefore, the TBS derivative **667** was prepared in a good yield by treatment of **654** with TBSOTf in the presence of 2,6-lutidine. The resulting silyl ether **667** was then subjected to the exposure of the HG-II catalyst and, to our delight, the macrocyclic product **668** was obtained in a reasonable 47% yield. The completion of the synthesis of the natural products should require an eventual removal of the TBS protecting group. With this future objective in mind, we proceeded with the desilylation reaction by treatment of **668** with HF•*pyr*. Surprisingly, the expected hydroxyl derivative **653** was not obtained, instead recovered starting material. Other fluoride-based reagents (TBAF, TBAF-AcOH) afforded the same frustrating result. Therefore, we decided to replace the TBS group with

[303] (a) Lin, Y. A.; Davis, B. G. *Beilstein J. Org. Chem.* **2010**, *6*, 1219–1228. (b) Fuwa, H.; Saito, A.; Sasaki, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3041–3044. (c) Schmidt, B.; Staude, L. *J. Org. Chem.* **2009**, *74*, 9237–9240. (d) Schmidt, B.; Nave, S. *Chem. Commun.* **2006**, 2489–2491.

a more labile protecting group, choosing TES as a suitable alternative. Then, compound **669** was prepared by reaction of **654** with TESOTf/2,6-lutidine and its suitability as a viable substrate for the preparation of **653** was evaluated. Gratifyingly, the RCM reaction of **669** provided **670** in a similar yield as for **668** (53%) and its desilylation, by treatment with TBAF, yielded the desired macrocyclic **653** in 85% yield (**Scheme 85**).

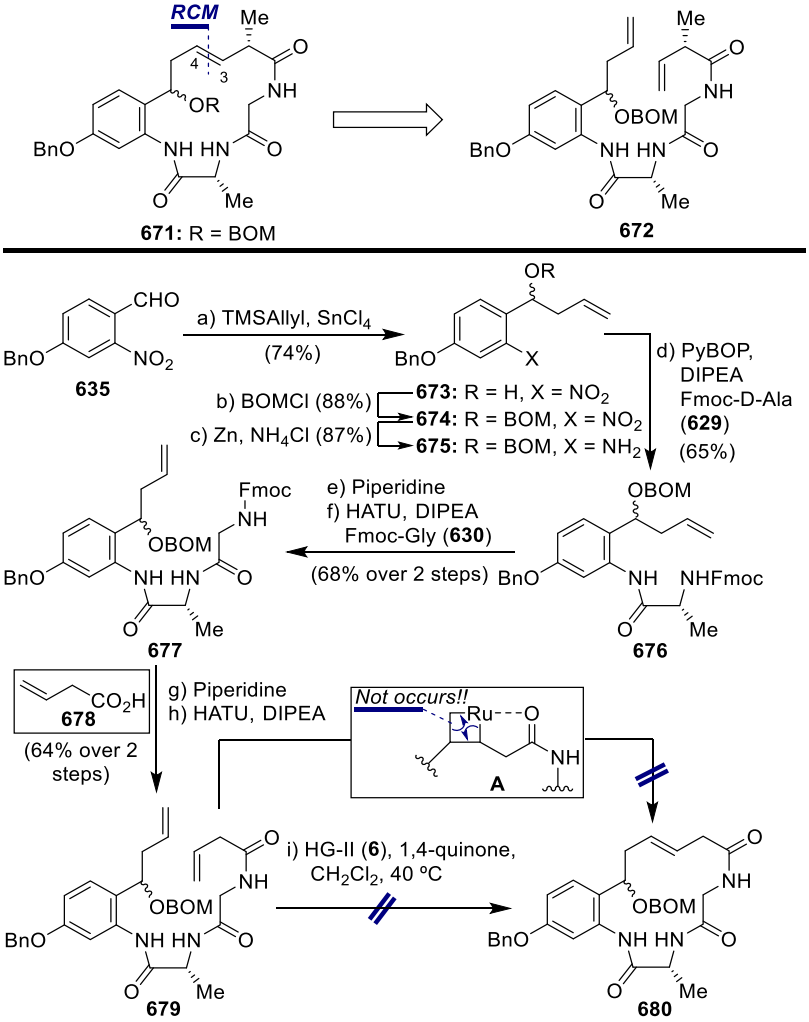


Scheme 85. RCM of the Acyclic Precursors **667** and **669**: Synthesis of **653**

4.3.3. Ring-Closing Metathesis at the C3-C4 Bond

Prior to the completion of the synthetic study towards the natural solomonamides, for which meaningful quantities of **653** or precursor **670** were required, we opted to complete the exploration of the RCM reaction by exploring the C6-C7 bond as another disconnection point to construct the macrocyclic system of the solomonamides. This new disconnection strategy would be based on the retrosynthetic analysis depicted in **Scheme 86**. Having established the viability of the RCM strategy for the construction of the macrocylic core of the solomonamides at two different sites, the C5-C6 and the C4-C5 bonds, we decided to extend the RCM-based strategy to the C3-C4 position, scanning all the options along the six-carbons chain contained in the ADMOA fragment. In this new scenario, the removal of the functional groups at the C3 and C4 positions revealed compound **671** as a potential precursor for solomonamide B, which could be obtained from the acyclic derivative **672** via RCM. Thus, aldehyde **635** was transformed into the amine **675** without problems according to the synthetic sequence described in **Scheme 86**. Our experience gathered during the synthetic campaign led us to choose BOM as the most suitable protecting group for the benzylic alcohol and to introduce sequentially the two amino acids (D-Ala and Gly) through the Fmoc derivatives **629** and **630** to obtain compound **677**. Prior to the preparation of the subtarget RCM precursor **672**, we

considered the use of the commercially available acid **678** to test the possibilities of this new strategy. Having prepared model compound **679**, treatment with HG-II catalyst under similar reaction conditions as previously used, did not provide the desired result with the no formation of the macrocyclic compound **680**. In fact, a rational explanation for this result could be the formation of a stable 5-membered ring chelate between the ruthenium carbene and the carbonyl group of the amide (intermediate **A**), which renders the metallacyclobutane intermediate unreactive toward the retro [2 + 2] cycloaddition[304] (**Scheme 86**).

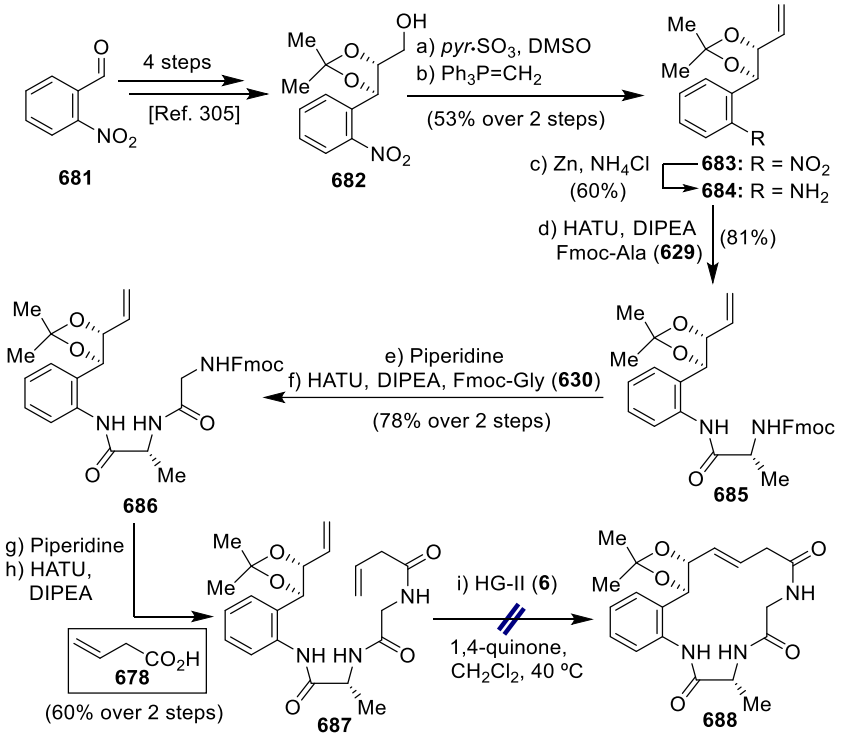


Scheme 86. Third Approach to the Solomonamides via RCM: The C3-C4 Disconnection towards Macrocycle **680**

In parallel with these dissapointing results directed towards the solomonamide B, we explored a synthetic pathway towards solomonamide A. In this sense, we decided firstly to target a model compound, represented by compound **687** in **Scheme 87**, as a suitable precursor that would allow to a rapid validation of the $\Delta^{3,4}$-strategy. With this

[304] (a) Fürstner, A.; Thiel, O. R.; Lehmann, C. W. *Organometallics* **2002**, *21*, 331–335. (b) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1277–1279. (c) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

aim, we started the synthetic plan from known alcohol **682**,[305] which was subjected to a Parikh-Doering oxidation followed by a Wittig reaction to obtain nitro derivative **683** in 53% over 2 steps, which was then reducted to aniline **684** by the action of Zn/NH_4Cl in 60% yield. From aniline **684**, we were able to obtain model precursor **687** in a similar way than previously described above for **679**. To our dismay, the desired macrocycle **688** was not obtained after treatment of **687** with HG-II catalyst under the same reaction conditions as before, thus confirming the formation of the unreactive metallacyclobutane intermediate as in the previous case (**Scheme 87**).

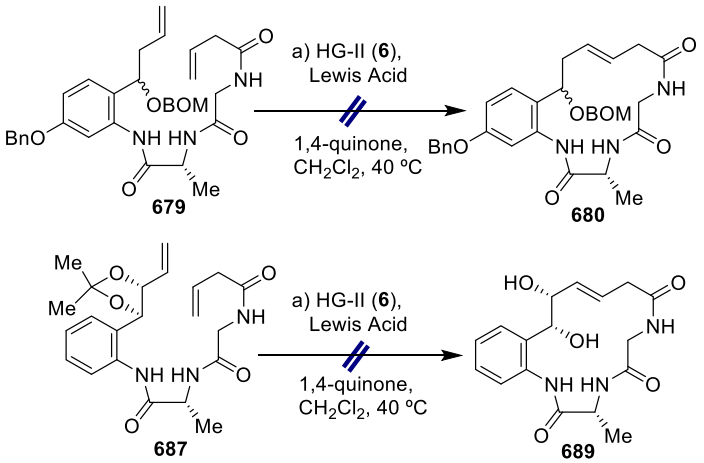


Scheme 87. Third Approach to the Solomonamides via RCM: The C3-C4 Disconnection towards Macrocycle **688**

In ligth of these results, we decided to explore the RCM by use of Lewis acids,[306] which are useful additives to promote the ring closure as demonstrated in cross-metathesis reactions bearing similar structural motifs. Then, we repeated the RCM reaction of dialkenes **679** and **687** under the presence of $Ti(OiPr)_4$. However, in both cases the result of the RCM reaction met with no success as in previous cases, detecting a mixture of starting material together degradation products. Attempts of these RCM reactions under the action of other Lewis acids as $La(OTf)_3$ or $Zn(OTf)_2$ were similar unfruitful, not detecting the desired macrocyclic compounds **680** or **689** (**Scheme 88**). With these

[305] Aeluri, M.; Gaddam, J.; Trinath, D. V. K. S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. *Eur. J. Org. Chem.* **2013**, 3955–3958.
[306] For representative examples see: (a) Lübbe, C.; Dumrath, A.; Neumann, H.; Beller, M.; Kadyrov, R. *ChemCatChem* **2014**, *6*, 105–108. (b) Nagarapu, L.; Gaikwad, H. K.; Bantu, R.; Manikonda, S. R.; Kumar, C. G.; Pombala, S. *Tetrahedron Lett.* **2012**, *53*, 1287–1291. (c) Pentzer, E. B.; Gadzikwa, T.; Nguyen, S. T. *Org. Lett.* **2008**, *10*, 5613–5615. (d) Vedrenne, E.; Dupont, H.; Oualef, S.; Elkaïm, L.; Grimaud, L. *Synlett* **2005**, 670–672.

dissapointing results, we decided to stop exploration of the $\Delta^{3,4}$-RCM in favor to the $\Delta^{5,6}$-RCM route described before.



Scheme 88. Attempts of RCM Reaction Assisted by Lewis Acids:$Ti(OiPr)_4$, $La(OTf)_3$ or $Zn(OTf)_2$

4.4. Biological Activity and Molecular Modelling of Selected Solomonamide Precursors.

At this stage of the synthetic work, with an efficient route defined to obtain the final natural products by the $\Delta^{5,6}$-RCM strategy, we were intrigued with the biological properties of the synthesized products, recognizing that the macrocyclic peptides represented unprecedented and novel molecular architectures of biological interest. For this reason, we decided to explore and investigate their biological activities in collaboration with the group of Prof. Ana R. Quesada from the Molecular Biology and Biochemistry Department of Málaga University. To this aim, we performed preliminary biological evaluations, which consisted of the measurement of the antitumor properties of selected compounds against a panel of various tumor cell lines. The chosen solomonamide derivatives for this study were **614**, **615**, **623**, **633**, **666**, **670** and **653** as representative compounds of the different scaffolds generated during the synthetic work. In addition, compound **690**, obtained from **615** by treatment with Na/NH_3 (See **Figure 2**), was included for this study to evaluate the effect of the protecting group upon biological activity.

As a first attempt to characterize the biological activities of the synthetic solomonamide analogues, the cytotoxicity profile of the aforementioned compounds was examined using nine different cancer cell lines (see **Table 2**), as well as a primary culture of non transformed bovine aorta endothelial (BAEC) cells. The results of these biological evaluations, summarized in **Table 2**, clearly revealed a relevant cytotoxic activity for only one compound, **653**, which displayed the best values of inhibition of the series in the low μM range, against all the tumor cell lines. In addition, **653** was also cytotoxic against the endothelial cells line (BAEC), which may indicate a putative antiangiogenic effect of this compound.[270] In contrast, the other compounds were practically devoid of antitumor

activity except compounds **623** and **666**, which displayed cytotoxicity, particularly against the HL60 tumor cell line albeit moderately. From these results, a highlight is the notable enhancement of activity observed upon introduction of functional groups in the polyketide fragment contained in these compounds, as concluded when biological activities of **666** and **653** are compared, or **615** and **623** for the case of the HL60 cell line. In addition, the isomeric derivative of **653**, compound **623**, displayed similar antiproliferative activity as **653** against HL60, but, in contrast, was inactive against the other cell lines, including BAEC, revealing the importance of the position of the double bond of the molecule upon biological activities. This structural effect is also reflected when the biological activities of the isomeric compounds **615** and **666** are compared.

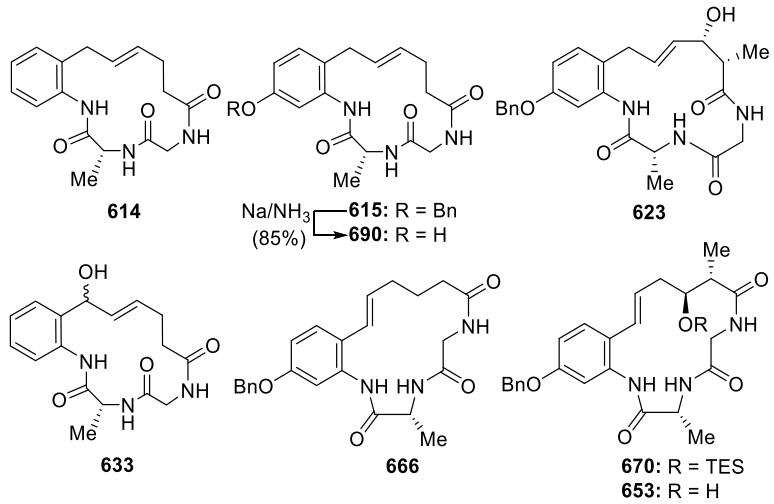


Figure 13. Synthetic Solomonamide Precursors Submitted to Biological Evaluations

Table 2. *In vitro* Antitumor Activities of Solomonamide Precursors against Various Tumor Cell Lines and BAEC (IC_{50}, μM)[a]

Compd.	HL60[b]	KU812F[c]	U937[d]	HT-1080[e]	MDA-MB-231[f]	U87MG[g]	HepG2[h]	HT-29[i]	U2OS[j]	BAEC[k]
614	> 50	> 50	> 50	> 100	> 100	> 100	> 100	> 100	> 100	> 100
615	> 50	n.d.	n.d.	> 100	> 100	> 100	> 100	> 100	> 100	43,8 ± 1,2
690	> 50	> 50	> 50	> 100	> 100	> 100	> 100	> 100	> 100	> 100
623	17,2 ± 6,6	n.d.	n.d.	> 50	> 50	n.d.	n.d.	n.d.	n.d.	> 100
633	> 50	> 50	> 50	> 100	> 100	> 100	> 100	> 100	> 100	> 100
666	20,5 ± 5.2	> 50	> 50	31,1 ± 2,8	> 100	> 100	> 100	> 100	> 100	69,6 ± 12,5
670	> 50	> 50	> 50	> 100	> 100	> 100	> 100	> 100	> 100	> 100
653	14,7 ± 4,4	14,0 ± 3.05	7,02 ± 2.32	16,3 ± 2.9	16,5 ± 1,01	34,8 ± 5,1	18,9 ± 1,5	13,3 ± 0,6	12,9 ± 3,1	18,1 ± 2,2

[a] *In vitro* cytotoxicities were determined according to the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide dye reduction assay as detailed in experimental part. The IC_{50} values were obtained from semilogarithmic dose-response plots as the concentration of compound yielding a 50% of cell survival. [b] HL60: Human promyelocytic leukemia. [c] KU812F: Chronic Myelogenous leukemia. [d] U937: Histiocytic lymphoma. [e] HT1080: Human fibrosarcoma. [f] MDA-MB-231: Human breast adenocarcinoma. [g] U87MG: Gioblastoma. [h] HepG2: Hepatocellular carcinoma. [i] HT-29: Colorectal adenocarcinoma. [j] U2OS: Osteosarcoma. [k] BAEC: Non transformed bovine aortic endothelial cells.

In an attempt to make sense of this result, molecular modelling studies were conducted for compounds **615**, **623**, **666** and **653** to obtain the corresponding minimized structures (**Figure 14**).[307] The resulting models revealed a certain structural distorsion when **615** and **666**, on one side, and **623** and **653**, on the other, are compared, respectively. Thus, whereas **666** and **653** are almost flat, **615** and **623** displayed considerable twisting. These differences in the resulting minimized molecular structures may explain the differences observed for the biological activities found for these compounds. Additionally, the overall shape of **615** is very similar to **623**, and the same is evident also for **666** and **653**. In this case, despite these conformational similarities, it is clear that the functional groups incorporated in **623** and **653**, in particular the hydroxy group, may exert a key biological interaction through a hydrogen bonding interaction with an acceptor-type residue located at the active site of the biological targets. These interactions may justify the greater activities displayed by **623** and **653** compared with **615** and **666**, respectively. In addition, the importance of the hydroxy group can be further deduced from the loss of the biological activities of compound **670** with the TES-protected hydroxy group.

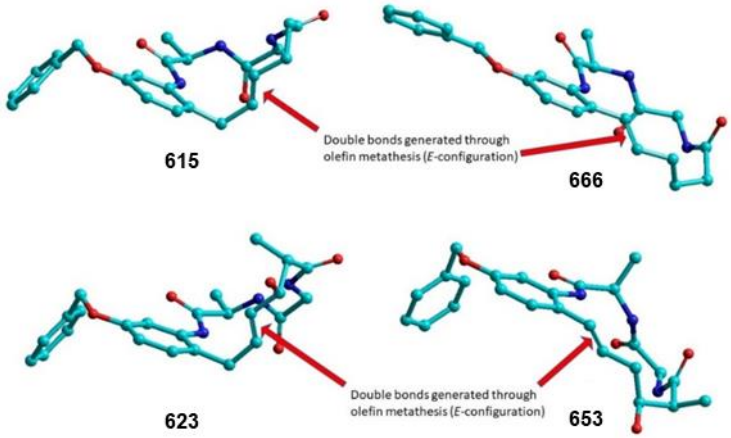


Figure 14. Computer-generated Minimum-Energy Conformations for Compounds **615**, **623**, **653** and **666**

4.5. In vitro and in vivo Antiangiogenic Potential of Solomonamide Precursors

The promising *in vitro* antitumor activity reported above for compound **653** prompted us to evaluate the antiangiogenic potential of the complete series of solomonamide precursors, with the collaboration of the group of Prof. Ana R. Quesada. Angiogenesis involves the generation of new capillaries by sprouting of pre-existing vessels. Although in a healthy situation this process is tightly regulated by a balance of stimulators and inhibitors, being restricted to specific situations such as embryonic development, endometrial regulation, reproductive cycle, and wound repair, a persistent and deregulated angiogenesis is related to the course of many pathologies[308,309] and is

[307] Minimum energy conformations were calculated using the PM3 method found in HyperChem 5.0 software. Optimization was performed using Polak-Ribiere algorithm until the RMS gradient reached a value below 0.001 kcal/(Å·mol).
[308] Potente, M.; Gerhardt, H.; Carmeliet, P. *Cell* **2011**, *146*, 873−887.
[309] Quesada, A.R., Medina, M.Á., Muñoz-Chápuli, R., Ponce, Á.L. *Curr. Pharm. Des.* **2010**, *16*, 3932-3957.

considered as one of the hallmarks of cancer.[310] In consequence, the pharmacological regulation of angiogenesis emerges as an attractive strategy for the treatment of cancer and other angiogenesis-dependent diseases.[311] Attending to this evidence, the active search for new compounds able to modulate angiogenesis is a crucial research strategy in order to discover potential antiangiogenic drugs with possible clinical applications.

With the aim to study the antiangiogenic potential of the previously synthesized solomonamide precursors **614**, **615**, **690**, **623**, **633**, **666**, **670** and **653**, we performed a primary screening *in vitro* based on the analysis of their inhibitory activity in the formation of endothelial tubular-like structures, measuring their minimum inhibitory concentration (MIC). In this primary screening, we identified compound **653** as the solomonamide precursor that showed the best MIC value (1 μM) compared to the rest of analogues tested (>50 μM) (**Figure 15, part A**). This markedly low MIC value confirmed the unique bioactivity of this compound. Current approaches to target tumor vessels include two strategies: (a) the inhibition of the formation of new blood vessels following the activation of the endothelial cells (antiangiogenic drugs), and (b) the disruption and destruction of the pre-existing vasculature (tumor vascular disrupting drugs).[312] As shown in **Figure 15 part B**, **653** is not able to disrupt the tubule-like structures already formed, discarding a possible vascular disrupting activity of this compound. These results prompted us to select compound **653** for further analysis of its antiangiogenic potential.

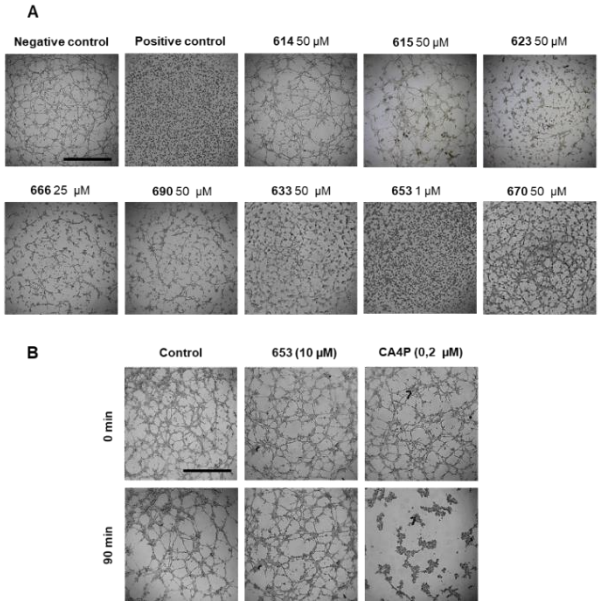


Figure 15. Compound **653** Exhibits a Strong Inhibitory Effect on Tubulogenesis *in vitro*, without Affecting Already Formed Structures. A) Effect of solomonamide precursors on endothelial tubular-like structures formation on Matrigel. BAEC were seeded on Matrigel in presence of the compounds and structures formation was evaluated after 5 hours. Vehicle (DMSO) was added to the negative control; staurosporine 2 μM was used as positive inhibition control. B) Vascular disruption assay *in vitro*. Compounds were added to already formed BAEC tubular-like structures on Matrigel. Effects were evaluated after 90 minutes. Combrestatin (CA4P) 0.2 μM was used as a positive control (Scale bar = 1000 μm). Each experimental condition was conducted in duplicates, and three independent assays were performed in each case.

[310] Hanahan, D.; Weinberg, R. A. *Cell* **2011**, *144*, 646−674.
[311] (a) Folkman, J. *N. Engl. J. Med*. **1971**, *285*, 1182−1186. (b) Folkman, J. *Nat. Rev. Drug Discov.* **2007**, *6*, 273−286. (c) Carmeliet, P. *Nature* **2005**, *438*, 932−936.
[312] Tozer, G.M., Kanthou C., Baguley B.C. *Nat. Rev. Cancer* **2005**, *5*, 423–435.

During angiogenesis, migration is an indispensable step by which endothelial cells activate their migratory and invasive potential, moving towards the pro-angiogenic signal, making the formation of new vessels possible in the tissue. A wound-healing assay was performed in order to evaluate the possible effect of the solomonamide precursor on endothelial cell migration *in vitro*. As shown in **Figure 16**, **653** significantly reduced the migratory capabilities of BAEC at not toxic doses (MIC for migration =10 μM).

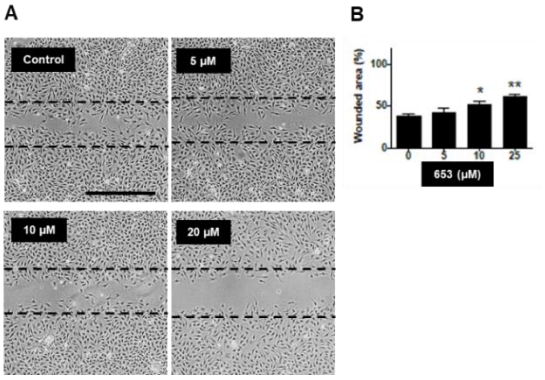


Figure 16. Compound **653** Decreases Endothelial Cell Migration Capability. A) Representative photographs of wound healing assay after 7 h of treatment with **653**. Vehicle (DMSO) was added to control condition. Discontinued lines point the free-cell area at time 0 h in each experimental condition. (Scale bar = 500 μm). B) Quantification of the non-recovered area in the wound-healing assay after 7 hours of treatment with **653**. Data are showed as percentages of the free-cell area at time 0 h and are expressed as the mean ±SD of three independent experiments (*p<0.05,**p<0.01).

In addition to the migratory potential, during angiogenesis activated endothelial cells must be able to degrade extracellular matrix components in order to allow the invasion through the tissue. The possible effect of **653** on the invasive capability of endothelial cells was studied. **653** was able to inhibit the invasive potential of BAEC in a dose-response manner, reaching a 50% of inhibition at a concentration close to 5 μM (**Figure 17**, **part A**). We studied also the effect of **653** on the capability of endothelial cells to degrade the proteins of extracellular matrix (ECM). Our results showed that the presence of matrix metalloproteinase-2 (MMP-2), the main MMP expressed in endothelial cells, was reduced both in cell extracts and in conditioned media of BAEC treated with **653** at 20 μM (**Figure 17**, **part C**). These results supported the observed inhibitory effect of this compound on endothelial cell invasion. In order to study the cell specificity of the protease modulation by this compound, the effect of **653** on the proteolytic potential of HT1080 tumor cells was examined. While endothelial cells only express one gelatin degrading MMP, HT1080 cells express both gelatinases: MMP-2 and MMP-9. As shown in **Figure 17 part D**, both MMP activities were decreased when these cells were treated with **653**, suggesting that the inhibitory effect of **653** on the ECM degrading potential is not specific for endothelial cells. In order to better understand the inhibitory effect of **653** on ECM degradation capability, MMP-2 gelatinase activity was measured in the gel in absence or presence of the compound. The gelatin degradation bands corresponding to MMP-2 in control endothelial conditioned media were unaffected when gels were incubated in presence of the compound (**Figure 17**, **part E**), indicating that **653** was not able to directly inhibit MMP-2.

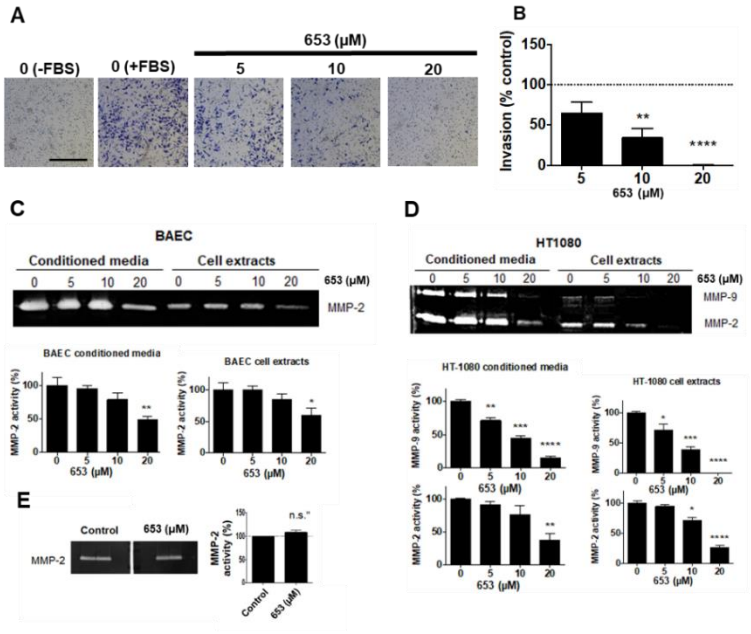


Figure 17. Compound **653** Inhibits Endothelial Cell Invasion and ECM Degradation Capability. A) Representative photographs of invading endothelial cells through Matrigel-coated transwells after 16 hours of treatment (Scale bar = 500 μμm). B) Quantification of the cell invasion assay. The number of invading cells stained in the control stimulated with FBS was considered as 100% of invasion. C) Representative gelatin zymography and quantification of MMP-2 presence in conditioned media and cell extracts of BAEC treated with **653**. D) Representative gelatin zymographies and quantifications of MMP-9 and MMP-2 presence in conditioned media and cell extracts of HT-1080 treated with **653**. E) Representative *in situ* gelatin zymography of untreated BAEC conditioned media, and quantification of MMP-2 activity in absence (control) or presence of **653** 20 μM added to the incubation buffer. For all quantifications, data are the mean ±SD of at least three independent experiments (*p<0.05,**p<0.01, ***p<0.001, ****p<0,0001).

The *in vitro* observed evidences of the inhibitory activity of **653** on key steps of angiogenesis observed *in vitro* prompted us to study the *in vivo* effect of this compound in two different animal models: the chick chorioallantoic membrane (CAM) and the zebrafish yolk membrane (ZFYM) assays. In the chick CAM assay, that allowed us to evaluate the *in vivo* effect in a context of physiological angiogenesis which occurs during the development of the chick embryo, **653** was able to inhibit angiogenesis in a dose-dependent manner between 0.1-10 nmol/CAM (**Figure 18 part A** and **Table 3**), which is a very low concentration range in comparison with those reported for other known antiangiogenic compounds (~30 nmol/CAM).[313]

Then, the *in vivo* antiangiogenic activity of compound **653** was confirmed by using the zebrafish yolk membrane (ZFYM) assay, that allow us to evaluate the *in vivo* effect in a background of induced angiogenesis by the injection of the fibroblast growth factor-2 (FGF-2) in the zebrafish embryo, mimicking a pathological situation. As shown in **Figure 18 part B** and **Table 4**, the treatment of embryos with different doses of **653** diminished the angiogenic response of subintestinal vessels to exogenous FGF-2 in

[313] (a) Castro, M. E.; González-Iriarte, M.; Barrero, A. F.; Salvador-Tormo, N.; Muñoz-Chápuli, R.; Medina, M. Á.; Quesada, A. R. *Int. J. Cancer* **2004**, *110*, 31–38. (b) Martínez-Poveda, B.; Quesada, A. R.; Medina, M. Á. *Int. J. Cancer* **2005**, *117*, 775−780. (c) Cárdenas, C.; Quesada, A. R.; Medina, M. Á. *PLoS One* **2011**, *6*, e23407. (d) Garcia-Caballero, M.; Mari-Beffa, M.; Medina, M. Á.; Quesada, A. R. J. *Invest. Dermatol*. **2011**, *131*, 1347−1355.

zebrafish, manifested by a decreased number of embryos which presented a strong or mild angiogenic response and increased number of embryos unresponsive to FGF-2 stimulus.

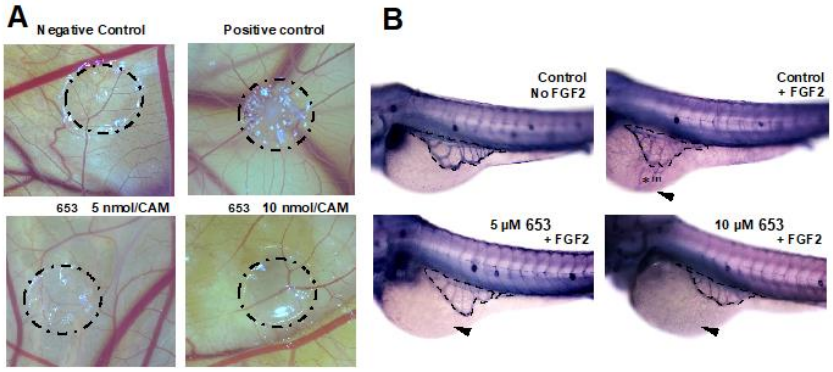


Figure 18. Compound **653** Shows a Potent Antiangiogenic Effect *in vivo*. A) Representative photographs of CAM assay testing **653**. Negative control condition containing vehicle (DMSO) and positive control condition containing Apl-1 3 nmol/CAM, were used in the assay. Circles show the locations of the methyl cellulose discs. B) Representative photographs of ZFYM assay. The response of subintestinal vessels of zebrafish embryos to FGF-2-induced angiogenesis in presence of **653** was evaluated. Zebrafish embryos were stained for alkaline phosphatase (AP) activity. Dashes lines delimit subintestinal vessels basket; arrow heads points to the FGF-2 injection site, and asterisks marks the angiogenic response to FGF-2.

Table 3. Inhibition of *in vivo* angiogenesis in the CAM assay by **653**. Table summarizes the evaluation of the effect of different doses of the compound in the CAM of chicken embryos. When angiogenesis inhibition was observed the CAM was scored positive.

CAM assay

653 (nmol/CAM)	Positive/ total	% Inhibition
0	0/11	0
0.1	1/7	14
0.5	2/7	29
1	6/9	67
5	9/12	75
10	10/10	100

Table 4. Inhibition of *in vivo* angiogenesis in the ZFYM assay by **653**. Table summarizes the observed effect of different doses of the compound in FGF-2-induced angiogenesis on the SIVs of zebrafish embryos. Embryos were scored as – (no response to FGF-2), + (mild response) or ++ (strong response).

ZFYM assay

FGF-2 Induction	653 (µM)	SCORE (%)		
		- / total(%)	+ / total(%)	++ / total(%)
None	0	20/20 (100)	0/20 (0)	0/20 (0)
2 ng	0	5/21 (23.8)	10/21 (47.6)	6/21 (28.6)
2 ng	5	9/19 (47.4)	7/19 (36.8)	3/19 (15.8)
2 ng	10	13/23 (56.5)	9/23 (39.1)	1/23 (4.3)

Cellular processes related to angiogenesis are controlled by a complex network of signaling pathways in endothelial cells. The pharmacological interference of this signaling system constitutes a very interesting strategy in order to design new therapeutic approaches.[314] Since PI3K/Akt and ERK-MAPK are two of the main signaling cascades implicated in the transduction of pro-angiogenic signals and play an essential role in the regulation of many processes such proliferation, migration, differentiation and morphogenesis,[315] we studied the effect of **653** in the activation of Akt and ERK1/2. Our results revealed that **653** prevents Akt and ERK1/2 phosphorylation in response to serum induction, therefore inhibiting the activation of both pathway at a concentration of 20 μM. These results throw some light about the mechanism of action of **653**, pointing to PI3K/Akt and ERK-MAPK pathway as major targets of the compound (**Figure 19**).

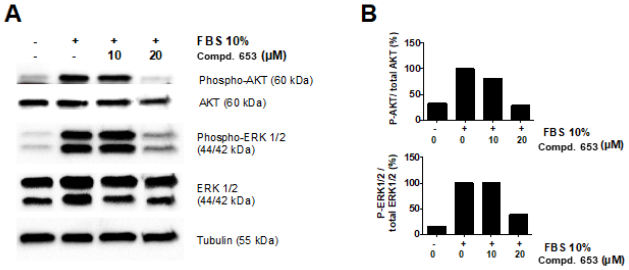
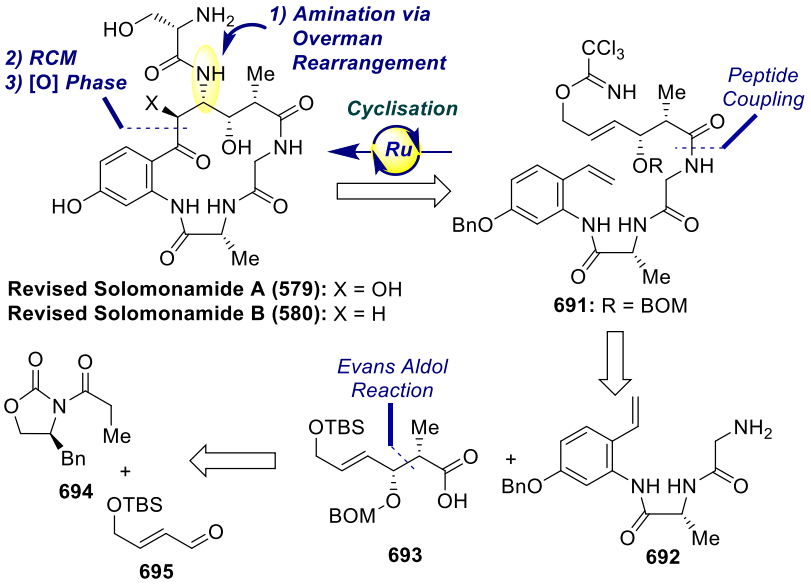


Figure 19. Compound **653** Inhibits Akt and ERK1/2 Phosphorylation in Endothelial Cells. A) Representative Western-blots of phosphorylated Akt, total Akt, phosphorylated ERK1/2, total ERK1/2 and tubulin in protein extracts from BAEC induced with serum in absence or presence of **653**. B) Western-blots were quantified by densitometry, and the pAkt/total Akt and P-ERK1/2 / ERK-1/2 ratios were expressed as the percentage of ratio in serum-stimulated BAECs (in presence of serum, in absence of **653**). Data are means of two independent experiments.

4.6. Towards the Total Synthesis of the Revised Structure of the Solomonamides

In order to complete our synthetic campaign towards the natural solomonamides, we planned to carry out the total synthesis of the corrected structure of the solomonamides A and B, as Reddy et al. revised.[283, 284] In this sense, we envisioned the introduction of the amino group via an Overman rearrangement,[316] and the cyclisation of the macrocycle through a RCM reaction from the key trichloroacetimidate **691**, which could be obtained by a peptidic coupling of carboxylic acid **693** and amine **692**. In turn, acid **693** could be achieved by a Bu_2BOTf mediated stereoselective Evans aldol reaction, involving Evans chiral auxiliary **694** and aldehyde **695** (**Scheme 89**).

[314] Muñoz-Cápuli, R.; Quesada, A. R.; Medina, M. Á. *Cell. Mol Life Sci.* **2004**, *61*, 2224−2243.
[315] (a) Shiojima, I. Walsh, K. *Circ. Res.* **2002**, *90*, 1243−1250. (b) Somanath, P. R.; Razorenova , O. V.; Chen, J.; Byzova, T. V. *Cell Cycle* **2006**, *5*, 512−518.
[316] For recent advances in the Overman rearrangement see: Fernandes, R. A.; Kattanguru, P.; Gholap, S. P.; Chaudhari, D. A. *Org. Biomol. Chem.* **2017**, *15*, 2672−2710.

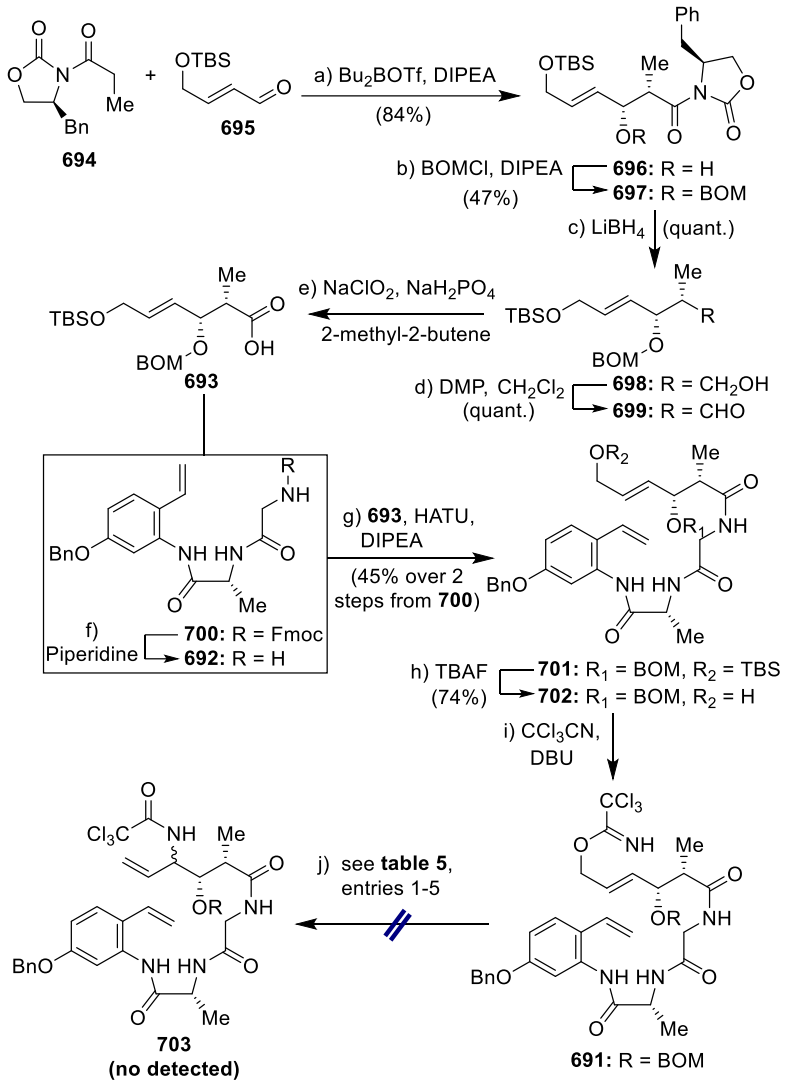


Scheme 89. Retrosynthetic Analysis of the Revised Structures of the Solomonamides

Thus, we started our designed strategy with the Bu_2BOTf mediated Evans aldol reaction of **694** and **695** to obtain oxazolidinone **696** in 84% yield. Protection of the free alcohol as a BOM derivative was achieved using BOMCl and DIPEA in a moderate 47% yield. Next, reduction of the oxazolidinone **697** by the use of $LiBH_4$ afforded alcohol derivative **698** in quantitative yield. Alcohol **698** was then oxidized to the acid in two steps, Dess-Martin periodinane (DMP) oxidation in quantitative yield followed by a final treatment of the resulting aldehyde with sodium chlorite under Pinnick conditions to furnish acid **693**. The obtained acid did not required further purification and was subsequently coupled with amine **692** to yield peptide **701** in 45% over two steps. Deprotection of the TBS protecting group in **701** by the use of TBAF afforded alcohol **702** in 74% yield, and was then reacted with CCl_3CN in presence of catalytic amount of DBU to obtain trichloroacetimidate **691** (**Scheme 90**).

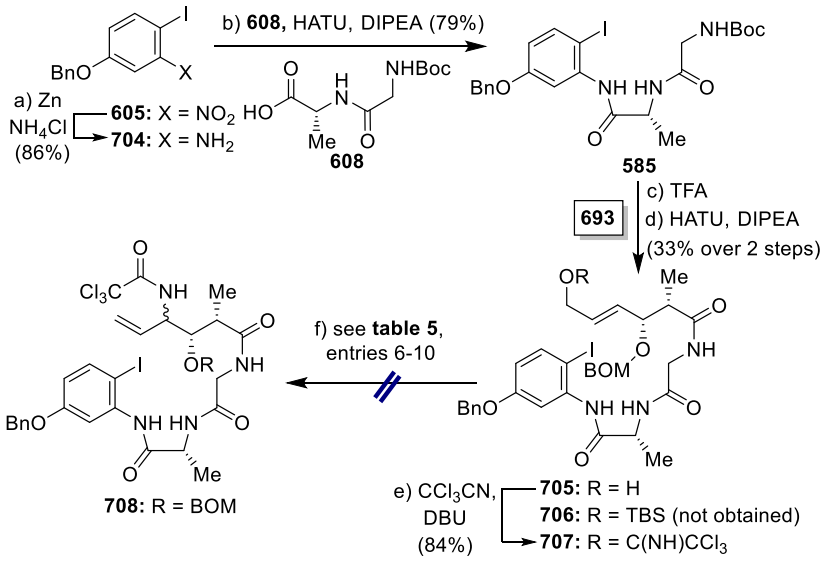
At this point of the synthesis, we were able to attempt the key Overman rearrangement of trichloroacetimidate **691**. In a first attempt, we tried the rearrangement reaction by the action of $PdCl_2(PhCN)_2$ as catalyst in the presence of 1,4-quinone as additive[317] and refluxing CH_2Cl_2 for 15 h. However, under these reaction conditions we did not observed the desired rearrangement product, instead starting material was recovered (**Table 5**, entry 1). Other reactions conditions were attempted, changing the catalyst, by the use of COPCl, temperature, solvent and/or additive, but the reactions met with failure, recovering starting material and/or obtaining unidentified degradations products in all the cases tested (**Table 5**, entries 2-5). These discouraging results could be explained by a coordination of the palladium catalyst with the styryl double bond during the Overman rearrangement. Having in mind this hypothesis, we decided to change the styryl group by a iodide to avoid these possible coordination effects.

[317] Sutherland, A.; Zaed, A. M. *Org. Biomol. Chem.* **2010**, *8*, 4394−4399.



Scheme 90. Synthesis of Trichloroacetimidate **691** and Attempts to the Synthesis of Trichloroacetamide **703** via Overman Rearrangement

With this purpose, we started the synthesis of the required iodo trichloroacetimidate **707** from nitro derivative **605** (**Scheme 91**). Reduction of the nitro group by the action of Zn/NH_4Cl was followed by a peptide coupling of the resulting amine **704** with acid **608** to obtain peptide **585** in 79% yield. Then, a two-steps sequence, involving a Boc deprotection and a subsequent peptide coupling with acid **693**, yielded **705** in 33% yield over two steps with the unexpected cleavage of the silyl protecting group. The final conversion of **705** into iodo trichloroacetimidate **707** was achieved in 84% yield by the reaction with CCl_3CN in presence of DBU (**Scheme 91**). Once we had in our hands compound **707**, we attempted the Overman rearrangement under the same reaction conditions employed above (**Table 5**, entry 6). However, the result of the reaction was the same than the previous cases, not detecting the desired trichloroacetamide **708**, instead recovering starting material. Different attempts to optimize this rearrangement reaction by the change of catalyst, temperature, solvent and/or additive were unsuccessful, recovering trichloroacetimidate **707** in all cases (**Table 5**, entries 6-10).



Scheme 91. Synthesis of Trichloroacetimidate **707** and Attempts to the Synthesis of Trichloroacetamide **708** via Overman Rearrangement

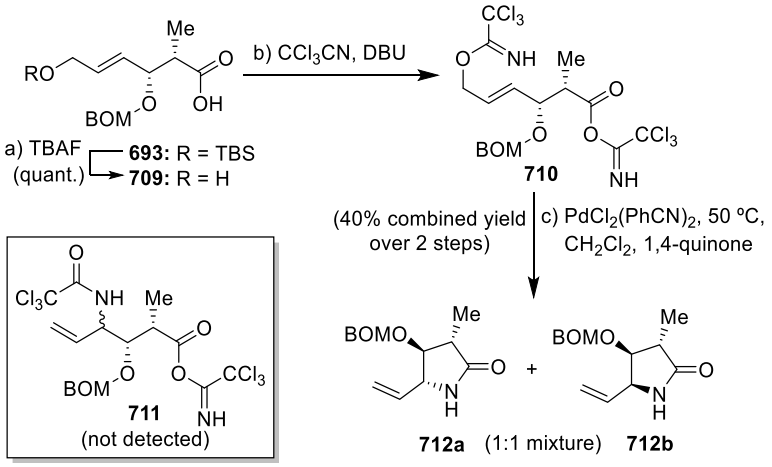
Table 5. Attempts for Overman Rearrangement of **691** and **707** [a]

Entry	Compd.	Catalyst	Temperature	Solvent	Additive	Product
1[b]	**691**	$PdCl_2(PhCN)_2$	45 ºC	CH_2Cl_2	1,4-quinone	Recoverd **691**
2[b]	**691**	$PdCl_2(PhCN)_2$	45 ºC	CH_2Cl_2	none	Recoverd **691**
3[b]	**691**	$PdCl_2(PhCN)_2$	80 ºC	Toluene	1,4-quinone	Degradation
4[b]	**691**	(*R*)-COPCl	80 ºC	Toluene	1,4-quinone	Recoverd **691**
5[b]	**691**	none	160 ºC	Xylene	anh. K_2CO_3	Degradation
6[b]	**707**	$PdCl_2(PhCN)_2$	45 ºC	CH_2Cl_2	1,4-quinone	Recovered **707**
7[b]	**707**	(*R*)-COPCl	25 ºC	CH_2Cl_2	none	Recovered **707**
8[c]	**707**	(*R*)-COPCl	25 ºC	CH_2Cl_2	1,4-quinone	Recovered **707**
9[c]	**707**	(*R*)-COPCl	45 ºC	CH_2Cl_2	1,4-quinone	Recovered **707**
10[c]	**707**	(*R*)-COPCl	80 ºC	Toluene	1,4-quinone	Recovered **707**

[a] All reactions were carried out with 1.0 equiv of **691** or **707**, 10 mol% of catalyst and 50 mol% of 1,4-quinone or 2 mg of anhydrous K_2CO_3/mL solvent. Dry solvents were used in all cases, with a final molar concentration of ~0.03 M. All the reactions were stirred overnight. [b] The reaction was carried out with crude trichloroacetimidate in presence of DBU. [c] The reaction was carried out with pure trichloroacetimidate previously purified by flash column chromatography, 30% EtOAc in hexanes → 80% EtOAc in hexanes. COP = Di-μ-chlorobis[η^5-(*R*)-(*pR*)-2-(2′-(4′-methylethyl)oxazolinyl) cyclopentadienyl,1-*C*,3′-*N*)(η^4 tetraphenylcyclobutadiene)cobalt]dipalladium

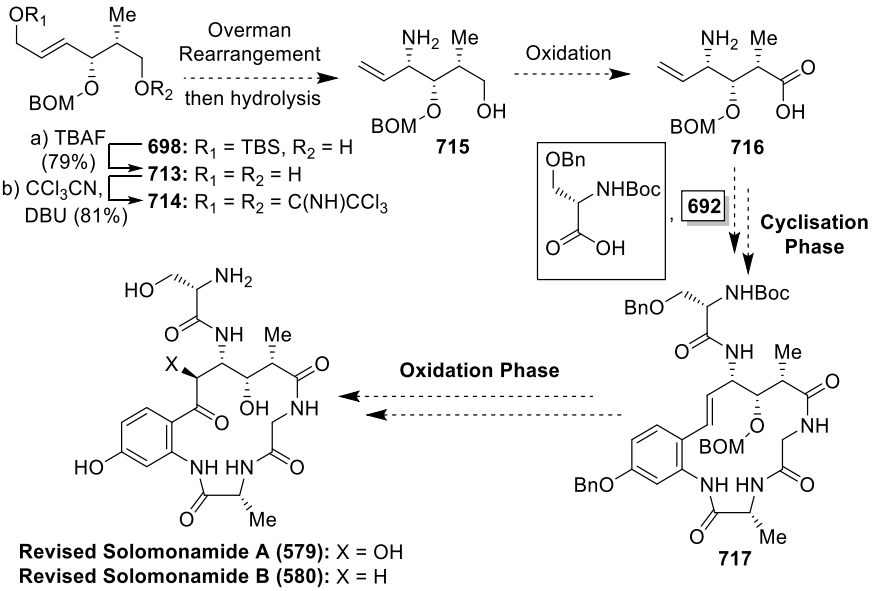
At this point, no further work was required to recognize that the Overman rearrangement in our system was extremely hard to accomplish. Having demonstrated that the styryl double bond was not the problem for the failure of the Overman rearrangement, a plausible explanation could be the chelation of the palladium with the nitrogen groups along the peptide structure found in **691** or **707**. Therefore, a new approach was considered. Our new approach was based on the introduction of the amino group at the early stages of the synthesis in order to avoid the problematic Overman rearrangement by the time the peptidic structure is already installed. With this aim, we started from the previously synthesized acid **693**, which was transformed into hydroxy acid **709**. Treatment of **709** with CCl_3CN in presence of DBU afforded bis-

trichloroacetimidate **710**, which was subjected to the Overman rearrangement by the use of $PdCl_2(PhCN)_2$ as catalyst in refluxing dichloromethane and in the presence of 1,4-quinone as additive. However, the expected trichloroacetamide **711** was not detected, obtaining instead a separable 1:1 mixture of lactames **712a** and **712b** in a 40% combined yield (**Scheme 92**).



Scheme 92. Attempts to the Synthesis of Trichloroacetamide **711**

Considering that the presence of the second trichloroacetimidate group in **710** could favour the cyclisation to form the lactame, we decided to start the synthesis from allylic alcohol **698** to avoid this undesired cyclisation reaction. As shown in **Scheme 93**, TBS deprotection in **698** yielded diol **713** in 79%, which was then treated with CCl_3CN/DBU to obtain trichloroacetimidate **714** in 81% yield. Unfortunately, the Overman rearrangement of **714** as well as the subsequent steps depicted in **Scheme 93** still remain incomplete due to the lack of time. Thus, the results from this new approach towards the solomonamides are not included in the current PhD Thesis, and it will be reported in due time.



Scheme 93. Planned Strategy Towards the Total Synthesis of the Revised Structures of the Solomonamides

4.7. Summary

In conclusion, an extensive synthetic exploration directed towards the solomonamides was conducted based on a ring-closing metathesis as the key reaction for the rapid and efficient access to their macrocyclic cores. The result of this synthetic study was the establishment of an efficient ring closure process which proceeded in high yields and complete stereoselectivity. During the course of these efforts, unexpected hurdles arose along the way, mainly with: 1) the reactivity of the hydroxyl group at the benzylic position (compounds **626** and **636**); 2) the reactivity of diolefins containing allylic and homoallylic alcohols (compounds **600**, **601**, **627**, **642**, **654**, **659**, **667** and **669**) or containing a β,γ-unsaturated carbonyl system (case of compounds **679** and **687**) toward the ruthenium catalysts, and 3) the reactivity of macrocyclic olefins (compounds **615**, **623** and **643**) toward oxidative reagents. Although many of these synthetic problems were overcome, others remained elusive and represent synthetic challenges for future works. In relation to the ring-closing metathesis reactions, many of the described findings support the observations and results reported by other authors for this reaction on this class of structural systems.

More importantly, not only did we explore the scope and limitations of the ring-closing metathesis in the synthesis of the macrocyclic core of the solomonamides, but we also identified several structurally related solomonamide precursors possessing significant cytotoxicities against various tumor cell lines, including endothelial cells, in the low μM range. In addition, the putative antiangiogenic potential of the solomonamide synthetic precursors has been evaluated. Through a preliminary *in vitro* screening, based in the inhibitory activity of endothelial tube formation, the compound **653** was selected for a deeper characterization of its antiangiogenic potential, and we found that **653** is able to inhibit some key steps of the angiogenic process, including the proliferation, migration and invasion of endothelial cells, and to diminish their capability to degrade the extracellular matrix proteins. Furthermore, the antiangiogenic potential of **653** was confirmed by two different *in vivo* models, the chorioallantoic membrane (CAM) and the zebrafish yolk membrane (ZFYM) assays, respectively. The reduction in ERK1/2 and Akt phosphorylation in endothelial cells treated with **653** indicated that the mechanism of action of this compound could target the upstream components that are common to both pathways. Thus, our results show a new and interesting biological activity of **653** as an inhibitor of the persistent and deregulated angiogenesis that characterizes cancer and other pathologies. In addition, these results suggest the potential therapeutic application of solomonamide derivatives and reinforce the value of marine products as drug candidates for the treatment of angiogenesis-related malignances.

In summary, the described chemistry highlights the benefits of the olefin metathesis reaction in the field of the total synthesis of natural products, featuring convergency and flexibility for structural diversity and has allowed the identification of bioactive compounds with interesting antitumor properties. In addition, these biological

evaluations of relatively simple compounds, devoid of the functional groups present in the natural counterparts, portend promising antitumor properties for the natural products and qualify them as new scaffolds of biological and medicinal interest. Finally, several synthetic efforts towards the total synthesis of the revised structures of the solomonamides have been initiated based on an Overman rearrangement strategy. The completion of the synthesis of the natural products, the design of new analogues based upon compound **653**, and further biological studies to elucidate the mechanism of its antiangiogenic activities are currently in progress and they will be reported in due course.

Chapter 5

Celebeside Campaign

5.1. Isolation, Structure and Biology of the Celebesides

As mentioned before, Nature represents a striking and a huge source of new natural products which are key in drug discovery.[318] In particular, cyclodepsipeptides[286] are secondary metabolites that comprise a wide variety of cyclic peptides of natural origin characterized by the occurrence of at least one ester linkage.[319] The wide spectrum of biological activities that this class of natural product display, including immunosuppressant, antibiotic, antifungi, antiinflammatory or antitumoral activities, together with their atractive molecular structures, have elicited great interest to the biological, medical and chemical community.[320] As a new demonstration of the impressive source of secondary metabolites type-cyclodepsipeptide from marine enviroment, three unprecedented cyclic depsipeptides termed celebesides A-C (**718**-**720**) were isolated by Bewley et al.[321] from the marine sponge *Siliquariaspongia mirabilis* collected from the Sulawesi Island, in Indonesia (**Figure 20**).

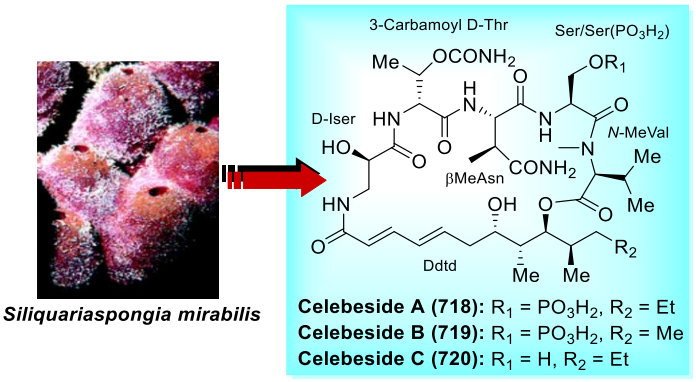


Figure 20. Molecular Structures of Celebesides A-C

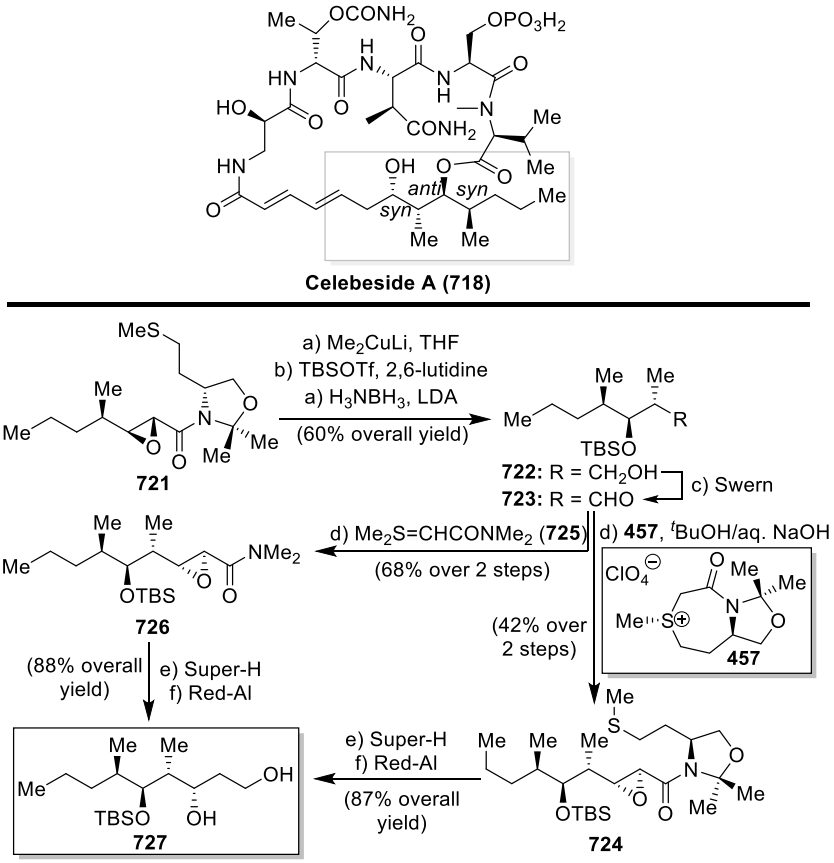
The structure of these compounds were elucidated by extensive spectroscopic methods. The absolute configurations of the amino acids were determined by Marfey's method[322] and chiral HPLC, while the relative configuration of the polyketide moiety was resolved by combination of *J*-based analysis and quantic mechanic (QM) calculations. These natural products are unusual [26]-membered cyclic depsipeptides that contain a polyketide chain namely 7,9-dihydroxy-8,10-dimethyltrideca-2,4-dienoic acid (Ddtd), and a peptide chain comprises by five amino acids residues, including a *N*-methyl valine, a β-methyl L-asparagine, a D-isoserine, a 3-carbamoyl D-threonine and a L-serine in celebeside C (**720**), and a phosphoserine residue in celebesides A (**718**) and B (**719**). Interestingly, the 3-carbamoyl threonine and phosphoserine are uncommon aminoacids contained in marine natural products. From the biological standpoint, celebeside A (**718**)

[318] (a) *Drug Discovery from Nature*; Grabley, S.; Thiericke, R.; Eds.; Springer-Verlag: Berlin, **2000**. (b) Samuelsson, G. *Drugs of Natural Origin*; Swedish Pharmaceutical Press: Stockholm, **1992**. (c) Nicolaou, K. C.; Chen, J. S.; Dalby, S. M. *Bioorg. Med. Chem.* **2009**, *17*, 2290–2303.
[319] (a) Faulkner, D. J. *Nat. Prod. Rep.* **1994**, *11*, 355–394. (b) Burja, A. M.; Banaigs, B.; Abou-Mansour, E.; Burgess, J. G.; Wright, P. C. *Tetrahedron*, **2001**, *57*, 9347–9377. (c) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1–48.
[320] Ballard, C. E.; Yu, H.; Wang, B. *Curr. Med. Chem.* **2002**, *9*, 471–498.
[321] Plaza, A.; Bifulco, G.; Keffer, J. L.; Lloyd, J. R.; Baker, H. L.; Bewley, C. A. *J. Org. Chem.* **2009**, *74*, 504–512.
[322] Fujii, K.; Ikai, Y.; Oka, H.; Suzuki, M.; Harada, K.-I.; *Anal. Chem.* **1997**, 69, 5146–5151.

showed anti-HIV activity, with an IC_{50} of 1.9 μg/ml. In addition, **718** was cytotoxic against a human colon cancer cell line (HTC-116) in the low μM range. In contrast, celebeside C (**720**) was inactive, while celebeside B (**719**) was not biologically evaluated. Once again, the scarcity of the isolated cyclodepsipeptides from the natural sources is a drawback for further pharmacological assays. This difficulty to access large amounts of these compounds makes quite difficult to gain insight into their biological profiles and mechanism of biological action and justifies the chemical synthesis of these unexplored marine cyclodepsipeptides.

5.2. Chemistry of the Celebesides

The synthesis of the lipidic chain of celebeside A (**718**) carried out by our group in 2014 represents the only synthetic approach towards the polyketide fragment contained in celebesides reported to date.[250e] Our synthesis was based on the use of a new class of sulfonium salts to obtain glycidic amides in a stereoselective fashion (**Scheme 94**).



Scheme 94. Synthesis of the Polyketide Chain of the Celebeside A (Sarabia et al. 2014)[250e]

The oxirane ring-opening reactions of the obtained epoxy amides let to obtain the *syn,anti,syn* dipropionate-acetate stereopentad unit contained in the celebesides, as well

as in many other natural products as YM-47522,[323] the anti-fungal basiliskamide[324] and the cyclodepsipeptide langunamide A.[325] As depicted in **Scheme 94**, the oxirane ring opening of **721** with Me_2CuLi was followed by TBS protection of the resulting alcohol, and subsequent amide reduction with $NH_3{\cdot}BH_3$/LDA to obtain alcohol **722** in 60% overall yield from **721**. Then, Swern oxidation afforded aldehyde **723** which was treated with chiral sulfonium salt **457** under basic conditions to afford epoxy amide **724** in 42% yield over 2 steps. This reaction was performed with the known non-chiral sulfur ylide **725** to gave epoxy amide **726** as the major isomer (ratio 9:1) in 68% yield over 2 steps. The efficient stereocontrol during the nucleophilic addition was due to the starting chiral aldehyde **723**. Reduction of epoxy amide **724** or **726** with Super-H® gave the corresponding epoxy alchols wich were treated with Red-Al to obtain diol **727** which represent the complete polyketide fragment of celebeside A (**718**).

5.3. An Olefin Metathesis Approach Towards the Celebesides

5.3.1. Synthesis of the Peptide Fragment of the Celebesides

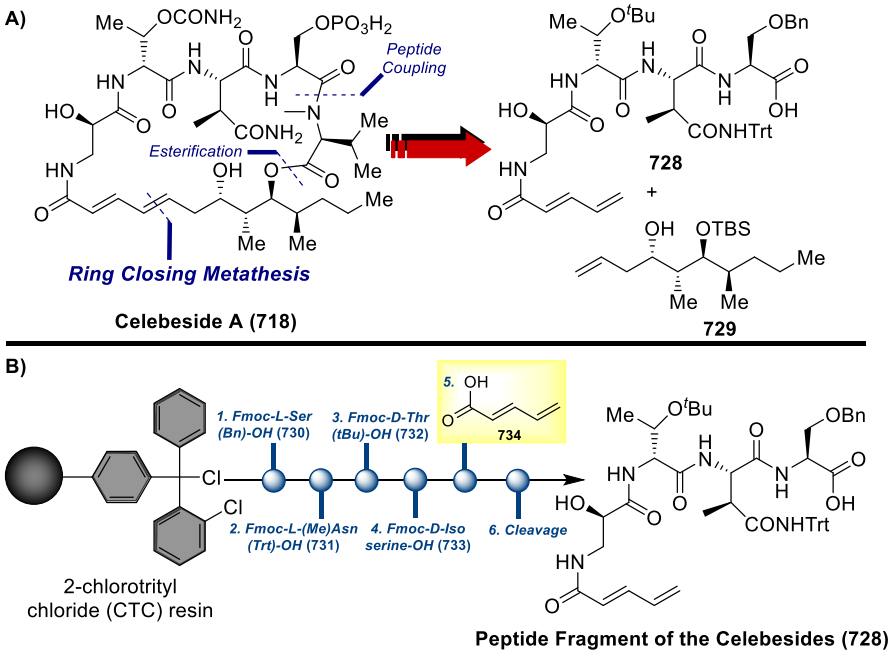
We decided to initiate a research programme towards the total synthesis of the celebesides, which is justified by the following reasons: (1) Intriguing biological properties displayed by these natural compounds; (2) The need to have and supply enough material for further biological evaluations; (3) To confirm their novel structures; (4) To pave the synthetic scheme for generation of related compounds as novel scaffolds with potential therapeutic applications. In particular, among the three celebesides, we firstly focused our efforts on the synthesis of celebeside A (**718**) due to the attractive biological profile displayed.

To this aim, we designed a retrosynthetic analysis of the celebeside A (**718**) based on an olefin ring-closing metathesis reaction as the key step for the construction of the macrocycle. Thus, as depicted in **Scheme 95**, **part A**, our analysis began with the amide and ester disconnections of the L-serine residue and the *N*-Me-valine residue, respectively, to render two key fragments: the peptidic fragment **728** and the polyketide fragment **729**. For the consecution of the peptide fragment of the celebesides (**728**), we decided to use the solid phase peptide synthesis (SPPS) methodology as a suitable technology for rapid and advantageous access to the linear peptide chain. We selected the 2-chlorotrityl chloride (CTC) resin due to its resistence in the basic media employed in peptide coupling conditions. The general strategy is depicted in **Scheme 95**, **part B**.

In our first approach towards celebeside A, we initially targeted a more simple derivative for a rapid validation of our RCM strategy. In this sense, we planned to produce a model peptidic fragment that possessed a β-alanine aminoacid intead of the D-isoserine residue which is contained in the natural products. In addition, the proposed model did

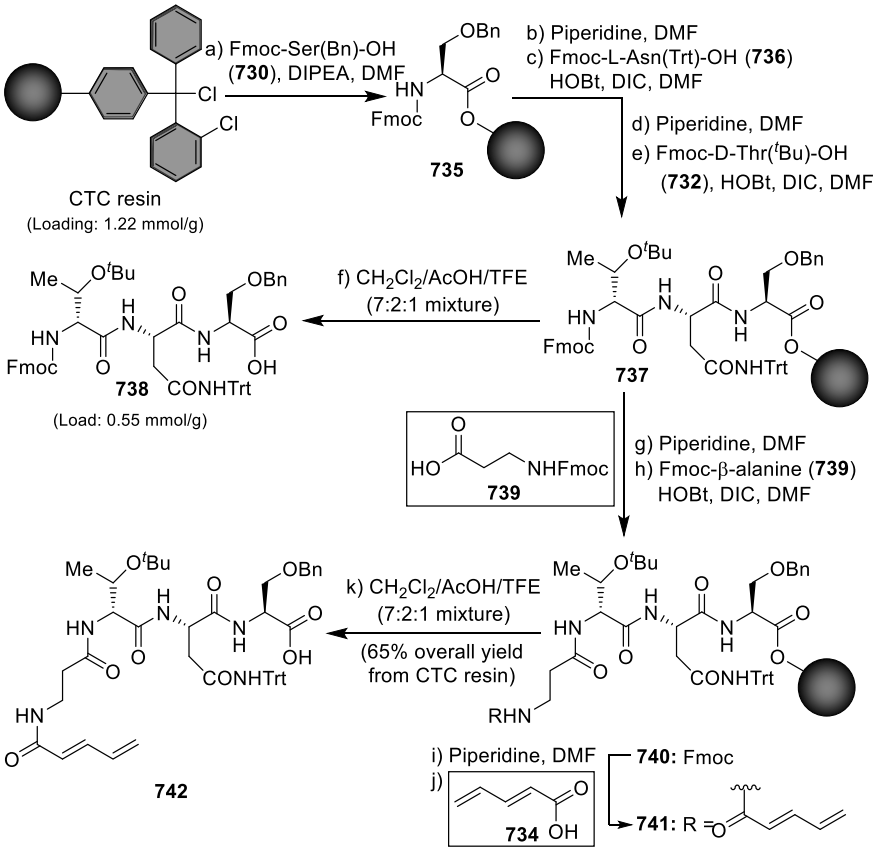
[323] Ermolenko, M. S. *Tetrahedron Lett.* **1996**, *37*, 6711–6712.
[324] Barsby, T.; Kelly, M. T.; Andersen, R. J. *J. Nat. Prod*. **2002**, *65*, 1447–1451.
[325] Huang, W.; Ren, R.-G.; Dong, H.-Q.; Wei, B.-G.; Lin, G.-Q. *J. Org. Chem*. **2013**, *78*, 10747–10762.

not contain the methyl group upon the asparagine residue, avoiding the preparation of this complex amino acid.



Scheme 95. Retrosynthetic Analysis of Celebeside A (A) and Solid Phase Peptide Synthesis (SPPS) Strategy (B)

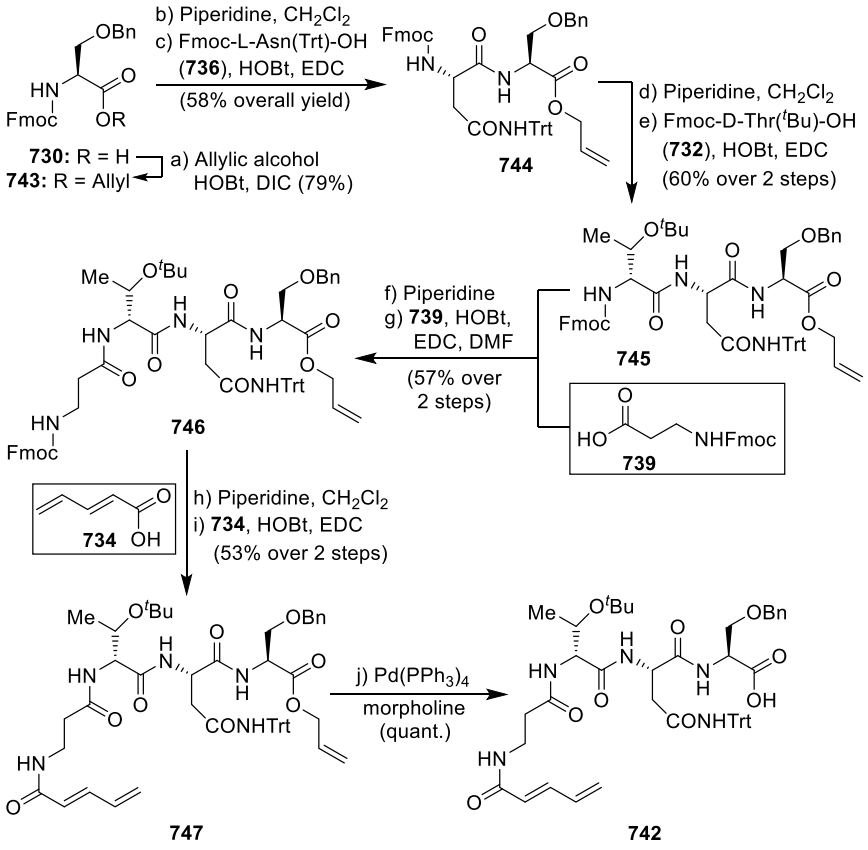
With this purpose, we started the solid phase synthesis from the CTC resin which was properly derivatized with the Fmoc-L-Ser(Bn)-OH (**730**) using HOBt and DIPEA in dimethylformamide (DMF) for 30 h to produce the resin-bound peptide **735**. The Fmoc group of **735** was removed by treatment with 20% solution of piperidine in DMF and the Fmoc-L-Asn(Trt)-OH (**736**) was loaded onto the resulting resin using HOBt and DIC in DMF. The same sequence to remove the Fmoc groups and to couple amino acids was repeated to introduce the Fmoc-D-Thr(^{t}Bu)-OH (**732**). To check the loading of the amino acid and to ensure the effectiveness of the chosen coupling procedure, we decided to cleave the tripeptide by treatment of **737** with AcOH/CF_3CH_2OH (TFE)/CH_2Cl_2 (7:2:1), which gave pure tripeptide **738**. The synthesis was continued from **737**, repeating the procedure of coupling and Fmoc deprotection steps for the sequentially introduction of Fmoc-β-Ala-OH (**739**), and the commercial 2,4-pentadienoic acid **734**, to obtain the resin-bound peptide **741**. At the end of the solid phase peptide synthesis, the resin-bound peptide **741** was cleaved from the resin by treatment with a AcOH:TFE:CH_2Cl_2 (7:2:1) mixture to obtain the model peptide chain of the celebesides **742** in 65% overall yield from CTC resin in a high degree of purity as determined by its NMR spectra and did not required further purification (**Scheme 96**).



Scheme 96. Solid Phase Synthesis of **742**

In order to ensure that during the solid phase synthesis of **742** any process of epimerization took place,[326] we decided to repeat the synthesis via solution phase, and then compare the spectroscopic data of both products, which should match. Thus, the synthesis of **742** via solution phase began with the protection of the Fmoc-L-Ser(Bn)-OH (**730**) as allyl ester derivative. From protected compound **743**, deprotection of the Fmoc group by treament with a solution of piperidine in CH_2Cl_2 afforded the corresponding free amine, which was subjected to a peptide coupling with the Fmoc-L-Asn(Trt)-OH (**736**) in presence of HOBt and EDC to obtain peptide **744** in 58% over 2 steps. Then, an iterative process to deprotect the Fmoc groups and to couple the Fmoc aminoacids derivatives was repeated three times under the same reaction conditions than previously employed to introduce sequentially the amino acids Fmoc-D-Thr(ᵗBu)-OH (**732**) and Fmoc-β-Ala-OH (**739**) and the 2,4-pentadienoic acid **734** in 60%, 57% and 53% over 2 steps, respectively (**Scheme 97**). Final deprotection of the allyl group in presence of $Pd(PPh_3)_4$ and morpholine gave the model peptidic chain of the celebesides (**747**) in quantitative yield. Spectroscopic properties of **747** obtained from solid phase and from solution phase were identical, thus confirming that epimerization process did not occur during the solid phase synthesis. Thus, with these results, we have established a solid phase synthesis strategy for the construction of the peptide fragment of the celebesides.

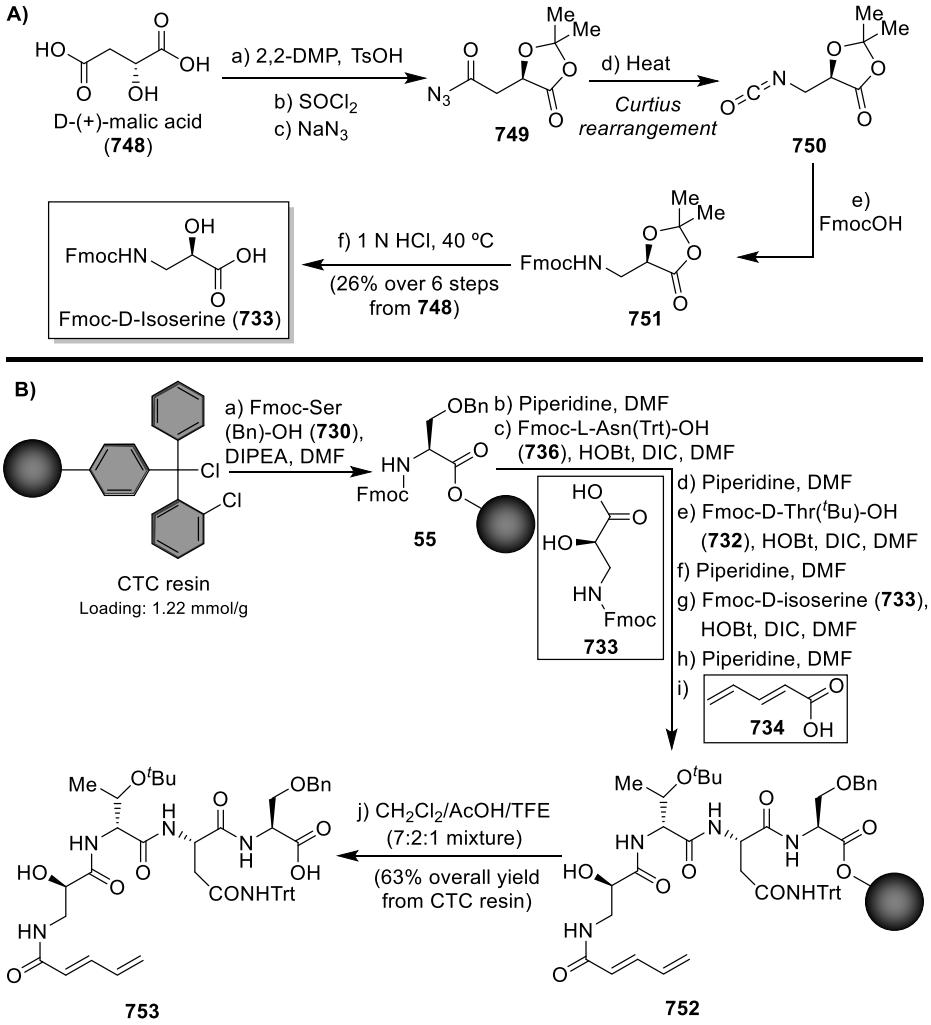
[326] For an example of epimerization process in solid phase peptide synthesis see: Spatola, A. F.; Darlak, K.; Romanovskis *Tetrahedron Lett.* **1996**, *37*, 591–594.



Scheme 97. Synthesis of **742** by Solution Phase

With the aim to extend the previous established solid phase strategy to a more advanced celebeside peptide chain, we decided to include in the peptidie fragment the amino acid D-isoserine that is contained in the structure of the natural celebesides. With this purpose, we first carried out the synthesis of the required Fmoc-D-isoserine **733.** Thus, the synthesis of **733** started from D-(+)-malic acid (**748**), which was transformed in three steps into acylc acide **749**, as shown in **Scheme 98**, **part A**. Then, the Curtius rearrangement was used to introduce the isocyanate group through the termal decomposition of the carboxylic azide intermediate. The resulting isocyanate **750** was reacted with FmocOH to afford carbamate **751**, which was subsequent treated with HCl at 40 ºC to obtain Fmoc-D-isoserine (**733**)[327] in 26% over 6 steps (**Scheme 98**, **part A**). With **733** in hand, we proceeded with the solid phase synthesis of the more advanced peptidic chain of celebesides, represented by compound **753** in **Scheme 98, part B**. Starting again from the 2-chlorotrityl chloride (CTC) resin, we repeated the same steps for the solid phase synthesis of **742**, but in this case we included the Fmoc D-isoserine **733** instead the Fmoc-β-alanine (**739**), thus obtaining the corresponding peptide fragment **753** in 63% overall yield from CTC resin (**Scheme 98, part B**).

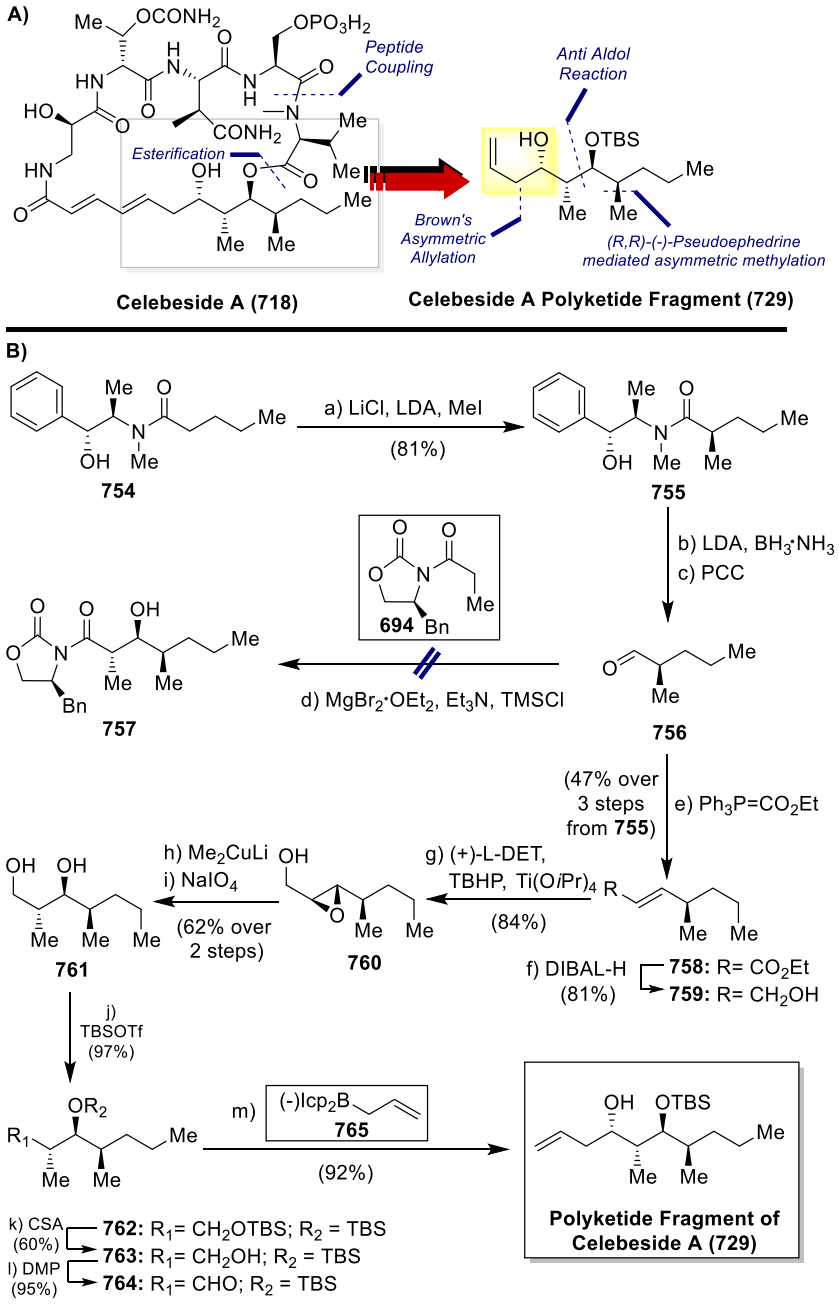
[327] The synthesis of D-isoserine has been described in the literature according to a slightly modified protocol (a) Kodra, J. T.; Jorgensen, A. S.; Andersen, B.; Behrens, C.; Brand, C. L.; Christensen, I. T.; Guldbrandt, M.; Jeppesen, C. B.; Knudsen, L. B.; Madsen, P.; Nishimura, E.; Sams, C.; Sidelmann, U. G.; Pedersen, R. A.; Lynn, F. C.; Lau, J. *J. Med. Chem*. **2008**, *51*, 5387–5396.(b) Böttcher, C.; Burger, K. *Tetrahedron Lett*. **2003**, *44*, 4223–4226.



Scheme 98. Synthesis of Fmoc-D-Isoserine **733** (A) and Solid Phase Synthesis of **753** (B)

5.3.2. Synthesis of the Polyketide Fragment of Celebeside A

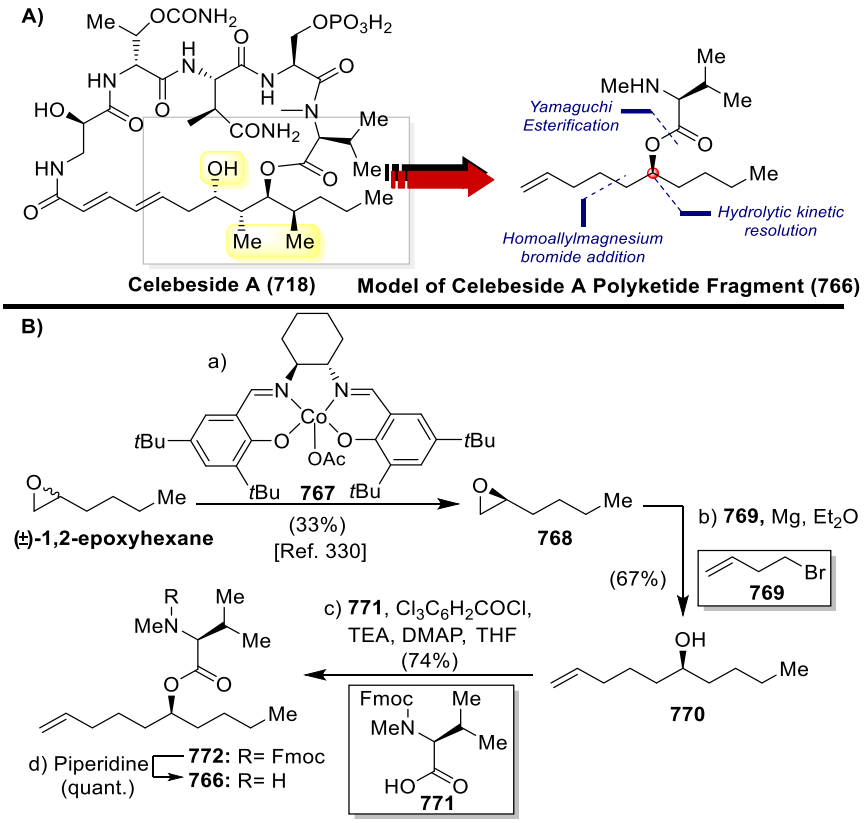
At this point of the synthesis, where we were able to establish a synthetic strategy for the consecution of the peptidic fragment of the celebesides by solid and solution phase, we focused on the synthesis of the polyketide fragment of celebeside A. As previously showed in **Scheme 94**, our goup achieved the synthesis of the polyketide fragment of celebeside A by oxirane ring-opening reactions of epoxy amides obtained by sulfonium ylides. Now, with the aim to explore new strategies, we planned a different approach without the use of sulfoniums ylides. In this sense, the new approach was based on the combined asymmetric methylation, anti-aldol reaction, and Brown's asymmetric allylation to obtain the required *syn,anti,syn* dipropionate-acetate stereopentad unit (**Scheme 99**, **part A**).



Scheme 99. Retrosynthetic Analysis (A) and Synthesis of the Polyketide Fragment of the Celebeside A (**729**) (B)

Thus, this new synthetic plan started with the conversion of aldehyde **756** in α,β-unsaturated ester **758** via a Wittig reaction by the use of [(Ethoxycarbonyl)methylene]triphenylphosphorane. Reduction of the ester **758** with DIBAL-H afforded allylic alcohol **759** in 81% yield. Subsequent Sharpless asymmetric epoxidation by the use of (+)-L-DET gave epoxy alcohol **760** in 84% yield, which was subjected to the oxirane opening employing Me_2CuLi to obtain a 3:1 mixture of opening products in 2- and 3- positions, respectively. Therefore, the oxirane opening step was followed by a periodic cleavage employing $NaIO_4$ to obtain diol **761** in 62% over two steps (**Scheme 99**). From **761**, a sequence of protection of the diol as silyl ethers and

selective deprotection of the primary alcohol was achieved in 60% overall yield to obtain alcohol **763**, which was subjected to a oxidation reaction with Dess-Martin periodinane to obtain aldehyde **764** in 95% yield. Final Brown's asymmetric allylation of aldehyde **764** by the use of (-)-Ipc_2B(allyl) gave **729** in excellent 92% yield and complete stereoselectivity, which represents the complete polyketide fragment of the celebeside A.



Scheme 100. Synthesis of Celebeside A Polyketide Fragment Model **766**

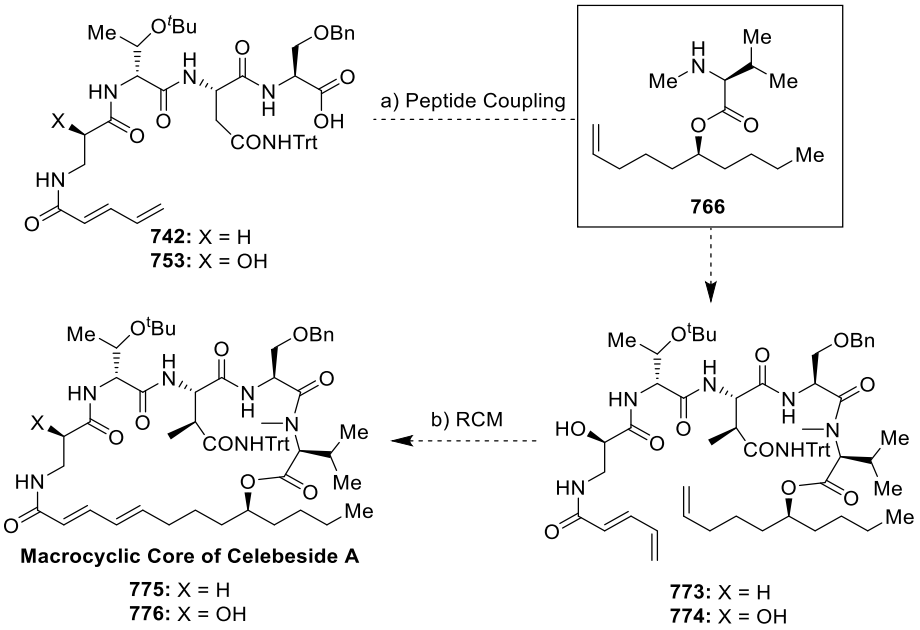
At this point where we were able to establish a solid strategy to access to the polyketide fragment of the celebeside A, we decided to focus on the preparation of a more simple derivative for a rapid validation of our RCM strategy, represented by compound **766** in **Scheme 100**, avoiding the use of the complex chain **729** contained in the natural product which required more steps for its synthesis.

The synthesis of the polyketide chain model **766** started with the known hydrolytic kinetic resolution of the corresponding racemic 1,2-epoxyhexane by the action of cobalt catalyst **767**, to afford enationmeric pure **768** in 33% yield.[328] Then, epoxide opening of **768** by use of homoallylmagnesium bromide gave alohol **770** in 67% yield, which was subjected to a Yamaguchi esterification with Fmoc-*N*-Me-Valine-OH (**771**) to obtain ester **772** in 74% yield. Finally, Fmoc deprotection by treatment of **772** with piperdine yielded **766** in quantitative yield (**Scheme 100**).

[328] Haase, B.; Schneider, M. *Tetrahedron: Asymmetry* **1993**, *4*, 1017–1026.

5.3.3. Towards the Macrocyclic Core of Celebeside A

With model amine **766** in our hands, we would be able to complete the last steps of towards the celebeside A in order to try our RCM strategy (**Scheme 101**). However, this task still remains incomplete due to the lack of time. Thus, the last steps towards the celebesides are not included in the current PhD Thesis, and it will be reported in due time.



Scheme 101. Planned Strategy towards the Macrocyclic Core of the Celebeside A via RCM

5.4. Summary

In conclusion, we have envisioned a synthetic strategy directed towards the celebesides utilizing an olefin metathesis reaction to form the [26]-membered ring contained in these natural products. In our strategy, we have used the solid phase synthesis as a suitale technology for a rapid and efficient access to the peptide fragment contained in the celebesides (compounds **742** and **753**), while the polyketide chain of the celebeside A, represented by compound **729**, has been achieved in a stereoselective fashion, featuring an asymmetric methylation, epoxide opening and Brown's asymmetric allylation as the key steps. The described synthetic strategy for the celebesides would allow for access to the natural products, as well as would offer the opportunity for the generation of a wide array of celebeside analogues by modifing the amino acids contained in the peptide chain during the solid phase-based synthesis in an easy and rapid manner. The completion of the synthesis of the celebeside A is currently in progress and will be reported in due course.

Chapter 6

Conclusions

6.1. Conclusions

The conclusions of the current PhD Thesis are summarized as the following:

1) We have established a new total synthesis of (-)-depudecin (**442**) utilizing an olefin cross-metathesis reaction as the key step, which was successfully achieved in a convergent manner to provide (-)-depudecin (**442**) in only 12 steps and 26% overall yield from (+)-methyl-D-lactate. This new convergent approach greatly improves upon our previous linear synthesis (17 steps, 19% overall yield) as well as the Schreiber synthesis (23 steps, 0.7% overall yield).

2) The developed synthetic route was amenable to stereochemical and functional modifications, allowing the preparation of two stereoisomers of (-)-depudecin, the 10-*epi*-depudecin (**498**) and its enantiomer (*ent*-**442**), as well as homodepudecin (**506**). In addition, we have complemented the set of analogues with the preparation of truncated analogues **540**, **541** and **555**.

3) The synthesized depudecin analogues were biologically evaluated against several tumor cell lines, including endothelial cells and the results led us to complete a preliminary structure-activity relationship (SAR) study for this natural product concluding that: a) the C-10 stereochemistry of the product is not essential upon the biological activity; b) the presence of at least one of the epoxide groups is key upon the biological activity, but it is not necessary the simultaneous presence of both epoxides; and c) the terminal allylic alcohol system is not essential, and it can be substitued by its isomer.

4) An extensive synthetic exploration directed towards the solomonamides was conducted based on a ring-closing metathesis as the key reaction for the rapid and efficient access to their macrocyclic cores, which proceeded in high yields and complete stereoselectivity.

5) We identified several structurally related solomonamide precursors possessing significant cytotoxicities against various tumor cell lines, including endothelial cells, in the low μM range. In particular, we found that compound **653** exhibits a potent antiangiogenic effect *in vitro* and *in vivo*, and the results suggest the potential therapeutic application of solomonamide derivatives as inhibitors of the persistent and deregulated angiogenesis that characterizes cancer and other pathologies.

6) We envisioned a synthetic strategy directed towards the celebesides utilizing an olefin metathesis reaction to form the [26]-membered ring contained in these natural products. In our strategy, we used the solid phase synthesis as a suitable technology for a rapid and efficient access to the peptide fragment contained in

the celebesides, while the polyketide chain of the celebeside A was achieved in a stereoselective fashion.

7) The described chemistry highlights the benefits of the olefin metathesis reaction in the field of the total synthesis of natural products, featuring convergency and flexibility for structural diversity and has allowed the identification of bioactive compounds with interesting antitumor properties.

Chapter 7

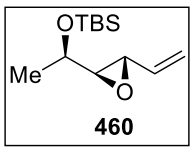
Experimental Part

7.1. General Techniques

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless using aqueous reagents or otherwise noted. All solvents used in reactions were dried and distilled using standard procedures. Tetrahydrofuran (THF) was distilled from sodium benzophenone, methylene chloride (CH_2Cl_2) from calcium hydride, diethyl ether from sodium. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All solutions used in workup procedures were saturated unless otherwise noted. All reagents were purchased at highest commercial quality and used without further purification unless otherwise stated. All reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm silica gel plates (60F-254) using UV light (254 nm) as visualizing agent and acidic ceric ammonium molybdate/phosphomolybdic acid or potassium permanganate solutions and heat as developing agents. Flash column chromatography (FCC) was performed using silica gel (60 Å, particle size 230-400 mesh) under air pressure. All solvents used for chromatographic purifications were distilled prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 MHz instrument and calibrated using residual undeuterated solvent as an internal reference. Chemical shifts are reported in ppm with the resonance resulting from incomplete deuteration of the solvent as the internal standard ($^{13}CDCl_3$: 7.26 ppm, s and 77.0 ppm, t; $^{13}CD_3OD$: 4.87 ppm, s, 3.31 ppm, quin and 49.1 ppm, sep; $^{13}C_2D_6OS$: 2.49 ppm, quin and 39.52 ppm, sep). Data are reported as follows: chemical shift δ/ppm (multiplicity, coupling constants *J* (Hz) and integration (^{1}H only)). The following abbreviations were used to explain the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; b = broad; m = multiplet or combination thereof. ^{13}C signals are singles, unless otherwise stated. High resolution mass spectrometry (HRMS) was performed on a H-ESI and APCI mass spectrometer in positive mode and using an ion trap (Orbitrap) as the mass analyzer type. HRMS signals are reported to 4 decimal places and are within ± 5 ppm of theoretical values. Specific optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a sodium halogen lamp (ƛ = 589 nm) and a cell path length of 100 mm (*c* given in g/100 mL). Melting points were collected using a Gallenkamp melting point system using a gradient of 0.5 ºC per min.

7.2. Experimental Procedures and Compound Characterization Related to Depudecin

7.2.1. Synthesis of Epoxy Alkene 460

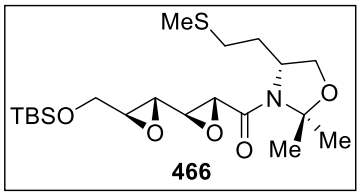


460

Epoxy Alkene 460. A solution of epoxy alcohol **464**[253] (220 mg, 0.95 mmol, 1.0 equiv) in a 1:1 DMSO:CH_2Cl_2 mixture (20 mL) was treated with Et_3N (0.4 mL, 14.20 mmol, 3.0 equiv) and SO_3·pyr (375 mg, 2.37 mmol, 2.5 equiv) at 0 ºC. The mixture was stirred until complete conversion of the alcohol (~ 3 h). After this time, the reaction mixture was quenched by

addition of a buffer solution (pH = 7) and diluted with Et_2O. The aqueous phase was extracted with Et_2O twice and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to give the crude aldehyde (~0.95 mmol) which was used in the next step without further purification. To a stirred suspension of methyl triphenylphosphonium bromide (693 mg, 1.90 mmol, 2.0 equiv) in THF (10 mL) at 0 ºC was added dropwise NaHMDS (0.95 mL, 2.0 M in THF, 1.87 mmol, 2.0 equiv). The resulting suspension was stirred for 30 min at this temperature, and after this time, a solution of the crude aldehyde (~0.95 mmol) in THF (5 mL) was added dropwise, and the resulting mixture stirred for 1 h. After this time, the crude mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain epoxy alkene **460** (100 mg, 50% over two steps) as a pale yellow oil: R_f = 0.74 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 35.2 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63–5.53 (m, 1 H), 5.45 (dd, *J* = 17.2, 1.5 Hz, 1 H), 5.26 (ddd, *J* = 10.2, 1.5, 0.5 Hz, 1 H), 3.66–3.58 (m, 1 H), 3.20 (dd, *J* = 7.5, 2.2 Hz, 1 H), 2.85 (dd, *J* = 5.9, 2.2 Hz, 1 H), 1.21 (d, *J* = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 118.9, 67.5, 63.5, 56.5, 25.8, 20.8, 18.1, –4.7, –4.9; HRMS (H-ESI) *m/e* calcd for $C_{12}H_{24}O_2Si$ $[M + H]^+$ 229.1624, found 229.1618.

7.2.2. Synthesis of Diepoxy Amide 466

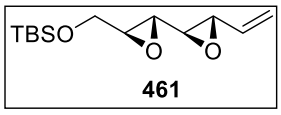


466

Diepoxy Amide 466. Epoxy alcohol **465**[254] (640 mg, 2.96 mmol 1.0 equiv) was dissolved in a CH_2Cl_2/DMSO (1:1) mixture (12 mL) and cooled at 0 ºC. At this temperature, Et_3N (1.2 mL, 8.88 mmol, 3.0 equiv) was added followed by SO_3·pyr (840 mg, 5.20 mmol, 1.8 equiv). The reaction mixture was allowed to reach room temperature and, after 5 h, was quenched by addition of a buffer solution (pH = 7) and diluted with Et_2O. The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were washed with water and brine, then dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The resulting crude aldehyde was used in the next step without further purification. To a suspension of sulfonium salt **457**[249, 250] (1.0 g, 3.40 mmol, 1.1 equiv) in *t*-BuOH (40 mL) was added a 5.0 M aqueous NaOH solution (0.6 mL, 3.0 mmol, 1.0 equiv) at 25 ºC. After 1 h at this temperature, a solution of crude aldehyde in *t*-BuOH (10 mL) was added and the resulting reaction mixture was stirred overnight. The crude mixture was then diluted with CH_2Cl_2 and H_2O and, after decantation, the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain diepoxy amide **466** (920 mg, 73% over 2 steps) as a pale yellow oil and whose spectroscopic and physical properties matched with those described in the literature:[250f] R_f = 0.20 (Silica

gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = −17.1 (*c* 0.34, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.27 (ddd, *J* = 8.8, 4.7, 3.5 Hz, 1 H), 3.97 (ddd, *J* = 9.1, 5.2, 1.3 Hz, 1 H), 3.89–3.86 (m, 1 H), 3.85 (d, *J* = 2.0 Hz, 1 H), 3.69 (dd, *J* = 12.3, 3.7 Hz, 1 H), 3.54 (d, *J* = 2.0 Hz, 1 H), 3.30 (dd, *J* = 3.4, 2.0 Hz, 1 H), 3.11–3.06 (m, 2 H), 2.59–2.50 (m, 1 H), 2.48–2.39 (m, 1 H), 2.08 (s, 3 H), 2.05–2.00 (m, 1 H), 1.83–1.73 (m, 1 H), 1.59 (s, 3 H), 1.48 (s, 3 H), 0.84 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 162.9, 95.9, 67.0, 61.6, 56.3, 55.9, 55.5, 51.7, 51.2, 34.4, 30.6, 26.2, 25.8, 22.9, 18.3, 15.7, –5.4, –5.4; HRMS (H-ESI) *m/e* calcd for $C_{20}H_{37}NO_5SSi$ $[M + H]^+$ 432.2240, found 432.2239.

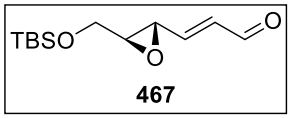
7.2.3. Synthesis of Diepoxy Alkene 461



461

Diepoxy Alkene 461. To a solution of diepoxy amide **466** (95 mg, 0.34 mmol, 1.0 equiv) in THF (1.5 mL) was added dropwise Red-Al (0.03 mL, 70% w/v in toluene, 0.09 mmol, 0.5 equiv) at 0 ºC. After 30 min at this temperature, the reaction mixture was quenched by addition of a saturated aqueous Na^+/K^+ tartrate solution and diluted with EtOAc. The resulting mixture was vigorously stirred until a clear separation of both oganic and aqueous phases. After separation of both layers, the aqueous phase was extracted with EtOAc and the combined organic extracts washed with H_2O and brine, dried over anhydrous $MgSO_4$, and the solvent evaporated under reduced pressure. The resulting crude aldehyde was used in the next step without further purification. To a stirred suspension of methyl triphenylphosphonium bromide (123 mg, 0.35 mmol, 1.75 equiv) in THF (1.0 mL) at 0 ºC was added dropwise NaHMDS (0.18 mL, 2.0 M in THF, 0.35 mmol, 1.75 equiv). The resulting suspension was stirred for 15 min at this temperature, and after this time, a solution of the crude aldehyde (~0.20 mmol) in THF (3.0 mL) was added dropwise, and the resulting mixture was stirred for 30 min. After this time, the crude mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain the epoxy alkene **461** (33 mg, 50% over two steps) as a colorless oil: R_f = 0.89 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = –20.2 (*c* 0.39, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 5.59–5.49 (m, 2 H), 5.35–5.30 (m, 1 H), 3.88 (dd, *J* = 12.2, 2.9 Hz, 1 H), 3.75 (dd, *J* = 12.2, 4.0 Hz, 1 H), 3.36 (dd, *J* = 7.0, 2.1 Hz, 1 H), 3.11 (ddd, *J* = 4.0, 2.8, 2.2 Hz, 1 H), 3.00 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.92 (dd, *J* = 4.4, 2.1 Hz, 1 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 128.5, 62.1, 57.7, 56.0, 55.9, 53.3, 29.7, 25.8, 18.3, –5.4; HRMS (H-ESI) *m/z* calcd for $C_{13}H_{24}O_3Si$ $[M + H]^+$ 257.1573, found 257.1567.

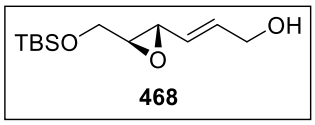
7.2.4. Synthesis of Aldehyde 467



467

Aldehyde 467. To a solution of epoxy alcohol **465** (4.0 g, 18.32 mmol, 1.0 equiv) in a 1:1 DMSO:CH_2Cl_2 mixture (36 mL) was added Et_3N (7.7 mL, 54.95 mmol, 3.0 equiv) followed by SO_3·pyr (7.3 g, 45.79 mmol, 2.5 equiv) at 0 ºC. The reaction mixture was stirred at this temperature until depletion of the starting alcohol as judged by TLC (~ 5 h). After this time, the reaction mixture was quenched by addition of a buffer solution (pH = 7) and diluted with Et_2O. The aqueous phase was extracted with Et_2O (2 x 30 mL) and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to give the crude aldehyde (~18 mmol) which was used in the next step without further purification. To a solution of the crude aldehyde in CH_2Cl_2 (95 mL) was added (formylmethylene)triphenylphosphorane (7.0 g, 23.08 mmol, 1.2 equiv) and the mixture was stirred for 12 h. After this time the solvent was removed under reduced pressure and the residue purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain aldehyde **467** (3.3 g, 74% over two steps) as a pale yellow oil: R_f = 0.51 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = –24.8 (*c* 0.21, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, *J* = 7.7 Hz, 1 H), 6.57 (dd, *J* = 15.8, 6.9 Hz, 1 H), 6.40 (ddd, *J* = 15.8, 7.7, 0.6 Hz, 1 H), 3.94–3.89 (m, 1 H), 3.81 (dd, *J* = 12.2, 3.8 Hz, 1 H), 3.55 (dd, *J* = 6.9, 2.0 Hz, 1 H), 3.12 (ddd, *J* = 3.8, 3.0, 2.0 Hz, 1 H), 0.90 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 152.3, 133.9, 61.9, 61.5, 53.4, 25.8, 18.3, –5.3; HRMS (H-ESI) *m/z* calcd for $C_{12}H_{22}O_3Si$ $[M + H]^+$ 243.1416, found 243.1398.

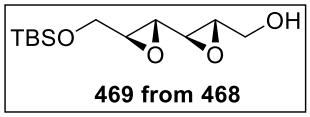
7.2.5. Synthesis of Allylic Alcohol 468



468

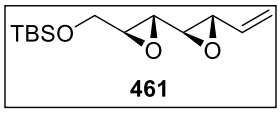
Allylic Alcohol 468. A solution of aldehyde **467** (3.3 g, 13.61 mmol, 1.0 equiv) in CH_2Cl_2 (120 mL) was cooled at -78 ºC and treated with DIBAL-H (13.6 mL, 1.0 M in toluene, 13.61 mmol, 1.0 equiv). After 20 min, the reaction was quenched by addition of MeOH at -78 ºC and the mixture was allowed to reach room temperature, treated with a saturated aqueous Na^+/K^+ tartrate solution and diluted with CH_2Cl_2. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 15% EtOAc in hexanes) to obtain allylic alcohol **468** (3.0 g, 90%) as a yellow oil: R_f = 0.35 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = –31.8 (*c* 0.64, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (dt, *J* = 15.7, 5.3 Hz, 1 H), 5.51 (ddt, *J* = 15.6, 7.9, 1.7 Hz, 1 H), 4.19 (td, *J* = 5.7, 1.6 Hz, 2 H), 3.86 (dd, *J* = 12.0, 3.3 Hz, 1 H), 3.73 (dd, *J* = 12.0, 4.4 Hz, 1 H), 3.32 (dd, *J* = 7.9, 2.1 Hz, 1 H), 3.02 (ddd, *J* = 4.4, 3.2, 2.2 Hz, 1 H), 1.39 (t, *J* = 5.9 Hz, 1 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5, 128.2, 62.9, 62.8, 60.4, 55.3, 25.9, 18.4, –5.3; HRMS (H-ESI) *m/z* calcd for $C_{12}H_{24}O_3Si$ $[M + H]^+$ 245.1573, found 245.1595.

7.2.6. Synthesis of Diepoxy Alcohol 469



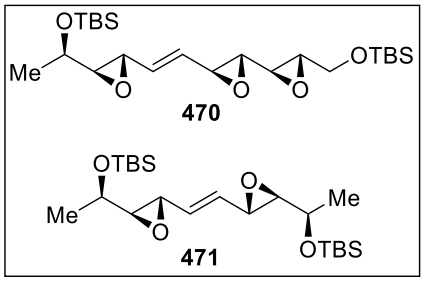
Diepoxy Alcohol 469. To a suspension of titanium tetraisopropoxide (1.27 mL, 4.29 mmol, 0.35 equiv) and 4Å molecular sieves (8.0 g) in CH_2Cl_2 (85 mL) was added (+)-L-DET (0.74 mL, 4.29 mmol, 0.35 equiv) at -20 ºC. After 15 min at this temperature, a solution of allylic alcohol **468** (3.0 g, 12.27 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) was added dropwise, followed by the addition, after additional 30 min, of TBHP (5.0 mL, 5.5 M solution in decane, 24.55 mmol, 2.0 equiv) at the same temperature. After 12 h at this temperature, the reaction mixture was quenched with Me_2S (4.2 mL, 56.47 mmol, 4.6 equiv) at 0 ºC, filtered off and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain diepoxy alcohol **469** (2.49 g, 78%) as a colourless oil: R_f = 0.40 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = –22.4 (*c* 0.51, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (ddd, *J* = 12.8, 4.9, 2.3 Hz, 1 H), 3.88 (dd, *J* = 12.2, 2.9 Hz, 1 H), 3.75 (dd, *J* = 12.2, 4.0 Hz, 1 H), 3.73–3.68 (m, 1 H), 3.17–3.15 (m, 1 H), 3.11 (ddd, *J* = 4.0, 2.9, 2.2 Hz, 1 H), 3.08 (dd, *J* = 4.6, 2.2 Hz, 1 H), 2.98 (dd, *J* = 4.7, 2.2 Hz, 1 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.5, 62.0, 56.1, 55.8, 53.5, 53.4, 25.8, 18.3, –5.4; HRMS (H-ESI) *m/z* calcd for $C_{12}H_{24}O_4Si$ $[M + H]^+$ 261.1522, found 261.1523.

7.2.7. Synthesis of Diepoxy Alkene 461 from Diepoxy Alcohol 469



Diepoxy Alkene 461 from Diepoxy Alcohol 469. Diepoxy alcohol **469** (1.8 g, 6.91 mmol, 1.0 equiv) was converted to diepoxy alkene **461** (1.0 g, 60% over two steps) according to the procedure described above for **460** by sequential treatments with Et_3N (2.9 mL)/SO_3·pyr (2.8 g) and methyl triphenylphosphonium bromide (5.0 g)/NaHMDS (7.0 mL). The spectroscopic properties of the resulting diepoxy alkene were indetical with those exhibited by **461** obtained above from **466**.

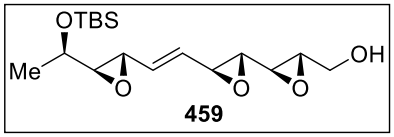
7.2.8. Synthesis of Bis(silyl ether) 470 and Dimer 471. Cross-Metathesis of Olefins 460 and 461



Bis(silyl ether) 470 and Dimer 471. Cross-Metathesis of Olefins 460 and 461. Hoveyda-Grubbs 2nd generation catalyst (16 mg, 0.02 mmol, 0.2 equiv), diepoxy alkene **461** (23 mg, 0.09 mmol, 1.0 equiv) and epoxy alkene **460** (60 mg, 0.27 mmol, 3.0 equiv) were dissolved in degassed CH_2Cl_2 (8 mL) and the reaction mixture was heated at 40 ºC for 12 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain dimer **471** (23 mg, 60%) and bis(silyl ether) **470** (6 mg, 15%) as a colourless and a pale yellow oils, respectively. **[470]:** R_f = 0.57 (silica gel, 10% EtOAc in hexanes);

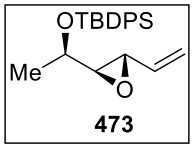
$[\alpha]^{25}_D$ = –31.4 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (dd, *J* = 15.7, 7.0 Hz, 1 H), 5.64 (dd, *J* = 15.6, 7.0 Hz, 1 H), 3.88 (dd, *J* = 12.2, 2.7 Hz, 1 H), 3.74 (dd, *J* = 12.2, 4.0 Hz, 1 H), 3.67–3.60 (m, 1 H), 3.37 (dd, *J* = 7.0, 2.1 Hz, 1 H), 3.23 (dd, *J* = 6.9, 2.1 Hz, 1 H), 3.11–3.07 (m, 1 H), 3.00 (dd, *J* = 4.2, 2.2 Hz, 1 H), 2.93 (dd, *J* = 4.2, 2.1 Hz, 1 H), 2.86 (dd, *J* = 5.7, 2.1 Hz, 1 H), 1.20 (d, *J* = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 130.8, 69.2, 64.7, 61.9, 58.1, 56.1, 54.8, 54.8, 53.0, 25.8, 20.3, 18.3, 18.2, –4.8, –5.4; HRMS (APCI) *m/e* calcd for $C_{23}H_{44}O_5Si_2$ $[M + Na]^+$ 479.2625, found 479.2621; **[471]:** R_f = 0.77 (silica gel, 10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (dd, *J* = 4.4, 2.4 Hz, 2 H), 3.77 (dd, *J* = 6.2, 4.3 Hz, 2 H), 3.31 (dt, *J* = 4.4, 2.2 Hz, 2 H), 2.78 (dd, *J* = 4.2, 2.1 Hz, 2 H), 1.23 (d, *J* = 6.3 Hz, 6 H), 0.88 (s, 18 H), 0.05 (s, 6 H), 0.04 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 67.2, 63.9, 55.1, 25.8, 20.8, 18.1, –4.7, –4.8; HRMS (APCI) *m/e* calcd for $C_{22}H_{44}O_4Si_2$ $[M + H]^+$ 429.2856, found 429.2862.

7.2.9. Synthesis of Epoxy Alcohol 459



Epoxy Alcohol 459. Silyl derivative **470** (30 mg, 0.07 mmol, 1.0 equiv) was dissolved in a mixture THF-H_2O (20:1) (5 mL) and over this solution was added *p*-TsOH (2 mg, 0.01 mmol, 0.1 equiv) at 25 ºC. After stirring for 40 min at the same temperature, the solvent was removed under vacuum and the crude mixture purified by flash column chromatography (silica gel, 40% EtOAc in hexanes) to obtain diepoxy alcohol **459** (11 mg, 50%) as a pale colourless oil: R_f = 0.38 (Silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$ = –35.2 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (dd, *J* = 15.6, 7.1 Hz, 1 H), 5.64 (dd, *J* = 15.7, 7.2 Hz, 1 H), 3.72 (dd, *J* = 13.2, 3.1 Hz, 1 H), 3.67–3.59 (m, 1 H), 3.39 (dd, *J* = 7.2, 2.1 Hz, 1 H), 3.24 (dd, *J* = 7.1, 2.0 Hz, 1 H), 3.19–3.15 (m, 1 H), 3.10 (dd, *J* = 4.3, 2.2 Hz, 1 H), 3.05–3.01 (m, 1 H), 2.94 (dd, *J* = 4.3, 2.1 Hz, 1 H), 2.87 (dd, *J* = 5.7, 2.1 Hz, 1 H), 1.60 (bs, 1 H), 1.20 (d, *J* = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.8, 130.5, 69.1, 64.7, 61.7, 60.4, 57.9, 55.7, 54.8, 53.0, 25.8, 20.3, 18.2, –4.7, –4.8; HRMS (APCI) *m/e* calcd for $C_{17}H_{30}O_5Si$ $[M + H]^+$ 343.1941, found 343.1936.

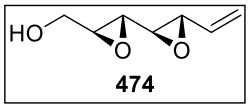
7.2.10. Synthesis of Epoxy Alkene 473



Epoxy Alkene 473. Epoxy olefin **473** was prepared from epoxy alcohol **472**[248] (2.7 g, 7.57 mmol, 1.0 equiv) by sequential treatments with SO_3·pyr and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **460**, to obtain epoxy alkene **473** (2.2 g, 85% over two steps) as a colourless oil: R_f = 0.66 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 12.7 (*c* 0.59, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.68 (m, 4 H), 7.44–7.36 (m, 6 H), 5.56 (ddd, *J* = 17.3, 10.2, 7.7 Hz, 1 H), 5.44–5.38 (m, 1 H), 5.25 (ddd, *J* = 10.3, 1.5, 0.5 Hz, 1 H), 3.76–3.68 (m, 1 H), 3.19 (dd, *J* = 7.7, 2.2 Hz, 1 H), 2.96 (dd, *J* = 5.7, 2.2 Hz, 1 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.08 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.8, 135.3, 134.3, 133.7, 129.7, 129.6, 127.6, 127.5, 119.3, 69.9, 64.3, 56.1,

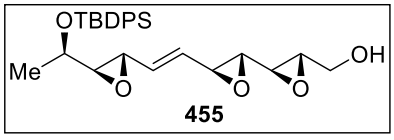
26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{22}H_{28}O_2Si$ $[M + H]^+$ 353.1937, found 353.1933.

7.2.11. Synthesis of Diepoxy Alkene 474



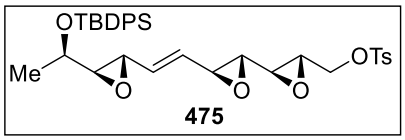
Diepoxy Alkene 474. To a solution of silyl ether **461** (700 mg, 2.73 mmol, 1.0 equiv) in THF (70 mL) was added TBAF (5.5 mL, 1.0 M in THF, 5.45 mmol, 2.0 equiv) at 0 ºC. The reaction mixture was stirred at 25 ºC for 1 h and, after this time, diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was then extracted with Et_2O twice and the organic extracts were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes → 30% EtOAc in hexanes) to obtain diepoxy alkene **474** (314 mg, 81%) as a colourless oil: R_f = 0.33 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = –15.8 (*c* 0.27, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47–5.37 (m, 2 H), 5.24–5.18 (m, 1 H), 3.79 (ddd, *J* = 11.4, 9.0, 2.5 Hz, 1 H), 3.53 (dd, *J* = 12.9, 4.3 Hz, 1 H), 3.29–3.25 (m, 1 H), 3.05 (dd, *J* = 4.3, 2.3 Hz, 1 H), 2.95–2.90 (m, 1 H), 2.81 (dd, *J* = 4.8, 2.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 120.4, 60.7, 57.9, 56.0, 55.9, 53.5; HRMS (H-ESI) *m/z* calcd for $C_7H_{10}O_3$ $[M + H]^+$ 143.0708, found 143.0696.

7.2.12. Synthesis of Triepoxy Alcohol 455. Cross-Metathesis of Olefins 473 and 474



Triepoxy Alcohol 455. Cross-Metathesis of Olefins 473 and 474. Hoveyda-Grubbs 2nd generation catalyst (35 mg, 0.06 mmol, 0.10 equiv), diepoxy alkene **474** (80 mg, 0.56 mmol, 1.0 equiv) and epoxy alkene **473** (595 mg, 1.69 mmol, 3.0 equiv) were dissolved in degassed CH_2Cl_2 (6 mL) and the reaction mixture was heated at 40 ºC for 12 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 40% EtOAc in hexanes) to obtain triepoxy alcohol **455** (129 mg, 50%) as a colourless oil: R_f = 0.51 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$ = –30.3 (*c* 0.45, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.66 (m, 4 H), 7.44–7.35 (m, 6 H), 5.69 (dd, *J* = 15.7, 7.3 Hz, 1 H), 5.57 (dd, *J* = 15.6, 7.3 Hz, 1 H), 3.98 (dd, *J* = 10.7, 2.2 Hz, 1 H), 3.76–3.68 (m, 2 H), 3.37 (dd, *J* = 7.3, 2.0 Hz, 1 H), 3.21–3.16 (m, 2 H), 3.11 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.94 (ddd, *J* = 6.4, 4.9, 2.1 Hz, 2 H), 1.34 (t, *J* = 7.1 Hz, 1 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 134.2, 133.6, 132.8, 130.5, 129.7, 127.6, 127.6, 69.7, 64.6, 62.5, 60.4, 57.9, 55.7, 54.7, 52.9, 26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_5Si$ $[M + Na]^+$ 489.2073, found 489.2073.

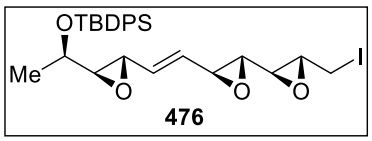
7.2.13. Synthesis of Tosyl Derivative 475



475

Tosyl Derivative 475. Triepoxy alcohol **455** (57 mg, 0.12 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (7 mL) and cooled at 0 ºC. Over this solution was then added *p*-TsCl (28 mg, 0.15 mmol, 1.2 equiv), TEA (30 μL, 0.18 mmol, 1.5 equiv) and 4-DMAP (0.3 mg, 0.002 mmol, 0.02 equiv). After 3 h, the reaction mixture was quenched by addition of water and the aqueous phase was extracted with CH_2Cl_2 three times. The organic phase was washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to obtain tosyl derivative **475** (90 mg, ~0.12 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (5.0 mg, ~0.007 mmol) was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to provide pure tosyl derivative **475** (3.8 mg, 87%) as a colourless oil: R_f = 0.33 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= –18.6 (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.78 (m, 2 H), 7.71–7.65 (m, 4 H), 7.43–7.34 (m, 8 H), 5.67 (dd, *J* = 15.7, 7.3 Hz, 1 H), 5.54 (dd, *J* = 15.6, 7.6 Hz, 1 H), 4.20 (dd, *J* = 11.6, 3.7 Hz, 1 H), 4.08 (dd, *J* = 11.6, 5.2 Hz, 1 H), 3.76–3.68 (m, 1 H), 3.32 (dd, *J* = 7.4, 1.9 Hz, 1 H), 3.22–3.17 (m, 2 H), 2.98 (dd, *J* = 4.0, 2.0 Hz, 1 H), 2.94 (dd, *J* = 5.5, 2.2 Hz, 1 H), 2.88 (dd, *J* = 4.0, 2.0 Hz, 1 H), 2.46 (s, 3 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 135.9, 135.8, 134.2, 134.1, 133.6, 133.1, 130.2, 130.0, 129.7, 129.6, 127.9, 127.6, 127.5, 69.7, 68.5, 64.6, 57.1, 54.8, 54.6, 53.8, 52.3, 26.9, 21.7, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{34}H_{40}O_7SSi$ $[M + Na]^+$ 643.2162, found 643.2161.

7.2.14. Synthesis of Iodide Derivative 476

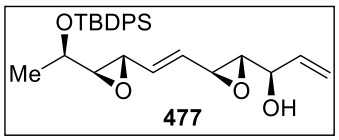


476

Iodide Derivative 476. To a solution of crude tosyl derivative **475** (~85 mg, ~0.11 mmol, 1.0 equiv) in dry acetone (7 mL) was added dry KI (28 mg, 0.17 mmol, 1.5 equiv) at room temperature, and the resulting crude mixture was refluxed for 5.5 hours. The reaction mixture was then allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The resulting crude was diluted with H_2O and extracted with Et_2O. After separation of both phases, the organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to obtain iodide derivative **476** (80 mg, ~0.11 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (4.5 mg, ~0.006 mmol) was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford the iodide derivative **476** (3.2 mg, 93%) as a colourless oil: R_f = 0.56 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$= –19.4 (*c* 0.45 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.66 (m, 4 H), 7.44–7.34 (m, 6 H), 5.69 (dd, *J* = 15.7, 7.3 Hz, 1 H), 5.56 (dd, *J* = 15.7, 7.4 Hz, 1 H), 3.76–3.69 (m, 1 H), 3.35 (d, *J* = 7.2 Hz, 1 H), 3.28–3.21 (m, 2 H), 3.20 (dd, *J* = 7.2, 2.1 Hz, 1 H), 3.10 (dd, *J* = 12.4, 8.8 Hz, 1 H), 2.96–2.93 (m, 3 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.8, 134.2, 133.6, 132.9, 130.3, 129.7, 129.6,

127.6, 127.5, 69.7, 64.6, 59.4, 57.3, 55.7, 54.8, 54.6, 26.9, 19.9, 19.3, 3.2; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{33}IO_4Si$ $[M + Na]^+$ 599.1091, found 599.1088.

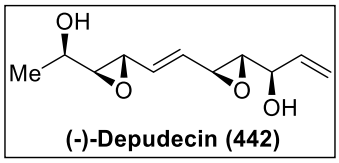
7.2.15. Synthesis of Allylic Alcohol 477



477

Allylic Alcohol 477. To a solution of the crude iodide derivative **476** (~80 mg, ~0.10 mmol, 1.0 equiv) in THF (10 mL) was added *n*-BuLi (0.13 mL, 1.6 M in hexane, 0.20 mmol, 2.0 equiv) at -78 ºC, and the reaction mixture was stirred for 5 min. After this time, the reaction mixture was then quenched at -78 ºC with MeOH followed by addition of a saturated aqueous NH_4Cl solution at 0 ºC. The resulting mixture was extracted with EtOAc (3 x 10 mL) and the organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The solvent was then removed under reduced pressure and the resulting crude mixture purified by flash column chromatogaphy (silica gel, 20% EtOAc in hexanes) to obtain allylic alcohol **477** (41 mg, 90% over 3 steps from **455**) as a colourless oil: R_f = 0.57 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= –20.9 (*c* 0.28, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.66 (m, 4 H), 7.43–7.34 (m, 6 H), 5.94 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.67 (dd, *J* = 15.7, 7.1 Hz, 1 H), 5.58 (dd, *J* = 15.7, 7.2 Hz, 1 H), 5.40 (dt, *J* = 17.3, 1.3 Hz , 1 H), 5.28 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.15–4.09 (m, 1 H), 3.76–3.70 (m, 1 H), 3.40 (dd, *J* = 7.1, 2.2 Hz, 1 H), 3.20 (dd, *J* = 7.0, 2.1 Hz, 1 H), 2.99 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.95 (dd, *J* = 5.5, 2.1 Hz, 1 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.9, 135.8, 134.2, 133.6, 132.7, 130.9, 129.7, 129.6, 127.6, 127.5, 117.0, 71.5, 69.7, 64.5, 62.4, 55.0, 54.8, 26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_4Si$ $[M + H]^+$ 451.2305, found 451.2301.

7.2.16. Synthesis of (-)-Depudecin (442)

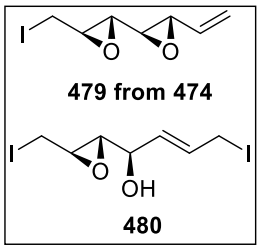


(-)-Depudecin (442)

(-)-Depudecin (442). Silyl derivative **477** (11 mg, 0.02 mmol, 1.0 equiv) was dissolved in THF (3 mL) and over this solution was added TBAF (29 µL, 1.0 M in THF, 0.03 mmol, 1.2 equiv) at 25 ºC. After 90 min, the reaction mixture was diluted with EtOAc and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was then extracted with EtOAc and the organic extracts were washed with H_2O, brine, dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 60% EtOAc in hexanes) to afford (-)-depudecin (**442**) (4.5 mg, 90%) as a colourless oil: R_f = 0.52 (silica gel, EtOAc); $[\alpha]^{25}_D$= –31.1 (*c* 0.17, CH_2Cl_2) (*lit.*[236] $[\alpha]^{24}_D$= –35.8 (*c* 0.52, MeOH); (*lit.*[245] $[\alpha]^{23}_D$= –31.0 (*c* 0.08, $CHCl_3$); (*lit.*[248] $[\alpha]^{25}_D$= –29.6 (*c* 0.12, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.72–5.69 (m, 2 H), 5.40 (dt, *J* = 17.3, 1.3 Hz, 1 H), 5.28 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.13 (d, *J* = 4.4 Hz, 1 H), 3.74 (dd, *J* = 11.3, 6.2 Hz, 1 H), 3.45–3.42 (m, 1 H), 3.40–3.36 (m, 1 H), 3.01 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.91 (dd, *J* = 4.5, 2.2 Hz, 1 H), 1.93 (d, *J* = 6.5 Hz, 1 H), 1.80 (d, *J* = 6.1 Hz, 1 H), 1.31 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1,

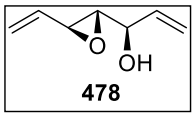
132.0, 131.5, 117.1, 71.5, 66.9, 64.1, 62.4, 55.3, 54.9, 20.0; HRMS (H-ESI) *m/z* calcd for $C_{11}H_{16}O_4$ $[M + H]^+$ 213.1127, found 213.1115.

7.2.17. Synthesis of Diepoxy Iodide 479 and Diiodide 480. Iodination of Diepoxy Alcohol 474.



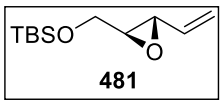
Diepoxy Iodide 479 and Diiodide 480. Iodination of Diepoxy Alcohol 474. To a solution of diepoxy alcohol **474** (50 mg, 0.35 mmol, 1.0 equiv) in THF (10 mL) at 0 ºC was added imidazole (72 mg, 1.05 mmol, 3.0 equiv), PPh_3 (138 mg, 0.53 mmol, 1.5 equiv) and iodine (134 mg, 0.53 mmol, 1.5 equiv) at 25 ºC. The mixture was vigorously stirred at 25 ºC for 20 min. After this time, the solvent was evaporated under reduced pressure and the crude residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes→10% EtOAc in hexanes) to obtain diepoxy iodide **479** (22 mg, 25%) and diiodide **480** (42 mg, 47%) as yellow oils. **[479]**: R_f = 0.90 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = –35.8 (*c* 0.87, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58–5.53 (m, 2 H), 5.35–5.31 (m, 1 H), 3.37–3.32 (m, 1 H), 3.28–3.22 (m, 2 H), 3.12–3.05 (m, 1 H), 2.96–2.94 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 120.5, 60.1, 59.6, 57.1, 55.6, 3.2; HRMS (H-ESI) *m/z* calcd for $C_7H_9IO_2$ $[M + H]^+$ 252.9726, found 252.9698. **[480]**: R_f = 0.81 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = –29.4 (*c* 0.31, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (dtd, *J* = 15.4, 7.9, 1.4 Hz, 1 H), 5.76 (ddt, *J* = 15.2, 5.7, 1.0 Hz, 1 H), 4.09 (dd, *J* = 10.2, 4.9 Hz, 1 H), 3.90–3.86 (m, 2 H), 3.29–3.24 (m, 2 H), 3.10–3.06 (m, 1 H), 2.94 (dd, *J* = 4.6, 1.9 Hz, 1 H), 2.23 (d, *J* = 6.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.0, 130.8, 70.3, 64.0, 55.9, 3.7, 3.4; HRMS (H-ESI) *m/z* calcd for $C_7H_{10}I_2O_2$ $[M + H]^+$ 380.8848, found 380.8856.

7.2.18. Synthesis of Dialkene 478



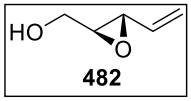
Dialkene 478. To a solution of iodide derivative **479** (13 mg, 0.04 mmol, 1.0 equiv) in THF (3 mL) was added *n*-BuLi (50.0 µL, 1.6 M in hexane, 0.08 mmol, 2.0 equiv) at -78 ºC, and the reaction was stirred for 5 min. The reaction mixture was then quenched at -78 ºC with MeOH followed by addition of a saturated aqueous NH_4Cl solution at 0 ºC. The resulting mixture was extracted with EtOAc and the organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The solvent was then removed under reduced pressure and the resulting crude mixture purified by flash column chromatogaphy (silica gel, 25% EtOAc in hexanes) to obtain dialkene **478** (6.3 mg, 97%) as a colourless oil: R_f = 0.51 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = –12.35 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.58 (dd, *J* = 9.9, 7.3 Hz, 1 H), 5.53 (d, *J* = 1.8 Hz, 1 H), 5.40 (dt, *J* = 17.3, 1.4 Hz, 1 H), 5.34–5.30 (m, 1 H), 5.27 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.13 (t, *J* = 4.7 Hz, 1 H), 3.41 (dd, *J* = 7.1, 2.2 Hz, 1 H), 3.00 (dd, *J* = 4.4, 2.2 Hz, 1 H), 2.01 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 134.5, 120.2, 116.9, 71.6, 62.2, 56.3; HRMS (H-ESI) *m/z* calcd for $C_7H_{10}O_2$ $[M + H]^+$ 127.0759, found 127.0780.

7.2.19. Synthesis of Epoxy Alkene 481



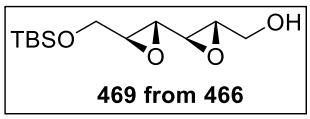
Epoxy Alkene 481. Epoxy olefin **481** was prepared from epoxy alcohol **465** (700 mg, 3.21 mmol, 1.0 equiv) by sequential treatments with SO_3·pyr and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **460**, to obtain epoxy alkene **481** (424 mg, 66% over two steps) as a colourless oil: R_f = 0.67 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D$= –29.2 (*c* 0.56, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64–5.55 (m, 1 H), 5.47 (dd, *J* = 17.2, 1.3 Hz, 1 H), 5.27 (ddd, *J* = 10.2, 1.6, 0.6 Hz, 1 H), 3.86 (dd, *J* = 12.0, 3.2 Hz, 1 H), 3.71 (dd, *J* = 12.0, 4.5 Hz, 1 H), 3.27 (dd, *J* = 7.5, 2.1 Hz, 1 H), 2.99 (ddd, *J* = 4.5, 3.2, 2.2 Hz, 1 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 119.4, 62.96, 60.3, 56.1, 25.9, 18.3, –5.3; HRMS (H-ESI) *m/z* calcd for $C_{11}H_{22}O_2Si$ $[M + H]^+$ 215.1467, found 215.1465.

7.2.20. Synthesis of Epoxy Alcohol 482



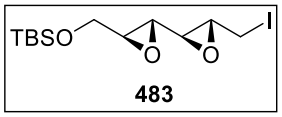
Epoxy Alcohol 482. Silyl ether **481** (424 mg, 1.98 mmol, 1.0 equiv) was dissolved in THF (40 mL) and to this solution was added TBAF (4.0 mL, 1.0 M in THF, 3.96 mmol, 2.0 equiv) at 0 ºC. The reaction mixture was stirred at 25 ºC for 1 h and, after this time, the reaction mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was then extracted with Et_2O and the organic extracts were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain epoxy alcohol **482** (108 mg, 55%) as a colourless oil: R_f = 0.27 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= –19.8 (*c* 0.31, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (ddd, *J* = 17.3, 10.0, 7.4 Hz, 1 H), 5.50 (dd, *J* = 17.2, 1.6 Hz, 1 H), 5.31 (dd, *J* = 10.4, 1.7 Hz, 1 H), 3.95 (d, *J* = 12.7 Hz, 1 H), 3.68 (d, *J* = 12.6 Hz, 1 H), 3.40 (dd, *J* = 7.4, 2.2 Hz, 1 H), 3.08 (dt, *J* = 4.1, 2.4 Hz, 1 H), 2.01 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 120.0, 61.2, 59.9, 55.8; HRMS (H-ESI) *m/z* calcd for $C_5H_8O_2$ $[M + H]^+$ 101.0603, found 101.0597.

7.2.21. Synthesis of Diepoxy Alcohol 469. Reduction of Diepoxy Amide 466



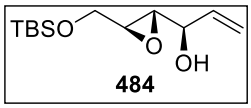
Diepoxy Alcohol 469. Reduction of Diepoxy Amide 466. Diepoxy amide **466** (700 mg, 1.62 mmol, 1.0 equiv) in THF (30 mL) was treated with $LiEt_3BH$ (3.2 mL, 3.20 mmol, 1.0 M in THF, 2.0 equiv) at 0 ºC. After 1 h at this temperature, the reaction mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was separated, extracted with Et_2O twice and the combined organic layers washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% EtOAc in hexanes) provided diepoxy alcohol **469** (371 mg, 88%) whose physical and spectroscopic properties were identical to those obtained from **468**.

7.2.22. Synthesis of Iodide Derivative 483



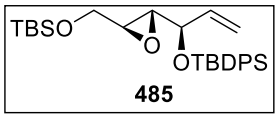
Iodide Derivative 483. To a solution of diepoxy alcohol **469** (200 mg, 0.768 mmol, 1.0 equiv) in THF (20 mL) at 0 ºC was added imidazole (157 mg, 2.30 mmol, 3.0 equiv), PPh_3 (302 mg, 1.15 mmol, 1.5 equiv) and iodine (292 mg, 1.15 mmol, 1.5 equiv) at 25 ºC. The mixture was vigorously stirred at 25 ºC for 20 min. After this time, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain iodide derivative **483** (196 mg, 69%) as a pale yellow oil: R_f = 0.68 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = –24.2 (*c* 0.62, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (dd, *J* = 12.2, 2.7 Hz, 1 H), 3.77–3.71 (m, 1 H), 3.29–3.21 (m, 2 H), 3.15–3.06 (m, 2 H), 3.00 (dd, *J* = 4.2, 2.1 Hz, 1 H), 2.92 (dd, *J* = 4.3, 1.7 Hz, 1 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.9, 59.9, 56.1, 55.7, 52.8, 25.9, 18.4, 3.5, –5.3; HRMS (H-ESI) *m/z* calcd for $C_{12}H_{23}IO_3Si$ $[M + H]^+$ 371.0539, found 371.0540.

7.2.23. Synthesis of Allylic Alcohol 484



Allylic Alcohol 484. A solution of diepoxy iodide **483** (196 mg, 0.53 mmol, 1.0 equiv) in THF (40 mL) was reacted with *n*-BuLi (0.7 mL, 1.6 M in hexane, 1.06 mmol, 2.0 equiv) at -78 ºC, according to the same procedure as described above for the preparation of **477**, to afford, after similar processing, allylic alcohol **484** (116 mg, 90%) as a colourless oil: R_f = 0.47 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}{}_D$= –33.1 (*c* 0.87, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95–5.78 (m, 1 H), 5.36 (ddd, *J* = 17.3, 1.7, 1.2 Hz, 1 H), 5.22 (ddd, *J* = 10.6, 1.2, 0.7 Hz, 1 H), 4.08–4.01 (m, 1 H), 3.84 (ddd, *J* = 12.2, 3.0, 1.6 Hz, 1 H), 3.67 (tdd, *J* = 4.6, 3.8, 1.1 Hz, 1 H), 3.10 (ddd, *J* = 4.6, 2.0, 0.8 Hz, 1 H), 3.00–2.97 (m, 1 H), 2.41 (bs, 1 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 116.7, 71.9, 62.7, 58.2, 56.4, 25.8, 18.3, –5.3; HRMS (H-ESI) *m/z* calcd for $C_{12}H_{24}O_3Si$ $[M + H]^+$ 245.1573, found 245.1568.

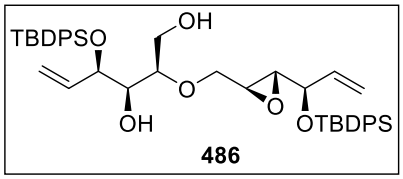
7.2.24. Synthesis of Bis(silyl ether) 485



Bis(silyl ether) 485. A solution of allylic alcohol **484** in CH_2Cl_2 (15 mL) was treated with imidazole (49 mg, 0.71 mmol, 1.5 equiv) and TBDPSCl (0.15 mL, 0.57 mmol, 1.2 equiv) at 0 ºC. The resulting solution was stirred for 12 h and then poured into CH_2Cl_2, washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain bis(silyl ether) derivative **485** (229 mg, quant.) as a colourless oil: R_f = 0.89 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = –9.45 (*c* 0.12, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4 H), 7.43–7.38 (m, 6 H), 5.80 (ddd, *J* = 17.2, 10.5, 5.8 Hz, 1 H), 5.19–5.13 (m, 1 H), 5.07 (dt, *J* = 10.6, 1.4 Hz, 1 H), 4.09 (t, *J* = 5.6 Hz, 1 H), 3.75 (dd, *J* = 11.9, 3.4 Hz, 1 H), 3.64 (dd, *J* = 11.9, 4.5 Hz, 1 H), 2.98 (dd, *J* = 5.5, 2.2 Hz, 1 H), 2.94–2.90 (m, 1 H), 1.16 (s, 9 H), 1.09 (s, 9 H), 0.90 (s, 3

H), 0.90 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.2, 134.8, 132.6, 130.3, 129.7, 127.9, 127.7, 127.5, 127.5, 74.9, 62.9, 58.8, 55.9, 27.0, 25.9, 20.7, 19.0, –5.3; HRMS (H-ESI) *m/z* calcd for $C_{28}H_{42}O_3Si_2$ $[M + H]^+$ 483.2751, found 483.2752.

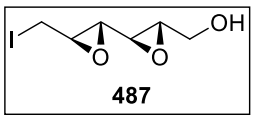
7.2.25. Synthesis of Epoxy Ether 486



486

Epoxy Ether 486. A solution of bis(silyl ether) **485** (229 mg, 0.48 mmol, 1.0 equiv) in CH_2Cl_2/MeOH mixture (4:1, 10 mL) was treated with CSA (11 mg, 0.05 mmol, 0.1 equiv) at 0 ºC. The reaction mixture was stirred at 0 ºC until depletion of starting material as judged by TLC (4.5 h). Then, the reaction was quenched by addition of Et_3N (30 µL) and the resultant mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain epoxy ether **486** (262 mg, 75%) as a colourless oil: R_f = 0.65 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = +28.6 (*c* 0.52, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.65 (m, 8 H), 7.47–7.34 (m, 12 H), 5.97–5.86 (m, 1 H), 5.86–5.76 (m, 1 H), 5.29–4.83 (m, 4 H), 4.57–4.48 (m, 1 H), 4.11 (t, *J* = 5.7 Hz, 1 H), 4.04–3.90 (m, 2 H), 3.90–3.76 (m, 2 H), 3.75–3.59 (m, 1 H), 3.57–3.32 (m, 1 H), 3.08 (dd, *J* = 5.6, 2.3 Hz, 1 H), 3.04–2.93 (m, 2 H), 2.65–2.45 (m, 1H), 1.12 (s, 9 H), 1.10 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 137.0, 136.1, 136.1, 136.0, 135.9, 135.9, 135.8, 133.8, 133.7, 130.1, 129.9, 129.8, 129.7, 127.8, 127.8, 127.6, 127.5, 117.8, 116.7, 75.5, 74.8, 74.5, 73.5, 64.8, 61.2, 58.6, 55.8, 27.2, 26.9, 19.6, 19.4; HRMS (H-ESI) *m/z* calcd for $C_{44}H_{56}O_6Si_2$ $[M + Na]^+$ 759.3513, found 759.3506.

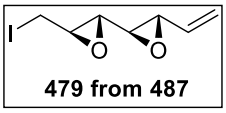
7.2.26. Synthesis of Diepoxy Alcohol 487



487

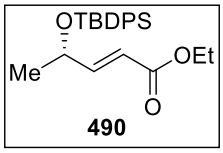
Diepoxy Alcohol 487. Silyl derivative **483** (212 mg, 0.57 mmol, 1.0 equiv) was dissolved in THF (10 mL) and to this solution was added TBAF (1.14 mL, 1.0 M in THF, 1.14 mmol, 2.0 equiv) at 0 ºC. The reaction mixture was stirred at 25 ºC for 1.15 h and, after this time, the reaction mixture was diluted with Et_2O and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was then extracted with Et_2O three times and the combined organic extracts were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 30% EtOAc in hexanes) to obtain diepoxy alcohol **487** (127 mg, 87%) as a colourless oil: R_f = 0.33 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$ = –21.4 (*c* 0.24, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (d, *J* = 12.8 Hz, 1 H), 3.69 (d, *J* = 11.8 Hz, 1 H), 3.27 (dd, *J* = 2.5, 1.9 Hz, 1 H), 3.25 (dd, *J* = 1.6, 1.1 Hz, 1 H), 3.17 (ddd, *J* = 7.3, 4.4, 2.0 Hz, 1 H), 3.13 (ddd, *J* = 8.5, 3.5, 1.3 Hz, 1 H), 3.12–3.06 (m, 1 H), 2.98 (dd, *J* = 3.6, 1.3 Hz, 1 H), 2.35 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 60.4, 59.8, 55.9, 55.8, 52.8, 3.5; HRMS (H-ESI) *m/z* calcd for $C_6H_9IO_3$ $[M + H]^+$ 256.9675, found 256.9675.

7.2.27. Synthesis of Diepoxy Iodide 479. Olefination of Diepoxy Alcohol 487



Diepoxy Iodide 479. Olefination of Diepoxy Alcohol 487. Diepoxy olefin **479** was prepared from diepoxy alcohol **487** (70 mg, 0.27 mmol, 1.0 equiv) by sequential treatments with SO_3·pyr and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **460**, to obtain diepoxy alkene **479** (31 mg, 47% over two steps) whose physical and spectroscopic properties were identical to those obtained from **474**.

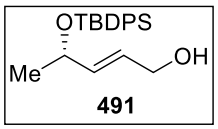
7.2.28. Synthesis of α,β-Unsaturated Ester 490



α,β-Unsaturated Ester 490. To a solution of (-)-ethyl-L-lactate **488** (3.2 mL, 27.94 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added TEA (8.30 mL, 61.47 mmol, 2.2 equiv), TBDPSCl (7.89 mL, 30.73 mmol, 1.1 equiv) and 4-DMAP (683 mg, 5.59 mmol, 0.2 equiv) at 0 ºC. The mixture was stirred for 12 h and then diluted with brine and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to obtain silyl derivative **489** (10 g, quant.) as a colourless oil which was used in the next step without further purification. A solution of silyl derivative **489** (10.0 g, 28.04 mmol, 1.0 equiv) in CH_2Cl_2 (60 mL) was cooled at -78 ºC and then treated with DIBAL-H (28 mL, 1.0 M in toluene, 28.04 mmol, 1.0 equiv). After 20 min, the reaction was quenched by dropwise addition of MeOH at -78 ºC and the mixture was allowed to reach room temperature, treated with a saturated aqueous Na^+/K^+ tartrate solution and diluted with CH_2Cl_2. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The aqueous phase was then separated, the organic extract washed with water and brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The resulting crude aldehyde (~28 mmol) was used in the next step without purification. A solution of tributyl(ethoxycarbonylmethylene)phosphonium bromide (11.0 g, 35.0 mmol, 1.25 equiv) in CH_2Cl_2 (40 mL) was washed twice with a 1.0 M aqueous NaOH solution (60 mL), then dried over $MgSO_4$ and diluted with toluene (40 mL). After removing CH_2Cl_2 under reduced pressure, the resulting solution was added to a stirred solution of the crude aldehyde and benzoic acid (682 mg, 5.60 mmol, 0.2 equiv) in toluene (100 mL) at 95 ºC. After 30 min at this temperature, the solvent was evaporated under reduced pressure and the resulting residue purified by flash column chromatography (silica gel, 10 % EtOAc in hexanes) to provide the corresponding α,β-unsaturated ester **490** (9.2 g, 86% over two steps) as a colourless oil and whose spectroscopic and physical properties matched with those described in the literature:[261] R_f = 0.69 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = +11.2 (*c* 0.89, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.66 (m, 4 H), 7.48–7.37 (m, 6 H), 6.96 (ddd, *J* = 15.5, 4.5, 2.4 Hz, 1 H), 6.07 (ddd, *J* = 15.5, 2.6, 1.7 Hz, 1 H), 4.56–4.48 (m, 1 H), 4.24 (qdd, *J* = 7.0, 3.1, 1.0 Hz, 2 H), 1.33 (t, *J* = 7.1 Hz, 3 H), 1.18 (d, *J* = 6.5 Hz, 3 H), 1.15 (s, *J* = 2.2 Hz, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 151.5, 135.9, 135.8, 134.1, 133.5, 129.1, 128.3,

127.7, 127.6, 119.2, 68.7, 60.3, 27.0, 23.4, 19.3, 14.3; HRMS (H-ESI) *m/z* calcd for $C_{23}H_{30}O_3Si$ $[M + H]^+$ 383.2043, found 383.2040.

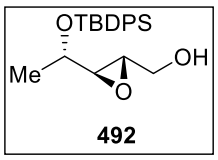
7.2.29. Synthesis of Allylic Alcohol 491



491

Allylic Alcohol 491. A solution of α,β-unsaturated ester **490** (9.0 g, 23.53 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was cooled at -78 ºC and treated with DIBAL-H (70 mL, 1.0 M in toluene, 70.58 mmol, 3.0 equiv). After 20 min, the reaction was quenched by addition of MeOH at -78 ºC and the mixture was allowed to reach room temperature, treated with a saturated aqueous Na^+/K^+ tartrate solution and diluted with CH_2Cl_2. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain allylic alcohol **491** (7.2 g, 90%) as a colourless oil and whose spectroscopic and physical properties matched with those described in the literature:[261] R_f = 0.20 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = –15.6 (*c* 0.43, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4 H), 7.46–7.33 (m, 6 H), 5.65 (dd, *J* = 15.4, 5.6 Hz, 1 H), 5.56 (dt, *J* = 15.4, 4.9 Hz, 1 H), 4.35 (p, *J* = 5.7 Hz, 1 H), 3.99 (d, *J* = 4.8 Hz, 2 H), 1.55 (bs, 1 H), 1.17 (d, *J* = 6.3 Hz, 3 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.9, 135.8, 134.5, 134.4, 129.6, 129.5, 127.8, 127.5, 127.4, 69.7, 63.1, 27.0, 24.2, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{21}H_{28}O_2Si$ $[M + H]^+$ 341.1937, found 341.1938.

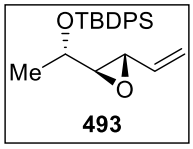
7.2.30. Synthesis of Epoxy Alcohol 492



492

Epoxy Alcohol 492. To a suspension of titanium tetraisopropoxide (2.4 mL, 8.22 mmol, 0.35 equiv) and 4Å molecular sieves (15.0 g) in CH_2Cl_2 (100 mL) was added (+)-L-DET (1.4 mL, 8.22 mmol, 0.35 equiv) at -50 ºC. After 15 min at this temperature, a solution of allylic alcohol **491** (8.0 g, 23.49 mmol, 1.0 equiv) in CH_2Cl_2 (80 mL) was added dropwise, followed by the addition, after additional 30 min, of TBHP (8.5 mL, 5.5 M solution in decane, 46.99 mmol, 2.0 equiv) at the same temperature. After 12 h at this temperature, the reaction mixture was quenched with Me_2S (6.5 mL, 108 mmol, 4.6 equiv) at 0 ºC, filtered off and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain epoxy alcohol **492** (7.4 g, 88%) as a colourless oil: R_f = 0.40 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = –3.7 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.67 (m, 4 H), 7.45–7.37 (m, 6 H), 3.71 (dd, *J* = 12.8, 1.8 Hz, 1 H), 3.68–3.63 (m, 1 H), 3.41 (dd, *J* = 12.7, 4.3 Hz, 1 H), 2.91 (dd, *J* = 5.4, 1.9 Hz, 1 H), 2.71–2.67 (m, 1 H), 1.23 (d, *J* = 6.2 Hz, 3 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.8, 133.9, 133.8, 129.8, 129.7, 127.7, 127.6, 68.7, 61.3, 58.8, 57.4, 26.9, 20.9, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{21}H_{28}O_3Si$ $[M + H]^+$ 357.1886, found 357.1876.

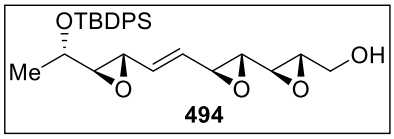
7.2.31. Synthesis of Epoxy Alkene 493



493

Epoxy Alkene 493. Epoxy olefin **493** was prepared from epoxy alcohol **492** (4.6 g, 12.90 mmol, 1.0 equiv) by sequential treatments with SO_3·pyr and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **460**, to obtain epoxy alkene **493** (3.6 g, 80% over two steps) as a pale yellow oil: R_f = 0.69 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = –11.7 (*c* 0.67, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.65 (m, 4 H), 7.43–7.36 (m, 6 H), 5.56–5.44 (m, 1 H), 5.32 (dd, *J* = 17.2, 1.5 Hz, 1 H), 5.21 (dd, *J* = 10.3, 1.5 Hz, 1 H), 3.60 (p, *J* = 6.1 Hz, 1 H), 2.90 (dd, *J* = 7.5, 2.1 Hz, 1 H), 2.81 (dd, *J* = 5.7, 2.1 Hz, 1 H), 1.21 (d, *J* = 6.3 Hz, 3 H), 1.06 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.97, 135.88, 135.2, 134.8, 134.0, 133.7, 129.8, 129.7, 127.7, 119.3, 69.1, 63.5, 57.7, 26.9, 20.9, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{22}H_{28}O_2Si$ $[M + H]^+$ 353.1937, found 353.1935.

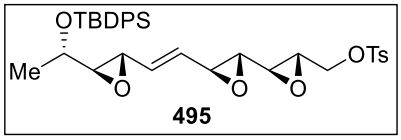
7.2.32. Synthesis of Triepoxy Alcohol 494



494

Triepoxy Alcohol 494. A solution of diepoxy olefin **474** (100 mg, 0.70 mmol, 1.0 equiv) and epoxy olefin **493** (744 mg, 2.11 mmol, 3.0 equiv) in degassed CH_2Cl_2 (7 mL) was reacted with Hoveyda-Grubbs 2nd generation catalyst (44 mg, 0.10 mmol, 0.10 equiv) according to the same procedure as described above for the synthesis of **455**, to afford triepoxy alcohol **494** (179 mg, 55%) as a colourless oil: R_f = 0.56 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$ = +26.5 (*c* 0.39, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4 H), 7.45–7.34 (m, 6 H), 5.60 (dd, *J* = 15.6, 7.1 Hz, 1 H), 5.45 (dd, *J* = 15.6, 7.4 Hz, 1 H), 3.76–3.67 (m, 2 H), 3.66–3.58 (m, 1 H), 3.34 (dd, *J* = 7.5, 1.9 Hz, 1 H), 3.19 (dt, *J* = 3.5, 2.3 Hz, 1 H), 3.11 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.93–2.89 (m, 2 H), 2.79 (dd, *J* = 5.6, 2.0 Hz, 1 H), 1.22 (d, *J* = 6.3 Hz, 3 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.8, 133.8, 133.7, 132.7, 130.2, 129.8, 129.7, 127.67, 127.6, 68.9, 63.9, 60.5, 57.9, 56.0, 55.8, 54.8, 53.1, 26.8, 20.8, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_5Si$ $[M + Na]^+$ 489.2074, found 489.2073.

7.2.33. Synthesis of Tosyl Derivative 495

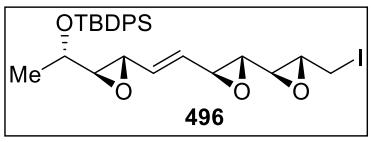


495

Tosyl Derivative 495. The tosylation of triepoxy alcohol **494** (65 mg, 0.14 mmol, 1.0 equiv) was achieved in exactly the same way as described above fot **475**, to obtain tosyl derivative **495** (105 mg, ~0.14 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (7.0 mg, ~0.009 mmol) was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to provide pure tosyl derivative **495** (5.5 mg, 95%) as a colourless oil: R_f = 0.83 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$= +20.6 (*c* 0.34, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.78 (m, 2 H), 7.69–7.64 (m, 4 H), 7.44–7.40 (m, 2 H), 7.40–7.34 (m, 6 H), 5.61–5.52 (m, 1 H), 5.41 (dd, *J* = 15.7, 7.5

Hz, 1 H), 4.22 (dd, *J* = 11.7, 3.6 Hz, 1 H), 4.09 (dd, *J* = 11.6, 5.3 Hz, 1 H), 3.64–3.57 (m, 1 H), 3.32–3.27 (m, 1 H), 3.23–3.20 (m, 1 H), 3.00 (dd, *J* = 3.9, 2.0 Hz, 1 H), 2.91–2.86 (m, 2 H), 2.78 (dd, *J* = 5.6, 2.0 Hz, 1 H), 2.46 (s, 3 H), 1.21 (d, *J* = 6.3 Hz, 3 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 135.9, 135.8, 133.9, 133.8, 133.7, 133.0, 132.6, 130.0, 129.8, 129.7, 127.9, 127.7, 127.6, 68.9, 68.5, 63.8, 57.1, 55.9, 54.9, 53.8, 52.3, 26.9, 21.7, 20.8, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{34}H_{40}O_7SSi$ $[M + Na]^+$ 643.2162, found 643.2160.

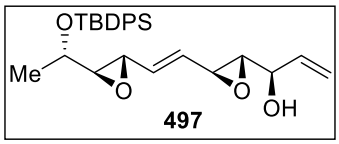
7.2.34. Synthesis of Iodide Derivative 496



496

Iodide Derivative 496. The iodination of crude tosyl derivative **495** (~98 mg, ~0.13 mmol, 1.0 equiv) was carried out according to the procedure described above for **476**, to afford iodide derivative **496** (97 mg, ~0.13 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (6.5 mg, ~0.009 mmol) was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain pure iodide **496** (4.5 mg, 91%) as a colourless oil: R_f = 0.66 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$= +12.1 (*c* 0.34 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4 H), 7.44–7.34 (m, 6 H), 5.59 (dd, *J* = 15.6, 7.1 Hz, 1 H), 5.43 (dd, *J* = 15.6, 7.9 Hz, 1 H), 3.63–3.57 (m, 1 H), 3.32 (dd, *J* = 7.4, 1.7 Hz, 1 H), 3.28–3.24 (m, 2 H), 3.14–3.07 (m, 1 H), 2.98–2.91 (m, 2 H), 2.90 (dd, *J* = 7.3, 2.1 Hz, 1 H), 2.79 (dd, *J* = 5.6, 2.0 Hz, 1 H), 1.22 (d, *J* = 6.2 Hz, 3 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.8, 133.8, 133.7, 132.9, 130.0, 129.9, 129.8, 127.7, 127.6, 68.9, 63.9, 59.4, 57.3, 55.9, 55.7, 54.8, 26.9, 20.8, 19.2, 3.1; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{33}IO_4Si$ $[M + Na]^+$ 599.1091, found 599.1090.

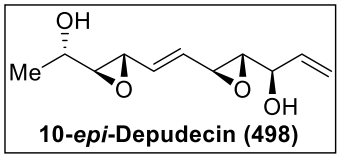
7.2.35. Synthesis of Allylic Alcohol 497



497

Allylic Alcohol 497. A solution of diepoxy iodide **496** (~91 mg, ~0.12 mmol, 1.0 equiv) in THF (10 mL) was reacted with *n*-BuLi (0.15 mL, 1.6 M in hexane, 0.24 mmol, 2.0 equiv) at -78 ºC, according to the same procedure as described above for the preparation of **477**, to afford, after similar processing, allylic alcohol **497** (50 mg, 91% over 3 steps): R_f = 0.50 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= +18.9 (*c* 0.23, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4 H), 7.42–7.34 (m, 6 H), 5.96 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.57 (dd, *J* = 15.7, 7.2 Hz, 1 H), 5.45 (dd, *J* = 12.3, 4.4 Hz, 1 H), 5.29 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.15–4.09 (m, 1 H), 3.60 (p, *J* = 6.1 Hz, 1 H), 3.38 (dd, *J* = 7.5, 2.1 Hz, 1 H), 2.97 (dd, *J* = 4.4, 2.2 Hz, 1 H), 2.90 (dd, *J* = 7.2, 1.9 Hz, 1 H), 2.80 (dd, *J* = 5.7, 2.0 Hz, 1 H), 2.05 (bs, 1 H), 1.22 (d, *J* = 6.2 Hz, 3 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.9, 135.8, 133.8, 133.7, 132.6, 130.6, 129.8, 129.7, 127.7, 127.6, 117.0, 71.6, 69.0, 63.8, 62.4, 56.2, 55.1, 26.9, 20.8, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_4Si$ $[M + H]^+$ 451.2305, found 451.2315.

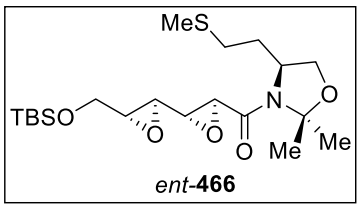
7.2.36. Synthesis of 10-epi-Depudecin (498)



10-*epi*-Depudecin (498)

10-*epi*-Depudecin (498). Silyl derivative **497** (16 mg, 0.04 mmol, 1.0 equiv) was desilylated by the action of TBAF (0.04 mL, 1.0 M in THF, 0.04 mmol, 1.2 equiv) in the same way as desrcribed above for (-)-depudecin (**442**) to afford 10-*epi*-depudecin (**498**) (6.0 mg, 85%) as a colourless oil: R_f = 0.52 (silica gel, EtOAc); $[\alpha]^{25}_D$= +33.3 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.73–5.70 (m, 2 H), 5.39 (dt, *J* = 17.2, 1.4 Hz, 1 H), 5.27 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.13 (dd, *J* = 10.3, 5.6 Hz, 1 H), 4.01 (dd, *J* = 4.4, 1.8 Hz, 1 H), 3.48–3.45 (m, 1 H), 3.44–3.41 (m, 1 H), 3.01 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.94 (dd, *J* = 3.0, 2.2 Hz, 1 H), 1.98 (d, *J* = 6.5 Hz, 1 H), 1.87 (bs, 1 H), 1.27 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 132.2, 131.4, 117.1, 71.5, 64.6, 63.5, 62.4, 54.9, 53.5, 18.7; HRMS (H-ESI) *m/z* calcd for $C_{11}H_{16}O_4$ $[M + H]^+$ 213.1127, found 213.1129.

7.2.37. Synthesis of Diepoxy Amide ent-466

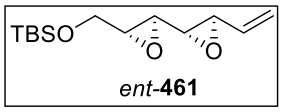


ent-**466**

Diepoxy Amide *ent*-466. Epoxy alcohol *ent*-**465**[329] (133 mg, 0.62 mmol 1.0 equiv) was dissolved in a CH_2Cl_2/DMSO (1:1) mixture (2.5 mL) and cooled at 0 ºC. At this temperature, Et_3N (0.25 mL, 1.83 mmol, 3.0 equiv) was added followed by SO_3·pyr (175 mg, 1.08 mmol, 1.8 equiv). The reaction mixture was allowed to reach 25 ºC and, after 5 h, was quenched by addition of a buffer solution (pH = 7) and diluted with Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with water and brine, then dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The resulting crude aldehyde was used in the next step without further purification. The crude aldehyde (1.0 equiv) was reacted with sulfonium salt *ent*-**457**[249,250] (221 mg, 0.71 mmol, 1.1 equiv) and NaOH (5.0 M aqueous solution, 0.13 mL, 0.63 mmol, 1.0 equiv) according to the procedure described above for epoxy amide **466** to yield diepoxy amide *ent*-**466** (179 mg, 68% over 2 steps) as a pale yellow oil: Flash column chromatography (silica gel, 20% EtOAc in hexanes); R_f = 0.21 (Silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = +26.7 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (ddd, *J* = 8.4, 4.7, 3.3 Hz, 1 H), 3.96 (ddd, *J* = 9.2, 5.2, 1.2 Hz, 1 H), 3.88–3.86 (m, 1 H), 3.85 (d, *J* = 2.4 Hz, 1 H), 3.68 (dd, *J* = 12.3, 3.7 Hz, 1 H), 3.54 (d, *J* = 2.0 Hz, 1 H), 3.29 (dd, *J* = 3.4, 2.0 Hz, 1 H), 3.07 (dq, *J* = 3.5, 2.2 Hz, 2 H), 2.58–2.49 (m, 1 H), 2.47–2.39 (m, 1 H), 2.07 (s, 3 H), 1.80–1.73 (m, 1 H), 1.58 (s, 3 H), 1.47 (s, 3 H), 0.83 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 95.9, 67.0, 61.6, 56.3, 55.9, 55.5, 51.7, 51.2, 34.4, 30.6, 26.2, 25.6, 22.9, 18.3, 15.7, –3.6, –5.4; HRMS (H-ESI) *m/e* calcd for $C_{20}H_{37}NO_5SSi$ $[M + H]^+$ 432.2240, found 432.2242.

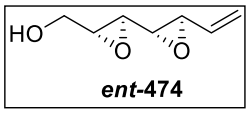
[329] (a) Shibuya, H.; Kawashima, K.; Narita, N.; Ikeda, M.; Kitagawa *Chem. Pharm. Bull.* **1992**, *40*, 1154-1165. (b) Hayashi, Y.; Shoji, M.; Mukaiyama, T.; Gotoh, H.; Yamaguchi, S.; Nakata, M.; Kakeya, H.; Osada, H. *J. Org. Chem.* **2005**, *70*, 5643-5654.

7.2.38. Synthesis of Diepoxy Alkene ent-461



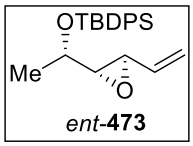
Diepoxy Alkene *ent*-461. Diepoxy olefin *ent*-**461** (67 mg, 52% over two steps) was prepared from epoxy amide *ent*-**466** (190 mg, 0.34 mmol, 1.0 equiv) by sequential treatments with Red-Al and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **461**. **[*ent*-461]:** colorless oil; R_f = 0.87 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = +29.9 (*c* 0.45, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63–5.47 (m, 2 H), 5.33–5.29 (m, 1 H), 3.87 (dd, *J* = 12.2, 2.9 Hz, 1 H), 3.74 (dd, *J* = 12.2, 4.1 Hz, 1 H), 3.35 (dd, *J* = 7.1, 2.1 Hz, 1 H), 3.10 (ddd, *J* = 4.0, 2.8, 2.2 Hz, 1 H), 2.99 (dd, *J* = 4.4, 2.1 Hz, 1 H), 2.91 (dd, *J* = 4.4, 2.1 Hz, 1 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 120.2, 62.1, 57.9, 56.0, 55.9, 53.3, 25.8, 18.3, –5.4; HRMS (H-ESI) *m/z* calcd for $C_{13}H_{24}O_3Si$ $[M + H]^+$ 257.1573, found 257.1576.

7.2.39. Synthesis of Diepoxy Alcohol ent-474



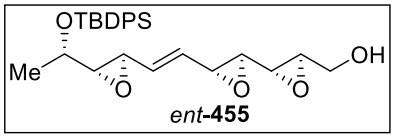
Diepoxy alcohol *ent*-474. Diepoxy alcohol *ent*-**474** (33 mg, 85%) was prepared from silyl ether *ent*-**461** (67 mg, 0.26 mmol, 1.0 equiv) by treatment with TBAF according to the same procedure described above for the preparation of **474**. **[*ent*-474]:** colourless oil; R_f = 0.32 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 23.3 (*c* 0.33, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47–5.37 (m, 2 H), 5.24–5.18 (m, 1 H), 3.79 (ddd, *J* = 11.4, 9.0, 2.5 Hz, 1 H), 3.53 (dd, *J* = 12.9, 4.3 Hz, 1 H), 3.29–3.25 (m, 1 H), 3.05 (dd, *J* = 4.3, 2.3 Hz, 1 H), 2.95–2.90 (m, 1 H), 2.81 (dd, *J* = 4.8, 2.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 120.4, 60.7, 57.9, 56.0, 55.9, 53.5; HRMS (H-ESI) *m/z* calcd for $C_7H_{10}O_3$ $[M + H]^+$ 143.0708, found 143.0712.

7.2.40. Synthesis of Epoxy Alkene ent-473



Epoxy Alkene *ent*-473. Epoxy olefin *ent*-**473** was prepared from epoxy alcohol *ent*-**472** (3.8 g, 10.66 mmol, 1.0 equiv) by sequential treatments with SO_3·pyr and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **460**, to obtain epoxy alkene *ent*-**473** (3.3 g, 87% over two steps) whose spectroscopic and physical properties were identical to epoxy alkene **473**, except for its specific rotation: $[\alpha]^{25}_D$ = –11.5 (*c* 0.45, CH_2Cl_2); HRMS (H-ESI) *m/z* calcd for $C_{22}H_{28}O_2Si$ $[M + H]^+$ 353.1937, found 353.1936.

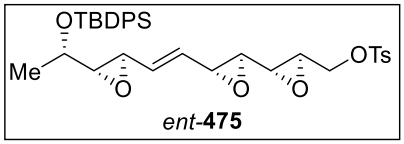
7.2.41. Synthesis of Triepoxy Alcohol ent-455



Triepoxy Alcohol *ent*-455. A solution of diepoxy olefin *ent*-**474** (33 mg, 0.23 mmol, 1.0 equiv) and epoxy olefin *ent*-**473** (245 mg, 0.70 mmol, 3.0 equiv) in degassed CH_2Cl_2 (7 mL) was reacted with Hoveyda-Grubbs 2nd generation catalyst (14 mg, 0.03 mmol, 0.10 equiv) according to the same procedure as described above for the synthesis of **455**, to afford triepoxy alcohol *ent*-**455** (53 mg, 52%)

as a colourless oil: R_f = 0.56 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$= +28.7 (*c* 0.41, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.65 (m, 4 H), 7.46–7.34 (m, 6 H), 5.70 (dd, *J* = 15.7, 7.3 Hz, 1 H), 5.58 (dd, *J* = 15.7, 7.3 Hz, 1 H), 3.97 (dd, *J* = 12.9, 2.3 Hz, 1 H), 3.76–3.68 (m, 2 H), 3.37 (dd, *J* = 7.3, 2.0 Hz, 1 H), 3.20 (dd, *J* = 7.3, 2.2 Hz, 1H), 3.19– 3.17 (m, 1 H), 3.10 (dd, *J* = 4.3, 2.3 Hz, 1 H), 2.95 (dd, *J* = 5.5, 2.1 Hz, 1 H), 2.93 (dd, *J* = 4.3, 2.1 Hz, 1 H), 1.54–1.49 (bs), 1.11 (d, *J* = 6.4 Hz, 3 H), 1.08 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.8, 134.2, 133.6, 132.8, 130.5, 129.7, 129.6, 127.6, 127.5, 69.7, 64.6, 60.5, 57.9, 55.8, 54.8, 54.6, 53.0, 26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_5Si$ $[M + Na]^+$ 489.2073, found 489.2066.

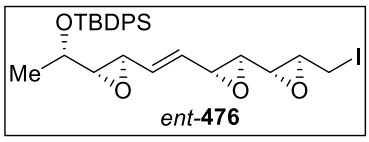
7.2.42. Synthesis of Tosyl Derivative ent-475



ent-**475**

Tosyl Derivative *ent*-475. The tosylation of triepoxy alcohol *ent*-**455** (19 mg, 0.04 mmol, 1.0 equiv) was achieved in exactly the same way as described above for **475**, to obtain tosyl derivative *ent*-**475** (35 mg, ~0.04 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (2.5 mg, ~0.0029 mmol) was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain tosyl derivative *ent*-**475** (1.7 mg, 94%) as a colourless oil: R_f = 0.74 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$= +11.3 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.77 (m, 2 H), 7.72–7.66 (m, 4 H), 7.45–7.34 (m, 8 H), 5.68 (dd, *J* = 15.6, 7.3 Hz, 1 H), 5.54 (dd, *J* = 15.7, 7.5 Hz, 1 H), 4.21 (dd, *J* = 11.7, 3.7 Hz, 1 H), 4.08 (dd, *J* = 11.6, 5.2 Hz, 1 H), 3.76–3.69 (m, 1 H), 3.32 (dd, *J* = 7.4, 1.8 Hz, 1 H), 3.23–3.20 (m, 1 H), 3.19 (dd, *J* = 7.2, 2.1 Hz, 1 H), 2.98 (dd, *J* = 4.0, 2.0 Hz, 1 H), 2.95 (dd, *J* = 5.5, 2.1 Hz, 1 H), 2.89 (dd, *J* = 4.0, 2.0 Hz, 1 H), 2.46 (s, 3 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 135.9, 135.8, 134.2, 133.6, 133.1, 132.6, 130.2, 130.0, 129.7, 129.6, 127.9, 127.6, 127.5, 69.7, 68.5, 64.6, 57.1, 54.8, 54.6, 53.8, 52.3, 26.9, 26.8, 21.7, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{34}H_{40}O_7SSi$ $[M + Na]^+$ 643.2162, found 643.2153.

7.2.43. Synthesis of Iodide Derivative ent-476

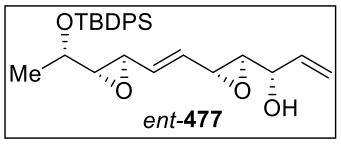


ent-**476**

Iodide Derivative *ent*-476. The iodination of crude tosyl derivative *ent*-**475** (~32 mg, ~0.037 mmol, 1.0 equiv) was carried out according to the procedure described above for **476**, to afford iodide derivative *ent*-**476** (30 mg, ~0.037 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (3.0 mg, ~0.0037 mmol) was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain pure iodide *ent*-**476** (2.0 mg, 95%) as a colourless oil: R_f = 0.83 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= +11.1 (*c* 0. 30 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.66 (m, 4 H), 7.46–7.34 (m, 6 H), 5.69 (dd, *J* = 15.7, 7.3 Hz, 1 H), 5.56 (dd, *J* = 15.7, 7.4 Hz, 1 H), 3.78–3.69 (m, 1 H), 3.35 (d, *J* = 7.2 Hz, 1 H), 3.28–3.23 (m, 2 H), 3.20 (dd, *J* = 7.2, 2.1 Hz, 1 H), 3.14–3.08 (m, 1 H), 2.97–2.94 (m, 3 H), 1.11 (d, *J* = 6.4 Hz, 3 H), 1.08 (s, 9 H); ^{13}C NMR (100 MHz,

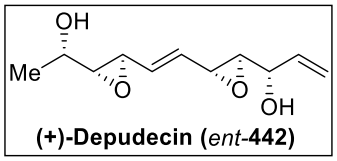
$CDCl_3$) δ 135.88, 135.84, 134.19, 133.64, 132.96, 130.31, 129.69, 129.67, 127.60, 127.6, 69.7, 64.6, 59.4, 57.3, 55.7, 54.7, 54.6, 26.9, 19.9, 19.3, 3.1; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{33}IO_4Si$ $[M + H]^+$ 577.1271, found 577.1259.

7.2.44. Synthesis of Allylic Alcohol ent-477



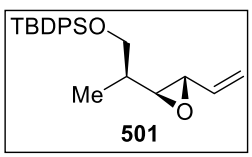
Allylic Alcohol *ent*-477. A solution of crude iodide *ent*-**476** (~24 mg, ~0.033 mmol, 1.0 equiv) in THF (4 mL) was reacted with *n*-BuLi (41.0 µL, 1.6 M in hexane, 0.066 mmol, 2.0 equiv) at -78 ºC, according to the same procedure as described above for the preparation of **477**, to afford, after similar processing, allylic alcohol *ent*-**477** (13 mg, 89% over 3 steps) as a colourless oil: R_f = 0.48 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= +16.9 (*c* 0.19, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.66 (m, 4 H), 7.46–7.34 (m, 6 H), 5.94 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.67 (dd, *J* = 15.7, 7.1 Hz, 1 H), 5.59 (dd, *J* = 15.7, 7.1 Hz, 1 H), 5.43–5.37 (m, 1 H), 5.28 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.17–4.10 (m, 1 H), 3.76– 3.70 (m, 1 H), 3.40 (dd, *J* = 7.1, 2.2 Hz, 1 H), 3.20 (dd, *J* = 7.0, 2.1 Hz, 1 H), 2.99 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.95 (dd, *J* = 5.5, 2.1 Hz, 1 H), 1.88 (d, *J* = 6.6 Hz, 1 H), 1.11 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.9, 135.8, 133.1, 133.0, 132.6, 130.9, 129.7, 129.6, 127.6, 127.5, 117.0, 71.5, 69.7, 64.5, 62.4, 54.9, 54.7, 26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_4Si$ $[M + H]^+$ 451.2305, found 451.2315.

7.2.45. Synthesis of (+)-Depudecin (ent-442)



(+)-Depudecin (*ent*-442). Silyl derivative *ent*-**477** (8 mg, 0.02 mmol, 1.0 equiv) was desilylated by the action of TBAF (0.02 mL, 1.0 M in THF, 0.02 mmol, 1.2 equiv) in the same way as desrcribed above for (-)-depudecin (**1**) to afford (+)-depudecin (*ent*-**442**) (3.0 mg, 88%) as a colourless oil: R_f = 0.50 (silica gel, EtOAc); $[\alpha]^{25}_D$= +35.6 (*c* 0.38, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.2, 10.6, 5.5 Hz, 1 H), 5.73–5.71 (m, 2 H), 5.41 (dt, *J* = 17.3, 1.3 Hz, 1 H), 5.29 (dt, *J* = 10.6, 1.2 Hz, 1 H), 4.15 (d, *J* = 5.4 Hz, 1 H), 3.79–3.74 (m, 1 H), 3.46–3.44 (m, 1 H), 3.41–3.39 (m, 1 H), 3.03 (dd, *J* = 4.2, 2.2 Hz, 1 H), 2.92 (dd, *J* = 4.5, 2.2 Hz, 1 H), 1.90 (d, *J* = 6.4 Hz, 1 H), 1.77 (d, *J* = 6.0 Hz, 1 H), 1.32 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 132.0, 131.5, 117.1, 71.5, 66.9, 64.1, 62.4, 55.3, 54.9, 20.0; HRMS (H-ESI) *m/z* calcd for $C_{11}H_{16}O_4$ $[M + H]^+$ 213.1127, found 213.1118.

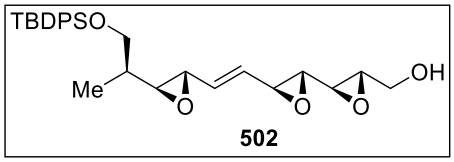
7.2.46. Synthesis of Epoxy Alkene 501



Epoxy Alkene 501. Epoxy alkene **501** was prepared from epoxy alcohol **500**[249c] (400 mg, 1.08 mmol, 1.0 equiv) by sequential treatments with SO_3·pyr and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **460**, to obtain epoxy alkene **501** (312 mg, 79% over two steps) as a pale yellow oil: R_f= 0.73 (silica gel,

20% EtOAc in hexanes); $[\alpha]^{25}_D$ = –35.5 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 4 H), 7.45 – 7.36 (m, 6 H), 6.03 (dtd, *J* = 15.6, 5.3, 0.5 Hz, 1 H), 5.50 (dt, *J* = 8.0, 1.6 Hz, 1 H), 5.47 (dt, *J* = 8.0, 1.6 Hz, 1 H), 3.64 (dd, *J* = 10.2, 5.2 Hz, 1 H), 3.58 (dd, *J* = 10.2, 7.7 Hz, 1 H), 3.29 (dd, *J* = 7.9, 2.1 Hz, 1 H), 2.79 (dd, *J* = 7.3, 2.2 Hz, 1 H), 1.71 – 1.60 (m, 1 H), 1.05 (s, 9 H), 0.99 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 135.8, 133.7, 129.7, 127.7, 118.9, 65.9, 62.1, 57.2, 38.1, 26.9, 19.4, 12.7; HRMS (H-ESI) *m/z* calcd for $C_{23}H_{31}O_2Si$ $[M + H]^+$ 367.2093, found 367.2090.

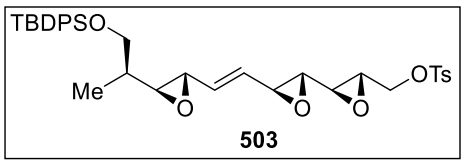
7.2.47. Synthesis of Triepoxy Alcohol 502



502

Triepoxy Alcohol 502. A solution of epoxy olefin **501** (158 mg, 0.43 mmol, 1.0 equiv) and diepoxy olefin **474** (184 mg, 1.29 mmol, 3.0 equiv) in degassed CH_2Cl_2 (4 mL) was reacted with Hoveyda-Grubbs 2nd generation catalyst (54 mg, 0.08 mmol, 0.20 equiv) according to the same procedure as described above for the synthesis of **455**, to afford triepoxy alcohol **502** (103 mg, 50%) as a colourless oil: R_f = 0.60 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$= –12.9 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 4 H), 7.46 – 7.33 (m, 6 H), 5.74 (dd, *J* = 15.7, 7.2 Hz, 1 H), 5.62 (dd, *J* = 15.7, 7.4 Hz, 1 H), 3.97 (d, *J* = 12.7 Hz, 1 H), 3.74 – 3.66 (m, 4 H), 3.39 (dd, *J* = 7.4, 2.0 Hz, 1 H), 3.22 (dd, *J* = 7.2, 2.2 Hz, 1 H), 3.10 (dd, *J* = 4.4, 2.2 Hz, 1 H), 2.91 (ddd, *J* = 8.8, 5.5, 2.1 Hz, 2 H), 1.75 – 1.68 (m, 1 H), 1.06 (s, 9 H), 0.99 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.8, 133.6, 130.2, 129.7, 127.7, 65.8, 62.5, 60.5, 57.9, 55.8, 54.9, 53.1, 38.0, 29.7, 26.9, 19.3, 12.7; HRMS (H-ESI) *m/z* calcd for $C_{28}H_{37}O_5Si$ $[M + H]^+$ 481.2410, found 481.2408.

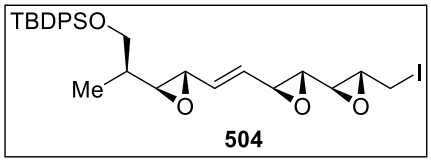
7.2.48. Synthesis of Tosyl Derivative 503



503

Tosyl Derivative 503. The tosylation of triepoxy alcohol **502** (32 mg, 0.07 mmol, 1.0 equiv) was achieved in exactly the same way as described above for **475**, to obtain tosyl derivative **503** (44 mg, ~0.07 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (10 mg, ~0.01 mmol) was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain tosyl derivative **503** (9.6 mg, 96%) as a colourless oil: R_f = 0.76 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$= –30.5 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.76 (m, 2 H), 7.69 – 7.60 (m, 4 H), 7.45 – 7.28 (m, 8 H), 5.73 (dd, *J* = 15.7, 7.2 Hz, 1 H), 5.58 (dd, *J* = 15.6, 7.4 Hz, 1 H), 4.21 (dd, *J* = 11.7, 3.7 Hz, 1 H), 4.08 (dd, *J* = 11.6, 5.2 Hz, 1 H), 3.76 – 3.62 (m, 3 H), 3.35 (dd, *J* = 7.5, 2.1 Hz, 1 H), 3.25 – 3.19 (m, 2 H), 3.16 – 3.07 (m, 2 H), 2.92 – 2.85 (m, 1 H), 2.46 (s, 3 H), 1.75 – 1.67 (m, 1 H), 1.06 (s, 9 H), 0.99 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.6, 130.0, 129.7, 128.0, 127.7, 68.5, 65.7, 62.6, 55.7, 52.3, 45.9, 38.0, 29.7, 26.9, 21.7, 19.3, 12.7, 8.6; HRMS (H-ESI) *m/z* calcd for $C_{35}H_{43}O_7SSi$ $[M + H]^+$ 635.2499, found 635.2496.

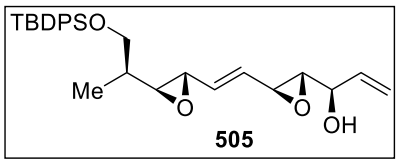
7.2.49. Synthesis of Iodide Derivative 504



504

Iodide Derivative 504. The iodination of crude tosyl derivative **503** (~34 mg, ~0.05 mmol, 1.0 equiv) was carried out according to the procedure described above for **476**, to afford iodide derivative **504** (30 mg, ~0.037 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (10 mg, ~0.02 mmol) was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain pure iodide **504** (9.4 mg, 94%) as a colourless oil: R_f = 0.86 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= –10.2 (*c* 0. 20 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 4 H), 7.45 – 7.34 (m, 6 H), 5.74 (dd, *J* = 15.7, 7.4 Hz, 1 H), 5.61 (dd, *J* = 15.7, 7.5 Hz, 1 H), 3.74 – 3.62 (m, 3 H), 3.37 (dd, *J* = 7.2, 3.5 Hz, 1 H), 3.28 – 3.20 (m, 3 H), 2.97 – 2.92 (m, 2 H), 2.90 (dd, *J* = 6.6, 2.2 Hz, 1 H), 1.77 – 1.66 (m, 1 H), 1.06 (s, 9 H), 1.00 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.9, 133.6, 130.0, 129.7, 127.7, 65.8, 62.5, 59.5, 57.3, 55.7, 54.9, 38.0, 29.7, 26.9, 19.3, 12.7, 3.2; HRMS (H-ESI) *m/z* calcd for $C_{28}H_{36}IO_4Si$ $[M + H]^+$ 591.1428, found 591.1425.

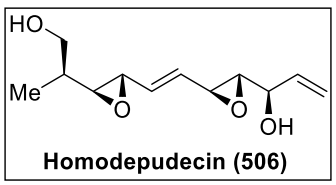
7.2.50. Synthesis of Allylic Alcohol 505



505

Allylic Alcohol 505. A solution of crude iodide **504** (~22 mg, ~0.037 mmol, 1.0 equiv) in THF (3 mL) was reacted with *n*-BuLi (50 µL, 1.6 M in hexane, 0.074 mmol, 2.0 equiv) at -78 ºC, according to the same procedure as described above for the preparation of **477**, to afford, after similar processing, allylic alcohol **505** (15 mg, 85% over 3 steps) as a colourless oil: R_f = 0.50 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= –12.8 (*c* 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.60 (m, 4 H), 7.45 – 7.32 (m, 6 H), 5.94 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.71 (dd, *J* = 9.0, 6.7 Hz, 1 H), 5.64 (dd, *J* = 11.0, 4.7 Hz, 1 H), 5.43 – 5.36 (m, 1 H), 5.27 (dt, *J* = 10.6, 1.3 Hz, 1 H), 3.68 (ddd, *J* = 22.0, 10.0, 5.0 Hz, 3 H), 3.43 (dd, *J* = 7.2, 2.2 Hz, 1 H), 3.22 (dd, *J* = 7.1, 2.0 Hz, 1 H), 3.00 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.92 – 2.88 (m, 1 H), 1.75 – 1.65 (m, 1 H), 1.06 (s, 9 H), 0.99 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.6, 133.6, 130.6, 130.0, 129.7, 127.7, 117.0, 71.6, 65.8, 62.4, 55.1, 38.0, 29.7, 26.9, 19.3, 14.1, 12.6; HRMS (H-ESI) *m/z* calcd for $C_{28}H_{37}O_4Si$ $[M + H]^+$ 465.2461, found 465.2460.

7.2.51. Synthesis of Homodepudecin (506)

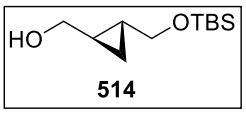


Homodepudecin (506)

Homodepudecin (506). Silyl derivative **505** (15 mg, 0.03 mmol, 1.0 equiv) was desilylated by the action of TBAF (0.04 mL, 1.0 M in THF, 0.04 mmol, 1.2 equiv) in the same way as desrcribed above for (-)-depudecin (**442**) to afford homodepudecin (**506**) (7 mg, 97%) as a colourless oil: R_f = 0.52 (silica gel, EtOAc); $[\alpha]^{25}_D$= –21.1 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ

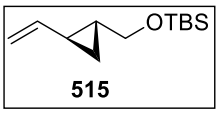
5.94 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1 H), 5.72 – 5.68 (m, 2 H), 5.43 – 5.37 (m, 1 H), 5.28 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.17 – 4.09 (m, 1 H), 3.74 – 3.63 (m, 2 H), 3.43 (dd, *J* = 7.0, 2.1 Hz, 1 H), 3.26 – 3.19 (m, 1 H), 3.01 (dd, *J* = 4.3, 2.2 Hz, 1 H), 2.82 (dd, *J* = 7.2, 2.2 Hz, 1 H), 1.92 (d, *J* = 5.9 Hz, 1 H), 1.73 (bs, 1 H), 1.72 – 1.63 (m, 1 H), 1.02 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 132.9, 131.0, 117.1, 71.5, 65.9, 63.4, 62.4, 55.9, 54.9, 38.0, 13.0; HRMS (H-ESI) *m/z* calcd for $C_{12}H_{19}O_4$ $[M + H]^+$ 227.1283, found 227.1280.

7.2.52. Synthesis of Cyclopropyl Alcohol 514



Cyclopropyl Alcohol 514. Et_2Zn (10.9 mL, 1.0 M in hexane, 10.9 mmol, 2.2 equiv) was added to a solution of dimethoxyethane (1.1 mL) in CH_2Cl_2 (36 mL) at -15 ºC and over the resulting solution was added CH_2I_2 (1.75 mL, 21.74 mmol, 4.4 equiv) dropwise over 20 min. After stirring the reaction mixture for 10 min at -15 ºC, a solution of borolane **512** (1.5 mL, 5.93 mmol, 1.2 equiv) in CH_2Cl_2 (6 mL) was added dropwise over 5 min followed by the inmediate addition of a solution of allylic alcohol **513** (1 g, 4.94 mmol, 1.0 equiv) in CH_2Cl_2 (5.5 mL). Then, the reaction mixture was stirred for 15 h at -20 ºC. After this time, the reaction was quenched by sequential addition of a saturated NH_4Cl solution and an aqueous 1.0 N HCl solution, and the aqueous phase was extracted with Et_2O. Then, a mixture of a 2 N NaOH solution (20 mL)/30% H_2O_2 (4 mL) was added to the ether phase and the mixture was stirred for 5 min at 25 ºC. After this time, the ether layer was separate and was washed sequentially with saturated NH4Cl solution, saturated $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to afford cyclopropyl **514** (952 mg, 89%) as a colorless oil: R_f = 0.76 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = –9.9 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 – 3.58 (m, 2 H), 3.50 – 3.41 (m, 2 H), 1.36 – 1.25 (m, 2 H), 0.89 (s, 9 H), 0.50 (dt, *J* = 8.3, 5.0 Hz, 1 H), 0.44 (dt, *J* = 8.5, 5.0 Hz, 1 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.6, 65.8, 25.9, 19.4, 19.3, 7.8, -5.2, -5.2; HRMS (H-ESI) *m/z* calcd for $C_{11}H_{25}O_2Si$ $[M + H]^+$ 217.1624, found 217.1622.

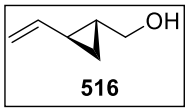
7.2.53. Synthesis of Cyclopropyl Alkene 515



Cyclopropyl Alkene 515. Cyclopropyl alkene **515** was prepared from cyclopropyl alcohol **514** (950 mg, 4.39 mmol, 1.0 equiv) by sequential treatments with SO_3·pyr and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **460**, to obtain cyclopropyl alkene **515** (420 mg, 45% over two steps) as a pale yellow oil: Flash column chromatography (silica gel, 5% EtOAc in hexanes); R_f = 0.85 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 15.9 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (ddd, *J* = 17.1, 10.2, 8.6 Hz, 1 H), 5.04 (ddd, *J* = 17.1, 1.7, 0.6 Hz, 1 H), 4.85 (dd, *J* = 10.2, 1.8 Hz, 1 H), 3.61 (dd, *J* = 10.8, 5.8 Hz, 1 H), 3.54 (dd, *J* = 5.9, 4.5 Hz, 1 H), 1.33 (ddd, *J* = 13.2, 8.7, 4.8 Hz, 2 H), 0.89 (s, 9 H), 0.71 – 0.65 (m, 1 H), 0.60 (dt, *J* = 8.5, 4.8 Hz, 1 H), 0.05 (s, 6 H); ^{13}C NMR (100

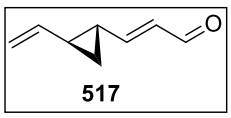
MHz, $CDCl_3$) δ 141.2, 111.8, 65.6, 25.9, 22.9, 20.2, 18.4, 11.5, -5.1; HRMS (H-ESI) *m/z* calcd for $C_{12}H_{25}OSi$ $[M + H]^+$ 213.1675, found 213.1672.

7.2.54. Synthesis of Cyclopropyl Alcohol 516



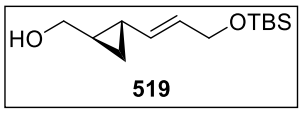
Cyclopropyl Alcohol 516. Silyl derivative **515** (420 mg, 1.98 mmol, 1.0 equiv) was dissolved in THF (15 mL) and to this solution was added TBAF (4 mL, 1.0 M in THF, 3.96 mmol, 2.0 equiv) at 25 ºC. After 1 h, the reaction mixture was diluted with EtOAc and washed with a saturated aqueous NH_4Cl solution. The aqueous phase was then extracted with EtOAc and the organic extracts were washed with H_2O, brine, dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the crude product was purified by flash column chromatography (silica gel, 15% EtOAc in hexanes) to afford cyclopropyl alcohol **516** (107 mg, 55%) as a pale yellow oil: R_f = 0.30 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$= –30.2 (*c* 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (ddd, *J* = 17.1, 10.2, 8.6 Hz, 1 H), 5.07 (ddd, *J* = 17.1, 1.6, 0.5 Hz, 1 H), 4.88 (dd, *J* = 10.2, 1.6 Hz, 1 H), 3.51 (dd, *J* = 6.9, 3.2 Hz, 2 H), 1.35 (ddd, *J* = 13.4, 8.4, 4.6 Hz, 1 H), 1.21 – 1.12 (m, 1 H), 0.71 – 0.63 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 112.4, 66.3, 22.9, 20.6, 11.6; HRMS (H-ESI) *m/z* calcd for $C_6H_{11}O$ $[M + H]^+$ 99.0809, found 99.0808.

7.2.55. Synthesis of Aldehyde 517



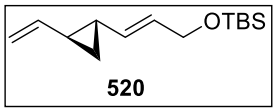
Aldehyde 517. To a solution of cyclopropyl alcohol **516** (105 mg, 1.07 mmol, 1.0 equiv) in a 1:1 DMSO:CH_2Cl_2 mixture (2.2 mL) was added Et_3N (0.45 mL, 3.21 mmol, 3.0 equiv) followed by SO_3·pyr (426 mg, 2.67 mmol, 2.5 equiv) at 0 ºC. The reaction mixture was stirred at this temperature until depletion of the starting alcohol as judged by TLC (~ 4 h). After this time, the reaction mixture was quenched by addition of a buffer solution (pH = 7) and diluted with Et_2O. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to give the crude aldehyde (~1.1 mmol) which was used in the next step without further purification. To a solution of the crude aldehyde in CH_2Cl_2 (5 mL) was added (formylmethylene) triphenylphosphorane (671 mg, 2.14 mmol, 2.0 equiv) and the mixture was stirred for 12 h. After this time the solvent was removed under reduced pressure at 25 ºC and the residue purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain aldehyde **517** (10 mg, 1% over two steps) as a colorless oil: R_f = 0.30 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = –10.8 (*c* 0.09, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (d, *J* = 7.8 Hz, 1 H), 6.38 – 6.29 (m, 1 H), 6.18 (dd, *J* = 15.4, 7.8 Hz, 1 H), 5.45 (ddd, *J* = 17.0, 10.2, 8.3 Hz, 1 H), 5.15 (ddd, *J* = 17.0, 1.3, 0.6 Hz, 1 H), 5.03 – 4.96 (m, 1 H), 1.83 – 1.76 (m, 1 H), 1.76 – 1.69 (m, 1 H), 1.21 – 1.14 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 161.1, 138.2, 130.4, 114.5, 27.5, 24.7, 17.4; HRMS (H-ESI) *m/z* calcd for $C_8H_{11}O$ $[M + H]^+$ 123.0809, found 123.0807.

7.2.56. Synthesis of Cyclopropyl Alcohol 519



Cyclopropyl Alcohol 519. Cyclopropyl alcohol **519** was prepared from alcohol **518** (2.1 g, 9.19 mmol, 1.0 equiv) according to the same procedure described above for the preparation of **514** to obtain cyclopropyl alcohol **519** (2.2 g, 98%) as a colorless oil: Flash column chromatography (silica gel, 10% EtOAc in hexanes); R_f = 0.70 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = –39.5 (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 – 5.57 (m, 1 H), 5.24 (ddt, *J* = 15.2, 8.6, 1.5 Hz, 1 H), 4.10 (dd, *J* = 5.5, 1.5 Hz, 2 H), 3.53 – 3.46 (m, 1 H), 3.47 – 3.40 (m, 1 H), 1.37 – 1.25 (m, 2 H), 0.90 (s, 9 H), 0.69 – 0.61 (m, 2 H), 0.06 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 127.6, 66.4, 63.8, 26.0, 22.9, 19.2, 18.5, 11.6, -5.1; HRMS (H-ESI) *m/z* calcd for $C_{13}H_{27}O_2Si$ $[M + H]^+$ 243.1780, found 243.1781.

7.2.57. Synthesis of Cyclopropyl Alkene 520

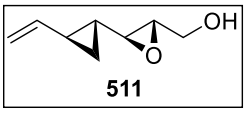


Cyclopropyl Alkene 520. Cyclopropyl alkene **520** was prepared from cyclopropyl alcohol **519** (2.2 g, 9.08 mmol, 1.0 equiv) by sequential treatments with SO_3·pyr and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **460**, to obtain cyclopropyl alkene **520** (1 g, 46% over two steps) as a colorless oil: Flash column chromatography (silica gel, 100% hexanes) to obtain cyclopropyl alkene **520** (1 g, 46% over two steps) as a colorless oil: R_f = 0.95 (silica gel, 5% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 25.1 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (dt, *J* = 15.2, 5.4 Hz, 1 H), 5.46 – 5.34 (m, 1 H), 5.25 (ddt, *J* = 15.2, 8.3, 1.5 Hz, 1 H), 5.05 (dd, *J* = 17.1, 1.7 Hz, 1 H), 4.87 (dd, *J* = 10.2, 1.6 Hz, 1 H), 4.11 (dd, *J* = 5.4, 1.5 Hz, 2 H), 1.48 – 1.37 (m, 2 H), 0.91 (s, 9 H), 0.49 (ddd, *J* = 8.4, 5.6, 2.6 Hz, 1 H), 0.36 – 0.30 (m, 1 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 132.9, 127.6, 112.2, 63.8, 26.0, 24.4, 23.3, 18.5, 14.9, -5.1; HRMS (H-ESI) *m/z* calcd for $C_{14}H_{27}OSi$ $[M + H]^+$ 239.1831, found 239.1830.

7.2.58. Synthesis of Allylic Alcohol 521

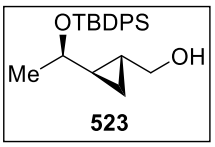
Allylic Alcohol 521. Silyl derivative **520** (1 g, 4.19 mmol, 1.0 equiv) was desilylated by the action of TBAF (8.4 mL, 1.0 M in THF, 8.40 mmol, 2.0 equiv) in the same way as desrcribed above for **516** to afford **521** (513mg, 98%) as a pale yellow oil: Flash column chromatography (silica gel, 2.5% EtOAc in hexanes → 10% EtOAc in hexanes); R_f = 0.20 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$= –26.3 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 – 5.67 (m, 1 H), 5.46 – 5.34 (m, 1 H), 5.34 – 5.23 (m, 1 H), 5.10 – 5.03 (m, 1 H), 4.89 (dd, *J* = 10.2, 1.6 Hz, 1 H), 4.11 – 4.04 (m, 2 H), 1.49 – 1.41 (m, 2 H), 0.91 – 0.83 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 135.1, 127.2, 112.5, 63.6, 24.6, 23.3, 15.0; HRMS (H-ESI) *m/z* calcd for $C_8H_{13}O$ $[M + H]^+$ 125.0966, found 125.0964.

7.2.59. Synthesis of Epoxy Cyclopropyl Alkene 511



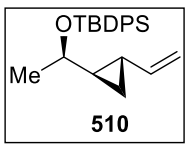
Epoxy Cyclopropyl Alkene 511. To a suspension of titanium tetraisopropoxide (0.28 mL, 0.95 mmol, 0.23 equiv) and 4Å molecular sieves (5.0 g) in CH_2Cl_2 (50 mL) was added (+)-L-DET (0.18 mL, 1.03 mmol, 0.25 equiv) at -50 ºC. After 15 min at this temperature, a solution of allylic alcohol **521** (513 mg, 4.13 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added dropwise, followed by the addition, after additional 30 min, of TBHP (1.13 mL, 5.5 M solution in decane, 6.19 mmol, 1.5 equiv) at the same temperature. After 15 h at -20 ºC, the reaction mixture was quenched with Me_2S (1.4 mL, 19.00 mmol, 4.6 equiv) at 0 ºC, filtered off and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain epoxy alcohol **511** (603 mg, 71%) as a colourless oil: R_f = 0.40 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = –18.6 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (ddd, *J* = 17.1, 10.2, 8.6 Hz, 1 H), 5.01 (ddd, *J* = 17.0, 1.7, 0.6 Hz, 1 H), 4.83 (ddd, *J* = 10.2, 1.7, 0.4 Hz, 1 H), 3.43 (dd, *J* = 7.0, 3.3 Hz, 2 H), 1.23 – 1.14 (m, 1 H), 0.91 – 0.84 (m, 2 H), 0.82 – 0.74 (m, 1 H), 0.41 – 0.35 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 111.54, 66.9, 21.9, 21.2, 18.2, 12.3, 8.7; HRMS (H-ESI) *m/z* calcd for $C_8H_{13}O_2$ [M + H]$^+$ 141.0916, found 141.0913.

7.2.60. Synthesis of Cyclopropyl Alcohol 523



Cyclopropyl Alcohol 523. Cyclopropyl alcohol **523** was prepared from allylic alcohol **522** (1 g, 2.94 mmol, 1.0 equiv) according to the same procedure described above for the preparation of **514** to obtain cyclopropyl alcohol **523** (1 g, 96%) as a yellow oil: Flash column chromatography (silica gel, 15% EtOAc in hexanes); R_f = 0.50 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = –12.1 (*c* 0.45, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 4 H), 7.44 – 7.33 (m, 6 H), 3.64 (t, *J* = 6.0 Hz, 1 H), 3.39 – 3.33 (m, 1 H), 3.32 – 3.22 (m, 1 H), 1.35 – 1.31 (m, 2 H), 1.17 (d, *J* = 6.1 Hz, 3 H), 1.04 (s, 9 H), 0.92 – 0.86 (m, 1 H), 0.34 – 0.27 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.9, 134.5, 134.4, 129.6, 129.6, 127.6, 127.5, 72.4, 66.6, 26.9, 25.3, 19.8, 7.3; HRMS (H-ESI) *m/z* calcd for $C_{22}H_{31}O_2Si$ [M + H]$^+$ 355.2093, found 355.2091.

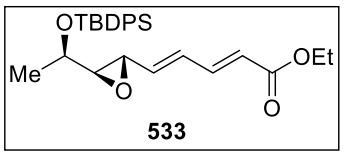
7.2.61. Synthesis of Cyclopropyl Alkene 510



Cyclopropyl Alkene 510. Cyclopropyl alkene **510** was prepared from cyclopropyl alcohol **523** (1 g, 2.82 mmol, 1.0 equiv) by sequential treatments with SO_3·pyr and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **460**, to obtain cyclopropyl alkene **510** (380 mg, 40% over two steps) as a yellow oil: Flash column chromatography (silica gel, 100% hexanes); R_f = 0.92 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 36.2 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 4 H), 7.47 – 7.32 (m, 6 H), 5.40 – 5.28 (m, 1 H), 4.94 (ddd, *J* = 17.1, 1.8, 0.6 Hz, 1 H), 4.84 – 4.78 (m, 1 H), 3.29 (dq, *J* = 12.4, 6.2 Hz, 1 H), 1.30 – 1.22 (m, 2 H), 1.15 (d, *J* = 6.1 Hz, 3 H), 1.05 (s, 9 H), 0.52 –

0.45 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 136.0, 135.9, 129.5, 129.5, 127.5, 127.5, 111.6, 72.5, 28.8, 27.0, 23.5, 21.0, 19.2, 10.8; HRMS (H-ESI) *m/z* calcd for $C_{23}H_{31}OSi$ $[M + H]^+$ 351.2144, found 351.2142.

7.2.62. Synthesis of Epoxy Ester 533



533

Epoxy Ester 533. To a solution of epoxy alcohol **473** (1.2 g, 3.37 mmol, 1.0 equiv) in a 1:1 DMSO:CH_2Cl_2 mixture (7 mL) was added Et_3N (1.4 mL, 10.10 mmol, 3.0 equiv) followed by SO_3·pyr (1.3 g, 8.41 mmol, 2.5 equiv) at 0 ºC. The reaction mixture was stirred at this temperature until depletion of the starting alcohol as judged by TLC (~ 5 h). After this time, the reaction mixture was quenched by addition of a buffer solution (pH = 7) and diluted with Et_2O. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to give the crude aldehyde (~3.4 mmol) which was used in the next step without further purification. The crude aldehyde (~3.4 mmol, 1.0 equiv), triethyl 4-phosphonocrotonate (**532**) (1.0 g, 4.76 mmol, 1.4 equiv), LiOH (113 mg, 4.71 mmol, 1.4 equiv) and 4 Å molecular sieves (5 g) were dissolved in THF (15 mL) and refluxed for 15 h. After this time, the mixture was filtered through a pad of SiO_2 and washed with Et_2O. The organic solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain ester **533** (707 mg, 47% over two steps) as a pale yellow oil: R_f = 0.54 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 10.8 (*c* 0.71, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 4 H), 7.44 – 7.36 (m, 6 H), 7.25 – 7.19 (m, 1 H), 6.41 (dd, *J* = 15.3, 11.2 Hz, 1 H), 5.89 (d, *J* = 15.4 Hz, 1 H), 5.78 (dd, *J* = 15.3, 7.7 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 3.77 (dd, *J* = 6.3, 5.5 Hz, 1 H), 3.26 (dd, *J* = 7.6, 2.1 Hz, 1 H), 2.98 (dd, *J* = 5.4, 2.1 Hz, 1 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.12 (d, *J* = 6.5 Hz, 3 H), 1.08 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 142.7, 138.4, 135.9, 135.9, 134.1, 133.6, 131.3, 129.7, 129.7, 127.6, 127.6, 122.3, 69.6, 65.0, 60.5, 55.0, 26.9, 19.9, 19.3, 14.3; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_4Si$ $[M + H]^+$ 451.2305, found 451.2303.

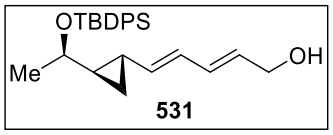
7.2.63. Synthesis of Cyclopropyl Ester 535

535

Cyclopropyl Ester 535. Cyclopropyl ester **535** was prepared from cyclopropyl alcohol **523** (500 mg, 1.40 mmol, 1.0 equiv) according to the same procedure described above for the preparation of **533**, to obtain cyclopropyl ester **535** (320 mg, 51% over two steps) as a pale yellow oil: Flash column chromatography (silica gel, 5% EtOAc in hexanes); R_f = 0.85 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 18.66 (*c* 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 4 H), 7.45 – 7.33 (m, 6 H), 7.25 – 7.16 (m, 1 H), 6.03 (dd, *J* = 19.0, 7.2 Hz, 1 H), 5.74 (d, *J* = 15.3 Hz, 1 H), 5.56 (dd, *J* = 15.0, 9.3 Hz, 1 H), 4.21 (q, *J* = 7.2 Hz, 3 H), 3.36 – 3.28 (m, 1 H), 1.34 – 1.28 (m, 2 H), 1.21 – 1.16 (m, 4 H), 1.08 (d, *J* = 5.6 Hz, 3 H), 1.04 (s, 9 H), 0.71 – 0.60 (m, 2

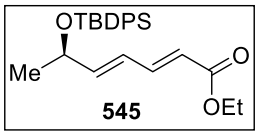
H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 147.6, 145.0, 135.9, 135.9, 135.9, 134.3, 134.2, 129.6, 129.6, 127.6, 117.9, 72.3, 69.6, 60.1, 30.4, 27.0, 21.2, 19.3, 14.4, 12.6; HRMS (H-ESI) *m/z* calcd for $C_{28}H_{37}O_3Si$ $[M + H]^+$ 449.2512, found 449.2511.

7.2.64. Synthesis of Allylic Alcohol 531



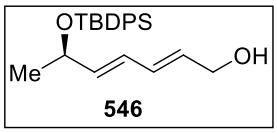
Allylic Alcohol 531. A solution of ester **535** (100 mg, 0.22 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was cooled at -78 ºC and treated with DIBAL-H (0.6 mL, 1.0 M in toluene, 0.56 mmol, 2.5 equiv). After 20 min, the reaction was quenched by addition of MeOH at -78 ºC and the mixture was allowed to reach room temperature, treated with a saturated aqueous Na^+/K^+ tartrate solution and diluted with CH_2Cl_2. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain allylic alcohol **531** (70 mg, 77%) as a colorless oil: R_f = 0.75 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 15.7 (*c* 0.15, CH_2Cl_2);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 4 H), 7.44 – 7.34 (m, 6 H), 6.17 (dd, *J* = 15.1, 10.5 Hz, 1 H), 5.96 (dd, *J* = 15.1, 10.5 Hz, 1 H), 5.70 (ddd, *J* = 15.1, 10.5, 4.3 Hz, 1 H), 5.22 (dd, *J* = 15.1, 8.9 Hz, 1 H), 4.17 (d, *J* = 6.0 Hz, 2 H), 3.35 – 3.28 (m, 1 H), 1.19 – 1.15 (m, 2 H), 1.07 (d, *J* = 4.2 Hz, 3 H), 1.05 (s, 9 H), 0.59 – 0.49 (m, 1 H), 0.36 – 0.27 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 136.0, 135.9, 135.9, 134.5, 134.3, 132.1, 129.6, 129.5, 128.5, 127.5, 127.1, 72.4, 66.6, 63.7, 29.4, 27.0, 23.6, 19.3, 11.6; HRMS (H-ESI) *m/z* calcd for $C_{26}H_{35}O_2Si$ $[M + H]^+$ 407.2406, found 407.2404.

7.2.65. Synthesis of Ester 545



Ester 545. Ester **545** was prepared from allylic alcohol **522** (500 mg, 1.47 mmol, 1.0 equiv) according to the same procedure described above for the preparation of **533**, to obtain ester **545** (525 mg, 88% over two steps) as a colorless oil: Flash column chromatography (silica gel, 10% EtOAc in hexanes); R_f = 0.60 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D$ = –10.1 (*c* 0.93, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 4 H), 7.44 – 7.33 (m, 6 H), 7.22 (dd, *J* = 15.4, 10.8 Hz, 1 H), 6.19 (dd, *J* = 15.4, 10.6 Hz, 1 H), 6.07 (dd, *J* = 15.2, 5.2 Hz, 1 H), 5.79 (d, *J* = 15.4 Hz, 1 H), 4.42 – 4.35 (m, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.16 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 146.5, 144.3, 135.8, 134.2, 133.7, 129.7, 129.7, 127.6, 126.2, 120.9, 69.4, 60.3, 26.9, 23.8, 19.3, 14.3; HRMS (H-ESI) *m/z* calcd for $C_{25}H_{32}O_3Si$ $[M + H]^+$ 409.2199, found 409.2197.

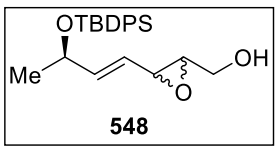
7.2.66. Synthesis of Allylic Alcohol 546



546

Allylic Alcohol 546. A solution of ester **545** (525 mg, 2.29 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was cooled at -78 ºC and treated with DIBAL-H (5.7 mL, 1.0 M in toluene, 5.72 mmol, 2.5 equiv). After 20 min, the reaction was quenched by addition of MeOH at -78 ºC and the mixture was allowed to reach room temperature, treated with a saturated aqueous Na^+/K^+ tartrate solution and diluted with CH_2Cl_2. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain allylic alcohol **546** (423 mg, 90%) as a pale colorless oil: R_f = 0.20 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 21.5 (*c* 0.66, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 4 H), 7.44 – 7.33 (m, 6 H), 6.19 (ddt, *J* = 15.1, 10.5, 1.3 Hz, 1 H), 6.03 (dd, *J* = 15.4, 10.7 Hz, 1 H), 5.72 (ddd, *J* = 13.6, 10.0, 5.9 Hz, 2 H), 4.38 – 4.30 (m, 1 H), 4.17 (t, *J* = 5.0 Hz, 2 H), 1.14 (d, *J* = 6.3 Hz, 3 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 135.9, 135.9, 134.5, 134.1, 131.3, 131.2, 129.6, 129.5, 127.7, 127.5, 127.5, 69.7, 63.5, 27.0, 24.2, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{23}H_{30}O_2Si$ $[M + H]^+$ 367.2093, found 367.2096.

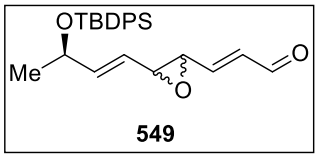
7.2.67. Synthesis of Epoxy Alcohol 548



548

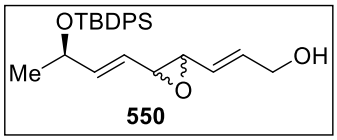
Epoxy Alcohol 548. To a solution of allylic alcohol **546** (1.1 g, 3.14 mmol, 1.0 equiv) and $NaHCO_3$ (600 mg, 7.22 mmol, 2.3 equiv) in CH_2Cl_2 (100 mL) was added *m*-CPBA (914 mg, 4.08 mmol, 1.3 equiv) at -15 ºC, and the resulting mixture was stirred at this temperature for 4 h. After this time the reaction was quenched by addition of Me_2S (0.23 mL, 3.14 mmol, 1.0 equiv) at 0 ºC. The mixture was stirred for 5 minutes at the same temperature. Then, a saturated aqueous $NaHCO_3$ solution was added and the aqueous phase was extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain epoxy alcohol **548** (1.0 g, 88%) as a colorless oil: R_f = 0.68 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 8 H), 7.45 – 7.34 (m, 12 H), 5.95 (dd, *J* = 11.2, 4.4 Hz, 1 H), 5.91 (dd, *J* = 11.1, 4.4 Hz, 1 H), 5.32 (ddd, *J* = 15.5, 8.0, 1.3 Hz, 1 H), 5.20 (ddd, *J* = 15.5, 8.1, 1.2 Hz, 1 H), 4.39 – 4.31 (m, 2 H), 3.95 (dd, *J* = 5.0, 2.3 Hz, 1 H), 3.92 (dd, *J* = 4.9, 2.3 Hz, 1 H), 3.70 – 3.61 (m, 1 H), 3.34 (ddd, *J* = 13.2, 8.1, 2.2 Hz, 1 H), 2.98 (dt, *J* = 4.4, 2.4 Hz, 1 H), 2.94 (dt, *J* = 4.4, 2.3 Hz, 1 H), 1.18 – 1.14 (m, 6 H), 1.09 – 1.07 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 140.2, 135.9, 135.9, 135.9, 134.3, 134.3, 133.9, 133.9, 129.7, 129.6, 127.6, 127.5, 125.3, 125.0, 69.4, 69.2, 61.2, 60.1, 60.1, 55.3, 55.2, 27.0, 23.9, 23.9, 19.3, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{23}H_{30}O_3Si$ $[M + H]^+$ 383.2043, found 383.2046.

7.2.68. Synthesis of Aldehyde 549



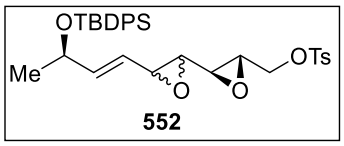
Aldehyde 549. Aldehyde **549** was prepared from epoxy alcohol **548** (574 mg, 1.50 mmol, 1.0 equiv) by sequential treatments with SO_3·pyr and Ph_3P=CHCHO according to the same procedure described above for the preparation of **467**, to obtain aldehyde **549** (387 mg, 63% over two steps) as a pale yellow oil: Flash column chromatography (silica gel, 5% EtOAc in hexanes); R_f = 0.75 (silica gel, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, *J* = 3.6 Hz, 1 H), 9.57 (d, *J* = 3.6 Hz, 1 H), 7.69 – 7.64 (m, 8 H), 7.44 – 7.33 (m, 12 H), 6.57 (dd, *J* = 6.6, 1.1 Hz, 1 H), 6.53 (dd, *J* = 6.6, 1.1 Hz, 1 H), 6.41 (ddd, *J* = 7.7, 3.8, 0.5 Hz, 1 H), 6.38 – 6.35 (m, 1 H), 5.97 (dd, *J* = 8.5, 5.4 Hz, 1 H), 5.93 (dd, *J* = 8.7, 5.6 Hz, 1 H), 5.32 (ddd, *J* = 15.5, 7.4, 1.4 Hz, 1 H), 5.24 (ddd, *J* = 15.5, 7.7, 1.4 Hz, 1 H), 4.40 – 4.32 (m, 2 H), 3.33 – 3.27 (m, 4 H), 1.18 – 1.15 (m, 6 H), 1.07 (s, 9 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 152.1, 141.1, 140.9, 135.9, 135.9, 134.2, 133.9, 133.6, 133.6, 129.7, 129.7, 127.6, 127.5, 124.3, 124.1, 69.2, 69.2, 61.1, 60.9, 58.1, 57.9, 26.9, 23.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{25}H_{30}O_3Si$ $[M + H]^+$ 407.2044, found 407.2041.

7.2.69. Synthesis of Allylic Alcohol 550



Allylic Alcohol 550. A solution of aldehyde **549** (387 mg, 0.95 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was cooled at -78 ºC and treated with DIBAL-H (1.0 mL, 1.0 M in toluene, 0.95 mmol, 1.0 equiv). After 20 min, the reaction was quenched by addition of MeOH at -78 ºC and the mixture was allowed to reach room temperature, treated with a saturated aqueous Na^+/K^+ tartrate solution and diluted with CH_2Cl_2. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain allylic alcohol **550** (265 mg, 68%) as a yellow oil: R_f = 0.25 (silica gel, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 8 H), 7.45 – 7.32 (m, 12 H), 6.09 (ddd, *J* = 5.6, 5.0, 3.7 Hz, 1 H), 6.05 (ddd, *J* = 5.7, 5.0, 3.4 Hz, 1 H), 5.91 (dd, *J* = 10.2, 5.4 Hz, 1 H), 5.87 (dd, *J* = 10.3, 5.5 Hz, 1 H), 5.52 (dt, *J* = 7.7, 1.6 Hz, 1 H), 5.31 (ddd, *J* = 15.5, 7.6, 1.4 Hz, 1 H), 5.20 (ddd, *J* = 15.5, 7.8, 1.3 Hz, 1 H), 4.38 – 4.29 (m, 2 H), 4.23 – 4.15 (m, 4 H), 3.16 (dtd, *J* = 18.0, 8.0, 2.0 Hz, 4 H), 1.18 – 1.12 (m, 6 H), 1.10 – 1.05 (m, 19 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 139.6, 135.9, 135.9, 135.9, 134.3, 134.3, 133.9, 133.9, 129.6, 129.6, 128.2, 128.1, 127.5, 127.5, 125.5, 125.2, 69.4, 69.3, 62.7, 62.7, 59.9, 59.8, 59.6, 59.6, 27.0, 23.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{25}H_{32}O_3Si$ $[M + H]^+$ 409.2199, found 409.2195.

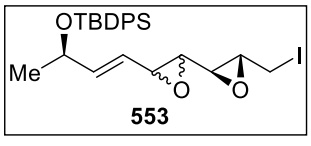
7.2.70. Synthesis of Tosyl Derivative 552



552

Tosyl Derivative 552. To a suspension of titanium tetraisopropoxide (0.04 mL, 0.15 mmol, 0.23 equiv) and 4Å molecular sieves (1.0 g) in CH_2Cl_2 (10 mL) was added (+)-L-DET (0.03 mL, 0.16 mmol, 0.25 equiv) at -50 ºC. After 15 min at this temperature, a solution of allylic alcohol **550** (265 mg, 0.65 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added dropwise, followed by the addition, after additional 30 min, of TBHP (0.2 mL, 5.5 M solution in decane, 0.97 mmol, 1.5 equiv) at the same temperature. After 15 h at -20 ºC, the reaction mixture was quenched with Me_2S (0.2 mL, 2.96 mmol, 4.6 equiv) at 0 ºC, filtered off and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) to obtain diepoxy alcohol **551** (300 mg, ~72%, impurified with ~100 mg of (+)-DET) as a colourless oil which was used in the next steps without further purification. Diepoxy alcohol **551** obtained above (300 mg, 0.71 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (20 mL) and cooled at 0 ºC. Over this solution was then added *p*-TsCl (162 mg, 0.85 mmol, 1.2 equiv), TEA (0.15 mL, 1.06 mmol, 1.5 equiv) and 4-DMAP (2 mg, 0.01 mmol, 0.02 equiv). After 3 h, the reaction mixture was quenched by addition of water and the aqueous phase was extracted with CH_2Cl_2 three times. The organic phase was washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to obtain tosyl derivative **552** (245 mg, ~0.42 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (35 mg, ~0.06 mmol) was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to provide pure tosyl derivative **552** (33 mg, 95%) as a colourless oil: R_f = 0.80 (silica gel, 60% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.77 (m, 4 H), 7.68 – 7.60 (m, 8 H), 7.45 – 7.32 (m, 16 H), 5.90 (td, *J* = 15.0, 5.4 Hz, 2 H), 5.22 (ddd, *J* = 15.6, 7.9, 1.4 Hz, 1 H), 5.12 (ddd, *J* = 15.4, 7.9, 1.3 Hz, 1 H), 4.32 (dd, *J* = 11.9, 6.6 Hz, 2 H), 4.22 – 4.12 (m, 2 H), 4.06 (dd, *J* = 11.6, 5.3 Hz, 1 H), 4.00 (dd, *J* = 11.6, 5.6 Hz, 1 H), 3.24 (dd, *J* = 7.9, 1.9 Hz, 1 H), 3.22 – 3.14 (m, 3 H), 2.93 (dd, *J* = 4.1, 2.0 Hz, 1 H), 2.89 (dd, *J* = 4.4, 2.0 Hz, 1 H), 2.72 (ddd, *J* = 9.8, 4.3, 2.1 Hz, 2 H), 2.46 (s, 6 H), 1.16 – 1.12 (m, 6 H), 1.07 – 1.04 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 140.9, 140.7, 135.9, 135.9, 134.2, 134.2, 133.9, 132.6, 130.0, 129.7, 128.6, 128.0, 128.0, 127.5, 127.5, 124.3, 124.2, 69.2, 69.2, 68.8, 68.7, 62.8, 61.6, 57.2, 57.0, 56.4, 55.4, 54.6, 54.1, 52.8, 52.3, 29.7, 26.9, 23.9, 21.8, 19.2, 1.0; HRMS (H-ESI) *m/z* calcd for $C_{32}H_{38}O_6SSi$ $[M + H]^+$ 579.2237, found 579.2235.

7.2.71. Synthesis of Iodide Derivative 553

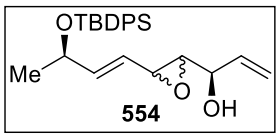


553

Iodide Derivative 553. The iodination of crude tosyl derivative **552** (~200 mg, ~0.34 mmol, 1.0 equiv) was carried out according to the procedure described above for **476**, to afford iodide derivative **553** (130 mg, ~0.24 mmol), which did not require further purification for the next step. For analytical purposes, a sample of this crude (65 mg, ~0.12 mmol) was purified by flash column chromatography (silica gel,

10% EtOAc in hexanes) to afford pure iodide derivative **553** (59 mg, 93%) as a colourless oil: R_f = 0.60 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 8 H), 7.44 – 7.35 (m, 12 H), 5.92 (dddd, *J* = 15.5, 11.6, 5.4, 0.5 Hz, 2 H), 5.24 (ddd, *J* = 15.5, 7.8, 1.5 Hz, 1 H), 5.14 (ddd, *J* = 15.5, 8.0, 1.3 Hz, 1 H), 4.36 – 4.29 (m, 2 H), 4.16 (dq, *J* = 15.6, 7.2 Hz, 2 H), 3.29 – 3.18 (m, 4 H), 3.13 – 3.04 (m, 2 H), 2.94 – 2.90 (m, 2 H), 2.80 (ddd, *J* = 8.9, 4.0, 2.1 Hz, 2 H), 1.17 – 1.13 (m, 6 H), 1.08 – 1.04 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 140.6, 135.9, 135.9, 134.2, 134.2, 133.9, 129.7, 127.6, 127.5, 124.5, 124.4, 69.3, 69.2, 60.1, 59.7, 57.4, 57.2, 56.5, 56.1, 55.6, 55.4, 26.9, 23.9, 19.2, 1.0; HRMS (H-ESI) *m/z* calcd for $C_{25}H_{31}IO_3Si$ $[M + H]^+$ 535.1165, found 535.1163.

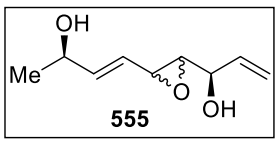
7.2.72. Synthesis of Allylic Alcohol 554



554

Allylic Alcohol 554. A solution of iodide **553** (~65 mg, ~0.12 mmol, 1.0 equiv) in THF (9 mL) was reacted with *n*-BuLi (0.15 mL, 1.6 M in hexane, 0.24 mmol, 2.0 equiv) at -78 ºC, according to the same procedure as described above for the preparation of **477**, to afford, after similar processing, allylic alcohol **554** (41 mg, 85% over 3 steps from **10**) as a colourless oil: Flash column chromatogaphy (silica gel, 15% EtOAc in hexanes); R_f = 0.60 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 8 H), 7.44 – 7.32 (m, 12 H), 5.98 – 5.79 (m, 4 H), 5.44 – 5.35 (m, 2 H), 5.33 – 5.25 (m, 3 H), 5.17 (ddd, *J* = 15.4, 8.1, 1.3 Hz, 1 H), 4.36 – 4.29 (m, 3 H), 4.13 – 4.06 (m, 1 H), 3.38 – 3.32 (m, 2 H), 2.90 – 2.84 (m, 2 H), 1.17 – 1.14 (m, 6 H), 1.07 – 1.05 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 140.3, 136.4, 135.9, 135.9, 135.4, 134.3, 133.9, 129.6, 129.6, 127.5, 127.5, 125.2, 124.8, 117.8, 116.8, 71.6, 70.1, 69.4, 69.2, 62.3, 61.6, 55.6, 54.5, 26.9, 23.9, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{25}H_{32}O_3Si$ $[M + H]^+$ 409.2199, found 409.2196.

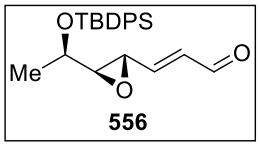
7.2.73. Synthesis of Depudecin Analogue 555



555

Depudecin Analogue 555. Silyl derivative **554** (25 mg, 0.06 mmol, 1.0 equiv) was desilylated by the action of TBAF (70 µL, 1.0 M in THF, 0.07 mmol, 1.2 equiv) in the same way as desrcribed above for (-)-depudecin (**442**) to afford depudecin analogue **555** (8.0 mg, 78%) as a colourless oil: Flash column chromatography (silica gel, 30% EtOAc in hexanes → 100% EtOAc); R_f = 0.56 (silica gel, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 – 5.99 (m, 1 H), 5.86 (ddd, *J* = 17.2, 10.5, 6.3 Hz, 1 H), 5.41 (dt, *J* = 17.3, 1.4 Hz, 2 H), 5.28 (dt, *J* = 10.5, 1.3 Hz, 1 H), 4.41 – 4.30 (m, 2 H), 3.46 (dd, *J* = 8.0, 2.3 Hz, 1 H), 3.04 (dd, *J* = 3.2, 2.3 Hz, 1 H), 1.98 (bs, 1 H), 1.52 (bs, 1 H), 1.29 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 140.2, 136.2, 135.3, 126.1, 125.9, 117.9, 116.9, 71.6, 70.0, 67.9, 62.3, 61.7, 55.5, 54.3, 54.2, 23.2, 23.1; HRMS (H-ESI) *m/z* calcd for $C_9H_{14}O_3$ $[M + H]^+$ 171.1021, found 171.1023.

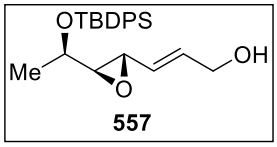
7.2.74. Synthesis of Aldehyde 556



556

Aldehyde 556. Aldehyde **556** was prepared from epoxy alcohol **472** (2.1 g, 5.89 mmol, 1.0 equiv) by sequential treatments with SO_3·pyr and Ph_3P=CHCHO according to the same procedure described above for the preparation of **467**, to obtain aldehyde **556** (1.7 g, 76% over two steps) as a pale yellow oil: Flash column chromatography (silica gel, 5% EtOAc in hexanes); R_f = 0.80 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 18.1 (*c* 0.82, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, *J* = 7.7 Hz, 1 H), 7.71 – 7.65 (m, 4 H), 7.46 – 7.35 (m, 6 H), 6.47 (dd, *J* = 15.8, 7.1 Hz, 1 H), 6.31 (dd, *J* = 15.8, 7.7 Hz, 1 H), 3.87 – 3.80 (m, 1 H), 3.43 (dd, *J* = 7.1, 2.0 Hz, 1 H), 3.05 (dd, *J* = 5.2, 2.0 Hz, 1 H), 1.15 (d, *J* = 6.4 Hz, 3 H), 1.08 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 152.3, 135.8, 133.9, 133.8, 133.4, 129.9, 129.8, 127.8, 127.7, 127.7, 69.2, 65.3, 53.7, 26.8, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{23}H_{28}O_3Si$ $[M + H]^+$ 381.1886, found 381.18861.

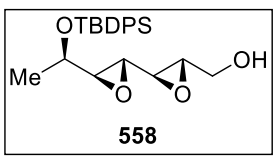
7.2.75. Synthesis of Allylic Alcohol 557



557

Allylic Alcohol 557. A solution of aldehyde **556** (1.7 g, 4.47 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) was cooled at -78 ºC and treated with DIBAL-H (4.5 mL, 1.0 M in toluene, 4.47 mmol, 1.0 equiv). After 20 min, the reaction was quenched by addition of MeOH at -78 ºC and the mixture was allowed to reach room temperature, treated with a saturated aqueous Na^+/K^+ tartrate solution and diluted with CH_2Cl_2. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain allylic alcohol **557** (1.69 g, 98%) as a pale yellow oil: R_f = 0.30 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 31.5 (*c* 0.65, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 4 H), 7.43 – 7.34 (m, 6 H), 6.01 (ddd, *J* = 15.6, 5.5, 5.1 Hz, 1 H), 5.46 (ddt, *J* = 15.6, 8.0, 1.6 Hz, 1 H), 4.17 (td, *J* = 5.7, 1.6 Hz, 2 H), 3.76 – 3.68 (m, 1 H), 3.22 (dd, *J* = 8.0, 2.1 Hz, 1 H), 2.97 (dd, *J* = 5.6, 2.2 Hz, 1 H), 1.11 (d, *J* = 6.4 Hz, 3 H), 1.08 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.9, 134.4, 133.6, 129.7, 129.7, 128.3, 127.6, 127.6, 125.3, 69.9, 64.4, 62.7, 55.3, 26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{23}H_{30}O_3Si$ $[M + H]^+$ 383.2043, found 383.2047.

7.2.76. Synthesis of Diepoxy Alcohol 558

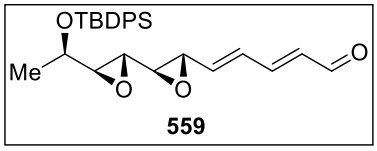


558

Diepoxy Alcohol 558. To a suspension of titanium tetraisopropoxide (0.3 mL, 1.02 mmol, 0.23 equiv) and 4Å molecular sieves (3.0 g) in CH_2Cl_2 (40 mL) was added (+)-L-DET (0.19 mL, 1.10 mmol, 0.25 equiv) at -50 ºC. After 15 min at this temperature, a solution of allylic alcohol **557** (1.69 g, 4.42 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added dropwise, followed by the addition, after additional 30 min, of TBHP

(1.2 mL, 5.5 M solution in decane, 6.63 mmol, 1.5 equiv) at the same temperature. After 15 h at -20 ºC, the reaction mixture was quenched with Me_2S (1.5 mL, 20.32 mmol, 4.6 equiv) at 0 ºC, filtered off and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain diepoxy alcohol **558** (1 g, 57% impurified with (+)-DET) as a colourless oil: R_f = 0.40 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = –11.3 (*c* 0.45, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 4 H), 7.46 – 7.34 (m, 6 H), 3.95 (ddd, *J* = 12.8, 4.7, 2.1 Hz, 1 H), 3.84 – 3.77 (m, 1 H), 3.67 (ddd, *J* = 12.8, 7.9, 3.5 Hz, 1 H), 3.07 (dt, *J* = 3.6, 2.3 Hz, 1 H), 3.03 (dd, *J* = 5.1, 2.2 Hz, 1 H), 2.99 (dd, *J* = 4.6, 2.3 Hz, 1 H), 2.87 (dd, *J* = 4.7, 2.2 Hz, 1 H), 1.11 (d, *J* = 6.4 Hz, 3 H), 1.06 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.8, 133.6, 133.6, 129.8, 129.7, 127.7, 127.6, 71.9, 62.5, 59.9, 55.7, 53.4, 26.9, 19.9, 19.3, 14.2; HRMS (H-ESI) *m/z* calcd for $C_{23}H_{30}O_4Si$ [M + H]$^+$ 399.1992, found 399.1994.

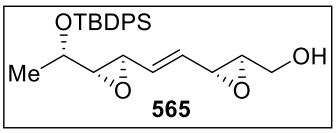
7.2.77. Synthesis of Aldehyde 559



559

Aldehyde 559. To a solution of epoxy alcohol **558** obtained above (1 g, 2.51 mmol, 1.0 equiv) in a 1:1 DMSO:CH_2Cl_2 mixture (5 mL) was added Et_3N (1 mL, 7.53 mmol, 3.0 equiv) followed by SO_3·pyr (1 g, 6.27 mmol, 2.5 equiv) at 0 ºC. The reaction mixture was stirred at this temperature until depletion of the starting alcohol as judged by TLC (~ 5 h). After this time, the reaction mixture was quenched by addition of a buffer solution (pH = 7) and diluted with Et_2O. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to give the crude aldehyde (~2.51 mmol) which was used in the next step without further purification. To a solution of the crude aldehyde in CH_2Cl_2 (10 mL) was added (formylmethylene)triphenylphosphorane (1.98 g, 6.52 mmol, 2.5 equiv) and the mixture was stirred for 15 h. After this time the solvent was removed under reduced pressure and the residue purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain aldehyde **559** (163 mg, 31% over two steps) as a pale yellow oil: R_f = 0.65 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = –15.6 (*c* 0.49, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, *J* = 7.9 Hz, 1 H), 7.73 – 7.64 (m, 4 H), 7.47 – 7.34 (m, 6 H), 7.08 (dd, *J* = 15.3, 11.0 Hz, 1 H), 6.64 (dd, *J* = 15.3, 11.0 Hz, 1 H), 6.19 (dd, *J* = 15.4, 7.9 Hz, 1 H), 5.94 (dd, *J* = 15.3, 7.5 Hz, 1 H), 3.83 (dd, *J* = 6.4, 5.0 Hz, 1 H), 3.38 (dd, *J* = 7.5, 1.4 Hz, 1 H), 3.04 (dd, *J* = 5.0, 1.8 Hz, 1 H), 2.95 – 2.93 (m, 2 H), 1.13 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 149.4, 139.5, 135.8, 134.8, 134.1, 133.5, 132.6, 131.9, 129.8, 129.8, 127.7, 127.6, 68.8, 60.1, 58.5, 54.7, 53.1, 26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{32}O_4Si$ [M + H]$^+$ 449.2148, found 449.2145.

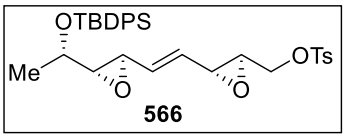
7.2.78. Synthesis of Allylic Alcohol 565



565

Allylic Alcohol 565. To a solution of diepoxy amide **564** (350 mg, 0.58 mmol, 1.0 equiv) in THF (7 mL) was added dropwise Red-Al (0.36 mL, 70% w/v in toluene, 1.17 mmol, 2.0 equiv) at 0 ºC. After 1 h at this temperature, the reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution. After separation of both layers, the aqueous phase was extracted twice with EtOAc and the combined organic extracts washed with H_2O and brine, dried over anhydrous $MgSO_4$, and the solvent evaporated under reduced pressure. The resulting crude diepoxy aldehyde (~0.58 mmol) was used in the next step without further purification. The crude aldehyde was dissolved in MeOH (10 mL) and reacted with $NaBH_4$ (44 mg, 1.16 mmol, 2.0 equiv) at 0 ºC. After 1 h, the reaction mixture was quenched by addition of H_2O and the solvent was removed under reduced pressure. The crude was then dissolved in EtOAc and washed with H_2O and brine. Removal of the solvent under reduced pressure followed by purification of the resiude by flash column chromatography (silica gel, 20% EtOAc in hexanes) provided diepoxy alcohol **565** (70 mg, 28% over 2 steps) as a colorless oil: R_f = 0.30 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = +13.8 (*c* 0.34, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 4 H), 7.46 – 7.36 (m, 6 H), 5.64 (qd, *J* = 15.7, 7.0 Hz, 2 H), 3.95 (d, *J* = 12.8 Hz, 1 H), 3.77 – 3.67 (m, 2 H), 3.42 (dd, *J* = 7.0, 2.2 Hz, 1 H), 3.21 (dd, *J* = 6.9, 2.1 Hz, 1 H), 3.07 (dt, *J* = 3.8, 2.4 Hz, 1 H), 2.96 (dd, *J* = 5.6, 2.1 Hz, 1 H), 1.11 (d, *J* = 6.4 Hz, 3 H), 1.08 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.9, 134.2, 133.6, 132.5, 131.2, 129.7, 129.7, 127.6, 127.6, 69.8, 67.4, 64.5, 60.9, 60.1, 54.8, 54.5, 26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_4Si$ $[M + H]^+$ 451.2305, found 451.2303.

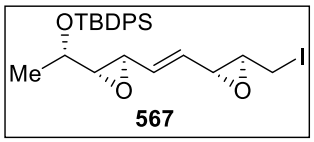
7.2.79. Synthesis of Tosyl Derivative 566



566

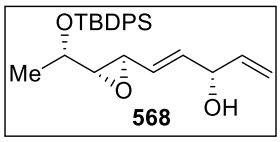
Tosyl Derivative 566. The tosylation of diepoxy alcohol **565** (70 mg, 0.16 mmol, 1.0 equiv) was achieved in exactly the same way as described above for **475**, to obtain tosyl derivative **566** (80 mg, 86%) as a colorless oil: Flash column chromatography (silica gel, 20% EtOAc in hexanes); R_f = 0.77 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = +15.6 (*c* 0.16, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.79 (m, 2 H), 7.71 – 7.66 (m, 4 H), 7.44 – 7.34 (m, 8H), 5.65 (dd, *J* = 15.7, 7.4 Hz, 1 H), 5.50 (dd, *J* = 15.7, 7.4 Hz, 1 H), 4.21 (dd, *J* = 11.5, 3.8 Hz, 1 H), 4.04 (dd, *J* = 11.5, 5.5 Hz, 1 H), 3.76 – 3.69 (m, 1 H), 3.24 (dd, *J* = 7.4, 2.0 Hz, 1 H), 3.18 (dd, *J* = 7.4, 2.0 Hz, 1 H), 3.10 (ddd, *J* = 5.7, 3.8, 2.0 Hz, 1 H), 2.93 (dd, *J* = 5.5, 2.1 Hz, 1 H), 2.46 (s, 3 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 135.9, 135.8, 134.2, 133.3, 129.9, 129.9, 129.7, 129.7, 128.0, 127.6, 127.6, 69.7, 69.2, 64.5, 60.4, 56.5, 55.4, 54.6, 29.7, 26.9, 21.7, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{32}H_{38}O_6SSi$ $[M + H]^+$ 579.2237, found 579.2236.

7.2.80. Synthesis of Iodide Derivative 567



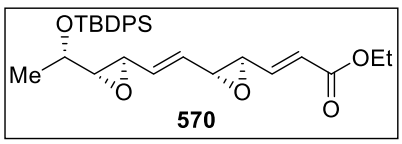
Iodide Derivative 567. The iodination of tosyl derivative **566** (30 mg, 0.05 mmol, 1.0 equiv) was carried out according to the procedure described above for **476**, to afford iodide derivative **567** (25 mg, 90%) as a colorless oil: Flash column chromatography (silica gel, 10% EtOAc in hexanes); R_f = 0.58 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$= +12.7 (*c* 0.35 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 4 H), 7.44 – 7.35 (m, 6 H), 5.67 (dd, *J* = 15.7, 7.2 Hz, 1 H), 5.57 (dd, *J* = 15.7, 7.0 Hz, 1 H), 3.77 – 3.70 (m, 1 H), 3.27 – 3.21 (m, 2 H), 3.20 (dd, *J* = 7.2, 2.1 Hz, 1 H), 3.17 – 3.08 (m, 2 H), 2.95 (dd, *J* = 5.5, 2.1 Hz, 1 H), 1.11 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.9, 135.8, 132.8, 130.5, 129.8, 129.7, 129.7, 127.6, 127.6, 69.7, 64.5, 61.1, 60.1, 54.7, 29.7, 26.9, 19.9, 19.3, 3.8; HRMS (H-ESI) *m/z* calcd for $C_{25}H_{31}IO_3Si$ $[M + H]^+$ 535.1165, found 535.1167.

7.2.81. Synthesis of Allylic Alcohol 568



Allylic Alcohol 568. A solution of iodide **567** (20 mg, 0.04 mmol, 1.0 equiv) in THF (3 mL) was reacted with *n*-BuLi (0.05 mL, 1.6 M in hexane, 0.08 mmol, 2.0 equiv) at -78 ºC, according to the same procedure as described above for the preparation of **477**, to afford, after similar processing, allylic alcohol **568** (13 mg, 87%) as a colorless oil: Flash column chromatogaphy (silica gel, 15% EtOAc in hexanes); R_f = 0.20 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$= +19.1 (*c* 0.39, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 4 H), 7.44 – 7.34 (m, 6 H), 5.89 (dddd, *J* = 17.2, 16.3, 8.1, 3.3 Hz, 2 H), 5.46 (ddd, *J* = 15.6, 7.9, 1.4 Hz, 1 H), 5.28 (dt, *J* = 17.2, 1.3 Hz, 1 H), 5.18 (dt, *J* = 10.4, 1.3 Hz, 1 H), 4.65 (t, *J* = 6.1 Hz, 1 H), 4.27 – 4.17 (m, 1 H), 3.76 – 3.69 (m, 1 H), 3.21 (dd, *J* = 8.0, 2.1 Hz, 1 H), 2.96 (dd, *J* = 5.6, 2.2 Hz, 1 H), 1.10 (d, *J* = 6.4 Hz,3), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 136.1, 135.9, 135.9, 132.5, 129.7, 129.6, 128.8, 128.3, 127.6, 127.6, 115.8, 72.9, 69.9, 68.2, 64.4, 55.2, 38.8, 26.9, 19.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{25}H_{32}O_3Si$ $[M + H]^+$ 409.2199, found 409.2197.

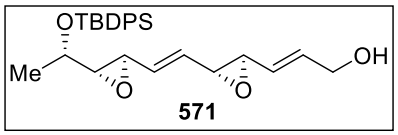
7.2.82. Synthesis of Ester 570



Ester 570. To a solution of diepoxy amide **564** (175 mg, 0.29 mmol, 1.0 equiv) in THF (5 mL) was added dropwise with Red-Al (0.20 mL, 70% w/v in toluene, 0.65 mmol, 2.2 equiv) at 0 ºC. After 1 h at this temperature, the reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution. After separation of both layers, the aqueous phase was extracted twice with EtOAc and the combined organic extracts washed with H_2O and brine, dried over anhydrous $MgSO_4$, and the solvent evaporated under reduced pressure. The resulting crude diepoxy aldehyde (~0.29 mmol) was used in the next step without further purification. A solution of tributyl(ethoxycarbonylmethylene)phosphonium bromide (134 mg, 0.36 mmol, 1.25 equiv) in CH_2Cl_2 (3 mL) was washed twice with a 1.0 M aqueous

NaOH solution (1 mL), dried and diluted with toluene (3 mL). After removing CH_2Cl_2, the resulting solution was then added to a stirred solution of crude aldehyde and benzoic acid (13 mg, 0.10 mmol, 0.2 equiv) in toluene (5 mL) at 95 ºC. After 30 min the solvent was evaporated and the resulting residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to provide the corresponding α,β-unsaturated ester **570** (40 mg, 28% over 2 steps) as a colourless oil: R_f = 0.44 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$= +10.5 (*c* 0.62, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 4 H), 7.44 – 7.35 (m, 6 H), 6.70 (dd, *J* = 15.7, 6.9 Hz, 1 H), 6.15 (d, *J* = 15.7 Hz, 1 H), 5.66 (qd, *J* = 15.7, 6.9 Hz, 2 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 3.79 – 3.70 (m, 1 H), 3.36 (dd, *J* = 6.9, 1.8 Hz, 1 H), 3.32 (dd, *J* = 6.7, 1.9 Hz, 1 H), 3.21 (dd, *J* = 6.9, 2.1 Hz, 1 H), 2.96 (dd, *J* = 5.5, 2.1 Hz, 1 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.11 (d, *J* = 6.4 Hz, 3 H), 1.08 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 143.3, 135.9, 135.9, 135.7, 132.9, 130.4, 129.7, 129.7, 127.8, 127.6, 127.6, 124.2, 69.7, 64.6, 60.7, 59.9, 58.3, 54.6, 26.9, 19.9, 19.3, 14.2; HRMS (H-ESI) *m/z* calcd for $C_{29}H_{36}O_5Si$ $[M + H]^+$ 493.2410, found 493.2413.

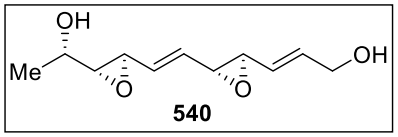
7.2.83. Synthesis of Allylic Alcohol 571



571

Allylic Alcohol 571. A solution of ester **570** (40 mg, 0.08 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was cooled at -78 ºC and treated with DIBAL-H (0.2 mL, 1.0 M in toluene, 0.20 mmol, 2.5 equiv). After 20 min, the reaction was quenched by addition of MeOH at -78 ºC and the mixture was allowed to reach room temperature, treated with a saturated aqueous Na^+/K^+ tartrate solution and diluted with CH_2Cl_2. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain allylic alcohol **571** (8.0 mg, 22%) as a pale colorless oil: R_f = 0.10 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = +20.3 (*c* 0.51, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 4 H), 7.44 – 7.35 (m, 6 H), 6.09 (ddd, *J* = 15.3, 7.7, 2.8 Hz, 1 H), 5.65 – 5.61 (m, 2 H), 5.51 (ddt, *J* = 15.6, 7.5, 1.7 Hz, 1 H), 4.19 (dd, *J* = 5.0, 1.3 Hz, 2 H), 3.78 – 3.67 (m, 1 H), 3.30 – 3.23 (m, 2 H), 3.23 – 3.18 (m, 1 H), 2.95 (dd, *J* = 5.6, 2.2 Hz, 1 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 1.07 (s, *J* = 2.6 Hz, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.9, 134.7, 134.2, 133.7, 133.6, 131.9, 131.4, 129.7, 129.7, 127.6, 127.6, 69.8, 64.6, 62.6, 59.8, 59.2, 54.8, 30.9, 26.9, 19.3; HRMS (H-ESI) *m/z* calcd for $C_{27}H_{34}O_4Si$ $[M + H]^+$ 451.2305, found 451.2302.

7.2.84. Synthesis of Depudecin Analogue 540

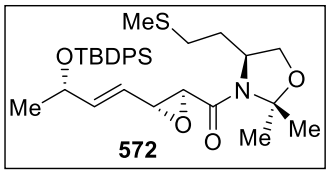


540

Depudecin Analogue 540. Silyl derivative **571** (8 mg, 0.02 mmol, 1.0 equiv) was desilylated by the action of TBAF (30 µL, 1.0 M in THF, 0.03 mmol, 1.2 equiv) in the same way as desrcribed above for (-)-depudecin

(**442**) to afford depudecin analogue **540** (1.5 mg, 40%) as a colorless oil: Flash column chromatography (silica gel, 2% MeOH in CH_2Cl_2); R_f = 0.51 (silica gel, 2% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$= +15.9 (*c* 0.47, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (dtd, *J* = 15.6, 5.1, 0.5 Hz, 1 H), 5.78 – 5.65 (m, 2 H), 5.52 (ddt, *J* = 15.6, 7.5, 1.7 Hz, 1 H), 4.20 (d, *J* = 3.6 Hz, 2 H), 3.75 (dd, *J* = 10.3, 5.2 Hz, 1 H), 3.39 (dd, *J* = 6.9, 2.2 Hz, 1 H), 3.33 – 3.26 (m, 2 H), 2.90 (dd, *J* = 4.6, 2.2 Hz, 1 H), 1.31 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 131.9, 131.3, 127.5, 66.9, 64.1, 62.6, 59.9, 59.1, 55.4, 20.0; HRMS (H-ESI) *m/z* calcd for $C_{11}H_{16}O_4$ $[M + H]^+$ 213.1127, found 213.1125.

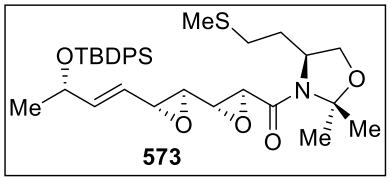
7.2.85. Synthesis of Epoxy Amide 572



572

Epoxy Amide 572. $(COCl)_2$ (0.23 mL, 2.60 mmol, 2.0 equiv) was dissolved in CH_2Cl_2 (7 mL) and cooled at -78 ºC. DMSO (0.38 mL, 5.30 mmol, 4.0 equiv) was then added dropwise and the mixture stirred for 10 min at the same temperature. Then, a solution of epoxy alcohol *ent*-**522** (450 mg, 1.32 mmol, 1.0 equiv) was added and the reaction mixture was stirred for 40 min at -78 ºC and quenched by addition of Et_3N (1.1 mL, 7.90 mmol, 6.0 equiv). The resulting mixture was vigorously stirred and diluted with H_2O and Et_2O. The aqueous and organic phases were then separated, the organic extract washed with water and brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure to afford the crude aldehyde (~1.30 mmol) that was used in the next step without further purification. The crude aldehyde (~1.30 mmol 1.0 equiv) was reacted with sulfonium salt *ent*-**457**[249,250] (460 mg, 1.45 mmol, 1.1 equiv) and NaOH (3.0 M aqueous solution, 0.44 mL, 1.32 mmol, 1.0 equiv) according to the procedure described above for epoxy amide **466** to yield epoxy amide **572** (420 mg, 57% over two steps) as a colourless oil: Flash column chromatography (silica gel, 20% EtOAc in hexanes); R_f = 0.30 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = +9.9 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 4 H), 7.43 – 7.33 (m, 6 H), 6.04 (dd, *J* = 15.5, 5.3 Hz, 1 H), 5.31 (ddd, *J* = 15.5, 8.0, 1.4 Hz, 1 H), 4.38 – 4.30 (m, 1 H), 4.29 – 4.22 (m, 1 H), 4.04 – 3.95 (m, 2 H), 3.53 (dd, *J* = 8.0, 1.8 Hz, 1 H), 3.42 (d, *J* = 2.0 Hz, 1 H), 2.56 – 2.47 (m, 1 H), 2.45 – 2.38 (m, 1 H), 2.01 (s, 3 H), 1.85 – 1.78 (m, 1 H), 1.75 – 1.68 (m, 1 H), 1.65 (s, 3 H), 1.54 (s, 3 H), 1.13 (d, *J* = 6.4 Hz, 3 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 141.9, 135.8, 135.8, 134.2, 133.8, 129.7, 127.6, 127.6, 127.6, 123.8, 95.9, 69.2, 67.1, 57.8, 55.9, 55.5, 34.4, 30.8, 27.0, 26.2, 23.0, 19.3, 15.9; HRMS (H-ESI) *m/z* calcd for $C_{31}H_{43}NO_4SSi$ $[M + H]^+$ 554.2760, found 554.2762.

7.2.86. Synthesis of Diepoxy Amide 573

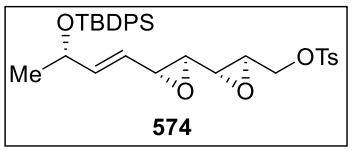


573

Diepoxy Amide 573. To a solution of diepoxy amide **572** (210 mg, 0.38 mmol, 1.0 equiv) in THF (5 mL) was added dropwise with Red-Al (0.23 mL, 70% w/v in toluene, 0.76 mmol, 2.0 equiv) at 0 ºC. After 1 h at this temperature, the reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution. After separation of both layers, the

aqueous phase was extracted twice with EtOAc and the combined organic extracts washed with H_2O and brine, dried over anhydrous $MgSO_4$, and the solvent evaporated under reduced pressure. The resulting crude diepoxy aldehyde (~0.38 mmol) was used in the next step without further purification. The crude aldehyde (~0.38 mmol, 1.0 equiv) was reacted with sulfonium salt *ent*-**457**[249,250] (132 mg, 0.42 mmol, 1.1 equiv) and NaOH (3.0 M aqueous solution, 0.08 mL, 1.0 equiv) according to the procedure described above for epoxy amide **466** to yield diepoxy amide **573** (85 mg, 38% over 2 steps) as a colorless oil: R_f = 0.40 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$= +23.1 (*c* 0.54, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 4 H), 7.45 – 7.32 (m, 6 H), 5.96 (ddd, *J* = 15.5, 5.3, 0.5 Hz, 1 H), 5.26 (ddd, *J* = 15.5, 7.9, 1.5 Hz, 1 H), 4.36 – 4.27 (m, 2 H), 4.02 (ddd, *J* = 9.1, 5.2, 1.2 Hz, 1 H), 3.91 (dd, *J* = 9.2, 0.5 Hz, 1 H), 3.58 (d, *J* = 1.9 Hz, 1 H), 3.37 – 3.34 (m, 2 H), 2.91 (dd, *J* = 3.3, 2.1 Hz, 1 H), 2.59 (ddd, *J* = 13.0, 7.7, 5.1 Hz, 1 H), 2.48 (ddd, *J* = 13.2, 8.3, 7.4 Hz, 1 H), 2.11 (s, *J* = 3.1 Hz, 3 H), 1.86 – 1.80 (m, 1 H), 1.75 (d, *J* = 2.5 Hz, 1 H), 1.66 (s, *J* = 6.6 Hz, 3 H), 1.54 (s, 3 H), 1.14 (d, *J* = 6.3 Hz, 3 H), 1.06 (s, *J* = 3.6 Hz, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 140.9, 135.9, 135.8, 134.2, 133.9, 129.7, 129.6, 127.5, 127.5, 124.3, 95.9, 69.2, 67.1, 56.5, 56.0, 55.6, 55.4, 51.3, 34.5, 30.7, 26.9, 26.2, 23.9, 19.2, 15.9; HRMS (H-ESI) *m/z* calcd for $C_{33}H_{45}NO_5SSi$ $[M + H]^+$ 596.2866, found 596.2869.

7.2.87. Synthesis of Tosyl Derivative 574

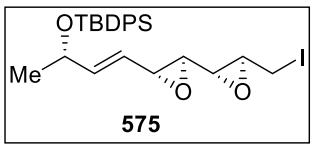


574

Tosyl Derivative 574. To a solution of diepoxy amide **573** (84 mg, 0.14 mmol, 1.0 equiv) in THF (3 mL) was added dropwise Red-Al (0.1 mL, 70% w/v in toluene, 0.31 mmol, 2.2 equiv) at 0 ºC. After 1 h at 0 ºC, the reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution. After separation of both layers, the aqueous phase was extracted with EtOAc, the organic extracts were washed with brine and dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The resulting crude aldehyde was dissolved in MeOH (3 mL) and reacted with $NaBH_4$ (11 mg, 0.28 mmol, 2.0 equiv) at 0 ºC. After 1 h, the reaction mixture was quenched by addition of H_2O and the solvent was removed under reduced pressure. The crude was then dissolved in EtOAc and washed with H_2O and brine. Removal of the solvent under reduced pressure provided crude diepoxy alcohol (~0.26 mmol) which was used in the next step without purification. Crude diepoxy alcohol obtained above (~0.26 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (5 mL) and cooled at 0 ºC. Over this solution was then added *p*-TsCl (59 mg, 0.31 mmol, 1.2 equiv), TEA (0.05 mL, 1.5 mmol, 1.5 equiv) and 4-DMAP (1 mg, 0.01 mmol, 0.02 equiv). After 3 h, the reaction mixture was quenched by addition of water and the aqueous phase was extracted with CH_2Cl_2 three times. The organic phase was washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The resiude was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to provide pure tosyl derivative **574** (40 mg, 27% over 3 steps) as a colourless oil: R_f = 0.83 (silica gel, 60% EtOAc in hexanes); $[\alpha]^{25}_D$= +26.6 (*c* 0.38, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 2 H), 7.75 – 7.71 (m, 2 H), 7.69 – 7.63 (m, 4 H), 7.43 – 7.30 (m, 6 H), 5.93 (dd, *J* = 15.5, 5.3 Hz, 1 H), 5.23 (ddd, *J*

= 15.5, 7.8, 1.4 Hz, 1 H), 4.38 – 4.28 (m, 1 H), 4.22 (dd, *J* = 11.6, 3.6 Hz, 1 H), 4.07 (dd, *J* = 11.6, 5.3 Hz, 1 H), 3.25 (dd, *J* = 7.7, 2.1 Hz, 1 H), 3.20 (ddd, *J* = 5.6, 3.6, 2.1 Hz, 1 H), 2.93 (dd, *J* = 4.1, 2.0 Hz, 1 H), 2.74 (dd, *J* = 4.1, 2.1 Hz, 1 H), 2.46 (s, 3 H), 1.15 (d, *J* = 6.4 Hz, 3 H), 1.06 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.8, 134.8, 129.9, 129.7, 128.0, 127.8, 127.7, 127.5, 124.3, 69.2, 68.7, 57.0, 55.3, 54.1, 52.3, 26.9, 23.9, 21.7, 19.2; HRMS (H-ESI) *m/z* calcd for $C_{32}H_{38}O_6SSi$ $[M + H]^+$ 579.2237, found 579.2234.

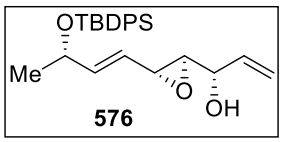
7.2.88. Synthesis of Iodide Derivative 575



575

Iodide Derivative 575. The iodination of tosyl derivative **574** (40 mg, 0.07 mmol, 1.0 equiv) was carried out according to the procedure described above for **476**, to afford iodide derivative **575** (32 mg, 87%) as a colourless oil: Flash column chromatography (silica gel, 10% EtOAc in hexanes); R_f = 0.60 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$= +19.8 (*c* 0.43 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.62 (m, 4 H), 7.46 – 7.33 (m, 6 H), 5.94 (dd, *J* = 15.5, 5.3 Hz, 1 H), 5.25 (ddd, *J* = 15.5, 7.8, 1.4 Hz, 1 H), 4.34 (ddd, *J* = 11.4, 6.2, 4.9 Hz, 1 H), 3.30 – 3.26 (m, 1 H), 3.26 – 3.22 (m, 2 H), 3.15 – 3.09 (m, 1 H), 2.92 (dd, *J* = 3.9, 1.6 Hz, 1 H), 2.81 (dd, *J* = 3.9, 2.1 Hz, 1 H), 1.15 (d, *J* = 6.3 Hz, 3 H), 1.06 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 135.9, 135.9, 134.8, 133.9, 129.7, 127.8, 127.7, 127.5, 124.4, 69.2, 59.7, 57.2, 55.6, 55.3, 26.9, 23.9, 19.2, 3.3; HRMS (H-ESI) *m/z* calcd for $C_{25}H_{31}IO_3Si$ $[M + H]^+$ 535.1165, found 535.1167.

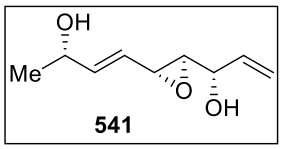
7.2.89. Synthesis of Allylic Alcohol 576



576

Allylic Alcohol 576. A solution of iodide **575** (20 mg, 0.04 mmol, 1.0 equiv) in THF (3 mL) was reacted with *n*-BuLi (0.05 mL, 1.6 M in hexane, 0.08 mmol, 2.0 equiv) at -78 ºC, according to the same procedure as described above for the preparation of **477**, to afford, after similar processing, allylic alcohol **576** (13 mg, 90%) as a colorless oil: Flash column chromatogaphy (silica gel, 15% EtOAc in hexanes); R_f = 0.60 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$= +26.9 (*c* 0.36 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.62 (m, 4 H), 7.46 – 7.31 (m, 6 H), 5.93 (dddd, *J* = 8.5, 6.2, 5.4, 4.3 Hz, 2 H), 5.42 – 5.35 (m, 1 H), 5.33 – 5.29 (m, 1 H), 5.29 – 5.25 (m, 1 H), 4.38 – 4.30 (m, 1 H), 3.33 (dd, *J* = 7.8, 2.1 Hz, 1 H), 2.87 (dd, *J* = 4.3, 2.2 Hz, 1 H), 1.15 (d, *J* = 6.3 Hz, 3 H), 1.06 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 136.4, 135.9, 135.9, 135.9, 134.8, 129.6, 129.6, 127.7, 127.5, 124.8, 116.7, 71.6, 69.2, 62.2, 60.4, 29.7, 26.9, 14.2; HRMS (H-ESI) *m/z* calcd for $C_{25}H_{32}O_3Si$ $[M + H]^+$ 409.2199, found 409.2196.

7.2.90. Synthesis of Depudecin Analogue 541

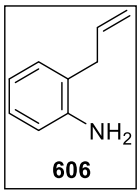


541

Depudecin Analogue 541. Silyl derivative **576** (11 mg, 0.03 mmol, 1.0 equiv) was desilylated by the action of TBAF (50 µL, 1.0 M in THF, 0.06 mmol, 2.0 equiv) in the same way as desrcribed above for (-)-depudecin (**442**) to afford depudecin analogue **541** (1 mg, 20%) as a colorless oil: Flash column chromatography (silica gel, 30% EtOAc in hexanes → 100% EtOAc); R_f = 0.56 (silica gel, EtOAc); $[\alpha]^{25}_D$= +27.5 (*c* 0.42 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (dddd, *J* = 17.3, 16.1, 8.2, 2.9 Hz, 2 H), 5.48 – 5.43 (m, 1 H), 5.43 – 5.37 (m, 1 H), 5.27 (dt, *J* = 10.6, 1.3 Hz, 1 H), 4.40 – 4.30 (m, 1 H), 4.17 – 4.08 (m, 1 H), 3.42 (dd, *J* = 8.0, 2.2 Hz, 1 H), 3.01 (dd, *J* = 4.4, 2.2 Hz, 1 H), 1.96 (d, *J* = 6.3 Hz, 1 H), 1.30 (d, *J* = 6.5 Hz, 3 H), 1.26 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 136.3, 125.9, 116.9, 71.6, 67.9, 62.3, 55.5, 23.1; HRMS (H-ESI) *m/z* calcd for $C_9H_{14}O_3$ $[M + H]^+$ 171.1021, found 171.1023.

7.3. Experimental Procedures and Compound Characterization Related to the Solomonamides

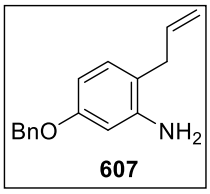
7.3.1. Synthesis of Aniline 606



606

Aniline 606. To a solution of bromoaniline **604** (1.0 g, 5.81 mmol, 1.0 equiv) and $Pd[PPh_3]_4$ (336 mg, 0.29 mmol, 0.05 equiv) in DMF (15 mL) was added dropwise allyltri-*n*-butyltin (2.2 mL, 6.97 mmol, 1.2 equiv). The solution was then heated at 80 ºC for 12 h. After this time, the mixture was diluted with diethyl ether and washed with water. The organic layer was separated and washed with water four times, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain aniline **606** (596 mg, 77%) as a yellow oil: R_f = 0.60 (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm) 7.13 – 7.05 (m, 2 H), 6.78 (td, *J* = 7.4, 1.1 Hz, 1 H), 6.72 – 6.69 (m, 1 H), 6.04 – 5.92 (m, 1 H), 5.18 – 5.09 (m, 2 H), 3.64 (bs, 2 H), 3.33 (d, *J* = 6.1 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* (ppm) 144.8, 136.0, 130.2, 127.6, 124.0, 118.9, 116.1, 115.9, 36.5; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_9H_{12}N$ 134.0970; found 134.0967.

7.3.2. Synthesis of Aniline 607

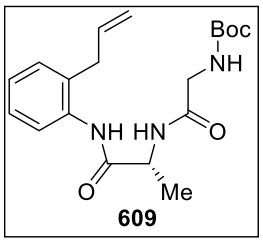


607

Aniline 607. To a solution of iodonitrobenzene **605**[287] (6.0 g, 16.90 mmol, 1.0 equiv) and $Pd[PPh_3]_4$ (3.0 g, 3.40 mmol, 0.15 equiv) in DMF (30 mL) was added dropwise allyltri-*n*-butyltin (6.4 mL, 20.30 mmol, 1.2 equiv). The solution was then heated at 60 ºC for 15 h. After this time, the mixture was diluted with Et_2O and water. The organic layer was separated and washed with water four times, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 100% Hexanes) to obtain the

corresponding allyl derivative (3.3 g, 73%) as a yellow oil: R_f = 0.56 (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.54 (d, J = 2.7 Hz, 1 H), 7.46 – 7.33 (m, 5 H), 7.28 – 7.25 (m, 1 H), 7.16 (dd, J = 8.5, 2.7 Hz, 1 H), 5.96 (ddt, J = 16.6, 10.1, 6.4 Hz, 1 H), 5.11 (s, 2 H), 5.09 – 5.07 (m, 1 H), 5.05 – 5.03 (m, 1 H), 3.62 (dt, J = 6.4, 1.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.4, 135.8, 135.4, 132.8, 128.7, 128.3, 127.5, 127.1, 120.4, 116.7, 110.3, 70.6, 36.3; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{16}NO_3$ 270.1130; found 270.1129. To a solution of the allyl derivative obtained above (1.5 g, 5.60 mmol, 1.0 equiv) in acetic acid (15 mL) was added Zn dust (1.0 g, 16.20 mmol, 3.0 equiv) in ten portions of 100 mg each over 30 min at 25 ºC. The reaction mixture was stirred at this temperature until completion monitoring by TLC (1 h) and then, quenched by addition of 10% NaOH solution at 0 ºC. The mixture was extracted with CH_2Cl_2, and the organic phase washed with water, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain **607** (773 mg, 65%) as an orange oil: R_f = 0.38 (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46 – 7.37 (m, 4 H), 7.35 – 7.30 (m, 1 H), 6.95 (d, J = 8.3 Hz, 1 H), 6.41 (dd, J = 8.2, 2.5 Hz, 1 H), 6.35 (d, J = 2.5 Hz, 1 H), 5.95 (ddt, J = 16.6, 10.5, 6.1 Hz, 1 H), 5.14 – 5.11 (m, 1 H), 5.11 – 5.08 (m, 1 H), 5.03 (s, 2 H), 3.67 (bs, 2 H), 3.26 (dt, J = 6.1, 1.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.6, 145.8, 137.3, 136.4, 130.9, 128.5, 127.8, 127.4, 116.9, 115.8, 104.9, 102.6, 69.9, 35.8; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{18}NO$ 240.1388; found 240.1392.

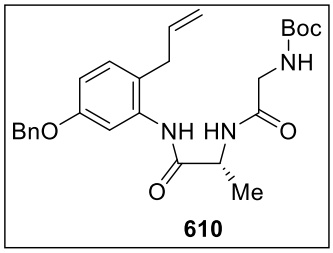
7.3.3. Synthesis of Dipeptide 609



609

Dipeptide 609. To a solution of aniline **606** (700 mg, 5.25 mmol, 1.0 equiv) and Boc-Gly-D-Ala-OH (**608**)[283] (1.3 g, 5.25 mmol, 1.0 equiv) in DMF (15 mL) was added HATU (3.0 g, 7.88 mmol, 1.5 equiv) and DIPEA (1.0 mL, 5.25 mmol, 1.0 equiv) at 0 ºC and the mixture was stirred for 12 h at 25 ºC. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 50% EtOAc in hexanes) to obtain dipeptide **609** (1.5 g, 81%) as a white foam: R_f = 0.60 (silica gel, 100% EtOAc); $[\alpha]^{25}_D$ = – 6.23 (*c* 0.45, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.96 (bs, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.23 (dd, J = 8.1, 1.7 Hz, 1 H), 7.18 (dd, J = 7.5, 1.5 Hz, 1 H), 7.15 – 7.10 (m, 1 H), 6.87 (s, 1 H), 5.97 (ddt, J = 16.2, 10.2, 6.0 Hz, 1 H), 5.15 (dd, J = 10.2, 1.6 Hz, 1 H), 5.06 (dd, J = 17.2, 1.6 Hz, 1 H), 4.64 – 4.55 (m, 1 H), 3.88 – 3.80 (m, 2 H), 3.41 – 3.33 (m, 2 H), 1.47 (d, J = 7.0 Hz, 3 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.4, 170.0, 156.2, 135.9, 135.4, 131.1, 130.2, 127.1, 125.8, 123.9, 116.5, 49.5, 38.7, 36.1, 31.3, 28.3, 17.8; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{28}N_3O_4$ 362.2080; found 362.2079.

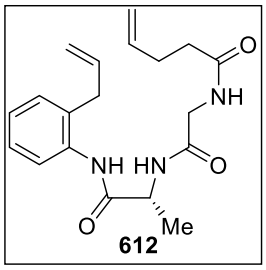
7.3.4. Synthesis of Dipeptide 610



610

Dipeptide 610. To a solution of aniline **607** (730 mg, 3.10 mmol, 1.0 equiv) and Boc-Gly-D-Ala-OH (**21**) (752 mg, 3.10 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added HATU (1.7 g, 4.60 mmol, 1.5 equiv) and DIPEA (0.5 mL, 3.10 mmol, 1.0 equiv) and the mixture was stirred for 12 h at 25 ºC. After this time, the reaction mixture was diluted with CH_2Cl_2 and washed sequentially with 1 N HCl and a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain dipeptide **610** (1.15 g, 81%) as a pale brown solid: R_f = 0.69 (silica gel, 100% EtOAc); $[\alpha]^{25}_D$ = – 3.41 (*c* 0.10, CH_2Cl_2); mp = 83-84 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.07 (bs, 1 H), 7.62 (d, *J* = 2.3 Hz, 1 H), 7.44 – 7.27 (m, 6 H), 7.05 (d, *J* = 8.5 Hz, 1 H), 6.94 (d, *J* = 7.3 Hz, 1 H), 6.73 (dd, *J* = 8.4, 2.6 Hz, 1 H), 5.94 (ddt, *J* = 16.2, 10.2, 5.9 Hz, 1 H), 5.14 – 5.04 (m, 2 H), 5.02 (s, 2 H), 4.59 (p, *J* = 7.0 Hz, 1 H), 3.91 – 3.77 (m, 2 H), 3.37 – 3.23 (m, 2 H), 1.46 (d, *J* = 7.0 Hz, 3 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.1, 169.9, 157.9, 156.0, 136.9, 136.3, 130.8, 128.5, 127.9, 127.7, 127.5, 122.3, 116.2, 112.2, 109.4, 80.6, 70.0, 49.6, 39.2, 36.5, 28.2, 17.6; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{34}N_3O_5$ 468.2498; found 468.2487.

7.3.5. Synthesis of Diolefin 612

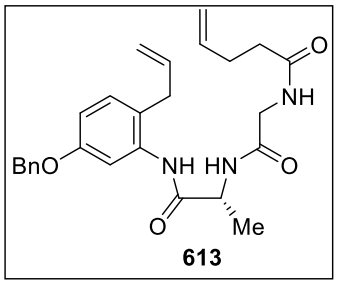


612

Diolefin 612. TFA (5.0 mL) was added to a solution of dipeptide **609** (360 mg, 0.99 mmol, 1.0 equiv) in CH_2Cl_2 (60 mL) at 0 ºC and the reaction mixture was stirred at 25 ºC until depletion of starting material as judged by TLC (3 h). Then, the TFA excess was removed under reduced pressure to obtain the corresponding ammonium trifluoroacetate salt as a brown solid which was dissolved in DMF (10 mL). To this solution, Kosher acid **611** (0.1 mL, 0.99 mmol, 1.0 equiv), HATU (379 mg, 0.99 mmol, 1.0 equiv) and DIPEA (0.52 mL, 2.99 mmol, 3.0 equiv) were added and the resulting solution was stirred at 25 ºC for 12 h. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) to obtain diolefin **612** (205 mg, 60% over two steps) as a white solid: R_f = 0.23 (silica gel, 100% EtOAc); $[\alpha]^{25}_D$ = – 8.50 (*c* 0.51, CH_2Cl_2); mp = 80-81 ºC ; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.82 (bs, 1 H), 7.29 – 7.27 (m, 1 H), 7.25 – 7.23 (m, 1 H), 7.21 – 7.17 (m, 1 H), 7.16 – 7.11 (m, 1 H), 6.64 (d, *J* = 6.4 Hz, 1 H), 6.17 (bs, 1 H), 5.98 (dt, *J* = 16.4, 6.3 Hz, 1 H), 5.83 (dt, *J* = 16.9, 5.8 Hz, 1 H), 5.19 – 5.14 (m, 1 H), 5.12 – 5.09 (m, 1 H), 5.08 – 5.01 (m, 2 H), 4.60 – 4.51 (m, 1 H), 3.98 (d, *J* = 5.4 Hz, 2 H), 3.41 – 3.35 (m, 2 H), 2.44 – 2.33 (m, 4 H), 1.48 (d, *J*

= 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.1, 169.9, 169.1, 136.7, 136.0, 135.3, 130.4, 130.3, 127.4, 125.7, 123.6, 116.6, 115.9, 49.7, 43.1, 36.4, 35.4, 29.4, 17.9; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{26}N_3O_3$ 344.1974; found 344.1965.

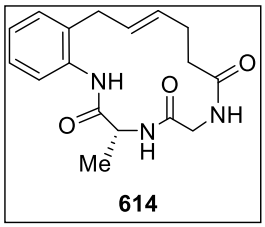
7.3.6. Synthesis of Diolefin 613



613

Diolefin 613. Dipeptide **610** (150 mg, 0.32 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was treated with TFA (1.6 mL) in exactly the same manner as previously described for synthesis of **612**. A solution of the ammonium salt and Kosher acid **611** (30 μL, 0.32 mmol, 1.0 equiv), in CH_2Cl_2 (10 mL) was treated with HATU (122 mg, 0.32 mmol, 1.0 equiv) and DIPEA (0.17 mL, 0.96 mmol, 3.0 equiv) and the resulting solution was stirred at 25 ºC for 12 h. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 80% EtOAc in hexanes) to obtain diolefin **613** (140 mg, 97% over two steps) as a white solid: R_f = 0.24 (silica gel, 100%); $[\alpha]^{25}_D$ = – 6.37 (*c* 0.06, CH_2Cl_2); mp = 87-88 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.02 (bs, 1 H), 7.63 (bs, 1 H), 7.45 – 7.28 (m, 6 H), 7.05 (d, *J* = 8.5 Hz, 1 H), 6.74 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.43 (bs, 1 H), 5.94 (ddd, *J* = 16.5, 11.1, 5.8 Hz, 1 H), 5.81 (ddd, *J* = 17.0, 11.2, 6.2 Hz, 1 H), 5.15 – 5.04 (m, 4 H), 5.03 (s, 2 H), 4.60 – 4.52 (m, 1 H), 4.04 – 3.93 (m, 2 H), 3.37 – 3.24 (m, 2 H), 2.43 – 2.31 (m, 4 H), 1.46 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.5, 170.8, 169.5, 157.7, 136.9, 136.7, 136.3, 136.0, 130.7, 128.5, 127.9, 127.5, 123.6, 116.1, 115.6, 112.2, 110.4, 70.0, 49.8, 43.1, 38.6, 36.2, 36.1, 29.3, 17.7; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{32}N_3O_4$ 450.2393; found 450.2390.

7.3.7. Synthesis of Cyclopeptide 614

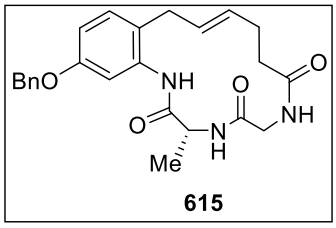


614

Cyclopeptide 614. Diolefin **612** (45 mg, 0.13 mmol, 1.0 equiv), Hoveyda-Grubbs 2nd generation catalyst (8 mg, 0.01 mmol, 0.10 equiv) and *p*-benzoquinone (1 mg, 0.01 mmol, 0.10 equiv) were dissolved in degassed CH_2Cl_2 (7 mL, 0.02 M) and the reaction mixture was heated at 40 ºC for 12 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 2% MeOH in CH_2Cl_2) to obtain macrocycle **614** (31 mg, 75%) as a white solid: R_f = 0.56 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ = – 6.11 (*c* 0.08, MeOH); mp = 188-189 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.50 (bs, 1 H), 8.45 (d, *J* = 7.3 Hz, 1 H), 8.37 (t, *J* = 5.9 Hz, 1 H), 7.46 (dd, *J* = 7.8, 0.9 Hz, 1 H), 7.23 – 7.09 (m, 3 H), 5.44 (dt, *J* = 15.9, 5.4 Hz, 1 H), 5.08 (dt, *J* = 15.9, 6.4 Hz, 1 H), 4.35 (p, *J* = 7.1 Hz, 1 H), 3.85 (dd, *J* = 14.7, 6.4 Hz, 1 H), 3.44 (dd, *J* = 14.7, 5.7 Hz, 1 H), 3.26 (dd, *J* = 15.8, 3.6 Hz, 1 H),

3.08 (dd, *J* = 15.5, 5.1 Hz, 1 H), 2.28 – 2.08 (m, 4 H), 1.31 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 173.1, 171.3, 170.8, 136.5, 134.4, 130.9, 130.3, 128.5, 127.1, 126.0, 125.9, 49.7, 43.7, 34.8, 31.1, 27.9, 17.1; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{22}N_3O_3$ 316.1661; found 316.1655.

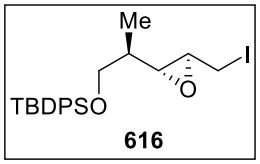
7.3.8. Synthesis of Cyclopeptide 615



615

Cyclopeptide 615. Diolefin **613** (135 mg, 0.30 mmol, 1.0 equiv), Hoveyda-Grubbs 2nd generation catalyst (20 mg, 0.03 mmol, 0.10 equiv) and *p*-benzoquinone (4.0 mg, 0.03 mmol, 0.10 equiv) were dissolved in degassed CH_2Cl_2 (16 mL, 0.02 M) and the reaction mixture was heated at 40 ºC for 12 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes → 3% MeOH in CH_2Cl_2) to obtain macrocycle **615** (100 mg, 79%) as a white solid: R_f = 0.5 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}{}_D$ = – 4.97 (*c* 0.07, MeOH); mp =198-199 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.54 (bs, 1 H), 8.52 (d, *J* = 7.3 Hz, 1 H), 8.37 (t, *J* = 6.0 Hz, 1 H), 7.46 – 7.31 (m, 5 H), 7.29 (d, *J* = 2.6 Hz, 1 H), 7.06 (d, *J* = 8.4 Hz, 1 H), 6.77 (dd, *J* = 8.4, 2.7 Hz, 1 H), 5.41 (dt, *J* = 15.9, 5.4 Hz, 1 H), 5.13 – 5.05 (m, 1 H), 5.04 (s, 2 H), 4.36 (p, *J* = 7.1 Hz, 1 H), 3.86 (dd, *J* = 14.8, 6.5 Hz, 1 H), 3.43 (dd, *J* = 14.7, 5.6 Hz, 1 H), 3.20 (dd, *J* = 16.4, 3.9 Hz, 1 H), 3.03 (dd, *J* = 16.2, 5.0 Hz, 1 H), 2.28 – 2.03 (m, 4 H), 1.30 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 173.1, 171.2, 171.0, 157.4, 137.6, 137.3, 131.5, 130.7, 128.8, 128.2, 128.1, 128.1, 128.0, 125.8, 111.8, 69.7, 49.7, 43.4, 34.7, 33.7, 27.9, 16.8; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{28}N_3O_4$ 422.2080; found 422.2074.

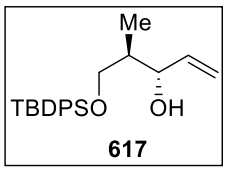
7.3.9. Synthesis of Epoxy Iodide 616



616

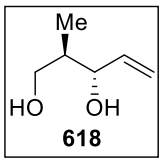
Epoxy Iodide 616. To a solution of *ent*-**500**[249c] (2.0 g, 5.39 mmol, 1.0 equiv) in THF (10 mL) at 0 ºC was added imidazole (1.1 g, 16.19 mmol, 3.0 equiv), PPh_3 (2.1 g, 8.09 mmol, 1.5 equiv) and iodine (2.0 g, 8.09 mmol, 1.5 equiv) at 25 ºC. The mixture was vigorously stirred at 25 ºC for 20 min. After this time the solvent was evaporated under reduced pressure and the crude residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain **616** (2.1 g, 84%) as pale yellow oil: R_f = 0.90 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = – 18.2 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 – 7.64 (m, 4 H), 7.40 (tdd, *J* = 8.5, 6.2, 2.5 Hz, 6 H), 3.72 – 3.62 (m, 2 H), 3.28 (dd, *J* = 9.5, 5.4 Hz, 1 H), 3.12 – 3.06 (m, 1 H), 3.03 (dd, *J* = 9.5, 7.0 Hz, 1 H), 2.85 (dd, *J* = 7.1, 2.0 Hz, 1 H), 1.07 (s, 9 H), 1.04 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 136.6, 133.5, 129.6, 127.6, 66.7, 64.1, 57.2, 38.1, 26.8, 19.3, 13.1, 5.1; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{29}IO_2Si$ $[M + H]^+$ 481,1059, found 481.1058.

7.3.10. Synthesis of Alcohol 617



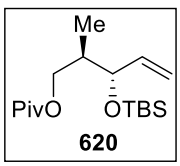
Alcohol 617. To a solution of **616** (1.7 g, 3.54 mmol, 1.0 equiv) in MeOH (40 mL) was added NaI (795 mg, 5.31 mmol, 1.5 equiv) and Zn dust (925 mg, 14.15 mmol, 4.0 equiv) and the reaction was heated at reflux for 2 h. After this time the reaction mixture was cooled to 25 ºC and filtered through a pad of celite. The solvent was evaporated under reduced pressure and the crude residue was purified by flash column chromatography (silica gel, 15% EtOAc in hexanes) to obtain **617** (1.1 g, 88%) as a colorless oil and whose spectroscopic and physical properties matched with those reported in the literature[330]: R_f = 0.76 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 17.90 (*c* 0.16, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71 – 7.66 (m, 4 H), 7.48 – 7.38 (m, 6 H), 5.87 (ddd, *J* = 17.0, 10.4, 6.5 Hz, 1 H), 5.35 – 5.28 (m, 1 H), 5.18 (ddd, *J* = 10.4, 1.8, 1.1 Hz, 1 H), 4.15 – 4.09 (m, 1 H), 3.80 (dd, *J* = 10.2, 4.0 Hz, 1 H), 3.62 (dd, *J* = 10.2, 7.3 Hz, 1 H), 1.84 (ddd, *J* = 14.1, 7.1, 4.0 Hz, 1 H), 1.06 (s, 9 H), 0.85 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 139.6, 136.5, 134.8, 129.8, 127.7, 115.7, 68.3, 40.1, 40.0, 26.8, 26.5, 13.3; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{30}O_2Si$ $[M + H]^+$ 355.2093, found 355.2095.

7.3.11. Synthesis of Diol 618



Diol 618. Silyl ether **617** (2.7 g, 7.62 mmol, 1.0 equiv) was dissolved in THF (20 mL) and to this solution was added TBAF (15 mL, 1.0 M in THF, 15.23 mmol, 2.0 equiv) at 0 ºC. The reaction mixture was stirred at 25 ºC for 3 h and, after this time, the solvent was evaporated under reduced pressure and the residue purified by flash column chromatography (silica gel, 10% EtOAc in hexanes → 30% EtOAc in hexanes) to obtain diol **618** (800 mg, 90%) as a colourless oil whose spectroscopic and physical properties matched with those reported in the literature[331]: R_f = 0.22 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 19.77 (*c* 0.12, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.90 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1 H), 5.30 – 5.17 (m, 2 H), 4.03 (dd, *J* = 16.6, 9.4 Hz, 1 H), 3.77 (dd, *J* = 10.9, 3.6 Hz, 1 H), 3.66 (dd, *J* = 10.9, 7.4 Hz, 1 H), 1.80 (dtd, *J* = 14.7, 7.2, 3.8 Hz, 1 H), 0.88 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 139.5, 116.2, 78.7, 67.2, 39.7, 13.4; HRMS (ESI-TOF) *m/z* calcd for $C_6H_{12}O_2$ $[M + H]^+$ 117.0916, found 117.0915.

7.3.12. Synthesis of Pivaloyl Silyl Ether 620

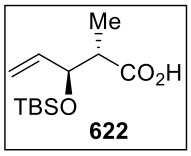


Pivaloyl Silyl Ether 620. To a solution of diol **618** (200 mg, 1.72 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added pyridine (2.8 mL, 34.40 mmol, 20 equiv) and PivCl (0.3 mL, 2.24 mmol, 1.3 equiv) at -30 ºC. The reaction mixture was stirred at this temperature until depletion of starting material (30 min). After this time a saturated aqueous $NaHCO_3$ solution was added to the reaction mixture and the organic layer was separated. The aqueous phase was extracted

[330] Habashita, H.; Kawasaki, T.; Takemoto, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1998**, *63*, 2392-2396.
[331] Heathcock, C. H.; Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. *J. Org. Chem.* **1988**, *53*, 1922-1942.

with CH_2Cl_2 and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting crude pivaloate (~1.71 mmol) was used in the next step without further purification. A solution of the crude pivaloate in DMF (10 mL) was treated with imidazole (235 mg, 3.44 mmol, 2.0 equiv) and TBSCl (389 mg, 2.58 mmol, 1.5 equiv). The resulting solution was stirred for 12 h and then poured into Et_2O, washed with a saturated aqueous NH_4Cl solution and brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain **620** (542 mg, quant. over two steps) as a colourless oil: R_f = 0.89 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = – 2.45 (*c* 0.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.77 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.19 – 5.10 (m, 2 H), 4.09 (dd, *J* = 10.9, 5.8 Hz, 1 H), 4.06 (dd, *J* = 6.8, 5.9 Hz, 1 H), 3.97 (dd, *J* = 10.9, 6.3 Hz, 1 H), 1.93 (qd, *J* = 6.8, 0.7 Hz, 1 H), 1.21 (s, *J* = 1.9 Hz, 9 H), 0.91 – 0.89 (m, 12 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 178.4, 134.8, 127.4, 75.2, 65.8, 36.4, 31.4, 27.2, 26.6, 19.0, 12.6; HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{34}O_3Si$ $[M + H]^+$ 315.2356, found 315.2354.

7.3.13. Synthesis of Acid 622

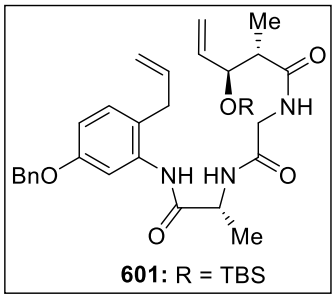


622

Acid 622. A solution of **620** (542 mg, 1.72 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was cooled at -78 ºC and treated with DIBAL-H (3.5 mL, 1.0 M in toluene, 3.45 mmol, 2.0 equiv). After 1 h, the reaction was quenched by addition of MeOH at -78 ºC and the mixture was allowed to reach room temperature, treated with a saturated aqueous Na^+/K^+ tartrate solution and diluted with CH_2Cl_2. The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phases. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting crude alcohol (~1.30 mmol) was used in the next step without further purification. To a solution of the crude alcohol in CH_2Cl_2 (10 mL) was added a solution of Dess-Martin periodinane (2.8 g, 6.51 mmol, 5.0 equiv) in CH_2Cl_2 (10 mL) at 0 ºC. The reaction mixture was stirred at 25 ºC for 12 h and, after this time, the reaction mixture was quenched with a 1:1 mixture of a saturated aqueous $NaHCO_3$ solution / $Na_2S_2O_3$ 1 M. The solution was stirred for 20 min and then, the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting crude aldehyde (~1.30 mmol) was used in the next step without further purification. A solution of crude aldehyde in ^{t}BuOH/H_2O (4:1, 30 mL) was treated with 2-methyl-2-butene (0.3 mL, 2.60 mmol, 2.0 equiv), $NaHPO_4$ (1.1 g, 9.11 mmol, 7.0 equiv) and $NaClO_2$ (825 mg, 9.11 mmol, 7.0 equiv). The reaction mixture was stirred for 12 h, then diluted with EtOAc and washed with brine. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to give the crude acid **622** (171 mg, 43% over three steps) as a colourless oil which did not require purification: R_f = 0.20 (silica gel, 70%

EtOAc in hexanes); $[\alpha]^{25}_{D} = -3.59$ (*c* 0.04, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.76 (ddd, *J* = 13.4, 10.2, 5.0 Hz, 1 H), 5.23 (dd, *J* = 17.0, 14.5 Hz, 2 H), 4.29 – 4.24 (m, 1 H), 2.67 – 2.54 (m, 1 H), 0.96 – 0.89 (m, 12 H), 0.10 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.5, 138.3, 116.9, 69.4, 46.6, 18.0, 12.9, -4.2, -5.2; HRMS (ESI-TOF) *m/z* calcd for $C_{12}H_{24}O_3Si$ $[M + H]^+$ 245.1573, found 245.1574.

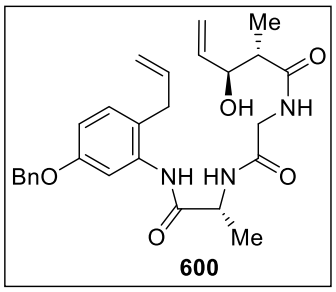
7.3.14. Synthesis of Diolefin 601



601: R = TBS

Diolefin 601. Dipeptide **610** (328 mg, 0.70 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was treated with TFA (3.5 mL) in exactly the same manner as previously described for synthesis of **612**. A solution of the ammonium salt and acid **622** (171 mg, 0.70 mmol, 1.0 equiv), in CH_2Cl_2 (15 mL) was treated with HATU (400 mg, 1.05 mmol, 1.0 equiv) and DIPEA (0.35 mL, 2.10 mmol, 3.0 equiv) and the resulting solution was stirred at 25 ºC for 12 h. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain diolefin **601** (250 mg, 74% over two steps) as a white solid: R_f = 0.73 (silica gel, 100% EtOAc); $[\alpha]^{25}_{D} = -6.06$ (*c* 0.05, CH_2Cl_2); mp = 98-99 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.12 (bs, 1 H), 7.68 (d, *J* = 7.3 Hz, 1 H), 7.54 (d, *J* = 2.6 Hz, 1 H), 7.44 – 7.27 (m, 5 H), 7.06 (m, 1 H), 6.78 – 6.71 (m, 1 H), 6.70 – 6.63 (m, 1 H), 5.92 (ddt, *J* = 16.5, 10.2, 6.1 Hz, 1 H), 5.79 (ddd, *J* = 17.3, 10.3, 7.2 Hz, 1 H), 5.27 (m, 1 H), 5.10 (m, 1 H), 5.01 (s, 2 H), 4.60 – 4.51 (m, 1 H), 4.33 (dd, *J* = 17.1, 7.4 Hz, 1 H), 4.15 – 4.04 (m, 2 H), 3.62 (dd, *J* = 17.1, 4.6 Hz, 1 H), 3.36 – 3.22 (m, 1 H), 2.32 (dq, *J* = 13.7, 6.8 Hz, 1 H), 1.42 (d, *J* = 7.0 Hz, 3 H), 1.10 (d, *J* = 6.9 Hz, 3 H), 0.94 (s, 9 H), 0.19 (s, 3 H), 0.17 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.5, 170.8, 169.8, 157.8, 138.2, 136.8, 136.3, 136.1, 130.9, 128.5, 127.9, 127.5, 122.7, 117.9, 116.3, 112.2, 109.9, 70.1, 49.8, 46.6, 43.1, 38.9, 38.5, 25.2, 18.1, 17.4, 16.2, 13.6, 2.9, -4.5, -4.7; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{33}H_{48}N_3O_5Si$ 594.3363; found 594.3365.

7.3.15. Synthesis of Diolefin 600

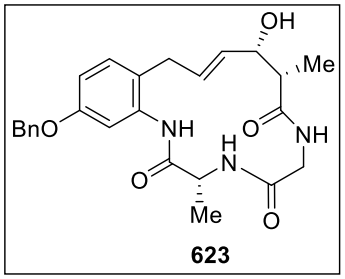


600

Diolefin 600. To a solution of diolefin **601** (90 mg, 0.15 mmol, 1.0 equiv) in THF (10 mL) was added HF•*pyr* (0.6 mL) at 0 ºC and the mixture was stirred for 12 h. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and diluted with EtOAc. The organic layer was separated and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 2% MeOH in CH_2Cl_2)

to obtain diolefin **600** (60 mg, 83%) as a white solid: R_f = 0.66 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ = – 4.91 (*c* 0.08, CH_2Cl_2); mp = 90-91 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.16 (bs, 1 H), 7.69 (d, *J* = 7.1 Hz, 1 H), 7.56 (d, *J* = 2.6 Hz, 1 H), 7.43 – 7.28 (m, 5 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 6.88 – 6.81 (m, 1 H), 6.73 (dd, *J* = 8.4, 2.6 Hz, 1 H), 5.93 (ddd, *J* = 16.3, 11.1, 6.0 Hz, 1 H), 5.80 (ddd, *J* = 17.3, 10.3, 7.2 Hz, 1 H), 5.28 (dd, *J* = 16.0, 2.2 Hz, 1 H), 5.20 (d, *J* = 10.3 Hz, 1 H); 5.14 – 5.04 (m, 2 H), 5.01 (s, 2 H), 4.59 – 4.48 (m, 1 H), 4.31 (dd, *J* = 17.2, 7.5 Hz, 1 H), 3.62 (dd, *J* = 17.1, 4.8 Hz, 1 H), 3.33 – 3.26 (m, 2 H), 2.35 (dq, *J* = 13.6, 6.8 Hz, 1 H), 1.41 (d, *J* = 7.1 Hz, 3 H), 1.09 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.5, 170.7, 169.9, 157.8, 138.4, 136.9, 136.3, 136.2, 130.8, 128.5, 127.9, 127.5, 122.8, 117.7, 116.3, 111.9, 109.9, 70.1, 49.8, 43.2, 36.4, 23.8, 19.6, 17.3, 13.5; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{34}N_3O_5$ 480.2498; found 480.2502.

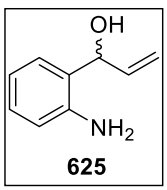
7.3.16. Synthesis of Cyclopeptide 623



623

Cyclopeptide 623. Diolefin **600** (30 mg, 0.06 mmol, 1.0 equiv), Hoveyda-Grubbs 2nd generation catalyst (4.0 mg, 0.01 mmol, 0.10 equiv) and *p*-benzoquinone (1.0 mg, 0.01 mmol, 0.10 equiv) were dissolved in degassed CH_2Cl_2 (3 mL, 0.02 M) and the reaction mixture was heated at 40 ºC for 12 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, CH_2Cl_2 → 5% MeOH in CH_2Cl_2) to obtain **623** (20 mg, 71%) as a white solid: R_f = 0.44 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ = – 8.4 (*c* 0.05, MeOH); mp = 203-204 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.67 (bs, 1 H), 8.49 (t, *J* = 5.5 Hz, 1 H), 7.46 – 7.29 (m, 6 H), 7.07 (d, *J* = 2.7 Hz, 1 H), 6.82 (dd, *J* = 8.3, 2.7 Hz, 1 H), 5.62 (dt, *J* = 15.9, 5.11 Hz, 1 H), 5.05 (s, 2 H), 4.98 (dd, *J* = 15.9, 7.0 Hz, 1 H), 4.32 – 4.23 (m, 1 H), 4.13 (dd, *J* = 6.6, 4.7 Hz, 1 H), 3.85 (dd, *J* = 14.3, 5.8 Hz, 1 H), 3.19 – 2.99 (m, 3 H), 2.68 – 2.64 (m, 1 H), 1.30 (d, *J* = 7.3 Hz, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 174.9, 171.5, 170.6, 157.5, 137.6, 137.5, 131.6, 131.0, 130.2, 128.8, 128.2, 128.1, 127.6, 113.3, 112.3, 72.7, 69.7, 49.6, 44.9, 43.6, 33.8, 16.9, 11.0; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{30}N_3O_5$ 452.2186; found 452.2188.

7.3.17. Synthesis of Aniline 625

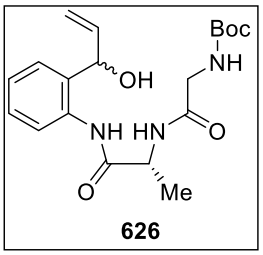


625

Aniline 625. To a solution of allylic alcohol **624**[293] (1.9 g, 10.60 mmol, 1.0 equiv) in EtOH (60 mL) was added a solution of NH_4Cl (2.8 g, 53.02 mmol, 5.0 equiv) in water (40 mL) followed by Zn dust (10 g, 159.06 mmol, 15.0 equiv) in ten portions of 1 g each over 30 min at 25 ºC. The mixture was stirred at this temperature for 12 h and then the reaction mixture was diluted with CH_2Cl_2 and water, then filtered and rinsed with CH_2Cl_2. The filtrate was diluted with water and extracted with CH_2Cl_2, and the organic phase washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under

reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain aniline **625** (1.4 g, 85%) as a yellow oil: R_f = 0.48 (silica gel, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.13 – 7.06 (m, 2 H), 6.75 (td, *J* = 7.5, 1.2 Hz, 1 H), 6.65 (dd, *J* = 7.9, 0.9 Hz, 1 H), 6.15 (ddd, *J* = 17.0, 10.4, 5.3 Hz, 1 H), 5.34 (dt, *J* = 17.2, 1.4 Hz, 1 H), 5.25 (dt, *J* = 10.4, 1.5 Hz, 1 H), 5.15 (d, *J* = 5.2 Hz, 1 H), 3.75 (bs, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 144.8, 138.3, 128.9, 128.0, 126.4, 118.6, 117.1, 115.4, 74.2; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_9H_{12}NO$ 150.0919; found 150.0907.

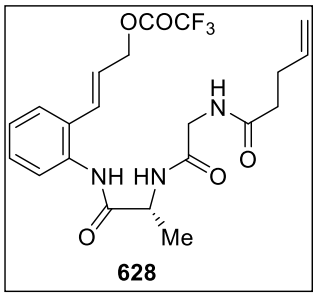
7.3.18. Synthesis of Dipeptide 626



626

Dipeptide 626. To a solution of aniline **625** (1.3 g, 8.71 mmol, 1.0 equiv) and Boc-Gly-D-Ala-OH (**608**) (2.1 g, 8.71 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added HATU (3.6 g, 13.07 mmol, 1.5 equiv) and DIPEA (1.5 mL, 8.71 mmol, 1.0 equiv) and the mixture was stirred for 12 h at 25 ºC. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 40% EtOAc in hexanes) to obtain dipeptide **626** (2.5 g, 76%, 1:1 mixture of diastereoisomers) as a white foam. Data assigned for the mixture of diastereoisomers: R_f = 0.56 (silica gel, 100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.75 (d, *J* = 8.6 Hz, 1 H), 7.96 (t, *J* = 8.2 Hz, 1 H), 7.39 – 7.28 (m, 1 H), 7.25 – 7.15 (m, 1 H), 7.10 (m, 1 H), 7.06 – 6.98 (m, 1 H), 6.08 – 5.92 (m, 1 H), 5.85 – 5.64 (m, 1 H), 5.20 (d, *J* = 5.7 Hz, 1 H), 5.16 – 5.07 (m, 1 H), 4.54 – 4.35 (m, 1 H), 3.89 – 3.62 (m, 2 H), 1.37 (s, 9 H), 1.33 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.5, 170.4, 170.4, 170.1, 170.1, 138.1, 138.1, 136.3, 128.6, 128.5, 128.1, 127.9, 124.4, 122.4, 122.3, 116.0, 115.9, 80.9, 60.4, 50.3, 50.1, 44.1, 44.0, 28.3, 28.3, 17.8, 17.8; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{28}N_3O_5$ 378.2029; found 378.2034.

7.3.19. Synthesis of Trifluoroacetate Derivative 628

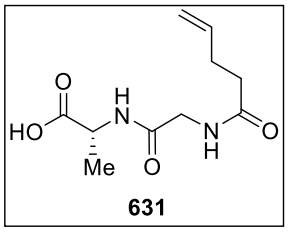


628

Trifluoroacetate Derivative 628. Dipeptide **626** (1.0 g, 2.65 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was treated with TFA (13 mL) in exactly the same manner as previously described for synthesis of **612**. A solution of the ammonium salt and Kosher acid **611** (0.27 mL, 2.65 mmol, 1.0 equiv), in CH_2Cl_2 (35 mL) was treated with HATU (1.0 g, 2.65 mmol, 1.0 equiv) and DIPEA (1.4 mL, 7.95 mmol, 3.0 equiv) and the resulting solution was stirred at 25 ºC for 12 h. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed

with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) to obtain trifluoroacetate derivative **628** (784 mg, 65%) as a white solid: R_f = 0.18 (silica gel, 100% EtOAc); $[\alpha]^{25}{}_D$ = – 9.14 (*c* 0.12, CH_2Cl_2); mp = 109-110 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.62 (bs, 1 H), 7.55 – 7.35 (m, 2 H), 7.25 – 7.20 (m, 1 H), 7.18 – 7.12 (m, 1 H), 6.85 (d, *J* = 15.4 Hz, 1 H), 6.15 (dt, *J* = 15.4, 6.6 Hz, 1 H), 5.77 – 5.66 (m, 1 H), 5.01 – 4.90 (m, 4 H), 4.69 – 4.58 (m, 1 H), 4.01 – 3.90 (m, 2 H), 2.37 – 2.22 (m, 4 H), 1.42 (d, *J* = 5.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.8, 171.2, 169.9, 157.7, 136.7, 134.3, 132.0, 129.7, 129.1, 126.7, 126.3, 125.1, 123.1, 115.7, 113.1, 68.5, 49.8, 43.3, 35.1, 29.3, 17.4; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{25}F_3N_3O_5$ 456.1746; found 456.1752.

7.3.20. Synthesis of Acid 631

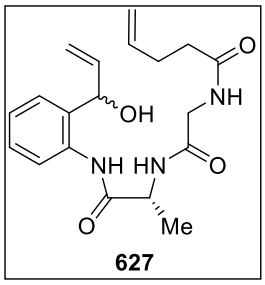


631

Acid 631. A 5 mL polypropylene syringe fitted with polyethylene porous disk charged with 2-chlorotrityl chloride (CTC) resin (300 mg, L=1.3 mmol/g, 1.0 equiv), was loaded with a solution of Fmoc-D-Ala-OH (**629**) (364 mg, 1.17 mmol, 3.0 equiv) and DIPEA (0.23 mL, 1.36 mmol, 3.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 30 h, then the solution was unloaded and the resin was washed by shaking with dry DMF (5 x 3 mL). The resulting yellow resin was used in the next step. The polypropylene syringe loaded with the yellow resin was treated with a solution of 20% piperidine in DMF (3 x 3 mL x 10 min at 280 rpm). After the last run, the resin was washed with dry DMF (5 x 3 mL) and loaded with a solution of Fmoc-Gly-OH (**630**) (232 mg, 0.78 mmol, 2.0 equiv), HOBt (105 mg, 0.78 mmol, 2.0 equiv) and DIC (0.15 mL, 0.97 mmol, 2.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 24 h, and then the solution was unloaded and the resin washed with dry DMF (5 x 3 mL). The resulting yellow resin was used in the next step. To a 5 mL polypropylene syringe fitted with polyethylene porus disk and loaded with the resulting Fmoc protected dipeptide was added a solution of 20% piperidine in DMF (3 x 3 mL x 10 min at 280 rpm). After the last run, the resin was washed with dry DMF (5 x 3 mL) and treated with a solution of Kosher acid **611** (80 µL, 0.78 mmol, 2.0 equiv) HOBt (105 mg, 0.78 mmol, 2.0 equiv) and DIC (0.2 mL, 0.97 mmol, 2.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 24 h, and then the solution was unloaded and the resinwashed with dry DMF (5 x 3 mL). The resulting yellow resin was treated with a solution of CH_2Cl_2/AcOH/TFE (7:2:1, 3 mL) for 30 min. After that, the solution was collected and the resin washed with CH_2Cl_2 (2 x 3 mL). All the collected organic solvents were evaporated under reduced pressure and the resulting acid **631** (71 mg, 81 % overall yield from CTC resin) was obtained as a white solid which not required further purification: R_f = 0.21 (silica gel, 100% EtOAc); $[\alpha]^{25}{}_D$ = – 5.21 (*c* 0.07, CH_2Cl_2); mp = 89-90 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.91 (bs, 1 H), 6.62 (bs, 1 H), 5.84 (ddd, *J* = 16.2, 11.1, 5.9 Hz, 1 H), 5.10 (dd, *J* = 17.1, 1.5 Hz, 1 H), 5.04 (dd, *J* = 10.3, 1.0 Hz, 1 H), 4.63 – 4.53 (m, 1 H), 4.10 (dd, *J* = 16.4, 5.5 Hz, 1 H), 3.94 (dd, *J* = 17.0, 4.9 Hz, 1 H), 2.46 – 2.35

(m, 4 H), 1.48 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.4, 175.3, 162.9, 136.7, 115.8, 42.5, 36.7, 31.6, 29.4, 23.3; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{17}N_2O_4$ 229.1188; found 229.1194.

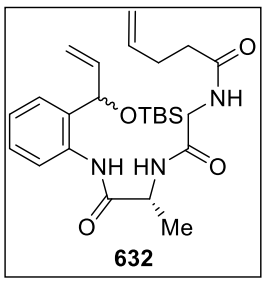
7.3.21. Synthesis of Diolefin 627



627

Diolefin 627. A solution of the aniline **625** (31 mg, 0.20 mmol, 1.0 equiv) and acid **631** (46 mg, 0.20 mmol, 1.0 equiv) in dry DMF (8 mL) was treated with HATU (76 mg, 0.20 mmol, 1.0 equiv) and DIPEA (40 µL, 0.20 mmol, 1.0 equiv) and the resulting solution was stirred at 25 ºC for 12 h. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 80% EtOAc in hexanes) to obtain diolefin **627** (55 mg, 77%, 1:1 mixture of diastereoisomers) as a white foam. Data assigned for the mixture of diastereoisomers: R_f = 0.37 (silica gel, 100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.83 (bs, 1 H), 9.66 (bs, 1 H), 8.16 (d, *J* = 8.1 Hz, 1 H), 8.11 (d, *J* = 8.1 Hz, 1 H), 7.32 – 7.23 (m, 4 H), 7.16 – 7.10 (m, 2 H), 7.06 (td, *J* = 7.5, 0.7 Hz, 2 H), 6.80 – 6.66 (m, 2 H), 6.14 – 5.99 (m, 2 H), 5.82 (dd, *J* = 11.6, 5.2 Hz, 1 H), 5.76 (dd, *J* = 10.3, 6.2 Hz, 1 H), 5.35 – 5.25 (m, 2 H), 5.24 – 5.22 (m, 2 H), 5.20 – 5.12 (m, 2 H), 5.07 (dd, *J* = 18.3, 2.9 Hz, 2 H), 5.04 – 4.99 (m, 2 H), 4.84 (bs, 2 H), 4.56 (dd, *J* = 14.7, 7.4 Hz, 1 H), 4.48 (dd, *J* = 14.1, 6.9 Hz, 1 H), 4.14 (dd, *J* = 6.6, 2.7 Hz, 1 H), 4.10 (dd, *J* = 6.2, 3.2 Hz, 1 H), 3.82 (d, *J* = 4.8 Hz, 1 H), 3.79 – 3.75 (m, 1 H), 2.40 – 2.29 (m, 8 H), 1.46 (d, *J* = 7.8 Hz, 3 H), 1.44 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.0, 173.9, 170.5, 170.4, 169.4, 169.3, 138.4, 138.2, 136.8, 136.5, 131.0, 130.8, 128.5, 128.4, 128.4, 128.3, 128.1, 127.8, 124.3, 124.2, 122.2, 122.1, 115.8, 115.7, 115.7, 115.6, 50.6, 50.2, 42.9, 42.8, 35.3, 35.2, 31.9, 31.4, 29.6, 29.3, 17.7, 17.6; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{26}N_3O_4$ 360.1923; found 360.1917.

7.3.22. Synthesis of Silyl Ether 632

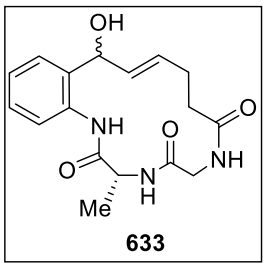


632

Silyl Ether 632. To a solution of **627** (45 mg, 0.14 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added 2,6-lutidine (30 µL, 0.25 mmol, 2.0 equiv) at 0 ºC and the mixture was stirred 10 min at this temperature. After this time TBSOTf (60 µL, 0.25 mmol, 2.0 equiv) was added at 0 ºC and the mixture was stirred 12 h at 25 ºC. Then, the reaction was quenched by addition of H_2O. After decantation of the organic layer, the aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 100% EtOAc) to obtain silyl ether **632** (50 mg, 85%, 1:1 mixture of diastereoisomers)

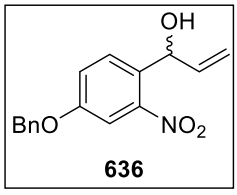
as a white solid. Data assigned for the mixture of diastereoisomers: R_f = 0.80 (silica gel, 100% EtOAc); mp = 121-122 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.16 (dd, *J* = 8.1, 7.9 Hz, 1 H), 7.31 – 7.27 (m, 1 H), 7.12 – 7.03 (m, 2 H), 7.01 – 6.95 (m, 1 H), 6.42 (d, *J* = 5.2 Hz, 1 H), 6.03 – 5.91 (m, 1 H), 5.88 – 5.76 (m, 1 H), 5.33 – 5.10 (m, 3 H), 5.10 – 4.98 (m, 2 H), 4.47 (p, *J* = 6.9 Hz, 1 H), 4.02 – 3.96 (m, 2 H), 2.44 – 2.36 (m, 2 H), 2.37 – 2.31 (m, 2 H), 1.50 – 1.42 (m, 3 H), 0.91 (s, 9 H), 0.14 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.7, 169.7, 169.7, 168.3, 168.2, 138.9, 138.7, 136.9, 136.4, 136.3, 130.5, 130.2, 128.7, 128.6, 127.9, 127.9, 124.4, 124.3, 122.3, 122.3, 115.7, 114.5, 114.4, 50.1, 49.9, 42.9, 38.6, 35.5, 29.4, 25.7, 19.1, 19.1, 18.3, 18.3, -4.9, -5.0, -5.1, -5.1; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{40}N_3O_4Si$ 474.2788; found 474.2775.

7.3.23. Synthesis of Cyclopeptide 633



Cyclopeptide 633. Diolefin **627** (30 mg, 0.08 mmol, 1.0 equiv), Hoveyda-Grubbs 2nd generation catalyst (5.0 mg, 0.01 mmol, 0.10 equiv) and *p*-benzoquinone (1.0 mg, 0.01 mmol, 0.10 equiv) were dissolved in degassed CH_2Cl_2 (4 mL, 0.02 M) and the reaction mixture was heated at 40 ºC for 15 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, CH_2Cl_2 → 5% MeOH in CH_2Cl_2) to obtain macrocycle **633** (21 mg, 73%, 1:1 mixture of diastereoisomers) as a white solid. Data assigned for the mixture of diastereoisomers: R_f = 0.46 (silica gel, 10% MeOH in CH_2Cl_2); mp = 153-154 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58 (dd, *J* = 14.1, 8.0 Hz, 2 H), 7.45 – 7.38 (m, 2 H), 7.30 – 7.20 (m, 4 H), 5.78 – 5.68 (m, 1 H), 5.58 – 5.51 (m, 1 H), 5.35 (dt, *J* = 14.6, 6.9 Hz, 1 H), 5.15 (d, *J* = 6.5 Hz, 1 H), 5.10 (d, *J* = 6.9 Hz, 1 H), 4.53 (q, *J* = 7.1 Hz, 1 H), 4.31 (q, *J* = 7.3 Hz, 1 H), 4.15 (d, *J* = 14.8 Hz, 1 H), 3.89 (d, *J* = 15.6 Hz, 1 H), 3.75 (d, *J* = 15.4 Hz, 1 H), 3.52 (d, *J* = 14.8 Hz, 1 H), 2.53 – 2.44 (m, 4 H), 2.41 – 2.26 (m, 4 H), 1.48 (d, *J* = 7.4 Hz, 3 H), 1.46 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.1, 174.9, 172.7, 171.7, 171.2, 171.2, 136.9, 136.7, 134.3, 133.9, 133.8, 133.5, 130.9, 129.9, 127.4, 127.3, 126.9, 126.4, 125.9, 125.8, 125.8, 125.3, 71.9, 71.6, 50.9, 49.6, 43.6, 42.7, 34.9, 33.5, 28.5, 26.8, 15.8, 15.5; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{22}N_3O_4$ 332.1610; found 332.1588.

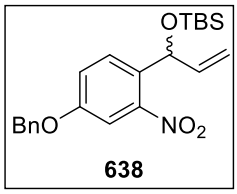
7.3.24. Synthesis of Allylic Alcohol 636



Allylic Alcohol 636. To a solution of nitrobenzaldehyde derivative **635**[295] (1.8 g, 6.99 mmol, 1.0 equiv) in THF (25 mL) was added vinylmagnesium bromide (10 mL, 1.0 M in THF, 9.79 mmol, 1.4 equiv) at -78 ºC. After being stirred for 3.5 h, the mixture was quenched with 25 mL of 0.01 N HCl, diluted and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes)

to obtain allylic alcohol **636** (1.8 g, 90%) as a yellow oil: R_f = 0.79 (silica gel, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.66 (d, *J* = 8.7 Hz, 1 H), 7.53 (d, *J* = 2.7 Hz, 1 H), 7.47 – 7.36 (m, 6 H), 7.25 (dd, *J* = 8.7, 2.7 Hz, 1 H), 6.08 (ddd, *J* = 17.2, 10.5, 5.1 Hz, 1 H), 5.75 – 5.70 (m, 1 H), 5.43 (dt, *J* = 17.2, 1.4 Hz, 1 H), 5.27 (dt, *J* = 10.5, 1.4 Hz, 1 H), 5.14 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.3, 148.9, 138.1, 135.7, 130.2, 129.8, 128.8, 128.5, 127.6, 120.7, 115.9, 110.3, 70.67, 69.7; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{16}NO_4$ 286.1079; found 286.1080.

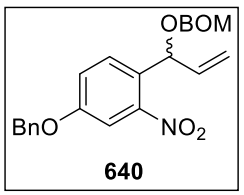
7.3.25. Synthesis of Silyl Ether 638



638

Silyl Ether 638. A solution of allylic alcohol **636** (800 mg, 4.47 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was treated with imidazole (395 mg, 5.80 mmol, 1.3 equiv) and TBSCl (875 mg, 5.80 mmol, 1.3 equiv) at 0 ºC. The resulting solution was stirred for 12 h at 25 ºC and then diluted with CH_2Cl_2, washed with a saturated aqueous NH_4Cl solution and brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain silyl ether **638** (1.2 g, 95%) as a colourless oil: R_f = 0.88 (silica gel, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.74 (d, *J* = 8.8 Hz, 1 H), 7.50 (d, *J* = 2.6 Hz, 1 H), 7.47 – 7.38 (m, 5 H), 7.25 (dd, *J* = 8.8, 2.7 Hz, 1 H), 5.98 (ddd, *J* = 17.0, 10.3, 5.0 Hz, 1 H), 5.84 (dt, *J* = 5.0, 1.4 Hz, 1 H), 5.35 (dt, *J* = 17.0, 1.6 Hz, 1 H), 5.13 (s, 2 H), 5.09 (dt, *J* = 10.3, 1.6 Hz, 1 H), 0.92 (s, 9 H), 0.13 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.8, 147.7, 139.7, 135.8, 131.6, 129.8, 128.8, 128.4, 127.6, 120.9, 113.9, 109.3, 70.6, 69.9, 25.8, 18.3, -3.5; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{30}NO_4Si$ 400.1944; found 400.1958.

7.3.26. Synthesis of Benzyloxymethyl Acetal 640

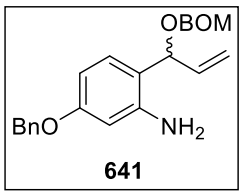


640

Benzyloxymethyl Acetal 640. To a solution of allylic alcohol **636** (460 mg, 1.61 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added DIPEA (1.12 mL, 6.45 mmol, 4.0 equiv) and BOMCl (1.2 mL, 6.45 mmol, 4.0 equiv) at 0 ºC and the mixture was stirred at 25 ºC for 15 h. After this time, the reaction was quenched by addition of a saturated aqueous Na_2CO_3 solution and the crude mixture was stirred for 30 min. Then, the aqueous phase was extracted with CH_2Cl_2 and the organic phase washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain benzyloxymethyl acetal **640** (528 mg, 88%) as a pale yellow oil: R_f = 0.56 (silica gel, 20% EtOAc in hexanes);^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.65 (d, *J* = 8.8 Hz, 1 H), 7.49 (d, *J* = 2.7 Hz, 1 H), 7.43 – 7.28 (m, 10 H), 7.22 (dd, *J* = 8.8, 2.7 Hz, 1 H), 5.95 (ddd, *J* = 17.1, 10.3, 6.0 Hz, 1 H), 5.79 (d, *J* = 6.1 Hz, 1 H), 5.35 (dt, *J* = 17.2, 1.4 Hz, 1 H), 5.23 (dt, *J* = 10.4, 1.3 Hz, 1 H), 5.11 (s, 2 H), 4.91 – 4.77 (m, 2 H), 4.71 (d, *J* = 6.9 Hz, 1 H), 4.62 – 4.51 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

(ppm) 158.2, 148.9, 137.6, 136.8, 135.8, 129.9, 128.8, 128.5, 128.4, 128.4, 127.9, 127.7, 127.5, 120.6, 117.0, 109.8, 92.6, 73.4, 70.7, 69.8; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{24}NO_5$ 406.1655; found 406.1651.

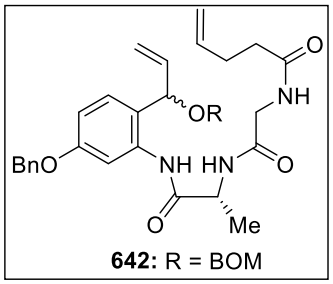
7.3.27. Synthesis of Aniline 641



641

Aniline 641. To a solution of benzyloxymethyl acetal **640** (480 mg, 1.18 mmol, 1.0 equiv) in EtOH (10 mL) was added a solution of NH_4Cl (317 mg, 5.92 mmol, 5.0 equiv) in water (7.5 mL) followed by Zn dust (1.2 g, 17.76 mmol, 15.0 equiv) in twelve portions of ~100 mg each over 30 min at 25 ºC. The mixture was stirred at this temperature for 12 h and then the reaction mixture was diluted with CH_2Cl_2 and water, filtered and rinsed with CH_2Cl_2. The filtrate was diluted with water and extracted with CH_2Cl_2, and the organic phase washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 15% EtOAc in hexanes) to obtain aniline **641** (351 mg, 79%) as a pale yellow oil: R_f = 0.35 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42 – 7.29 (m, 10 H), 7.01 (d, *J* = 8.4 Hz, 1 H), 6.35 (dd, *J* = 8.3, 2.5 Hz, 1 H), 6.29 (d, *J* = 2.5 Hz, 1 H), 6.12 (ddd, *J* = 17.2, 10.4, 5.7 Hz, 1 H), 5.33 (dt, *J* = 17.3, 1.6 Hz, 1 H), 5.25 (dt, *J* = 10.4, 1.6 Hz, 1 H), 5.16 (dt, *J* = 5.7, 1.5 Hz, 1 H), 5.02 (s, 2 H), 4.84 – 4.76 (m, 2 H), 4.67 – 4.62 (m, 2 H), 4.16 (bs, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.8, 146.7, 137.8, 137.2, 136.5, 130.6, 128.5, 128.4, 127.9, 127.9, 127.7, 127.4, 116.3, 104.2, 102.9, 91.9, 78.1, 77.2, 69.9, 69.8; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{26}NO_3$ 376.1913; found 376.1901.

7.3.28. Synthesis of Diolefin 642

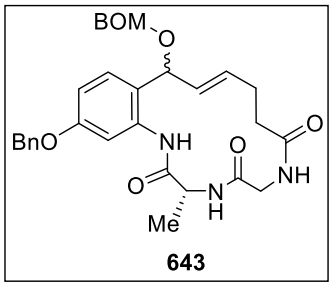


642: R = BOM

Diolefin 642. A solution of the aniline **641** (50 mg, 0.13 mmol, 1.0 equiv) and acid **631** (30 mg, 0.13 mmol, 1.0 equiv) in dry DMF (7 mL) was treated with HATU (50 mg, 0.13 mmol, 1.0 equiv) and DIPEA (22 µL, 0.13 mmol, 1.0 equiv) and the resulting solution was stirred at 25 ºC for 12 h. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) to obtain diolefin **642** (57 mg, 75%, 1:1 mixture of diastereoisomers) as a white solid. Data assigned for the mixture of diastereoisomers: R_f = 0.81 (silica gel, 80% EtOAc in hexanes); mp = 90-91 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.89 (d, *J* = 16.4 Hz, 1 H), 7.98 (d, *J* = 2.5 Hz, 1 H), 7.47 – 7.27 (m, 11 H), 7.08 (dd, *J* = 8.5, 1.8 Hz, 1 H), 6.70 (ddd, *J* = 8.5, 2.6, 1.2 Hz, 1 H), 6.00 (ddd, *J* = 18.5, 9.3, 4.1 Hz, 1 H), 5.83 (dddd, *J* = 12.6, 8.8, 6.1, 4.7 Hz, 1 H), 5.30 – 5.20 (m, 3 H), 5.12 – 4.99 (m, 5 H), 4.80 (ddd, *J* = 15.5, 11.0, 6.7 Hz, 2 H), 4.67 (dd, *J* = 14.2, 12.2 Hz, 1 H), 4.59 – 4.54 (m, 2 H), 2.44 –

2.37 (m, 2 H), 2.36 – 2.29 (m, 2 H), 1.45 – 1.38 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.3, 171.9, 171.9, 170.5, 170.4, 159.4, 137.5, 137.4, 137.2, 136.9, 136.8, 136.4, 136.4, 130.4, 128.6, 128.6, 128.5, 128.1, 128.1, 128.0, 127.6, 120.2, 120.2, 116.8, 116.8, 115.8, 115.7, 115.6, 111.1, 111.0, 108.6, 108.5, 92.2, 92.0, 78.2, 78.2, 70.2, 70.1, 49.8, 49.7, 38.6, 35.7, 33.0, 29.4, 28.7, 19.1, 18.9; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{34}H_{40}N_3O_6$ 586.2917; found 586.2921.

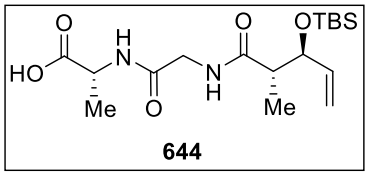
7.3.29. Synthesis of Cyclopeptide 643



643

Cyclopeptide 643. Diolefin **642** (15 mg, 0.03 mmol, 1.0 equiv), Hoveyda-Grubbs 2nd generation catalyst (1.6 mg, 0.003 mmol, 0.10 equiv) and *p*-benzoquinone (1.0 mg, 0.003 mmol, 0.10 equiv) were dissolved in degassed CH_2Cl_2 (2 mL, 0.02 M) and the reaction mixture was heated at 40 ºC for 15 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 60% EtOAc in hexanes) to obtain macrocycle **643** (12 mg, 84%, 1:1 mixture of diastereoisomers) as a white solid. Data assigned for the mixture of diastereoisomers: R_f = 0.21 (silica gel, 80% EtOAc in hexanes); mp = 207-208 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.81 (bs, 1 H), 8.53 (bs, 1 H), 8.51 (d, *J* = 2.6 Hz, 1 H), 8.35 (d, *J* = 2.6 Hz, 1 H), 7.46 – 7.28 (m, 23 H), 7.04 (d, *J* = 8.4 Hz, 1 H), 6.70 (dd, *J* = 8.5, 2.6 Hz, 1 H), 6.61 (dd, *J* = 8.3, 2.6 Hz, 1 H), 6.20 – 6.11 (m, 1 H), 6.08 – 5.98 (m, 2 H), 5.82 – 5.72 (m, 2 H), 5.60 (dd, *J* = 15.4, 5.7 Hz, 1 H), 5.20 – 5.16 (m, 1 H), 5.15 – 5.10 (m, 1 H), 5.07 (s, 4 H), 4.91 – 4.74 (m, 4 H), 4.71 – 4.63 (m, 4 H), 4.60 (d, *J* = 7.5 Hz, 2 H), 4.52 – 4.43 (m, 2 H), 2.51 (dd, *J* = 9.1, 4.1 Hz, 4 H), 2.39 – 2.20 (m, 4 H), 1.54 (d, *J* = 7.2 Hz, 3 H), 1.49 (d, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.7, 172.7, 172.2, 170.4, 170.3, 169.5, 159.8, 159.2, 138.7, 138.1, 137.7, 136.9, 136.9, 132.4, 132.3, 132.0, 131.6, 128.7, 128.6, 128.5, 128.5, 128.5, 128.1, 127.9, 127.9, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 119.8, 118.3, 110.7, 109.9, 106.9, 106.7, 91.5, 90.9, 75.9, 74.5, 69.9, 69.9, 69.7, 69.5, 51.8, 51.5, 50.9, 36.9, 36.4, 30.2, 29.7, 29.6, 17.9, 16.5; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{32}H_{36}N_3O_6$ 558.2604; found 558.2615.

7.3.30. Synthesis of Acid 644

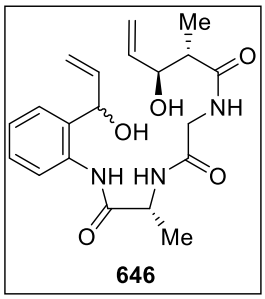


644

Acid 644. A 5 mL polypropylene syringe fitted with polyethylene porous disk charged with 2-chlorotrityl chloride (CTC) resin (363 mg, L=1.3 mmol/g, 1.0 equiv), was loaded with a solution of Fmoc-D-Ala-OH (**629**) (441 mg, 1.42 mmol, 3.0 equiv) and DIPEA (0.29 mL, 1.65 mmol, 3.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 30 h, then the solution was unloaded and the resin was washed by shaking with dry DMF (5 x 3 mL). The resulting yellow resin was used in the subsequent step. The polypropylene syringe loaded with the yellow resin was treated with a solution of 20%

piperidine in DMF (3 x 3 mL x 10 min at 280 rpm). After the last run, the resin was washed with dry DMF (5 x 3 mL) and loaded with a solution of Fmoc-Gly-OH (**630**) (281 mg, 0.94 mmol, 2.0 equiv), HOBt (128 mg, 0.94 mmol, 2.0 equiv) and DIC (0.18 mL, 1.18 mmol, 2.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 24 h, and then the solution was unloaded and the resin washed with dry DMF (5 x 3 mL). The resulting yellow resin was used in the next step. To a 5 mL polypropylene syringe fitted with polyethylene porous disk and loaded with the Fmoc protected dipeptide resin was added a solution of 20% piperidine in DMF (3 x 3 mL x 10 min at 280 rpm). After the last run, the resin was washed with dry DMF (5 x 3 mL) and treated with a solution of the acid **622** (231 mg, 0.94 mmol, 2.0 equiv), HOBt (127 mg, 0.94 mmol, 2.0 equiv) and DIC (0.18 mL, 1.18 mmol, 2.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 24 h, and then the solution was unloaded and the resin washed with dry DMF (5 x 3 mL). The resulting yellow resin was treated with a solution of CH_2Cl_2/AcOH/TFE (7:2:1, 3 mL) for 30 min. After that, the solution was collected and the resin washed with CH_2Cl_2 (2 x 3 mL). All the collected organic solvents were evaporated under reduced pressure and the resulting acid **644** (90 mg, 84% overall yield from CTC resin) was obtained as a colorless solid which not required further purification: R_f = 0.30 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}{}_D$ = – 5.44 (*c* 0.08, CH_2Cl_2); mp = 92-93 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.20 (d, *J* = 5.7 Hz, 1 H), 5.76 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.20 (d, *J* = 17.1 Hz, 1 H), 5.15 (d, *J* = 10.5 Hz, 1 H), 4.61 – 4.47 (m, 1 H), 4.17 (d, *J* = 6.5 Hz, 1 H), 4.08 (dd, *J* = 16.6, 5.7 Hz, 1 H), 3.86 (dd, *J* = 16.6, 4.8 Hz, 1 H), 2.41 (p, *J* = 6.9 Hz, 1 H), 1.42 (d, *J* = 7.0 Hz, 3 H), 1.11 (d, *J* = 7.1 Hz, 3 H), 0.86 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.9, 168.8, 163.2, 138.8, 116.6, 76.0, 47.8, 42.9, 36.8, 25.8, 18.1, 18.0, 14.7, -4.3, -5.1; HRMS (H-ESI) *m/z*: $[M + H]^+$calcd for $C_{17}H_{33}N_2O_5Si$ 373.2159; found 373.2164.

7.3.31. Synthesis of Diolefin 646

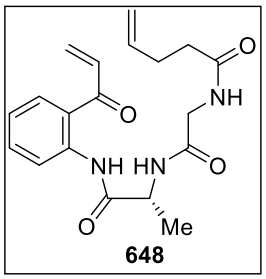


646

Diolefin 646. To a solution of aniline **625** (64 mg, 0.43 mmol, 1.0 equiv) and acid **644** (160 mg, 043 mmol, 1.3 equiv) in DMF (10 mL) was added HATU (163 mg, 0.43 mmol, 1.0 equiv) and DIPEA (0.10 mL, 0.43 mmol, 1.0 equiv) at 0 ºC and the mixture was stirred for 12 h at 25 ºC. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 25% EtOAc in hexanes → 100% EtOAc) to obtain diolefin **646** (60 mg, 36%, 1:1 mixture of diastereoisomers) as a white foam. Data assigned for the mixture of diastereoisomers: R_f = 0.23 (silica gel, 100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.28 – 7.19 (m, 2 H), 7.17 – 7.10 (m, 1 H), 7.05 (t, *J* = 7.3 Hz, 1 H), 6.14 – 5.96 (m, 1 H), 5.78 – 5.61 (m, 1 H), 5.32 – 5.06 (m, 5 H), 4.43 – 4.25 (m, 1 H), 4.18 – 4.07 (m, 1 H), 3.99 (s, 1 H), 3.69 – 3.55 (m, 1 H), 2.44 (s, 1

H), 2.35 – 2.22 (m, 1 H), 1.36 (d, *J* = 5.7 Hz, 3 H), 1.00 – 0.94 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.9, 176.5, 171.6, 171.2, 170.7, 170.5, 138.1, 137.9, 137.8, 136.1, 131.4, 131.1, 128.6, 128.5, 128.2, 128.1, 124.8, 124.8, 122.6, 122.3, 118.4, 118.0, 116.7, 116.2, 74.9, 74.3, 60.5, 50.5, 49.5, 46.8, 46.8, 30.7, 29.7, 17.4, 17.3, 13.8, 13.5; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{28}N_3O_5$ 390.2029; found 390.2037.

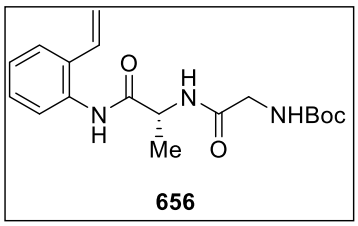
7.3.32. Synthesis of Ketone 648



648

Ketone 648. To a solution of diolefin **627** (27 mg, 0.08 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added MnO_2 (131 mg, 1.50 mmol, 20.0 equiv) and the dark solution was stirred at 25 ºC for 48 h. The mixture was filtered through a pad of celite and rinsed with CH_2Cl_2. The solvent was evaporated under reduced pressure to obtain ketone **648** (20 mg, 75%) as a white solid which did not require purification: R_f = 0.43 (silica gel, 100% EtOAc); $[\alpha]^{25}{}_D$ = – 6.98 (*c* 0.09, CH_2Cl_2); mp = 111-112 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.91 (bs, 1 H), 8.72 (dd, *J* = 8.5, 1.0 Hz, 1 H), 7.90 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.59 (ddd, *J* = 8.6, 7.5, 1.4 Hz, 1 H), 7.26 – 7.15 (m, 2 H), 7.04 (d, *J* = 7.2 Hz, 1 H), 6.73 (t, *J* = 4.9 Hz, 1 H), 6.42 (dd, *J* = 16.9, 1.6 Hz, 1 H), 5.98 (dd, *J* = 10.6, 1.6 Hz, 1 H), 5.91 – 5.77 (m, 1 H), 5.08 (ddd, *J* = 17.1, 3.2, 1.6 Hz, 1 H), 5.01 (ddd, *J* = 2.9, 2.4, 1.2 Hz, 1 H), 4.67 (p, *J* = 7.2 Hz, 1 H), 4.32 (dd, *J* = 16.8, 5.8 Hz, 1 H), 4.06 (dd, *J* = 16.8, 4.8 Hz, 1 H), 2.45 – 2.35 (m, 4 H), 1.54 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.2, 172.9, 171.3, 169.2, 140.7, 136.9, 135.3, 133.0, 131.3, 131.0, 122.9, 122.5, 121.0, 115.8, 50.4, 43.3, 35.5, 29.4, 18.2; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{24}N_3O_4$ 358.1767; found 358.1789.

7.3.33. Synthesis of Dipeptide 656

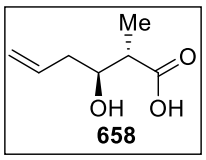


656

Dipeptide 656. To a solution of aniline **655**[299] (200 mg, 1.68 mmol, 1.0 equiv) and Boc-Gly-D-Ala-OH (**608**) (413 mg, 1.68 mmol, 1.0 equiv) in DMF (10 mL) was added HATU (960 mg, 2.52 mmol, 1.5 equiv) and DIPEA (0.30 mL, 1.68 mmol, 1.0 equiv) and the mixture was stirred for 12 h at 25 ºC. After this time, the reaction mixture was diluted with CH_2Cl_2 and washed sequentially with 1 N HCl and saturated aqueous $NaHCO_3$ solution. The organic layer was separated, washed with brine and dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) to obtain dipeptide **656** (455 mg, 78%) as a white solid: R_f = 0.52 (silica gel, 100% EtOAc); $[\alpha]^{25}{}_D$ = – 6.36 (*c* 0.06, CH_2Cl_2); mp = 84-85 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.13 (bs, 1 H), 7.78 (d, *J* = 8.1 Hz, 1 H), 7.45 (d, *J* = 7.8 Hz, 1 H), 7.15 (t, *J* = 7.5 Hz, 1 H), 6.85 – 6.79 (m, 1 H), 6.76 (d, *J* = 9.1 Hz, 1 H), 5.68 (dd, *J* = 17.4, 1.2 Hz, 1 H), 5.43 (dd, *J* = 11.0, 1.2 Hz, 1 H), 5.12 (bs, 1 H), 4.66 (q, *J* = 7.1 Hz, 1 H), 3.92 – 3.77 (m, 2 H), 1.50 (d, *J* = 7.0 Hz, 3 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.4,

170.0, 156.1, 136.9, 136.2, 131.1, 130.1, 127.2, 125.7, 123.9, 116.5, 49.5, 38.6, 36.1, 28.2, 17.7; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{26}N_3O_4$ 348.1923; found 348.1921.

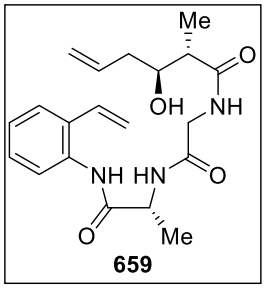
7.3.34. Synthesis of Acid 658



658

Acid 658. To a solution of diol **657**[300] (300 mg, 2.30 mmol, 1.0 equiv) in a 1:1 mixture CH_3CN/H_2O (50 mL) was added TEMPO (180 mg, 1.15 mmol, 0.5 equiv) and BAIB (3.7 g, 11.52 mmol, 5 equiv) at 25 ºC. The mixture was stirred until complete conversion of the alcohol (7 h). After this time, the reaction was diluted with EtOAc and quenched with a saturated aqueous $Na_2S_2O_3$ solution. The organic layer was separated and the aqueous phase was then extracted with EtOAc and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 40% EtOAc in hexanes) to obtain **658** (171 mg, 65%) as a colourless oil: R_f = 0.20 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = – 3.12 (*c* 0.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.59 (bs, 2 H), 5.90 – 5.75 (m, 1 H), 5.19 – 5.11 (m, 2 H), 4.05 (ddd , *J* = 7.7, 5.8, 3.9 Hz, 1 H), 3.79 (td, *J* = 7.4, 4.2 Hz, 1 H), 2.65 – 2.54 (m, 1 H), 2.44 – 2.36 (m, 1 H), 2.31 – 2.19 (m, 1 H), 1.24 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 180.7, 133.7, 118.5, 72.3, 44.6, 38.6, 13.9; HRMS (ESI-TOF) *m/z* calcd for $C_7H_{12}O_3$ $[M + H]^+$ 145.0865, found 145.0864.

7.3.35. Synthesis of Diolefin 659

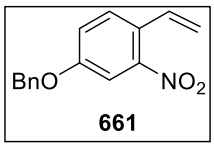


659

Diolefin 659. Dipeptide **656** (152 mg, 0.44 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) was treated with TFA (2.2 mL) in exactly the same manner as previously described for synthesis of **612**. A solution of the ammonium salt and acid **658** (50 mg, 0.44 mmol, 1.0 equiv), in DMF (15 mL) was treated with HATU (167 mg, 0.44 mmol, 1.0 equiv) and DIPEA (0.23 mL, 1.31 mmol, 3.0 equiv) and the resulting reaction mixture was stirred at 25 ºC for 12 h. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2 → 2% MeOH in CH_2Cl_2) to obtain diolefin **659** (150 mg, 92% over two steps) as a white solid: R_f = 0.60 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}{}_D$ = – 5.43 (*c* 0.07, CH_2Cl_2); mp = 104-105 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 (bs, 1 H), 7.67 – 7.57 (m, 1 H), 7.46 (d, *J* = 7.6 Hz, 1 H), 7.26 – 7.13 (m, 2 H), 6.82 – 6.71 (m, 1 H), 6.68 (t, *J* = 7.6 Hz, 1 H), 6.46 (bs, 1 H), 5.81 (td, *J* = 16.9, 7.7 Hz, 1 H), 5.67 (dd, *J* = 17.4, 1.1 Hz, 1 H), 5.42 – 5.34 (m, 2 H), 5.18 – 5.12 (m, 1 H), 4.67 – 4.51 (m, 1 H), 4.25 (dd, *J* = 16.7, 7.3 Hz, 1 H), 3.79 – 3.62 (m, 2 H), 3.14 (qd, *J* = 7.3, 4.4 Hz, 2 H), 2.17 (dd, *J* = 13.7, 8.2 Hz, 1 H), 1.42 (d, *J* = 6.7 Hz, 3 H), 1.39 (d, *J* = 6.6 Hz, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.1, 171.2, 170.2, 133.5, 131.8, 128.3, 126.4, 126.1, 126.0, 124.5, 124.1, 119.0, 117.5, 73.3, 55.6, 43.5, 39.2, 18.6, 17.2, 12.4. HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{28}N_3O_4$ 374.2080; found 374.2072.

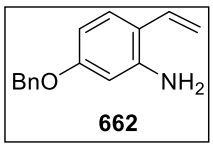
7.3.36. Synthesis of Styryl 661



661

Styryl 661. To a solution of iodonitrobenzene **605** (2.7 g, 7.60 mmol, 1.0 equiv) and $Pd[PPh_3]_4$ (1.3 g, 1.14 mmol, 0.15 equiv) in DMF (10 mL) was added dropwise tri-*n*-butyl(vinyl)tin (2.7 mL, 9.12 mmol, 1.2 equiv). The solution was then heated at 60 ºC for 48 h. After this time, the mixture was diluted with Et_2O and water. The organic layer was separated and washed with water four times, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 2% EtOAc in Hexanes) to obtain styryl **661** (1.4 g, 74%) as a yellow oil: R_f = 0.51 (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.54 (dd, *J* = 10.3, 5.7 Hz, 2 H), 7.46 – 7.34 (m, 5 H), 7.20 (ddd, *J* = 8.7, 2.7, 0.6 Hz, 1 H), 7.11 (ddd, *J* = 11.5, 10.9, 5.5 Hz, 1 H), 5.65 (dd, *J* = 17.3, 1.0 Hz, 1 H), 5.40 (dd, *J* = 11.0, 1.0 Hz, 1 H), 5.13 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.4, 135.7, 132.0, 129.5, 128.8, 128.7, 128.5, 127.6, 126.1, 120.8, 117.4, 109.8, 70.7; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{14}NO_3$ 256.0974; found 256.0981.

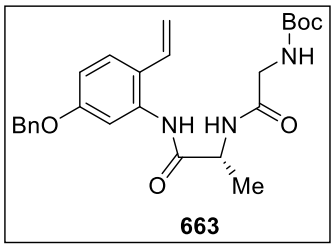
7.3.37. Synthesis of Aniline 662



662

Aniline 662. To a solution of styryl **661** (550 mg, 2.16 mmol, 1.0 equiv) in EtOH (20 mL) was added a solution of NH_4Cl (576 mg, 10.77 mmol, 5.0 equiv) in water (14 mL) followed by Zn dust (2.1 g, 32.32 mmol, 15.0 equiv) in ten portions of ~200 mg each over 30 min at 25 ºC. The mixture was stirred at this temperature for 12 h and then the reaction mixture was diluted with CH_2Cl_2 and water, filtered and rinsed with CH_2Cl_2. The filtrate was diluted with water and extracted with CH_2Cl_2, and the organic phase washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain aniline **662** (413 mg, 85%) as a yellow oil: R_f = 0.47 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45 – 7.31 (m, 5 H), 7.27 – 7.21 (m, 1 H), 6.71 (dd, *J* = 17.4, 11.1 Hz, 1 H), 6.44 (dd, *J* = 8.5, 2.4 Hz, 1 H), 6.32 (d, *J* = 2.5 Hz, 1 H), 5.54 (dd, *J* = 17.4, 1.5 Hz, 1 H), 5.22 (dd, *J* = 11.0, 1.5 Hz, 1 H), 5.04 (s, 2 H), 3.78 (bs, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.6, 144.9, 137.2, 132.2, 128.6, 128.5, 127.9, 127.4, 117.5, 113.8, 105.7, 102.3, 69.9; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{16}NO$ 226.1232; found 226.1229.

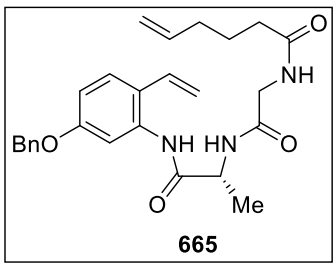
7.3.38. Synthesis of Dipeptide 663



663

Dipeptide 663. To a solution of aniline **662** (340 mg, 1.51 mmol, 1.0 equiv) and Boc-Gly-D-Ala-OH (**608**) (483 mg, 1.962 mmol, 1.0 equiv) in DMF (5 mL) was added HATU (861 mg, 2.26 mmol, 1.5 equiv) and DIPEA (0.5 mL, 3.02 mmol, 1.0 equiv) and the mixture was stirred for 12 h at 25 ºC. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 15% EtOAc in hexanes → 35% EtOAc in hexanes) to obtain dipeptide **663** (554 mg, 81%) as a yellow foam: R_f = 0.64 (silica gel, 100% EtOAc); $[\alpha]^{25}{}_D$ = – 3.96 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.30 (d, *J* = 13.1 Hz, 1 H), 7.60 (bs, 1 H), 7.46 – 7.30 (m, 7 H), 6.78 (d, *J* = 2.7 Hz, 1 H), 6.76 – 6.69 (m, 1 H), 5.56 (d, *J* = 17.3 Hz, 1 H), 5.31 (d, *J* = 11.6 Hz, 1 H), 5.18 (bs, 1 H), 5.04 (s, 2 H), 4.68 (p, *J* = 7.1 Hz, 1 H), 3.88 – 3.79 (m, 2 H), 1.47 (d, *J* = 6.3 Hz, 3 H), 1.43 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.2, 170.1, 158.8, 156.2, 136.8, 135.1, 131.4, 128.5, 127.9, 127.6, 123.2, 120.4, 116.0, 112.8, 109.1, 80.7, 70.1, 49.6, 44.4, 28.3, 17.5; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{32}N_3O_5$ 454.2342; found 454.2340.

7.3.39. Synthesis of Diolefin 665

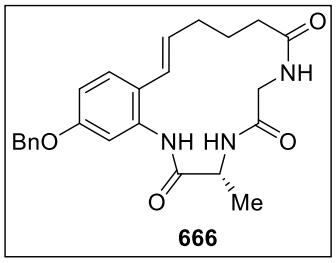


665

Diolefin 665. Dipeptide **663** (70 mg, 0.15 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was treated with TFA (2.2 mL) in exactly the same manner as previously described for synthesis of **612**. A solution of the resulting ammonium salt and hexenoic acid **664** (18 µL, 0.15 mmol, 1.0 equiv), in CH_2Cl_2 (15 mL) was treated with BOP (66 mg, 0.15 mmol, 1.0 equiv) and DIPEA (77 µL, 0.45 mmol, 3.0 equiv) and the resulting solution was stirred at 25 ºC for 12 h. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) to obtain diolefin **665** (51 mg, 74% over two steps) as a white solid: R_f = 0.45 (silica gel, 100% EtOAc); $[\alpha]^{25}{}_D$ = – 9.02 (*c* 0.11, CH_2Cl_2); mp = 82-83 ºC ; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.24 (bs, 1 H), 7.58 (bs, 1 H), 7.44 – 7.30 (m, 6 H), 7.06 (s, 1 H), 6.80 – 6.75 (m, 1 H), 6.72 (dd, *J* = 16.1, 9.7 Hz, 1 H), 6.34 (s, 1 H), 5.74 (ddt, *J* = 17.0, 10.0, 6.8 Hz, 1 H), 5.56 (d, *J* = 17.3 Hz, 1 H), 5.29 (d, *J* = 11.0 Hz, 1 H), 5.05 – 5.00 (m, 3 H), 5.00 – 4.93 (m, 1 H), 4.71 – 4.61 (m, 1 H), 4.06 – 3.93 (m, 2 H), 2.23 (td, *J* = 7.8, 1.7 Hz, 2 H), 2.10 – 2.02 (m, 2 H), 1.77 – 1.68 (m, 2 H), 1.48 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.8, 170.1, 169.4, 158.9, 137.7, 136.7, 135.1, 131.4, 128.6,

128.0, 127.6, 127.6, 123.0, 116.1, 115.5, 112.7, 109.0, 70.1, 49.8, 43.3, 35.4, 33.1, 24.5, 17.6; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{32}N_3O_4$ 450.2393; found 450.2391.

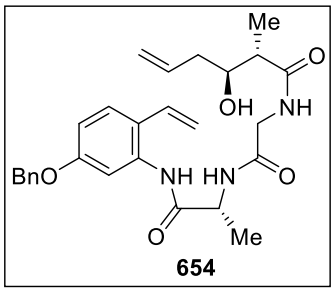
7.3.40. Synthesis of Cyclopeptide 666



666

Cyclopeptide 666. Diolefin **665** (19 mg, 0.08 mmol, 1.0 equiv), Hoveyda-Grubbs 2nd generation catalyst (3 mg, 0.004 mmol, 0.10 equiv) and *p*-benzoquinone (1.0 mg, 0.004 mmol, 0.10 equiv) were dissolved in degassed CH_2Cl_2 (2 mL, 0.02 M) and the reaction mixture was heated at 40 ºC for 12 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, CH_2Cl_2 → 3% MeOH in CH_2Cl_2) to obtain macrocycle **666** (6.1 mg, 43%) as a white solid: R_f = 0.76 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ = – 5.32 (*c* 0.09, MeOH); mp = 196-197 ; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.54 (bs, 1 H), 8.40 (t, *J* = 5.9 Hz, 1 H), 7.46 – 7.35 (m, 5 H), 7.32 (d, *J* = 7.0 Hz, 1 H), 7.29 (d, *J* = 2.5 Hz, 1 H), 7.06 (d, *J* = 8.5 Hz, 1 H), 6.77 (dd, *J* = 8.4, 2.6 Hz, 1 H), 5.42 (dt, *J* = 15.8, 5.2 Hz, 1 H), 5.04 (s, 2 H), 4.40 – 4.31 (m, 1 H), 3.85 (dd, *J* = 14.8, 6.3 Hz, 1 H), 3.45 (dd, *J* = 14.8, 5.6 Hz, 1 H), 3.20 (dd, *J* = 15.5, 5.1 Hz, 1 H), 3.03 (dd, *J* = 15.5, 5.2 Hz, 1 H), 2.34 – 2.04 (m, 4 H), 1.30 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 173.1, 171.4, 171.1, 157.4, 137.6, 137.3, 131.6, 130.7, 128.9, 128.2, 128.1, 128.09, 128.0, 125.8, 111.8, 69.7, 49.7, 43.4, 34.7, 33.7, 27.9, 16.8; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{28}N_3O_4$ 422.2079; found 422.2073.

7.3.41. Synthesis of Diolefin 654

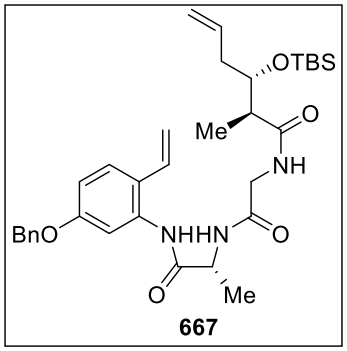


654

Diolefin 654. Dipeptide **663** (420 mg, 0.93 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was treated with TFA (4.6 mL) in exactly the same manner as previously described for synthesis of **612**. A solution of the corresponding ammonium salt and acid **658** (174 mg, 1.20 mmol, 1.3 equiv), in CH_2Cl_2 (15 mL) was treated with HATU (528 mg, 1.39 mmol, 1.0 equiv) and DIPEA (0.5 mL, 2.78 mmol, 3.0 equiv) and the resulting solution was stirred at 25 ºC for 12 h. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 50% EtOAc in hexanes → 100% EtOAc) to obtain diolefin **654** (67 mg, 86% over two steps) as a white solid: R_f = 0.46 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ = – 3.98 (*c* 0.07, MeOH); mp = 88-89 ºC; ^{1}H NMR (400 MHz, MeOD) δ (ppm) 7.53 (d, *J* = 8.7 Hz, 1 H), 7.44 – 7.27 (m, 6 H), 7.04 (d, *J* = 2.6 Hz, 1 H), 6.89 (dd, *J* = 8.7, 2.6 Hz, 1 H), 6.80 (dd, *J* = 17.5, 11.1 Hz, 1 H), 5.98 – 5.82 (m, 1 H), 5.62 (dd, *J* = 17.4, 1.2 Hz, 1 H), 5.20 (dd, *J* = 11.0, 1.3 Hz, 1 H), 5.11 (dd, *J* = 18.9, 1.7 Hz, 1 H), 5.07 (s, 2 H), 5.07 – 5.03 (m, 1 H), 4.55 – 4.47 (m, 1 H),

4.02 (d, *J* = 16.9 Hz, 1 H), 3.79 (d, *J* = 16.9 Hz, 1 H), 3.71 (td, *J* = 7.3, 4.0 Hz, 1 H), 2.48 – 2.38 (m, 2 H), 2.27 – 2.18 (m, 1 H), 1.46 (d, *J* = 7.2 Hz, 3 H), 1.11 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, MeOD) δ (ppm) 177.3, 172.7, 170.5, 163.5, 158.7, 137.1, 134.9, 134.2, 131.6, 128.1, 127.6, 127.2, 126.4, 116.5, 113.5, 112.9, 112.1, 73.1, 69.7, 42.3, 38.6, 35.6, 30.3, 16.5, 12.9; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{34}N_3O_5$ 480.2499; found 480.2501.

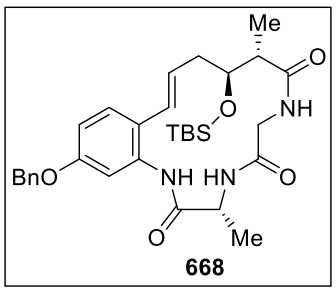
7.3.42. Synthesis of Diolefin 667



667

Diolefin 667. To a solution of diolefin **654** (35 mg, 0.07 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added 2,6-lutidine (20 µL, 0.15 mmol, 2.0 equiv) at 0 ºC and the mixture was stirred 10 min at this temperature. After this time TBSOTf (0.03 mL, 0.15 mmol, 2.0 equiv) was added at 0 ºC and the mixture was stirred for 12 h at 25 ºC. Then, the reaction was quenched by addition of H_2O. After decantation of the organic layer, the aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 100% EtOAc) to obtain diolefin **667** (31 mg, 72%) as a white solid: R_f = 0.80 (silica gel, 100% EtOAc); $[\alpha]^{25}_D$ = – 6.98 (*c* 0.06, MeOH); mp = 96-97 ºC; ^{1}H NMR (400 MHz, MeOD) δ (ppm) 7.52 (d, *J* = 8.7 Hz, 1 H), 7.44 – 7.40 (m, 2 H), 7.39 – 7.33 (m, 2 H), 7.33 – 7.27 (m, 1 H), 7.06 (d, *J* = 2.6 Hz, 1 H), 6.89 (dd, *J* = 8.7, 2.7 Hz, 1 H), 6.79 (dd, *J* = 17.5, 11.1 Hz, 1 H), 5.89 (dddd, *J* = 16.5, 10.4, 8.2, 6.0 Hz, 1 H), 5.62 (dd, *J* = 17.5, 1.3 Hz, 1 H), 5.19 (dd, *J* = 11.0, 1.3 Hz, 1 H), 5.11 – 5.07 (m, 1 H), 5.07 (s, 2 H), 5.06 – 5.03 (m, 1 H), 4.56 – 4.49 (m, 1 H), 4.07 (d, *J* = 16.5 Hz, 1 H), 3.98 – 3.89 (m, 1 H), 3.70 (d, *J* = 16.6 Hz, 1 H), 2.58 – 2.46 (m, 1 H), 2.40 – 2.22 (m, 2 H), 1.47 (d, *J* = 7.1 Hz, 3 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (100 MHz, MeOD) δ (ppm) 176.9, 172.6, 169.9, 158.7, 137.1, 134.9, 133.7, 131.6, 128.1, 127.5, 127.2, 126.4, 125.9, 116.6, 113.4, 112.9, 112.0, 73.3, 69.7, 49.4, 45.9, 42.0, 38.1, 24.9, 17.5, 16.8, 12.7, -5.6, -6.1; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{33}H_{48}N_3O_5Si$ 594.3363; found 594.3367.

7.3.43. Synthesis of Cyclopeptide 668

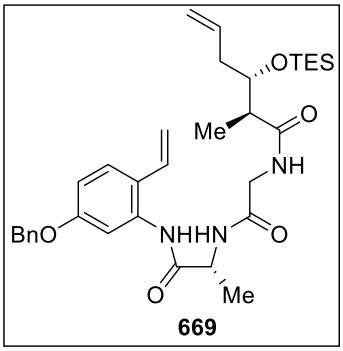


668

Cyclopeptide 668. Diolefin **667** (20 mg, 0.03 mmol, 1.0 equiv), Hoveyda-Grubbs 2nd generation catalyst (2 mg, 0.003 mmol, 0.10 equiv) and *p*-benzoquinone (1.0 mg, 0.003 mmol, 0.10 equiv) were dissolved in degassed CH_2Cl_2 (2 mL, 0.02 M) and the reaction mixture was heated at 40 ºC for 12 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 60% EtOAc in

hexanes) to obtain macrocycle **668** (9.0 mg, 47%) as a white solid: R_f = 0.51 (silica gel, 70% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 9.21 (*c* 0.08, MeOH); mp = 205-206 ºC; ^{1}H NMR (400 MHz, MeOD) δ (ppm) 7.44 – 7.27 (m, 6 H), 7.08 (d, *J* = 2.6 Hz, 1 H), 6.85 (dd, *J* = 8.7, 2.8 Hz, 1 H), 6.45 (d, *J* = 15.8 Hz, 1 H), 5.98 (ddd, *J* = 15.4, 7.5, 3.1 Hz, 1 H), 5.07 (s, 2 H), 4.25 (q, *J* = 7.2 Hz, 1 H), 4.13 (td, *J* = 6.6, 3.7 Hz, 1 H), 3.96 (d, *J* = 14.6 Hz, 1 H), 3.74 (d, *J* = 14.6 Hz, 1 H), 2.59 – 2.49 (m, 3 H), 1.54 (d, *J* = 7.2 Hz, 3 H), 1.15 (d, *J* = 7.2 Hz, 3 H), 0.95 (s, 9 H), 0.15 (overlap two singlets, 6 H); ^{13}C NMR (100 MHz, MeOD) δ (ppm) 176.8, 171.6, 171.3, 158.2, 137.2, 134.5, 128.6, 128.1, 127.5, 127.2, 126.3, 126.2, 125.4, 113.3, 112.3, 73.4, 69.7, 50.9, 46.3, 43.3, 38.9, 24.9, 17.5, 14.6, 12.0, -5.7, -6.1; HRMS (H-ESI) *m/z*: $[M + Na]^+$ calcd for $C_{31}H_{43}N_3O_5SiNa$ 588.2870; found 588.2868.

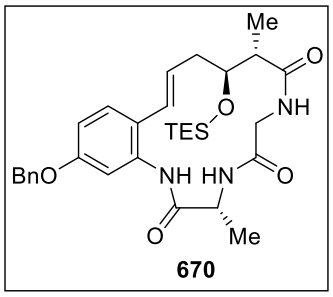
7.3.44. Synthesis of Diolefin 669



669

Diolefin 669. To a solution of diolefin **654** (53 mg, 0.11 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added 2,6-lutidine (30 µL, 0.28 mmol, 2.5 equiv) at 0 ºC and the mixture was stirred 10 min at this temperature. After this time TESOTf (0.06 mL, 0.30 mmol, 2.5 equiv) was added at 0 ºC and the mixture was stirred for 12 h at 25 ºC. Then, the reaction was quenched by addition of H_2O. After decantation of the organic layer, the aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 15% EtOAc in hexanes → 60% EtOAc) to obtain diolefin **669** (45 mg, 68%) as a white solid: R_f = 0.80 (silica gel, 100% EtOAc); $[\alpha]^{25}_D$ = – 9.41 (*c* 0.08, MeOH); mp = 92-93 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.53 (d, *J* = 8.7 Hz, 1 H), 7.45 – 7.40 (m, 2 H), 7.39 – 7.33 (m, 2 H), 7.31 (dt, *J* = 5.3, 2.1 Hz, 1 H), 7.06 (d, *J* = 2.6 Hz, 1 H), 6.89 (dd, *J* = 8.5, 2.4 Hz, 1 H), 6.80 (dd, *J* = 17.5, 11.0 Hz, 1 H), 5.89 (dddd, *J* = 16.5, 10.3, 8.1, 6.1 Hz, 1 H), 5.62 (dd, *J* = 17.5, 1.3 Hz, 1 H), 5.20 (dd, *J* = 11.0, 1.3 Hz, 1 H), 5.13 – 5.03 (m, 4 H), 4.53 (q, *J* = 7.0 Hz, 1 H), 4.06 (d, *J* = 16.6 Hz, 1 H), 3.97 – 3.91 (m, 1 H), 3.74 (d, *J* = 16.5 Hz, 1 H), 2.54 – 2.44 (m, 1 H), 2.40 – 2.22 (m, 2 H), 1.47 (d, *J* = 7.1 Hz, 3 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 0.61 (q, *J* = 7.6 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.9, 172.7, 169.9, 158.7, 137.1, 134.9, 133.9, 131.6, 128.1, 127.5, 127.2, 126.4, 125.9, 116.6, 113.4, 112.9, 112.0, 73.4, 69.7, 49.4, 46.1, 41.9, 38.5, 16.7, 12.9, 5.9, 4.5; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{33}H_{48}N_3O_5Si$ 594.3363; found 594.3359.

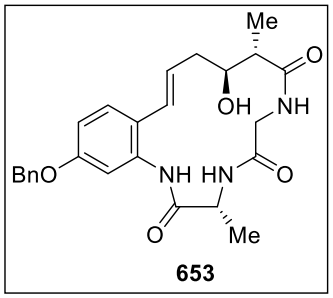
7.3.45. Synthesis of Cyclopeptide 670



670

Cyclopeptide 670. Diolefin **669** (22 mg, 0.04 mmol, 1.0 equiv), Hoveyda-Grubbs 2nd generation catalyst (2 mg, 0.004 mmol, 0.10 equiv) and *p*-benzoquinone (1.0 mg, 0.004 mmol, 0.10 equiv) were dissolved in degassed CH_2Cl_2 (2 mL, 0.02 M) and the reaction mixture was heated at 40 ºC for 12 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes → 60% EtOAc in hexanes) to obtain macrocycle **670** (11 mg, 53%) as a white solid: R_f = 0.28 (silica gel, 70% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 11.08 (*c* 0.09, MeOH); mp = 198-199 ºC; ^{1}H NMR (400 MHz, MeOD) δ (ppm) 7.44 – 7.40 (m, 2 H), 7.39 – 7.33 (m, 3 H), 7.33 – 7.27 (m, 2 H), 7.08 (d, *J* = 2.6 Hz, 1 H), 6.85 (dd, *J* = 8.6, 2.5 Hz, 1 H), 6.46 (d, *J* = 15.7 Hz, 1 H), 6.02 – 5.93 (m, 1 H), 5.07 (s, 2 H), 4.24 (q, *J* = 7.1 Hz, 1 H), 4.14 (dd, *J* = 10.2, 6.6 Hz, 1 H), 3.95 (d, *J* = 14.6 Hz, 1 H), 3.74 (d, *J* = 14.4 Hz, 1 H), 2.65 – 2.46 (m, 3 H), 1.54 (d, *J* = 7.2 Hz, 3 H), 1.17 (d, *J* = 7.2 Hz, 3 H), 1.02 (t, *J* = 7.9 Hz, 9 H), 0.70 (q, *J* = 7.5 Hz, 6 H); ^{13}C NMR (100 MHz, MeOD) δ (ppm) 176.8, 171.6, 171.3, 158.1, 137.2, 134.5, 128.7, 128.1, 127.5, 127.2, 126.3, 126.0, 125.4, 113.3, 112.3, 73.2, 69.9, 50.9, 46.3, 39.1, 29.3, 14.6, 12.2, 5.9, 4.4; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{31}H_{44}N_3O_5Si$ 566.3050; found 566.3067.

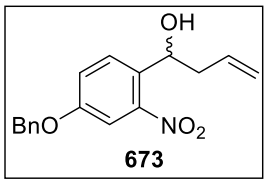
7.3.46. Synthesis of Cyclopeptide 653



653

Cyclopeptide 653. To a solution of macrocycle **670** (5.0 mg, 0.01 mmol, 1.0 equiv) in THF (3 mL) was added at 0 ºC TBAF (18 µL, 1.0 M in THF, 0.018 mmol, 2.0 equiv). After 95 min the solvent was removed under reduced pressure and the crude mixture was purified by preparative TLC (silica gel 60 F_{254}, 1 mm, 100% EtOAc) to obtain macrocycle **653** (3.4 mg, 85%) as a white solid: R_f = 0.27 (silica gel, 100% EtOAc); $[\alpha]^{25}_D$ = – 7.72 (*c* 0.04, MeOH); mp = 201-202 ºC; ^{1}H NMR (400 MHz, MeOD) δ (ppm) 7.44 – 7.40 (m, 2 H), 7.38 – 7.32 (m, 3 H), 7.32 – 7.27 (m, 1 H), 7.19 (d, *J* = 2.6 Hz, 1 H), 6.85 (dd, *J* = 8.6, 2.6 Hz, 1 H), 6.41 (d, *J* = 15.4 Hz, 1 H), 6.00 (dt, *J* = 15.4, 7.4 Hz, 1 H), 5.08 (s, 2 H), 4.55 (s, 1 H), 4.45 (q, *J* = 7.1 Hz, 1 H), 4.06 (d, *J* = 14.9 Hz, 1 H), 3.87 (td, *J* = 6.8, 2.9 Hz, 1 H), 3.72 (d, *J* = 14.9 Hz, 1 H), 2.56 – 2.50 (m, 3 H), 1.47 (d, *J* = 7.2 Hz, 3 H), 1.25 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, MeOD) δ (ppm) 176.7, 171.6, 170.7, 158.3, 137.1, 134.5, 128.9, 128.1, 127.6, 127.5, 127.2, 126.7, 125.1, 113.0, 111.3, 72.3, 69.8, 50.1, 44.9, 42.9, 39.2, 15.3, 13.5; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{30}N_3O_5$ 452.2186; found 452.2170.

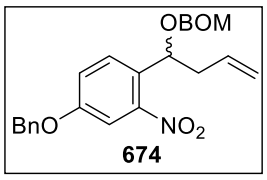
7.3.47. Synthesis of Homoallylic Alcohol 673



673

Homoallylic Alcohol 673. A solution of aldehyde **635** (395 mg, 1.54 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was cooled to 0 ºC and $SnCl_4$ (0.8 mL, 0.77 mmol, 0.5 equiv, 1.0 M in CH_2Cl_2) was added slowly over 10 min at this temperature and then stirred for 10 min at 25 ºC. Allyl trimethylsilane (0.35 mL, 2.30 mmol, 1.5 equiv) was added quickly and the reaction was stirred for 15 min, poured into Et_2O and after decantation the organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in Hexanes) to obtain the homoallylic alcohol **673** (340 mg, 74%) as a yellow solid: R_f = 0.67 (silica gel, 40% EtOAc in hexanes); mp = 74-75 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71 (d, J = 8.8 Hz, 1 H), 7.52 (d, J = 2.7 Hz, 1 H), 7.46 – 7.34 (m, 5 H), 7.26 – 7.23 (m, 1 H), 5.88 (dddd, J = 16.9, 10.5, 7.8, 6.4 Hz, 1 H), 5.26 – 5.19 (m, 2 H), 5.17 (t, J = 1.1 Hz, 1 H), 5.12 (s, 2 H), 2.67 (dddt, J = 14.0, 6.4, 3.8, 1.3 Hz, 1 H), 2.47 – 2.34 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.0, 148.4, 135.8, 134.2, 131.5, 129.3, 128.8, 128.4, 127.6, 120.8, 118.9, 109.9, 70.7, 68.2, 42.8; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{18}NO_4$ 300.1236; found 300.1238.

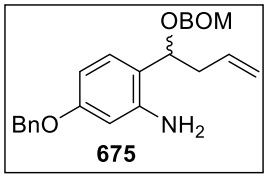
7.3.48. Synthesis of Benzyloxymethyl Acetal 674



674

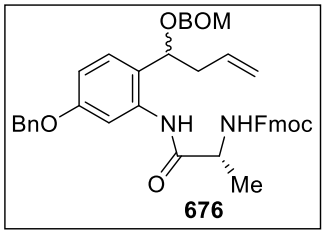
Benzyloxymethyl Acetal 674. To a solution of the homoallylic alcohol **673** (226 mg, 0.76 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added DIPEA (0.52 mL, 3.02 mmol, 4.0 equiv) and BOMCl (0.56 mL, 3.02 mmol, 4.0 equiv) at 0 ºC and the mixture was stirred at 25 ºC for 15 h. After this time, the reaction was quenched by addition of saturated aqueous Na_2CO_3 solution and the crude mixture was stirred for 30 min. Then, the aqueous phase was extracted with CH_2Cl_2 and the organic phase washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 3% EtOAc in hexanes) to obtain benzyloxymethyl acetal **674** (280 mg, 88%) as a pale yellow oil: R_f = 0.50 (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.67 (d, J = 8.7 Hz, 1 H), 7.53 (d, J = 2.6 Hz, 1 H), 7.46 – 7.22 (m, 11 H), 5.94 (ddt, J = 17.1, 10.1, 7.0 Hz, 1 H), 5.35 (dd, J = 8.0, 4.2 Hz, 1 H), 5.15 (dd, J = 17.0, 1.7 Hz, 2 H), 5.11 (s, 2 H), 4.91 (d, J = 9.0 Hz, 1 H), 4.71 (dd, J = 21.3, 5.5 Hz, 2 H), 4.66 (s, 1 H), 4.59 (d, J = 6.9 Hz, 1 H), 4.47 (d, J = 11.8 Hz, 1 H), 2.67 – 2.59 (m, 1 H), 2.57 – 2.48 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.1, 148.9, 137.6, 135.8, 134.3, 130.3, 129.7, 128.8, 128.4, 128.4, 127.8, 127.7, 127.6, 120.8, 117.8, 109.7, 93.1, 73.3, 70.7, 69.8, 42.0; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{26}NO_5$ 420.1811; found 420.1815.

7.3.49. Synthesis of Aniline 675



Aniline 675. To a solution of benzyloxymethyl acetal **674** (280 mg, 0.67 mmol, 1.0 equiv) in EtOH (6 mL) was added a solution of NH_4Cl (179 mg, 3.34 mmol, 5.0 equiv) in water (4 mL) followed by Zn dust (655 mg, 10.01 mmol, 15.0 equiv) in seven portions of ~100 mg each over 30 min at 25 ºC. The mixture was stirred at this temperature for 15 h and then the reaction mixture was diluted with CH_2Cl_2 and water, filtered and rinsed with CH_2Cl_2. The filtrate was diluted with water and extracted with CH_2Cl_2, and the organic phase washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain aniline **675** (217 mg, 87%) as a yellow oil: R_f = 0.60 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41 – 7.30 (m, 10 H), 6.94 (d, *J* = 8.4 Hz, 1 H), 6.34 (dd, *J* = 8.3, 2.5 Hz, 1 H), 6.28 (d, *J* = 2.5 Hz, 1 H), 5.81 (ddt, *J* = 17.2, 10.1, 7.0 Hz, 1 H), 5.12 (ddd, *J* = 17.1, 3.4, 1.4 Hz, 1 H), 5.05 (ddt, *J* = 10.2, 2.1, 1.0 Hz, 1 H), 5.01 (s, 2 H), 4.90 (d, *J* = 9.1 Hz, 1 H), 4.73 – 4.71 (m, 2 H), 4.67 – 4.63 (m, 1 H), 4.52 (d, *J* = 11.7 Hz, 1 H), 4.20 (bs, 2 H), 2.83 – 2.74 (m, 1 H), 2.62 – 2.53 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.5, 146.5, 137.8, 137.2, 135.3, 130.6, 128.6, 128.4, 128.0, 127.9, 127.7, 127.5, 117.1, 116.9, 104.1, 102.9, 91.9, 77.9, 69.8, 69.7, 38.7; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{28}NO_3$ 390.2069; found 390.2071.

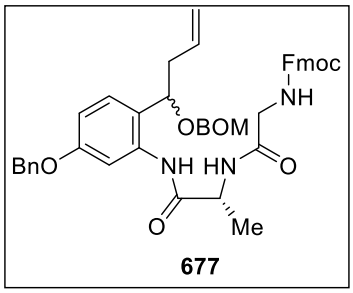
7.3.50. Synthesis of Peptide 676



Peptide 676. To a solution of aniline **675** (217 mg, 0.56 mmol, 1.0 equiv) and Fmoc-D-Ala-OH (**629**) (225 mg, 0.72 mmol, 1.3 equiv) in CH_2Cl_2 (10 mL) was added PyBOP (435 mg, 0.84 mmol, 1.5 equiv) and DIPEA (0.2 mL, 1.11 mmol, 2.0 equiv) at 0 ºC and the mixture was stirred for 15 h at 25 ºC. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) to obtain peptide **676** (247 mg, 65%, 1:1 mixture of diastereoisomers) as a white foam. Data assigned for the mixture of diastereoisomers: R_f = 0.20 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.32 (d, *J* = 11.0 Hz, 1 H), 8.03 (d, *J* = 8.7 Hz, 1 H), 7.77 (d, *J* = 7.4 Hz, 2 H), 7.61 (d, *J* = 6.0 Hz, 2 H), 7.47 – 7.27 (m, 13 H), 7.21 (dd, *J* = 7.2, 5.5 Hz, 2 H), 7.02 (d, *J* = 8.4 Hz, 1 H), 6.69 (dd, *J* = 8.4, 2.5 Hz, 1 H), 5.72 (td, *J* = 16.8, 6.9 Hz, 1 H), 5.40 (d, *J* = 6.5 Hz, 1 H), 5.13 – 5.01 (m, 4 H), 4.77 – 4.64 (m, 3 H), 4.64 – 4.56 (m, *J* = 11.4, 8.2 Hz, 1 H), 4.54 – 4.45 (m, 1 H), 4.43 – 4.32 (m, 2 H), 4.23 (dd, *J* = 14.3, 7.2 Hz, 1 H), 2.73 – 2.61 (m, 1 H), 2.53 – 2.40 (m, 1 H), 1.51 – 1.42 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.3, 159.1, 159.0, 155.8, 143.8, 141.3, 137.3, 137.2, 136.8, 134.2, 134.1, 129.9, 129.9, 128.5, 128.5, 128.4, 127.9, 127.9,

127.9, 127.9, 127.9, 127.8, 127.6, 127.1, 125.2, 125.0, 120.0, 117.9, 117.8, 111.1, 108.3, 108.1, 92.4, 78.6, 70.1, 70.0, 67.1, 51.6, 47.1, 39.9, 39.9, 18.9, 18.9; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{43}H_{43}N_2O_6$ 683.3121; found 683.3115.

7.3.51. Synthesis of Dipeptide 677

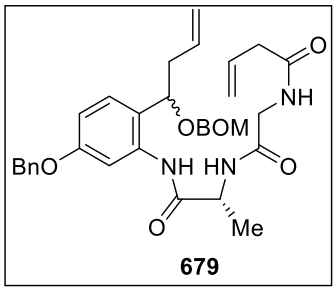


677

Dipeptide 677. To a solution of peptide **676** (176 mg, 0.26 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added piperidine (0.13 mL, 1.29 mmol, 5.0 equiv) and the reaction mixture was stirred at 25 ºC for 5 h. After this time, the organic solvent was removed under redued pressure and the resulting crude product was purified by fash column chromatography (silica gel, 30% EtOAc in hexanes → 60% EtOAc in hexanes) to obtain the corresponding amine (110 mg, 93%, 1:1 mixture of diastereoisomers) as a white solid. Data assigned for the mixture of diastereoisomers: R_f = 0.18 (silica gel, 80% EtOAc in hexanes); mp = 82-83 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.15 – 8.01 (m, 1 H), 7.48 – 7.21 (m, 12 H), 7.12 – 6.99 (m, 1 H), 6.74 – 6.62 (m, 1 H), 5.84 – 5.67 (m, 1 H), 5.13 – 4.99 (m, 5 H), 4.83 – 4.64 (m, 4 H), 4.58 – 4.45 (m, 1 H), 3.76 (bs, 1 H), 2.71 (dt, *J* = 14.8, 8.0 Hz, 1 H), 2.50 (dt, *J* = 13.6, 6.6 Hz, 1 H), 1.53 – 1.25 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 171.9, 159.1, 159.0, 137.6, 137.5, 137.5, 137.5, 137.4, 137.3, 137.3, 137.3, 136.9, 136.9, 134.5, 134.4, 128.5, 128.5, 128.5, 128.5, 128.1, 128.0, 127.9, 127.9, 127.6, 121.4, 121.2, 117.8, 117.7, 110.8, 110.6, 108.5, 108.2, 92.3, 92.3, 70.1, 70.0, 69.9, 61.4, 61.2, 51.4, 51.3, 40.1, 39.9, 16.4, 15.8. To a solution of the amine obtained above (105 mg, 0.23 mmol, 1.0 equiv) and Fmoc-Gly-OH (**630**) (88 mg, 0.30 mmol, 1.3 equiv) in CH_2Cl_2 (5 mL) was added HATU (130 mg, 0.34 mmol, 1.5 equiv) and DIPEA (0.1 mL, 0.46 mmol, 2.0 equiv) at 0 ºC and the mixture was stirred for 15 h at 25 ºC. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 15% EtOAc in hexanes → 40% EtOAc in hexanes) to obtain peptide **677** (123 mg, 73%, 1:1 mixture of diastereoisomers) as a white foam. Data assigned for the mixture of diastereoisomers: R_f = 0.27 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.99 – 7.96 (m, 1 H), 7.75 (dd, *J* = 7.5, 3.4 Hz, 2 H), 7.59 (d, *J* = 7.3 Hz, 2 H), 7.45 – 7.23 (m, 16 H), 7.03 (t, *J* = 8.9 Hz, 1 H), 6.71 – 6.66 (m, 1 H), 5.72 (ttd, *J* = 13.7, 7.0, 3.3 Hz, 1 H), 5.53 (bs, 1 H), 5.13 – 5.06 (m, 2 H), 5.04 (s, 2 H), 4.77 – 4.55 (m, 6 H), 4.44 (d, *J* = 6.8 Hz, 2 H), 4.22 (t, *J* = 6.9 Hz, 1 H), 3.97 – 3.78 (m, 2 H), 2.64 (dt, *J* = 16.3, 7.0 Hz, 1 H), 2.44 (ddd, *J* = 20.6, 13.8, 6.5 Hz, 1 H), 1.49 – 1.44 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.6, 170.1, 170.0, 165.6, 159.1, 159.1, 156.8, 156.7, 143.7, 143.7, 141.3, 141.3, 137.2, 136.8, 134.2, 134.2, 130.0, 129.9, 128.6, 128.1, 128.1, 128.0, 127.8, 127.7, 127.6, 127.1, 127.0, 125.1, 125.0, 121.3, 121.2, 120.0, 119.9, 117.9, 117.9, 111.2, 111.2, 108.5, 108.3, 92.6, 92.5, 78.3, 77.8, 70.3, 70.2, 70.1, 65.4, 49.9, 47.1, 44.5, 38.7,

18.4, 18.3; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{45}H_{46}N_3O_7$ 740.3336; found 740.3327.

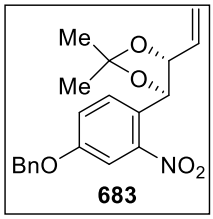
7.3.52. Synthesis of Diolefin 679



679

Diolefin 679. To a solution of peptide **677** (63 mg, 0.09 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added piperidine (0.04 mL, 0.43 mmol, 5.0 equiv) and the reaction mixture was stirred at 25 ºC 5 h. After this time, the organic solvent was removed under reduced pressure and the resulting crude amine was used in the next step without purification. To a solution of the crude amine (~0.09 mmol) and acid **678** (10 µL, 0.11 mmol, 1.3 equiv) in CH_2Cl_2 (5 mL) was added HATU (49 mg, 0.13 mmol, 1.5 equiv) and DIPEA (30 µL, 0.17 mmol, 2.0 equiv) at 0 ºC and the mixture was stirred for 12 h at 25 ºC. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes → 100% EtOAc) to obtain diolefin **679** (32 mg, 64% over 2 steps, 1:1 mixture of diastereoisomers) as a white solid. Data assigned for the mixture of diastereoisomers: R_f = 0.62 (silica gel, 100% EtOAc); mp = 95-96 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.95 (t, *J* = 2.6 Hz, 1 H), 7.46 – 7.27 (m, 12 H), 7.03 (t, *J* = 8.6 Hz, 1 H), 6.85 (s, 1 H), 6.69 (dt, *J* = 8.4, 2.8 Hz, 1 H), 5.99 – 5.84 (m, 1 H), 5.80 – 5.65 (m, 1 H), 5.27 – 5.19 (m, 2 H), 5.16 – 5.06 (m, 2 H), 5.05 (s, 2 H), 4.76 – 4.63 (m, 4 H), 4.56 – 4.46 (m, 2 H), 4.03 – 3.95 (m, 2 H), 3.07 – 3.00 (m, 2 H), 2.65 (ddd, *J* = 15.3, 13.9, 7.7 Hz, 1 H), 2.44 (ddd, *J* = 20.9, 13.1, 6.4 Hz, 1 H), 1.49 – 1.43 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.5, 171.8, 171.4, 170.1, 168.8, 165.7, 160.2, 159.1, 140.9, 137.2, 137.1, 136.8, 136.8, 134.3, 134.2, 130.7, 129.9, 129.9, 128.8, 128.6, 128.1, 128.1, 128.0, 127.7, 127.7, 127.6, 127.0, 120.2, 120.1, 117.9, 117.8, 111.2, 111.1, 108.6, 108.4, 92.7, 92.5, 78.8, 70.3, 70.3, 70.2, 70.1, 50.1, 50.1, 43.1, 43.0, 41.2, 41.2, 38.7, 18.3, 18.2; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{34}H_{40}N_3O_6$ 586.2917; found 586.2905.

7.3.53. Synthesis of Alkene 683

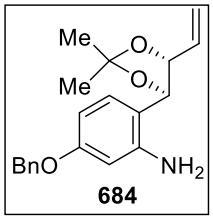


683

Alkene 683. Alkene **683** was prepared from alcohol **682**[305] (1.6 g, 4.46 mmol, 1.0 equiv) by sequential treatments with SO_3·pyr and $Ph_3P{=}CH_2$ according to the same procedure described above for the preparation of **460**, to obtain alkene **683** (840 mg, 53% over two steps) as a pale yellow oil: Flash column chromatography (silica gel, 5% EtOAc in hexanes); R_f = 0.20 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 18.51 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (ddd, *J* = 7.4, 5.9, 1.3 Hz, 2 H), 7.70 – 7.64 (m, 1 H), 7.49 – 7.44 (m, 1 H), 6.02 – 5.90 (m, 1 H), 5.50 (d, *J* = 8.2 Hz, 1 H), 5.24 (s, 1 H), 5.22 – 5.18 (m, 1 H), 4.17 (t, *J* = 8.0 Hz, 1 H), 1.60 (s, 3 H),

1.55 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7, 133.2, 132.4, 128.8, 128.5, 124.5, 119.7, 109.8, 85.6, 77.2, 77.2, 27.2, 26.9; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{22}NO_5$ 356.1498; found 356.1497.

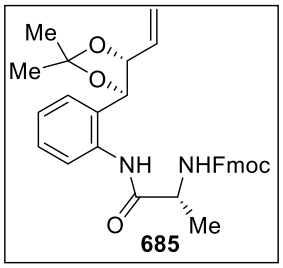
7.3.54. Synthesis of Aniline 684



684

Aniline 684. To a solution of nitro derivative **683** (532 mg, 2.14 mmol, 1.0 equiv) in EtOH (18 mL) was added a solution of NH_4Cl (570 mg, 10.68 mmol, 5.0 equiv) in water (13 mL) followed by Zn dust (2.0 g, 32.0 mmol, 15.0 equiv) in ten portions of ~200 mg each over 30 min at 25 ºC. The mixture was stirred at this temperature for 16 h and then the reaction mixture was diluted with CH_2Cl_2 and water, filtered and rinsed with CH_2Cl_2. The filtrate was diluted with water and extracted with CH_2Cl_2, and the organic phase washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain aniline **684** (417 mg, 60%) as a colorless oil: R_f = 0.55 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = + 9.43 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.11 (m, 1 H), 7.12 – 7.06 (m, 1 H), 6.84 – 6.74 (m, 2 H), 5.88 (ddd, *J* = 17.1, 10.4, 6.7 Hz, 1 H), 5.34 (dt, *J* = 17.2, 1.2 Hz, 1 H), 5.26 (dd, *J* = 10.4, 0.9 Hz, 1 H), 4.74 (d, *J* = 8.7 Hz, 1 H), 4.65 – 4.59 (m, 1 H), 1.60 (s, 3 H), 1.53 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 129.4, 129.0, 120.1, 119.3, 117.7, 109.2, 82.8, 80.4, 77.2, 27.3, 26.8; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{24}NO_3$ 326.1756; found 326.1755.

7.3.55. Synthesis of Peptide 685

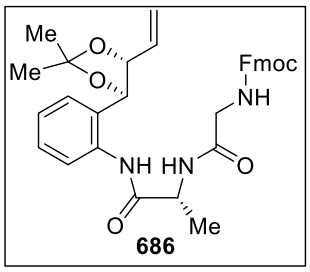


685

Peptide 685. Amine **684** (260 mg, 1.19 mmol, 1.0 equiv), Fmoc-D-Ala-OH (**629**) (480 mg, 1.54 mmol, 1.3 equiv), HATU (676 mg, 1.78 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (15 mL) and to the resulting solution was added DIPEA (0.41 mL, 2.37 mmol, 2.0 equiv). The reaction mixture was stirred at 25 ºC for 12 h. Then, a saturated aqueous NH_4Cl solution was added and the aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes → 20% EtOAc in hexanes) to obtain peptide **685** (490 mg, 81%) as a white foam: R_f = 0.50 (silica gel, 40% EtOAc); $[\alpha]^{25}{}_D$ = + 16.79 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (bs, 1 H), 8.16 (d, *J* = 8.3 Hz, 1 H), 7.76 (d, *J* = 7.5 Hz, 2 H), 7.59 (d, *J* = 4.0 Hz, 2 H), 7.45 – 7.27 (m, 6 H), 7.20 (d, *J* = 7.4 Hz, 1 H), 7.12 (dd, *J* = 11.2, 4.7 Hz, 1 H), 5.94 – 5.79 (m, 1 H), 5.68 – 5.54 (m, 1 H), 5.38 – 5.24 (m, 2 H), 4.78 (d, *J* = 8.8 Hz, 1 H), 4.53 – 4.28 (m, 5 H), 1.65 (s, 3 H), 1.57 – 1.49 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 155.8, 143.8, 141.3, 141.3, 136.4, 133.8, 129.2, 128.3, 127.8, 127.8, 127.1, 125.1, 125.0, 124.5, 124.5, 122.8,

120.0, 109.5, 82.2, 81.8, 67.1, 51.5, 47.2, 30.9, 27.3, 26.7, 19.3; HRMS (H-ESI) *m/z*: [M + H]$^+$ calcd for $C_{31}H_{33}N_2O_5$ 513.2389; found 513.2387.

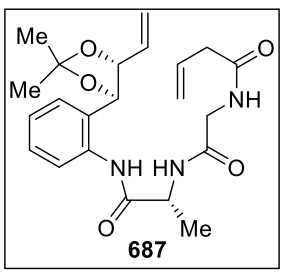
7.3.56. Synthesis of Dipeptide 686



686

Dipeptide 686. Piperidine (0.5 mL, 4.78 mmol, 5.0 equiv) was added to a solution of peptide **685** (490 mg, 0.96 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) and the reaction mixture was stirred at 25 ºC for 4 h. After this time, the organic solvent was removed under reduced pressure to obtain the corresponding crude amine (~0.90 mmol) which was used in the next step without further purification. The crude amine obtained above (~0.90 mmol), Fmoc-Gly-OH (**630**) (347 mg, 1.17 mmol, 1.3 equiv), HATU (513 mg, 1.35 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (20 mL) and to the resulting solution was added DIPEA (0.31 mL, 1.80 mmol, 2.0 equiv). The reaction mixture was stirred at 25 ºC for 12 h. Then, a saturated aqueous NH_4Cl solution was added and the aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes → 60% EtOAc in hexanes) to obtain dipeptide **686** (426 mg, 78% over 2 steps) as a white foam: R_f = 0.55 (silica gel, 80% EtOAc); $[\alpha]^{25}{}_D$ = + 9.13 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (bs, 1 H), 8.12 (d, *J* = 8.1 Hz, 1 H), 7.76 (d, *J* = 7.5 Hz, 2 H), 7.59 (d, *J* = 7.3 Hz, 2 H), 7.39 (t, *J* = 7.4 Hz, 2 H), 7.32 (dt, *J* = 10.9, 4.5 Hz, 3 H), 7.19 (d, *J* = 7.1 Hz, 1 H), 7.11 (t, *J* = 7.1 Hz, 1 H), 6.87 (d, *J* = 6.8 Hz, 1 H), 5.87 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.54 (bs, 1 H), 5.30 (t, *J* = 14.7 Hz, 2 H), 4.79 (d, *J* = 8.7 Hz, 1 H), 4.56 (p, *J* = 6.9 Hz, 1 H), 4.41 (d, *J* = 7.1 Hz, 3 H), 4.22 (t, *J* = 7.0 Hz, 1 H), 3.94 (p, *J* = 11.5 Hz, 2 H), 1.66 (s, 3 H), 1.56 (s, 3 H), 1.51 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 168.5, 165.8, 156.6, 143.8, 141.3, 136.3, 133.7, 129.2, 128.4, 127.8, 127.1, 125.1, 124.7, 124.5, 122.8, 120.0, 119.9, 109.5, 82.3, 81.9, 67.3, 49.9, 47.1, 44.4, 38.6, 27.3, 26.7, 18.9; HRMS (H-ESI) *m/z*: [M + H]$^+$ calcd for $C_{33}H_{36}N_3O_6$ 570.2604; found 570.2602.

7.3.57. Synthesis of Dialkene 687

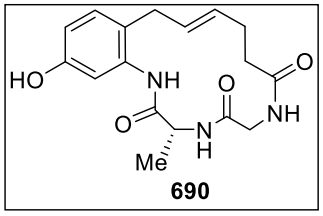


687

Dialkene 687. Piperidine (0.34 mL, 3.50 mmol, 5.0 equiv) was added to a solution of peptide **686** (400 mg, 0.70 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) and the reaction mixture was stirred at 25 ºC for 4.5 h. After this time, the organic solvent was removed under reduced pressure to obtain the corresponding crude amine (~0.70 mmol) which was used in the next step without further purification. The crude amine obtained above (~0.70 mmol), vinyl acetic acid **678** (0.1 mL, 0.91 mmol, 1.3 equiv), HATU (400 mg, 1.05 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (15 mL) and to the resulting solution was added DIPEA (0.28 mL, 1.40 mmol, 2.0 equiv). The reaction mixture was stirred at 25 ºC for 15 h. Then,

a saturated aqueous NH_4Cl solution was added and the aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes → 100% EtOAc in hexanes) to obtain peptide **687** (174 mg, 60% over 2 steps) as a white foam: R_f = 0.30 (silica gel, 100% EtOAc); $[\alpha]^{25}{}_D$ = + 13.48 (*c* 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (bs, 1 H), 8.10 (d, *J* = 8.0 Hz, 1 H), 7.37 – 7.30 (m, 1 H), 7.20 (d, *J* = 6.5 Hz, 1 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 6.93 (d, *J* = 6.7 Hz, 1 H), 6.44 (t, *J* = 4.9 Hz, 1 H), 6.00 – 5.81 (m, 2 H), 5.37 – 5.19 (m, 4 H), 4.79 (d, *J* = 8.7 Hz, 1 H), 4.53 (p, *J* = 7.0 Hz, 1 H), 4.47 – 4.37 (m, 1 H), 3.99 (dd, *J* = 5.1, 1.3 Hz, 2 H), 3.06 (d, *J* = 7.1 Hz, 2 H), 1.66 (s, 3 H), 1.56 (s, 3 H), 1.50 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.1, 168.4, 136.3, 133.7, 130.8, 129.2, 128.4, 124.7, 124.6, 122.9, 120.2, 119.9, 109.5, 82.2, 81.9, 49.9, 43.0, 41.2, 27.3, 26.7, 18.8; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{30}N_3O_5$ 416.2186; found 416.2184.

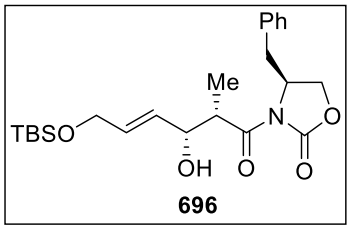
7.3.58. Synthesis of Cyclopeptide 690



690

Cyclopeptide 690. To a stirred solution of macrocycle **615** (28 mg, 0.07 mmol, 1.0 equiv) in THF (10 mL) at -78 ºC was added condensed liquid NH_3 (~8 mL) *via* cannula. Then, small pieces of Na (130 mg, 5.61 mmol, 85 equiv) were added to the mixture until the formation of a deep blue solution. The reaction was stirred at -78 ºC for 2 h and after this time it was quenched by slowly addition of MeOH at the same temperature. The mixture was allowed to reach room temperature and concentrated under reduced pressure to a volume of ~10 mL. The reaction was neutralized with Dowex-H^+, washed with MeOH and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 7% MeOH in CH_2Cl_2) to obtain macrocycle **690** (18 mg, 85%) as a white solid: R_f = 0.34 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}{}_D$ = – 6.77 (*c* 0.09, MeOH); mp = 125-126 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.30 (bs, 1 H), 8.51 (d, *J* = 7.2 Hz, 1 H), 8.38 (bs, 1 H), 7.03 (d, *J* = 2.4 Hz, 1 H), 6.91 (d, *J* = 8.2 Hz, 1 H), 6.49 (dd, *J* = 8.2, 2.5 Hz, 1 H), 5.40 (dt, *J* = 15.1, 5.0 Hz, 1 H), 5.07 (dt, *J* = 15.1, 5.7 Hz, 1 H), 4.32 (p, *J* = 7.0 Hz, 1 H), 4.11 (bs, 1 H), 3.84 (dd, *J* = 14.8, 6.4 Hz, 1 H), 3.43 (dd, *J* = 14.8, 5.6 Hz, 1 H), 3.16 – 3.09 (m, 1 H), 2.96 (dd, *J* = 16.4, 5.2 Hz, 1 H), 2.28 – 2.08 (m, 4 H), 1.29 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.1, 171.2, 170.9, 156.3, 136.9, 131.4, 131.0, 127.8, 123.7, 112.7, 112.4, 49.7, 49.1, 43.4, 33.8, 27.9, 16.9; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{22}N_3O_4$ 332.1610; found 332.1618.

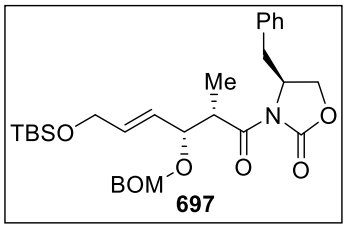
7.3.59. Synthesis of Oxazolidinone 696



696

Oxazolidinone 696. *n*-Bu_2BOTf (11.6 mL, 1.0 M in CH_2Cl_2, 11.63 mmol, 1.25 equiv) and freshly dry DIPEA (2.25 mL, 13.02 mmol, 1.4 equiv) was added sequentially over 15 min to a solution of oxazolidinone **694** (2.2 g, 9.30 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) at 0 ºC. The solution was cooled to -78 ºC and aldehyde **695** (2.2 g, 11.18 mmol, 1.2 equiv) was added slowly. After 30 min at -78 ºC, the reaction mixture was stirred at -20 ºC for 12 h. After this time, the system was placed in an ice bath at 0 ºC and quenched with pH 7 phosphate buffer (8 mL) followed by MeOH (20 mL). Then, a mixture of MeOH/30% H_2O_2 (3:1, 20 mL) was added over 30 min and the mixture was stirred for 30 min maintaining the temperature at 0 ºC. The organic solvent was removed under vaccum and the residue was extracted with CH_2Cl_2 three times. The combined organic layers were washed successively with 1 N HCl solution twice (14 mL), saturated aqueous $NaHCO_3$ solution (14 mL) and brine, then dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes → 10% EtOAc in hexanes) to obtain to obtain **696** (3.4 g, 84%) as a colorless oil: R_f = 0.30 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = + 12.9 (*c* 0.85, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 3 H), 7.23 – 7.19 (m, 2 H), 5.87 (dtd, *J* = 15.4, 4.5, 1.4 Hz, 1 H), 5.72 (ddt, *J* = 15.4, 5.6, 1.6 Hz, 1 H), 4.70 (ddt, *J* = 9.4, 7.3, 3.2 Hz, 1 H), 4.56 – 4.51 (m, 1 H), 4.27 – 4.17 (m, 4 H), 3.86 (qd, *J* = 7.0, 3.5 Hz, 1 H), 3.26 (dd, *J* = 13.4, 3.4 Hz, 1 H), 2.80 (dd, *J* = 13.3, 9.4 Hz, 1 H), 1.26 (d, *J* = 7.1 Hz, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 153.1, 135.1, 131.8, 129.5, 129.0, 128.7, 127.5, 72.0, 66.2, 63.1, 55.2, 42.8, 37.8, 25.9, 18.4, 11.1, -5.2; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{36}NO_5Si$ 434.2363; found 434.2364.

7.3.60. Synthesis of Oxazolidinone 697

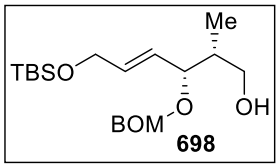


697

Oxazolidinone 697. To a solution of oxazolidinone **696** (580 mg, 1.34 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added DIPEA (0.93 mL, 5.35 mmol, 4.0 equiv) and BOMCl (1.0 mL, 5.35 mmol, 4.0 equiv) at 0 ºC and the mixture was stirred at 25 ºC for 15 h. After this time, the reaction was quenched by addition of saturated aqueous Na_2CO_3 solution and the crude mixture was stirred for 30 min. Then, the aqueous phase was extracted with CH_2Cl_2 and the organic phase washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain oxazolidinone **697** (346 mg, 47%) as a pale yellow oil: R_f = 0.60 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = + 22.1 (*c* 0.31, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 8 H), 7.20 – 7.16 (m, 2 H), 5.83 (ddd, *J* = 16.0, 4.7, 4.0 Hz, 1 H), 5.67 (ddt, *J* = 15.5, 7.7, 1.7 Hz, 1 H), 4.78 – 4.67 (m, 3 H), 4.52 – 4.38 (m, 3 H), 4.18 (dd, *J* = 4.3, 1.7 Hz, 2 H), 4.06 (ddd, *J* = 11.2, 7.9, 4.1 Hz, 2 H), 3.94 – 3.87 (m, 1 H), 3.26 (dd, *J* = 13.3, 3.2 Hz, 1 H),

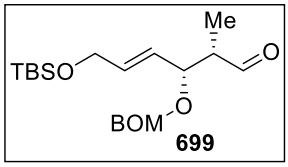
2.72 (dd, *J* = 13.3, 9.8 Hz, 1 H), 1.30 (d, *J* = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 153.3, 137.9, 135.4, 134.5, 129.4, 128.9, 128.4, 127.6, 127.6, 127.3, 126.7, 91.9, 77.5, 69.4, 65.9, 62.9, 55.6, 42.6, 37.8, 25.9, 18.4, 12.4, -5.2; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{31}H_{44}NO_6Si$ 554.2938; found 554.2937.

7.3.61. Synthesis of Alcohol 698



Alcohol 698. $LiBH_4$ (1.25 mL, 2.0 M THF, 2.50 mmol, 4.0 equiv) was added to a solution of oxazolidinone **697** (346 mg, 0.63 mmol, 1.0 equiv) in Et_2O (15 mL) at 0 ºC followed by MeOH (0.1 mL, 2.50 mmol, 4.0 equiv). The resulting reaction mixture was stirred for 1 h at 0 ºC. After this time, a saturated aqueous $NaHCO_3$ solution was added, and the residue was extracted with Et_2O three times. The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to obtain alcohol **698** (237 mg, quantitative) as a colorless oil which did not required further purification: R_f = 0.33 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 18.9 (*c* 0.45, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.34 (m, 4 H), 7.32 – 7.28 (m, 1 H), 5.79 (dtd, *J* = 15.5, 4.2, 0.6 Hz, 1 H), 5.66 (ddt, *J* = 15.4, 7.7, 1.7 Hz, 1 H), 4.79 – 4.69 (m, 3 H), 4.57 – 4.51 (m, 1 H), 4.28 (dd, *J* = 7.6, 4.4 Hz, 1 H), 4.20 (dd, *J* = 4.2, 1.6 Hz, 2 H), 3.69 (dd, *J* = 11.0, 8.0 Hz, 1 H), 3.54 (dd, *J* = 11.0, 4.8 Hz, 1 H), 2.03 – 1.94 (m, 1 H), 0.93 – 0.87 (m, 12 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 134.0, 128.5, 127.9, 127.8, 126.4, 91.9, 79.1, 69.8, 65.5, 62.9, 39.9, 25.9, 18.4, 12.1, -5.2; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{37}O_4Si$ 381.2461; found 381.2460.

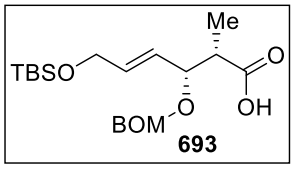
7.3.62. Synthesis of Aldehyde 699



Aldehyde 699. To a solution of alchol **698** (235 mg, 0.62 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added Dess-Martin periodinane (528 mg, 1.25 mmol, 2.0 equiv) at 0 ºC and the reaction mixture was stirred at this temperature for 2.5 h. Then the reaction was quenched by the addition of a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous $Na_2S_2O_3$ solution. The aqueous phase was extracted with EtOAc twice and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes → 20% EtOAc in hexanes) to obtain aldehyde **699** (235 mg, quantitative) as a pale yellow oil: R_f = 0.50 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 32.7 (*c* 0.80, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, *J* = 1.1 Hz, 1 H), 7.36 – 7.34 (m, 5 H), 5.85 (dtd, *J* = 15.4, 4.2, 0.8 Hz, 1 H), 5.64 (ddt, *J* = 15.4, 8.0, 1.9 Hz, 1 H), 4.82 – 4.78 (m, 1 H), 4.71 – 4.66 (m, 2 H), 4.57 (dd, *J* = 7.9, 4.5 Hz, 1 H), 4.52 – 4.46 (m, 1 H), 4.22 – 4.19 (m, 2 H), 2.60 – 2.53 (m, 1 H), 1.14 (d, *J* = 7.0 Hz, 3 H), 0.91 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 137.7,

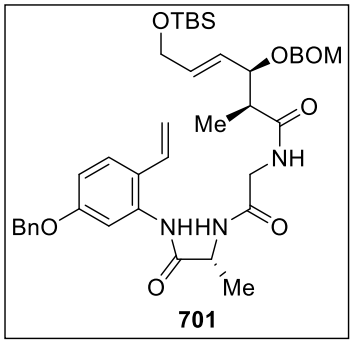
134.9, 128.5, 127.9, 127.8, 125.7, 91.7, 75.8, 69.8, 62.8, 51.1, 25.9, 18.3, 8.7, -5.3; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{35}O_4Si$ 379.2305; found 379.2303.

7.3.63. Synthesis of Acid 693



Acid 693. 2-methyl-2-butene (0.04 mL, 0.40 mmol, 2.0 equiv) was added to a solution of aldehyde **699** (75 mg, 0.20 mmol, 1.0 equiv) in a 4:1 mixture of ^{t}BuOH : H_2O (10 mL) followed by the addition of NaH_2PO_4 (166 mg, 1.40 mmol, 7.0 equiv)) and $NaClO_2$ (125 mg, 1.40 mmol, 7.0 equiv). The reaction mixture was stirred a 25 ºC for 4 h. After this time brine was added and the aqueous phase was extracted with EtOAc. The organic phase was washed with dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to obtain acid **693** (78 mg, quantitative) as a colorless oil which did not required further purification: R_f = 0.20 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = + 29.4 (*c* 0.35, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 5 H), 5.85 (dd, *J* = 15.4, 4.3 Hz, 1 H), 5.64 (dd, *J* = 15.4, 8.2 Hz, 1 H), 4.74 – 4.63 (m, 3 H), 4.56 – 4.42 (m, 2 H), 4.22 – 4.16 (m, 2 H), 2.72 – 2.63 (m, 1 H), 1.23 (d, *J* = 7.1 Hz, 3 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.06 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 137.7, 135.5, 128.4, 127.9, 127.8, 125.6, 91.7, 69.8, 62.7, 44.5, 25.9, 25.7, 18.3, 11.9, -5.3; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{35}O_5Si$ 395.2254; found 395.2252.

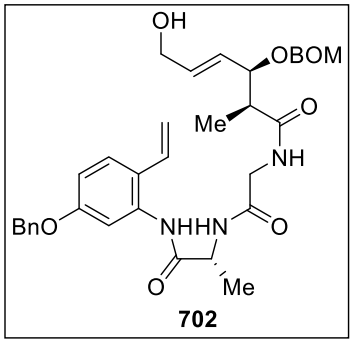
7.3.64. Synthesis of Peptide 701



Peptide 701. To a solution of peptide **700** (111 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added piperidine (0.12 mL, 1.25 mmol, 5.0 equiv) and the reaction mixture was stirred at 25 ºC 3 h. After this time, the organic solvent was removed under reduced pressure and the resulting crude amine (~0.25 mmol) was used in the next step without purification. DIPEA (0.1 mL, 0.62 mmol, 2.5 equiv) was added to a solution of crude amine **692** (~0.25 mmol), acid **693** (146 mg, 0.37 mmol, 1.5 equiv), HATU (234 mg, 0.62 mmol, 2.5 equiv) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 15 h and after this time, the reaction was diluted with CH2Cl2 and a saturated aqueous NH_4Cl solution was added. Ater decantation of the organic phase, the aqueous phase was extractes with EtOAc and the organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes → 60% EtOAc in hexanes) to obtain peptide **701** (80 mg, 45% over 2 steps) as a pale yellow oil: R_f = 0.55 (silica gel, 80% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = – 9.8 (*c* 0.18, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (bs, 1 H), 7.72 (d, *J* = 2.5 Hz, 1 H), 7.44 – 7.27 (m, 12 H), 7.09 (d, *J* = 7.5 Hz, 1 H), 6.83 – 6.73 (m, 2 H), 6.21 (t, *J* = 5.5 Hz, 1 H), 5.78 (dt, *J* = 15.6, 4.6 Hz, 1 H), 5.62 – 5.48 (m, 3 H), 5.34 (dd, *J* = 11.1, 1.0 Hz, 1 H),

4.84 (s, 2 H), 4.65 – 4.58 (m, 3 H), 4.22 – 4.14 (m, 3 H), 3.67 (dd, *J* = 17.1, 4.8 Hz, 1 H), 2.48 – 2.36 (m, 1 H), 1.40 (d, *J* = 7.0 Hz, 3 H), 1.04 (d, *J* = 7.1 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 170.1, 169.9, 158.9, 138.3, 136.7, 136.4, 135.4, 131.3, 128.6, 128.5, 128.0, 127.9, 127.6, 124.4, 122.6, 116.2, 112.5, 108.5, 92.8, 71.2, 70.1, 62.8, 49.6, 44.3, 38.6, 29.7, 25.8, 18.4, 12.8, -3.6, -5.3; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{41}H_{56}N_3O_7Si$ 730.3888; found 730.3886.

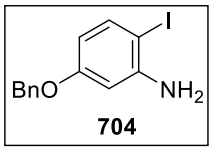
7.3.65. Synthesis of Allylic Alcohol 702



702

Allylic Alcohol 702. TBAF (0.2 mL, 1.0 M in THF, 0.20 mmol, 2.0 equiv) was added to a solution of silyl derivative **701** (75 mg, 0.10 mmol, 1.0 equiv) in THF (5 mL) at 25 ºC and the resulting reaction mixture was stirred at this temperature for 5 h. After this time, the organic solvent was removed under reduce pressure and the resulting residue was purified by flash column chromatography (silica gel, 8% MeOH in CH_2Cl_2) to obtain alcohol derivative **702** (47 mg, 74%) as a white solid: R_f = 0.15 (silica gel, 100% EtOAc); $[\alpha]^{25}{}_D$ = – 15.1 (*c* 0.20, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 7.53 (d, *J* = 8.7 Hz, 1 H), 7.44 – 7.39 (m, 2 H), 7.38 – 7.23 (m, 8 H), 7.06 (d, *J* = 2.6 Hz, 1 H), 6.89 (dd, *J* = 8.7, 2.6 Hz, 1 H), 6.79 (dd, *J* = 17.5, 11.0 Hz, 1 H), 5.82 (dddd, *J* = 8.5, 7.9, 4.0, 1.7 Hz, 1 H), 5.65 – 5.56 (m, 2 H), 5.19 (dd, *J* = 11.1, 1.3 Hz, 1 H), 5.06 (s, 2 H), 4.81 – 4.64 (m, 3 H), 4.61 – 4.48 (m, 2 H), 4.26 – 4.19 (m, 1 H), 4.04 (dd, *J* = 5.0, 1.4 Hz, 2 H), 3.87 (dt, *J* = 26.8, 16.6 Hz, 2 H), 2.63 (p, *J* = 6.9 Hz, 1 H), 1.45 (d, *J* = 7.2 Hz, 3 H), 1.17 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, MeOD) δ 175.4, 172.6, 170.1, 158.7, 138.0, 137.1, 134.9, 131.6, 128.1, 127.9, 127.6, 127.5, 127.3, 127.2, 126.9, 126.4, 125.9, 113.4, 112.9, 112.1, 91.5, 78.1, 69.7, 69.4, 61.4, 45.2, 42.2, 23.4, 16.9, 12.3; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{35}H_{42}N_3O_7$ 616.3023; found 616.3021.

7.3.66. Synthesis of Aniline 704

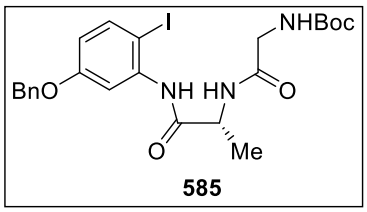


704

Aniline 704. To a solution of nitro derivative **605** (3.0 g, 8.45 mmol, 1.0 equiv) in EtOH (72 mL) was added a solution of NH_4Cl (2.3 g, 42.24 mmol, 5.0 equiv) in water (48 mL) followed by Zn dust (8.3 g, 126.7 mmol, 15.0 equiv) in ten portions of ~800 mg each over 30 min at 25 ºC. The mixture was stirred at this temperature for 12 h and then the reaction mixture was diluted with CH_2Cl_2 and water, filtered and rinsed with CH_2Cl_2. The filtrate was diluted with water and extracted with CH_2Cl_2, and the organic phase washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain aniline **704** (2.4 g, 86%) as a yellow oil: R_f = 0.40 (silica gel, 30% EtOAc in hexanes);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 5 H), 7.06 (t, *J* = 8.0 Hz, 1 H), 6.40 (dd, *J* = 8.0, 1.5 Hz, 1 H), 6.34 – 6.28 (m, 1 H), 5.03 (s, 2 H), 3.65 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 146.4, 137.2, 130.2, 128.6, 127.9, 127.5,

108.8, 105.8, 102.7, 69.9; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{13}INO$ 326.0042; found 326.0041.

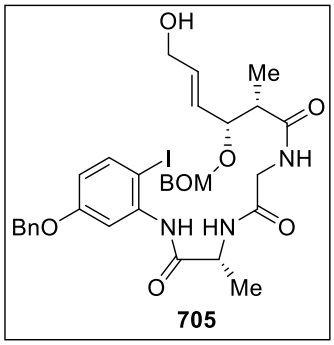
7.3.67. Synthesis of Dipeptide 585



585

Dipeptide 585. To a solution of aniline **704** (1.7 g, 5.44 mmol, 1.0 equiv) and Boc-Gly-D-Ala-OH (**608**) (1.7 mg, 7.08 mmol, 1.3 equiv) in DMF (5 mL) was added HATU (3.1 g, 8.17 mmol, 1.5 equiv) and DIPEA (1.88 mL, 10.89 mmol, 2.0 equiv) and the mixture was stirred for 15 h at 25 ºC. After this time, the reaction mixture was diluted with CH_2Cl_2 and washed sequentially with 1 N HCl and saturated aqueous $NaHCO_3$ solution. The organic layer was separated, washed with brine and dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) to obtain dipeptide **585** (2.3 g, 79%) as a white solid: R_f = 0.82 (silica gel, 100% EtOAc); $[\alpha]^{25}{}_D$ = + 18.44 (*c* 0.85, CH_2Cl_2); mp = 104-105 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (bs, 1 H), 7.48 – 7.32 (m, 5 H), 7.20 (t, *J* = 8.1 Hz, 1 H), 7.09 (d, *J* = 7.4 Hz, 1 H), 6.86 (bs, 1 H), 6.74 (dd, *J* = 8.2, 1.7 Hz, 1 H), 5.26 (t, *J* = 5.6 Hz, 1 H), 5.05 (s, 2 H), 4.67 (p, *J* = 7.2 Hz, 1 H), 3.85 (d, *J* = 5.5 Hz, 2 H), 1.48 (d, *J* = 7.0 Hz, 3 H), 1.46 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 163.6, 159.3, 156.4, 138.9, 136.9, 129.7, 128.6, 127.9, 127.5, 112.5, 111.3, 106.6, 69.9, 49.8, 34.5, 28.3, 24.1, 17.5; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{29}IN_3O_5$ 554.1152; found 554.1151.

7.3.68. Synthesis of Peptide 705

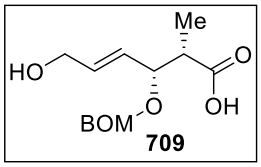


705

Peptide 705. Dipeptide **585** (560 mg, 1.01 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was treated with TFA (5.0 mL) in exactly the same manner as previously described for synthesis of **612**. A solution of the ammonium salt and acid **693** (559 mg, 1.42 mmol, 1.0 equiv), in CH_2Cl_2 (15 mL) was treated with HATU (962 mg, 2.53 mmol, 2.5 equiv) and DIPEA (0.4 mL, 4.05 mmol, 4.0 equiv) and the resulting reaction mixture was stirred at 25 ºC for 15 h. After this time, a saturated aqueous NH_4Cl solution was added and the organic layer was separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel 5% MeOH in CH_2Cl_2) to obtain **705** (238 mg, 33% over two steps) as a white foam: R_f = 0.20 (silica gel, 100% EtOAc); $[\alpha]^{25}{}_D$ = + 9.73 (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD) δ 7.44 – 7.39 (m, 3 H), 7.37 – 7.24 (m, 7 H), 7.21 – 7.14 (m, 2 H), 6.73 (dt, *J* = 7.1, 2.3 Hz, 1 H), 5.75 (dt, *J* = 15.5, 5.0 Hz, 1 H), 5.60 (dddd, *J* = 15.5, 8.3, 3.4, 1.8 Hz, 1 H), 5.05 (s, 2 H), 4.81 – 4.67 (m, 3 H), 4.57 – 4.46 (m, 2 H), 4.26 – 4.20 (m, 1 H), 4.01 (dd, *J* = 5.0, 1.4 Hz, 2 H), 3.93 (d, *J* = 16.4 Hz, 1 H), 3.76

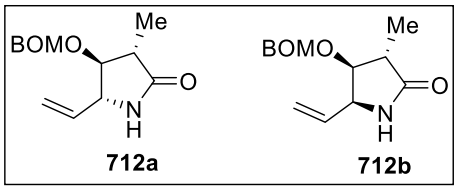
(d, *J* = 16.4 Hz, 1 H), 2.64 (p, *J* = 6.9 Hz, 1 H), 1.41 (d, *J* = 7.2 Hz, 3 H), 1.19 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, MeOD) δ 175.5, 171.7, 170.1, 159.2, 139.3, 138.0, 137.2, 135.0, 129.2, 128.1, 127.9, 127.7, 127.6, 127.5, 127.3, 127.2, 126.8, 112.4, 110.5, 106.8, 91.4, 78.1, 69.6, 69.4, 61.4, 49.6, 45.2, 42.4, 16.9, 12.4; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{33}H_{39}IN_3O_7$ 716.1833; found 716.1832.

7.3.69. Synthesis of Acid 709



Acid 709. TBAF (2.4 mL, 1.0 M in THF, 1.20 mmol, 2.0 equiv) was added to a solution of silyl derivative **693** (470 mg, 1.20 mmol, 1.0 equiv) in THF (10 mL) at 0 ºC. The reaction mixture was stirred at 25 ºC for 6 h. After this time, the organic solvent was removed under reduced pressure and the resulting crude residue was purified by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to obtain acid **709** (336 mg, quantitative) as a yellow oil: R_f = 0.12 (silica gel, 100% EtOAc); $[\alpha]^{25}_D$ = + 23.2 (*c* 0.46, MeOD); ^{1}H NMR (400 MHz, MeOD) δ 7.38 – 7.24 (m, 5 H), 5.87 (dtd, *J* = 15.6, 5.0, 0.7 Hz, 1 H), 5.66 (ddt, *J* = 15.5, 7.9, 1.6 Hz, 1 H), 4.78 (d, *J* = 6.9 Hz, 1 H), 4.71 – 4.66 (m, 2 H), 4.54 – 4.43 (m, 2 H), 4.13 – 4.06 (m, 2 H), 2.60 (qd, *J* = 7.1, 5.8 Hz, 1 H), 1.21 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, MeOD) δ 176.6, 137.9, 134.3, 127.9, 127.8, 127.5, 127.3, 91.3, 77.1, 69.2, 61.4, 23.4, 12.5; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{21}O_5$ 281.1389; found 281.1388.

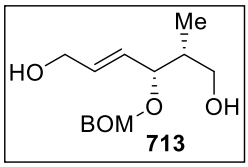
7.3.70. Synthesis of Lactames 712a and 712b



Lactames 712a and 712b. CCl_3CN (0.3 mL, 2.99 mmol, 2.5 equiv) and DBU (0.09 mL, 0.60 mmol, 0.5 equiv) were added to a solution of acid **709** (336 mg, 1.20 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) at 0 ºC. The reaction mixture was stirred at 25 ºC for 3 h. After this time, the organic solvent was removed under reduced pressure to obtain the corresponding crude bistrichloroacetoimidate **710** (~1.2 mmol) as a dark brown oil which was used in the next step without purification. Crude bistrichloroacetoimidate **710** obtained above (~26 mg, ~0.05 mmol, 1.0 equiv), $PdCl_2(PhCN)_2$ (2 mg, 0.005 mmol, 0.1 equiv) and p-benzoquinone (2.5 mg, 0.02 mmol, 0.5 equiv) were dissolved in CH_2Cl_2 (2 mL) and the reaction mixture was stirred at 45 ºC for 15 h. Then, the organic solvent was removed under reduced pressure and the obtained crude residue was purified by flash column chromatography (silica gel, 15% EtOAc in hexanes) to obtain lactames **712a** (60 mg, 20% over two steps) and **712b** (60 mg, 20% over two steps) as a colorless oils. Data for **712a**: R_f = 0.57 (30% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 22.56 (*c* 0.35, CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD) δ 7.36 – 7.25 (m, 5 H), 5.98 (ddd, *J* = 17.2, 10.5, 6.7 Hz, 1 H), 5.45 (dt, *J* = 17.2, 1.3 Hz, 1 H), 5.31 (dt, *J* = 10.5, 1.2 Hz, 1 H), 4.84 (d, *J* = 3.3 Hz, 2 H), 4.69 (tt, *J* = 6.6, 1.2 Hz, 1 H), 4.63 (d, *J* = 3.3 Hz, 2 H), 3.95 (dd, *J* = 7.7, 6.6 Hz, 1 H), 2.77 (p, *J* = 7.3 Hz, 1 H), 1.29 (d, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, MeOD) δ 177.3, 137.6, 134.3, 128.0, 127.6, 127.4, 118.1, 94.2, 84.1, 83.1, 69.5, 41.9, 12.5; Data for **712b:**

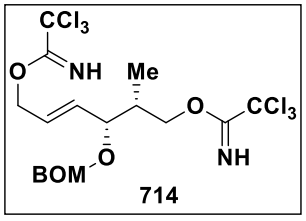
R_f = 0.55 (30% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 9.7 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD) δ 7.37 – 7.25 (m, 5 H), 6.05 (ddd, *J* = 17.3, 10.6, 6.9 Hz, 1 H), 5.42 (dt, *J* = 17.3, 1.4 Hz, 1 H), 5.37 (dt, *J* = 10.6, 1.3 Hz, 1 H), 5.11 – 5.06 (m, 1 H), 4.81 (d, *J* = 3.1 Hz, 2 H), 4.61 (s, 2 H), 4.26 (t, *J* = 5.7 Hz, 1 H), 2.71 (qd, *J* = 7.5, 5.7 Hz, 1 H), 1.27 (d, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, MeOD) δ 178.3, 137.7, 131.9, 128.1, 127.5, 127.4, 118.5, 93.9, 81.3, 80.4, 69.7, 40.7, 11.9; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{20}NO_3$ 262.1443; found 262.1441.

7.3.71. Synthesis of Diol 713



Diol 713. Silyl eter **698** (197 mg, 0.52 mmol, 1.0 equiv) was dissolved in THF (10 mL) and to this solution was added TBAF (1.0 mL, 1.0 M in THF, 1.04 mmol, 2.0 equiv) at 0 ºC. The reaction mixture was stirred at 25 ºC for 5.5 h and then the organic solvent was removed under reduced pressure to obtain a crude residue which was purified by flash column chromatography (70% EtOAc in hexanes) to obtain diol **713** (109 mg, 79%) as a colorless oil: R_f = 0.45 (100% EtOAc); $[\alpha]^{25}_D$ = + 27.7 (*c* 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD) δ 7.36 – 7.24 (m, 5 H), 5.82 (dt, *J* = 15.6, 5.1 Hz, 1 H), 5.63 (dd, *J* = 15.6, 7.9 Hz, 1 H), 4.78 (d, *J* = 6.8 Hz, 1 H), 4.69 (dd, *J* = 9.2, 2.4 Hz, 2 H), 4.53 (d, *J* = 11.7 Hz, 1 H), 4.19 (dd, *J* = 7.8, 5.1 Hz, 1 H), 4.08 (d, *J* = 5.1 Hz, 2 H), 3.64 (dd, *J* = 10.6, 6.0 Hz, 1 H), 3.42 (dd, *J* = 10.6, 6.7 Hz, 1 H), 3.31 (dt, *J* = 3.2, 1.6 Hz, 1 H), 1.84 – 1.73 (m, 1 H), 1.00 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, MeOD) δ 137.9, 133.4, 128.6, 127.9, 127.7, 127.3, 91.6, 77.3, 69.2, 63.8, 61.5, 40.7, 11.1; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{23}O_4$ 267.1596; found 267.1595.

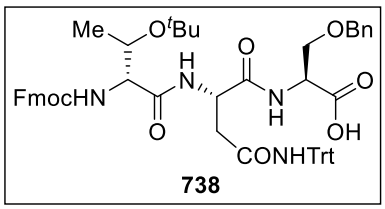
7.3.72. Synthesis of Bis(trichloroacetimidate) 714



Bis(trichloroacetimidate) 714. CCl_3CN (0.10 mL, 0.92 mmol, 2.5 equiv) and DBU (0.03 mL, 0.18 mmol, 0.5 equiv) were added to a solution of diol **713** (98 mg, 0.37 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 30 min and then at 25 ºC for 3.5 h. After this time, the solvent was removed under reduced pressure and the resulting crude mixture was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain bis(trichloroacetimidate) **714** (166 mg, 81%) as a pale yellow oil: R_f = 0.88 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 6.44 (*c* 0.35, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (bs, 1 H), 8.25 (bs, 1 H), 7.37 – 7.27 (m, 5 H), 5.93 (dt, *J* = 15.7, 5.4 Hz, 1 H), 5.82 (dd, *J* = 15.7, 7.4 Hz, 1 H), 4.85 – 4.78 (m, 3 H), 4.75 – 4.67 (m, 2 H), 4.54 (d, *J* = 11.7 Hz, 1 H), 4.31 (ddd, *J* = 12.7, 8.9, 5.8 Hz, 2 H), 4.21 (dd, *J* = 10.6, 5.7 Hz, 1 H), 2.24 – 2.12 (m, 1 H), 1.11 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 162.4, 137.8, 132.8, 128.5, 127.9, 127.7, 127.4, 92.3, 91.5, 91.4, 76.9, 70.9, 69.8, 68.5, 37.6, 12.3; HRMS (H-ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{23}Cl_6N_2O_4$ 552.9789; found 552.9788.

7.4. Experimental Procedures and Compound Characterization Related to the Celebesides

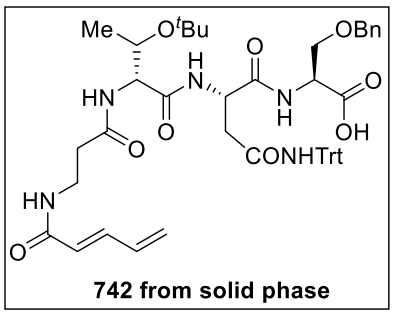
7.4.1. Synthesis of Peptide 738



738

Peptide 738. Release of a small amount of peptide from resin **737** (19 mg) by treatment with CH_2Cl_2/AcOH/TFE (3.0 mL, 7:2:1) gave the *N*-Fmoc protected tripeptide **738** (10 mg), which revealed a load of 0.55 mmol/g of resin **737**: white foam; $[\alpha]^{25}{}_D = -5.69$ (*c* 0.12, CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD) δ 8.55 (bs, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 7.5 Hz, 2 H), 7.61 (dd, *J* = 13.1, 7.5 Hz, 2 H), 7.37 (t, *J* = 7.5 Hz, 2 H), 7.31 – 7.15 (m, 20 H), 6.81 (d, *J* = 7.7 Hz, 1 H), 4.81 (dt, *J* = 8.0, 4.0 Hz, 1 H), 4.58 (t, *J* = 3.9 Hz, 1 H), 4.50 – 4.34 (m, 4 H), 4.29 (dd, *J* = 10.5, 6.5 Hz, 1 H), 4.21 – 4.08 (m, 2 H), 4.03 (dd, *J* = 6.2, 3.9 Hz, 1 H), 3.85 (dd, *J* = 9.7, 4.5 Hz, 1 H), 3.65 (dd, *J* = 9.7, 3.6 Hz, 1 H), 2.94 – 2.87 (m, 2 H), 2.83 – 2.75 (m, 1 H), 1.14 (s, 9 H), 1.06 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (100 MHz, MeOD) δ 171.6, 171.1, 170.7, 170.2, 156.8, 74.5, 72.8, 70.4, 69.1, 67.1, 66.6, 59.9, 52.9, 49.8, 38.2, 29.4, 27.3, 22.3, 18.1; HRMS (ESI-TOF) *m/z* calcd for $C_{56}H_{59}N_4O_9$ $[M + H]^+$ 931.4282 found 931.4280.

7.4.2. Synthesis of Peptide 742 from Solid Phase Synthesis

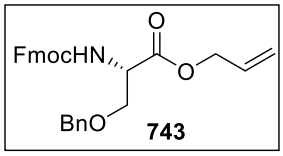


742 from solid phase

Peptide 742 from Solid Phase Synthesis. A 10 mL polypropylene syringe fitted with polyethylene porous disk charged with 2-chlorotrityl chloride (CTC) resin (200 mg, L=1.22 mmol/g, 1.0 equiv), was loaded with a solution of Fmoc-L-Ser(Bn)-OH **730** (200 mg, 0.48 mmol, 2.0 equiv) and DIPEA (0.10 mL, 0.60 mmol, 2.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 24 h, then the solution was unloaded and the resin was washed by shaking with dry DMF (5 x 3 mL). The resulting yellow resin was used in the next step. The polypropylene syringe loaded with the yellow resin was treated with a solution of 20% piperidine in DMF (3 x 3 mL x 10 min at 280 rpm). After the last run, the resin was washed with dry DMF (5 x 3 mL) and loaded with a solution of Fmoc-L-Asn(Trt)-OH **736** (286 mg, 0.48 mmol, 2.0 equiv), HOBt (65 mg, 0.48 mmol, 2.0 equiv) and DIC (0.10 mL, 0.60 mmol, 2.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 24 h, and then the solution was unloaded and the resin washed with dry DMF (5 x 3 mL). The resulting yellow resin was used in the next step. To a 10 mL polypropylene syringe fitted with polyethylene porus disk and loaded with the resulting Fmoc protected dipeptide was added a solution of 20% piperidine in DMF (3 x 3 mL x 10 min at 280 rpm). After the last run, the resin was washed with dry DMF (5 x 3 mL) and treated with a solution of Fmoc-D-Thr(^{t}Bu)-OH **732** (191 mg, 0.48 mmol, 2.0 equiv), HOBt (65 mg, 0.48 mmol, 2.0 equiv) and DIC (0.10 mL, 0.60 mmol, 2.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 24 h, and then the solution was unloaded and the resin washed with dry DMF

(5 x 3 mL). To the same polypropylene syringe was added a solution of 20% piperidine in DMF (3 x 3 mL x 10 min at 280 rpm). After the last run, the resin was washed with dry DMF (5 x 3 mL) and treated with a solution of β-Ala-OH (**739**) (149 mg, 0.48 mmol, 2.0 equiv), HOBt (65 mg, 0.48 mmol, 2.0 equiv) and DIC (0.10 mL, 0.60 mmol, 2.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 24 h, and then the solution was unloaded and the resin washed with dry DMF (5 x 3 mL). Then, to the same polypropylene syringe was added a solution of 20% piperidine in DMF (3 x 3 mL x 10 min at 280 rpm). After the last run, the resin was washed with dry DMF (5 x 3 mL) and treated with a solution of 2,4-pentadienoic acid **734** (47 mg, 0.48 mmol, 2.0 equiv), HOBt (65 mg, 0.48 mmol, 2.0 equiv) and DIC (0.10 mL, 0.60 mmol, 2.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 24 h, and then the solution was unloaded and the resin washed with dry DMF (5 x 3 mL). The resulting yellow resin was treated with a solution of CH_2Cl_2/AcOH/TFE (7:2:1, 3 mL) for 30 min. After that, the solution was collected and the resin washed with CH_2Cl_2 (2 x 3 mL). All the collected organic solvents were evaporated under reduced pressure and the resulting peptide **742** (134 mg, 65 % overall yield from CTC resin) was obtained as a pale yellow foam which not required further purification: R_f = 0.25 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}{}_D$ = – 15.2 (*c* 0.23, CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD) δ 8.60 (bs, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.80 (d, *J* = 7.6 Hz, 1 H), 7.29 – 7.17 (m, 20 H), 7.08 (dd, *J* = 15.2, 11.0 Hz, 1 H), 6.40 (dt, *J* = 16.9, 10.5 Hz, 1 H), 5.89 (d, *J* = 15.2 Hz, 1 H), 5.57 – 5.50 (m, 1 H), 5.43 – 5.38 (m, 1 H), 4.80 (dt, *J* = 11.0, 4.0 Hz, 1 H), 4.60 (t, *J* = 4.0 Hz, 1 H), 4.38 – 4.33 (m, 1 H), 4.10 (dd, *J* = 6.4, 3.4 Hz, 1 H), 3.87 (dd, *J* = 9.7, 4.4 Hz, 1 H), 3.67 (dd, *J* = 9.7, 3.6 Hz, 1 H), 3.49 (dt, *J* = 9.6, 6.3 Hz, 1 H), 3.37 – 3.32 (m, 2 H), 3.04 – 2.97 (m, 1 H), 2.77 (dd, *J* = 16.1, 5.0 Hz, 1 H), 2.44 (t, *J* = 6.4 Hz, 2 H), 1.14 (s, 9 H), 1.08 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, MeOD) δ 172.6, 171.7, 171.4, 170.5, 170.4, 167.2, 144.5, 140.5, 137.8, 135.1, 128.7, 127.9, 127.4, 127.3, 127.3, 126.4, 124.7, 123.1, 74.5, 72.8, 70.4, 69.3, 66.6, 58.7, 53.1, 49.6, 37.9, 35.6, 35.2, 27.3, 18.5; HRMS (ESI-TOF) *m/z* calcd for $C_{49}H_{58}N_5O_9$ $[M + H]^+$ 860.4235, found 860.4233.

7.4.3. Synthesis of Fmoc-L-Ser(Bn)-OAllyl 743

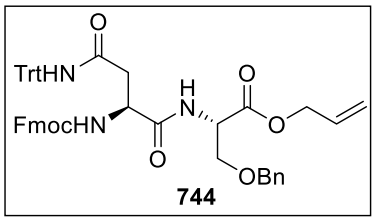


743

Fmoc-L-Ser(Bn)-OAllyl 743. To a solution of Fmoc-L-Ser(Bn)-OH **730** (2.5 g, 5.99 mmol, 1.0 equiv) and allylic alcohol (0.53 mL, 7.79 mmol, 1.3 equiv) in CH_2Cl_2 (120 mL) at 0 ºC was added sequentially HOBt·H_2O (1.6 g, 11.98 mmol, 2.0 equiv) and DIC (2.32 mL, 14.97 mmol, 2.5 equiv) and the mixture was stirred for 15 h at 25 ºC. After this time, the reaction was diluted with H_2O and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes → 10% EtOAc in hexanes) to obtain **743** (2.2 g , 79%) as a white foam: R_f = 0.25 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = – 9.1 (*c* 0.07, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.78 (d, *J* = 7.5 Hz, 1 H), 7.63 (d, *J* = 6.6 Hz, 1 H), 7.41 (t, *J* = 7.5 Hz, 1 H), 7.36 – 7.27 (m, 4 H), 5.90 (ddd, *J* = 22.7, 10.9, 5.7 Hz, 1 H), 5.72 (d, *J* = 8.7 Hz, 1 H), 5.34 (dd, *J* =

17.2, 1.0 Hz, 1 H), 5.25 (dd, *J* = 10.4, 0.9 Hz, 1 H), 4.68 (d, *J* = 5.6 Hz, 1 H), 4.55 (d, *J* = 13.8 Hz, 1 H), 4.44 (dd, *J* = 10.5, 7.3 Hz, 1 H), 4.37 (dd, *J* = 10.4, 7.4 Hz, 1 H), 4.26 (t, *J* = 7.1 Hz, 1 H), 3.96 (dd, *J* = 9.4, 3.0 Hz, 1 H), 3.75 (dd, *J* = 9.4, 3.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.0, 156.1, 143.8, 141.3, 137.5, 131.6, 128.5, 127.9, 127.7, 127.7, 127.1, 125.2, 120.0, 118.7, 73.4, 69.9, 67.3, 66.2, 54.5, 47.2; HRMS (ESI-TOF) *m/z* calcd for $C_{28}H_{28}NO_5$ $[M + H]^+$ 458.1968, found 458.11966.

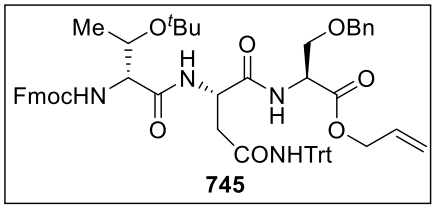
7.4.4. Synthesis of Fmoc-L-Asn(Trt)-L-Ser(Bn)-OAllyl 744



744

Fmoc-L-Asn(Trt)-L-Ser(Bn)-OAllyl 744. To a solution of Fmoc-L-Ser(Bn)-OAllyl **743** (1.0 g, 2.19 mmol, 1.0 equiv) in CH_2Cl_2 (60 mL) was added piperidine (1.1 mL, 10.93 mmol, 5.0 equiv) and the reaction mixture was stirred at 25 ºC for 2 h. After this time, the organic solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 60% EtOAc in hexanes) to obtain the corresponding amine (373 mg, 73%) as a colorless foam: R_f = 0.10 (silica gel, 80% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = – 18.7 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 5 H), 5.90 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1 H), 5.31 (dq, *J* = 17.2, 1.5 Hz, 1 H), 5.23 (dq, *J* = 10.5, 2.6, 1.3 Hz, 1 H), 4.65 – 4.62 (m, 2 H), 4.54 (d, *J* = 6.5 Hz, 2 H), 3.80 – 3.74 (m, 1 H), 3.74 – 3.66 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 137.9, 131.9, 128.4, 127.7, 127.6, 118.5, 73.3, 72.1, 65.7, 55.0; HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{18}NO_3$ $[M + H]^+$ 236.1287, found 236.1285. Amine obtained above (220 mg, 0.94 mmol, 1.0 equiv), Fmoc-L-Asn(Trt)-OH **736** (558 mg, 0.94 mmol, 1.0 equiv), HOBt·H_2O (190 mg, 1.40 mmol, 1.5 equiv) and EDC·HCl (358 mg, 1.87 mmol, 2.0 equiv) were dissolved in CH_2Cl_2 (40 mL) and the mixture was stirred at 25 ºC for 12 h. After this time, a saturated aqueous $NaHCO_3$ solution was added and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were washed sequentially with a saturated aqueous NH_4Cl solution and brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes → 40% EtOAc in hexanes) to obtain to obtain **744** (609 mg, 80%, 58% overall yield from **743**) as a white foam: R_f = 0.88 (silica gel, 80% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = – 12.4 (*c* 0.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.74 (m, *J* = 7.5, 0.7 Hz, 2 H), 7.55 (dd, *J* = 5.9, 1.6 Hz, 2 H), 7.39 (t, *J* = 7.4 Hz, 2 H), 7.32 – 7.16 (m, 23 H), 6.93 (bs, 1 H), 6.43 (d, *J* = 7.8 Hz, 1 H), 5.86 (ddd, *J* = 16.1, 10.9, 5.7 Hz, 1 H), 5.30 (dd, *J* = 17.2, 1.4 Hz, 1 H), 5.22 (ddd, *J* = 10.5, 2.5, 1.2 Hz, 1 H), 4.73 – 4.55 (m, 4 H), 4.46 – 4.40 (m, 1 H), 4.38 – 4.31 (m, 3 H), 4.18 (t, *J* = 7.2 Hz, 1 H), 3.88 (dd, *J* = 9.4, 3.3 Hz, 1 H), 3.53 (dd, *J* = 9.3, 3.3 Hz, 1 H), 3.12 (dd, *J* = 15.4, 2.9 Hz, 1 H), 2.69 (dd, *J* = 15.6, 5.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.3, 169.6, 156.3, 144.3, 143.9, 143.7, 141.3, 137.4, 131.6, 128.8, 128.7, 128.4, 128.0, 127.7, 127.6, 127.1, 125.2, 120.0, 118.6, 73.2, 70.9, 69.2, 67.4, 66.1, 53.1, 51.5, 47.1, 38.3; HRMS (ESI-TOF) *m/z* calcd for $C_{51}H_{48}N_3O_7$ $[M + H]^+$ 814.3492, found 814.3490.

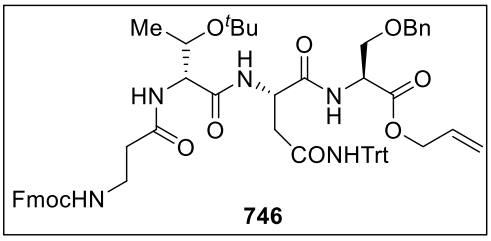
7.4.5. Synthesis of Fmoc-D-Thr(ᵗBu)-L-Asn(Trt)-L-Ser(Bn)-OAllyl 745



745

Fmoc-D-Thr(ᵗBu)-L-Asn(Trt)-L-Ser(Bn)-OAllyl 745. To a solution of Fmoc-L-Asn(Trt)-L-Ser(Bn)-OAllyl **744** (498 mg, 0.61 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added piperidine (0.2 mL, 1.84 mmol, 3.0 equiv) and the reaction mixture was stirred at 25 ºC for 4 h. After this time, the organic solvent was removed under reduced pressure to obtain the corresponding amine as a white solid which was used in the next step without purification. To a solution of the crude amine obtained above (~0.61 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added Fmoc-D-Thr(ᵗBu)-OH **732** (316 mg, 0.80 mmol, 1.3 equiv) and $HOBt{\cdot}H_2O$ (124 mg, 0.92 mmol, 1.5 equiv) and the mixture was cooled to 0 ºC. Then, EDC·HCl (235 mg, 1.22 mmol, 2.0 equiv) was added and the reaction mixture was stirred at 25 ºC for 15 h. After this time, a saturated aqueous $NaHCO_3$ solution was added and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were washed sequentially with a saturated aqueous NH_4Cl solution and brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes → 40% EtOAc in hexanes) to obtain **745** (340 mg, 60% over two steps) as a white foam: R_f = 0.50 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = – 5.88 (*c* 0.06, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 6.6 Hz, 1 H), 7.76 (d, *J* = 7.5 Hz, 2 H), 7.73 (d, *J* = 13.3 Hz, 1 H), 7.59 (dd, *J* = 7.3, 3.8 Hz, 2 H), 7.39 (t, *J* = 7.4 Hz, 2 H), 7.32 – 7.16 (m, 22 H), 6.84 (s, 1 H), 5.94 (d, *J* = 4.8 Hz, 1 H), 5.86 (ddd, *J* = 22.8, 10.8, 5.6 Hz, 1 H), 5.30 (dd, *J* = 17.2, 1.4 Hz, 1 H), 5.21 (dd, *J* = 10.5, 1.2 Hz, 1 H), 4.80 (bs, 1 H), 4.71 – 4.55 (m, 3 H), 4.45 – 4.32 (m, 4 H), 4.21 (t, *J* = 7.2 Hz, 1 H), 4.14 (d, *J* = 5.6 Hz, 2 H), 3.84 (dd, *J* = 9.5, 3.7 Hz, 1 H), 3.53 (dd, *J* = 9.3, 3.3 Hz, 1 H), 3.03 (d, *J* = 13.7 Hz, 1 H), 2.78 (dd, *J* = 15.6, 7.2 Hz, 1 H), 1.19 (s, 9 H), 1.03 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.8, 169.5, 169.5, 156.0, 144.4, 144.0, 143.7, 141.3, 141.3, 137.5, 131.7, 128.8, 128.3, 127.9, 127.7, 127.6, 127.1, 127.1, 125.2, 120.1, 118.5, 75.4, 73.2, 70.9, 69.0, 67.0, 66.3, 66.0, 59.0, 53.1, 49.6, 47.2, 38.9, 28.2, 17.7; HRMS (ESI-TOF) *m/z* calcd for $C_{59}H_{63}N_4O_9$ $[M + H]^+$ 971.4595, found 971.4593.

7.4.6. Synthesis of Fmoc-β-Ala-D-Thr(ᵗBu)-L-Asn(Trt)-L-Ser(Bn)-OAllyl 746

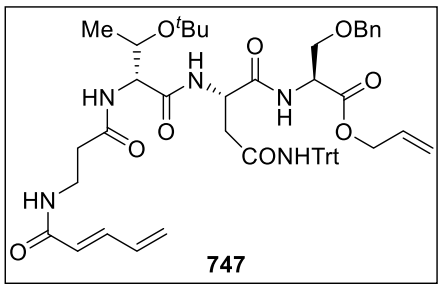


746

Fmoc-β-Ala-D-Thr(ᵗBu)-L-Asn(Trt)-L-Ser(Bn)-OAllyl 746. To a solution of Fmoc-D-Thr(ᵗBu)-L-Asn(Trt)-L-Ser(Bn)-OAllyl **745** (527 mg, 0.54 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added piperidine (0.16 mL, 1.63 mmol, 3.0 equiv) and the reaction mixture was stirred at 25 ºC for 3 h. After this time, the organic solvent was removed under reduced pressure to obtain the corresponding amine as a white foam which was used in the next step without purification. To a solution of the crude amine obtained above (~0.54 mmol, 1.0

equiv) in CH_2Cl_2 (20 mL) was added Fmoc-β-Ala-OH **739** (220 mg, 0.71 mmol, 1.3 equiv), HOBt·H_2O (110 mg, 0.82 mmol, 1.5 equiv), and EDC·HCl (208 mg, 1.09 mmol, 2.0 equiv) was added and the reaction mixture was stirred at 25 ºC for 15 h. After this time, a saturated aqueous $NaHCO_3$ solution was added and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were washed sequentially with a saturated aqueous NH_4Cl solution and brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes → 60% EtOAc in hexanes) to obtain **746** (285 mg, 57% over two steps) as a white foam: R_f = 0.40 (silica gel, 80% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = – 13.7 (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.0 Hz, 1 H), 7.74 (d, *J* = 7.1 Hz, 2 H), 7.68 (d, *J* = 8.1 Hz, 1 H), 7.59 (d, *J* = 7.5 Hz, 2 H), 7.38 (t, *J* = 7.3 Hz, 2 H), 7.32 – 7.17 (m, 22 H), 6.85 (bs, 1 H), 6.53 (d, *J* = 5.8 Hz, 1 H), 5.86 (ddd, *J* = 16.1, 11.0, 5.6 Hz, 1 H), 5.56 (t, *J* = 6.0 Hz, 1 H), 5.30 (dd, *J* = 17.2, 1.5 Hz, 1 H), 5.21 (dd, *J* = 10.4, 1.3 Hz, 1 H), 4.77 (td, *J* = 7.0, 3.1 Hz, 1 H), 4.67 (dt, *J* = 10.2, 3.0 Hz, 1 H), 4.61 (dd, *J* = 14.8, 5.6 Hz, 2 H), 4.45 – 4.32 (m, 4 H), 4.28 (dd, *J* = 5.8, 3.4 Hz, 1 H), 4.23 – 4.16 (m, 2 H), 3.84 (dd, *J* = 9.5, 3.7 Hz, 1 H), 3.53 (dd, *J* = 9.6, 3.7 Hz, 1 H), 3.45 – 3.40 (m, 2 H), 3.01 (dd, *J* = 15.7, 3.3 Hz, 1 H), 2.70 (dd, *J* = 15.8, 7.1 Hz, 1 H), 2.42 – 2.36 (m, 2 H), 1.18 (s, 9 H), 1.01 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 170.7, 169.9, 169.8, 169.5, 156.5, 144.4, 144.0, 141.3, 137.5, 131.6, 128.8, 128.4, 127.9, 127.7, 127.6, 127.1, 125.2, 119.9, 118.6, 75.3, 73.0, 70.9, 69.2, 66.7, 66.1, 65.8, 58.2, 53.1, 49.7, 47.3, 38.6, 36.9, 35.7, 28.2, 18.4; HRMS (ESI-TOF) *m/z* calcd for $C_{62}H_{68}N_5O_{10}$ $[M + H]^+$ 1042.4966, found 1042.4963

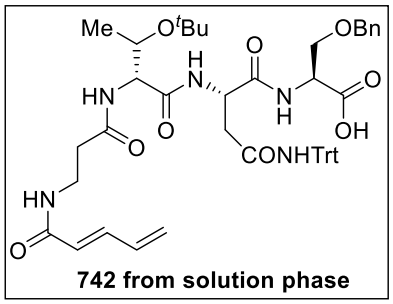
7.4.7. Synthesis of Peptide 747



Peptide 747. To a solution of Fmoc-β-Ala-D-Thr(^{t}Bu)-L-Asn(Trt)-L-Ser(Bn)-OAllyl **746** (100 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added piperidine (0.03 mL, 0.29 mmol, 3.0 equiv) and the reaction mixture was stirred at 25 ºC for 5 h. After this time, the organic solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 60% EtOAc in hexanes → 10% MeOH in CH_2Cl_2) to obtain the corresponding amine (80 mg, quantitative) as a colorless foam: R_f = 0.10 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}{}_D$ = – 8.11 (*c* 0.08, CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD) δ 8.04 (bs, 1 H), 7.30 – 7.18 (m, 20 H), 5.94 – 5.81 (m, 1 H), 5.35 – 5.27 (m, 1 H), 5.22 – 5.16 (m, 1 H), 4.79 (t, *J* = 5.6 Hz, 1 H), 4.68 (t, *J* = 4.0 Hz, 1 H), 4.65 – 4.55 (m, 2 H), 4.50 – 4.35 (m, 3 H), 4.09 (dd, *J* = 6.3, 3.5 Hz, 1 H), 3.88 (dd, *J* = 9.7, 4.4 Hz, 1 H), 3.66 (dd, *J* = 9.7, 3.8 Hz, 1 H), 3.13 – 3.07 (m, 1 H), 2.98 (t, *J* = 5.9 Hz, 2 H), 2.76 (dd, *J* = 15.9, 5.2 Hz, 1 H), 2.59 – 2.50 (m, 2 H), 1.16 (s, 9 H), 1.11 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (100 MHz, MeOD) δ 171.9, 171.7, 170.4, 170.3, 169.8, 144.5, 137.7, 131.8, 128.7, 128.7, 128.0, 127.5, 127.4, 126.4, 117.4, 74.5, 72.9, 70.4, 68.9, 65.7, 58.7, 53.1, 49.6, 44.5, 38.1, 36.3, 27.3, 18.3; HRMS (ESI-TOF) *m/z* calcd for $C_{47}H_{58}N_5O_8$ $[M + H]^+$ 820.4285, found 820.4283. To a solution of amine obtained

above (0.10 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added 2,4-pentadienoic acid **734** (13 mg, 0.13 mmol, 1.3 equiv), HOBt·H_2O (20 mg, 0.14 mmol, 1.5 equiv), and EDC·HCl (37 mg, 0.19 mmol, 2.0 equiv) was added and the reaction mixture was stirred at 25 ºC for 15 h. After this time, a saturated aqueous $NaHCO_3$ solution was added and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were washed sequentially with a saturated aqueous NH_4Cl solution and brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes → 100% EtOAc) to obtain **747** (45 mg, 53%) as a white foam: R_f = 0.35 (silica gel, 100% EtOAc); $[\alpha]^{25}{}_D$ = – 19.2 (*c* 0.21, CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD) δ 7.30 – 7.17 (m, 20 H), 7.08 (dd, *J* = 15.2, 11.0 Hz, 1 H), 6.41 (dt, *J* = 16.9, 10.5 Hz, 1 H), 5.93 – 5.80 (m, 2 H), 5.54 (d, *J* = 17.0 Hz, 1 H), 5.40 (d, *J* = 10.1 Hz, 1 H), 5.30 (ddd, *J* = 17.2, 3.1, 1.6 Hz, 1 H), 5.18 (ddd, *J* = 10.5, 2.7, 1.3 Hz, 1 H), 4.80 (t, *J* = 5.5 Hz, 1 H), 4.67 (t, *J* = 4.0 Hz, 1 H), 4.62 – 4.56 (m, 2 H), 4.52 – 4.38 (m, 2 H), 4.34 (d, *J* = 3.3 Hz, 1 H), 4.10 (dd, *J* = 6.3, 3.4 Hz, 1 H), 3.87 (dd, *J* = 9.7, 4.3 Hz, 1 H), 3.65 (dd, *J* = 9.7, 3.8 Hz, 1 H), 3.47 (dd, *J* = 13.4, 6.7 Hz, 1 H), 3.37 – 3.32 (m, 1 H), 3.00 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.75 (dd, *J* = 16.0, 5.2 Hz, 1 H), 2.44 (t, *J* = 6.5 Hz, 2 H), 1.14 (s, 9 H), 1.09 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (100 MHz, MeOD) δ 172.6, 171.7, 170.5, 170.4, 169.7, 167.2, 144.5, 140.5, 137.6, 135.1, 131.8, 128.7, 128.7, 128.0, 127.5, 127.3, 126.4, 124.7, 123.1, 117.4, 74.5, 72.8, 70.4, 68.9, 66.6, 65.7, 58.7, 53.1, 49.7, 38.1, 35.7, 35.1, 27.4, 18.4; HRMS (ESI-TOF) *m/z* calcd for $C_{52}H_{62}N_5O_9$ $[M + H]^+$ 900.4548, found 900.4546.

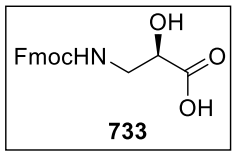
7.4.8. Synthesis of Peptide 742 from Solution Phase



742 from solution phase

Peptide 742 from Solution Phase. To a solution of peptide **747** (33 mg, 0.04 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added $Pd(PPh_3)_4$ (4 mg, 0.003 mmol, 0.1 equiv) and morpholine (0.01 mL, 0.04 mmol, 1.2 equiv). The resulting solution was stirred at 25 ºC for 1 h. Then, an aqueous 1M HCl solution was added and the aqueous phase was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford acid **742** (34 mg, quantitative) as a pale white foam which did not required further purification and whose spectroscopic and physical properties were identical to **742** obtained from solid phase synthesis: R_f = 0.25 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}{}_D$ = – 15.2 (*c* 0.23, CH_2Cl_2); HRMS (ESI-TOF) *m/z* calcd for $C_{49}H_{58}N_5O_9$ $[M + H]^+$ 860.4235 found 860.4233.

7.4.9. Synthesis of Fmoc-D-Isoserine 733

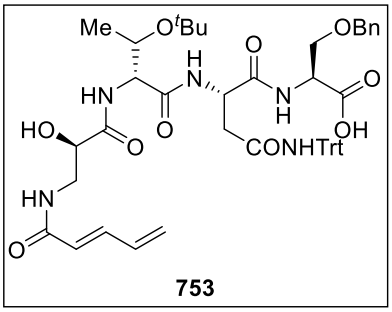


733

Fmoc-D-Isoserine 733. D-(+)-malic acid **748** (5.0 g, 37.31 mmol, 1.0 equiv) was dissolved in 2,2-DMP (37 mL) and TsOH (60 mg, 0.35 mmol, 0.01 equiv) was added. The reaction mixture was stirred for 5 h at 25 ºC. After this time, a saturated aqueous $NaHCO_3$

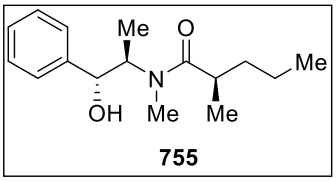
solution was added and the aqueous phase was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford the corresponding acetal (5.3 g) as a white solid which was used in the next step withouth further purification. Acetal obtained above (100 mg, 0.68 mmol, 1.0 equiv) was dissolved in $SOCl_2$ (0.8 mL) and the reaction mixture was refluxed for 1 h. After this time, excess of $SOCl_2$ was removed under reduced pressure to afford the corresponding acyl chloride (122 mg) as a brown oil which was used in the next step without further purification. Acyl chloride obtained above (122 mg, 0.64 mmol, 1.0 equiv) was dissolved in acetone (1 mL) and the mixture was cooled to 0 ºC. Then, a solution of NaN_3 (41 mg, 0.64 mmol, 1.0 equiv) in water (0.5 mL) was added dropwise and the reaction mixture was stirred for 1.5 h. After this time, the acetone was removed under reduced pressure. Then, the resulting residue was diluted with water and extracted with toluene three times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford acyl azide **749** as a yellow oil which was used in the next step without further purification. Acyl azide **749** obtained from the previous procedure (804 mg, 4.02 mmol, 1.0 equiv) was dissolved in toluene (12 mL) and the mixture was refluxed for 1 h. After this time, the solvent was removed under reduced pressure to obtain isocyanate **750** as a brown oil, which was used in the next step without further purification. Isocyanate **750** obtained above (583 mg, 3.41 mmol, 1.0 equiv) was dissolved in toluene (8 mL) and then FmocOH (1.0 g, 5.11 mmol, 1.5 equiv) was added. The reaction mixture was stirred for 15 h at 85 ºC. After this time, water was added and the aqueous phase was extracted with CH_2Cl_2. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford carbamate **751** (542 mg) as a white solid which was used in the next step without further purification. Carbamate **751** obtained above (542 mg, 1.48 mmol, 1.0 equiv) was dissolved in CH_3CN (10 mL) and to this solution was added 1N HCl solution (10 mL) at 25 ºC. The reaction mixture was heated slowly to 40 ºC and was stirred for 3 h at this temperature. After this time, the organic solvent was removed under reduced pressure to afford a white solid, which was recollected by filtration and washed with water. Then, the obtained solid was dissolved in acetone and stirred for 5 min. After this time, the solution was filter off and to the filtrate was added toluene (10 mL) and the resulting solution concentrated under reduced pressure until the precipitation of a white solid. Then, the solid was recollected by filtration, washed with toluene and dried under vaccumm to afford Fmoc-D-isoserine **733** (348 mg, 26% over 6 steps) as a white solid which did not required further purification: R_f = 0.1 (silica gel, 100% EtOAc); $[\alpha]^{25}{}_D$ = + 16.8 (*c* 0.35, MeOD); ^{1}H NMR (400 MHz, MeOD) δ 7.79 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.31 (td, *J* = 7.4, 1.1 Hz, 1H), 4.37 – 4.29 (m, 1H), 4.26 – 4.19 (m, 1H), 3.52 (dd, *J* = 13.9, 4.4 Hz, 1H), 3.37 (dd, *J* = 13.9, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, MeOD) δ 174.5, 157.6, 143.9, 141.2, 127.4, 126.8, 124.9, 119.5, 69.6, 66.6, 44.1; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{18}NO_5$ $[M + H]^+$ 328.1185, found 328.1184.

7.4.10. Synthesis of Peptide 753



Peptide 753. Peptide **753** was prepared from CTC resin (500 mg, L=1.22 mmol/g, 0.61 mmol, 1.0 equiv) according to the same procedure described above for the preparation of **742** by sequential coupling of Fmoc-L-Ser(Bn)-OH **730** (764 mg, 1.83 mmol, 3.0 equiv), Fmoc-L-Asn(Trt)-OH **736** (728 mg, 1.22 mmol, 2.0 equiv), Fmoc-D-Thr(^{t}Bu)-OH **732** (485 mg, 1.22 mmol, 2.0 equiv), Fmoc-D-isoserine **752** (399 mg, 1.22 mmol, 2.0 equiv) and 2,4-pentadienoic acid **734** (120 mg, 1.22 mmol, 2.0 equiv), to obtain peptide **753** (336 mg, 63%) as a pale yellow foam: R_f = 0.15 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}{}_D$ = – 5.71 (*c* 0.07, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 8.62 (bs, 1 H), 7.32 – 7.16 (m, 20 H), 7.16 – 7.08 (m, 1 H), 6.48 (dt, *J* = 17.3, 10.3 Hz, 1 H), 6.06 (d, *J* = 15.2 Hz, 1 H), 5.62 – 5.50 (m, 1 H), 5.48 – 5.41 (m, 1 H), 4.55 (t, *J* = 3.3 Hz, 1 H), 4.27 (d, *J* = 3.7 Hz, 1 H), 4.12 – 4.05 (m, 2 H), 3.87 (dd, *J* = 9.7, 4.4 Hz, 1 H), 3.69 (dd, *J* = 9.6, 3.4 Hz, 1 H), 3.62 (dd, *J* = 13.7, 5.8 Hz, 1 H), 3.52 (dd, *J* = 13.8, 4.0 Hz, 1 H), 2.99–2.94 (m, 1 H), 2.75 (dd, *J* = 16.1, 4.8 Hz, 1 H), 2.31 – 2.25 (m, 1 H), 2.22 – 2.16 (m, 1 H), 1.16 (s, 9 H), 1.02 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (100 MHz, MeOD) δ 173.4, 173.4, 171.4, 170.4, 170.1, 167.7, 144.5, 140.9, 137.9, 134.9, 128.7, 127.9, 127.5, 127.3, 127.2, 126.4, 124.4, 123.4, 74.7, 72.8, 70.9, 70.4, 69.3, 66.4, 57.9, 49.8, 42.9, 37.9, 29.4, 27.3, 18.2; HRMS (ESI-TOF) *m/z* calcd for $C_{49}H_{58}N_5O_{10}$ $[M + H]^+$ 876.4184, found 876.4182.

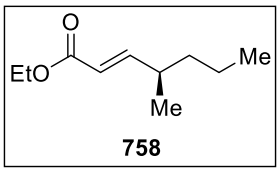
7.4.11. Synthesis of (R,R)-(-)-Pseudoephedrine 755



(*R*,*R*)-(-)-Pseudoephedrine 755. DIPA (13.5 mL, 96.12 mmol, 2.24 equiv) and *n*-BuLi (57 mL, 1.6 M in hexanes, 91.83 mmol, 2.14 equiv) were added to a solution of LiCl (10.8 g, 254 mmol, 5.93 equiv) in THF (60 mL) at -78 ºC. The resulting reaction mixture was stirred for 15 min at 0 ºC and after this time the reaction was cooled to -78 ºC. Then, a solution of **754** (10.7 g, 42.91 mmol, 1.0 equiv) in THF (30 mL) was added dropwise over 10 min and the reaction mixture was stirred for 1 h at -78 ºC, followed by 15 min at 0 ºC and 10 min at 25 ºC. After this time, the reaction was cooled to -78 ºC and MeI (4 mL, 64.37 mmol, 1.5 equiv) was added. The resulting mixture was stirred for 1 h at -78 ºC and 1 h at 0 ºC, quenched with a saturated aqueous NH_4Cl solution and the aqueous phase extracted with EtOAc twice. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 30% EtOAc in hexanes) to obtain **755** (9.2 g, 81%) as a colorless oil: R_f = 0.50 (silica gel, 70% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = – 14.3 (*c* 0.45, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 1H), 4.64 (d, *J* = 7.2 Hz, 1H), 4.28 (s, 1H), 2.79 (s, 1H), 2.59 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.72 – 1.58 (m, 1H), 1.33 – 1.23 (m, 1H), 1.20 (d, *J* = 7.0 Hz, 1H), 1.02 (d, *J* = 6.8 Hz, 1H), 0.92 – 0.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 142.7, 128.3, 127.5, 126.2, 77.2,

76.6, 36.4, 36.2, 20.6, 17.4, 14.5, 14.2; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{26}NO_2$ [M + H]$^+$ 264.1964, found 264.1962.

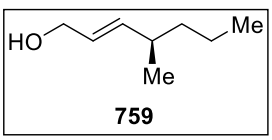
7.4.12. Synthesis of α,β-Unsaturated Ester 758



758

α,β-Unsaturated Ester 758. *n*-BuLi (87 mL, 1.6 M in hexanes, 140 mmol, 4.0 equiv) was added to a solution of DIPA (20 mL, 143 mmol, 4.1 equiv) in THF (60 mL) at -78 ºC and the resulting reaction mixture was stirred for 10 min at this temperature, followed by 10 min at 0 ºC. After this time, $BH_3{\cdot}NH_3$ (4.5 g, 147 mmol, 4.2 equiv) was added in one portion and the reaction mixture was stirred for 15 min at 0 ºC, 15 min at 25 ºC and then was cooled to 0 ºC. A solution of **755** (9.2 g, 34.93 mmol, 1.0 equiv) in THF (15 mL) was added over 30 min and the reaction mixture was stirred for 2 h at 25 ºC. After this time, the reaction was quenched by the addition of 3N HCl solution (90 mL) and was stirred for 30 min at 0 ºC. The aqueous phase was extracted with Et_2O four times and the combined organic layers were washed sequentially with 3N HCl solution (75 mL), 2N NaOH (75 mL) and brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to obtain the corresponding alcohol (~28.4 mmol) as a colorless oil which was used in the next step without purification. The crude alcohol obtained above (~28.4 mmol) was dissolved in CH_2Cl_2 (10 mL) and then PCC (10 g, 48.3 mmol, 1.7 equiv) was added to this solution. The reaction mixture was stirred for 2 h at 25 ºC and after this time, the crude mixture was filtered through a pad of celite and washed with CH_2Cl_2. To this solution of the crude aldehyde **756** in CH_2Cl_2 (~29 mmol, ~0.2 M solution) was added $Ph_3P{=}CO_2Et$ (20 g, 58.3 mmol, 2.0 equiv) and the resulting reaction mixture was stirred 15 h at 25 ºC. After this time the organic solvent was removed under reduced pressure and the resulting crude residue was purified by flash column chromatography (silica gel, 3% EtOAc in hexanes) to obtain **758** (2.8 g, 47% over 3 steps) as a colorless oil: R_f = 0.60 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = + 21.1 (*c* 0.35, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (dd, *J* = 15.7, 7.9 Hz, 1 H), 5.76 (dd, *J* = 15.7, 1.2 Hz, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 2.29 (dq, *J* = 13.5, 6.7 Hz, 1 H), 1.38 – 1.23 (m, 7 H), 1.03 (d, *J* = 6.7 Hz, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 154.7, 119.5, 60.2, 38.2, 36.3, 20.3, 19.4, 14.3, 14.1; HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{19}O_2$ [M + H]$^+$ 171.1385, found 171.1383.

7.4.13. Synthesis of Allylic Alcohol 759

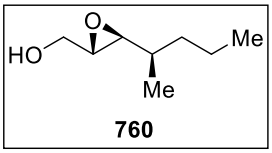


759

Allylic Alcohol 759. DIBAL-H (41 mL, 1.0 M in toluene, 41.0 mmol, 2.5 equiv) was added to a solution of **758** (2.8 g, 16.4 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) at -78 ºC and the reaction mixture was stirred for 1 h at this temperature. Then, the reaction was quenched by the dropwise addition of MeOH at -78 ºC and the mixture was allowed to reach 0 ºC, treated with a saturated aqueous Na^+/K^+ tartrate solution and diluted with CH_2Cl_2. The resulting mixture was vigorously stirred until a clear separation of both

organic and aqueous phases. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain allylic alcohol **759** (1.7 g, 81%) as a colorless oil: R_f = 0.35 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 5.91 (*c* 0.09, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 – 5.56 (m, 2 H), 4.11 – 4.08 (m, 2 H), 2.15 (dt, *J* = 12.6, 6.4 Hz, 1 H), 1.33 – 1.24 (m, 4 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 127.0, 63.9, 39.1, 36.1, 20.4, 20.4, 14.2; HRMS (ESI-TOF) *m/z* calcd for $C_8H_{17}O$ $[M + H]^+$ 129.1279, found 129.1277.

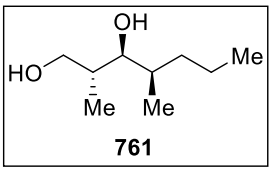
7.4.14. Synthesis of Epoxy Alcohol 760



760

Epoxy Alcohol 760. To a suspension of titanium tetraisopropoxide (0.9 mL, 3.05 mmol, 0.23 equiv) and 4Å molecular sieves (12 g) in CH_2Cl_2 (60 mL) was added (+)-L-DET (0.6 mL, 3.32 mmol, 0.25 equiv) at -50 ºC. After 15 min at this temperature, a solution of allylic alcohol **759** (1.7 g, 13.26 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was added dropwise, followed by the addition, after additional 30 min, of TBHP (3.6 mL, 5.5 M solution in decane, 19.89 mmol, 1.5 equiv) at the same temperature. After 15 h at this temperature, the reaction mixture was quenched with Me_2S (4.5 mL, 60.99 mmol, 4.6 equiv) at 0 ºC, filtered off and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain epoxy alcohol **760** (1.6 g, 84%) as a colourless oil: R_f = 0.45 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = – 21.0 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (d, *J* = 12.4 Hz, 1 H), 3.62 (d, *J* = 12.5 Hz, 1 H), 2.99 – 2.95 (m, 1 H), 2.72 (dd, *J* = 7.2, 2.4 Hz, 1 H), 1.86 (bs, 1 H), 1.39 – 1.29 (m, 4 H), 1.01 (d, *J* = 6.3 Hz, 3 H), 0.94 – 0.86 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.8, 60.6, 58.4, 35.9, 35.3, 20.4, 17.2, 14.3; HRMS (ESI-TOF) *m/z* calcd for $C_8H_{17}O_2$ $[M + H]^+$ 145.1229, found 145.1227.

7.4.15. Synthesis of Diol 761

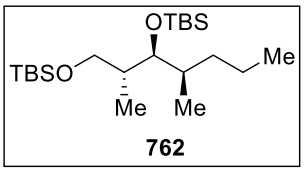


761

Diol 761. MeLi (69 mL, 1.6 M in Et_2O, 111 mmol, 10.0 equiv) was added at 0 ºC to a solution of CuI (10.6 g, 55.47 mmol, 5.0 equiv) in THF (100 mL) and the resulting mixture was stirred for 5 minutes. After this time, a solution of epoxy alcohol 24 (1.6 g, 11.09 mmol, 1.0 equiv) in THF (10 mL) was added at 0 ºC and the reaction was stirred at 25 ºC for 15 h. Then, the reaction was quenched by addition of MeOH at 0 ºC followed by the addition of saturated aqueous NH_4Cl solution. The aqueous phase was extracted with Et_2O twice and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to obtain a 3:1 mixture of opening products in 2- and 3- positions, respectively (~55.0 mmol). $NaIO_4$ (1.2 g, 5.55 mmol, 0.5 equiv) was added at 0 ºC to a solution of the

crude product obtained above in a 1:1 mixture of THF:H_2O (60 mL). The resulting suspension was stirred at 25 ºC for 15 h. After this time, the reaction mixture was diluted with water and the aqueous phase was extracted with Et_2O twice and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain diol **761** (1.1 g, 62% over 2 steps) as a colorless oil: R_f = 0.35 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 10.2 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (dd, *J* = 10.7, 3.3 Hz, 1 H), 3.66 (dd, *J* = 10.6, 7.9 Hz, 1 H), 3.48 (dd, *J* = 8.9, 2.6 Hz, 1 H), 2.44 (bs, 2 H), 1.92 – 1.81 (m, 1 H), 1.70 – 1.59 (m, 1 H), 1.40 – 1.25 (m, 3 H), 0.94 – 0.89 (m, 4 H), 0.87 (d, *J* = 6.8 Hz, 3 H), 0.81 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.8 60.6, 58.4, 35.9, 35.3, 20.4, 17.2, 14.3; HRMS (ESI-TOF) *m/z* calcd for $C_9H_{21}O_2$ $[M + H]^+$ 161.1542, found 161.1540.

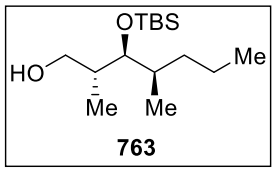
7.4.16. Synthesis of Bis(silyl ether) 762



762

Bis(silyl ether) 762. 2,6-Lutidine (2 mL, 17.16 mmol, 2.5 equiv) was added to a solution of diol **761** (1.1 g, 6.86 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at 0 ºC and the mixture was stirred for 10 min at this temperature. After this time, TBSOTf (3.9 mL, 17.16 mmol, 2.5 equiv) was added at 0 ºC and the reaction mixture was stirred at 25 ºC for 1.5 h. Then, the reaction mixture was diluted with water and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to obtain **762** (2.6 g, 97%) as a colorless oil: R_f = 0.80 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 11.5 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (dd, *J* = 9.8, 4.8 Hz, 1 H), 3.49 (dd, *J* = 6.6, 2.6 Hz, 1 H), 3.39 (dd, *J* = 9.8, 7.4 Hz, 1 H), 1.78 (ddd, *J* = 14.0, 6.9, 4.8 Hz, 1 H), 1.62 – 1.56 (m, 1 H), 1.36 – 1.12 (m, 5 H), 0.91 – 0.88 (m, 18 H), 0.88 – 0.86 (m, 4 H), 0.83 (d, *J* = 6.8 Hz, 3 H), 0.04 (d, *J* = 1.8 Hz, 6 H), 0.03 (d, *J* = 1.6 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.7, 40.3, 37.2, 35.7, 26.2, 25.9, 25.7, 20.8, 18.5, 18.3, 14.5, 14.3, -2.9, -3.8, -3.9, -5.3, -5.4; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{49}O_2Si_2$ $[M + H]^+$ 389.3271, found 389.3270.

7.4.17. Synthesis of Alcohol 763

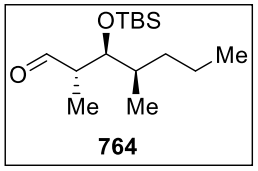


763

Alcohol 763. CSA (1.6 g, 6.79 mmol, 1.0 equiv) was added to a solution of **762** (2.6 g, 6.79 mmol, 1.0 equiv) in a mixture of CH_2Cl_2:MeOH (1:1, 150 mL) at 0 ºC and the reaction mixture was stirred at this temperature for 40 min. After this time, a saturated aqueous $NaHCO_3$ solution was added and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The

resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain **763** (1.1 g, 60%) as a colorless oil: R_f = 0.60 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 18.3 (*c* 0.60, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 – 3.55 (m, 2 H), 3.51 (dd, *J* = 5.4, 3.9 Hz, 1 H), 2.60 (bs, 1 H), 1.92 – 1.81 (m, 1 H), 1.68 – 1.58 (m, 1 H), 1.48 – 1.33 (m, 2 H), 1.29 – 1.07 (m, 3 H), 0.96 (d, *J* = 7.0 Hz, 3 H), 0.92 (s, *J* = 2.9 Hz, 9 H), 0.91 – 0.87 (m, 5 H), 0.11 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.3, 66.3, 38.1, 37.6, 35.3, 26.1, 20.9, 18.3, 16.4, 15.2, 14.4, -3.9, -4.1; HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{35}O_2Si$ $[M + H]^+$ 275.2406, found 275.2405.

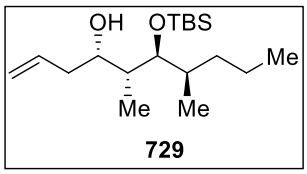
7.4.18. Synthesis of Aldehyde 764



764

Aldehyde 764. To a solution of alcohol **763** (1.0 g, 3.64 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was added Dess-Martin periodinane (3.0 g, 7.29 mmol, 2.0 equiv) at 0 ºC. The reaction mixture was stirred at 25 ºC for 3 h and, after this time, the reaction mixture was quenched with a 1:1 mixture of a saturated aqueous $NaHCO_3$ solution/$Na_2S_2O_3$ 1 M. The solution was stirred for 20 min and then, the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain **764** (940 mg, 95%) as a colorless oil: R_f = 0.80 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 11.4 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (d, *J* = 2.9 Hz, 1 H), 3.76 – 3.73 (m, 1 H), 2.58 – 2.50 (m, 1 H), 1.64 (dtd, *J* = 13.6, 6.8, 2.9 Hz, 1 H), 1.45 – 1.34 (m, 3 H), 1.29 – 1.19 (m, 2 H), 1.07 (d, *J* = 7.1 Hz, 3 H), 0.91 – 0.89 (m, 5 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.3, 66.3, 38.1, 37.6, 35.3, 26.1, 20.9, 18.3, 16.4, 15.2, 14.4, -3.9, -4.1; HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{33}O_2Si$ $[M + H]^+$ 273.2250, found 273.2251.

7.4.19. Synthesis of Polyketide Fragment 729

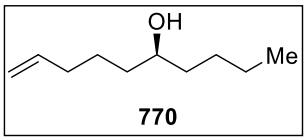


729

Polyketide Fragment 729. A solution of (-)-Icp_2BOMe (1.4 g, 4.31 mmol, 1.25 equiv) in Et_2O (5 mL) was cooled to 0 ºC and then allyl magnesium bromide (4.1 mL, 1.0 M in Et_2O, 4.14 mmol, 1.2 equiv) was added dropwise over 20 min and the mixture was stirred for 1 h at 25 ºC. After this time, the mixture was cooled to -78 ºC and then a solution of aldehyde **764** (940 mg, 3.45 mmol, 1.0 equiv) in Et_2O (2.5 mL) was added dropwise over 20 min. The resulting reaction mixture was stirred at -78 ºC for 1.5 h and then was stirred for 1h at 25 ºC. After this time, the system was cooled to 0 ºC and was added dropwise over 10 min a mixture a a 3.0 M aqueous NaOH solution (7 mL) and 30% H_2O_2 (3 mL), and was followed by the dropwise adittion over 3 min of a saturated queous $NaHCO_3$ solution (9 mL). The resulting mixture was stirred 15 h at 25 ºC. Then, the organic layer was separated and the aqueous phase was extracted with Et_2O twice. The combined organic layers were washed with brine, dried

over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 2% EtOAc in hexanes) to obtain polyketide fragment **729** (1.0 g, 92%) as a colorless oil: R_f = 0.50 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{25}_D$ = + 23.9 (*c* 0.21, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.1, 10.2, 7.1 Hz, 1 H), 5.15 – 5.03 (m, 2 H), 4.15 – 4.10 (m, 1 H), 3.56 (dd, *J* = 5.7, 3.0 Hz, 1 H), 2.35 – 2.26 (m, 1 H), 2.15 – 2.05 (m, 1 H), 1.78 – 1.64 (m, 2 H), 1.51 – 1.32 (m, 2 H), 1.26 – 1.05 (m, 3 H), 0.98 (d, *J* = 7.1 Hz, 3 H), 0.92 (s, 9 H), 0.91 – 0.87 (m, 5 H), 0.11 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 116.9, 82.7, 70.6, 39.5, 37.7, 37.5, 35.6, 26.2, 20.8, 18.3, 16.1, 14.4, 11.9, -3.8, -3.9; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{39}O_2Si$ $[M + H]^+$ 315.2719, found 315.2718.

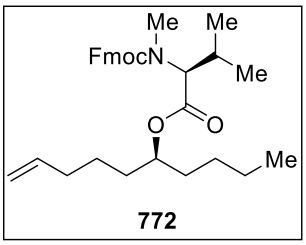
7.4.20. Synthesis of Alcohol 770



770

Alcohol 770. AcOH (0.03 mL, 0.59 mmol, 0.01 equiv) was added to a solution of (*S*,*S*)-*N*,*N*'-bis(3,5-di-tertbutylsalicyclidene-1,2-cyclohexanediamino)cobalt (II) (175 mg, 0.29 mmol, 0.005 equiv) in toluene (5 mL) and the reaction mixture was stirred for 1 h at 25 ºC. After this time, toluene and acetic acid in excess were removed under reduced pressure and (±)-1,2-epoxyhexane (6 g, 59.89 mmol, 1.0 equiv) was then added. The resulting mixture was stirred for 30 min and cooled to 0 ºC. Then, water (0.59 mL, 32.93 mmol, 0.55 equiv) was added and the reaction mixture was stirred for 15 h. The crude mixture was subjected to distillation and epoxide **768** was collected at 120 ºC (1 atm) (2.0 g, 33%): $[\alpha]^{25}_D$ = – 8.7 (c 1.0, $CHCl_3$), reported[330] $[\alpha]^{25}_D$ = – 9.0 (c 1.0, $CHCl_3$). A solution of 4-bromo-1-butene (1 mL, 9.98 mmol, 1.0 equiv) and Mg turnings (485 mg, 19,97 mmol, 2.0 equiv) in Et_2O (15 mL) was added into a stirred suspension of CuI (190 mg, 0.99 mmol, 0.1 equiv) in THF (35 mL) at -40 ºC. After 10 min, a solution of epoxide obtained above (1.0 g, 9.98 mmol, 1.0 equiv) in THF (10 mL) was added dropwise and the stirring was continued for 4 h at -40 ºC. After this time, the mixture was allowed to reach 25 ºC and a saturated aqueous NH_4Cl solution was added. The aqueous phase was extracted with Et_2O, washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain **770** (45 mg, 67%) as a colorless oil: R_f = 0.40 (silica gel, 40% EtOAc in hexanes); $[\alpha]^{25}_D$ = –15.5 (*c* 0.18, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1 H), 4.99 (dddd, *J* = 19.6, 10.2, 3.5, 1.4 Hz, 2 H), 3.65 – 3.54 (m, 1 H), 2.12 – 1.99 (m, 2 H), 1.58 – 1.24 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 114.6, 71.9, 37.2, 36.9, 33.8, 27.8, 25.7, 24.9, 22.8; HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{21}O$ $[M + H]^+$ 157.1592, found 157.1590.

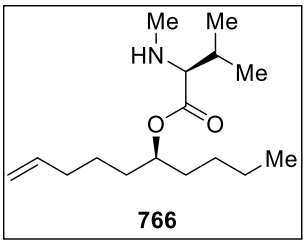
7.4.21. Synthesis of Ester 772



772

Ester 772. $Cl_3C_6H_2COCl$ (0.04 mL, 0.23 mmol, 1.2 equiv) was added to a solution of Fmoc-*N*-Methyl-L-Val-OH (**771**) (81 mg, 0.23 mmol, 1.2 equiv) and TEA (0.04 mL, 0.29 mmol, 1.5 equiv) in THF (2 mL) and the mixture was stirred for 30 min. Then, a solution of alcohol **770** (30 mg, 0.19 mmol, 1.0 equiv) and DMAP (47 mg, 0.38 mmol, 2.0 equiv) in toluene (1.0 mL) was added and the reaction mixture was stirred for 1 h. After this time, water was added and the aqueous phase was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain **772** (70 mg, 74%) as a colorless oil: R_f = 0.55 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = – 20.8 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers in 1.1/1 ratio) δ 7.77 (d, *J* = 7.5 Hz, 2 H), 7.68 – 7.57 (m, 2 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.31 (td, *J* = 7.5, 1.2 Hz, 2 H), 5.85 – 5.67 (m, 1 H), 5.05 – 4.84 (m, 2 H), 4.60 – 4.34 (m, 3 H), 4.26 (dd, *J* = 15.1, 6.9 Hz, 1 H), 2.91 (s, 3 H), 2.87 (s, 3 H), 2.10 – 1.97 (m, 2 H), 1.61 – 1.46 (m, 4 H), 1.44 – 1.34 (m, 1 H), 1.29 – 1.18 (m, 5 H), 1.00 (d, *J* = 6.5 Hz, 2 H), 0.92 – 0.87 (m, 4 H), 0.87 – 0.80 (m, 3 H), 0.74 (d, *J* = 6.7 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, both rotamers) δ 170.9, 170.4, 156.9, 156.3, 144.3, 144.1, 143.9, 143.9, 141.4, 141.4, 138.4, 138.3, 127.7, 127.1, 127.0, 125.0, 124.9, 124.9, 119.9, 119.9, 114.9, 114.8, 74.8, 74.8, 67.7, 67.6, 64.5, 64.2, 47.3, 33.6, 33.5, 33.4, 33.4, 30.1, 29.9, 29.7, 27.4, 27.3, 27.1, 24.6, 22.5, 19.7, 19.6, 18.8, 18.6, 13.9; HRMS (ESI-TOF) *m/z* calcd for $C_{31}H_{42}NO_4$ $[M + H]^+$ 492.3114, found 492.3115.

7.4.22. Synthesis of Amine 766



766

Amine 766. To a solution of **772** (69 mg, 0.14 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added piperidine (0.04 mL, 0.42 mmol, 3.0 equiv) and the reaction mixture was stirred at 25 ºC for 3 h. After this time, the solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to obtain amine **766** (37 mg, quantitative) as a colorless oil: R_f = 0.30 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{25}{}_D$ = – 12.6 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1 H), 5.07 – 4.95 (m, 2 H), 4.95 – 4.92 (m, 1 H), 2.93 (d, *J* = 5.7 Hz, 1 H), 2.40 (s, 3 H), 2.11 – 2.00 (m, 3 H), 1.58 (td, *J* = 10.0, 4.7 Hz, 4 H), 1.50 – 1.37 (m, 2 H), 1.37 – 1.29 (m, 6 H), 1.00 – 0.94 (m, 4 H), 0.91 – 0.87 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 138.3, 114.8, 74.5, 69.7, 35.4, 33.7, 33.5, 33.4, 31.5, 27.5, 24.5, 22.5, 19.5, 18.5, 13.9; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{32}NO_2$ $[M + H]^+$ 270.2433, found 270.2431.

Resumen

Introducción

Esta Tesis Doctoral propone el descubrimiento y desarrollo de nuevos fármacos inspirados en productos naturales bioactivos que representan plataformas válidas para la generación de nuevas entidades químicas de interés farmacéutico. De esta forma, la combinación de diversidad estructural y funcional permitiría la identificación de nuevos compuestos con mejores perfiles biológicos. Con el fin de seleccionar objetivos sintéticos adecuados, nos hemos centrado en productos naturales que pueden ofrecer prometedoras expectativas en el campo biomédico, bien por actuar sobre dianas biológicas novedosas o bien por contener nuevas estructuras moleculares que pueden representar las bases de nuevos *scaffolds* de interés farmacéutico. Por tanto, este proyecto de Tesis Doctoral presenta un programa de trabajo que integraría formación y generación de nuevos conocimientos a través del desarrollo de nuevos compuestos con potencial valor terapéutico. En particular, los productos naturales seleccionados son compuestos tipo policétido, como la (-)-depudecina y ciclopéptidos y ciclodepsipéptidos como las solomonamidas A-B y los celebésidos A-C. Además, estos compuestos han sido recientemente descubiertos de fuentes naturales poco accesibles que hacen que, por un lado, no haya muchos estudios respecto a su química y biología, y, por otro, que, dada la escasez de material suficiente y su difícil accesibilidad de sus fuentes naturales, no se pueda profundizar mucho sobre su perfil biológico. A pesar de la escasez de materia, las primeras pruebas biológicas de estos productos revelaron interesantes propiedades biológicas. Estos perfiles biológicos preliminares, unido a la necesidad de disponer de más materia para profundizar en el conocimiento de sus actividades biológicas y mecanismos de acción, y confirmar sus estructuras y el hecho de que tales compuestos presentan esqueletos moleculares totalmente novedosos y sin precedentes, justifican una acción investigadora que puede arrojar nuevos conocimientos desde los puntos de vista químico y biológico. En esta Tesis Doctoral hemos establecido estrategias sintéticas orientadas al objetivo pero con la posibilidad de extender dichas estrategias a la construcción de diversidad estructural a través de la generación de análogos. Estas estrategias sintéticas comparten una reacción de metátesis de olefinas como etapa clave hacia la síntesis de los productos naturales seleccionados.

Las reacciones de metátesis incluyen las reacciones de alquenos, eninos y alquinos, junto con múltiples variantes de sistemas de polialquenos o polialquinos como precursores involucrados en procesos de cascada. De entre todos ellos, la reacción de metátesis de alquenos es la más empleada, en la cual olefinas cíclicas o alquenos lineales se forman a través de una metátesis con cierre de anillo (*ring-closing metathesis*, RCM), metátesis cruzada (*cross-metathesis*, CM), o a través de sus diferentes versiones (estereoselectiva, con transposición, RCM con atadura temporal o RRCM). De hecho, estas transformaciones ocupan una posición privilegiada en la síntesis orgánica moderna. Menos frecuente en uso pero no menos importante son las metátesis de eninos y alquinos, que también se han convertido en valiosas reacciones sintéticas con ventajas adicionales sobre las metátesis de alquenos, como en el caso de las metátesis de eninos involucradas en procesos en cascada o el caso de las metátesis de alquinos debido a la versatilidad del

grupo alquino, que permite posteriores transformaciones para expandir la diversidad estructural de los productos que pueden ser formados.

Sin duda, detrás del éxito de todos estos procesos se encuentran los catalizadores excepcionales que permiten estas transformaciones. Desde el descubrimiento del primer catalizador de wolframio-carbeno llevado a cabo por Katz y de la elucidación del mecanismo de la metátesis de alquenos realizada por Chauvin en los años 70, las innovaciones claves han sido los descubrimientos del catalizador de Schrock en 1990 y del catalizador basado en rutenio por Grubbs en 1993. Estos descubrimientos marcaron el comienzo de una extraordinaria y emergente carrera hacia catalizadores más eficientes en términos de actividad, estabilidad y tolerancia de grupos funcionales. Estos catalizadores altamente eficientes son miembros representativos de tres generaciones de complejos de rutenio, en las que la introducción de un ligando de carbeno *N*-heterocíclico (NHC) resultó en un incremento de la actividad catalítica y estabilidad térmica de los catalizadores. Los catalizadores desarrollados entre 1996-2007 dieron lugar al diseño racional de nuevas versiones para permitir procesos de metátesis estereoselectivos y estereoretentivos. Como añadido a este amplio arsenal de valiosos catalizadores se encuentran el catalizador soluble en agua en forma de complejos de polietilenglicol o los catalizadores basados en rutenio soportados sobre superficies activadas, que expanden el alcance y las aplicaciones de la química, particularmente respecto a abordar problemas medioambientales. Todos estos catalizadores son apropiados para metátesis de alquenos y eninos. Interesantemente, para el último caso, el proceso puede ser efectuado también por otros catalizadores basados en otros metales de transición, como aquellos basados en Pt, Pd o Ir a través de un mecanismo totalmente diferente.

Un caso aparte es la reacción de metátesis de alquinos, la cual a pesar de poseer una similitud mecanística con la metátesis de alquenos, requiere de un tipo diferente de catalizador. De hecho, en este caso, la variedad de catalizadores disponibles no es tan amplia como los desarrollados para metátesis de alquenos. Junto con la destacada actividad y estabilidad de los catalizadores mencionados, otras características que han sido mejoradas durante la evolución del diseño de los catalizadores es la excepcional tolerancia frente a los grupos funcionales que todos estos catalizadores muestran, que a su vez los ha posicionado como una de las herramientas sintéticas más poderosas en la síntesis orgánica moderna. Consecuentemente, la síntesis total se ha beneficiado enormemente de estas reacciones de metátesis, como se ha demostrado por el uso extensivo de estas reacciones en sus versiones intra- e intermoleculares. De hecho, el número de contribuciones en las que una reacción de metátesis representa la etapa clave que permite completar con éxito una síntesis, o bien una herramienta sintética útil y eficiente empleada a lo largo del curso sintético, no deja de crecer en la literatura de la química orgánica.

De esta forma, las reacciones de metátesis, en sus varias versiones, se han convertido en herramientas poderosas y extremadamente valiosas para la formación de enlaces carbono-carbono en síntesis orgánica. La multitud de catalizadores disponibles

para llevar a cabo estas reacciones, combinado con las distintas transformaciones que pueden ser realizadas, ha posicionado a las reacciones de metátesis como una de las más importantes de este siglo, reconociendo a sus principales inventores con el Premio Nobel de Química en el año 2005. El valor sintético y el gran potencial de estas reacciones se deben al tremendo progreso presenciado en los últimos años respecto al diseño y desarrollo de catalizadores estables y eficientes basados en complejos metal-carbeno. Como consecuencia, estas reacciones presentan un gran alcance, generalidad y gran flexibilidad para la diversificación estructural. Además, como prueba de estas características se encuentra su uso extensivo en el campo de la química orgánica, con particular impacto en la síntesis total de productos naturales. Estas reacciones, en sus diferentes modalidades y estrategias se han convertido en una herramienta estándar en los laboratorios de química orgánica moderna, siendo determinante en la finalización de una amplia gama de productos naturales.

Objetivos

El objetivo general de este proyecto sería, por tanto, el descubrimiento y desarrollo de nuevos fármacos inspirados en productos naturales bioactivos y mediante la generación de análogos que, combinando diversidad estructural y funcional, permitan la identificación de nuevos compuestos con mejores perfiles biológicos. De esta forma, se establecerían los siguientes objetivos específicos que marcarían el desarrollo de este proyecto de tesis: (1) Establecimiento de estrategias sintéticas flexibles y convergentes para la síntesis total de los productos naturales seleccionados, (2) Implementación de las rutas sintéticas establecidas en el objetivo anterior, para la generación de análogos de los productos naturales seleccionados, y (3) Evaluación biológica de los productos naturales y análogos sintetizados.

Campaña de la Depudecina

El reconocimiento del rol crucial que poseen las histonas deacetilasas (HDACs) y las histonas acetil transferasas (HAT) en la regulación de la expresión genética, que ocurre a través de un control estricto del estado de acetilación de las histonas, ha generado un gran interés en su uso como nuevos objetivos prometedores para terapias contra el cáncer. De esta forma, mientras las histonas acetiladas provocan una expansión local de la cromatina, incrementando la accesibilidad de proteínas reguladoras al ADN, las histonas deacetiladas cargadas positivamente incrementan sus afinidades con el ADN y, por consiguiente, bloquean la transcripción de genes antitumorales. Las HDACs son las enzimas responsables de la eliminación del grupo acetilo presente en residuos de lisina de histonas y otras proteínas; y están compuestas por 18 isoformas agrupadas en cuatro clases diferentes (I-IV). La inhibición de estas enzimas en el contexto de un estado epigenético de neoplasia, donde están sobreexpresadas y juegan papeles importantes en la progresión del cáncer, lleva a la restauración de un estado epigenético normal e induce la expresión de genes supresivos del tumor. Consecuentemente, los inhibidores de

HDACs han atraído una considerable atención de la comunidad científica como potentes agentes anticancerígenos novedosos. Una indicación de este interés es la gran actividad dirigida hacia el diseño y síntesis de inhibidores de HDACs, que han sido clasificados en cinco categorías de acuerdo a sus modos de acción. Como consecuencia de esta actividad tan intensa, tres de ellos (vorinostat, belinostat y romidespina) han sido aprobados recientemente por la FDA para terapias clínicas anticancerígenas, mientras que un número importante de otros inhibidores de HDACs se han sometido a ensayos clínicos para el tratamiento de una variedad de neoplasias hematológicas y tumores sólidos malignos. El hecho de que otras proteínas, incluyendo factores de transcripción, enzimas reparadoras del ADN, transductores de señales y mediadores de inflamación, entre otros, son también sustratos de las HDACs, demuestra claramente su participación en una enorme variedad de procesos biológicos, tales como el ciclo celular y mitosis, reparación del ADN dañado, respuestas de estrés celular, degradación proteica, regulación de la citoquina, inmunidad, inflamación, angiogénesis, apoptósis e invasión celular. De hecho, las HDACs no solo están involucradas en el cáncer, también en otras patologías como las enfermedades neurológicas, desórdenes inmunitarios e infecciones. Por otro lado, la falta general de selectividad mostrada por los inhibidores actuales de la familia HDAC explica los efectos biológicos tan diversos que pueden producir, reduciendo por tanto la ventana terapéutica al fomentar efectos secundarios indeseados.

En este contexto, la (-)-depudecina, aislada desde el cultivo del hongo *Alternaria brassicicola* en 1992 y más tarde, desde el patógeno de la hierba *Nimbya scirpicola*, ha sido identificada como un inhibidor selectivo de las histonas deacetilasas I y II con un valor de IC_{50} en el rango de μM bajo, de acuerdo a los estudios biológicos llevados a cabo por Schreiber *et al*. Al contrario que en el caso de los inhibidores más representativos de HDACs, la depudecina representa un inhibidor único de estas enzimas en virtud de su estructura molecular, caracterizada por la presencia de dos anillos de oxirano separados por un doble enlace *trans*. Descubierta originalmente como parte de un *screening* biológico dirigido hacia la identificación de agentes antitumorales con actividad detransformadora, la depudecina se identificó como un metabolito bioactivo capaz de revertir la morfología de las células tumorales NIH3T3 (firoblasto), que pasó de una forma redondeada en las células transformadas a la morfología plana de las células no transformadas. La habilidad de la depudecina de regular la arquitectura citoesquelética de las células tumorales se debe a la restauración del estrés de la fibra de actina. Esta actividad biológica mostrada suscitó un gran interés biomédico y biológico debido a su gran potencial como agente antitumoral y como sonda molecular para la investigación de secuencias de señalización que regulan el estrés de las fibras de actina, así como para entender mejor los roles de las HDACs. Además, la depudecina no solo induce cambios morfológicos sino también parada del ciclo celular y diferenciación celular, que podrían atribuirse a la inhibición de la HDAC como se mencionó anteriormente. Probablemente, la acción inhibidora de la depudecina contra la HDAC es debido a la presencia de los anillos de oxirano biológicamente reactivos que bloquearían el sitio activo de las enzimas a través de la formación irreversible de un enlace covalente entre los residuos nucleofílicos presentes en el sitio activo y los anillos de oxirano. Además, la depudecina

también muestra una importante actividad anti-angiogénica que la dota con una potente actividad anti-proliferativa contra HUVEC (células endoteliales de las venas umbilicales humanas). Finalmente, además de sus propiedades antitumorales, la depudecina también fue identificada como un potente agente anti-protozoo contra el *Neospora caninum*, sin provocar ningún efecto secundario a la célula huésped.

A pesar de las interesantes actividades biológicas de la depudecina, así como su estructura molecular única, es bastante sorprendente que solo una síntesis total haya sido publicada hasta la fecha por el grupo de Schreiber en 1995. Aunque esta síntesis fue un síntesis lineal muy larga, pudo proveer de cantidades suficientes de (-)-depudecina sintética para realizar más estudios biológicos. Impulsados por sus impresionantes actividades biológicas y atractiva estructura, decidimos iniciar un programa de investigación dirigido hacia la síntesis de la depudecina natural y análogos. Nuestro plan sintético culminó recientemente con una síntesis total lineal basada en el uso de una nueva clase de sales de sulfonio quirales, desarrollados en nuestros laboratorios, para la construcción estereoselectiva de los anillos de oxirano contenidos en el producto natural. La síntesis contó con 17 etapas y un 19% de rendimiento global desde el (+)-metil D-lactato. Con el objeto de mejorar y facilitar el acceso a la depudecina natural, así como a análogos adicionales para realizar más ensayos biológicos, decidimos explorar una alternativa sintética basada en una estrategia de metátesis de olefinas cruzada como una aproximación más corta y convergente.

En nuestro proyecto de la depudecina hemos llevado a cabo una nueva síntesis de la (-)-depudecina, que mejora ampliamente a nuestra síntesis lineal previa. Mientras la primera síntesis total, publicada por Schreiber, requirió 23 etapas lineales desde el (-)-dietil D-tartrato, con un rendimiento global del 0.7%, nuestra primera síntesis lineal desde (+)-Methyl D-lactato se consiguió en 17 etapas con un 19% de rendimiento global. Como continuación de nuestro trabajo previo, hemos desarrollado una segunda ruta sintética hacia la depudecina utilizando una reacción de metátesis de olefinas cruzada como la etapa clave, que fue completada con éxito en una manera convergente para proveer la (-)-depudecina en solo 12 etapas y con un 26% de rendimiento global desde (+)-Methyl D-lactato. Además, la ruta sintética permite modificaciones estereoquímicas y funcionales, permitiendo la preparación de dos estereoisómeros de la (-)-depudecina, la 10-*epi*-depudecina y su enantiómero, que representan análogos únicos que permitirán evaluar la influenca de la estereoquímica sobre la actividad biológica, así como la homodepudecina. Además, hemos completado el set de análogos con la preparación de varios análogos truncados. Los productos sintetizados (-)-depudecina, (+)-depudecina y los análogos truncados han sido evaluados biológicamente contra varias líneas celulares tumorales, incluyendo células endoteliales. Los resultados obtenidos de las evaluaciones biológicas nos han permitido completar un estudio preliminar de relación estructura-actividad (SAR) para este interesante producto natural, concluyendo que: a) la estereoquímica en C-10 del producto no es esencial para la actividad biológica, b) la presencia de al menos un grupo epóxido es clave en la actividad biológica, no siendo necesaria la presencia simultánea de

ambos grupos epóxidos, y c) el sistema de alcohol alílico terminar no es esencial, pudiendo ser susituido por su isómero.

Campaña de las Solomonamidas

El descubrimiento de nuevos productos naturales ofrece oportunidades importantes para la identificación y desarrollo de nuevos *leads* y *scaffolds* en química médica, así como un reto fascinante para los químicos orgánicos en virtud de su diversidad estructural y complejas estructuras moleculares que muchos de ellos presentan. En particular, el mundo marino representa una fuente excepcional rica de nuevos metabolitos bioactivos con estructuras sin precedentes, fascinantes perfiles biológicos y potencial valor terapéutico. Los organismos marinos y más específicamente las esponjas, que son consideradas las mayores fuentes de productos naturales sin descubrir, producen una variedad de metabolitos únicos con unos perfiles biológicos muy amplios, debido a las condiciones que difieren significativamente de los ambientes terrestres, incluyendo entornos agresivos, exigentes y competitivos que permiten la producción de potentes moléculas activas.

Entre la infinidad de fuentes marinas de productos naturales, particularmente productiva es la esponja marina *Theonella swinhoei*, que ha demostrado ser una fuente impesionante de metabolitos secundarios, proveyendo al menos nueve clases diferentes de productos naturales. Además del importante y muy conocido policétido swinhólido, descubierto hace 30 años, el género *Theonella* es conocido por proveer una gama enorme de productos naturales tipo peptídicos bioactivos, incluyendo péptidos acíclicos (politeonamidas y koshikamidas), ciclopéptidos (kombamida, orbiculamida, barangamida, cupolamida o pertamidas, entre otros), péptidos bicíclicos de gran tamaño de anillo como las teonellamidas, depsipéptidos (koshikamidas, papuamidas, nagahamida o teopapuamida) y glicopéptidos. Como una prueba más del valor del género *Theonella* como una fuente excelente de nuevos péptidos, Zampella *et al*. recientemente aislaron dos nuevos ciclopéptidos denominados solomonamidas A y B, desde una colección de las islas Solomon. Estos ciclopéptidos de 15 miembros poseen estructuras moleculares únicas y, además, la solomonamida A mostró una potente actividad anti-inflamatoria, provocando una importante reducción del 60% de la inflamación en modelos animales con una muy baja dosis de 100 μg/Kg. Desafortunadamente, la extrema escasez de las solomonamidas ha impedido una evaluación biológica completa. De hecho, la actividad anti-inflamatoria de la solomonamida B no fue evaluada debido a la limitada cantidad que se aisló. Es importante destacar que los descubridores de estos compuestos, tras recolectar unos 207 gramos de esponja seca *Theonella Swinhoei* en una región cerca de las islas Solomon, en el océano Pacífico, solo obtuvieron 6.5 mg de solomonamida A y 3.6 mg de solomonamida B, tras un laborioso proceso de aislamiento y purificación. Un análisis espectroscópico exhaustivo de ambos compuestos facilitó la elucidación de sus complejas estructuras cíclicas, revelando la presencia de tres amino ácidos convencionales (D-Ala, Gly and L-Ser) y una unidad sin precedentes, el ácido 4-amino(2'-amino-4'-hidroxifenil)-

3,5-dihidroxi-2-metil-6-oxohexanoico (ADMOA) y el correspondiente 5-deoxi derivado (AHMOA) para las solomonamidas A y B, respectivamente, y para las cuales Zampella *et al.* propusieron una biosíntesis cuyo posible origen sería una unidad de 6-hidroxi triptófano. Las configuraciones absolutas de las solomonamidas naturales fueron establecidas de manera provisional, como las más probables, a través del empleo de una combinación de métodos espectroscópicos y teóricos.

La escasez de las solomonamidas aisladas desde la fuente natural es un inconveniente para realizar ensayos biológicos más profundos. La dificultad de acceder a grandes cantidades de estos compuestos hace muy difícil conocer con más detalle sus perfiles biológicos y mecanismos de acción, y justifica una síntesis química en el laboratorio de estos productos naturales. De esta forma, la síntesis química de estos inexplorados compuestos podría representar la solución para proveer suficiente cantidad de material como para llevar a cabo estudios biológicos más extensos, así como para confirmar sus estructuras inicialmente propuestas. Como consecuencia, cuando iniciamos este proyecto de investigación en el año 2016, las solomonamidas habían suscitado interés con la publicación de algunas aproximaciones sintéticas, incluyendo la síntesis de un deoxi análogo de la solomonamida B. En paralelo con el desarrollo de nuestro trabajo de investigación, nuevas aproximaciones sintéticas fueron publicadas, culminando con la síntesis total de la solomonamida B y, más tarde, con la síntesis total de la solomonamida A, llevadas a cabo por el grupo de Reddy. Recientemente, el mismo grupo ha publicado la preparación de varios estereoisómeros de macrociclos de solomonamidas, por variación de la estereoquímica del fragmento no peptídico AHMOA. Más importante, la síntesis total de la solomonamida B permitió una revisión de la estructura inicialmente propuesta, con la corrección de las configuraciones en las posiciones C-3 y C-4 llevando al isómero-(3*S*, 4*S*) en lugar de la configuración propuesta (3*R*, 4*R*) para la solomonamida B. Desde el punto de vista sintético, la síntesis se basó en una reacción clave de Heck intramolecular para obtener el núcleo macrocíclico de las solomonamidas. Teniendo en cuenta que la configuración relativa y absoluta de los tres estereocentros presentes en el fragmento policétido fueron establecidos por métodos computacionales por Zampella *et al.*, el grupo de Reddy decidió realizar la síntesis del isómero-(3*S*, 4*S*) en lugar del inicialmente propuesto (3*R*, 4*R*), confirmando la nueva estructura propuesta para la Solomonamida B.

Como la estructura de la solomonamida B fue inicialmente establecida derivada de la solomonamida A, esta última también necesitaba una revisión. Como ambos productos comparten la misma ruta biosintética, los tres estereocentros (2*S*, 3*S* y 4*S*) presentes en la solomonamida B deberían estar presentes en la solomonamida A, dejando un único estereocentro en la posición C5 del fragmento ADMOA cuya estereoquímica absoluta debía ser confirmada, siendo establecida inicialmente como 5*R*. Con este objetivo, Reddy *et al.* llevaron a cabo la síntesis del isómero-(3*S*, 4*S*, 5*S*), en lugar de la configuración inicialmente propuesta (3*R*, 4*S*, 5*R*), confirmando la nueva estructura asignada para la solomonamida A.

Nuestro interés en el descubrimiento y desarrollo de nuevos potenciales *leads* basados en compuestos tipo ciclopeptídicos y ciclodepsipeptídicos nos incitó a iniciar un programa de investigación dirigido hacia la síntesis total de esta nueva e inexplorada clase de ciclopéptido. Con el fin de establecer una estrategia sintética flexible y divergente capaz de proveer no solo los productos naturales, sino también acceder a una serie de análogos para estudios biológicos, buscamos explorar la reacción de metátesis con cierre de anillo (RCM) como la etapa clave para la construcción del macrociclo de 15 miembros. Esta etapa de ciclación sería seguida por una fase de oxidación, que incorporaría los grupos funcionales necesarios para alcanzar el estado de oxidación final encontrado en los productos naturales. Desde una perspectiva estratégica, consideramos que la construcción del núcleo macrocíclico en el enlace 4,5 sería capaz de proveer un rápido acceso no solo a los productos finales, sino también a análogos desde intermedios avanzados, permitiendo la obtención fácil de numerosos *scaffolds*. Además, es digno de mencionar que esta estrategia sintética utiliza materias de partidas simples, evitando la construcción del residuo complejo de ADMOA, que puede ser generado en estapas más avanzadas de la síntesis a través de una epoxidación de las olefinas precursoras, seguido de un proceso de apertura del anillo de oxirano para introducir el grupo amina. De acuerdo a esto, nuestra estrategia diseñada en términos retrosintéticos se basa en la desconexión de la amida del residuo de L-serina, seguido por la eliminación de los grupos funcionales, que serían introducidos mediante manipulaciones oxidativas (fase de oxidación) de los productos de metátesis resultantes (fase de ciclación). Como los presentes estudios sintéticos se iniciaron antes de la publicación de Reddy, tomamos como objetivo las estructuras inicialmente propuestas para las solomonamidas.

En esta Tesis Doctoral se ha llevado a cabo una exploración sintética extensa dirigida hacia las solomonamidas basada en una metátesis con cierre de anillo como reacción clave para un rápido y eficiente acceso a los núcleos macrocíclicos de estos productos naturales. Como resultado de este estudio sintético se ha establecido un proceso de cierre de anillo eficiente que procede en altos rendimientos y con completa estereoselectividad. Durante el curso de estos esfuerzos sintéticos nos hemos encontrado con obstáculos inesperados que han surgido a lo largo de la ruta sintética, principalmente los siguientes: 1) la reactividad del grupo hidroxilo en la posición bencílica; 2) la reactividad de las diolefinas que contienen alcoholes alílicos y homoalílicos o que contienen un sistema de carbonilo β,γ-insaturado en la catálisis de rutenio; y 3) la reactividad de las olefinas macrocíclicas respecto a los reactivos oxidantes. Además, no solamente hemos explorado el alcance y limitaciones de la metátesis con cierre de anillo en la síntesis del núcleo macrocíclico de las solomonamidas, también hemos identificado varios precursores estructuralmente relacionados con las solomonamidas que poseen significantes citotoxicidades contra varias líneas celulares tumorales, incluyendo células endoteliales, en el rango de μM bajo. De esta forma, hemos llevado a cabo un estudio del potencial antiangiogénico de los precursores sintéticos de solomonamidas. Uno de precursores fue seleccionado para una caracterización más profunda de su potencial antiangiogénico *in vitro*, mostrando que puede inhibir algunas etapas clave del proceso de angiogénesis, incluyendo la proliferización, migración e invasión de células

endoteliales, y disminuye su capacidad de degradar las proteínas de la matriz extracelular. Además, el potencial antiangiogénico de este compuesto se confirmó a través de dos modelos *in vivo*, la membrana corioalantoidea de pollo y la membrana de pez zebra. Nuestros resultados muestran una actividad biológica nueva e interesante de este precursor de solomonamida como un inhibidor de la persistente y desregulada angiogénesis que caracteriza al cáncer y otras patologías. En conclusión, la química descrita destaca los beneficios de la reacción de metátesis de olefinas en el campo de la síntesis total de productos naturales, destacando convergencia y flexibilidad para la diversidad estructural y ha permitido la identificación de compuestos bioactivos con interesantes propiedades antitumorales. Además, estas evaluaciones biológicas preliminares de compuestos relativamente simples, ausentes de algunos grupos funcionales presentes en los productos naturales, presagian prometedoras propiedades antitumorales para las solomonamidas naturales y los califica como nuevos *scaffolds* de interés biológico y medicinal. Finalmente, se han iniciado varios esfuerzos sintéticos hacia la síntesis total de las estructuras revisadas de las solomonamidas basados en una estrategia de transposición de Overman. La finalización de la síntesis de los productos naturales, el diseño de nuevos análogos y estudios biológicos más profundos que permitan elucidar el mecanismo de su actividad anti-tumoral y anti-angiogénica se encuentran en progreso.

Campaña de los Celebésidos

La naturaleza es una enorme fuente de nuevos productos naturales que son clave en el descubrimiento de nuevos fármacos. Como una nueva demostración de la impresionante fuente de metabolitos secundarios de origen marino, tres nuevos ciclodepsipéptidos denominados celebésidos A-C han sido aislados de la esponja marina *Siliquariaspongia mirabilis* recolectada en la isla Sulawesi, en Indonesia, por el grupo de Bewley. La estructura de estos compuestos ha sido establecida mediante extensivos análisis espectroscópicos. Mientras que la configuración absoluta de los amino ácidos se determinó a través del método avanzado de Marfey y HPLC quiral, las configuraciones relativas del fragmento policétido fueron resueltas por análisis combinado de las constantes de acoplamiento $J_{2,3}$ homonucleares (H-H) y heteronucleares (C-H), ROE y cálculos computacionales. Estos productos naturales se caracterizan por ser ciclodepsipéptidos de 26 miembros que contienen una cadena policétida denominada ácido 7,9-dihidroxi-8,10-dimetiltrideca-2,4-dienoico (Ddtd), y una cadena peptídica que presenta cinco residuos de amino ácidos, que incluyen una *N*-metil valina, una β-metil asparagina, una D-isoserina, una 3-carbamoil treonina y una serina en el caso del celebésido C, y un residuo de fosfoserina en los celebésidos A y B. Curiosamente, la 3-carbamoil treonina y la fosfoserina son amino ácidos nunca vistos en productos naturales de origen marino.

Desde el punto de vista biológico, el celebésido A mostró actividad anti-VIH, con un valor de IC_{50} de 1.9 μg/mL, además de citotoxicidad frente a una línea celular de

cáncer de colon humano (HTC-116) en el rango de μM bajo. Por su parte, el celebésido C fue inactivo, mientras que el celebésido B no pudo ser evaluado biológicamente. Una vez más, la escasez de estos ciclodepsipéptidos aislados desde la fuente natural es un problema para realizar ensayos biológicos más profundos. Por tanto, la síntesis química de estos inexplorados ciclodepsipéptidos marinos podría ser la solución para acceder a cantidades suficientes de materia para indagar más en sus perfiles biológicos, así como en sus mecanismos de acción, y poder confirmar sus estructuras inicialmente propuestas.

La síntesis del fragmento policétido del celebésido A llevada a cabo por nuestro grupo de investigación en 2014 representa la única aproximación sintética hacia la cadena policétida de los celebésidos hasta la fecha. Nuestra síntesis se basó en el uso de las sales de sulfonio para, mediante reacción con los correspondientes aldehídos, obtener amidas glicídicas de manera estereoselectiva, cuyas posteriores reacciones de apertura de los anillos de oxirano permitieron generar la unidad policétida con configuración relativa *syn,anti,syn* contenida en los celebésidos, así como en otros productos naturales como el YM-47522, el antifúngico basiliskamida y el ciclodepsipéptido langunamida A.

En la presente Tesis Doctoral hemos planeado una estrategia sintética dirigida hacia la síntesis de los celebésidos basada en una metátesis de olefinas con cierre de anillo para generar el núcleo macrocíclico de 26 miembros de estos productos naturales. En nuestra estrategia, hemos empleado la síntesis en fase sólida como una tecnología adecuada para un rápido y eficiente acceso al fragmento peptídico contenido en los celebésidos, mientras que la cadena policétida del celebésido A ha sido sintetizada de manera estereoselectiva a través de una metilación asimétrica, apertura de epóxido y alilación asimétrica de Brown como etapas claves. La estrategia sintética descrita para los celebésidos permite el acceso a los productos naturales, además de ofrecer la oportunidad de generar una amplia gama de análogos de celebésidos a través de la modificación de los aminoácidos contenidos en la cadena peptídica durante la síntesis en fase sólida en una manera rápida y fácil. La finalización de la síntesis del celebésido A está actualmente en marcha y representa nuestra prioridad.

Conclusiones

Las conclusiones de la Tesis Doctoral se pueden resumir como las siguientes:

1) Hemos establecido una nueva síntesis total de la (-)-depudecina utilizando una reacción de metátesis de olefinas cruzada como etapa clave, llevada a cabo con éxito en una manera convergente para proveer (-)-depudecina en solo 12 etapas y un 26% de rendimiento global desde (+)-metil-D-lactato. Esta nueva aproximación convergente mejora ampliamente a nuestra síntesis lineal previa (17 etapas, 19% rendimiento global) así como a la síntesis de Schreiber (23 etapas, 0.7% rendimiento global).

2) La ruta sintética desarrollada es susceptible a modificaciones estereoquímicas y funcionales, permitiendo la preparación de dos estereoisómeros, la 10-*epi*-depudecina y su enantiómero, así como la homodepudecina. Además, hemos completado el set de análogos con la preparación de varios análogos truncados de depudecina.

3) Los análogos de depudecina sintetizados fueron evaluados biológicamente contra varias líneas celulares tumorales, incluyendo células endoteliales, y los resultados nos han permitido completar un estudio preliminar de relación estructura-actividad para este producto natural, concluyendo que: a) la estereoquímica en C-10 del producto no es esencial en la actividad biológica; b) la presencia de al menos uno de los grupos epóxidos es clave en la actividad biológica, pero no es necesario la presencia simultánea de ambos; y c) el sistema de alcohol alílico terminal no es esencial en la actividad biológica, y puede ser sustituido por su isómero.

4) Una exploración sintética muy extensa dirigida hacia las solomonamidas se ha realizado basada en una metátesis de olefinas con cierre de anillo como reacción clave para un rápido y eficiente acceso a sus núcleos macrocíclicos, procediendo en altos rendimientos y con completa estereoselectividad.

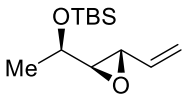
5) También hemos identificado varios precursores de solomonamidas que poseen una citotoxicidad importante contra varias líneas celulares tumorales, incluyendo células endoteliales, en el rango de μM bajo. En particular, hemos encontrado que un precursor de solomonamida exhibe un potente efecto antiangiogénico *in vitro* e *in vivo*, y nuestros resultados sugieren la aplicación potencial de los derivados de solomonamidas como inhibidores de la persistente y desregulada angiogénesis que caracteriza el cáncer y otras patologías.

6) Hemos diseñado una estrategia sintética dirigida hacia los celebésidos que se basa en el uso de una metátesis de olefinas con cierre de anillo para generar el anillo macrocíclico de 26 miembros que caracteriza a estos productos naturales. En nuestra estrategia, hemos utilizado la síntesis en fase sólida como una tecnología adecuada para un rápido y eficiente acceso a la cadena peptídica contenida en los celebésidos, mientras que el fragmento policétido ha sido sintetizado de manera estereoselectiva.

7) La química descrita destaca los beneficios de la reacción de metátesis de olefinas en el campo de la síntesis total de productos naturales, otorgando convergencia y flexibilidad para la diversidad estructural y ha permitido la identificación de compuestos bioactivos con interesantes propiedades antitumorales.

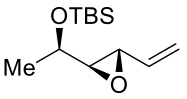
Appendix I

^{1}H and ^{13}C NMR Spectra Related to Depudecin



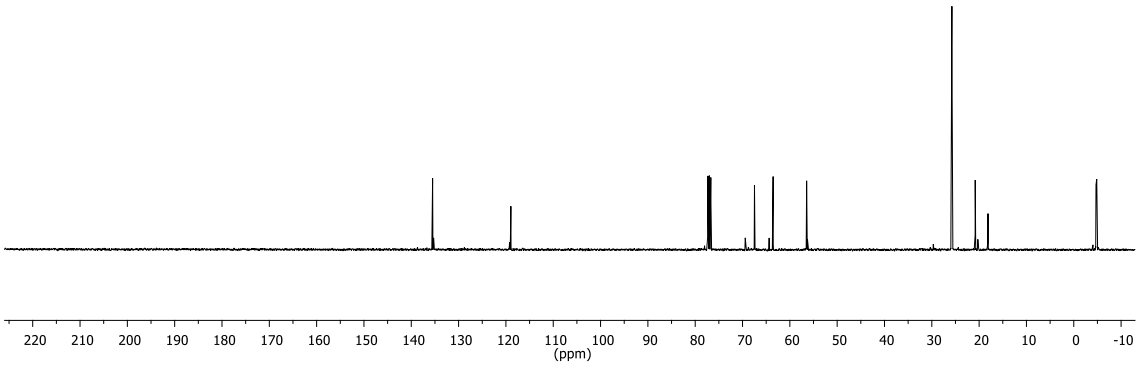
460

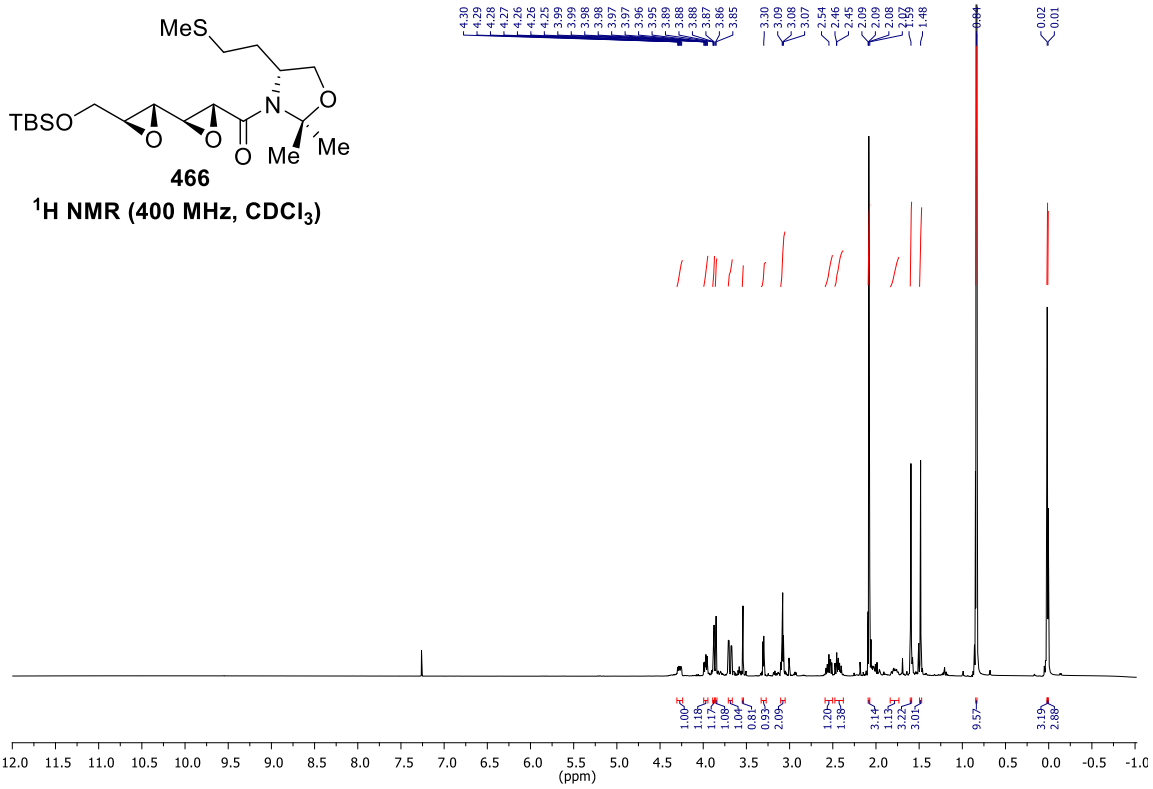
^{1}H NMR (400 MHz, $CDCl_3$)

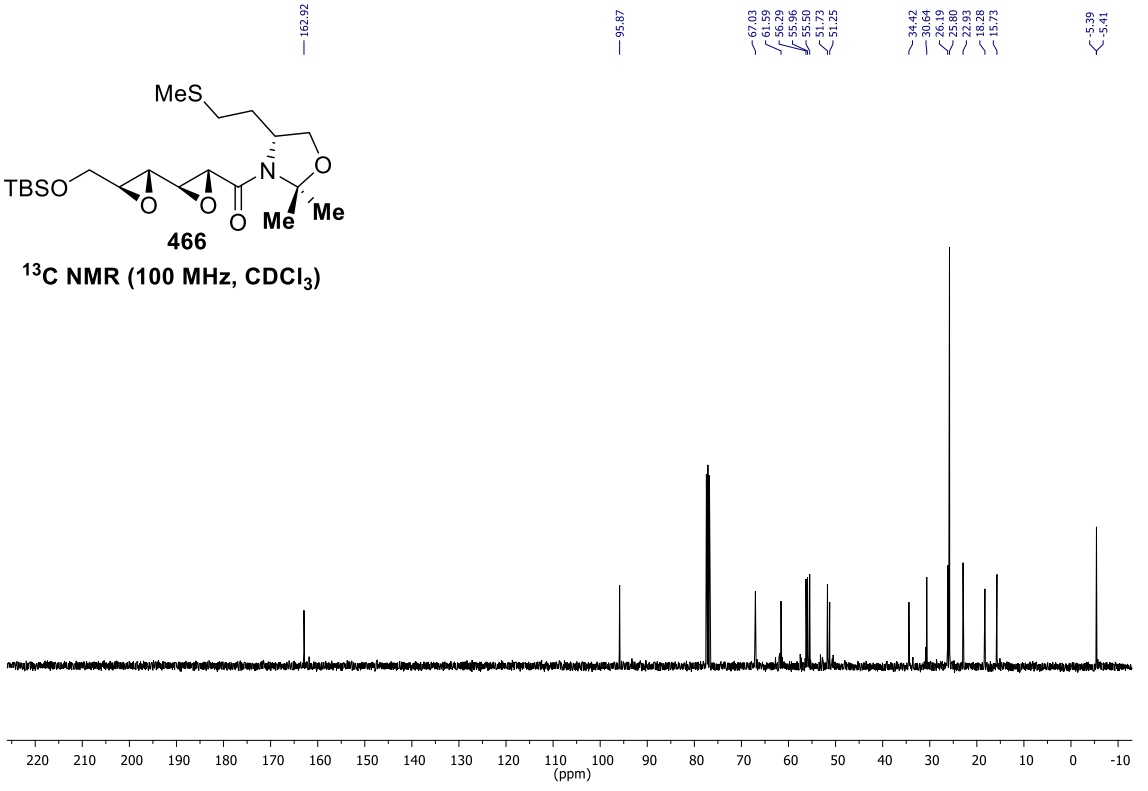


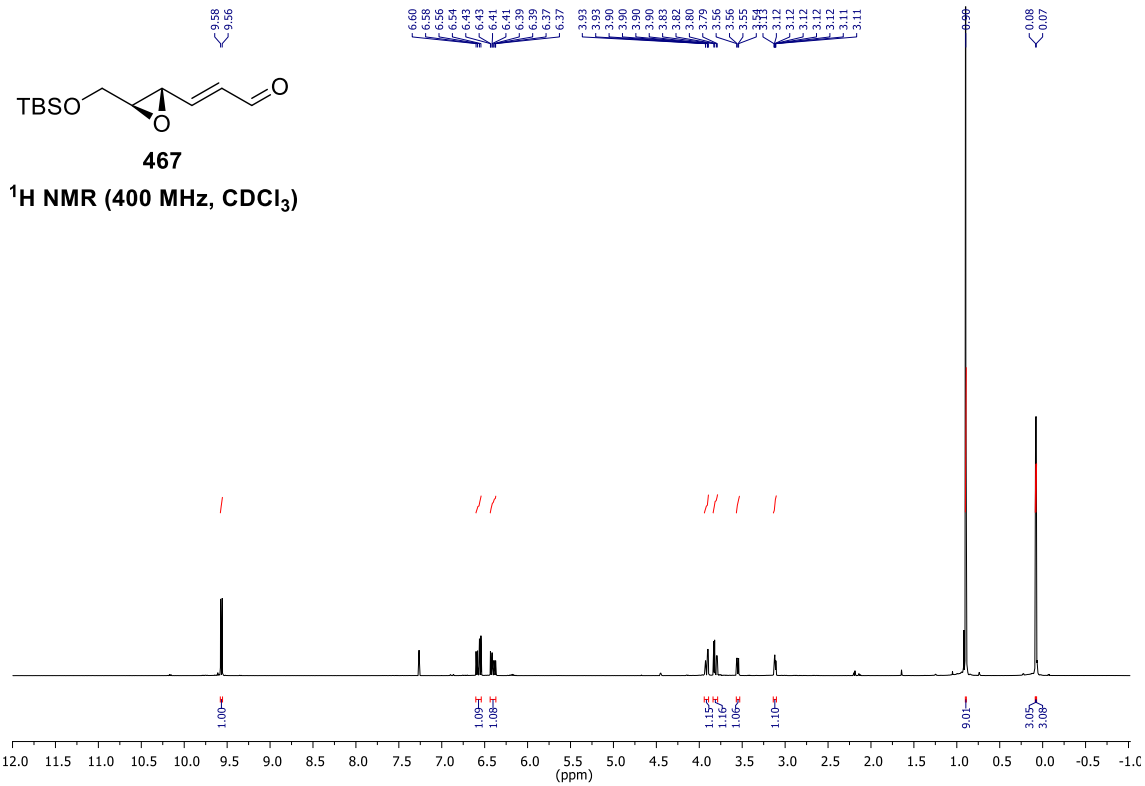
460

^{13}C NMR (100 MHz, $CDCl_3$)









467

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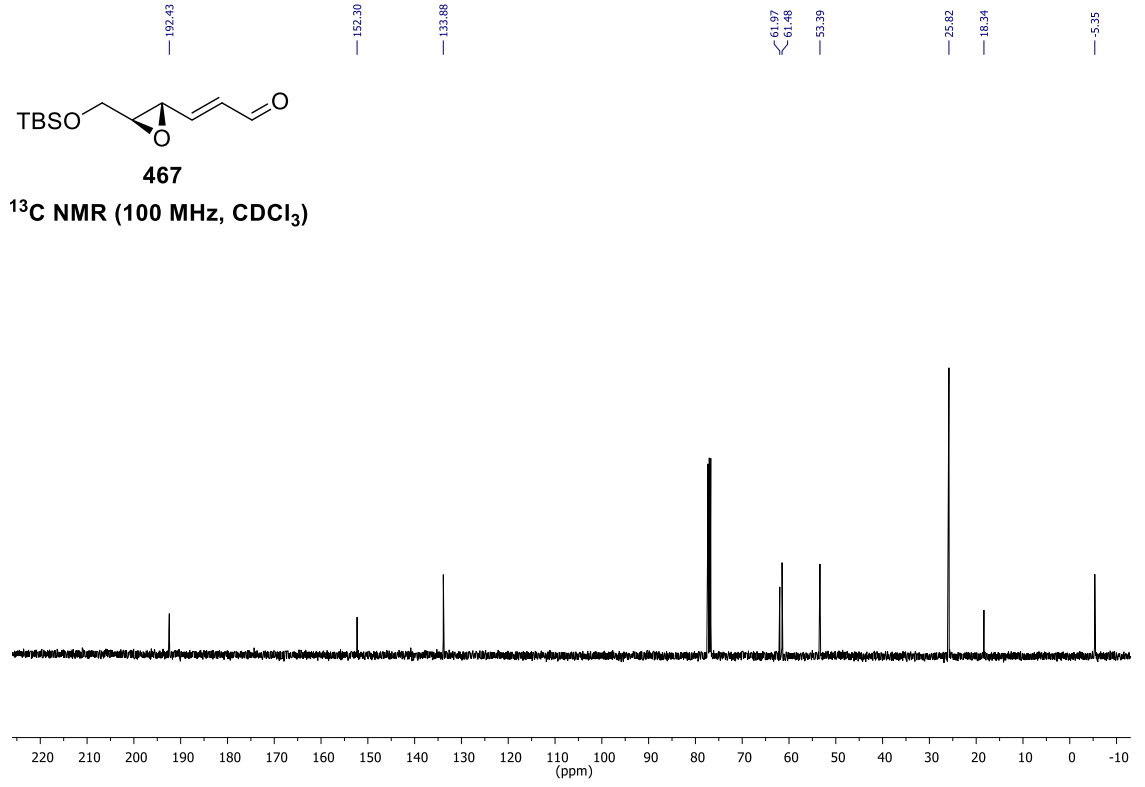
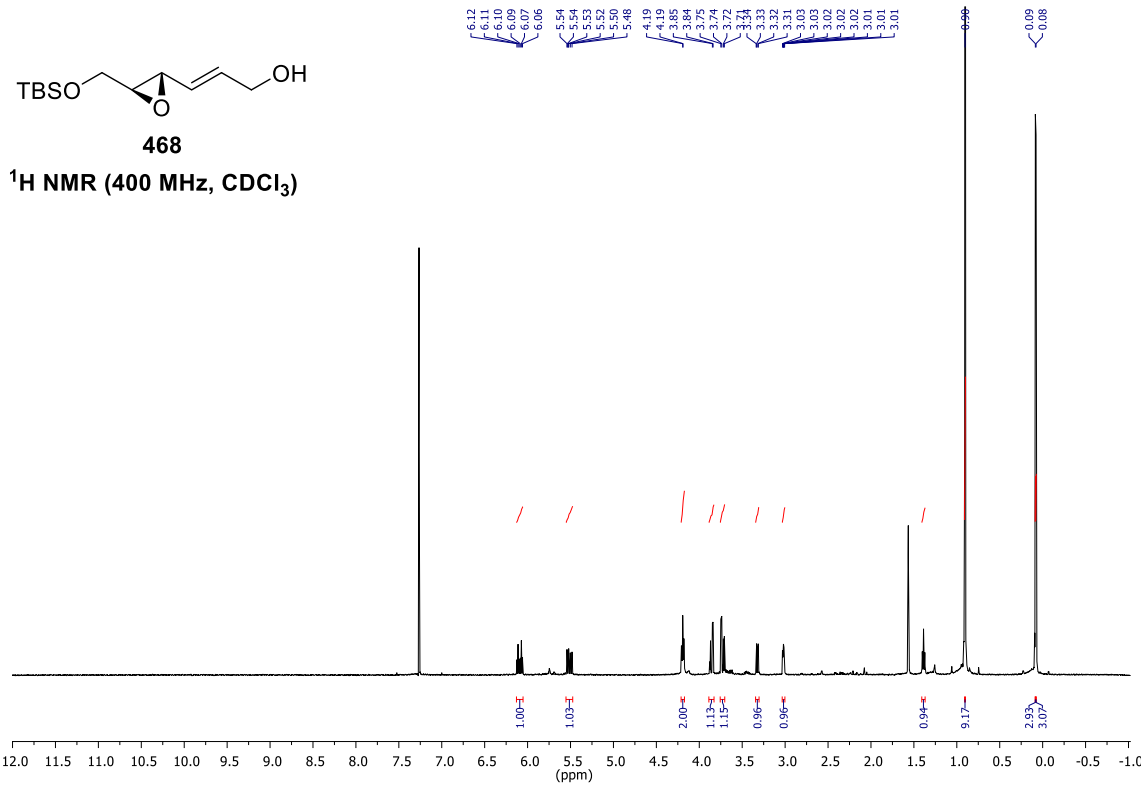


467

^{13}C NMR (100 MHz, $CDCl_3$)



468

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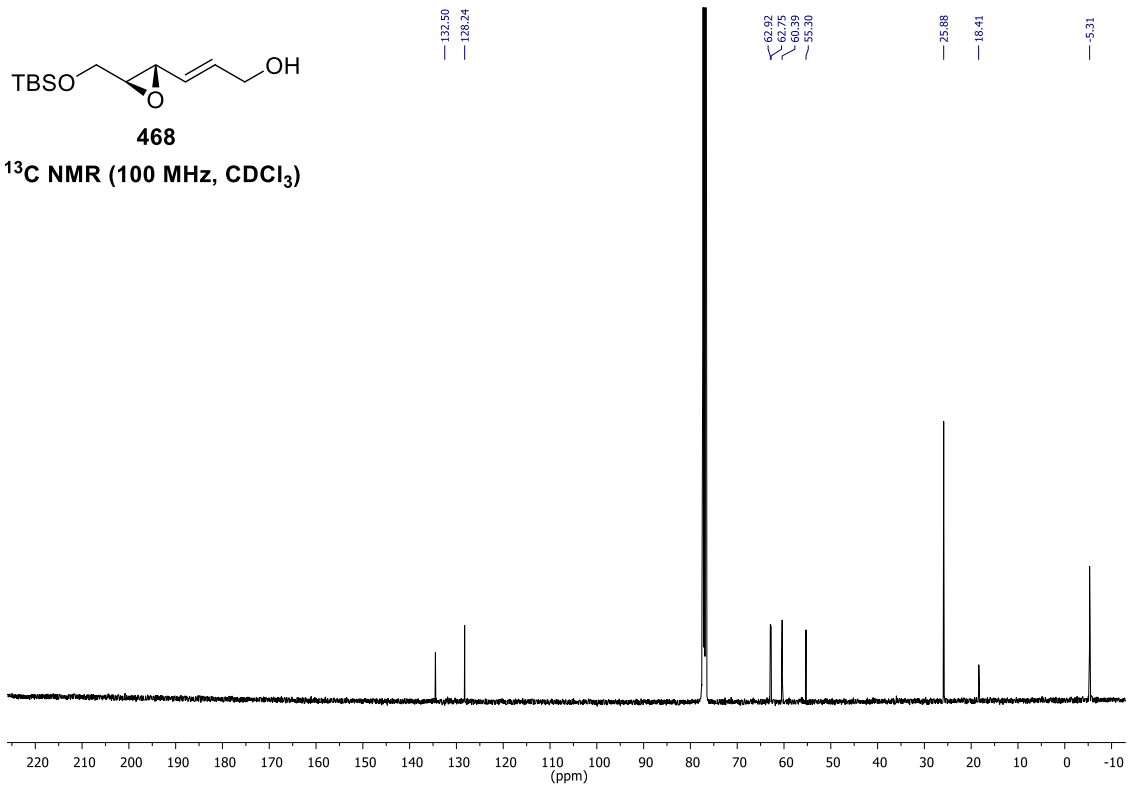

468

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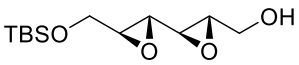
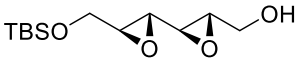


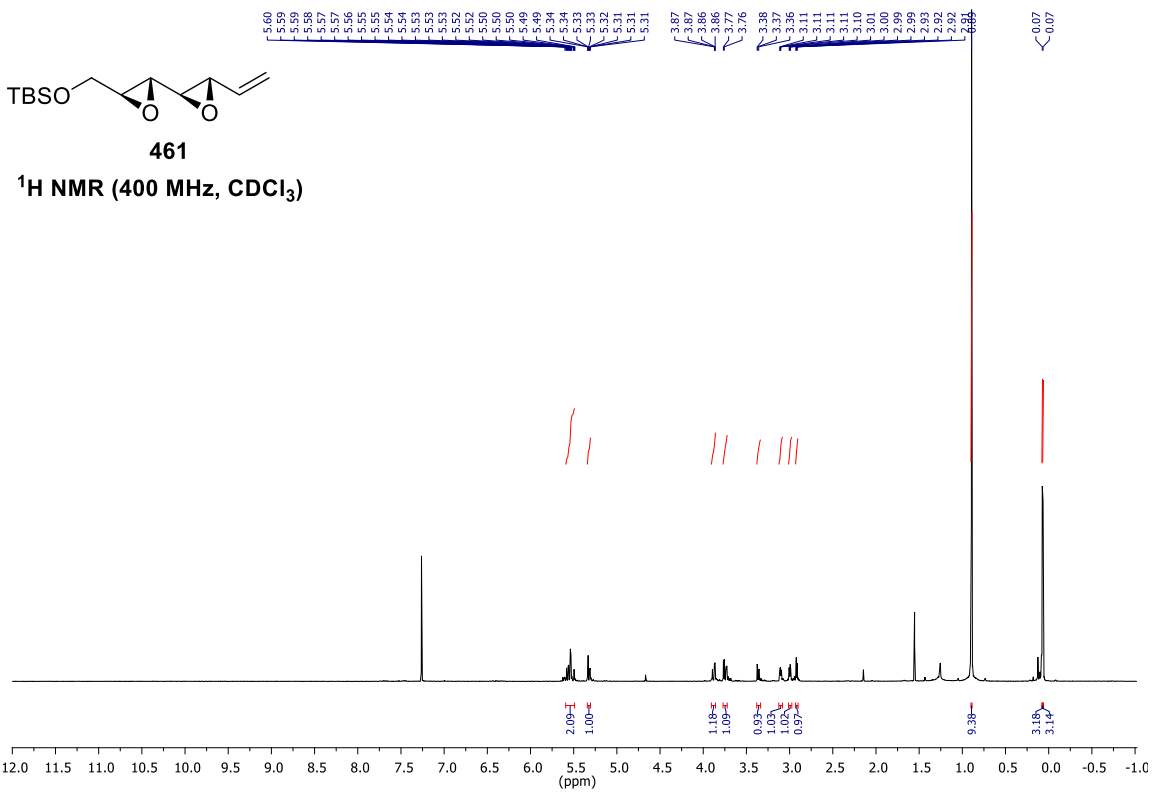
469 from 468

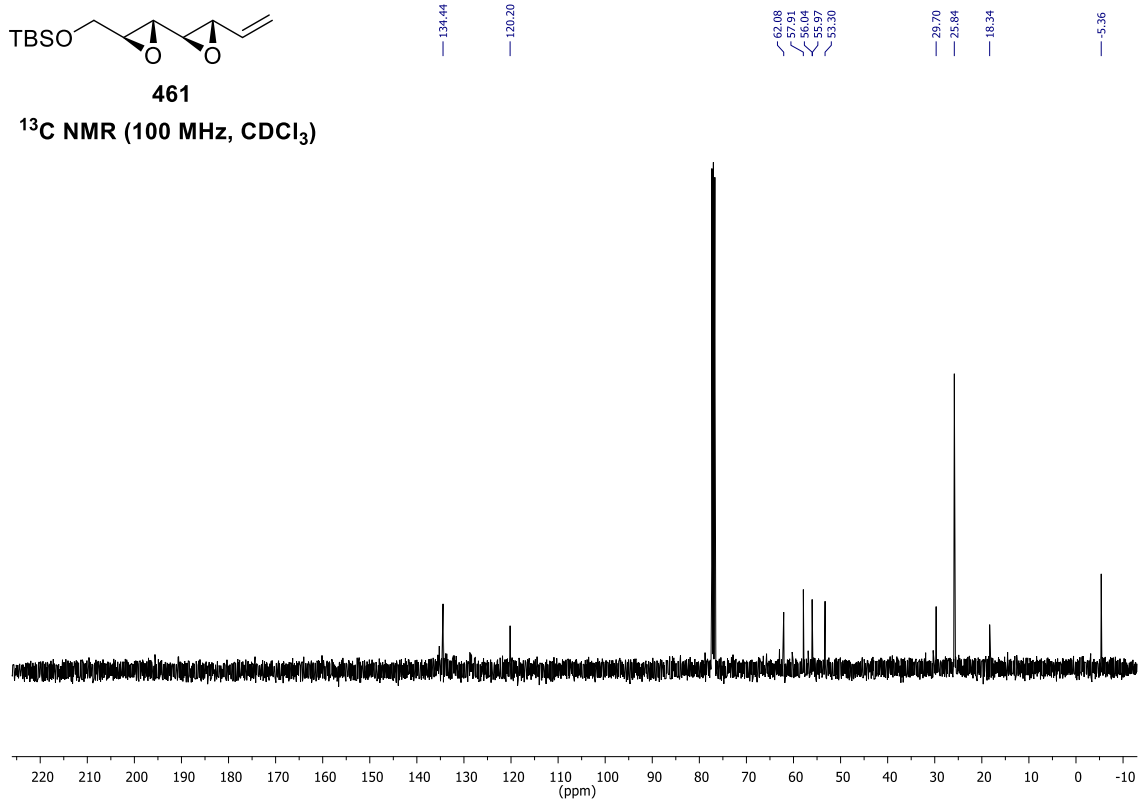
^{1}H NMR (400 MHz, $CDCl_3$)

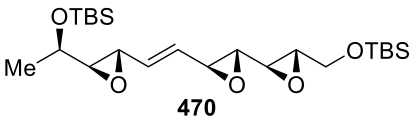


469 from 468

^{13}C NMR (100 MHz, $CDCl_3$)

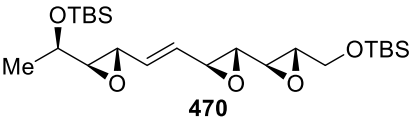






470

^{1}H NMR (400 MHz, $CDCl_3$)



470

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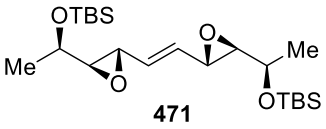

471

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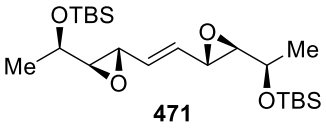

471

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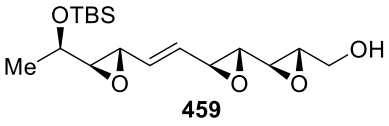

459

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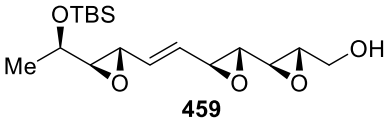
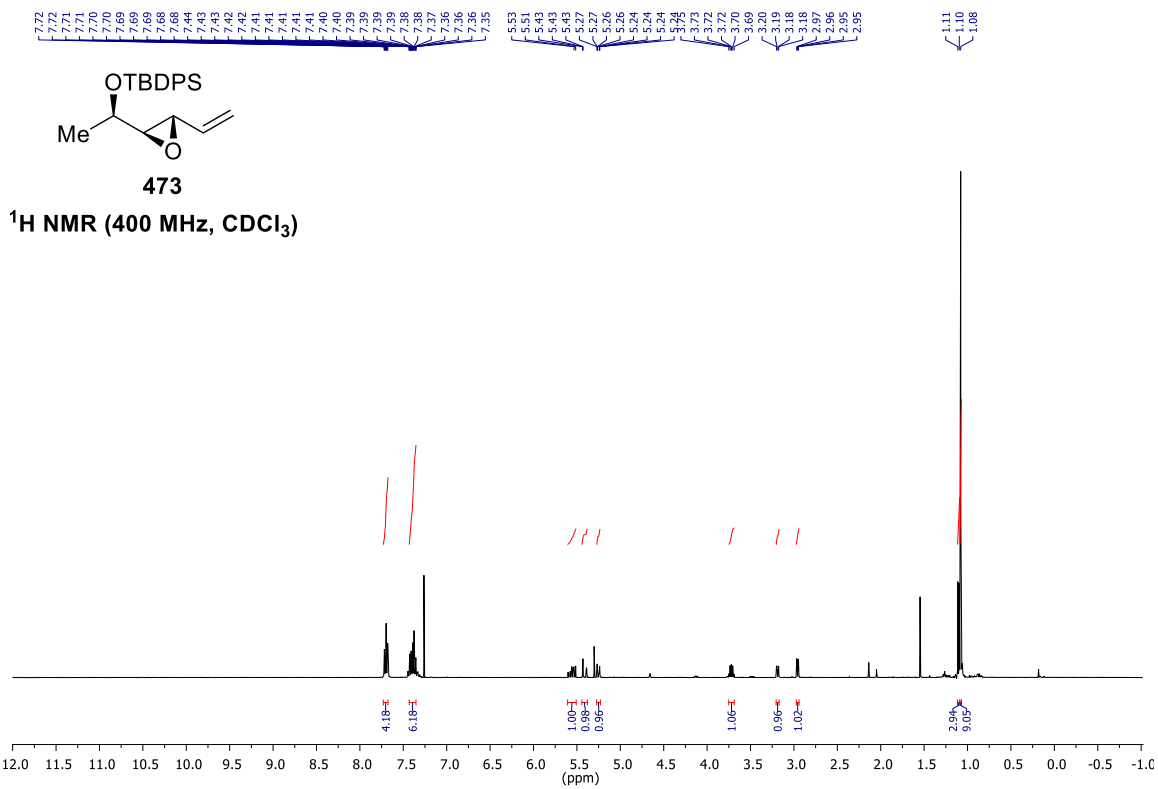


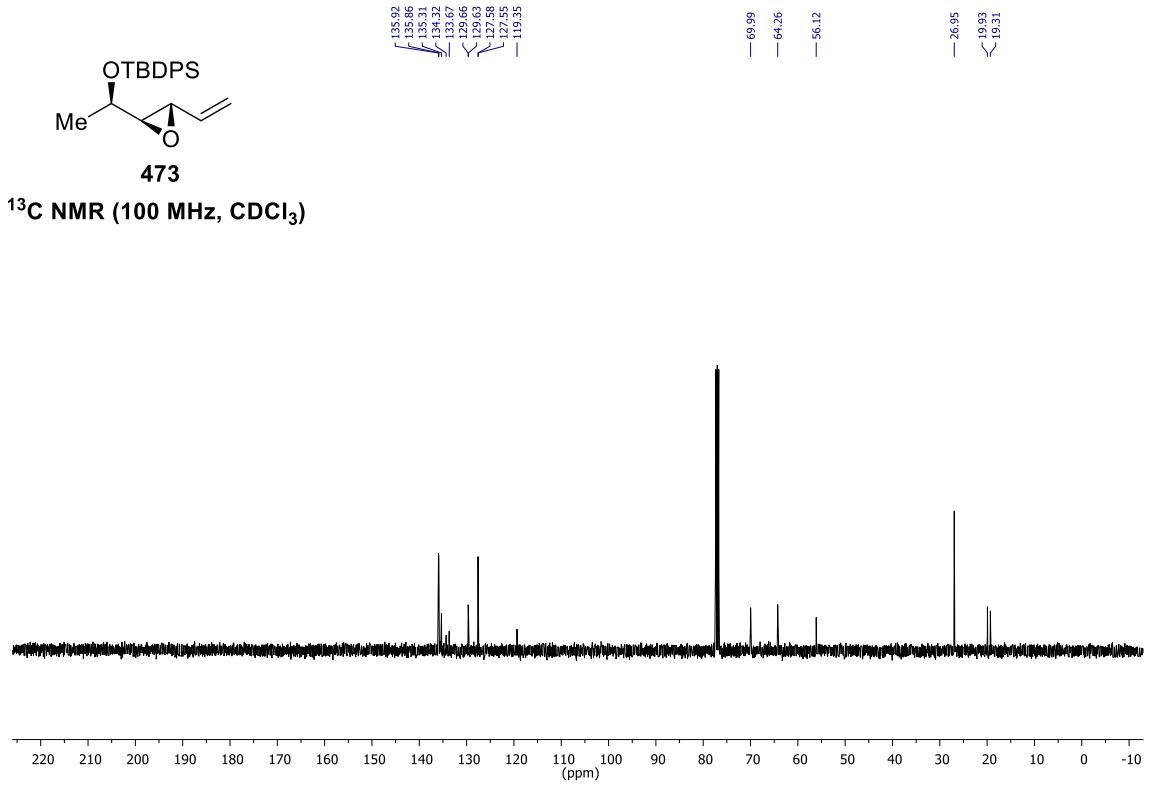
459

^{13}C NMR (100 MHz, $CDCl_3$)



473

^{1}H NMR (400 MHz, $CDCl_3$)



473

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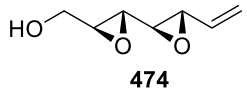

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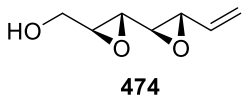

474

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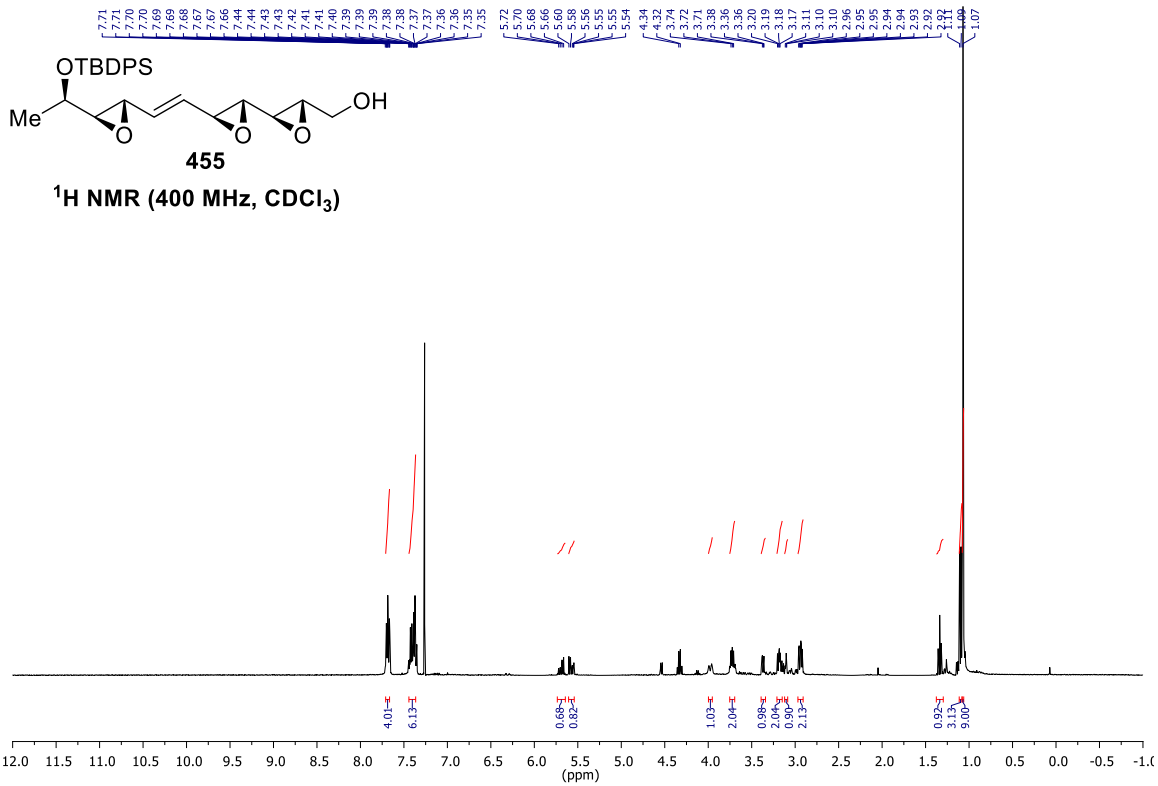

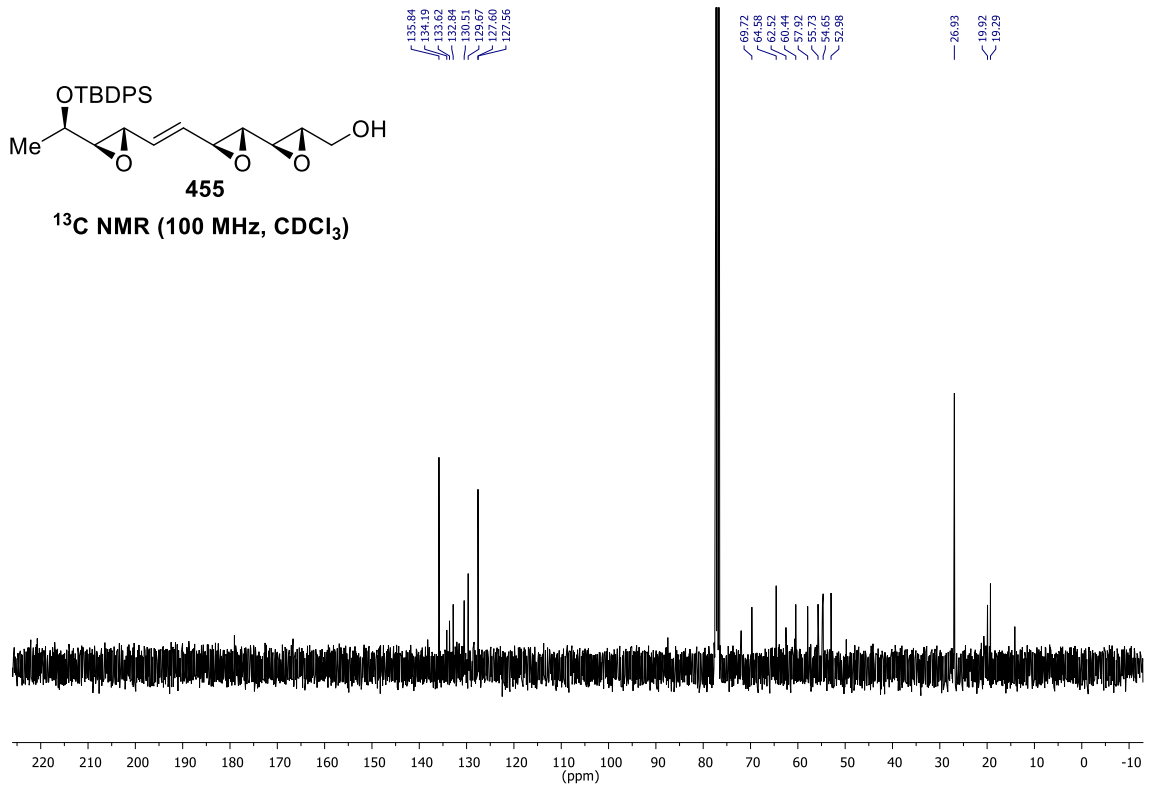

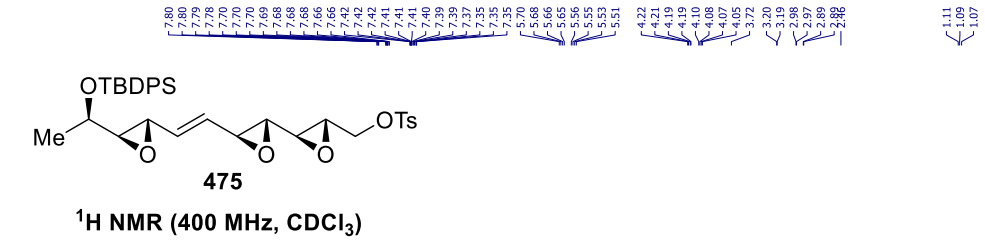

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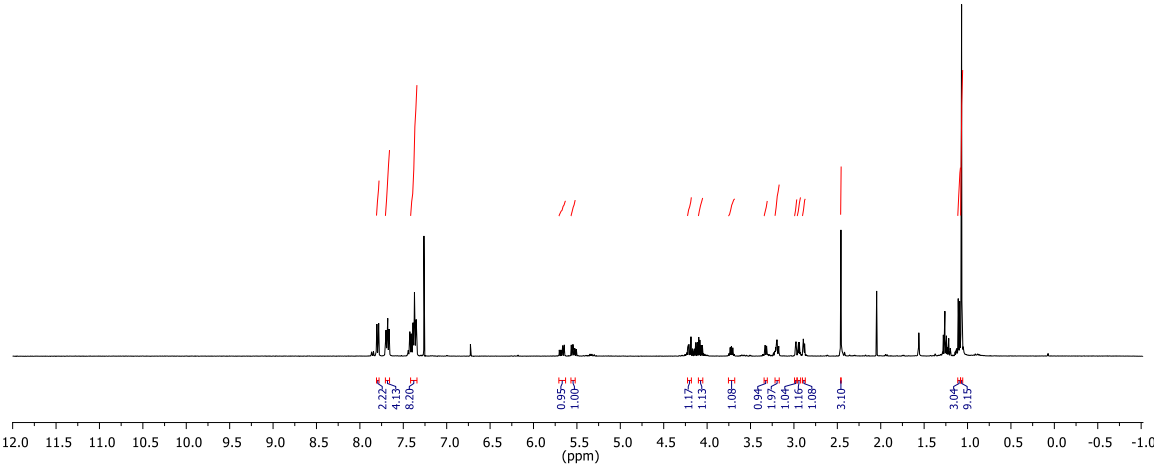

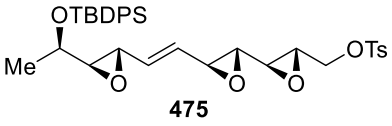

475

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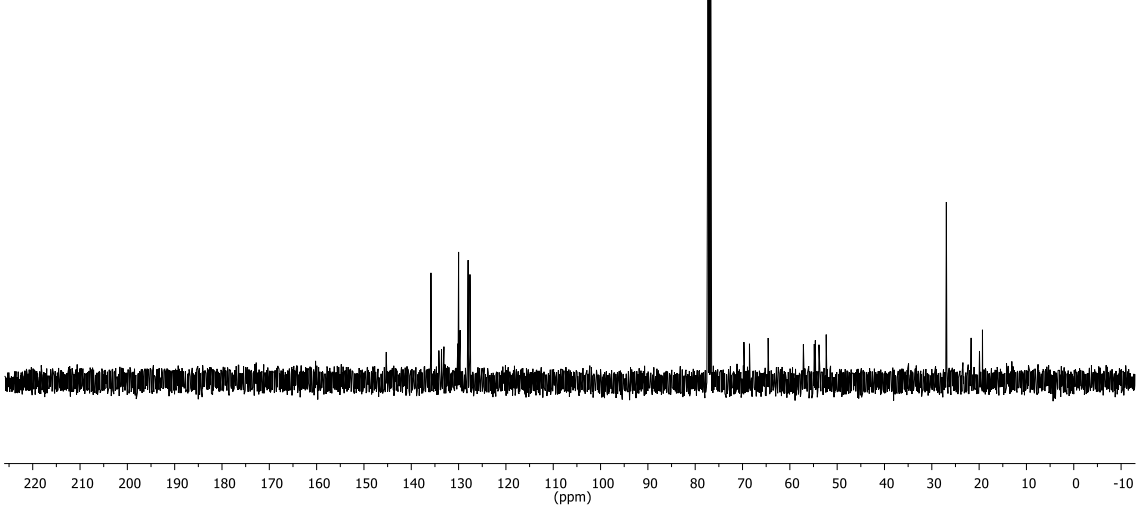
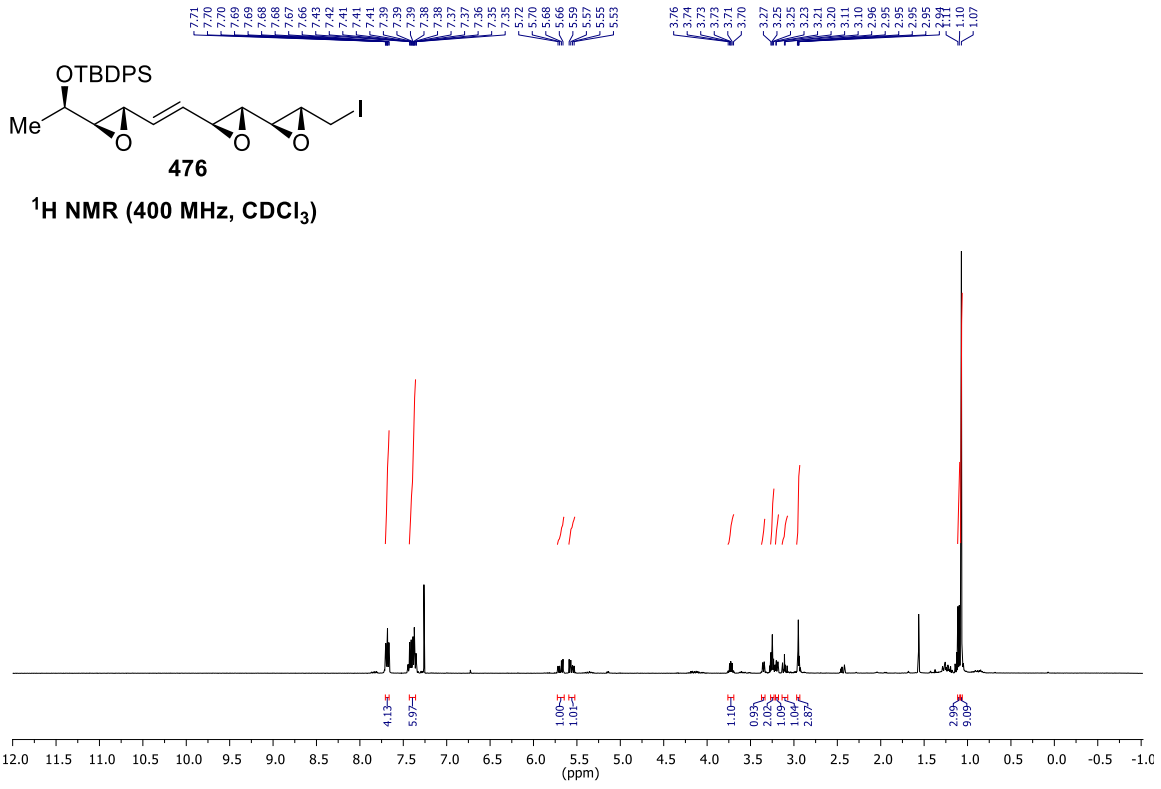
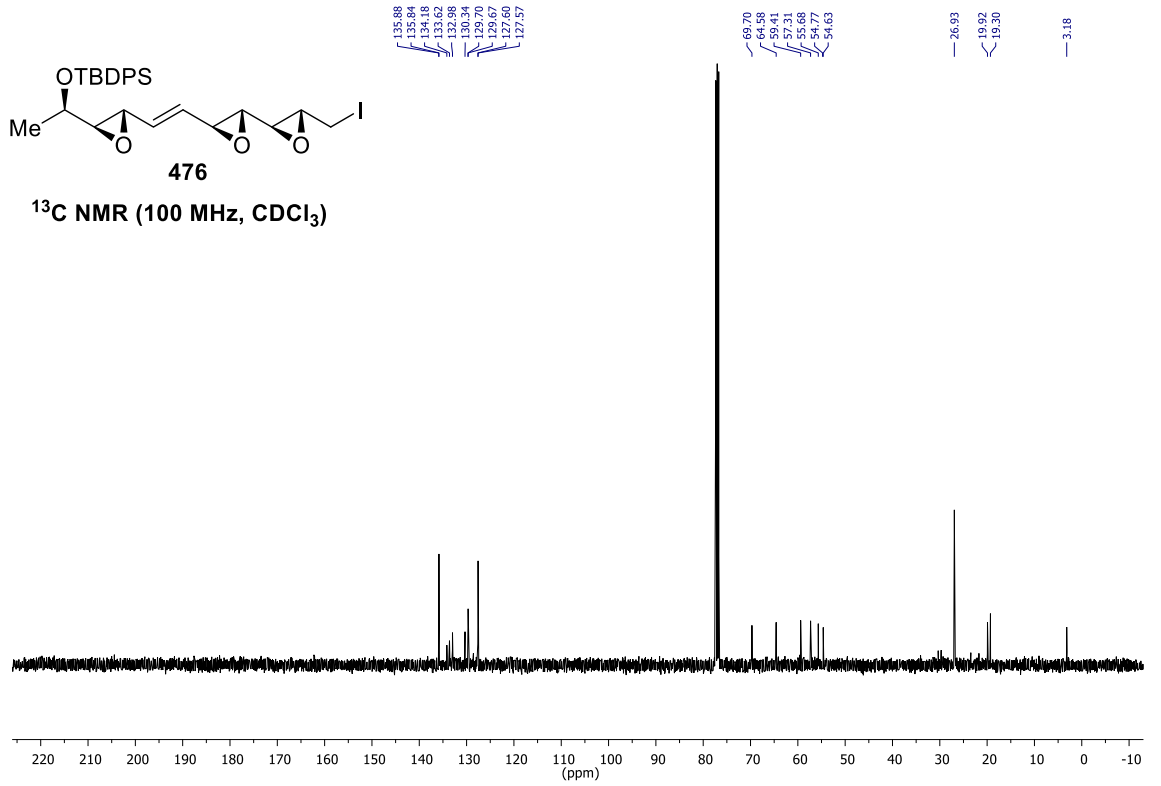
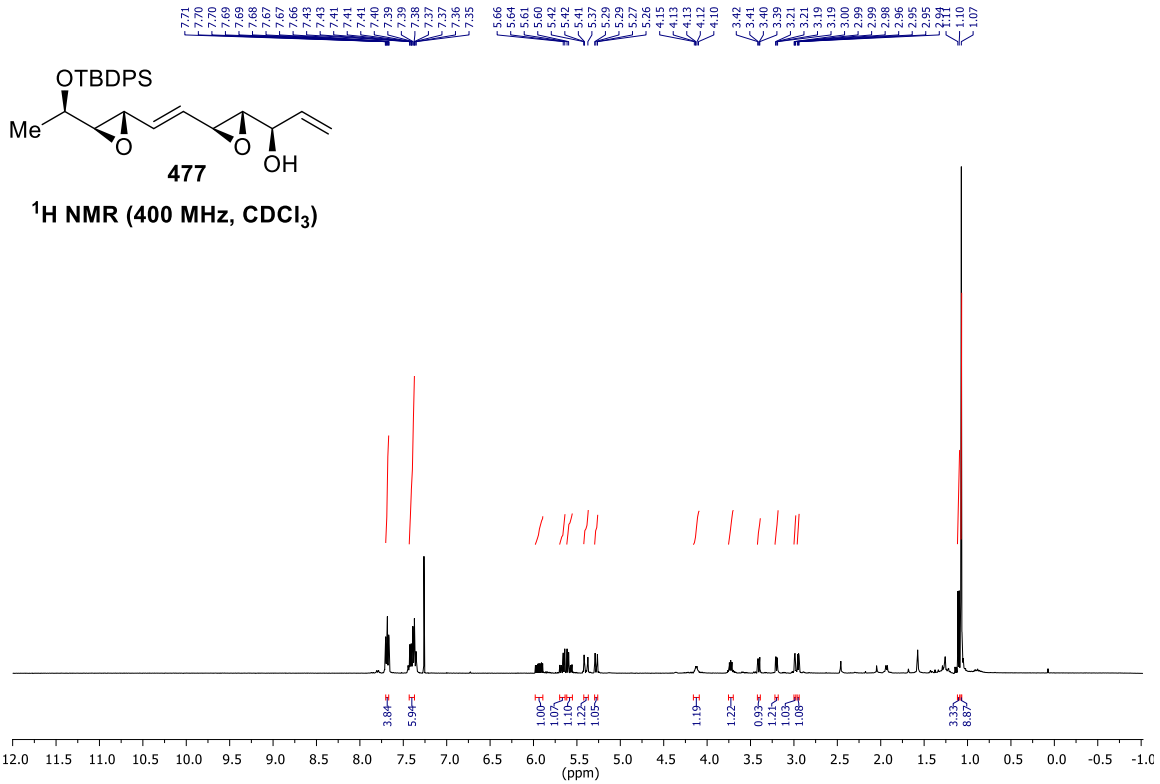


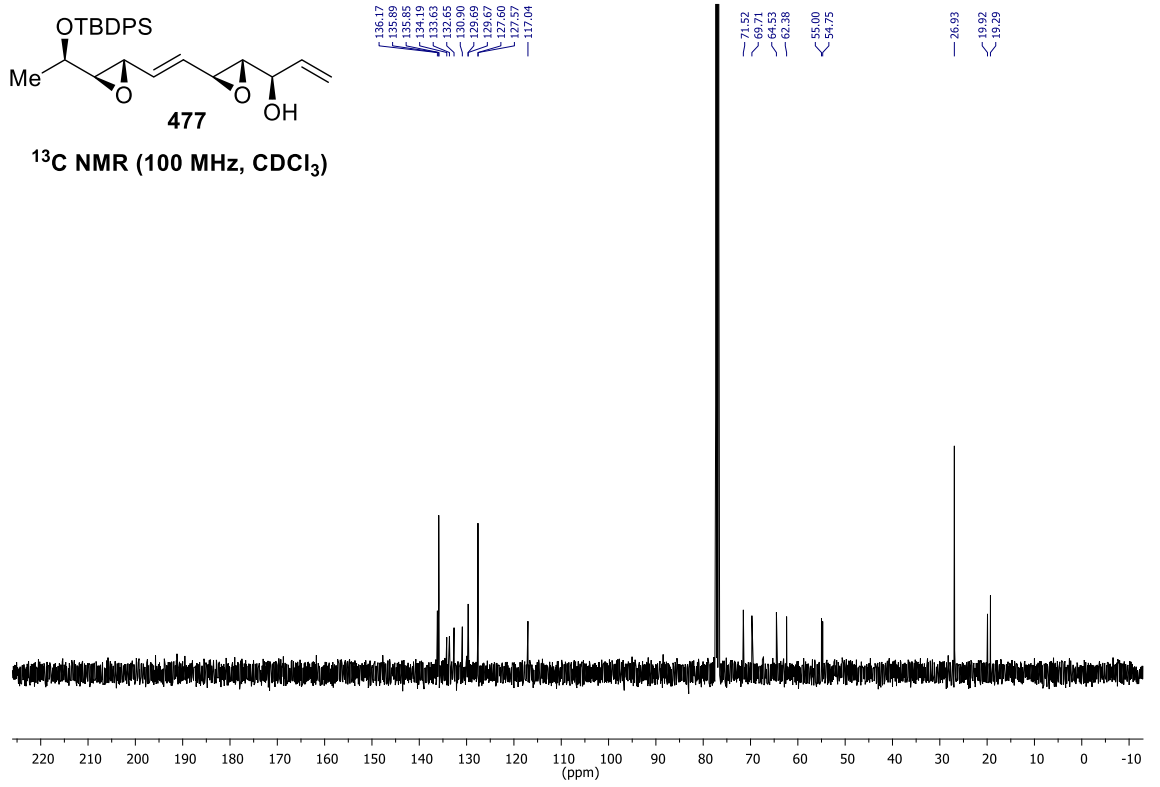


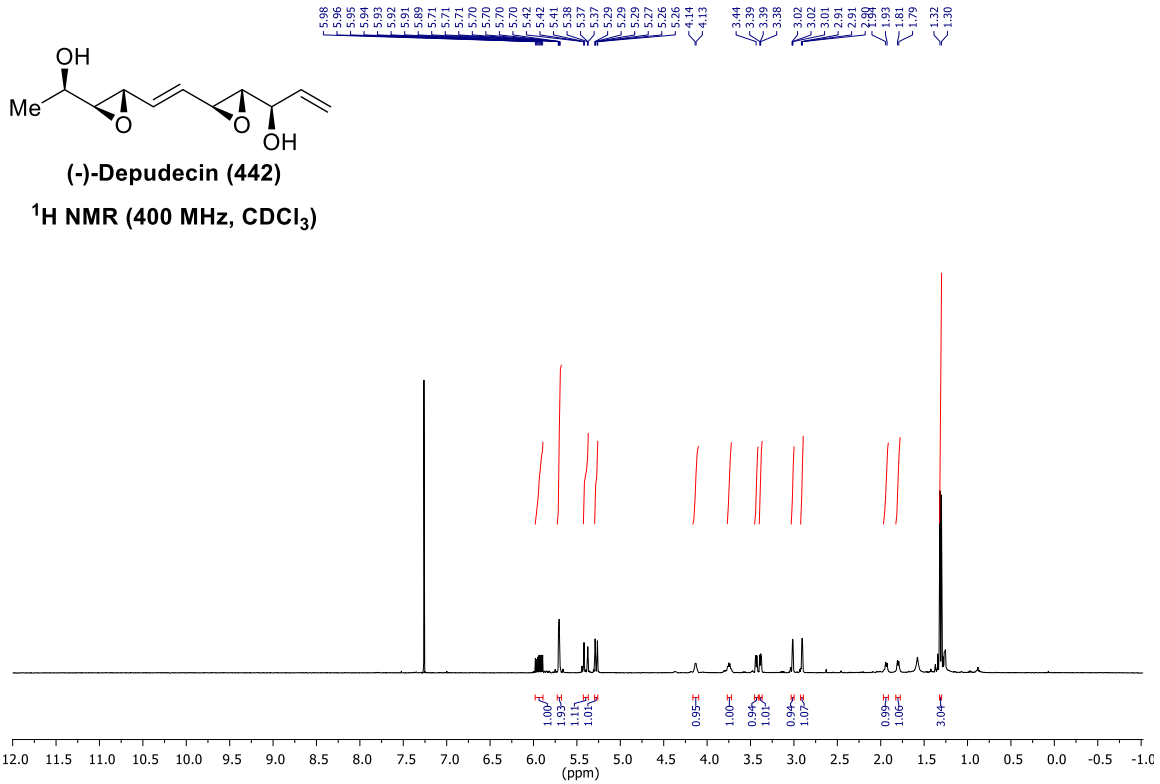
^{1}H NMR (400 MHz, $CDCl_3$)

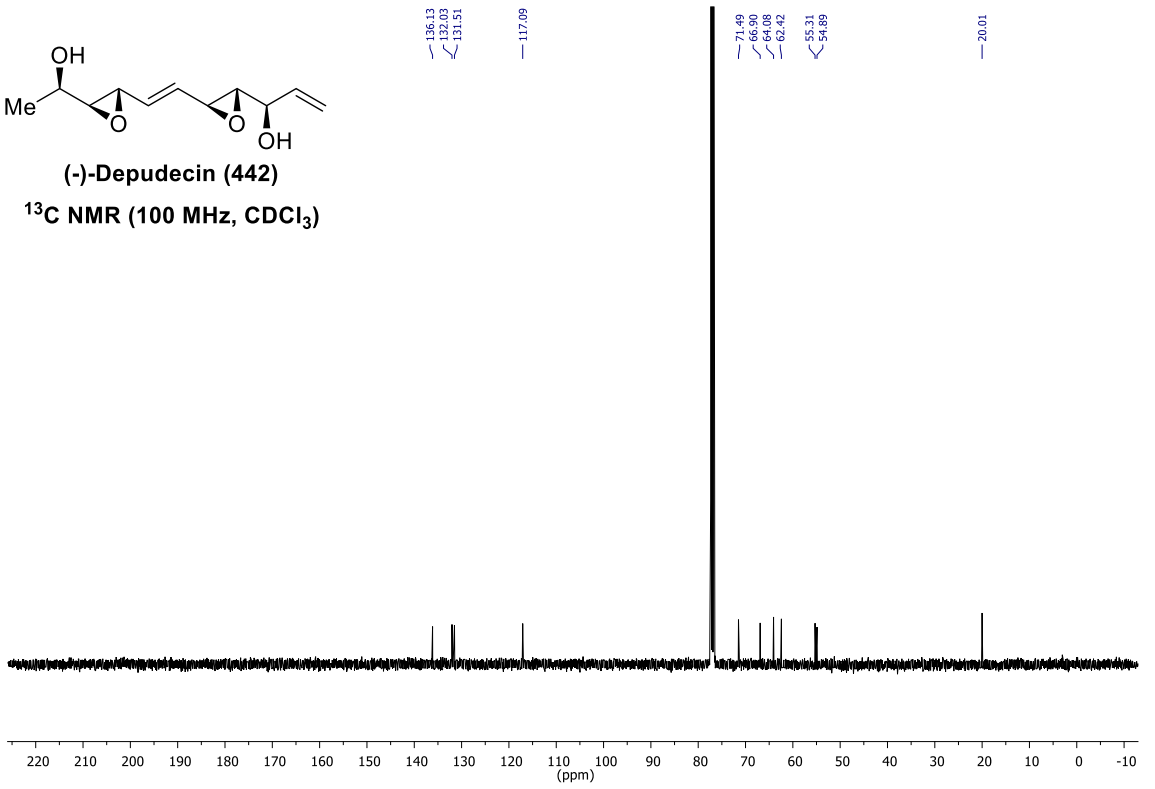


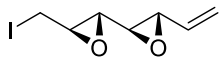
^{13}C NMR (100 MHz, $CDCl_3$)





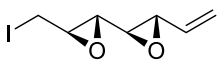






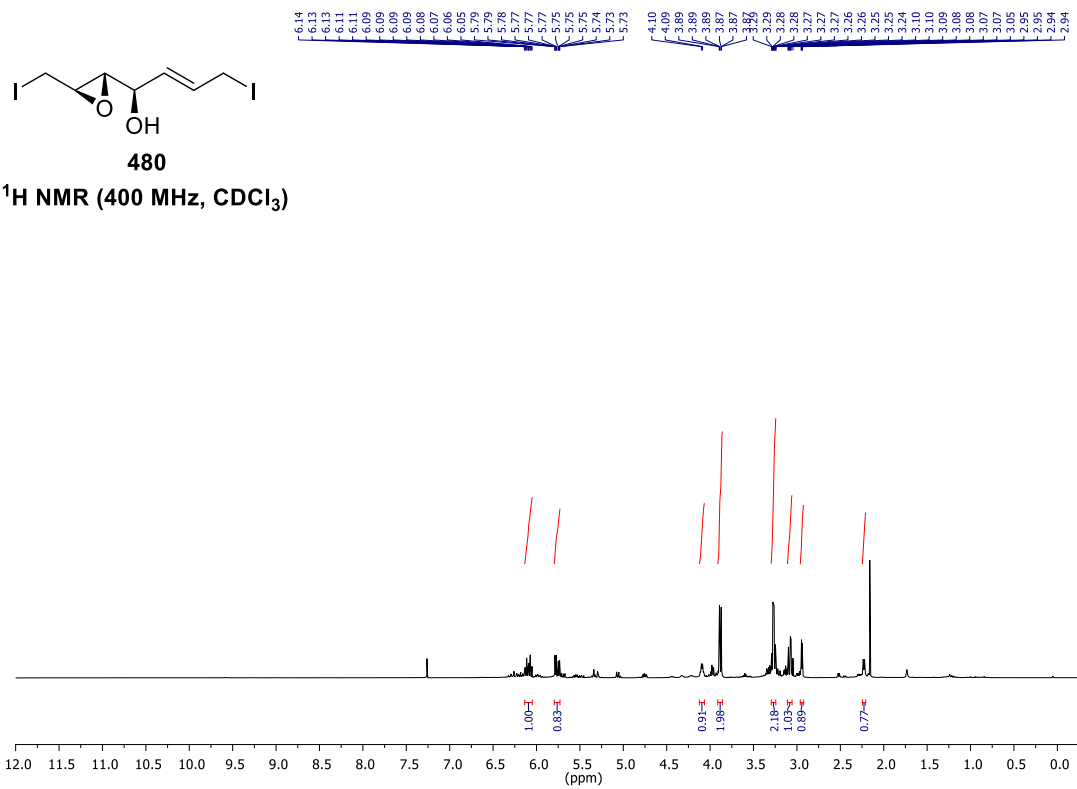
479 from 474

^{1}H NMR (400 MHz, $CDCl_3$)



479 from 474

^{13}C NMR (100 MHz, $CDCl_3$)



480

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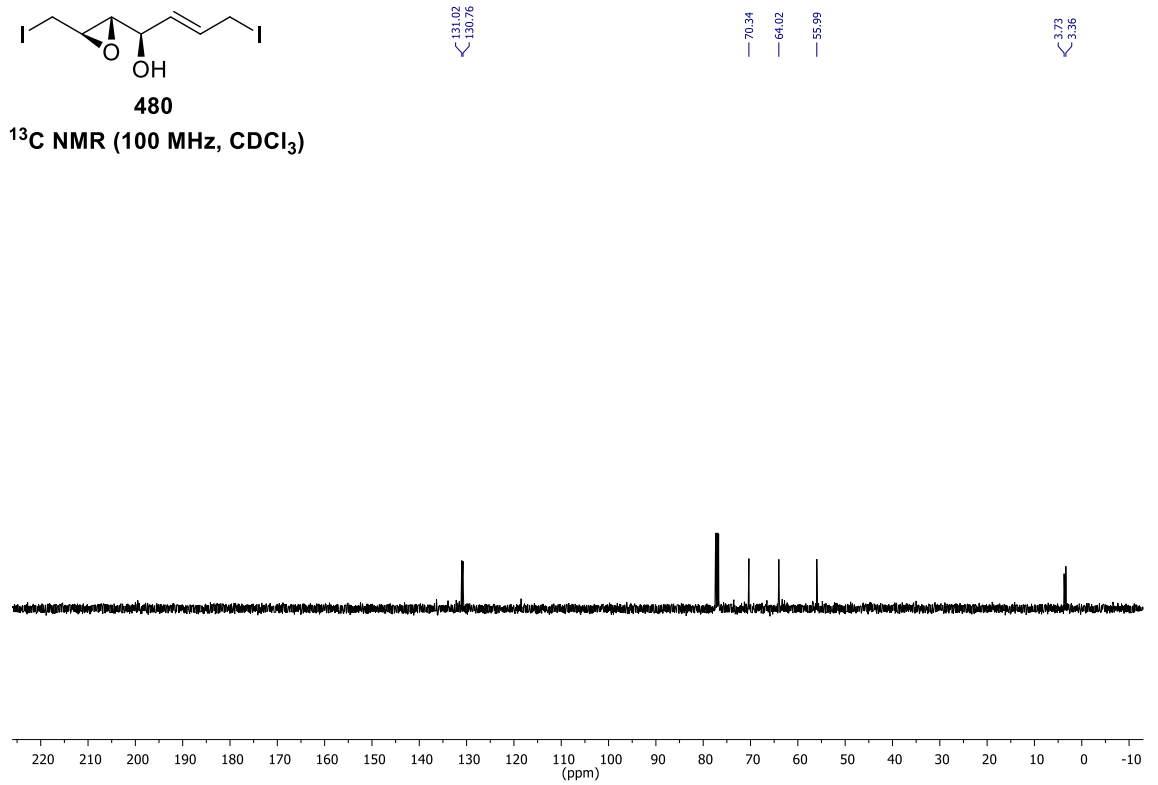
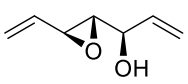


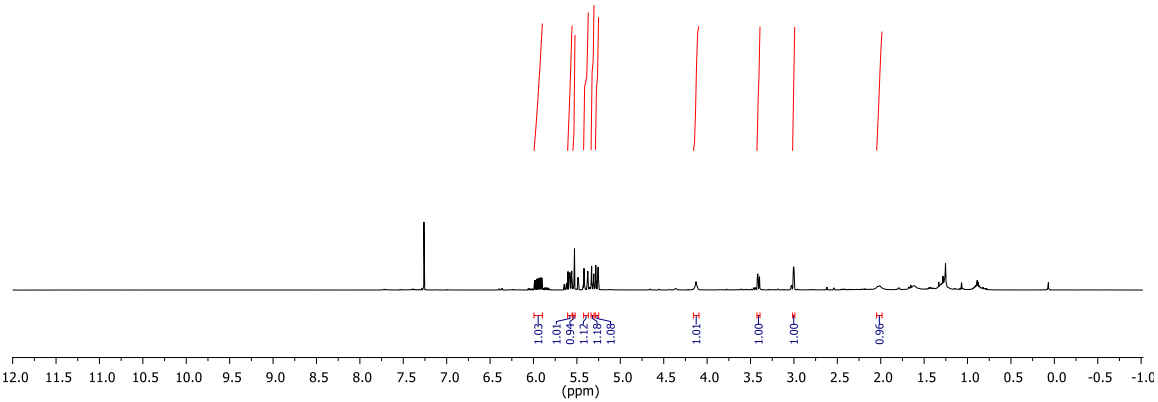
480

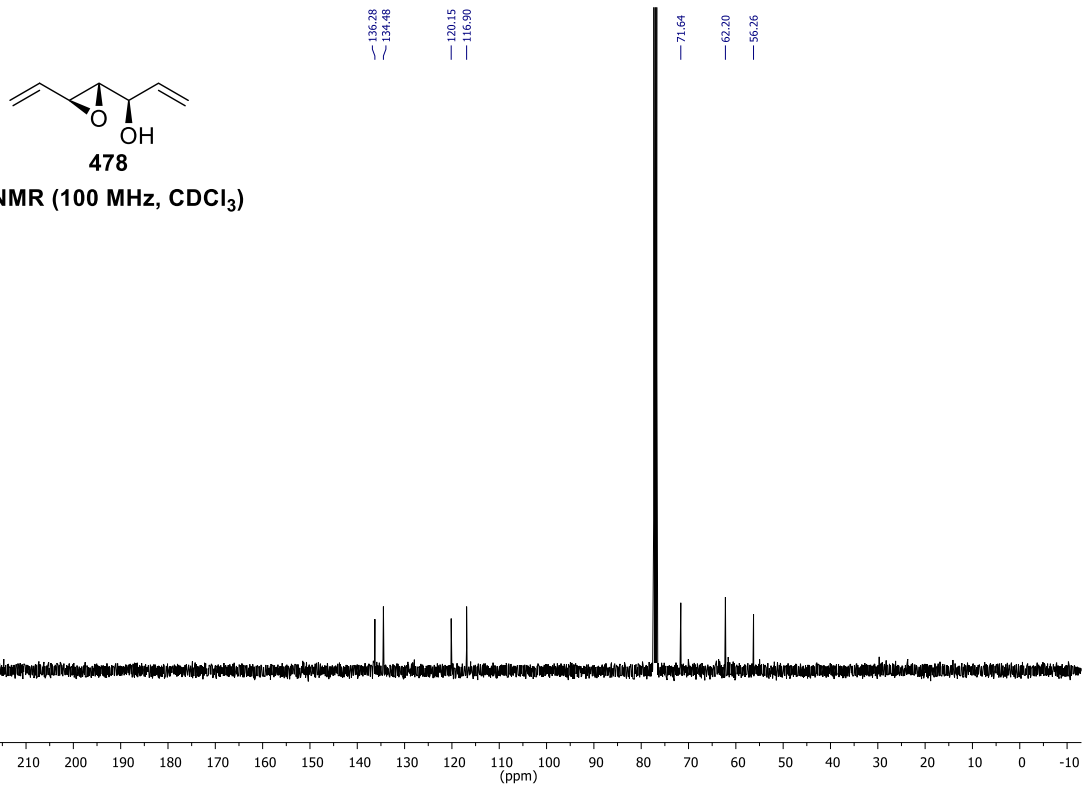
^{13}C NMR (100 MHz, $CDCl_3$)



478

^{1}H NMR (400 MHz, $CDCl_3$)





478

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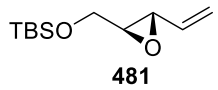
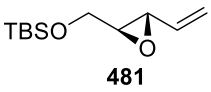


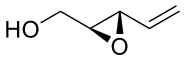
481

^{1}H NMR (400 MHz, $CDCl_3$)



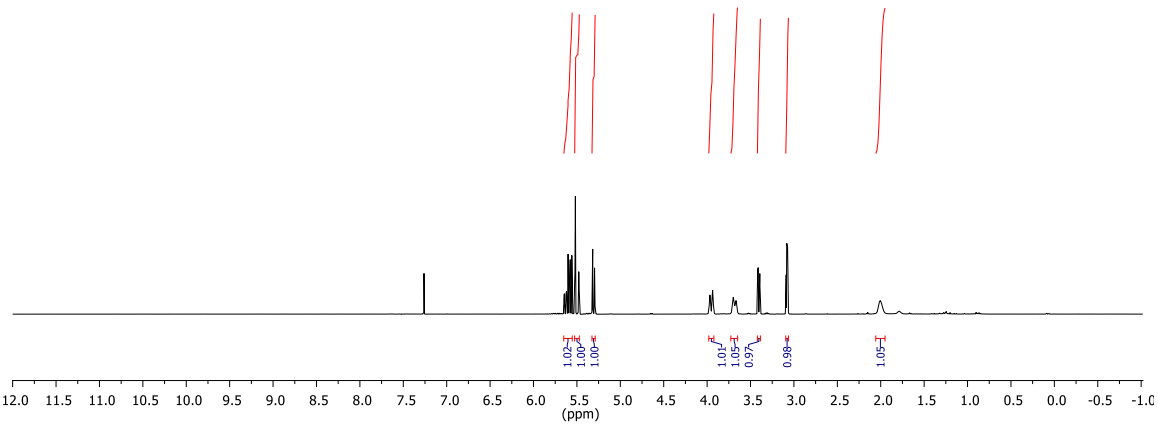
481

^{13}C NMR (100 MHz, $CDCl_3$)



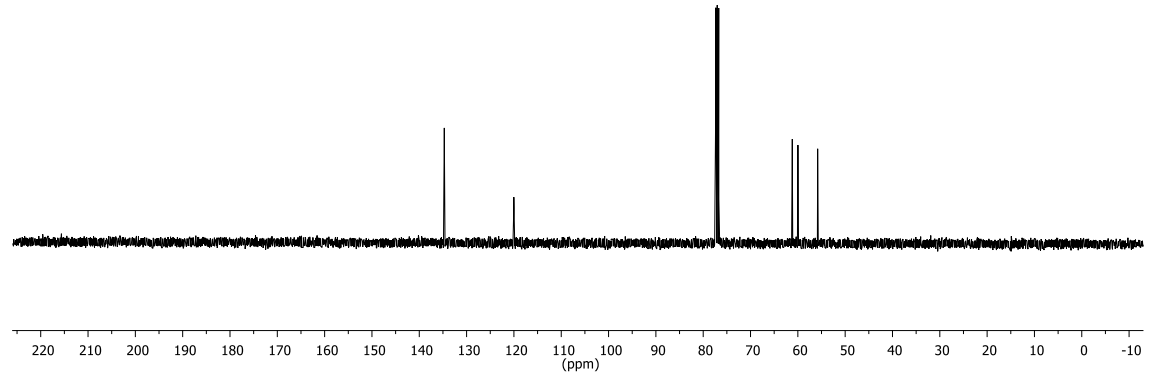
482

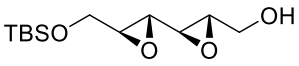
^{1}H NMR (400 MHz, $CDCl_3$)



482

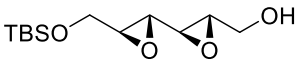
^{13}C NMR (100 MHz, $CDCl_3$)





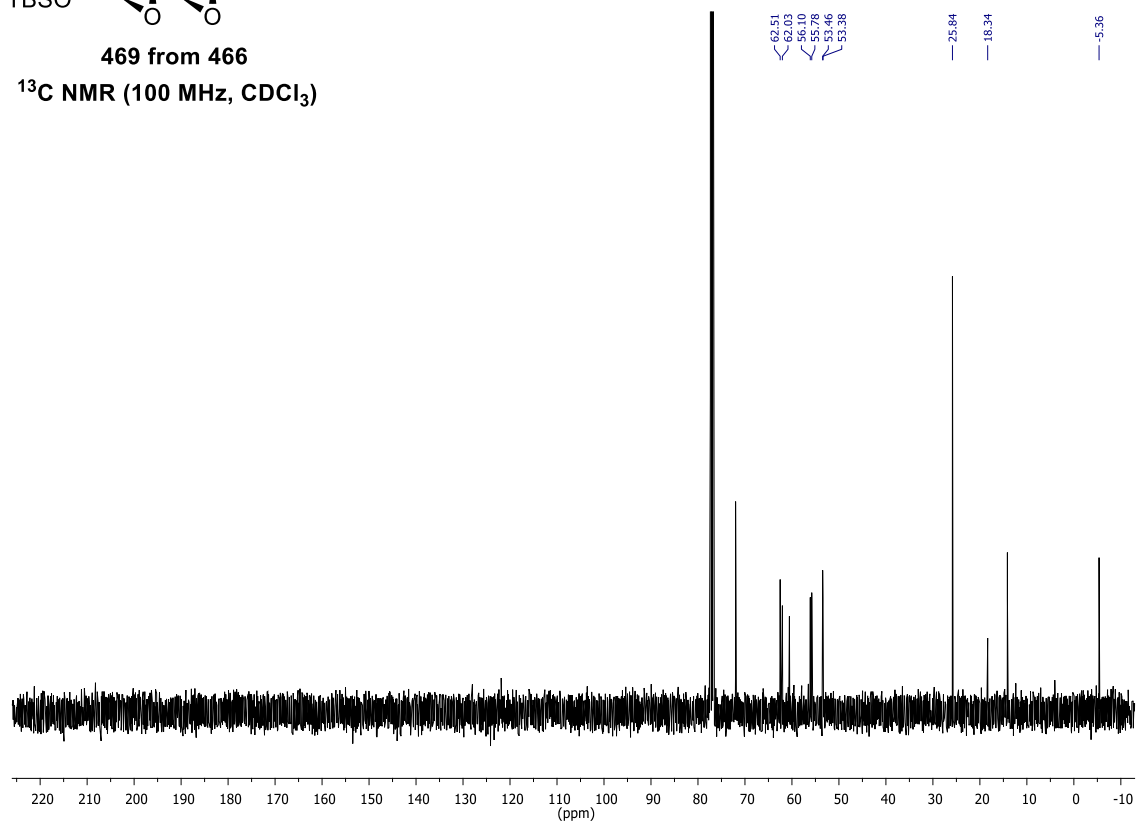
469 from 466

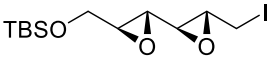
^{1}H NMR (400 MHz, $CDCl_3$)



469 from 466

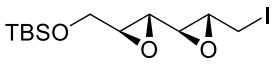
^{13}C NMR (100 MHz, $CDCl_3$)





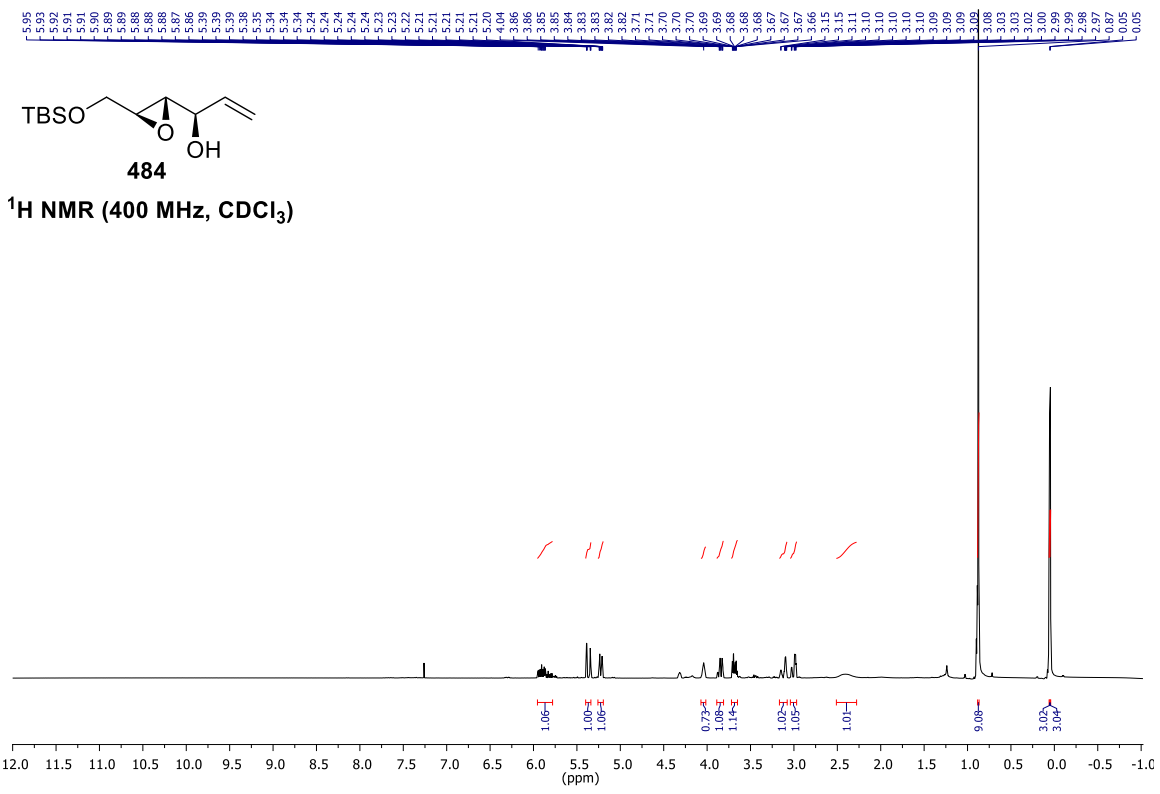
483

^{1}H NMR (400 MHz, $CDCl_3$)

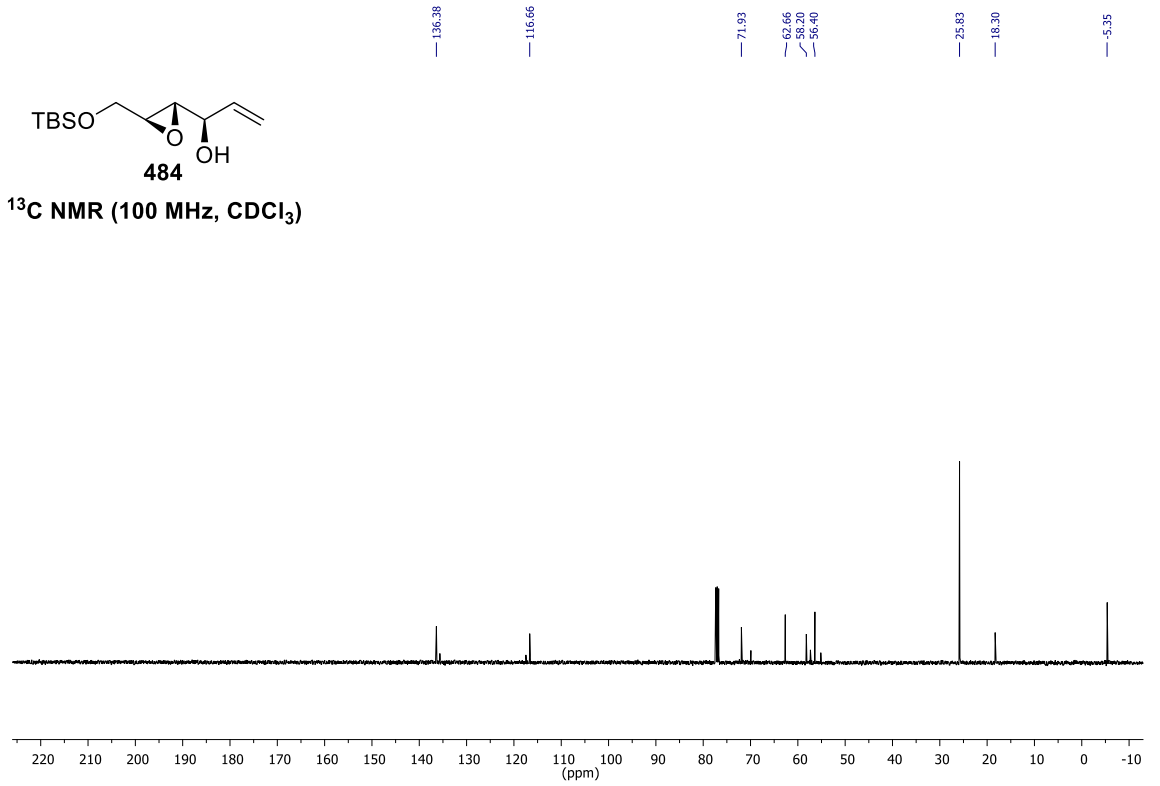


483

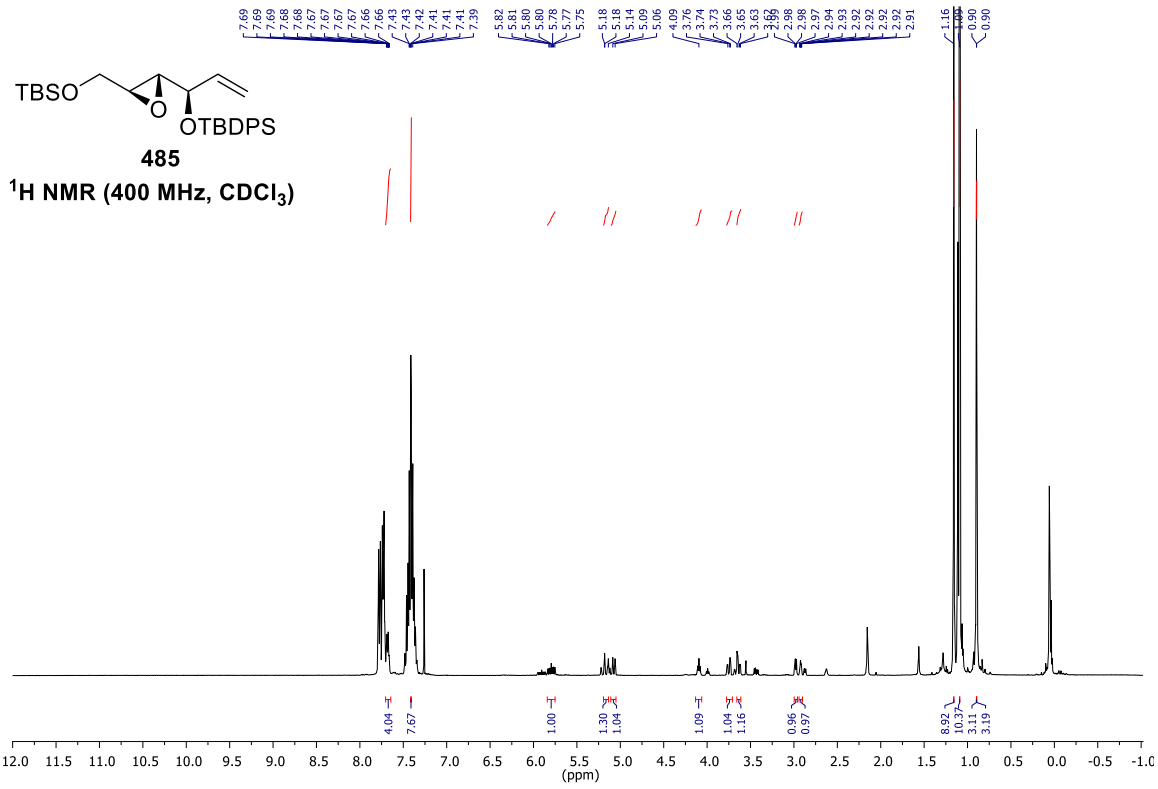
^{13}C NMR (100 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)

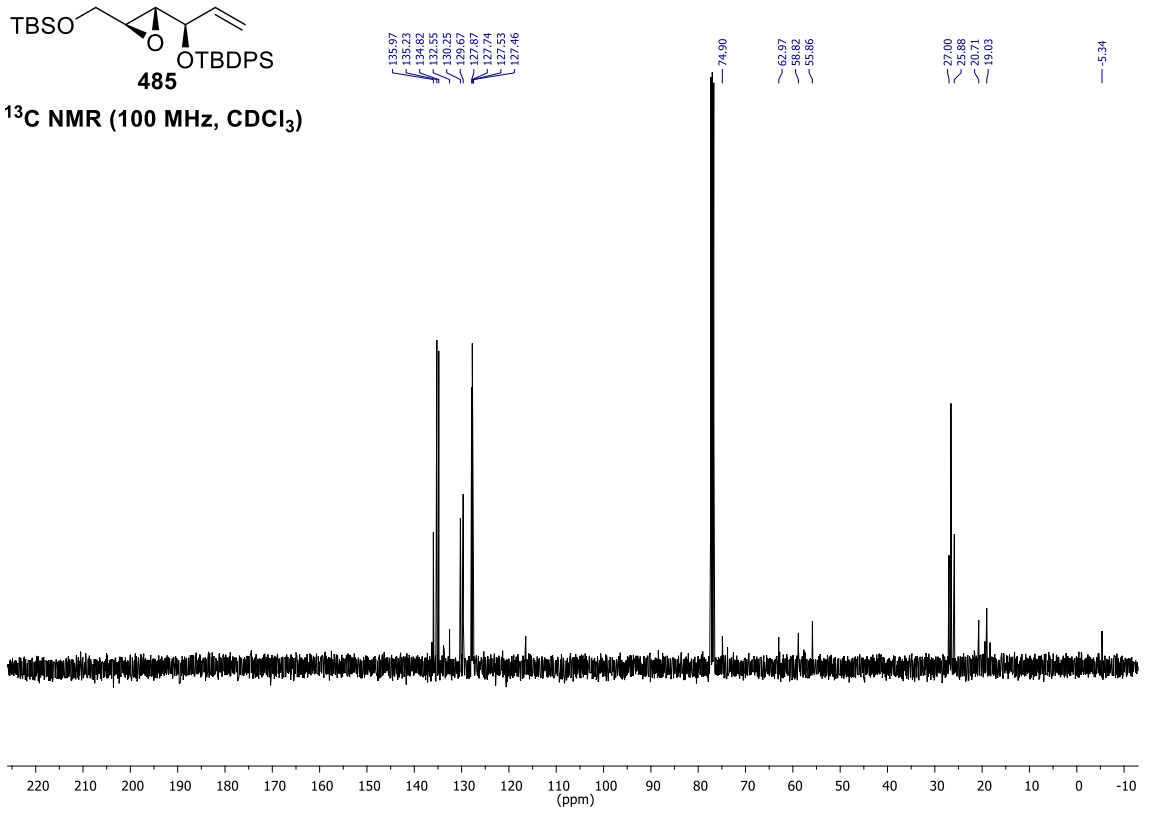


^{13}C NMR (100 MHz, $CDCl_3$)



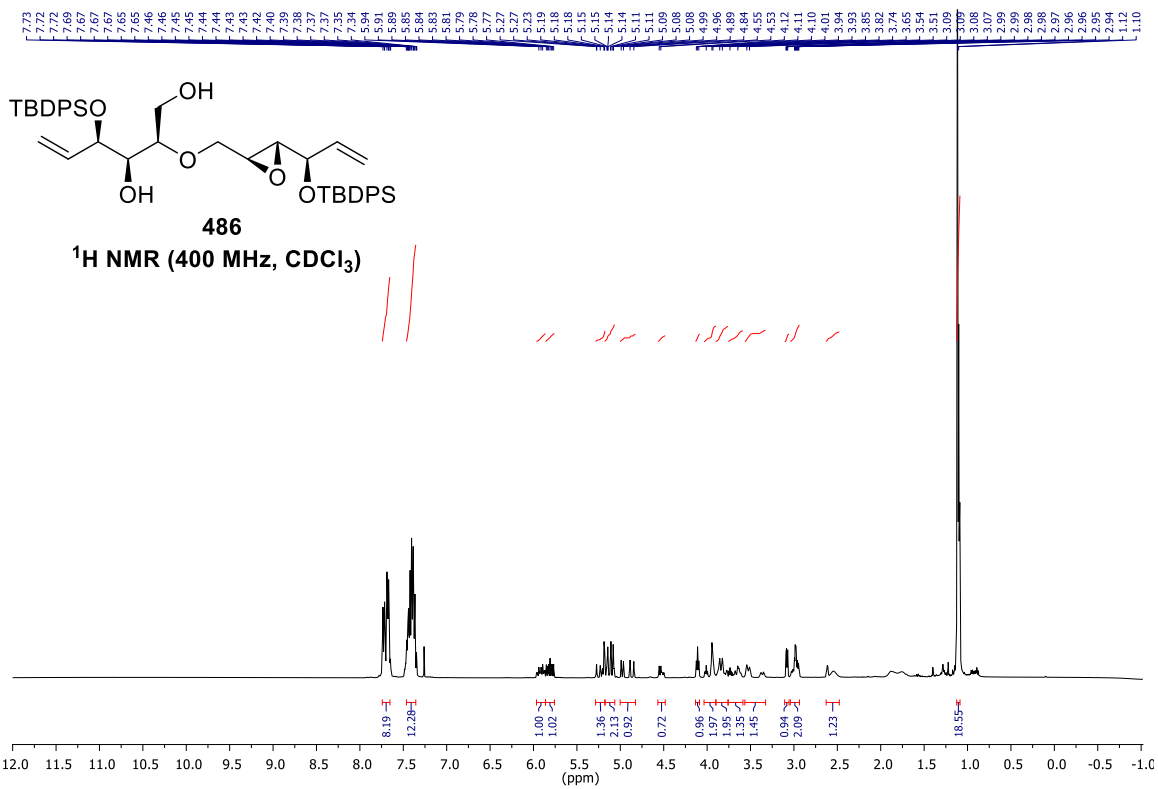
485

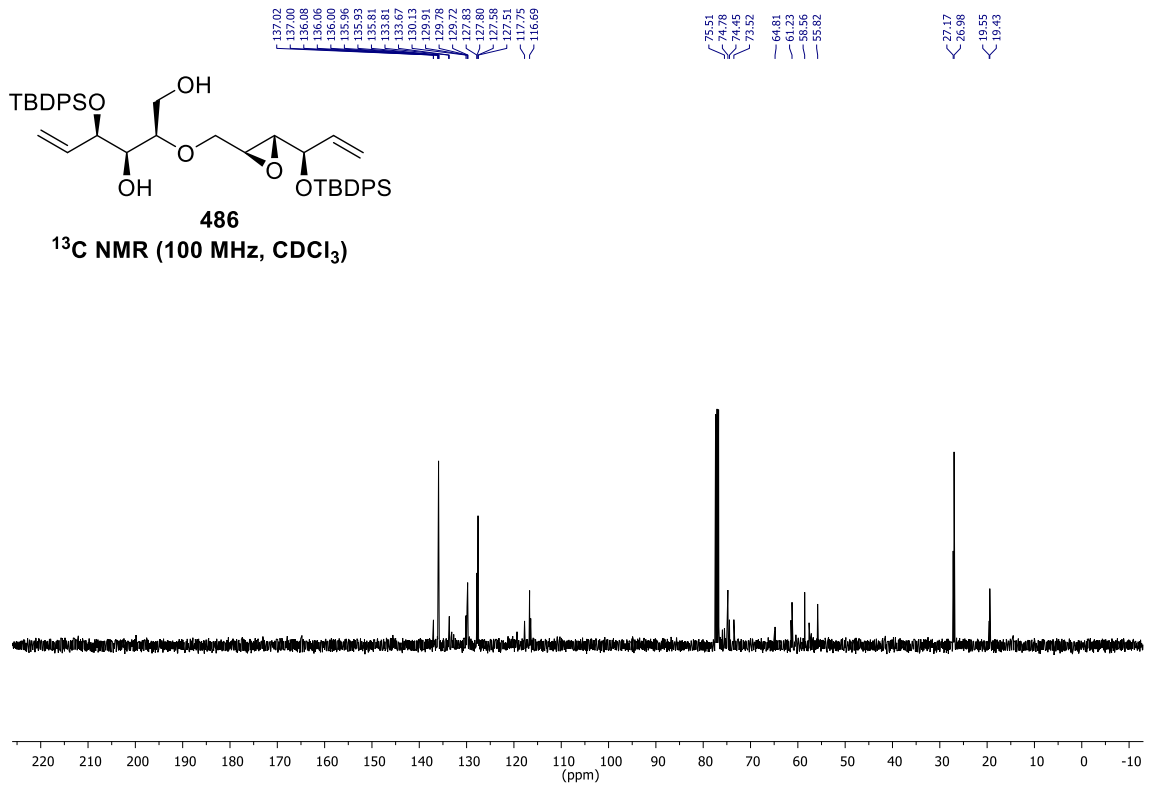
^{1}H NMR (400 MHz, $CDCl_3$)

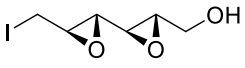


485

^{13}C NMR (100 MHz, $CDCl_3$)

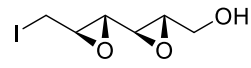






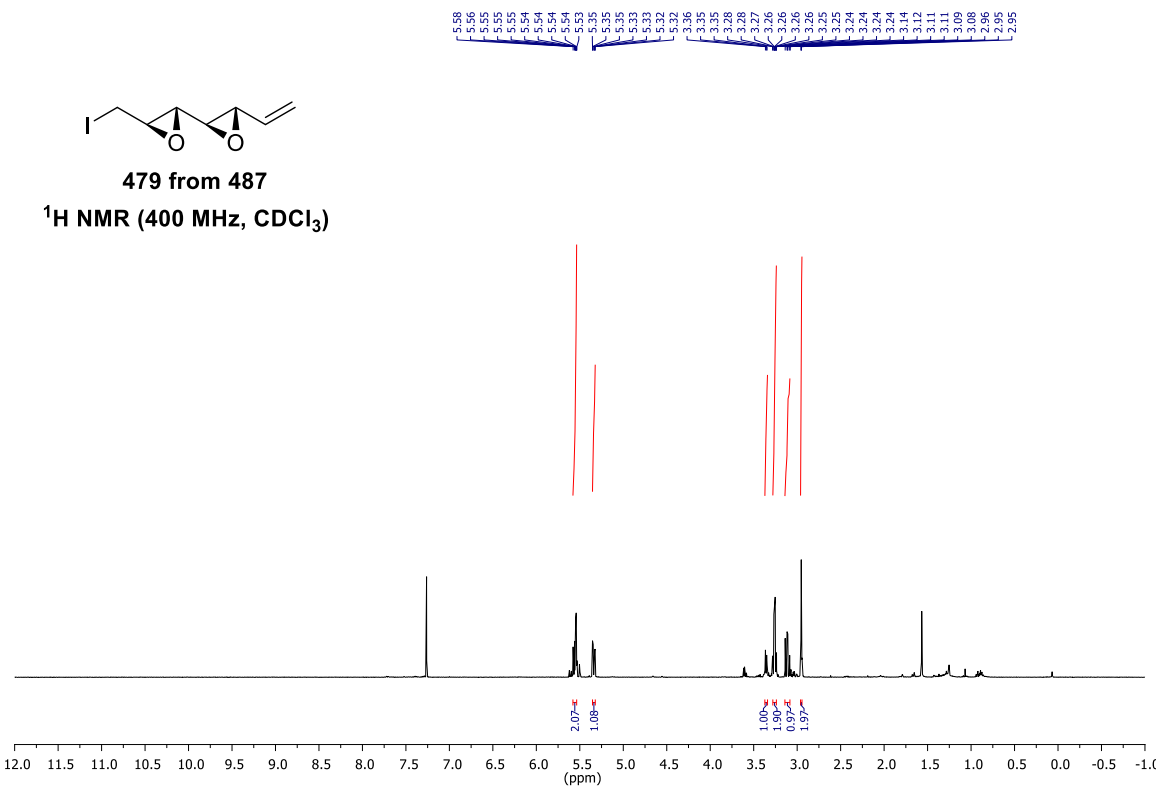
487

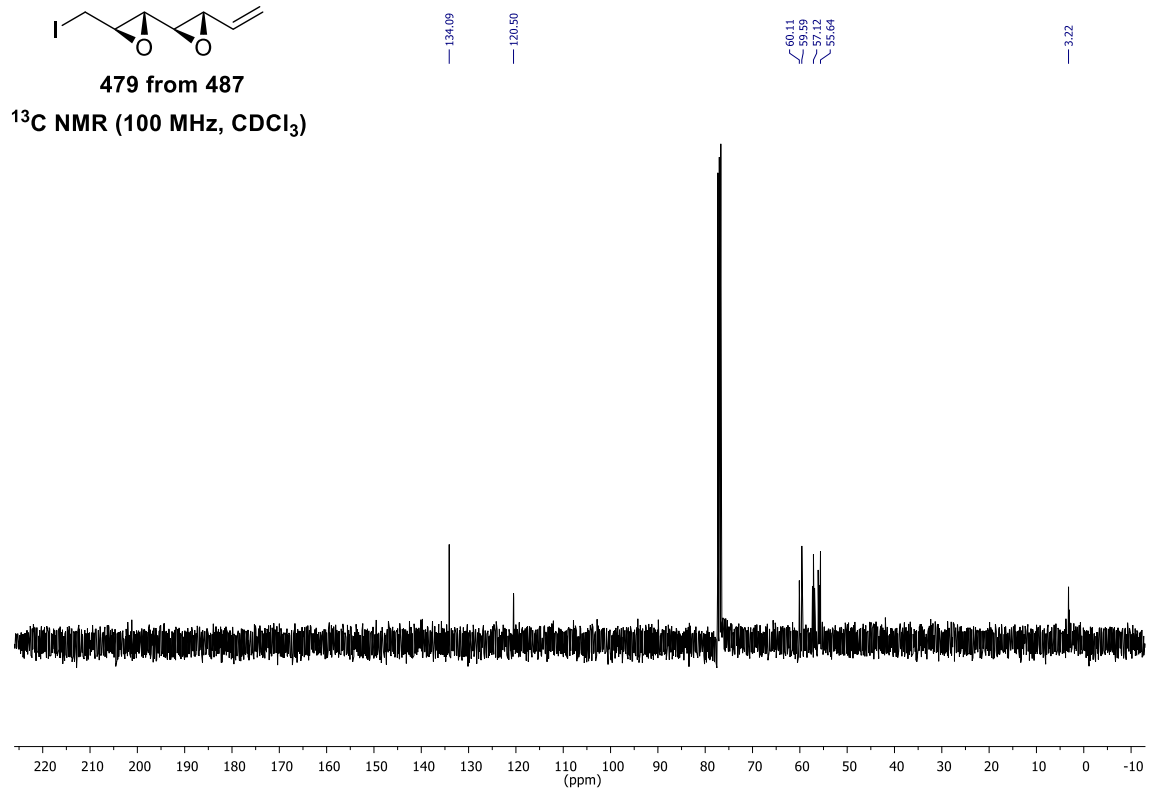
^{1}H NMR (400 MHz, $CDCl_3$)

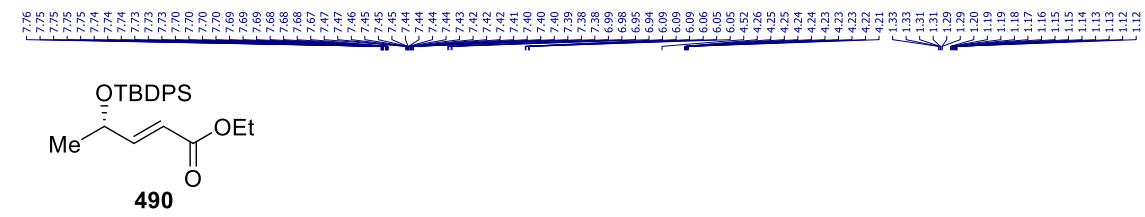


487

^{13}C NMR (100 MHz, $CDCl_3$)

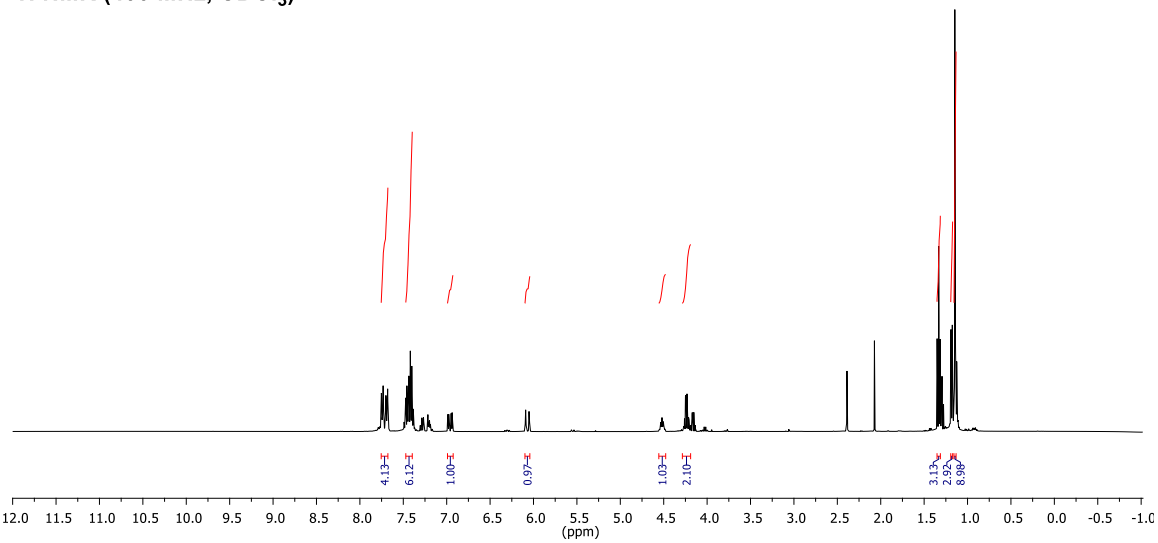


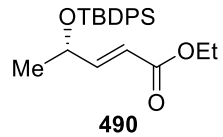




490

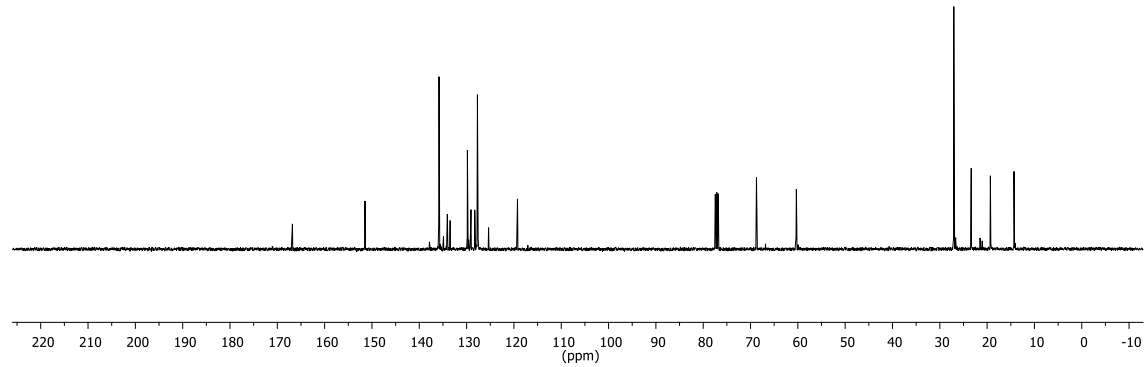
^{1}H NMR (400 MHz, $CDCl_3$)

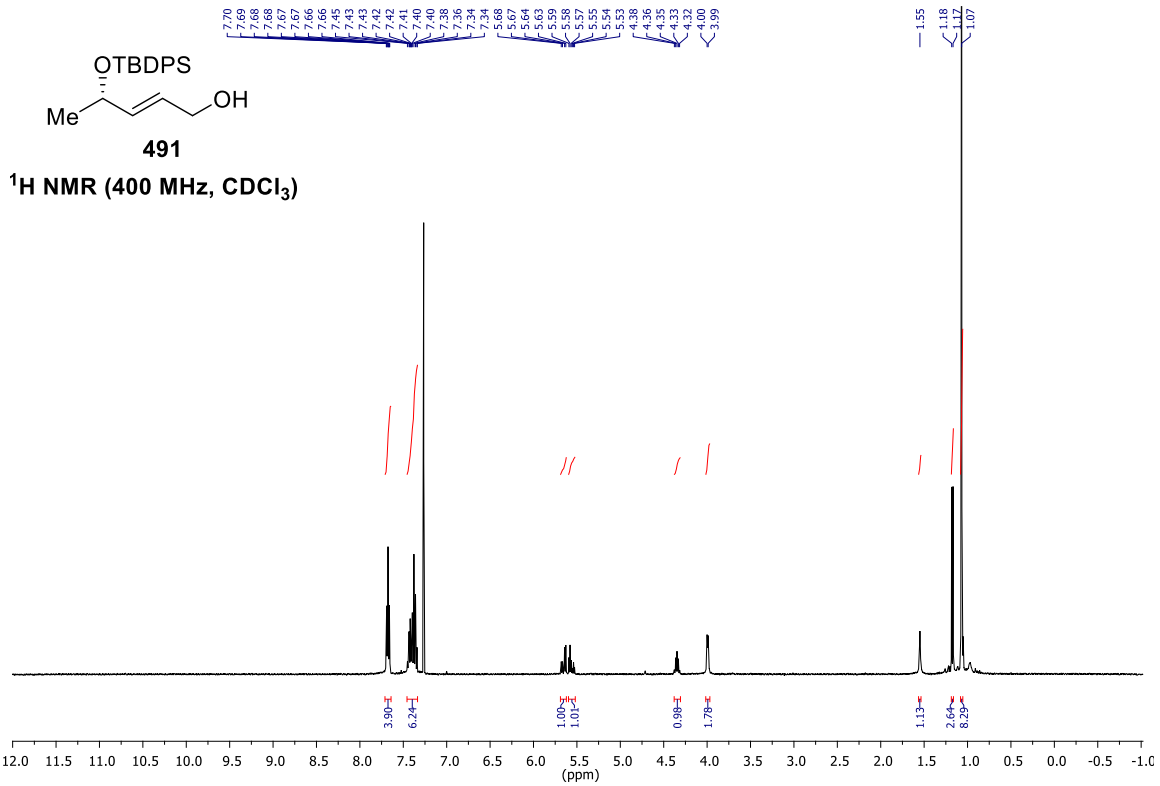




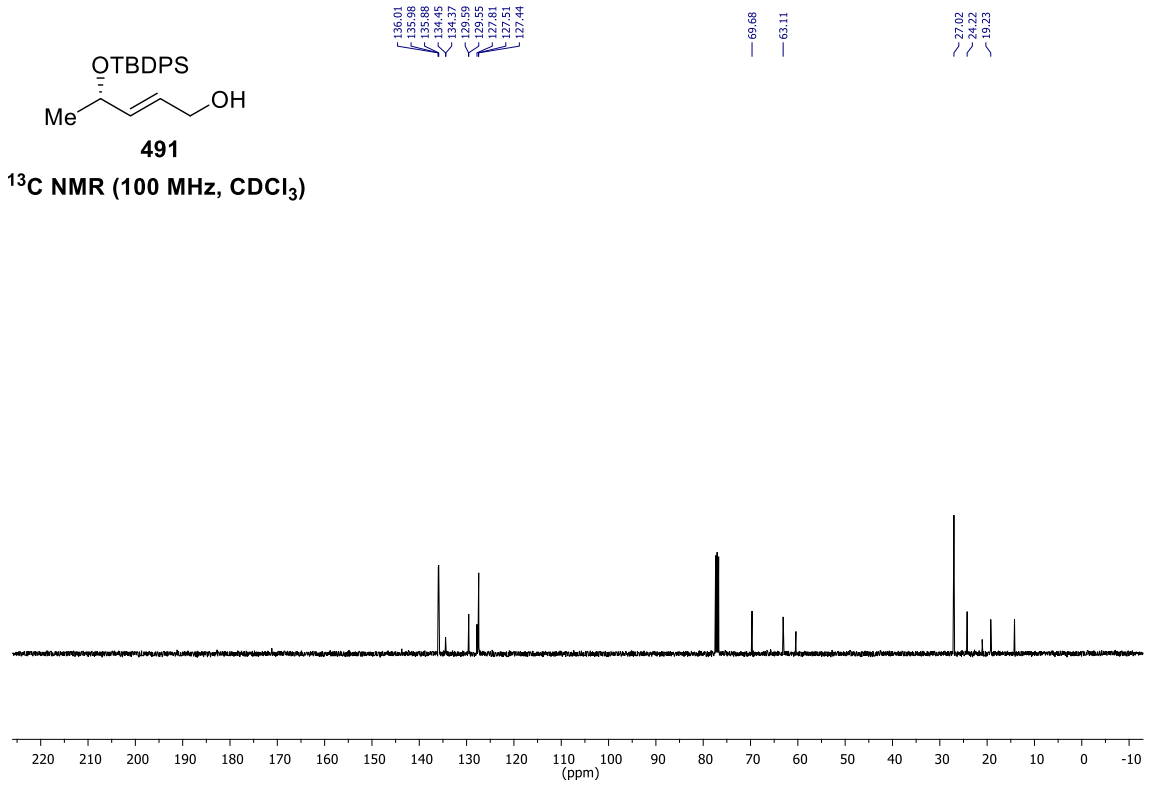
490

^{13}C NMR (100 MHz, $CDCl_3$)

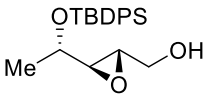




^{1}H NMR (400 MHz, $CDCl_3$)

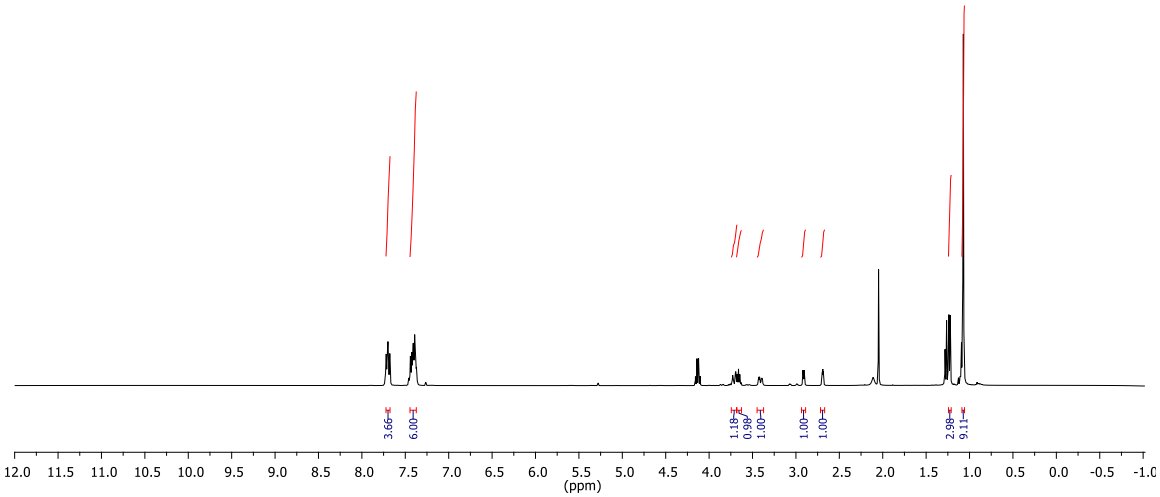


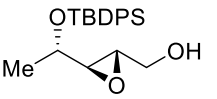
^{13}C NMR (100 MHz, $CDCl_3$)



492

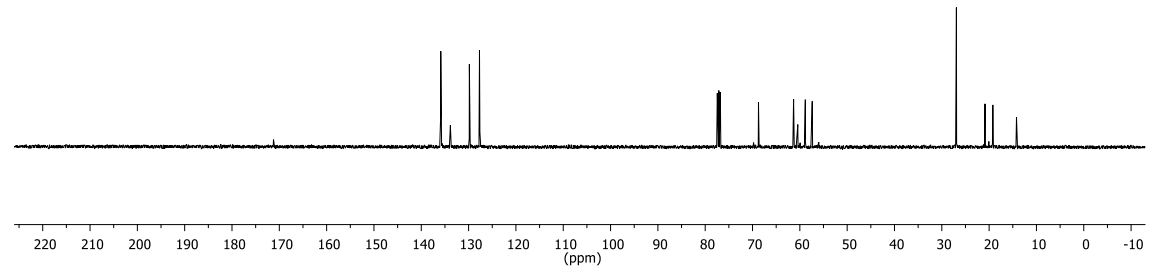
^{1}H NMR (400 MHz, $CDCl_3$)

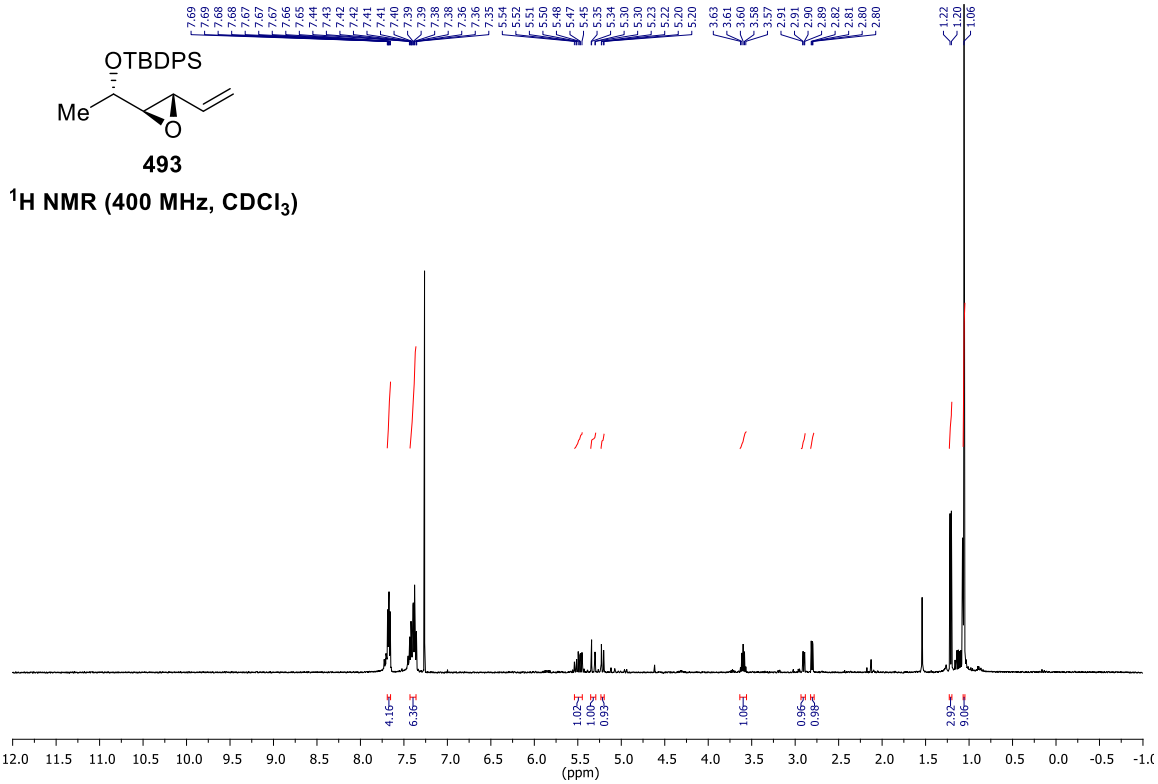




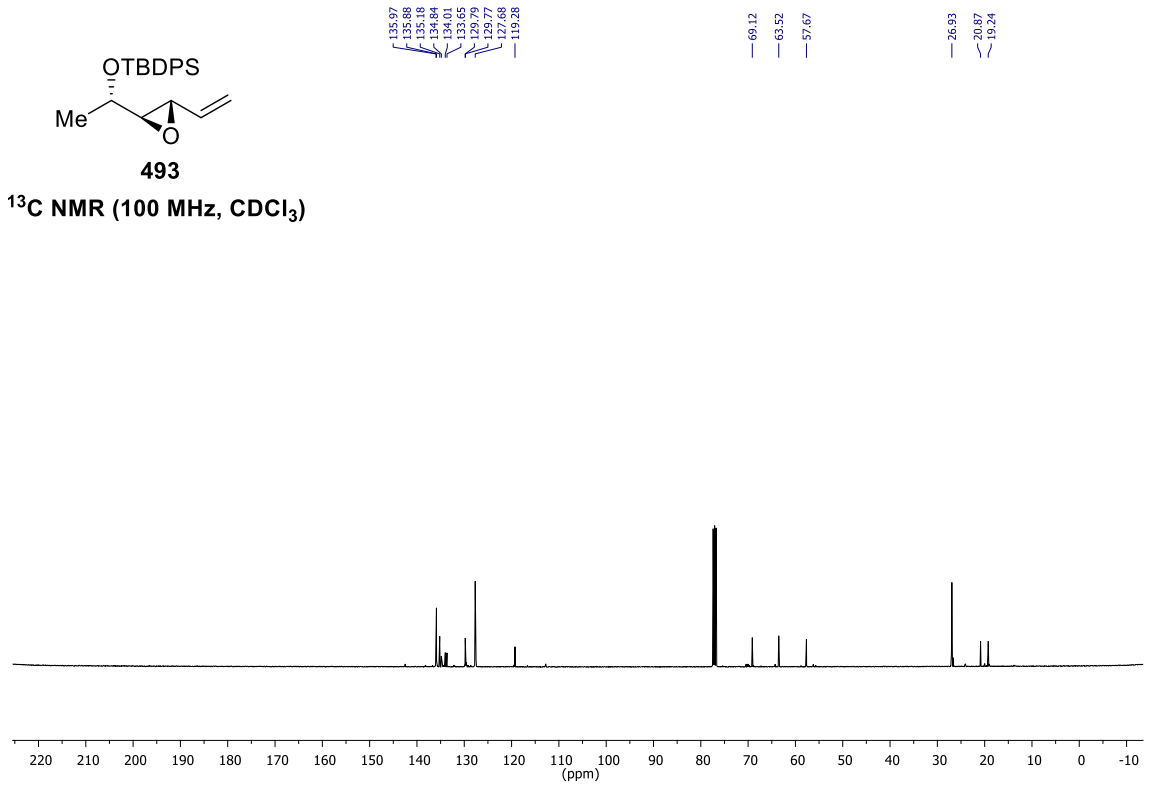
492

^{13}C NMR (100 MHz, $CDCl_3$)

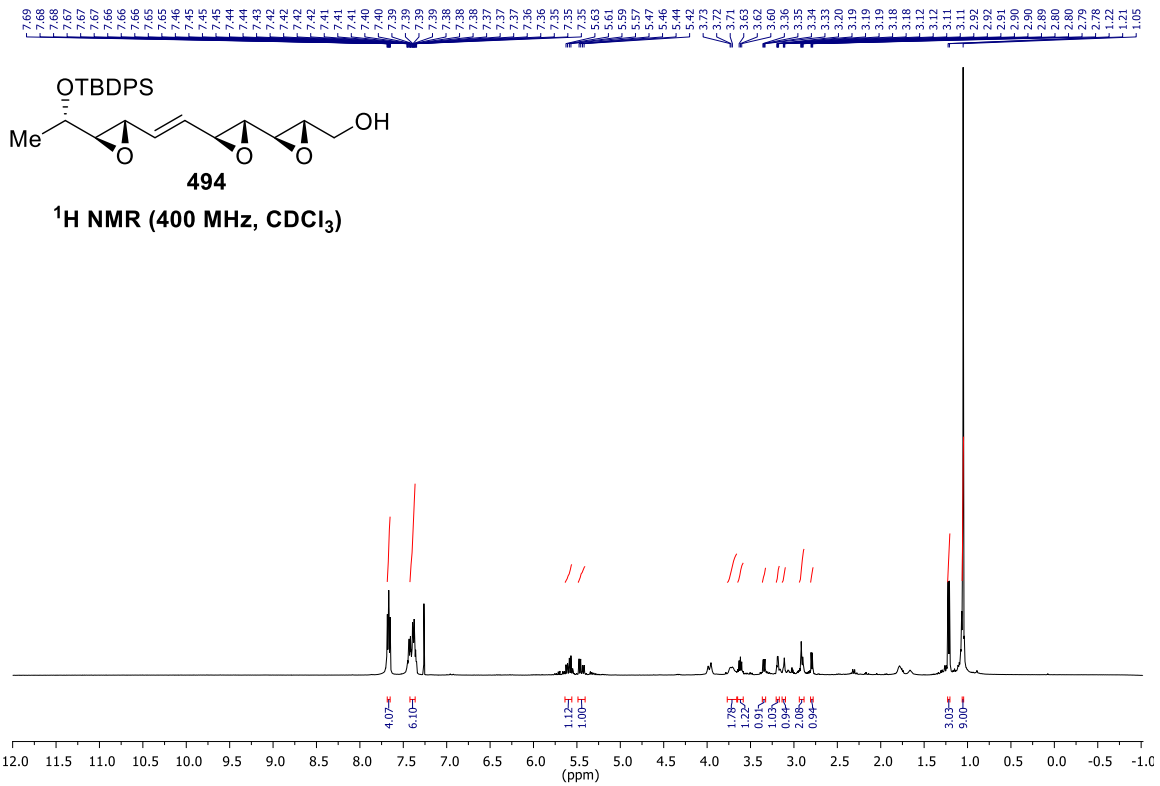




[1]H NMR (400 MHz, $CDCl_3$)

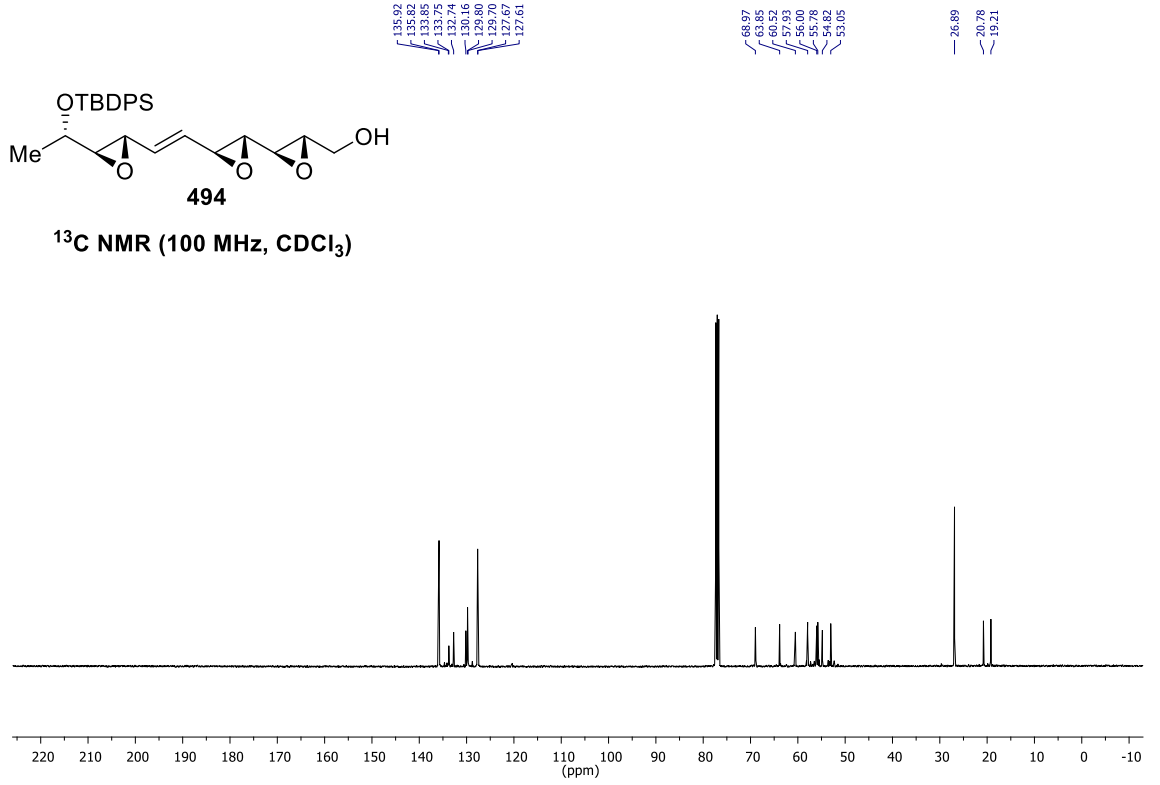


[13]C NMR (100 MHz, $CDCl_3$)



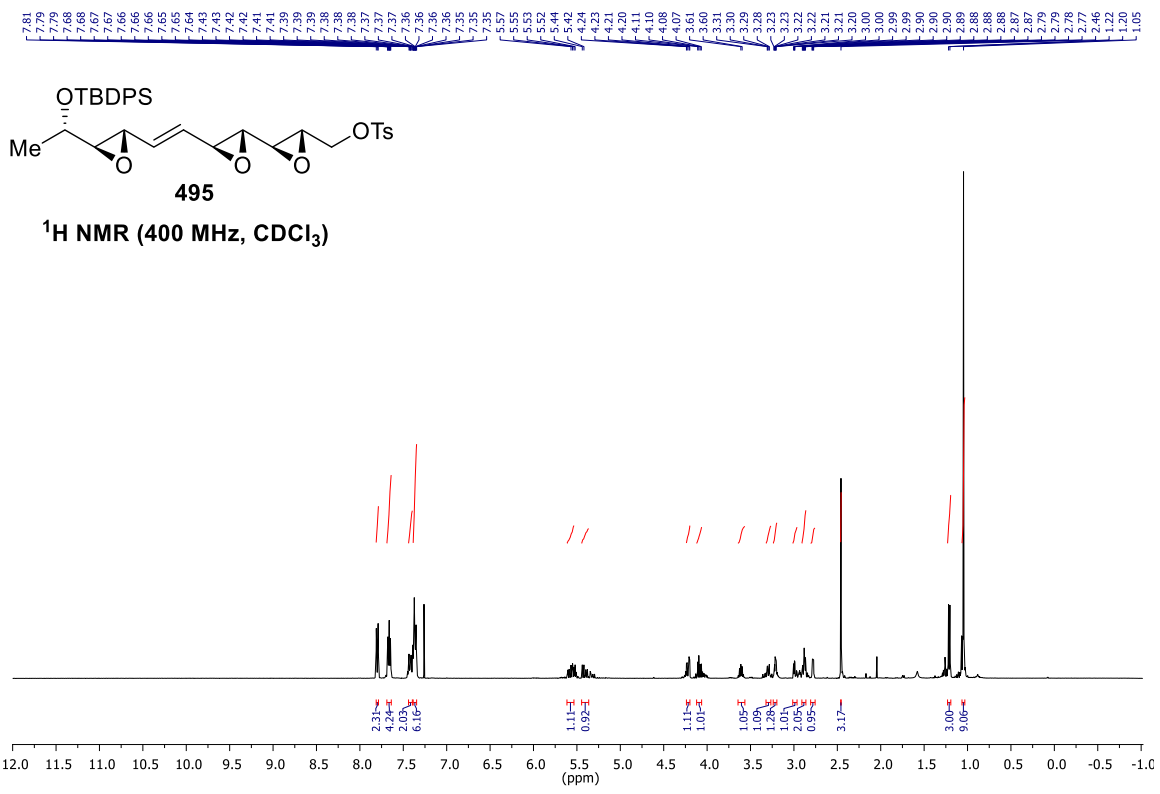
494

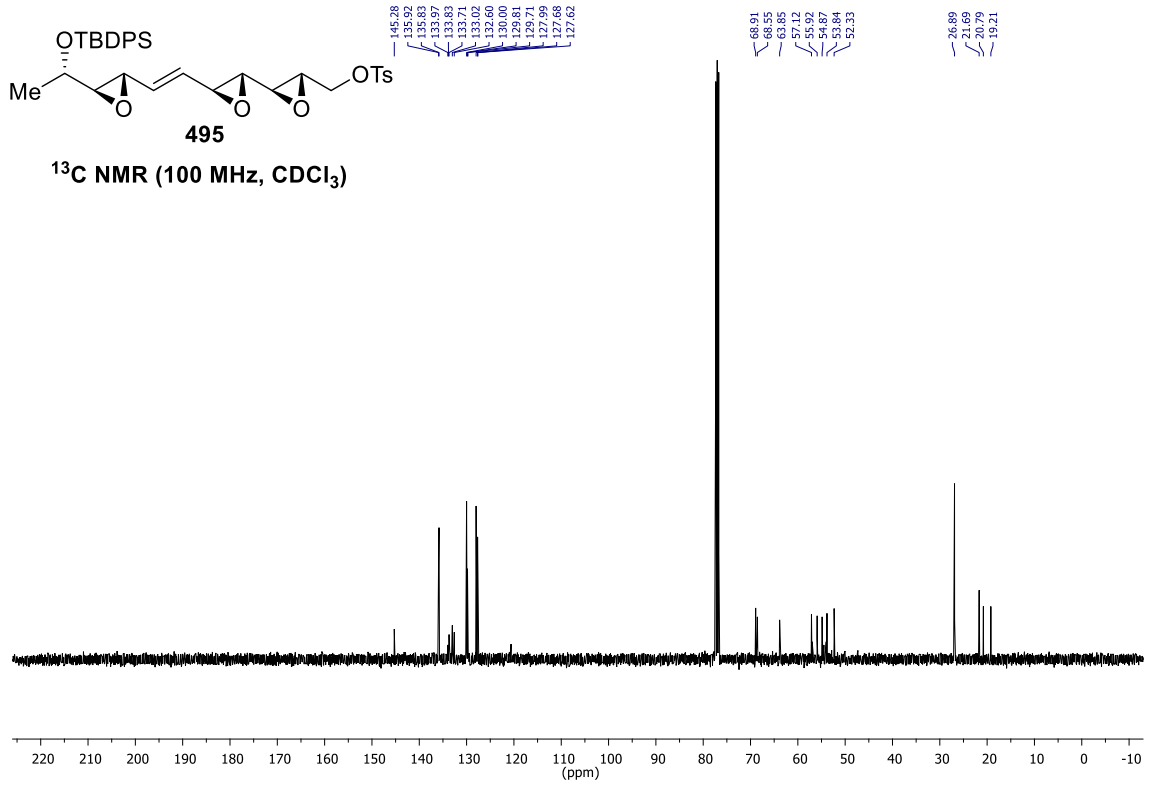
^{1}H NMR (400 MHz, $CDCl_3$)

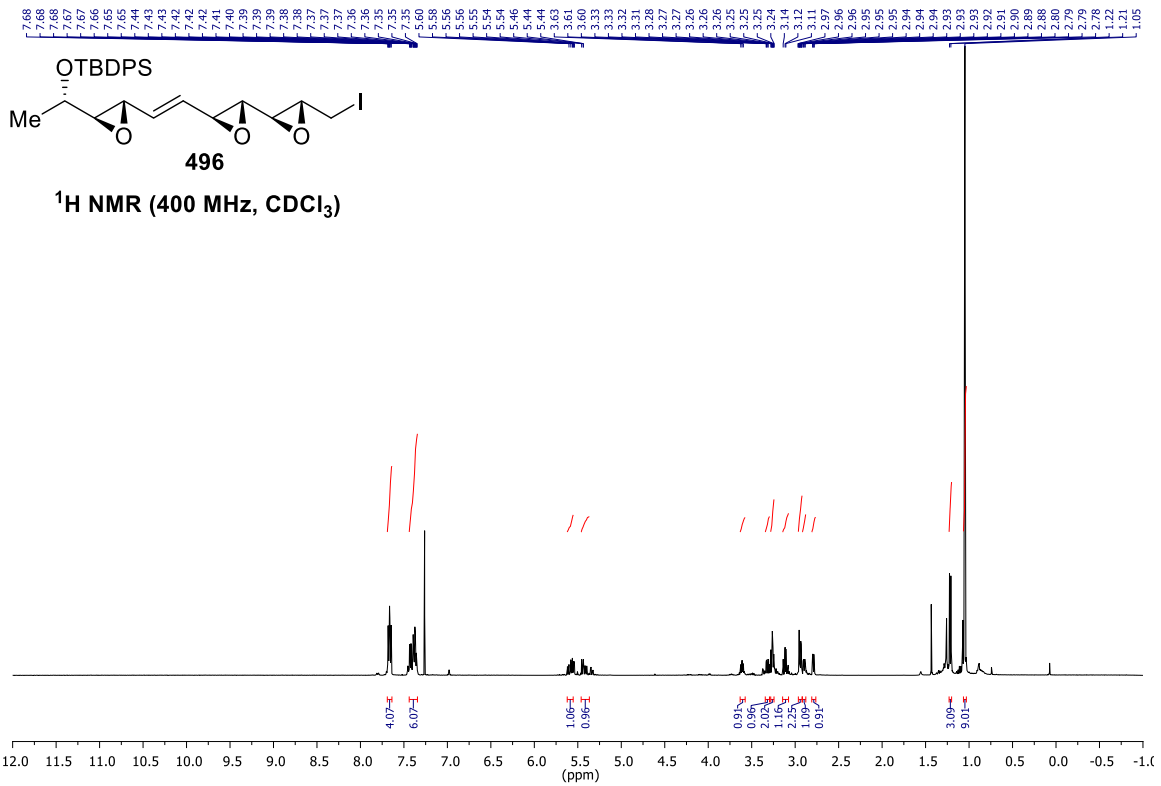


494

^{13}C NMR (100 MHz, $CDCl_3$)

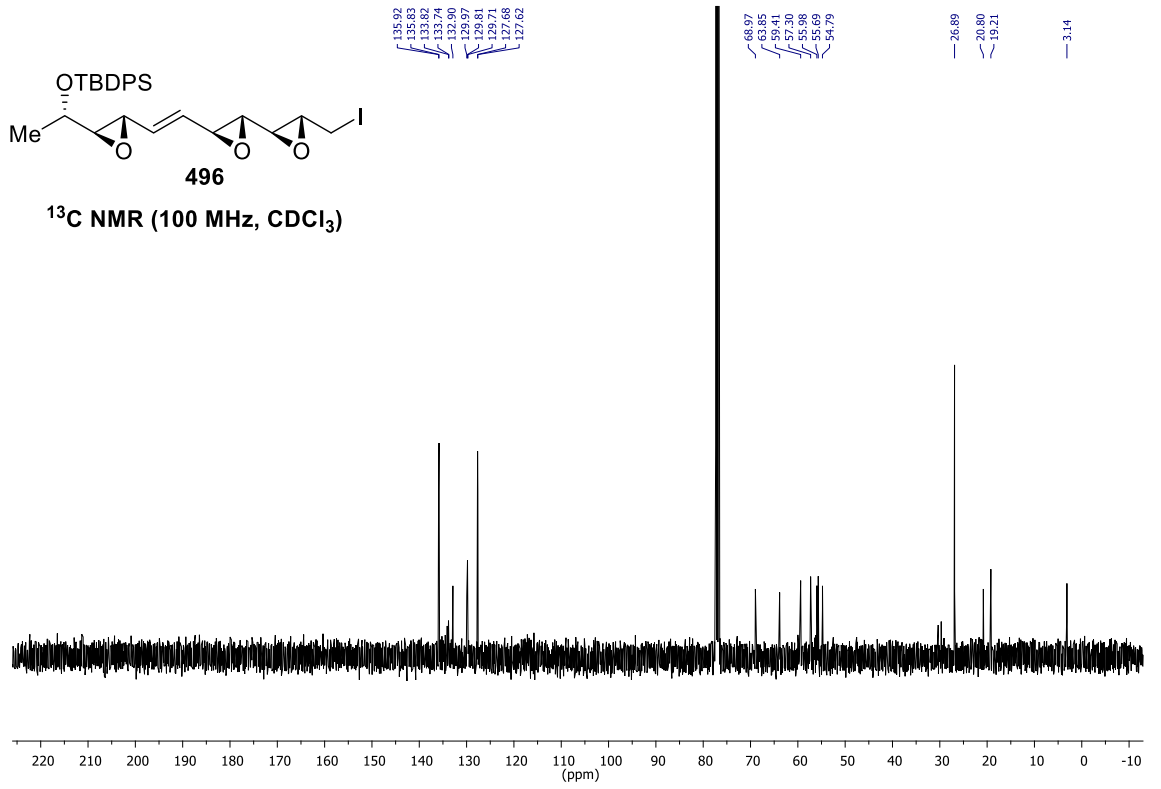






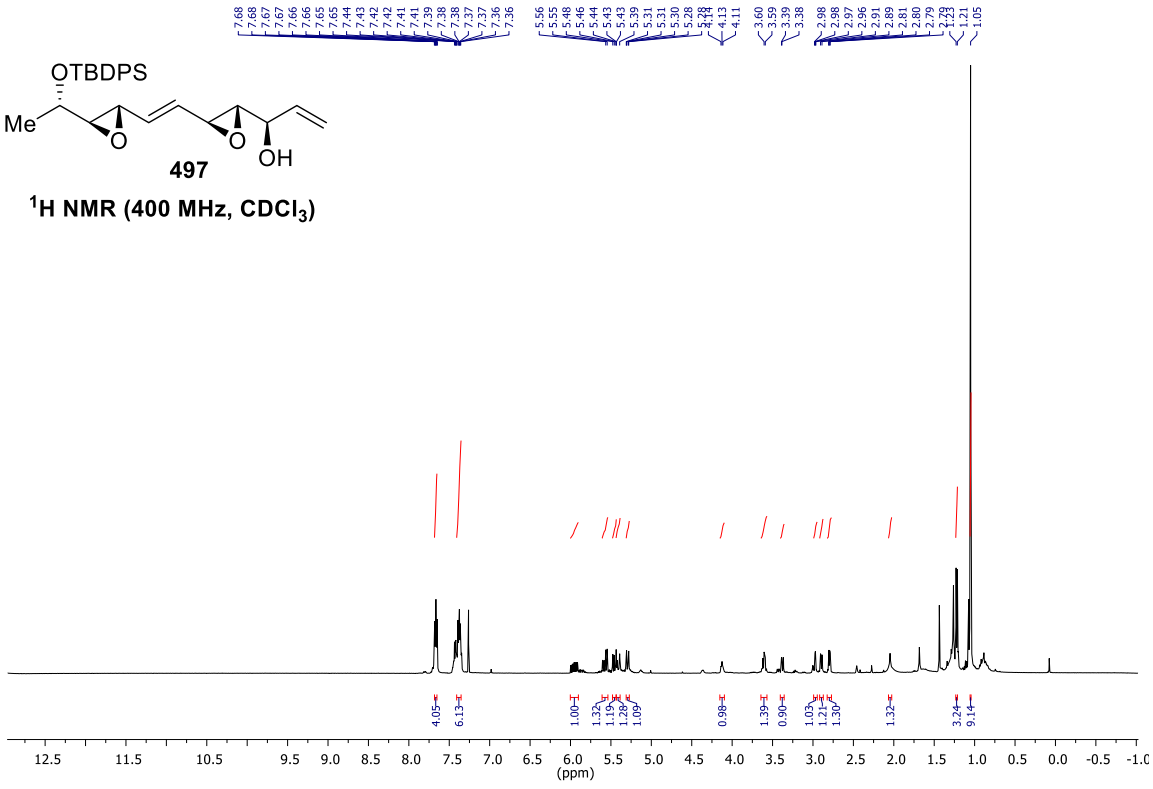
496

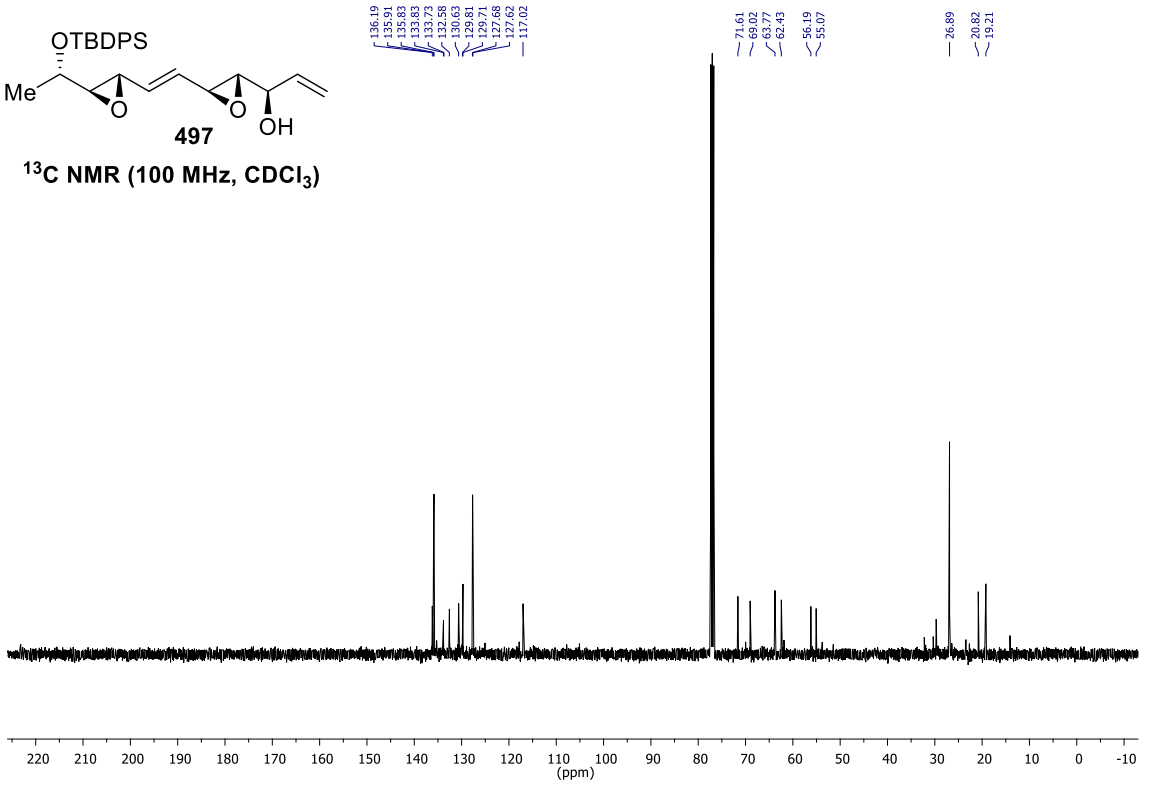
^{1}H NMR (400 MHz, $CDCl_3$)

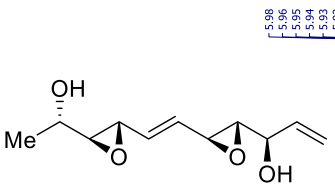


496

^{13}C NMR (100 MHz, $CDCl_3$)

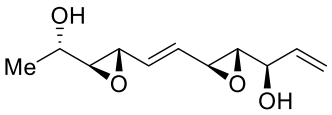






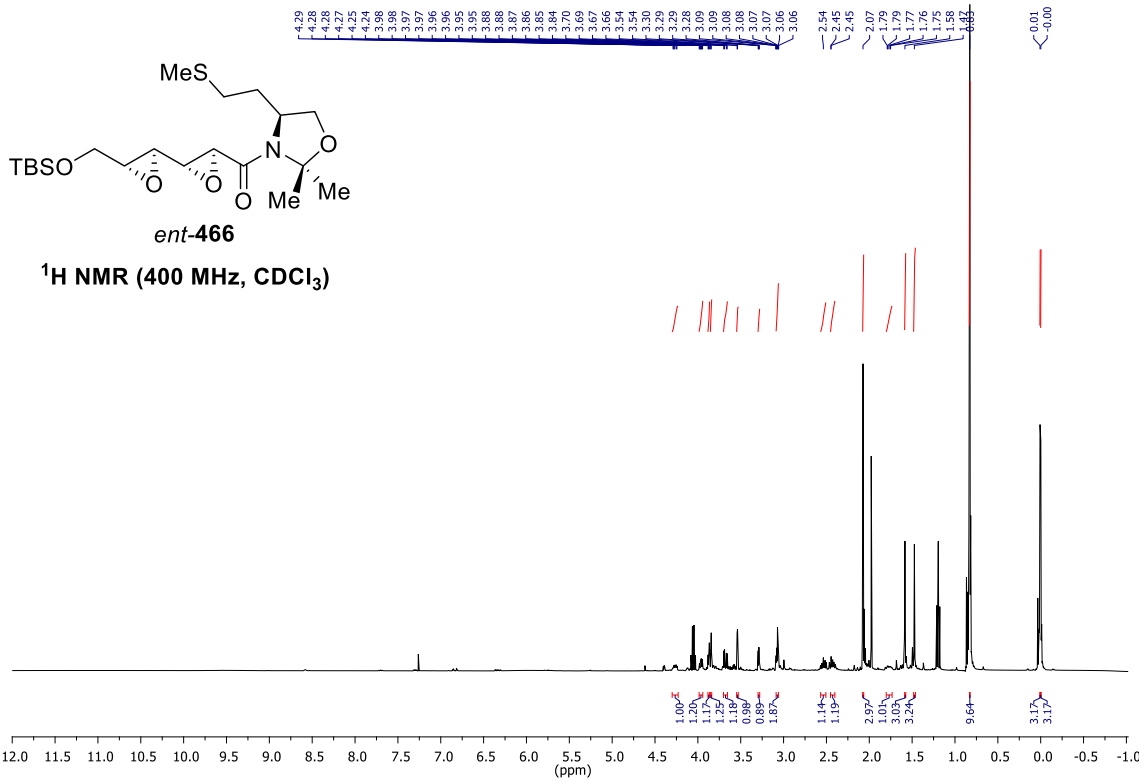
10-*epi*-Depudecin (498)

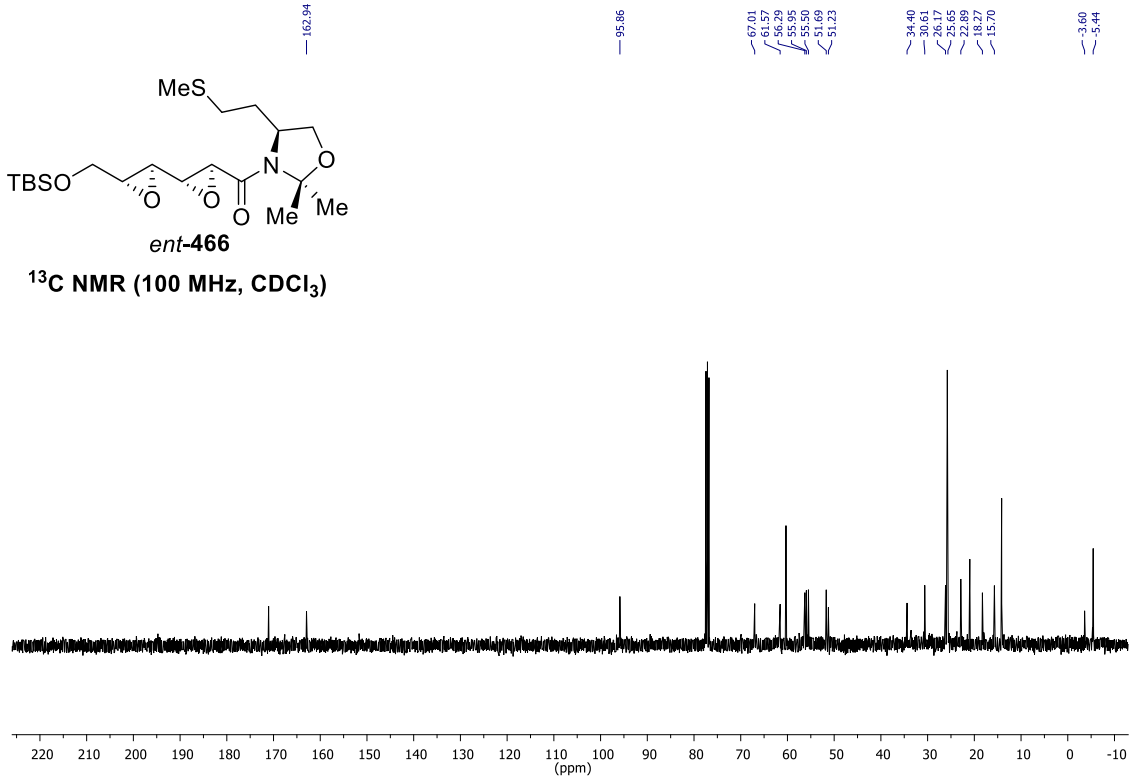
^{1}H NMR (400 MHz, $CDCl_3$)

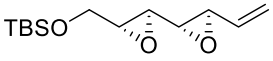


10-*epi*-Depudecin (498)

^{13}C NMR (100 MHz, $CDCl_3$)

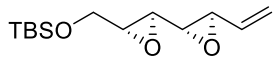






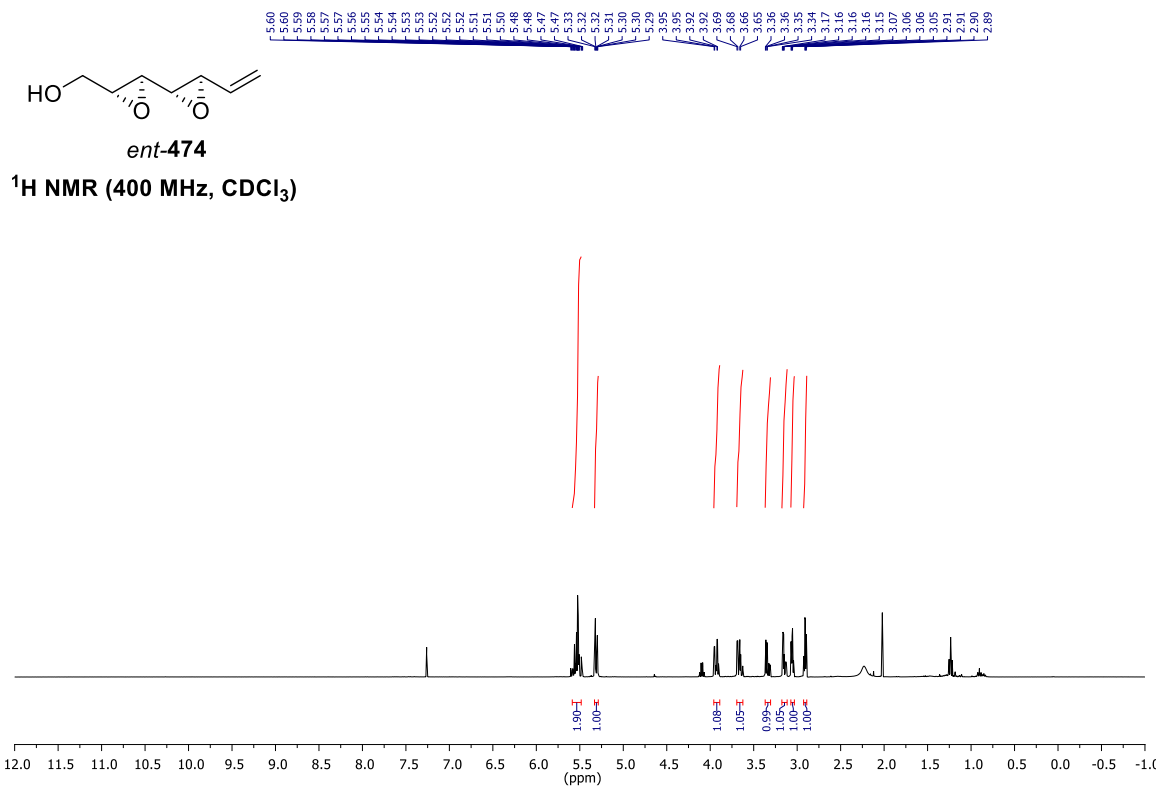
ent-**461**

^{1}H NMR (400 MHz, $CDCl_3$)



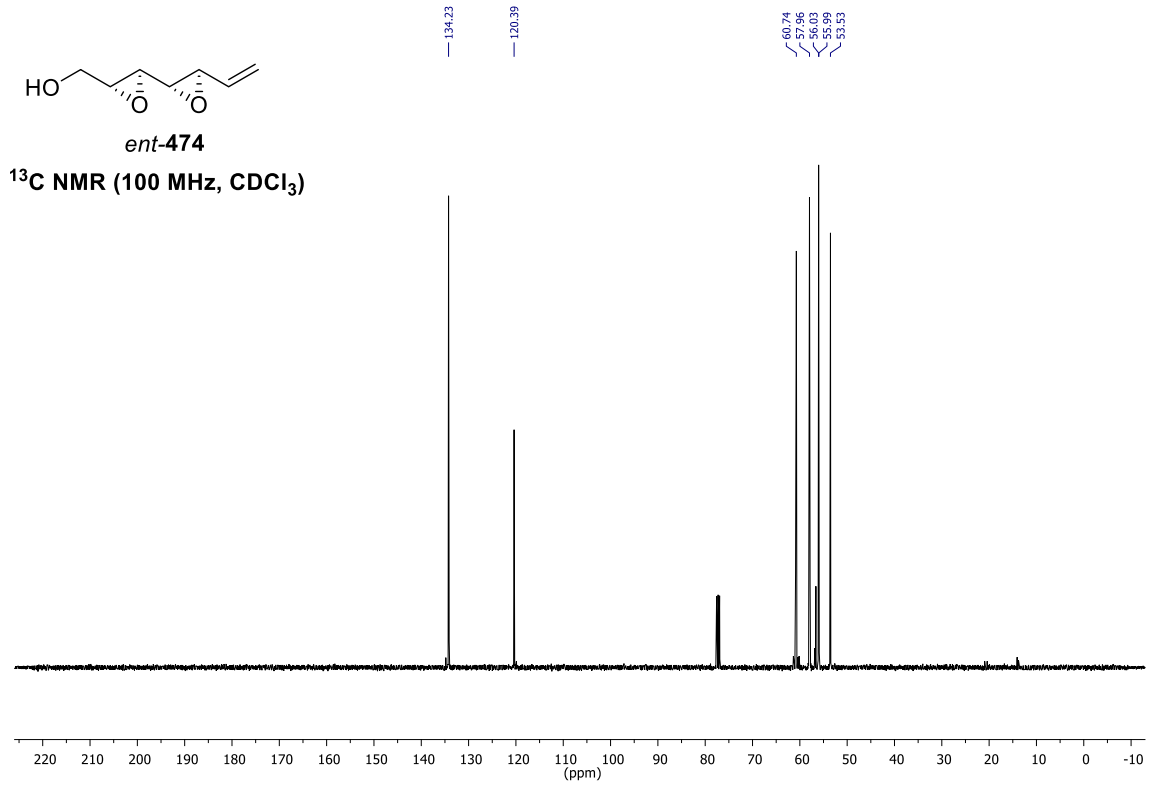
ent-**461**

^{13}C NMR (100 MHz, $CDCl_3$)



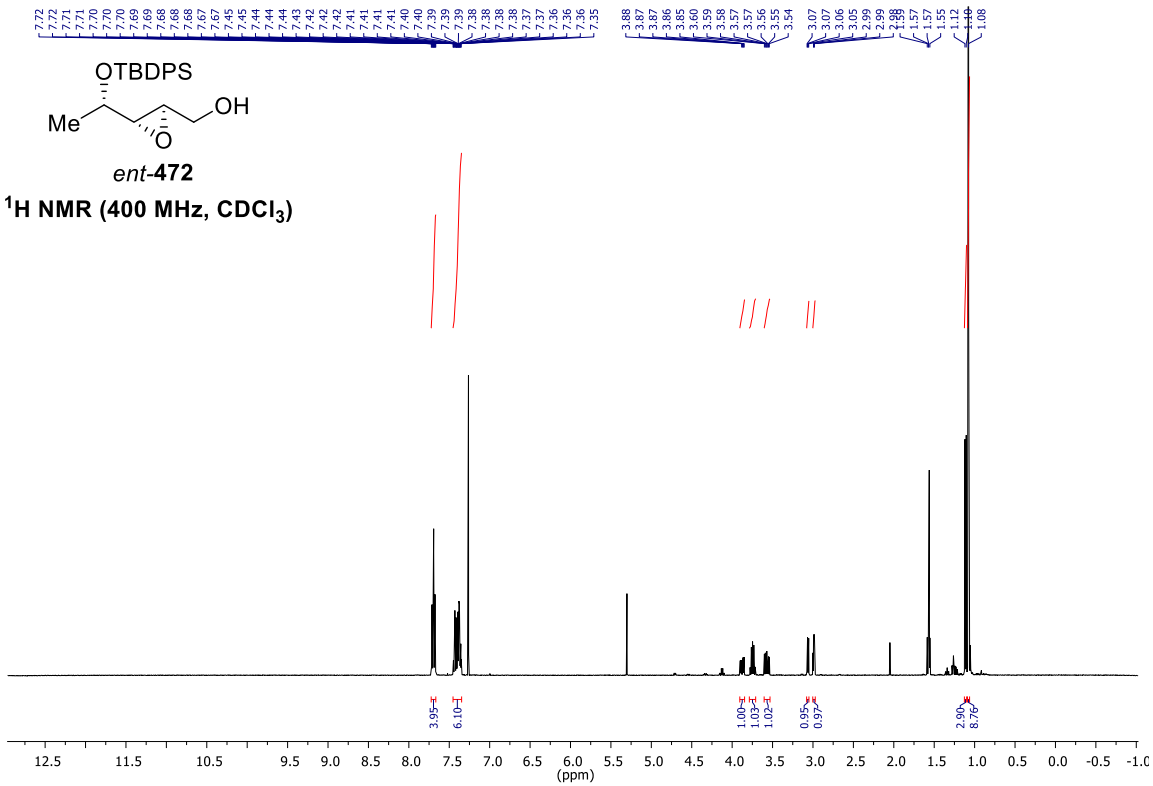
ent-**474**

^{1}H NMR (400 MHz, $CDCl_3$)



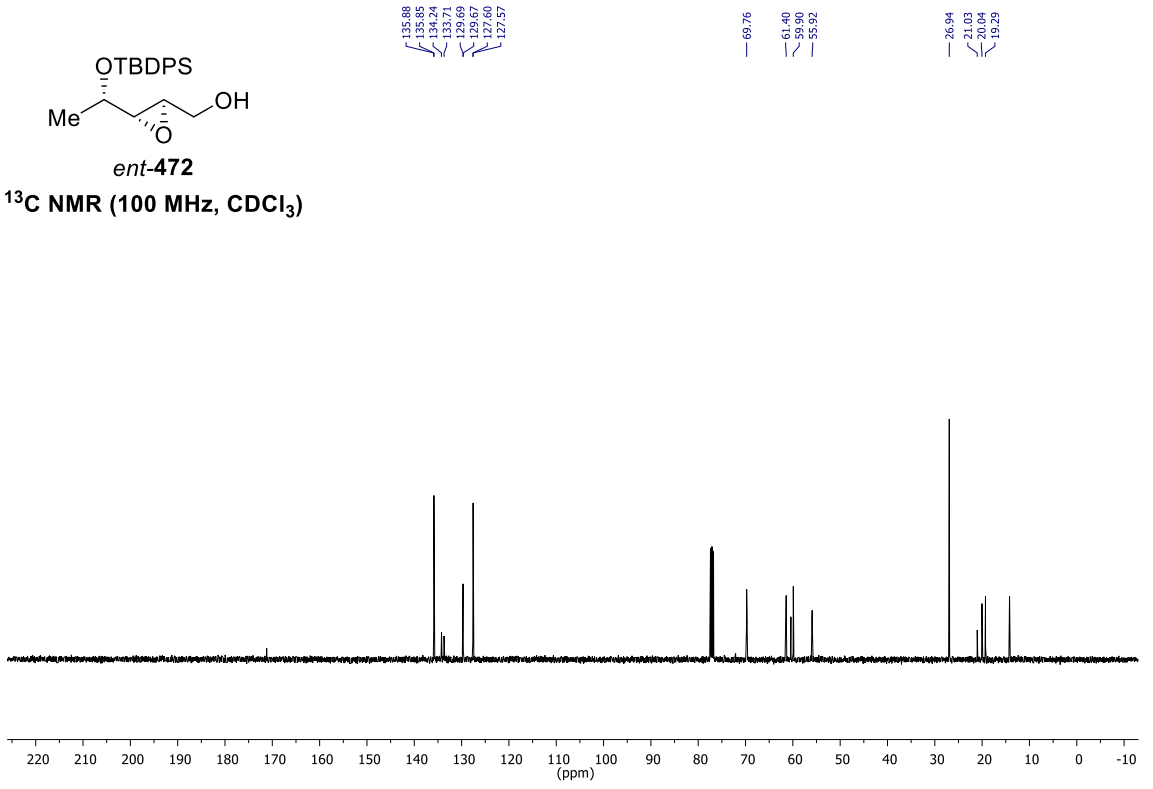
ent-**474**

^{13}C NMR (100 MHz, $CDCl_3$)



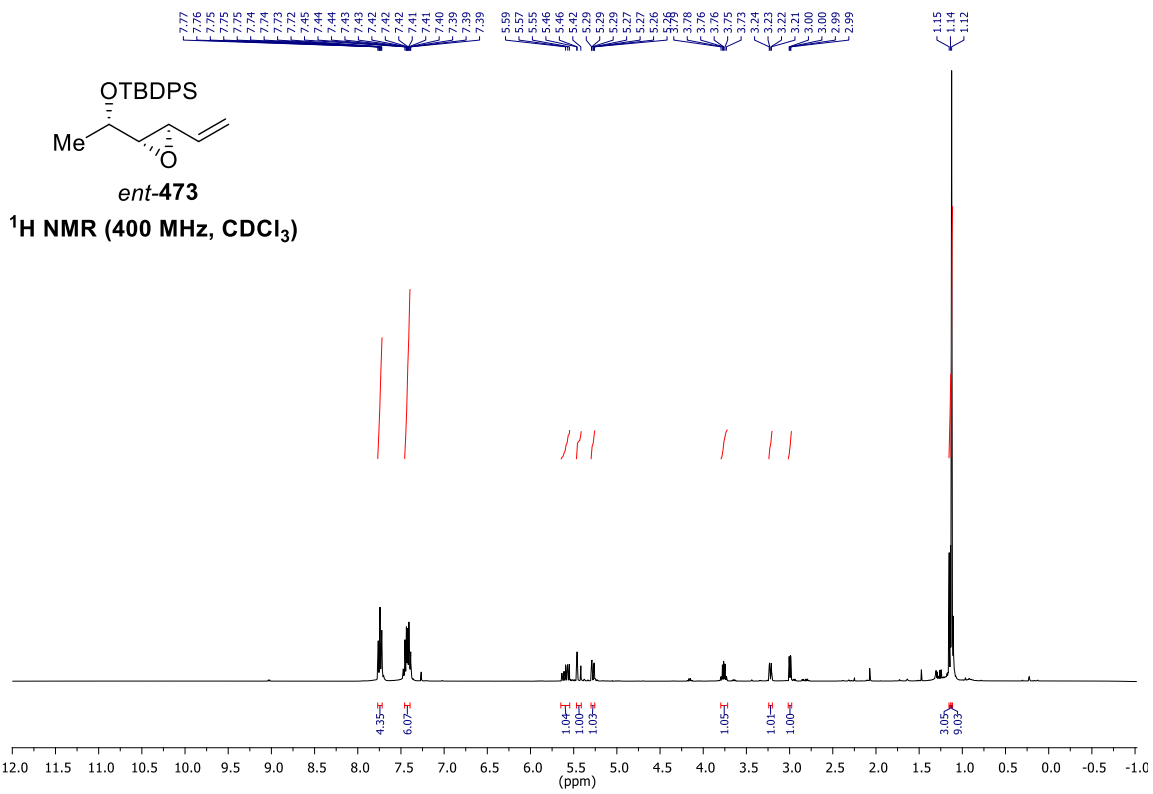
ent-**472**

^{1}H NMR (400 MHz, $CDCl_3$)



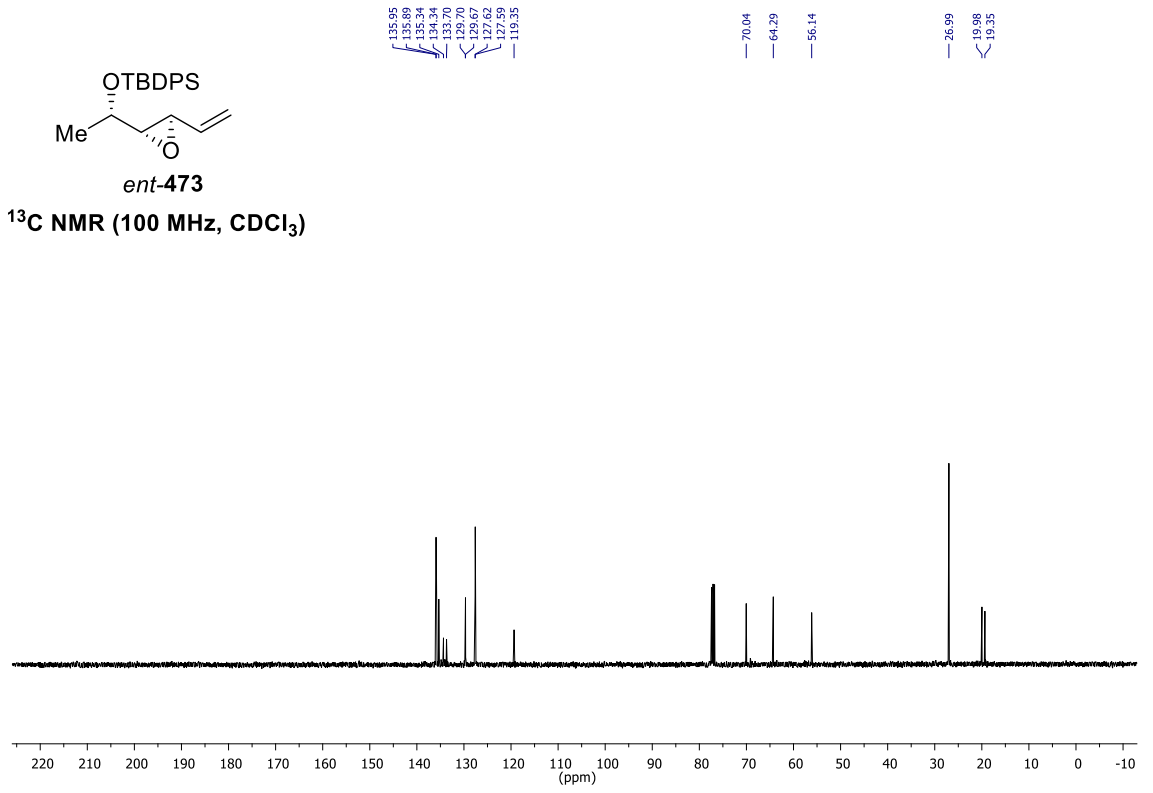
ent-**472**

^{13}C NMR (100 MHz, $CDCl_3$)



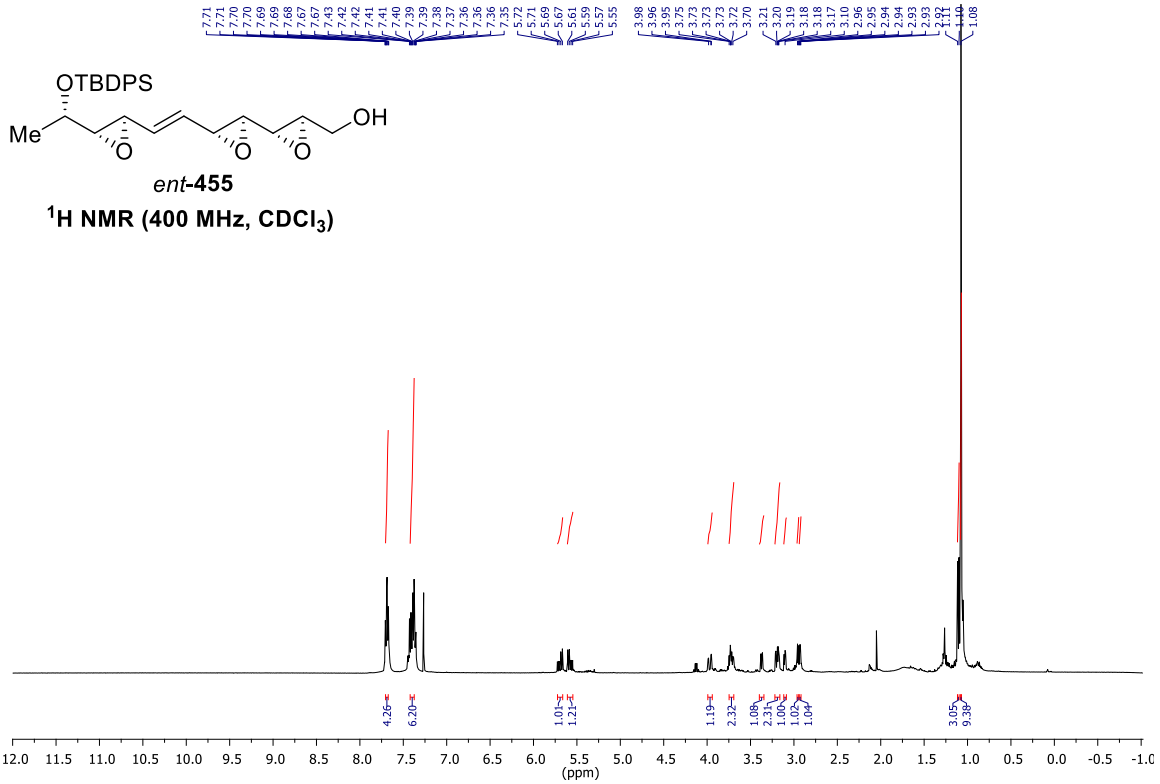
ent-**473**

^{1}H NMR (400 MHz, $CDCl_3$)



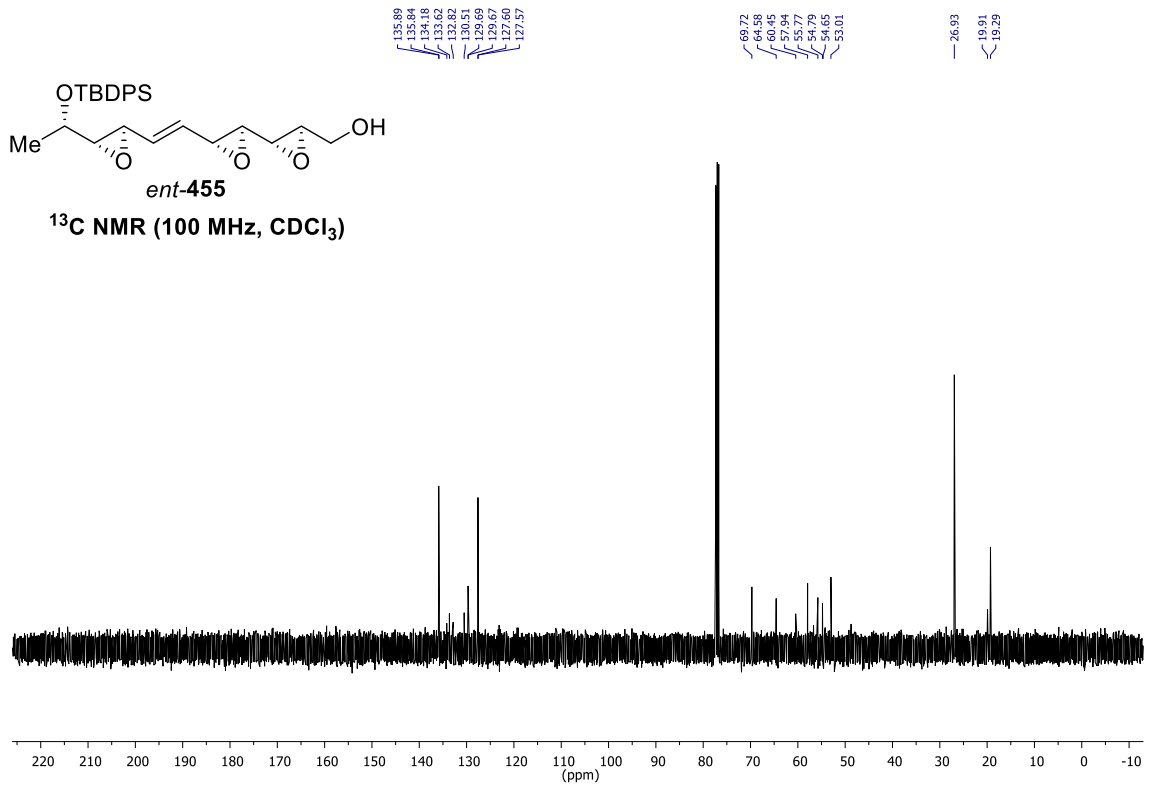
ent-**473**

^{13}C NMR (100 MHz, $CDCl_3$)



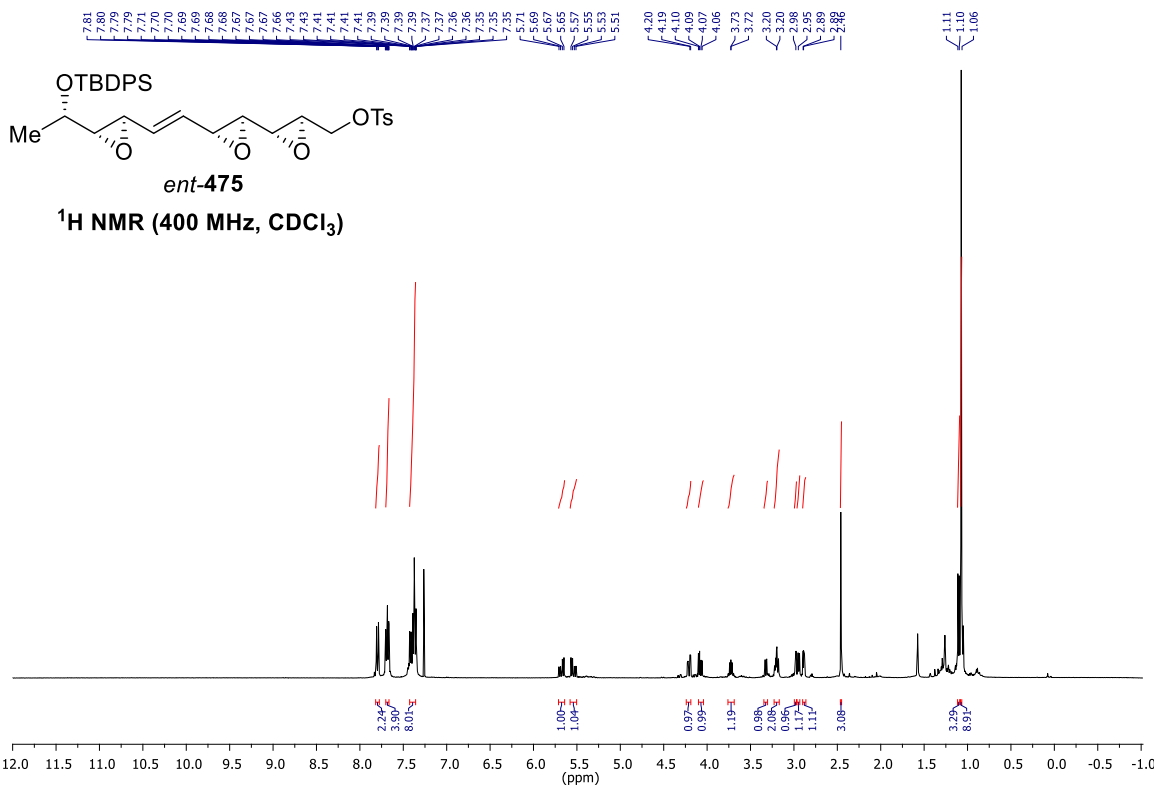
ent-**455**

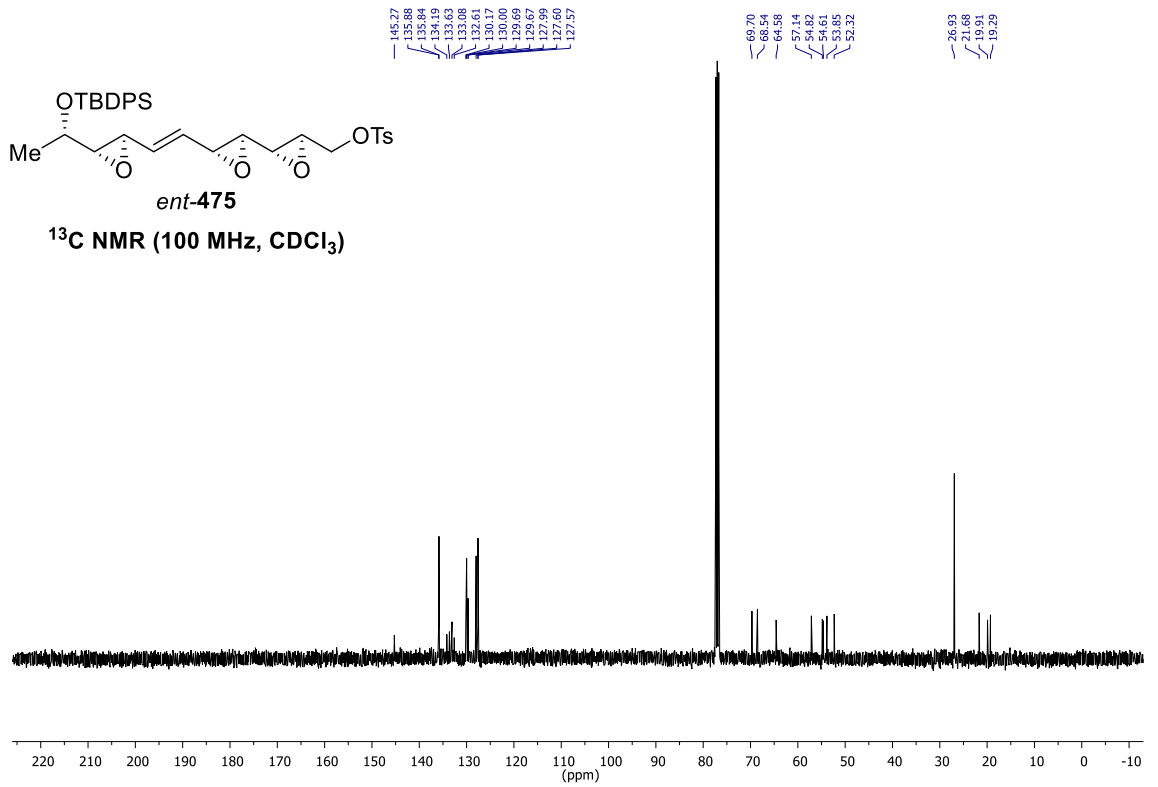
^{1}H NMR (400 MHz, $CDCl_3$)

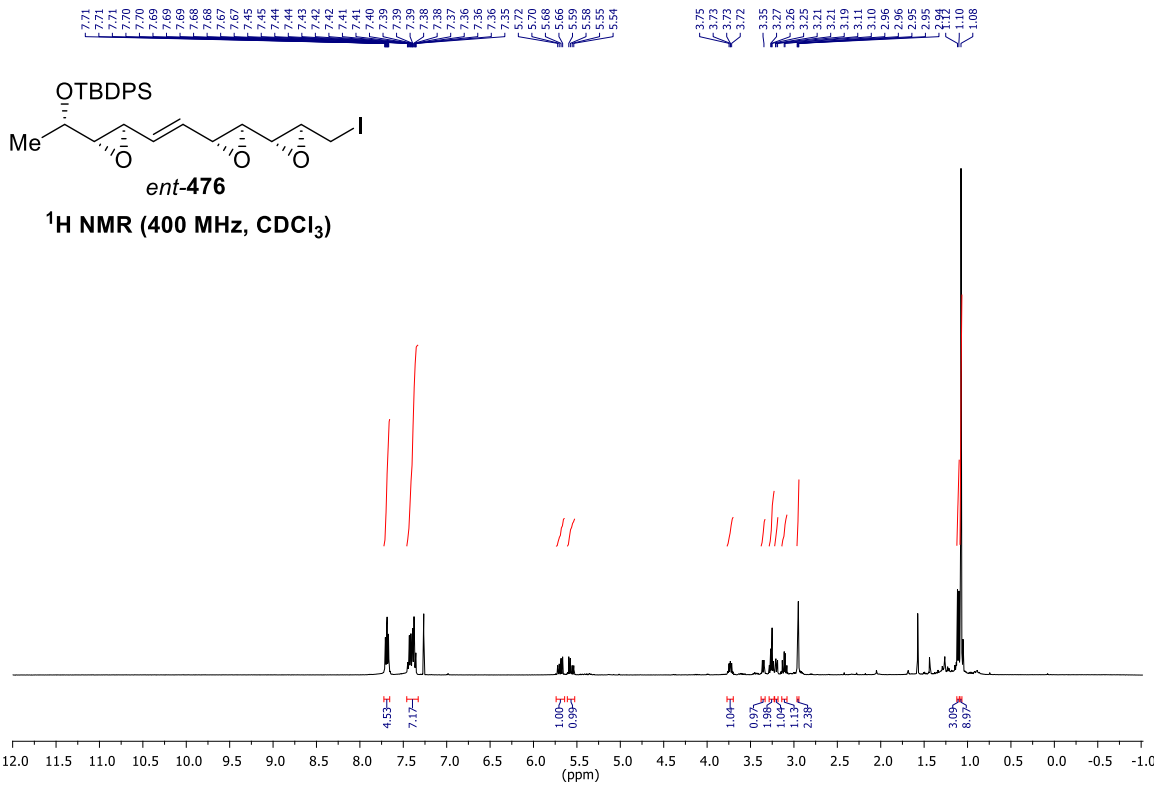


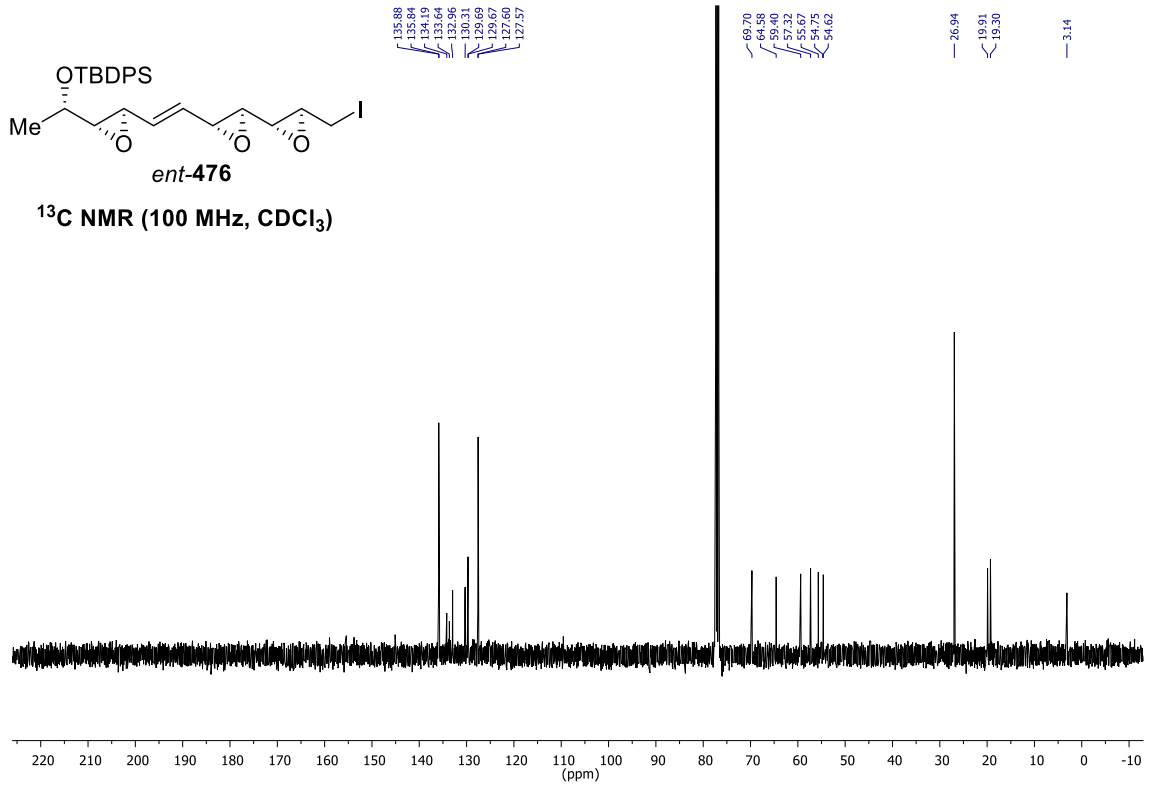
ent-**455**

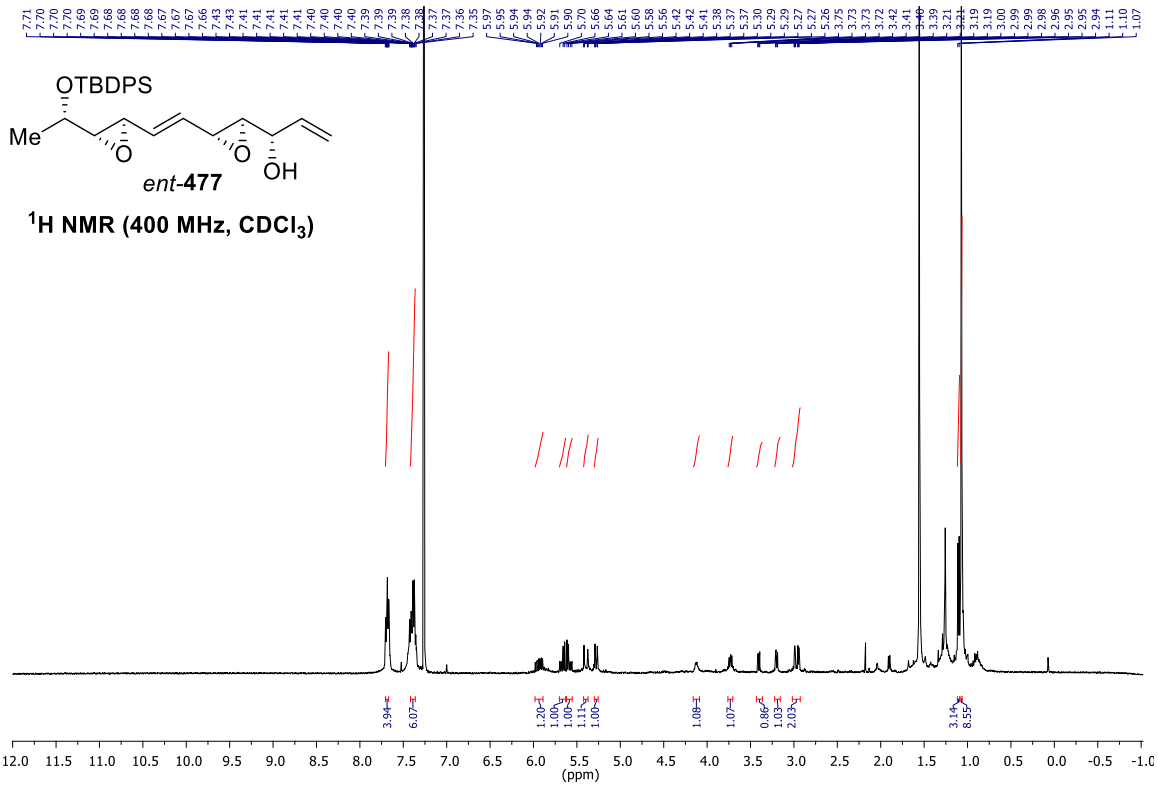
^{13}C NMR (100 MHz, $CDCl_3$)

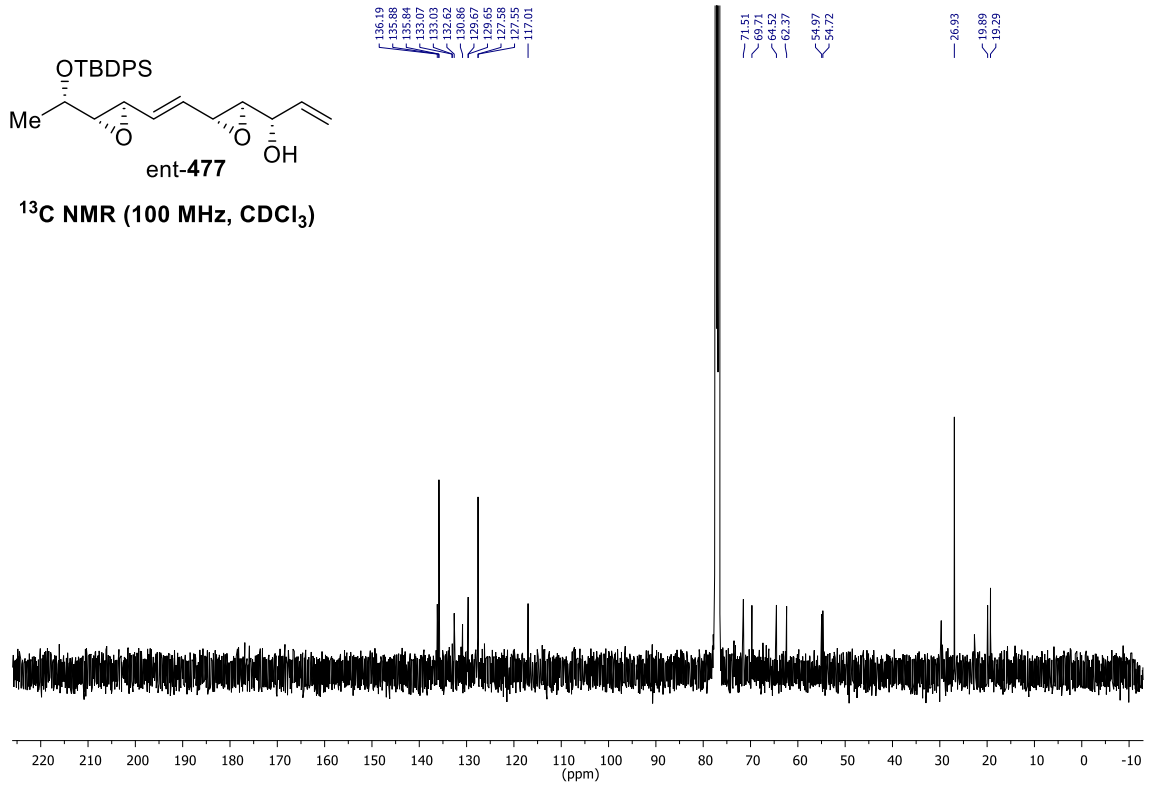


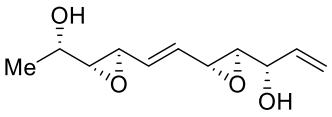






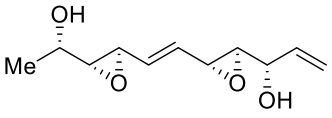






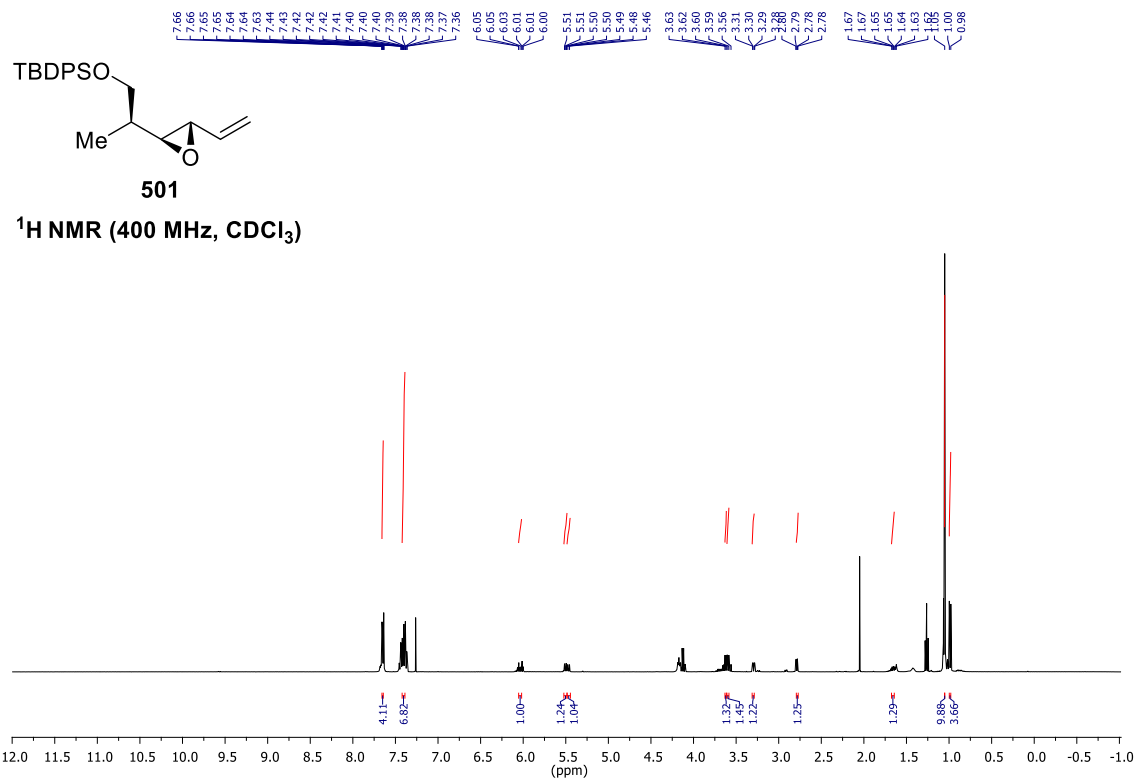
(+)-Depudecin (*ent*-442)

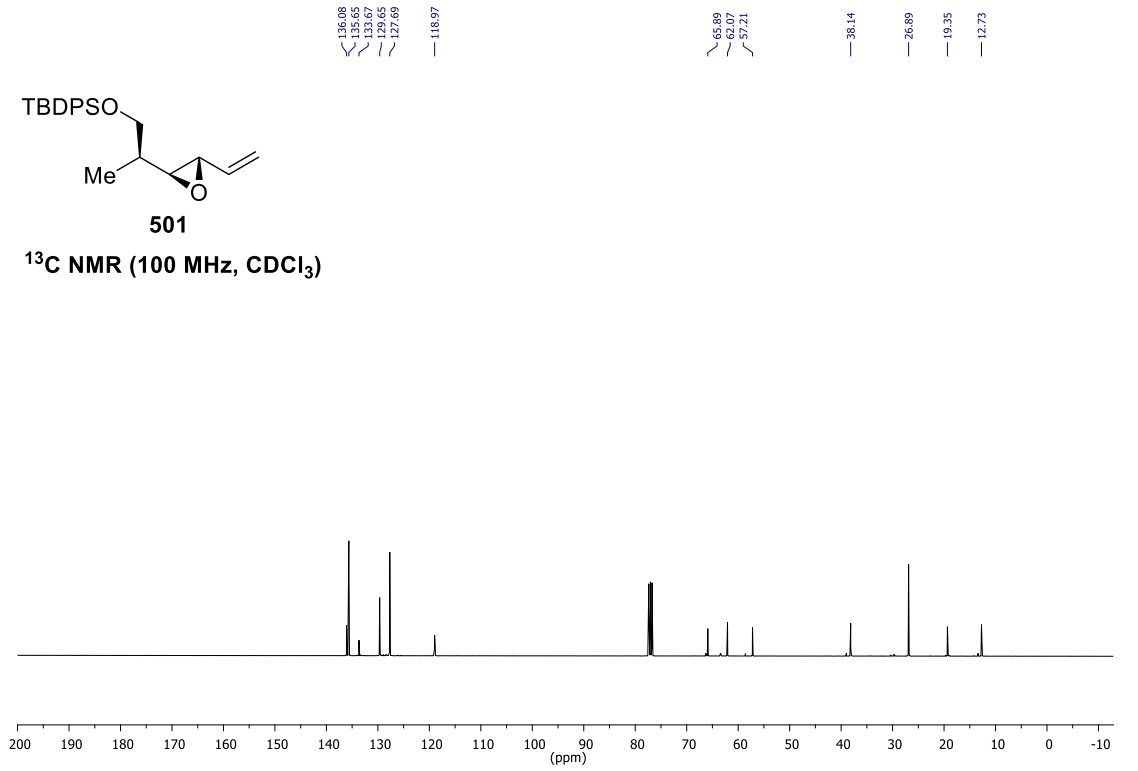
^{1}H NMR (400 MHz, $CDCl_3$)

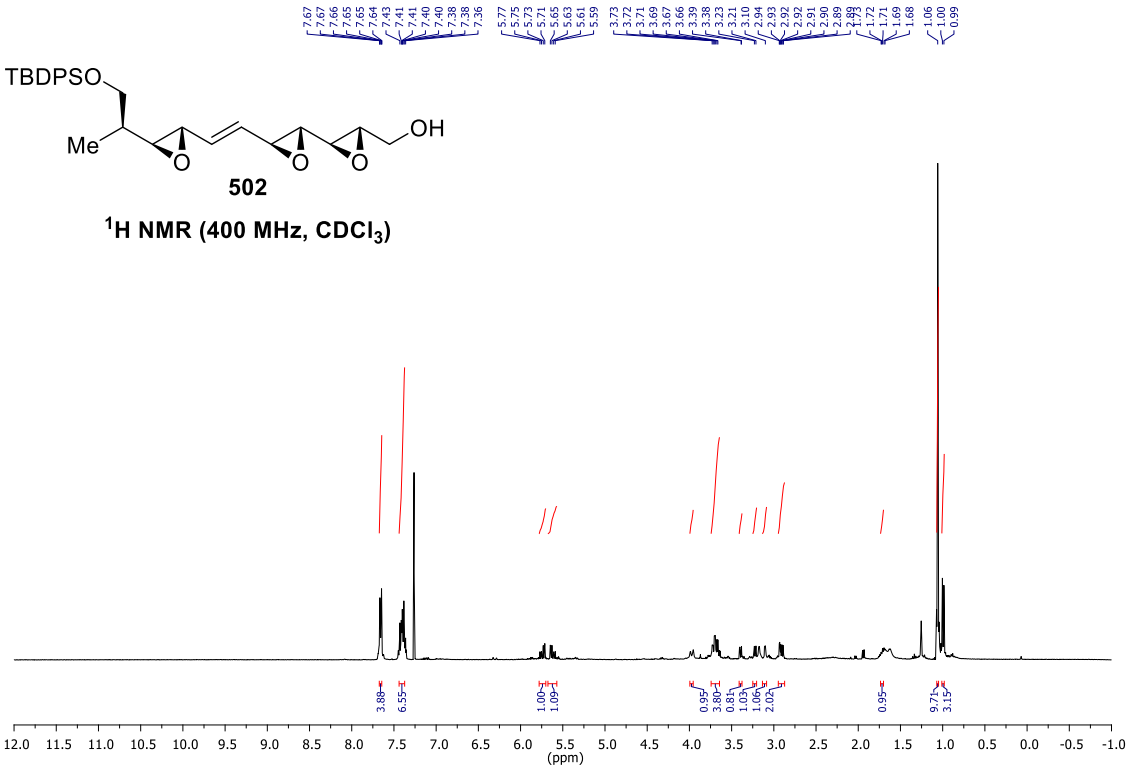


(+)-Depudecin (*ent*-442)

^{13}C NMR (100 MHz, $CDCl_3$)

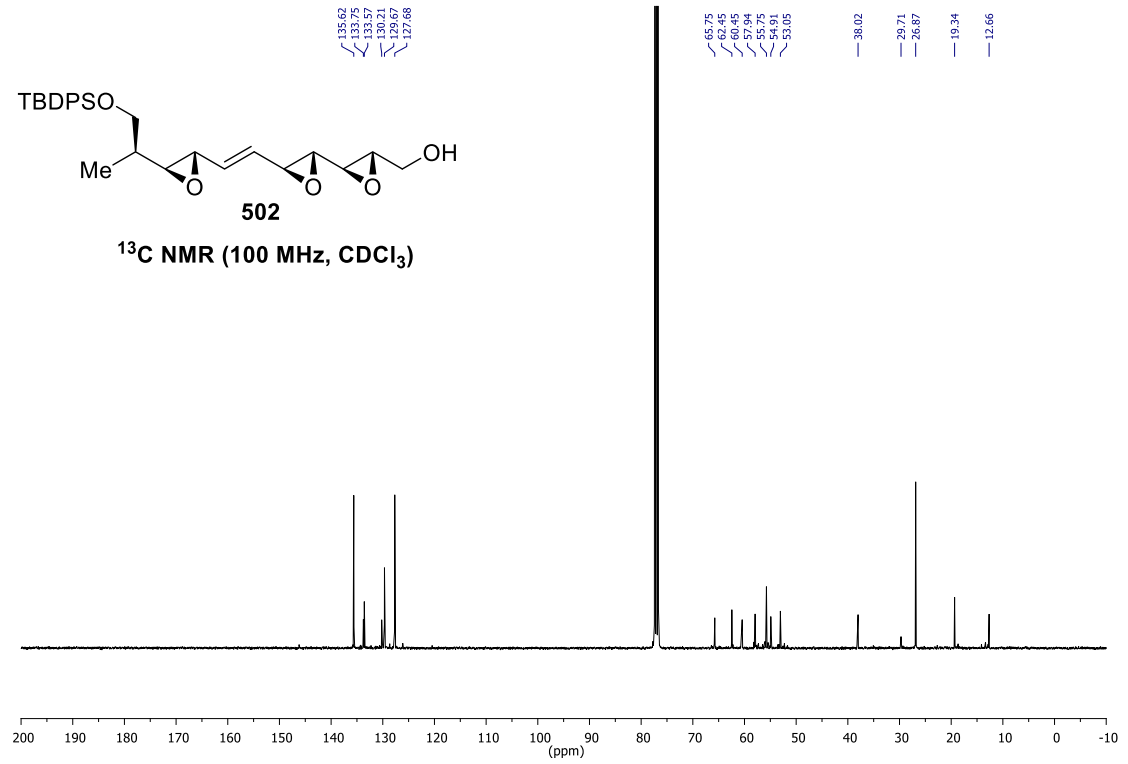






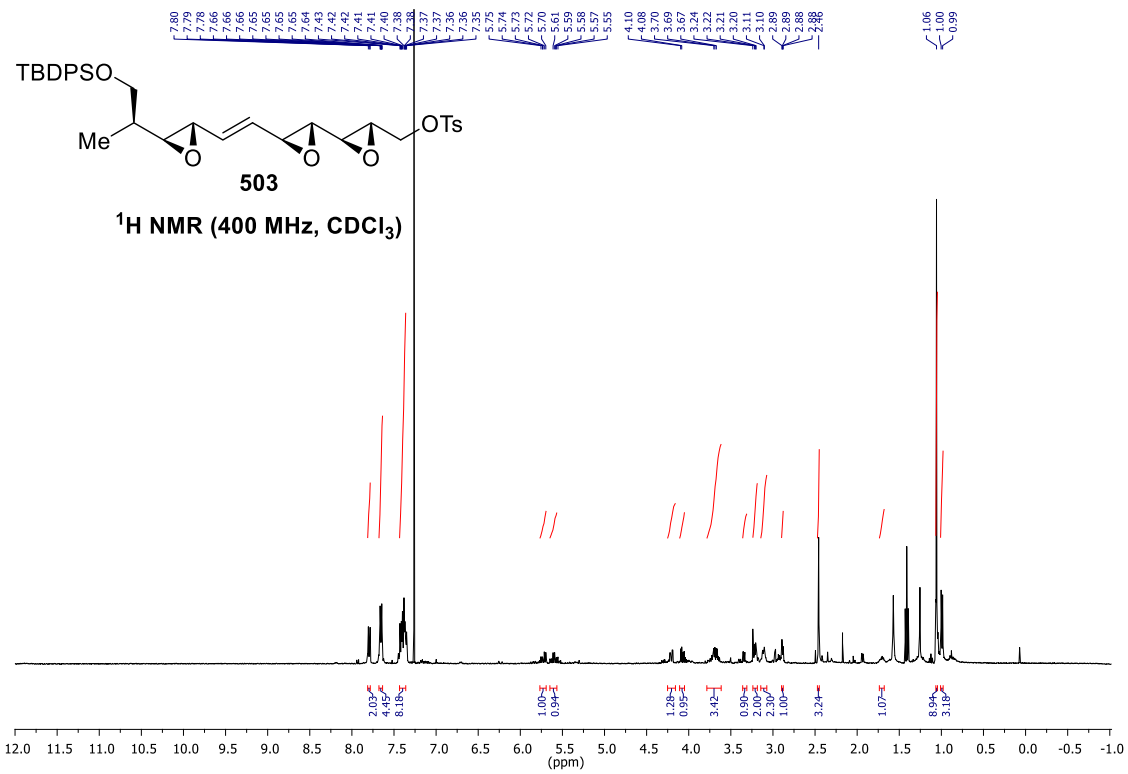
502

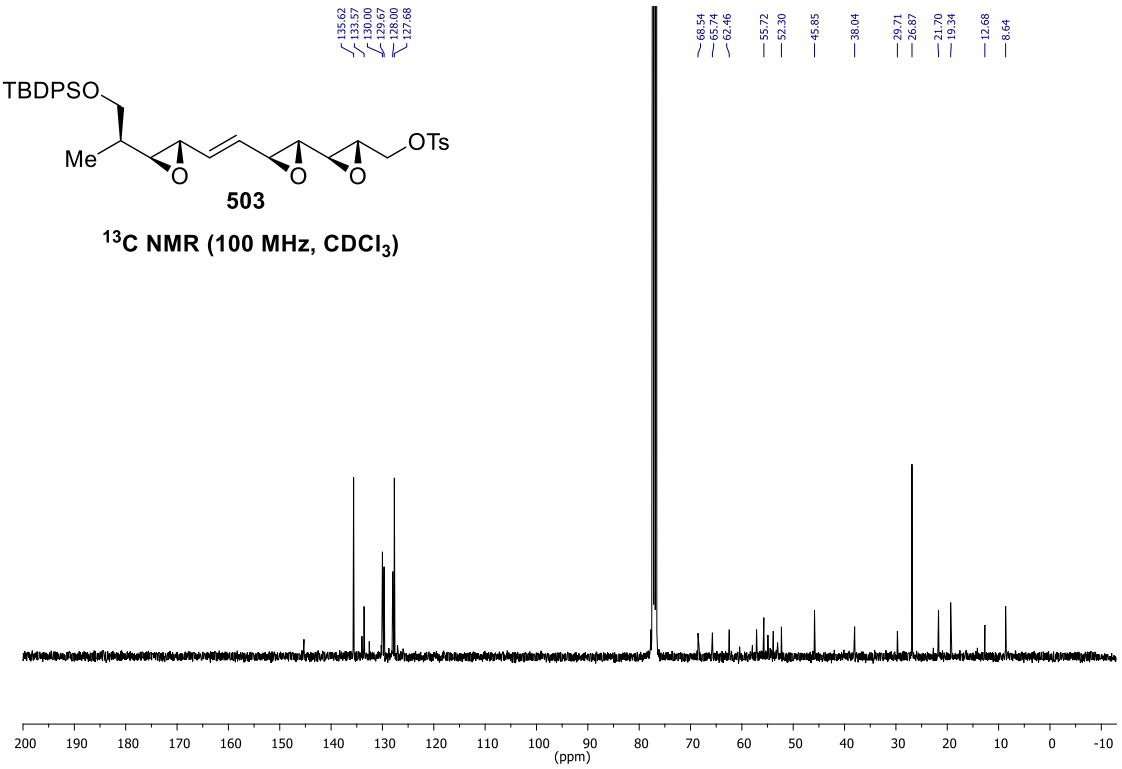
^{1}H NMR (400 MHz, $CDCl_3$)

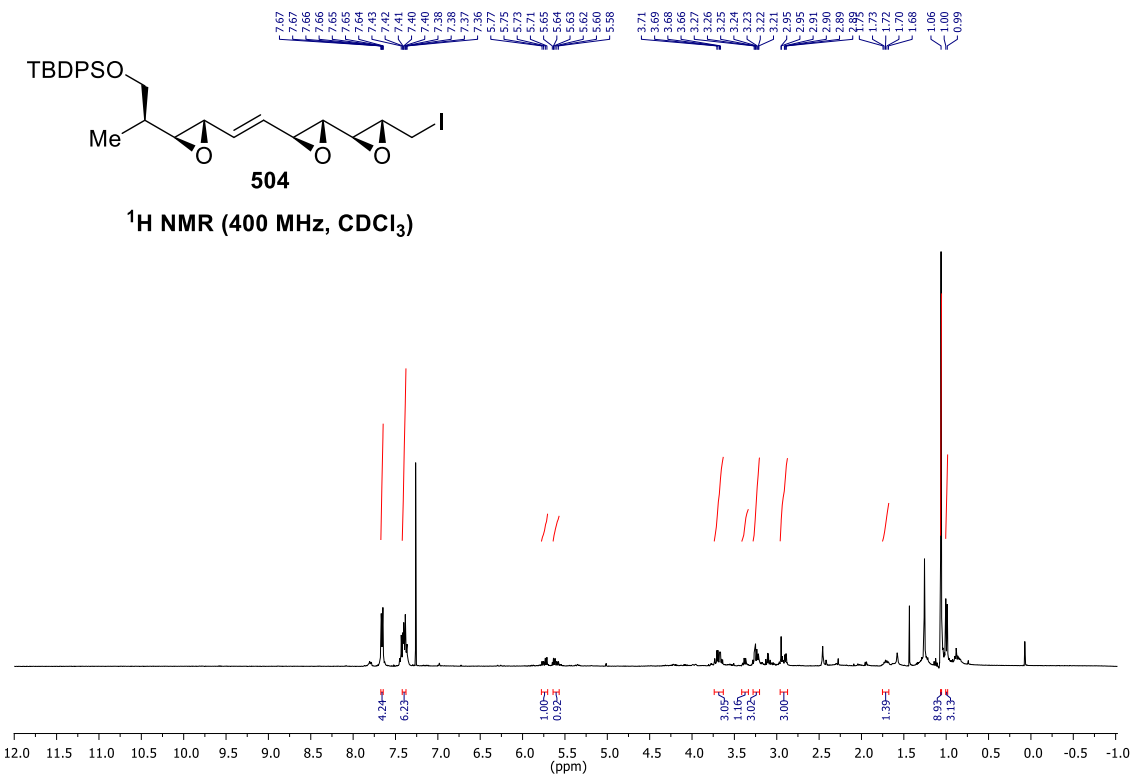


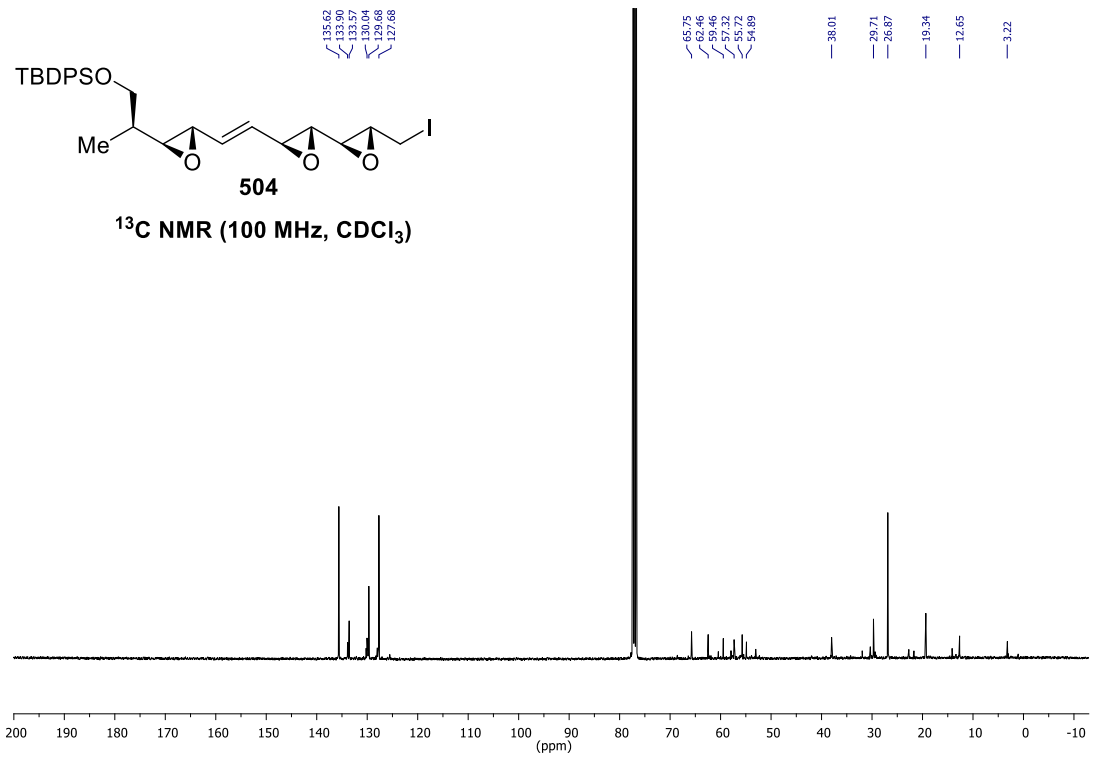
502

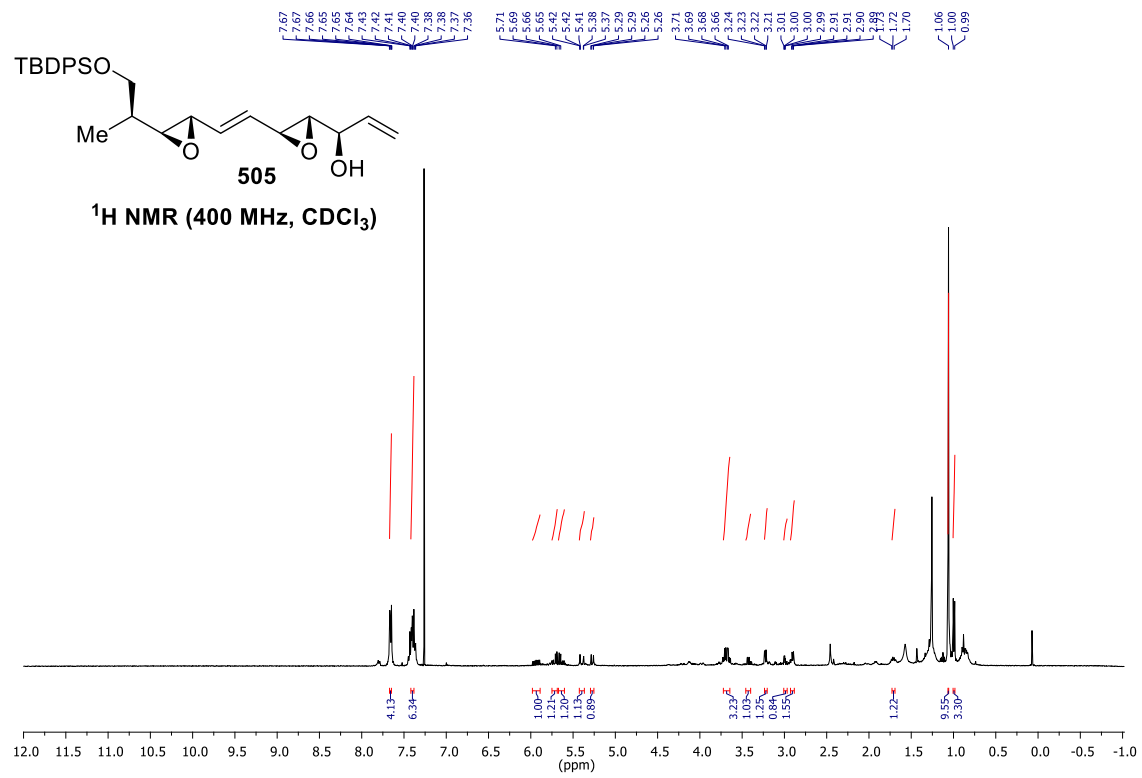
^{13}C NMR (100 MHz, $CDCl_3$)

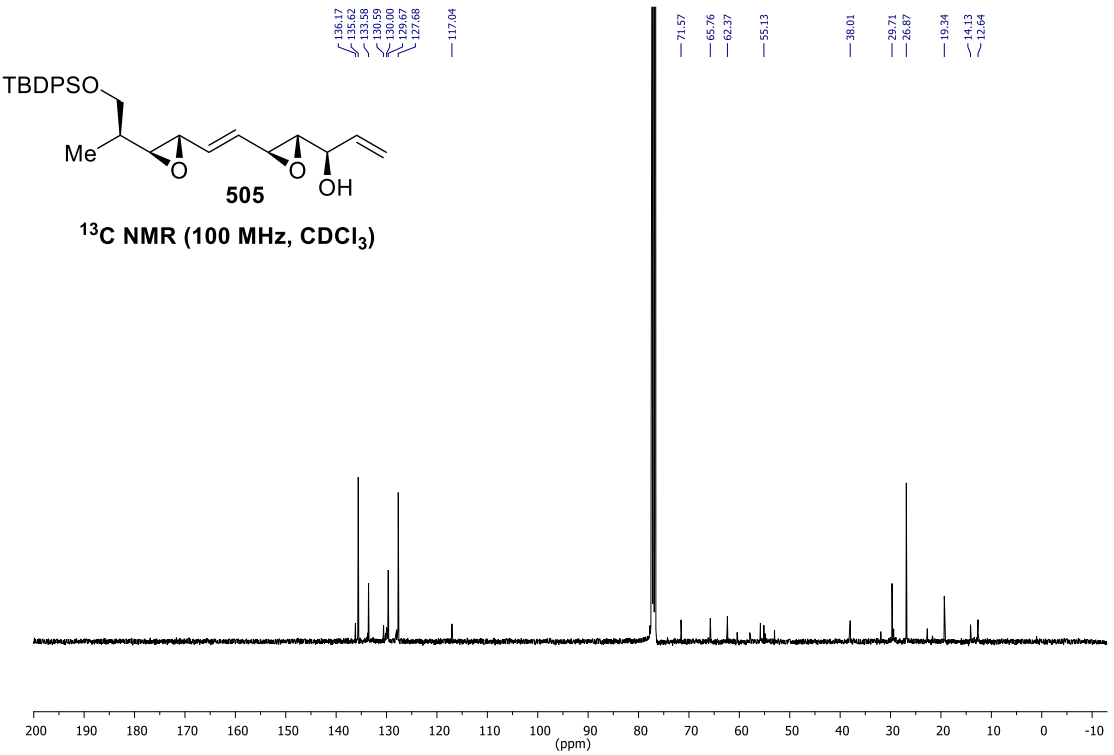


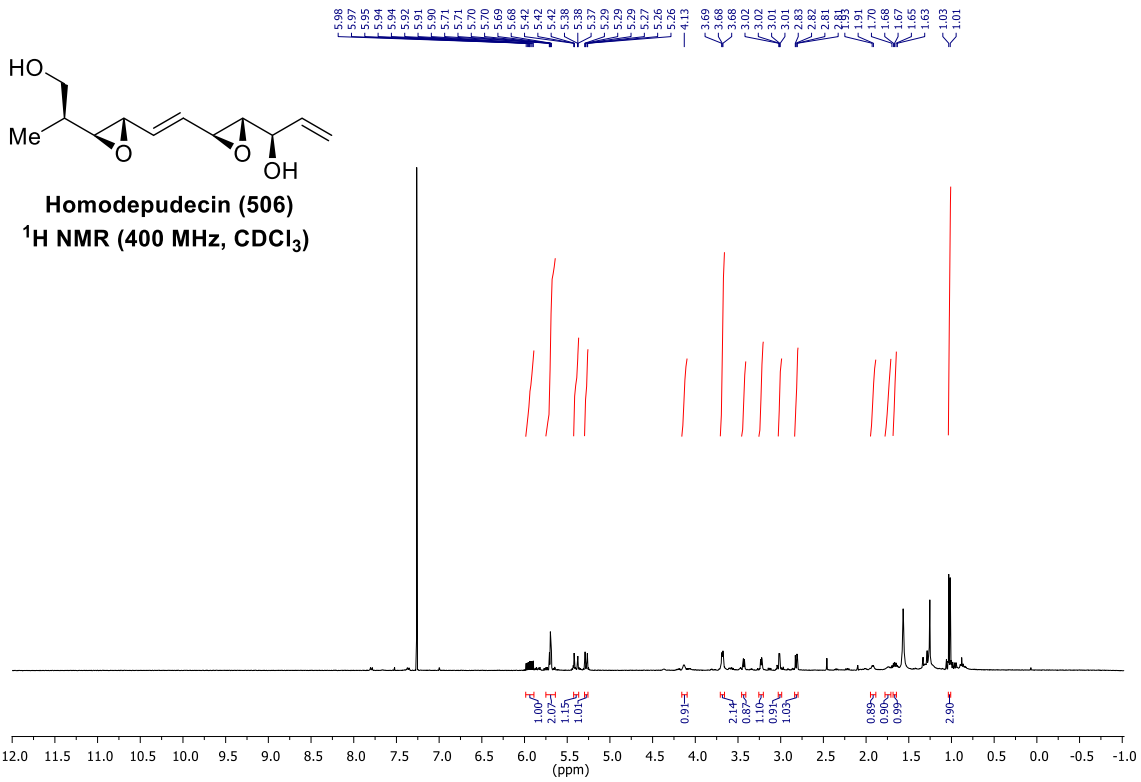


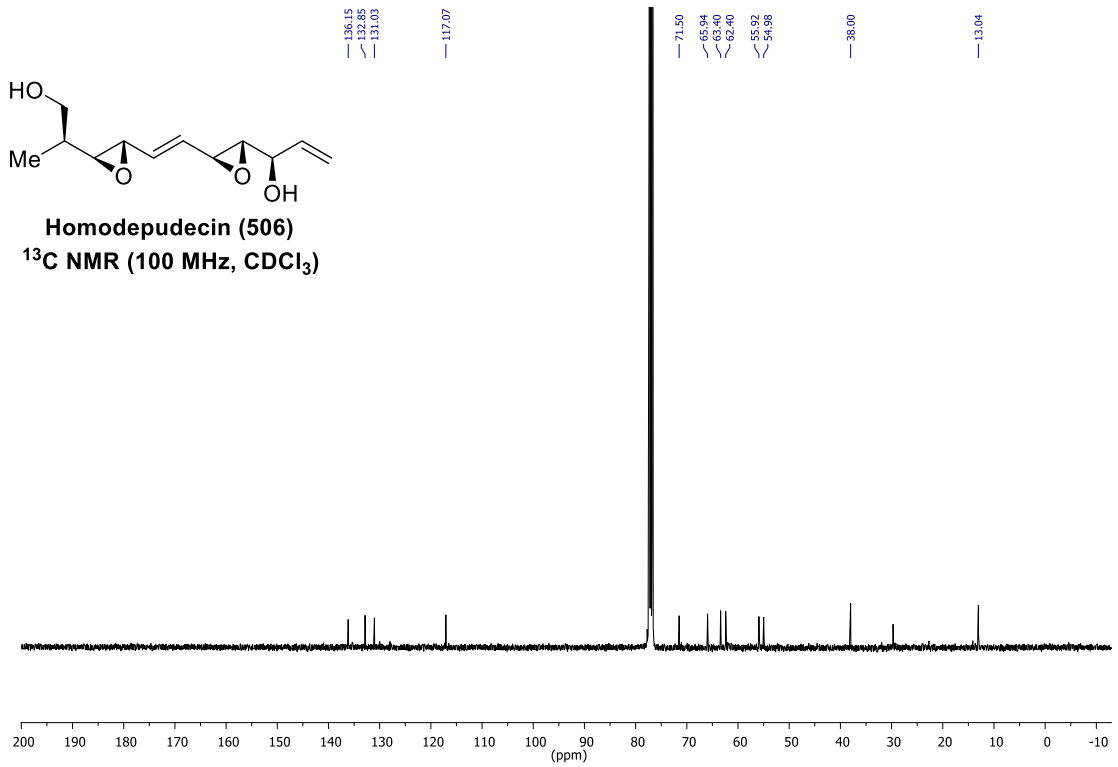










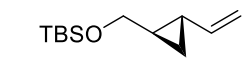


514

^{1}H NMR (400 MHz, $CDCl_3$)

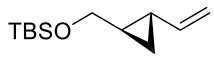
514

^{13}C NMR (100 MHz, $CDCl_3$)



515

^{1}H NMR (400 MHz, $CDCl_3$)



515

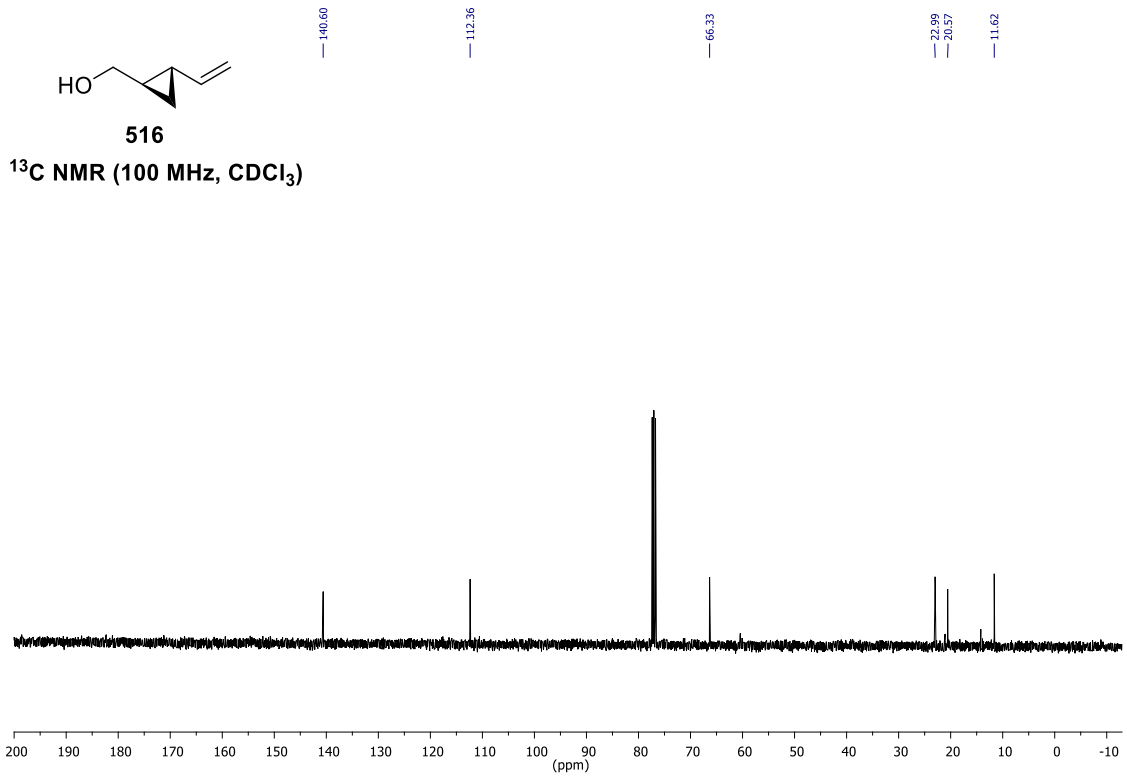
^{13}C NMR (100 MHz, $CDCl_3$)

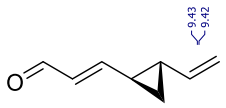
516

^{1}H NMR (400 MHz, $CDCl_3$)

516

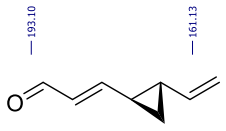
^{13}C NMR (100 MHz, $CDCl_3$)





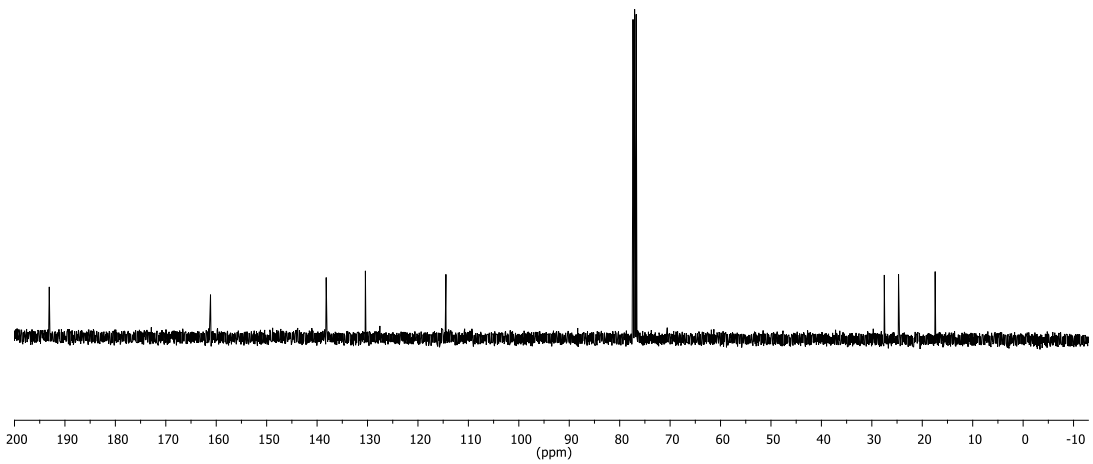
517

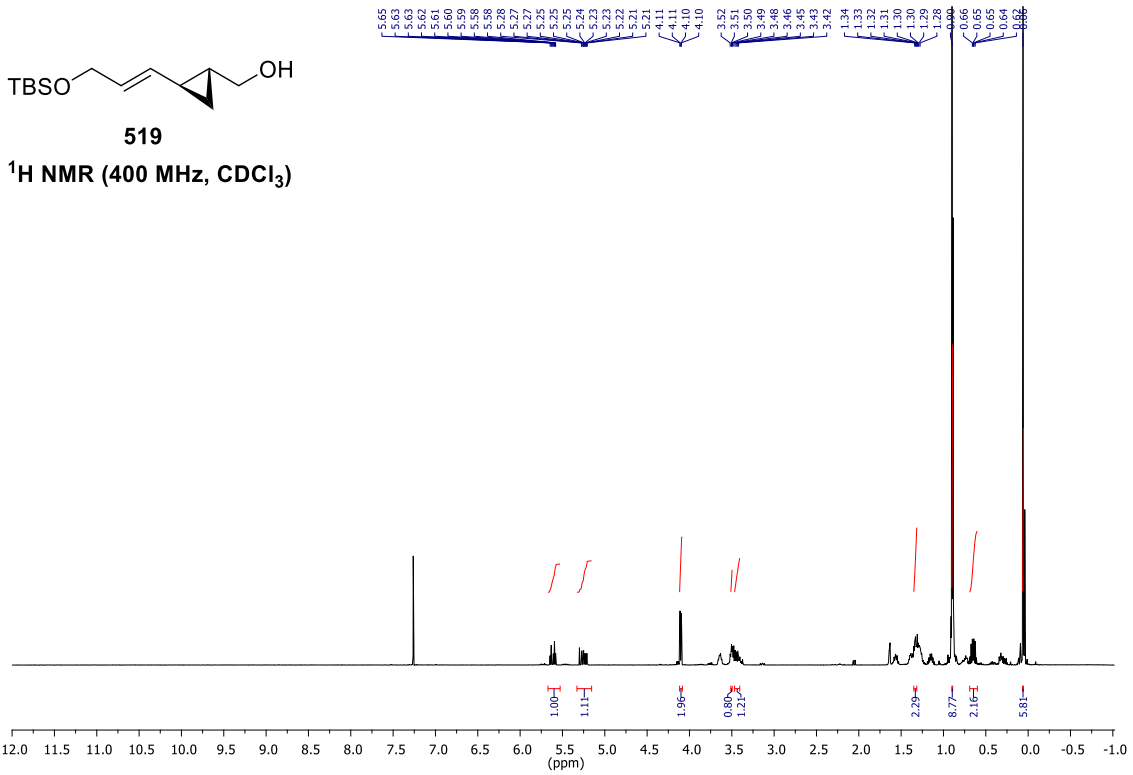
^{1}H NMR (400 MHz, $CDCl_3$)

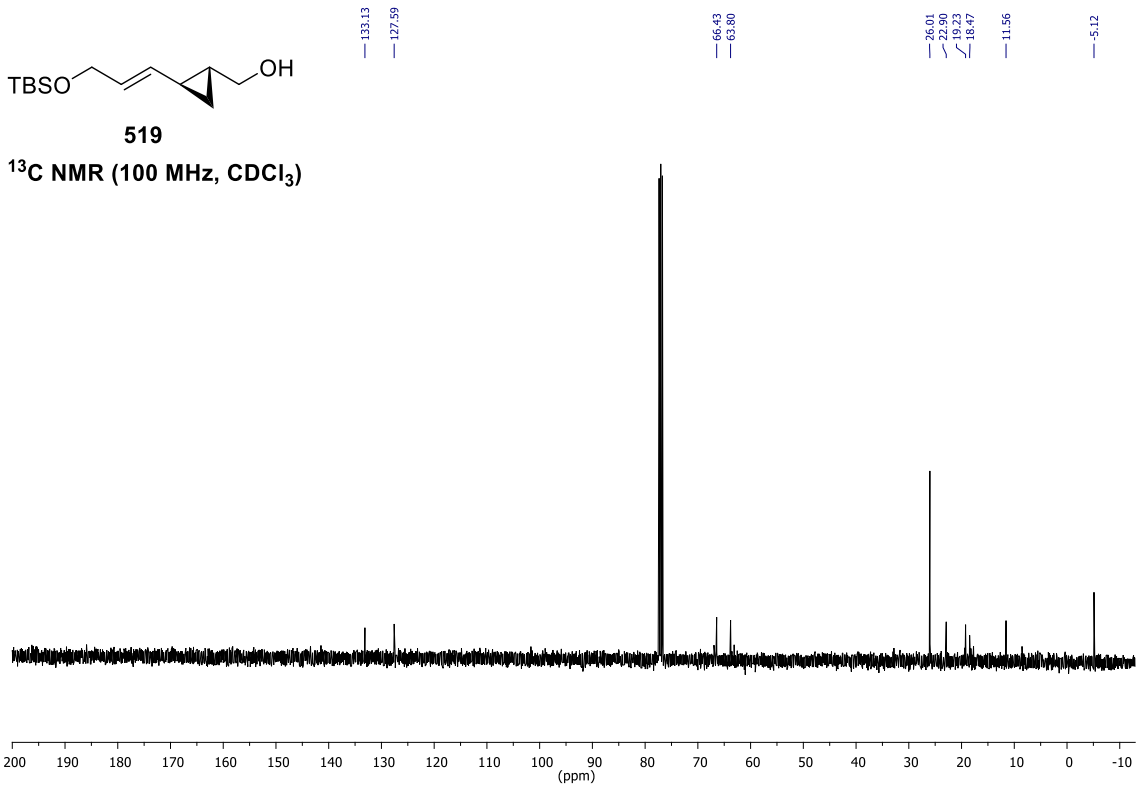


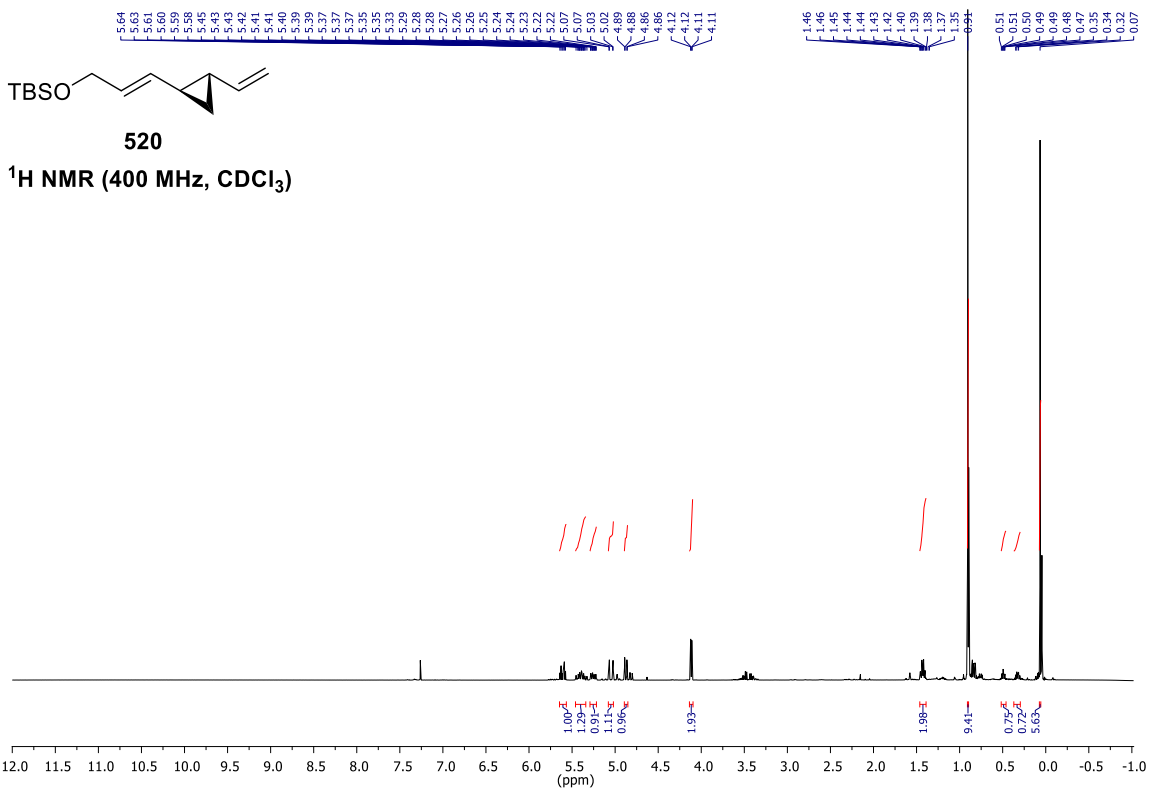
517

^{13}C NMR (100 MHz, $CDCl_3$)



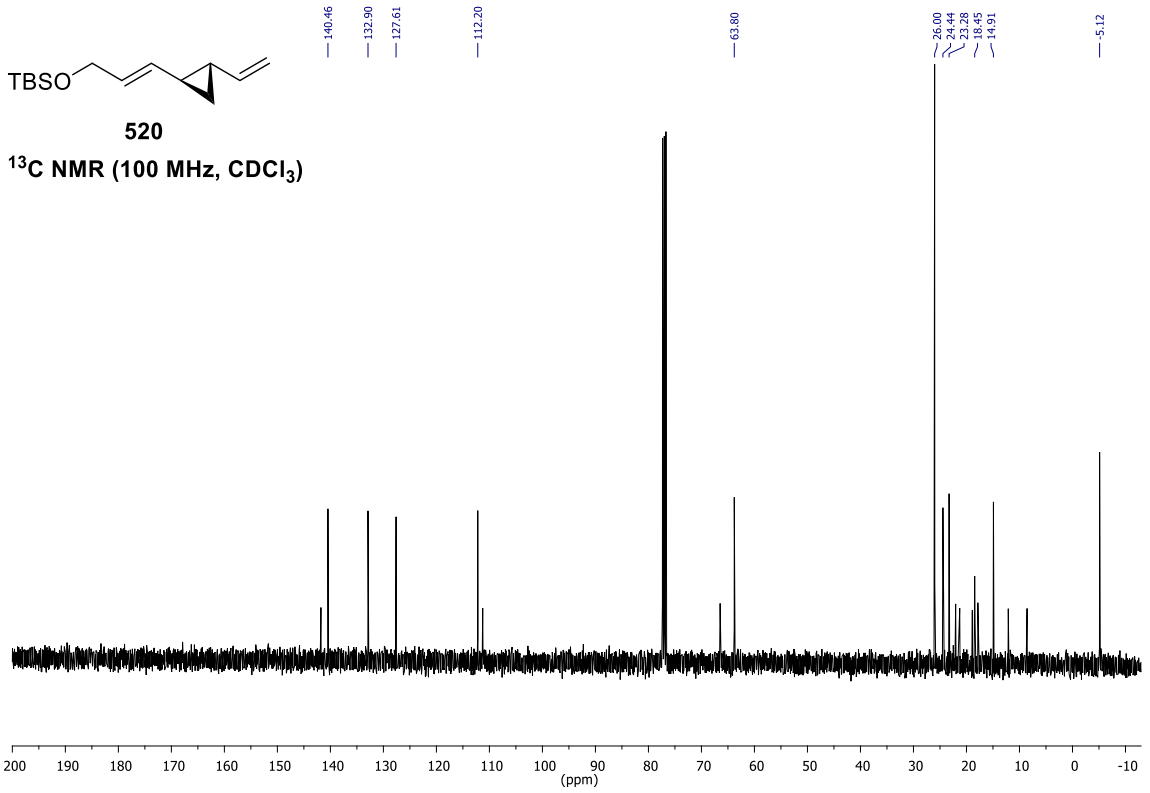






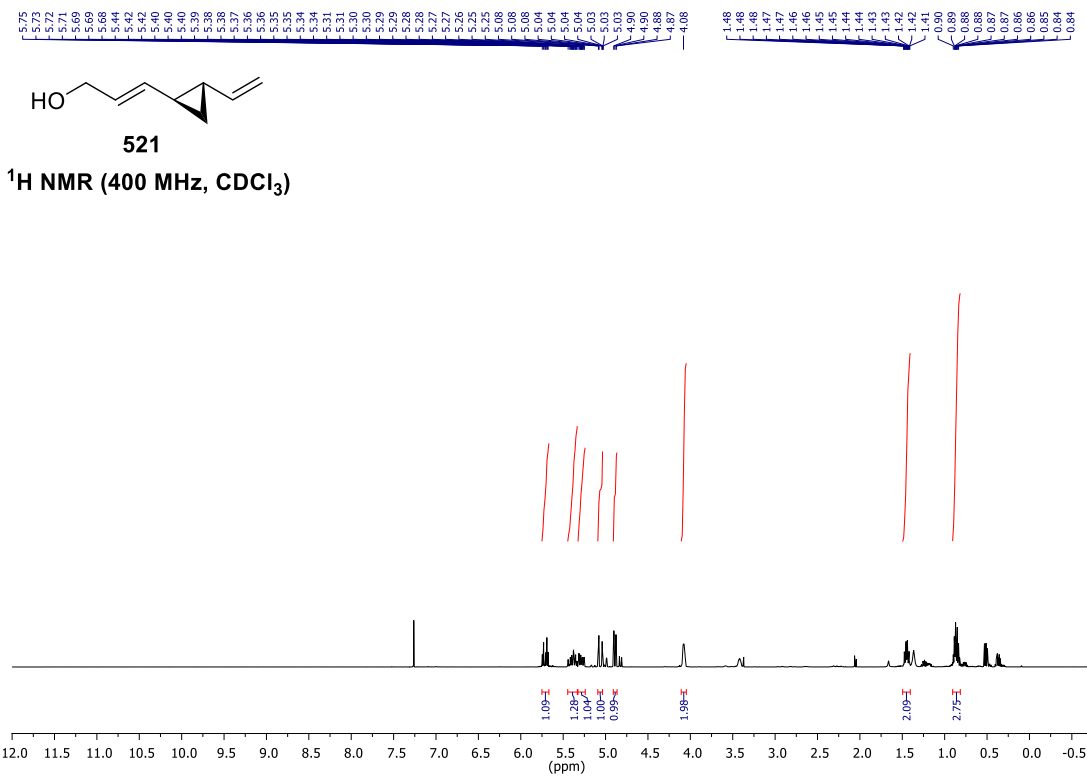
520

^{1}H NMR (400 MHz, $CDCl_3$)



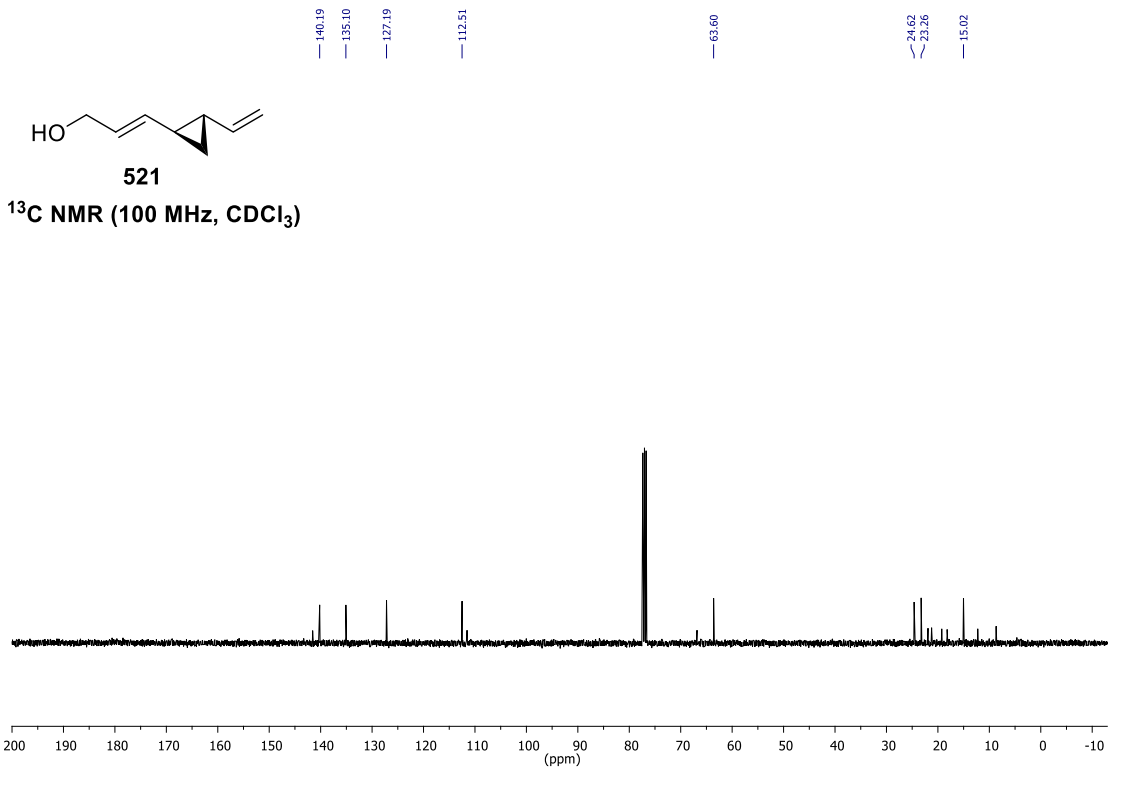
520

^{13}C NMR (100 MHz, $CDCl_3$)



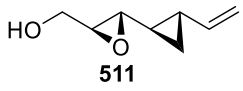
521

^{1}H NMR (400 MHz, $CDCl_3$)



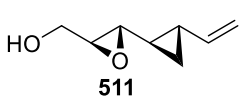
521

^{13}C NMR (100 MHz, $CDCl_3$)



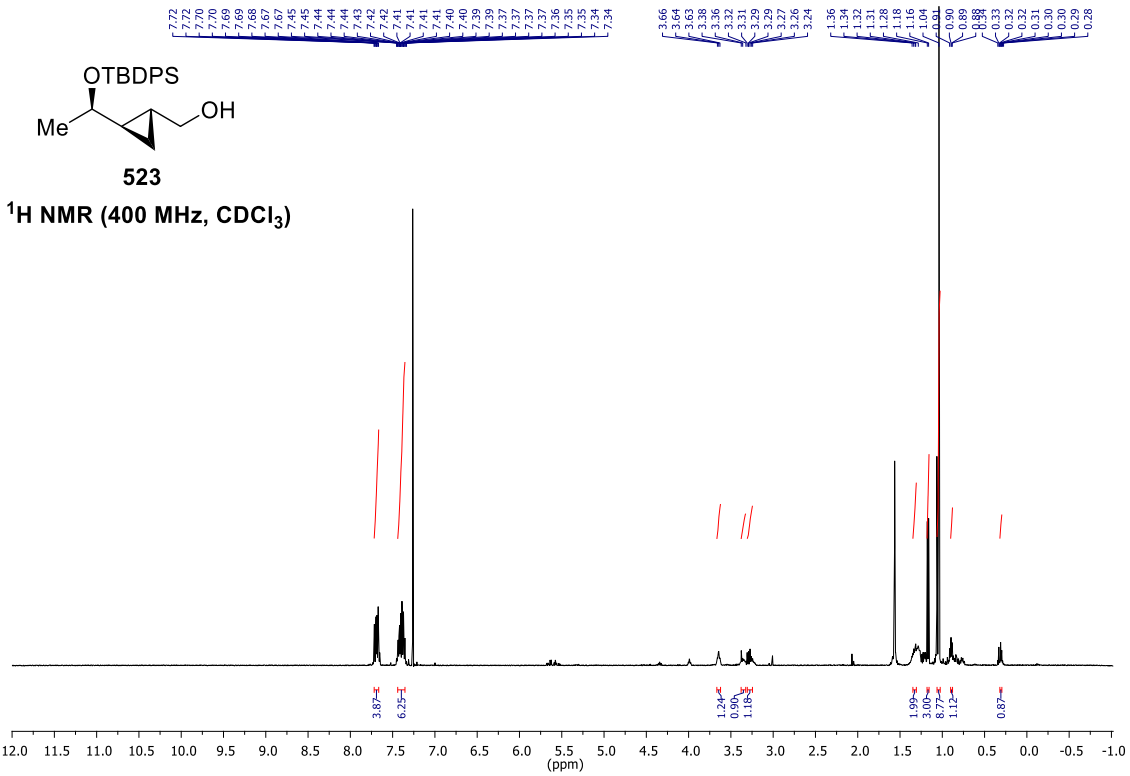
511

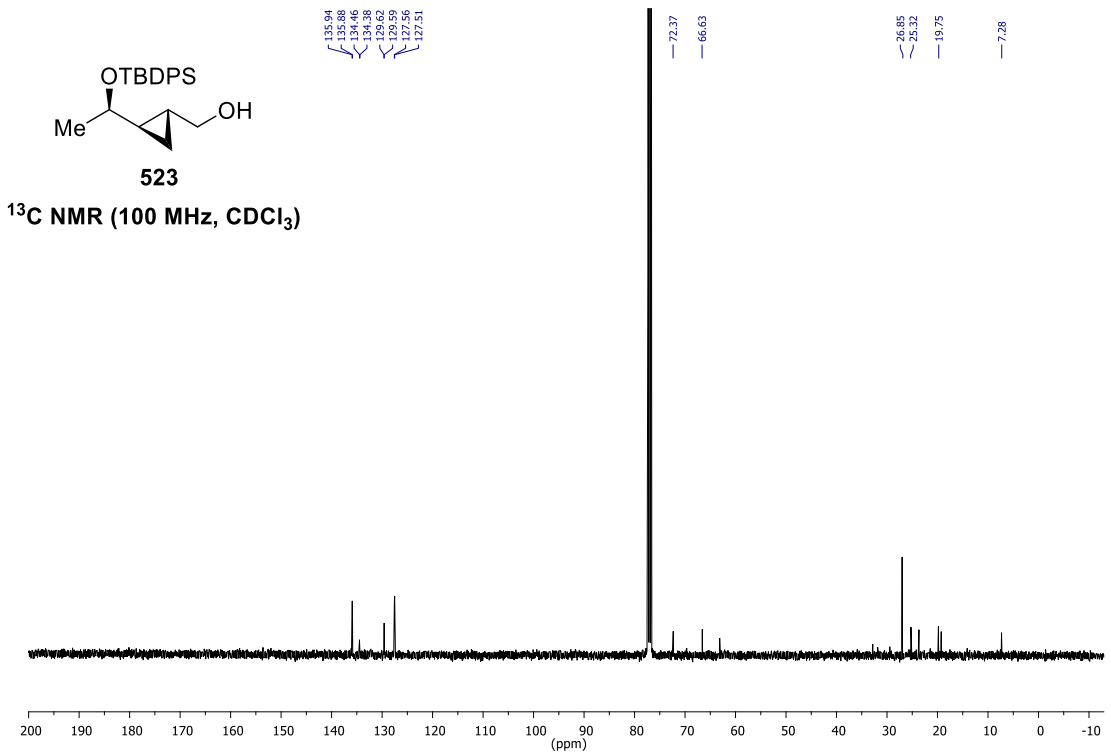
^{1}H NMR (400 MHz, $CDCl_3$)

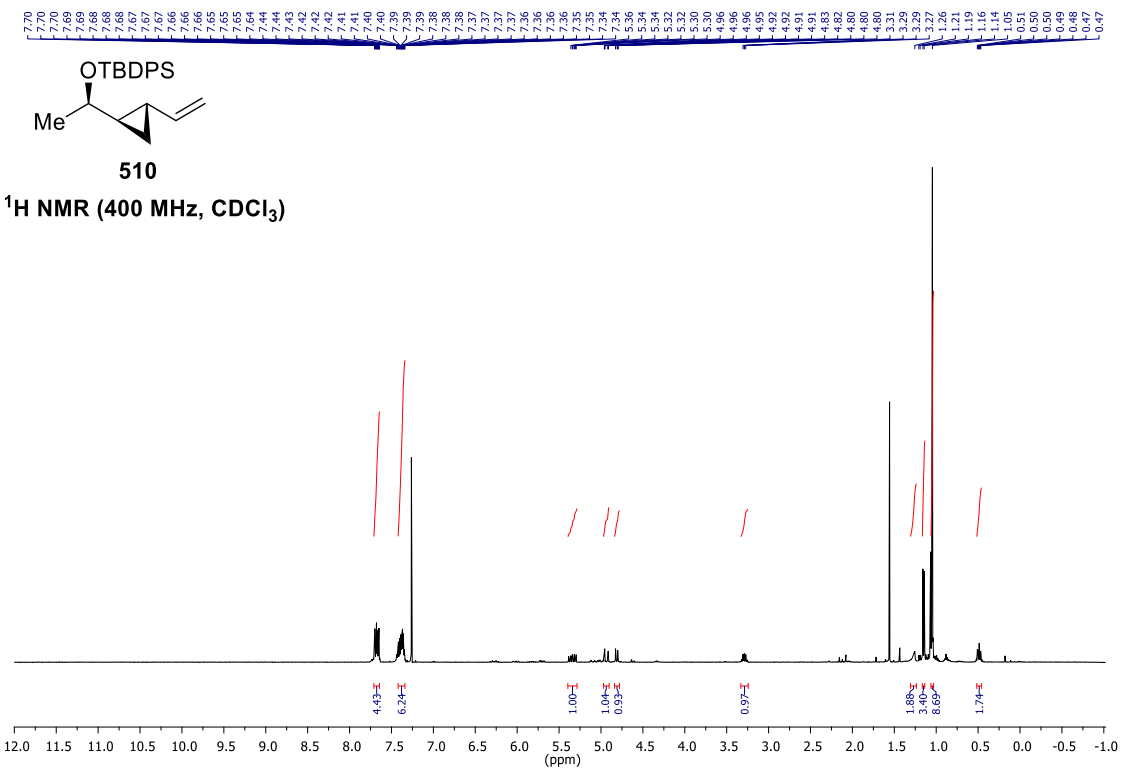


511

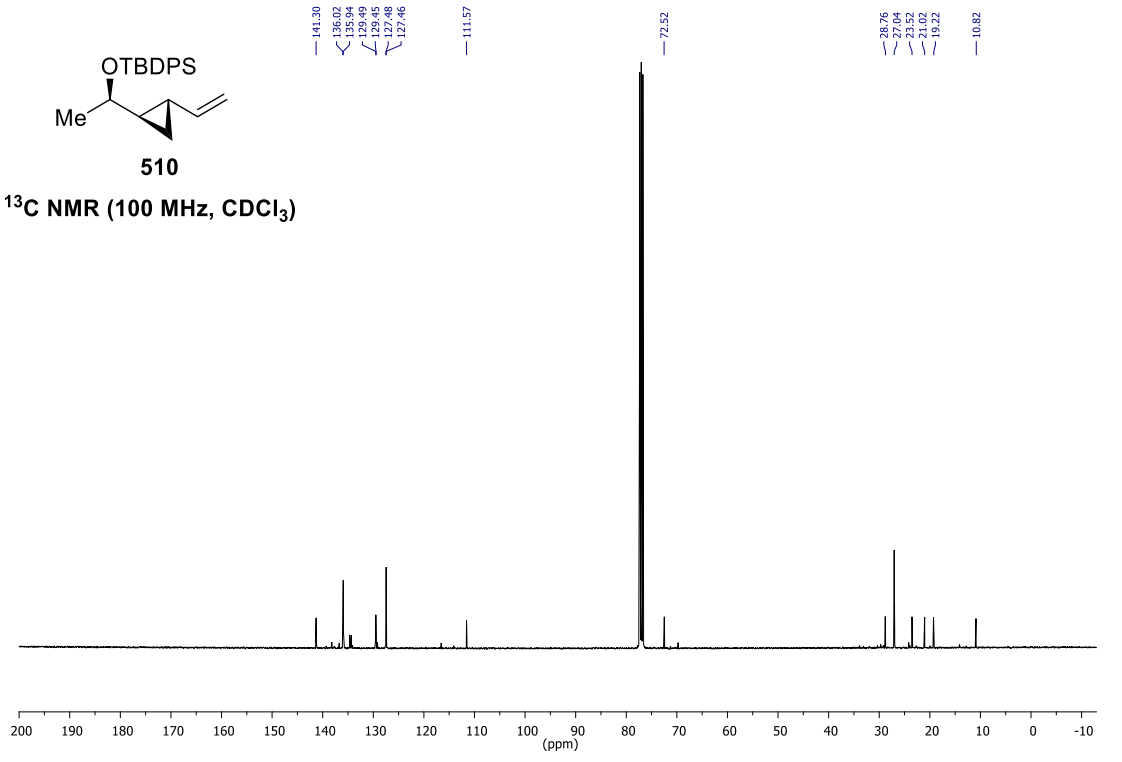
^{13}C NMR (100 MHz, $CDCl_3$)



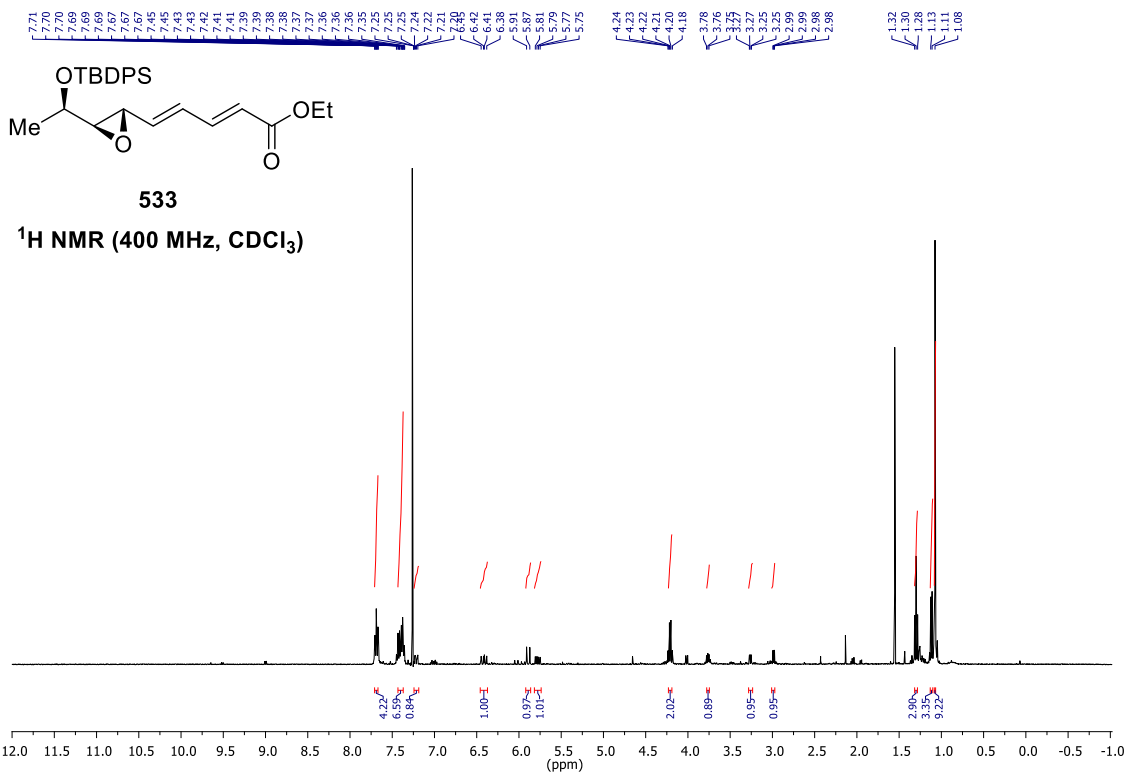


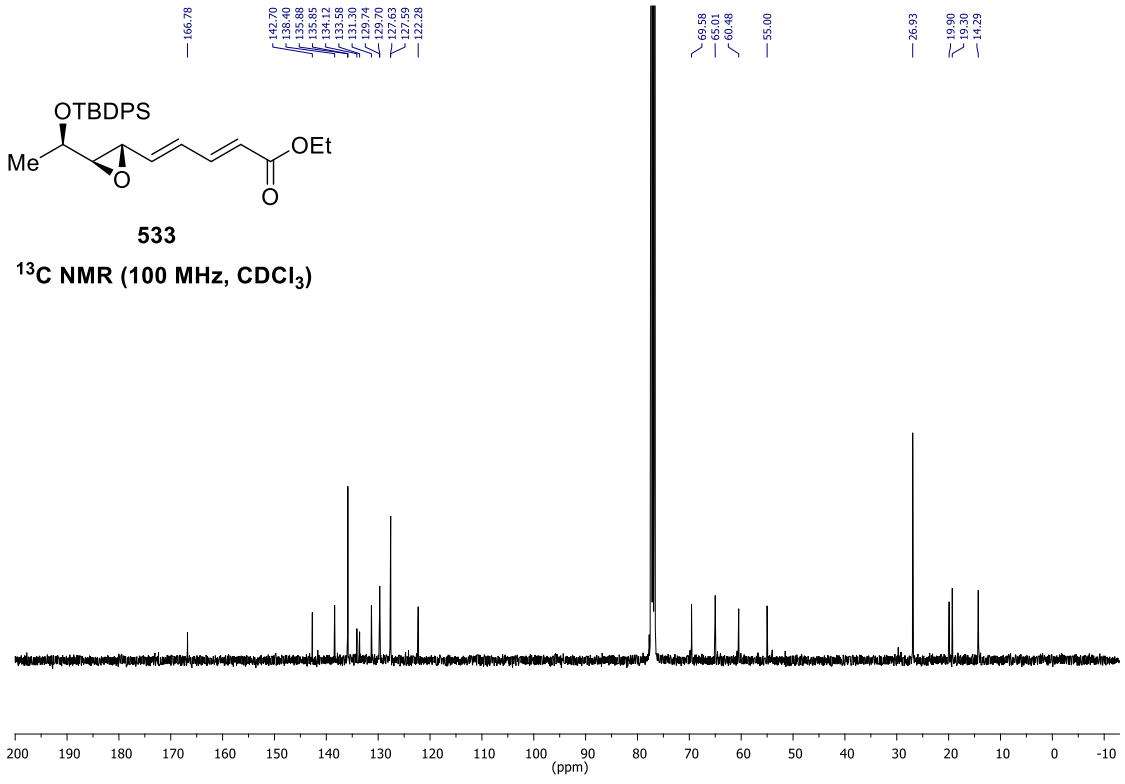


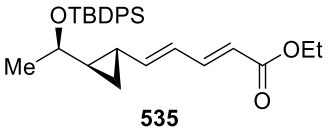
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

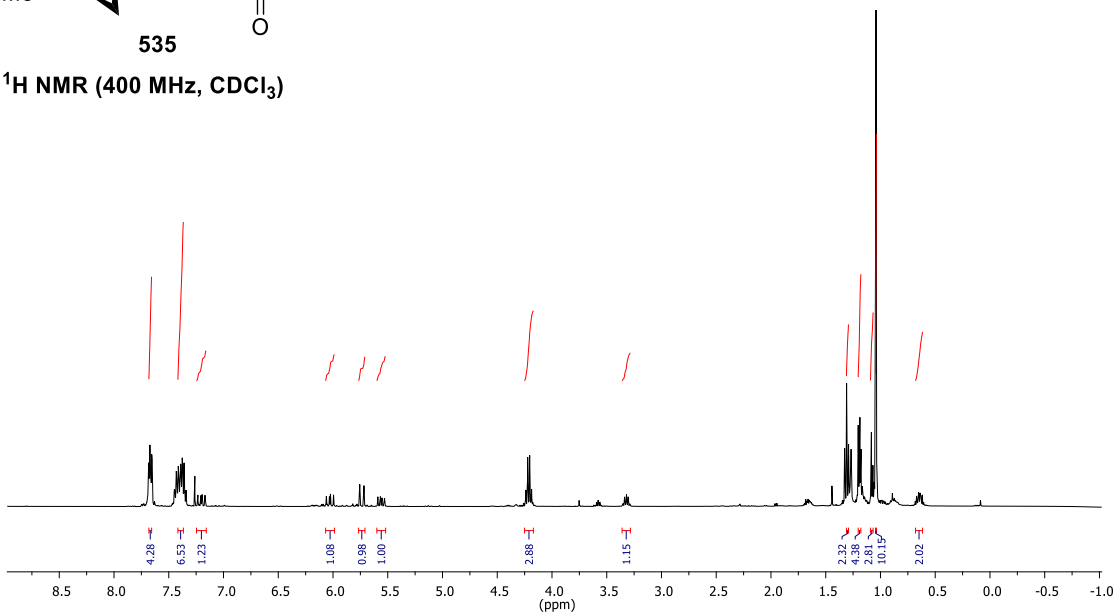


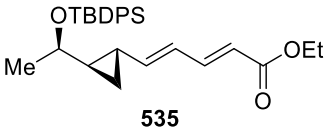




535

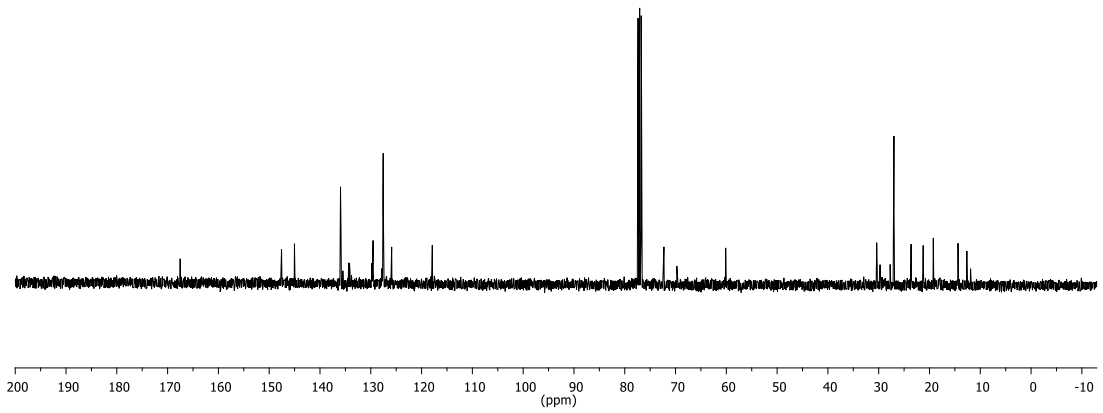
^{1}H NMR (400 MHz, $CDCl_3$)

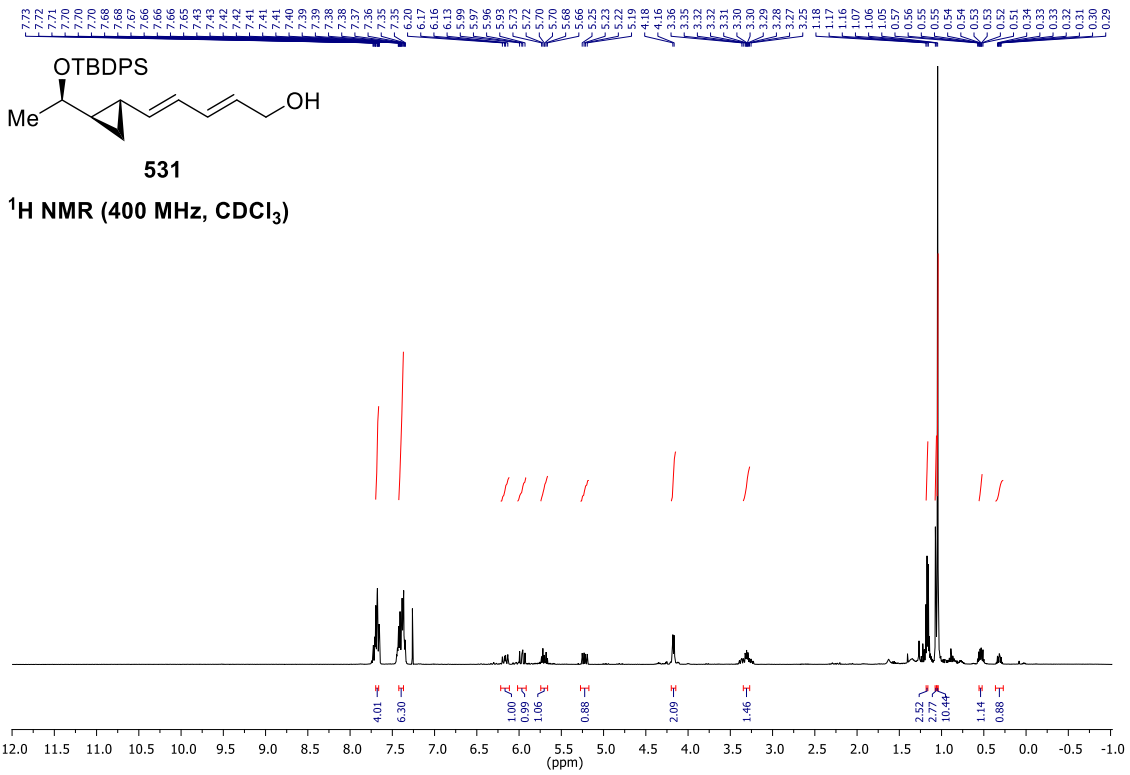




535

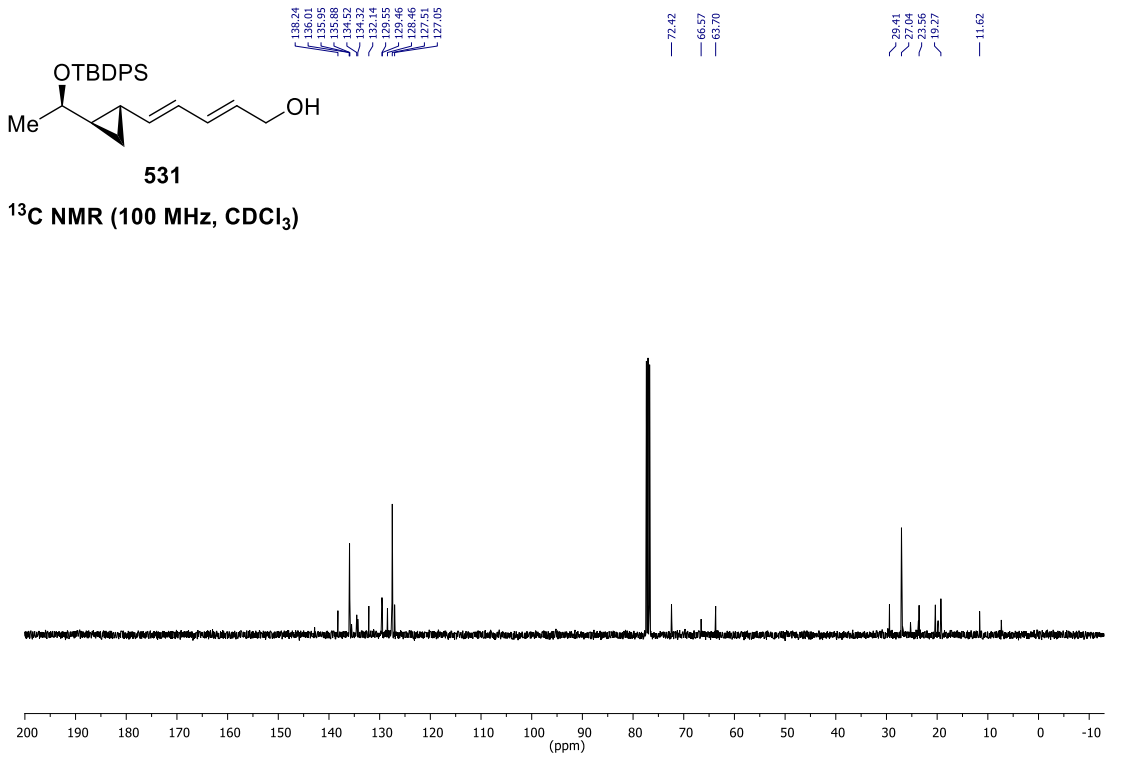
^{13}C NMR (100 MHz, $CDCl_3$)





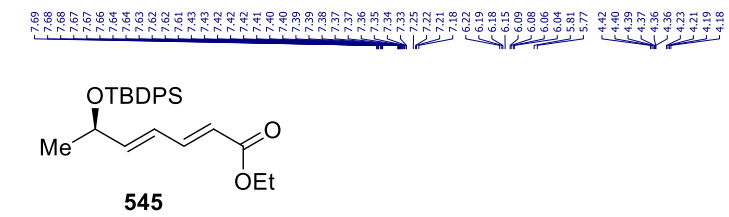
531

^{1}H NMR (400 MHz, $CDCl_3$)



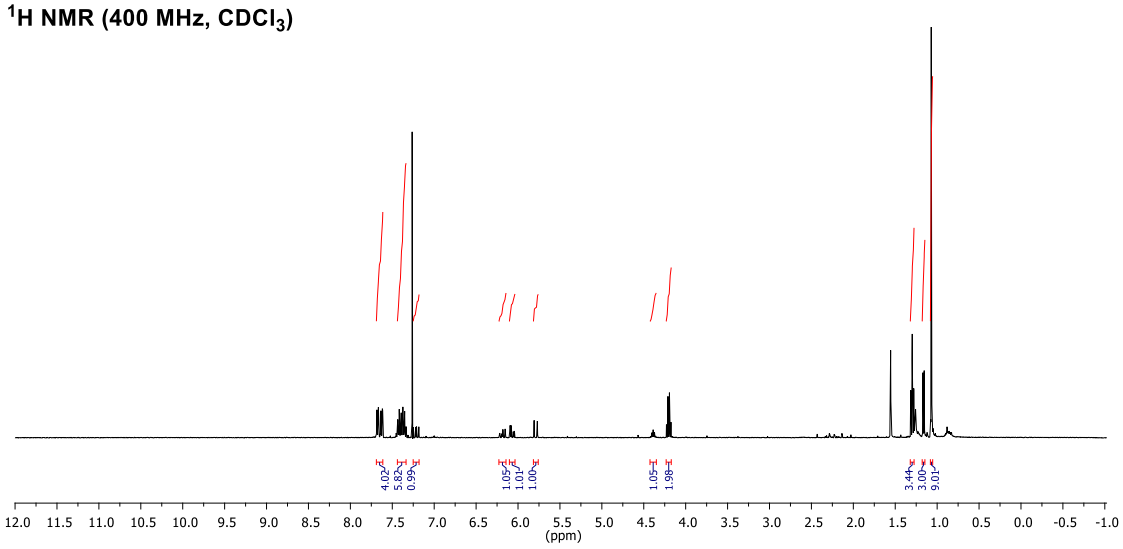
531

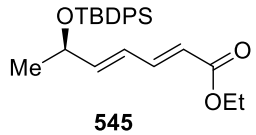
^{13}C NMR (100 MHz, $CDCl_3$)



545

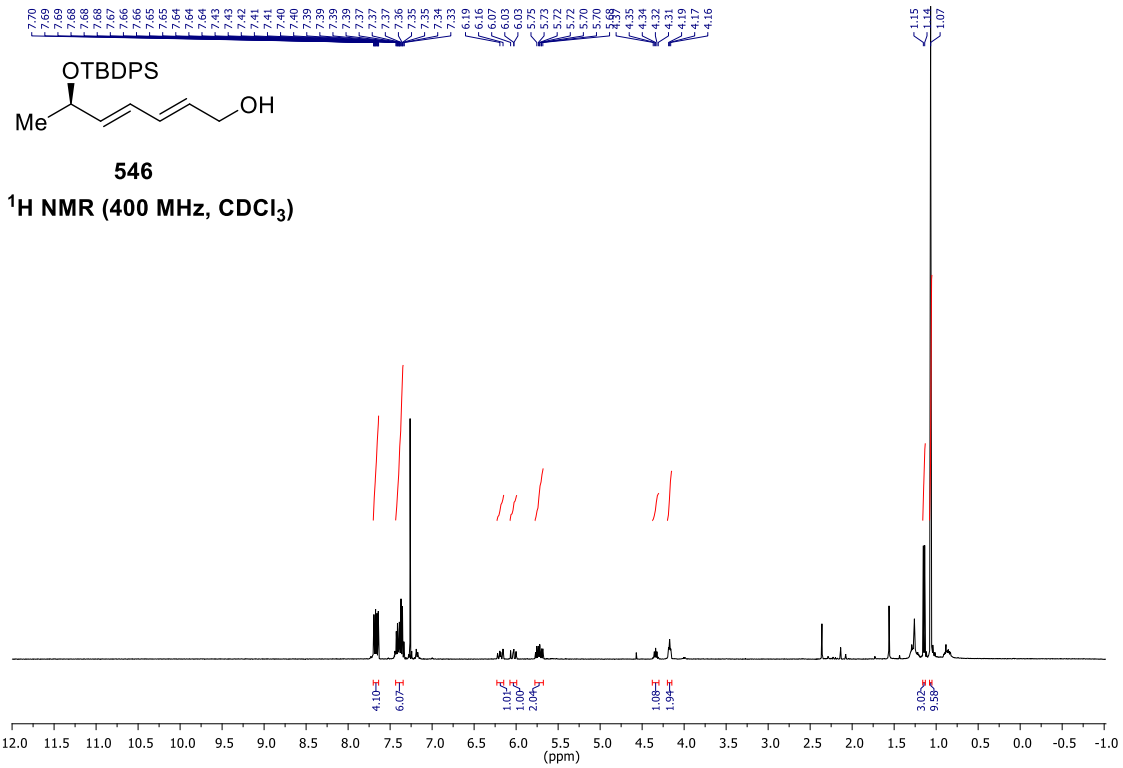
^{1}H NMR (400 MHz, $CDCl_3$)





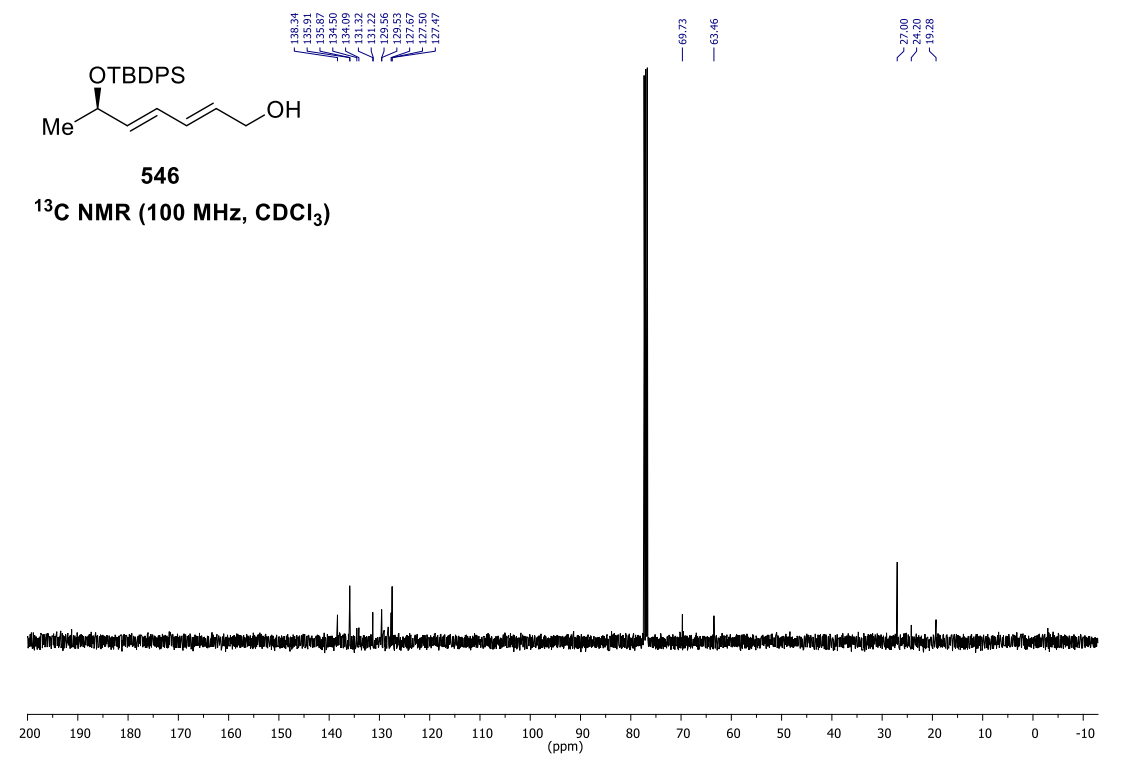
545

^{13}C NMR (100 MHz, $CDCl_3$)



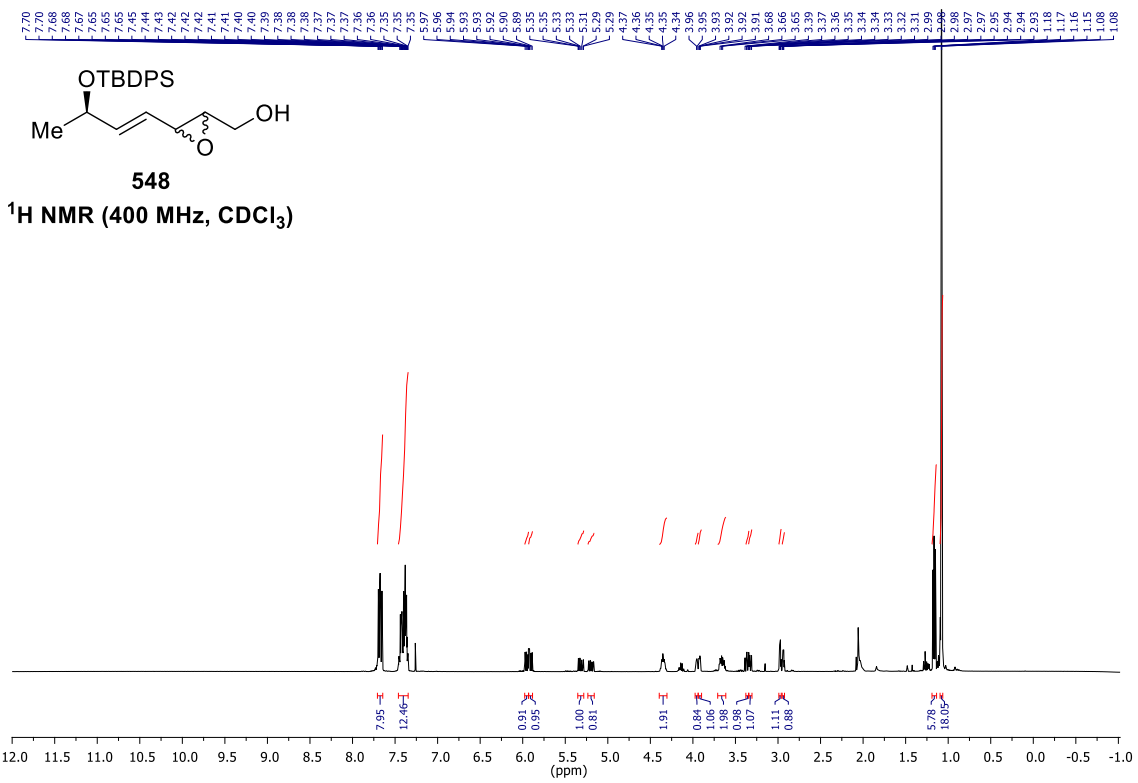
546

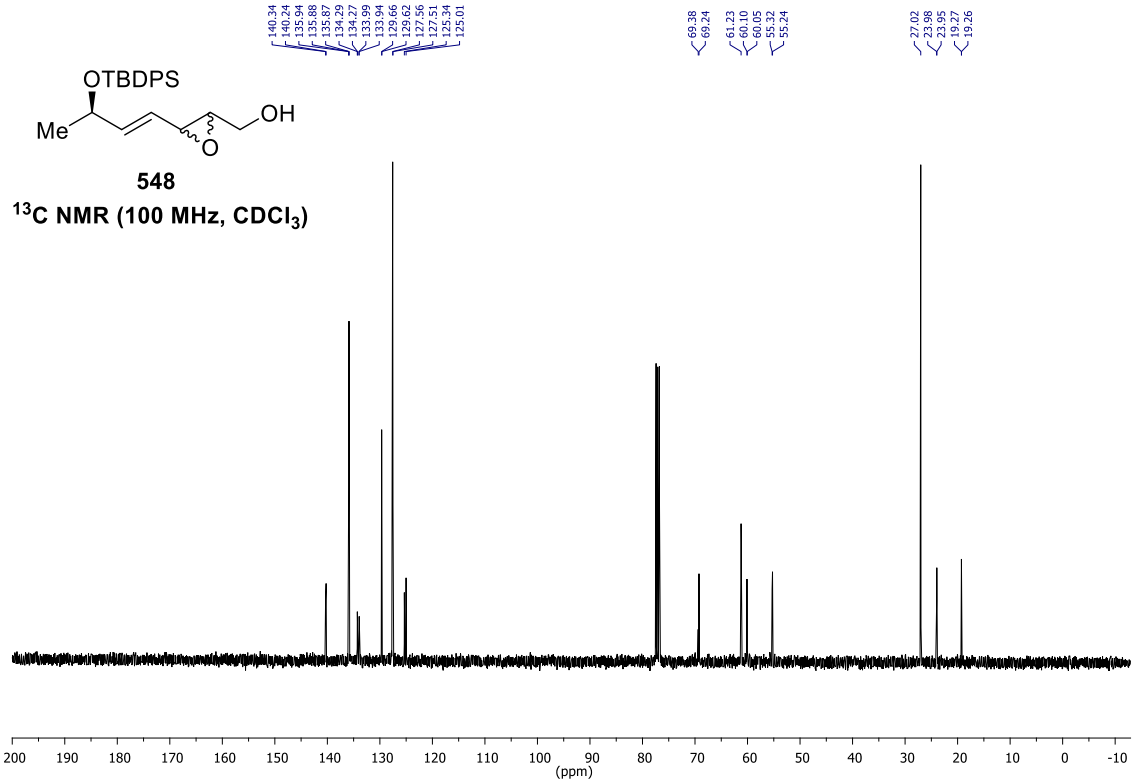
^{1}H NMR (400 MHz, $CDCl_3$)

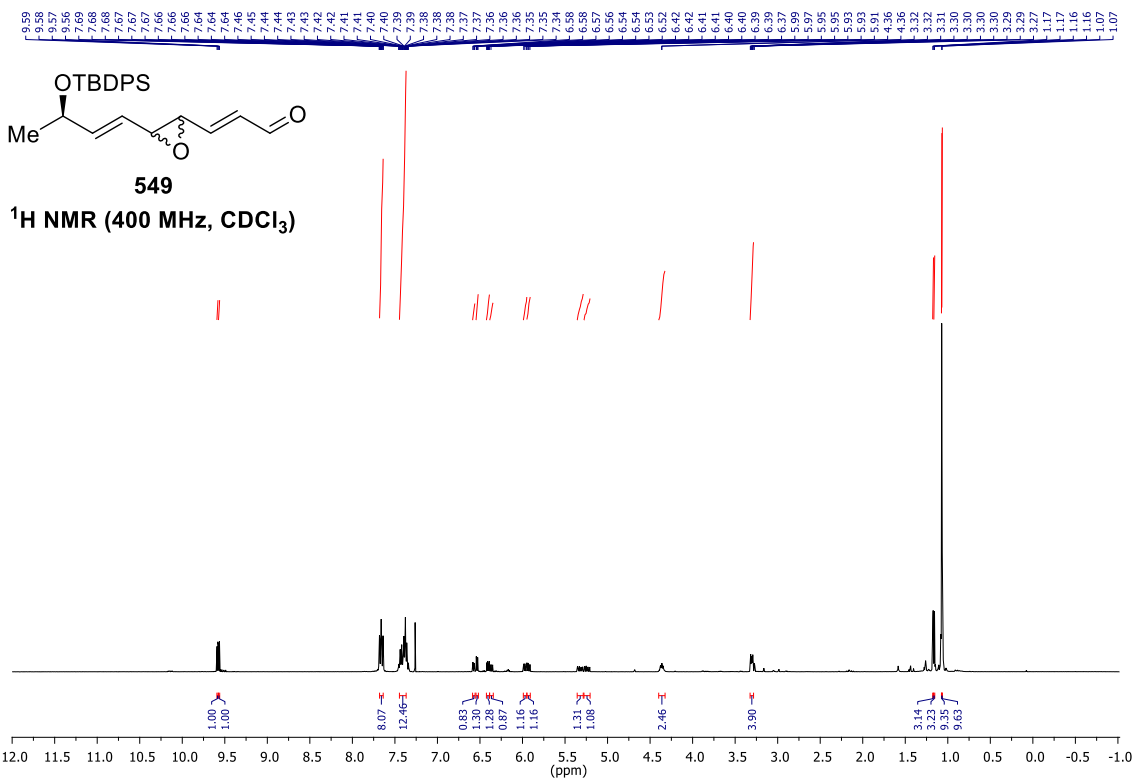


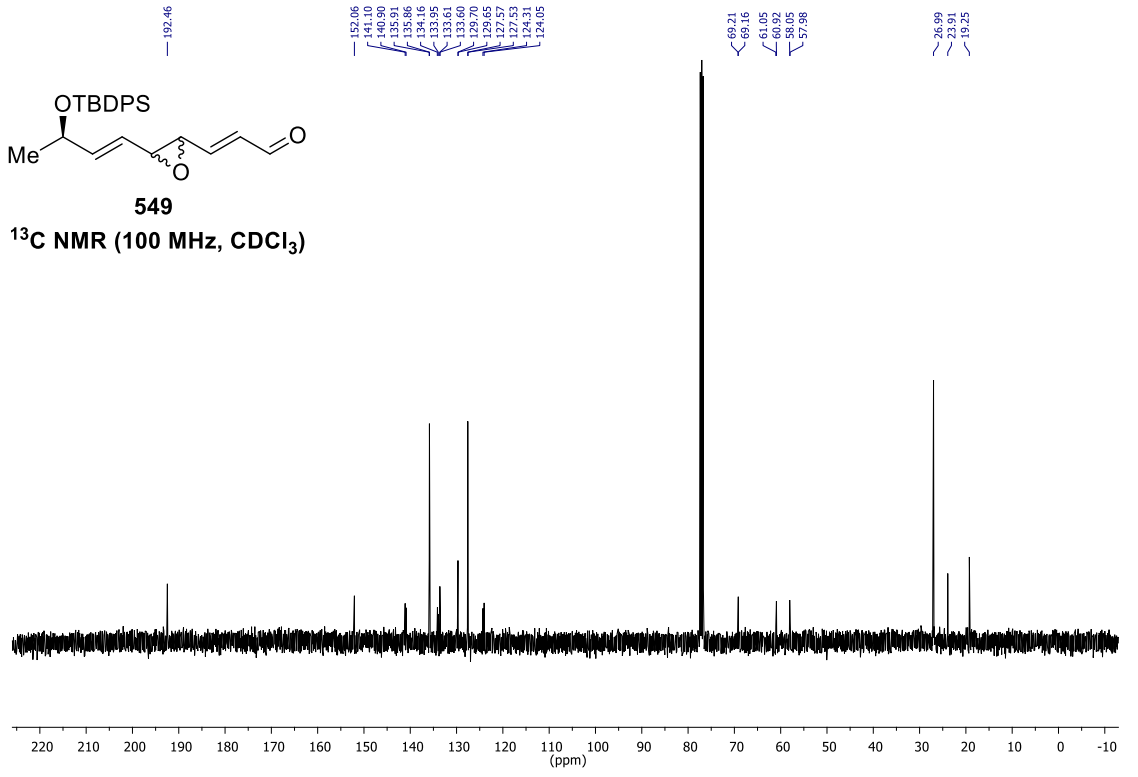
546

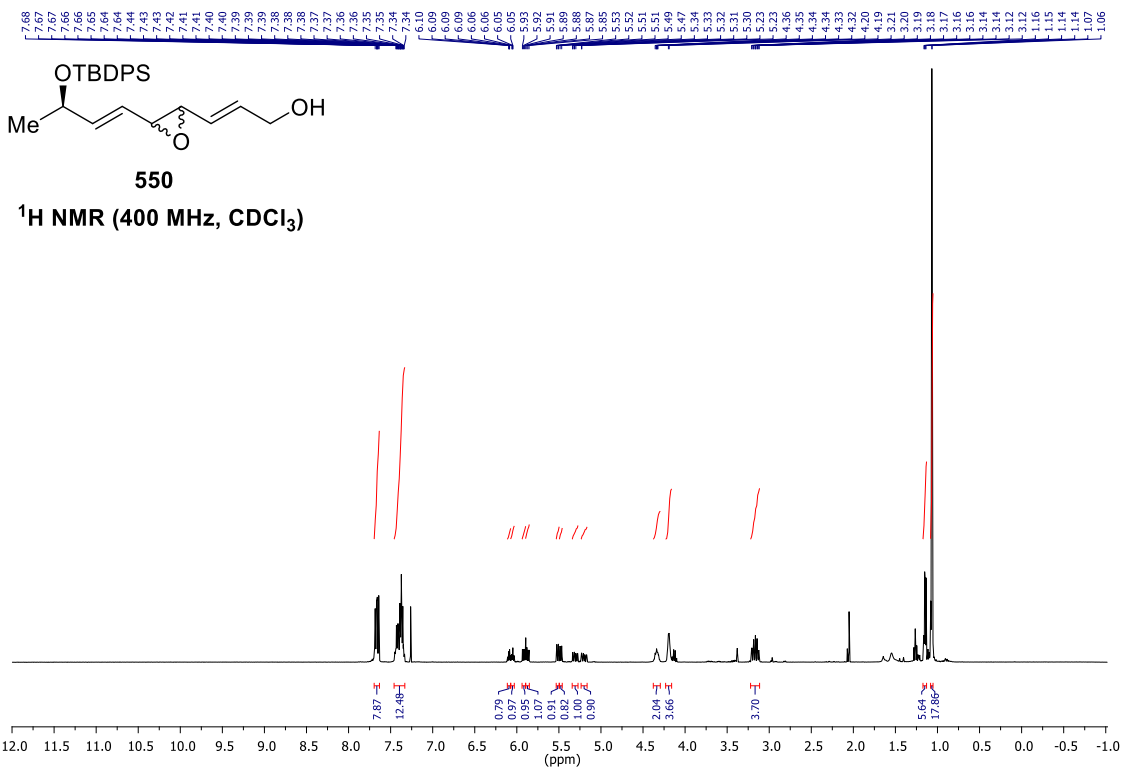
^{13}C NMR (100 MHz, $CDCl_3$)

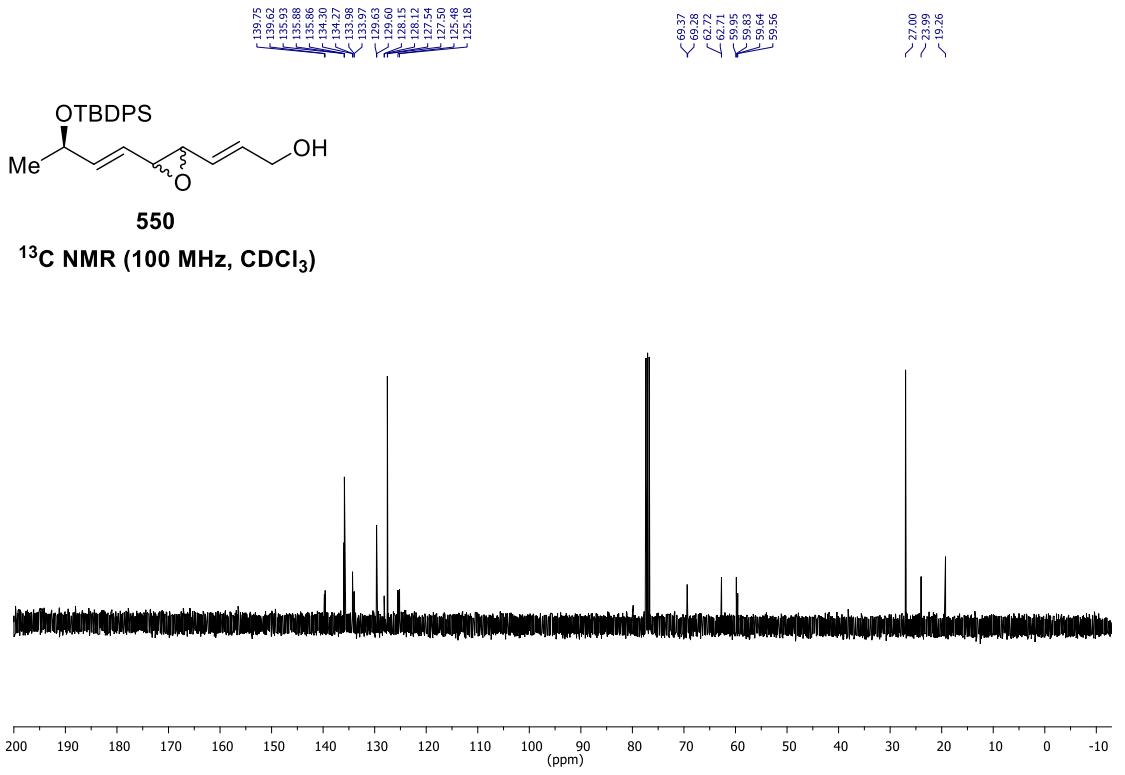


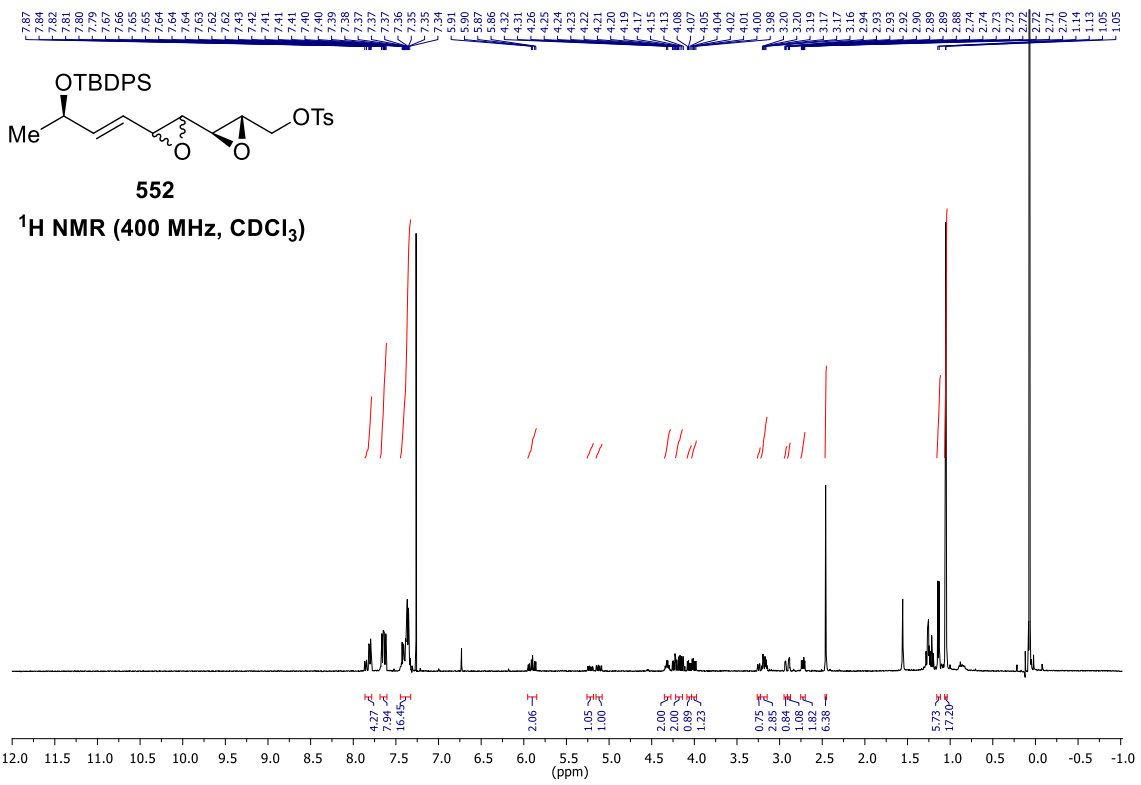


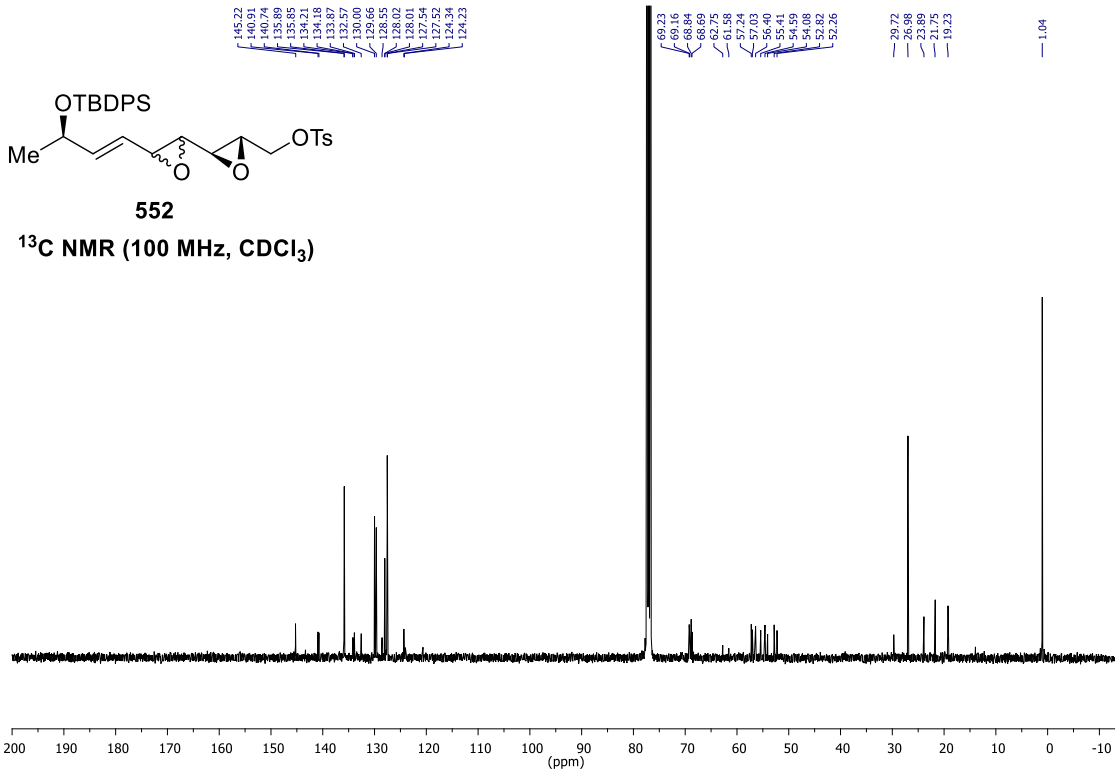


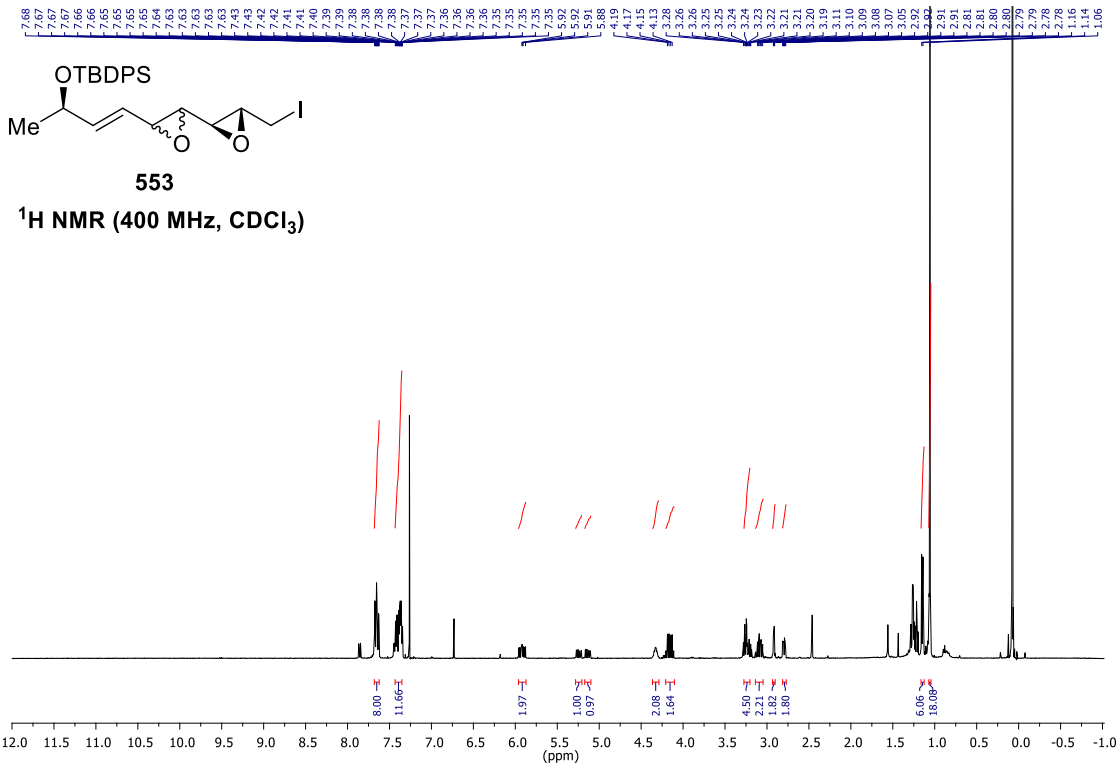






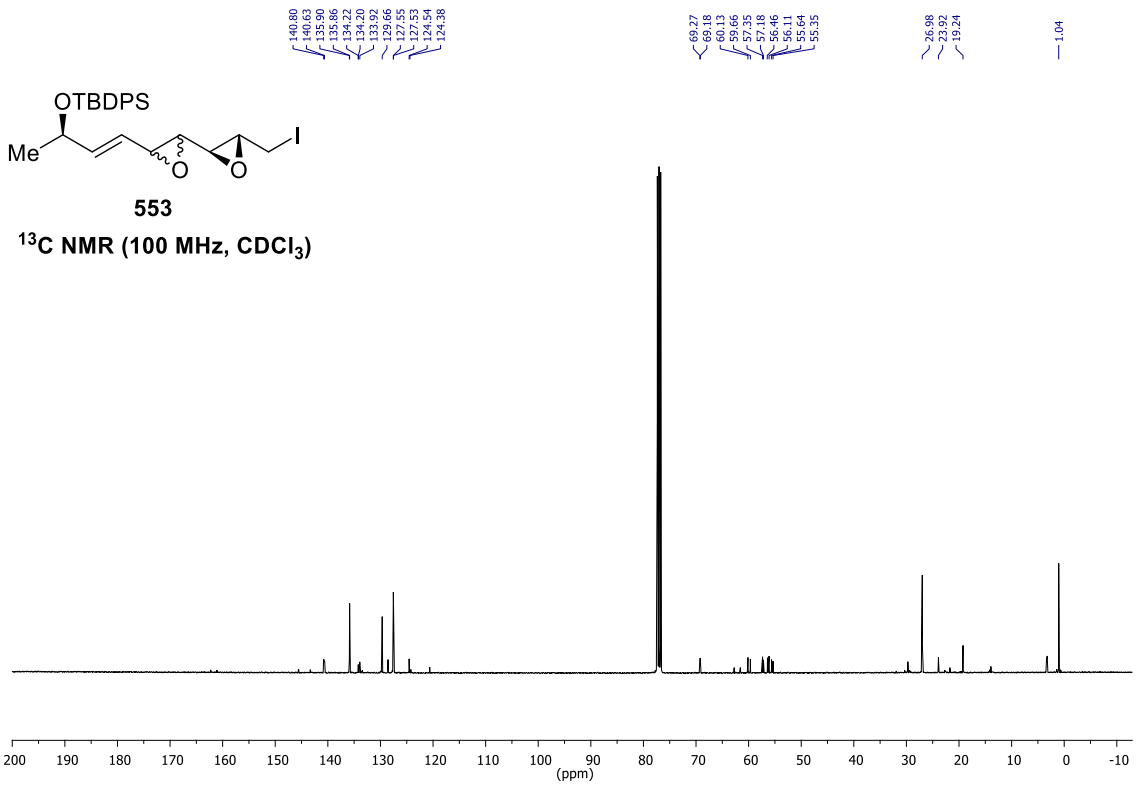






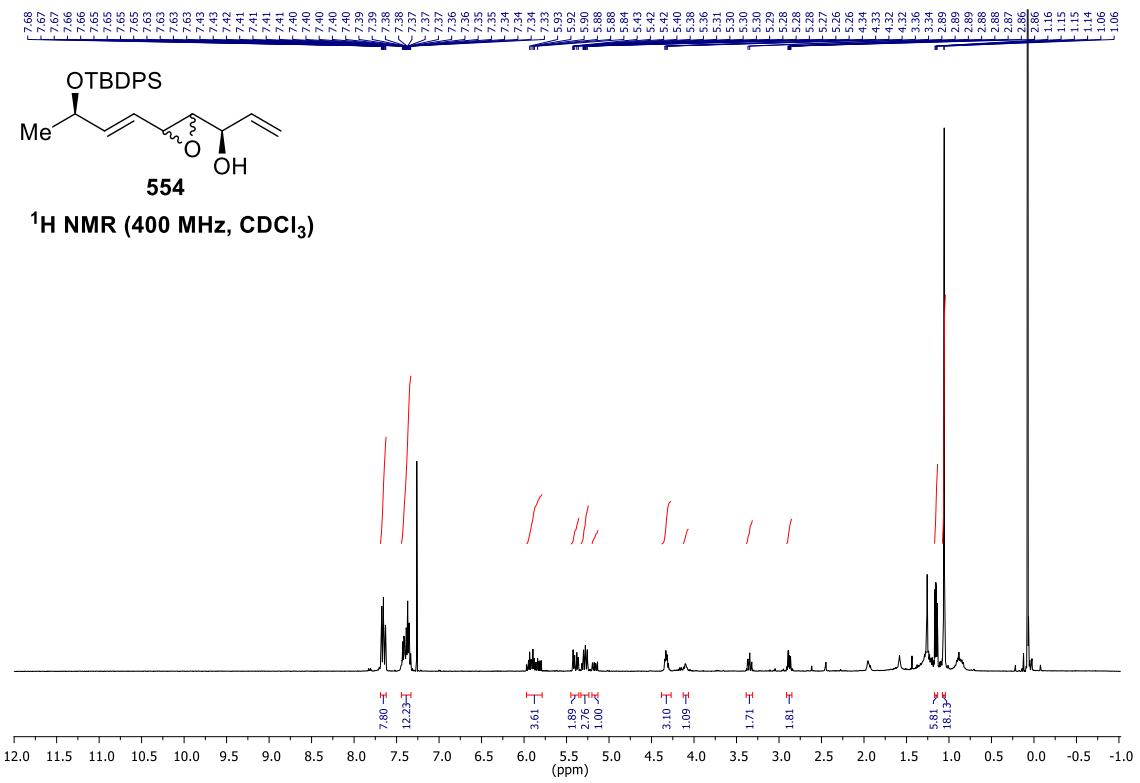
553

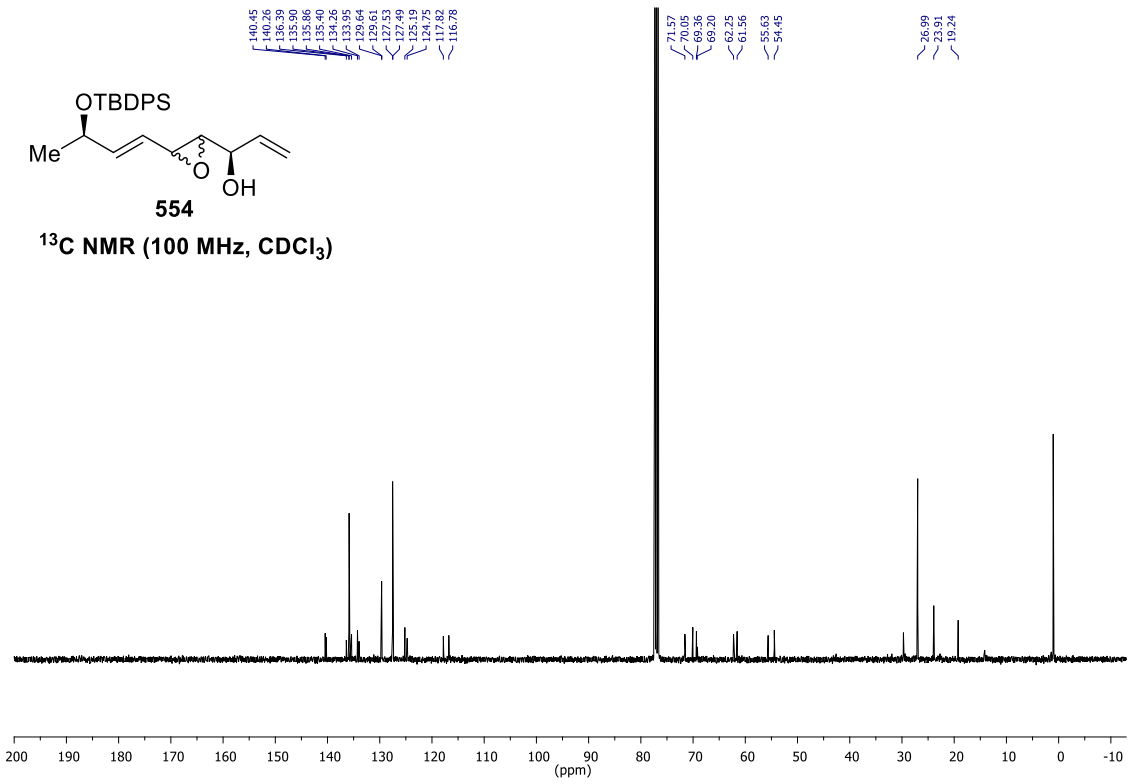
^{1}H NMR (400 MHz, $CDCl_3$)

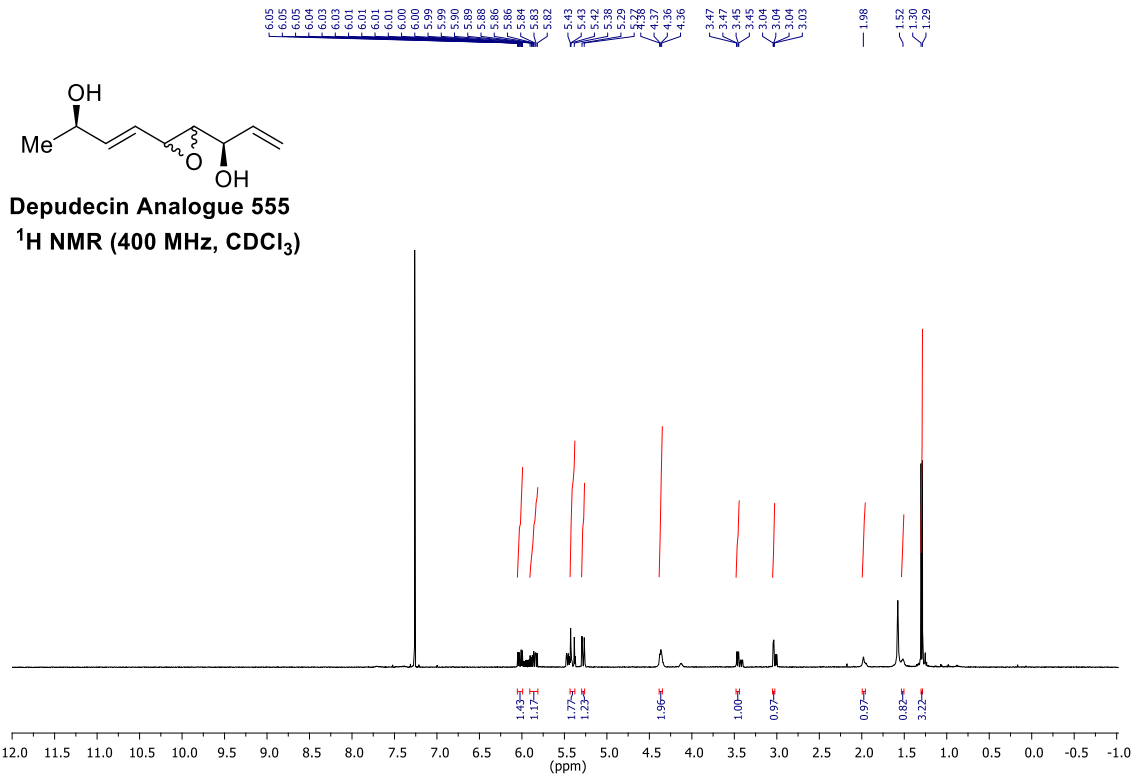


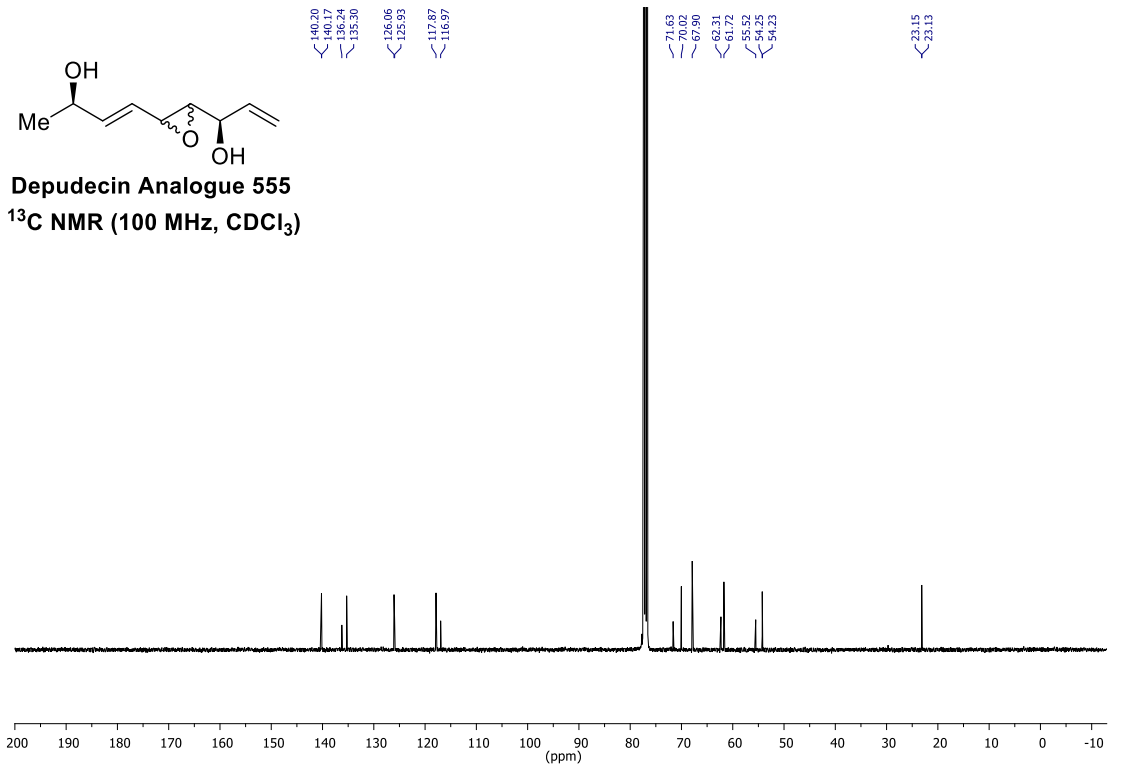
553

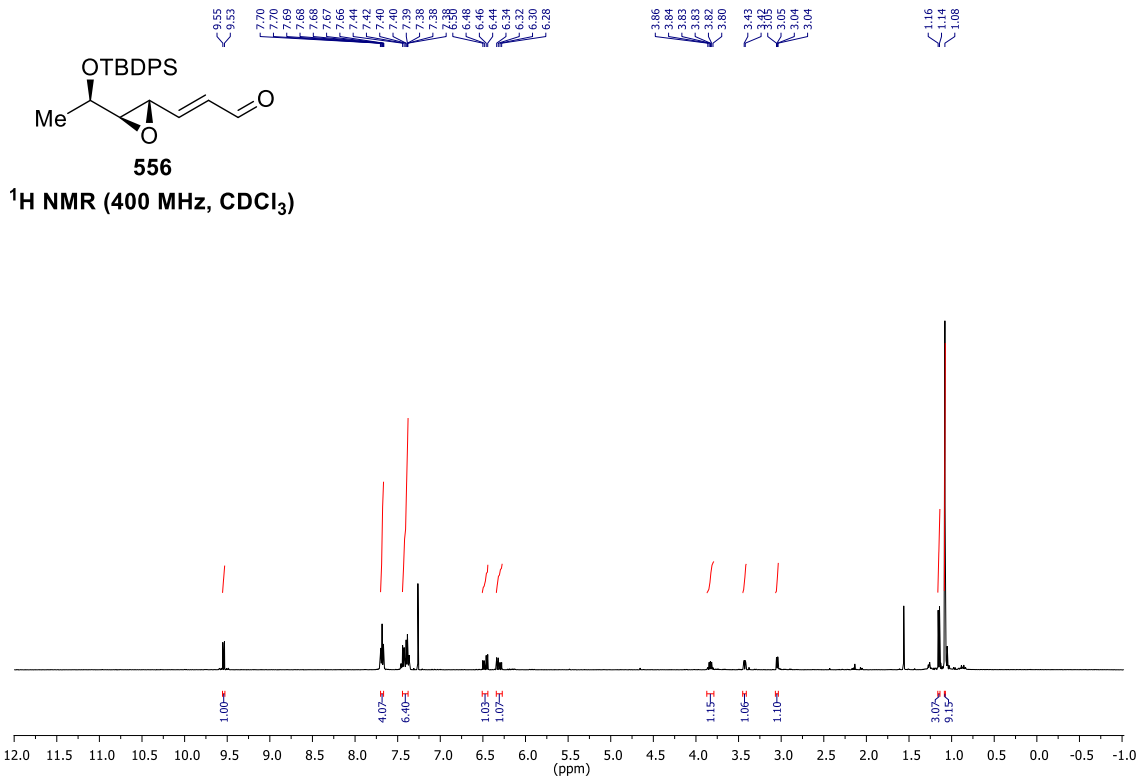
^{13}C NMR (100 MHz, $CDCl_3$)

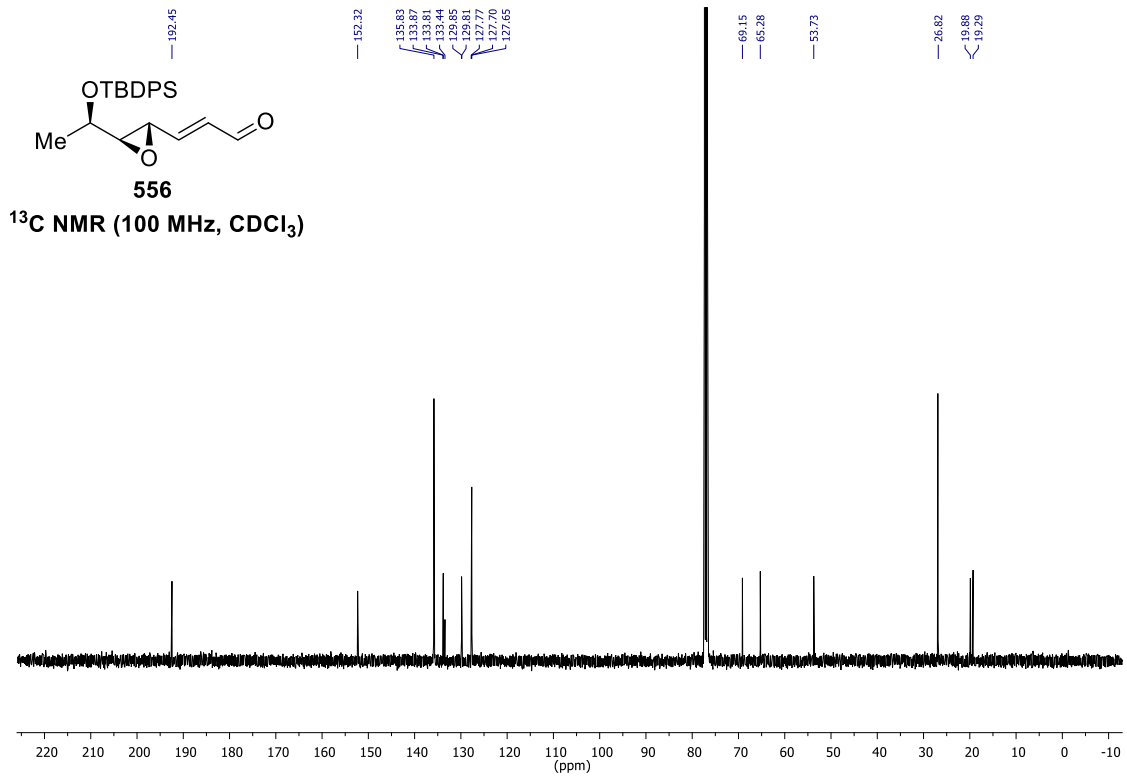


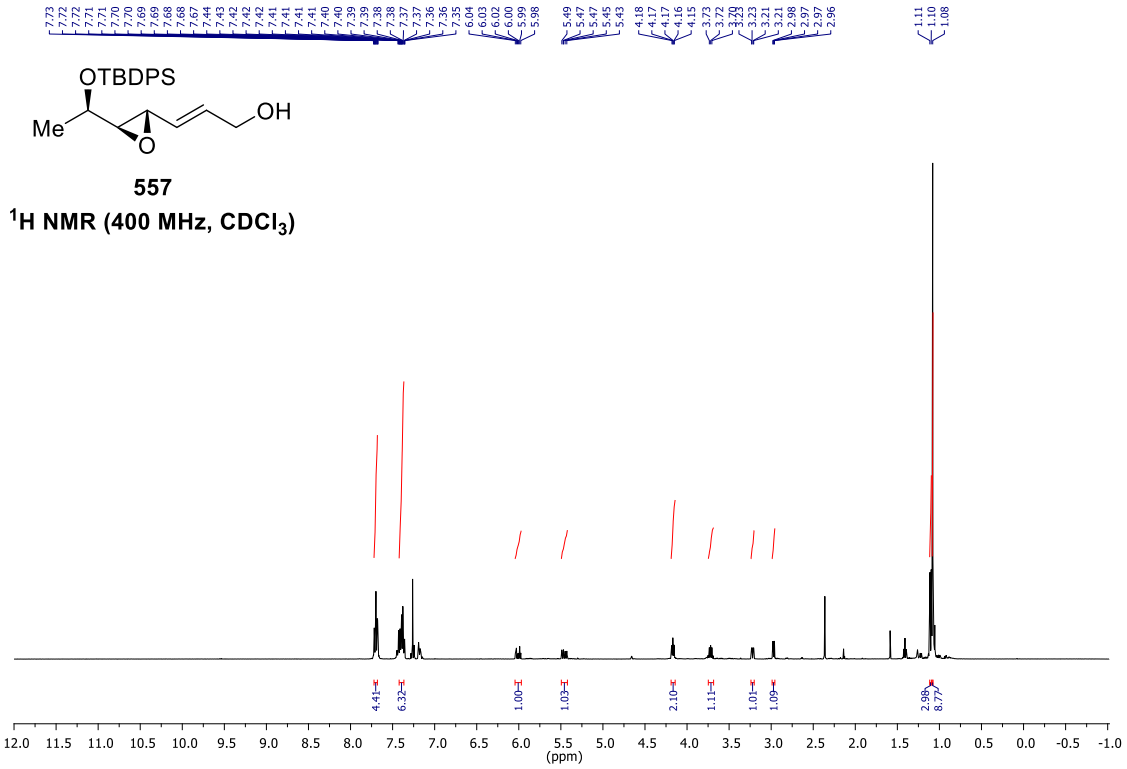






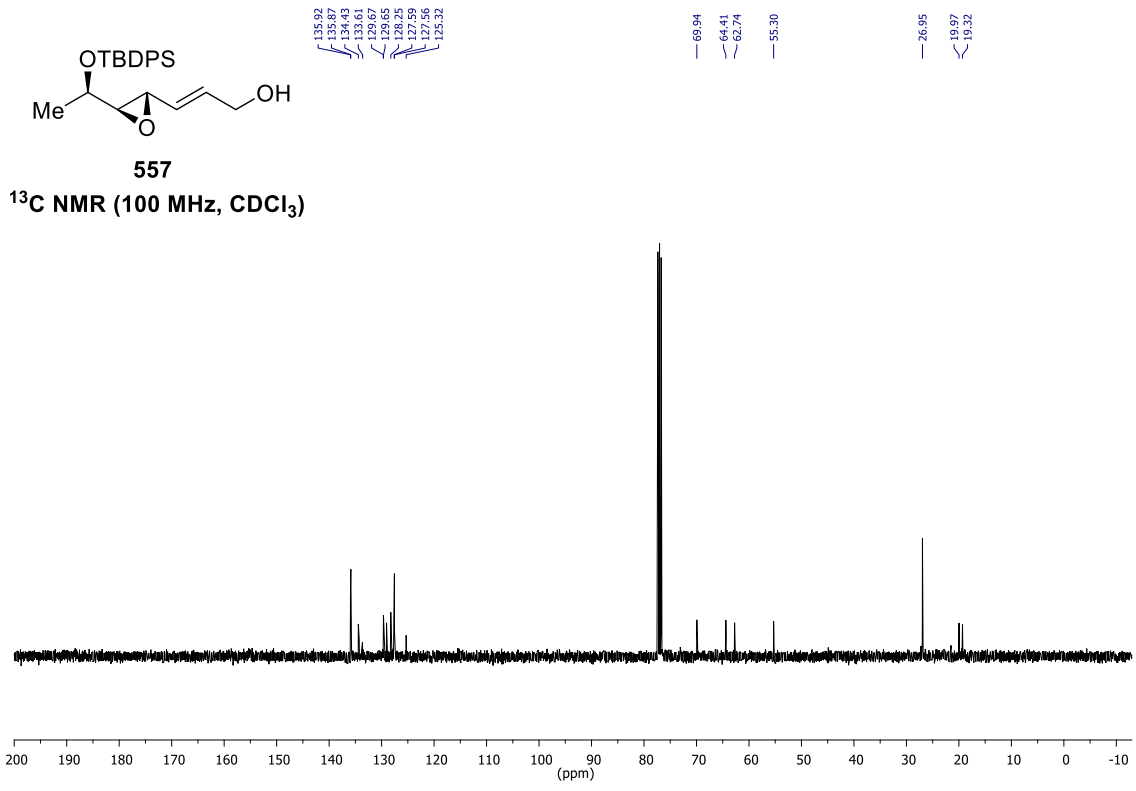






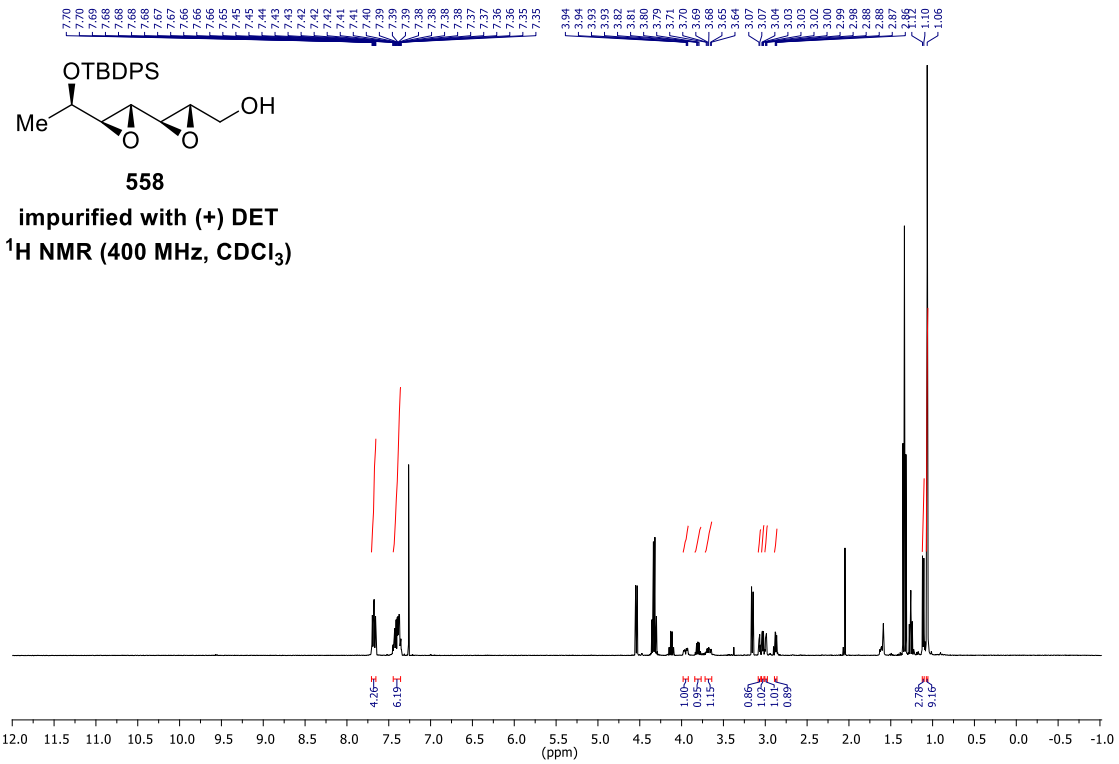
557

^{1}H NMR (400 MHz, $CDCl_3$)



557

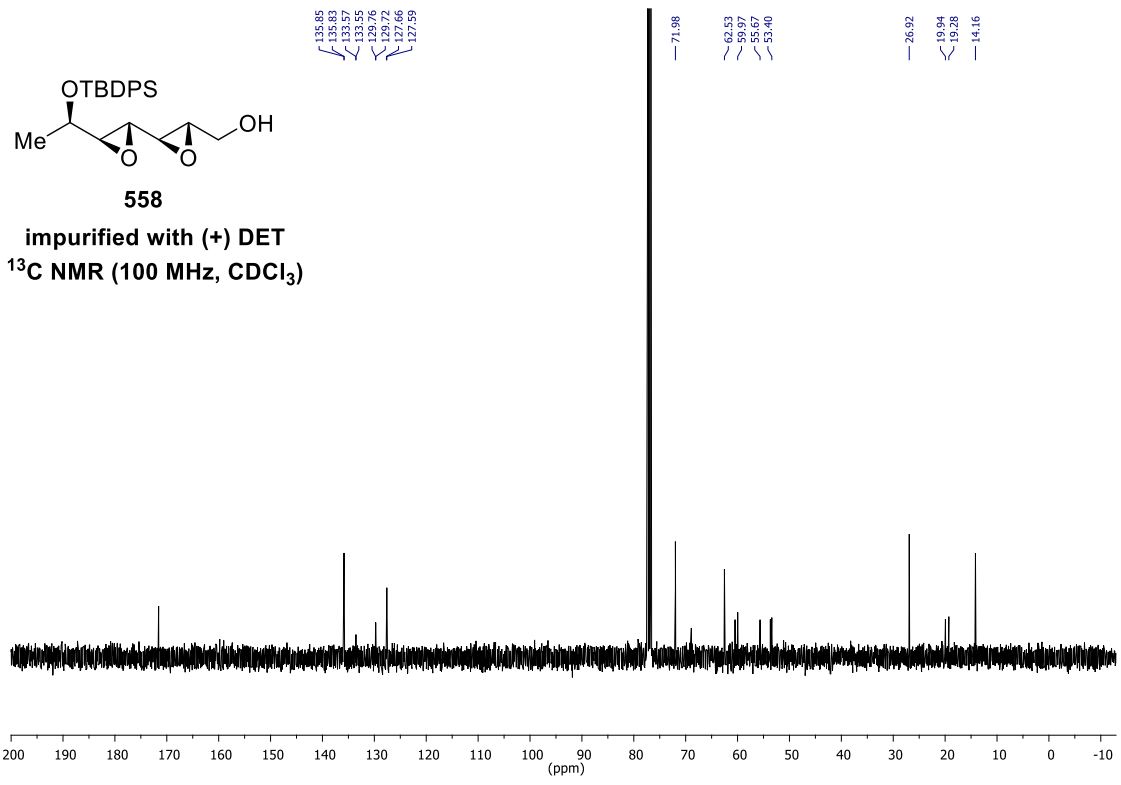
^{13}C NMR (100 MHz, $CDCl_3$)



558

impurified with (+) DET

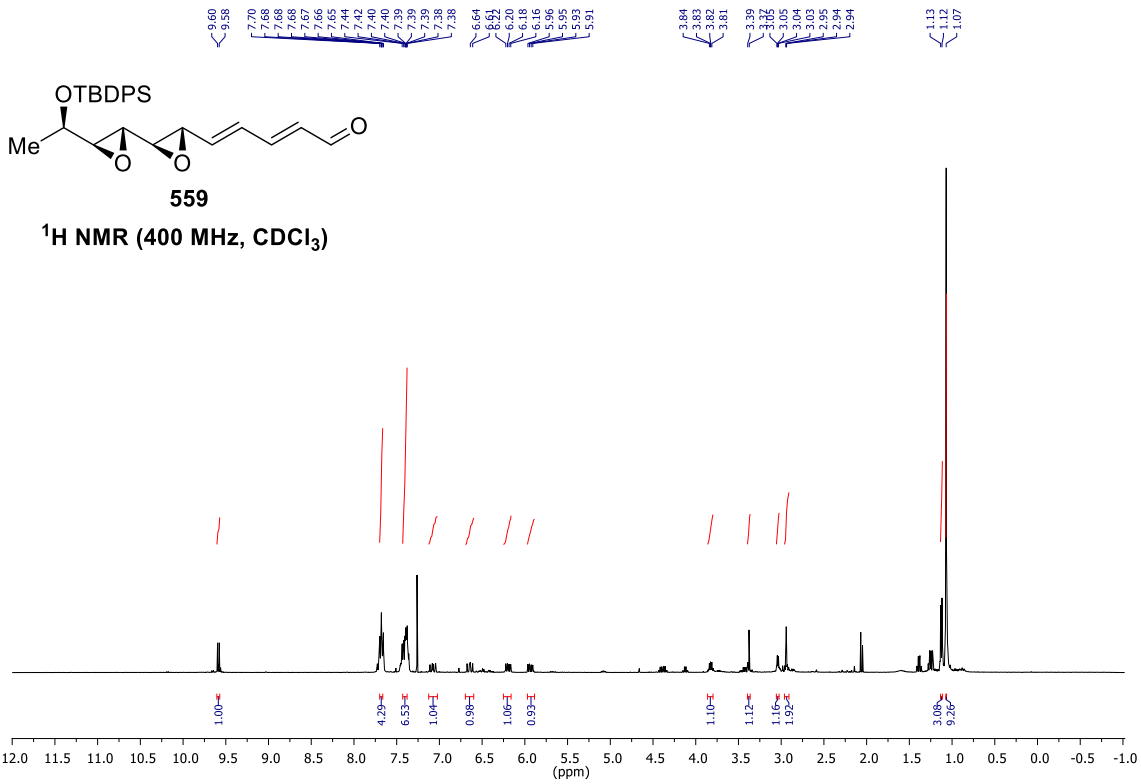
^{1}H NMR (400 MHz, $CDCl_3$)

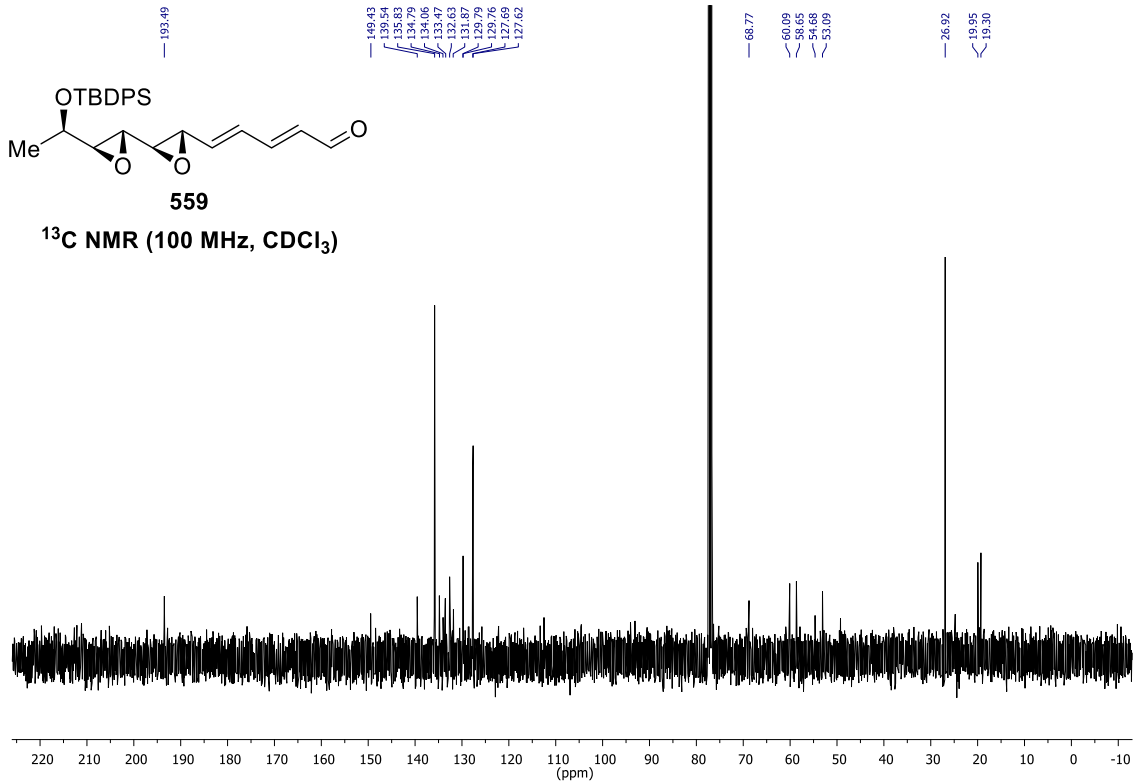


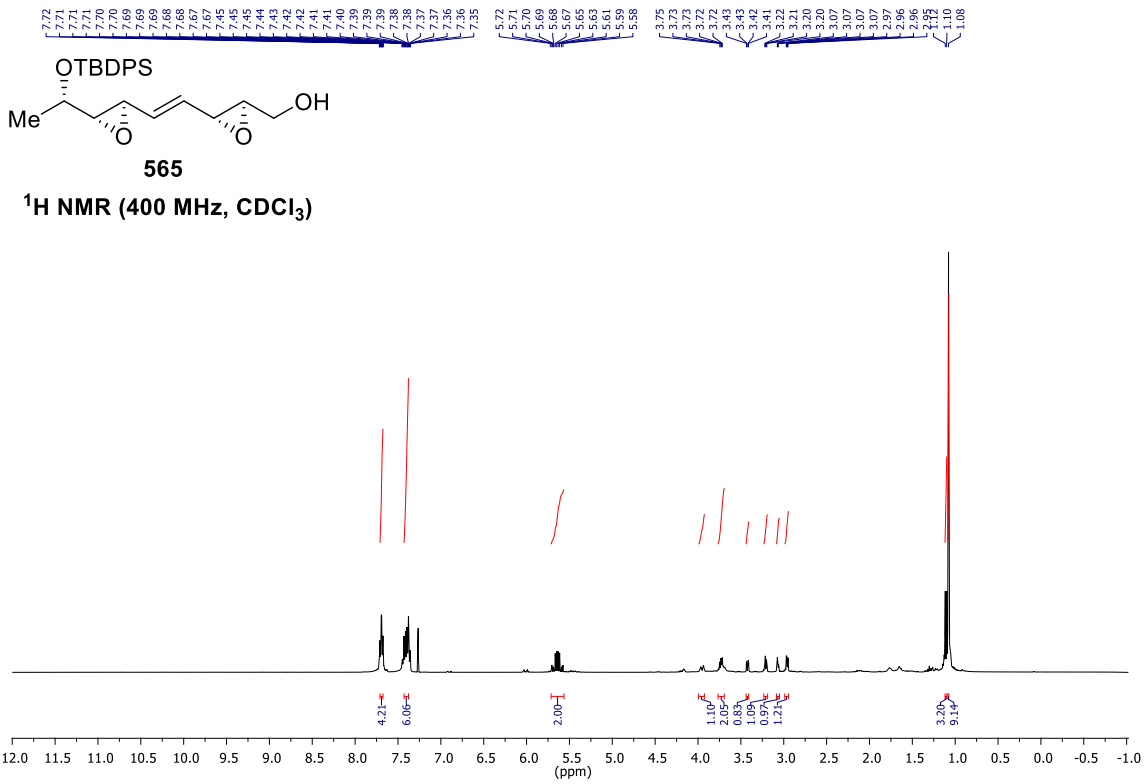
558

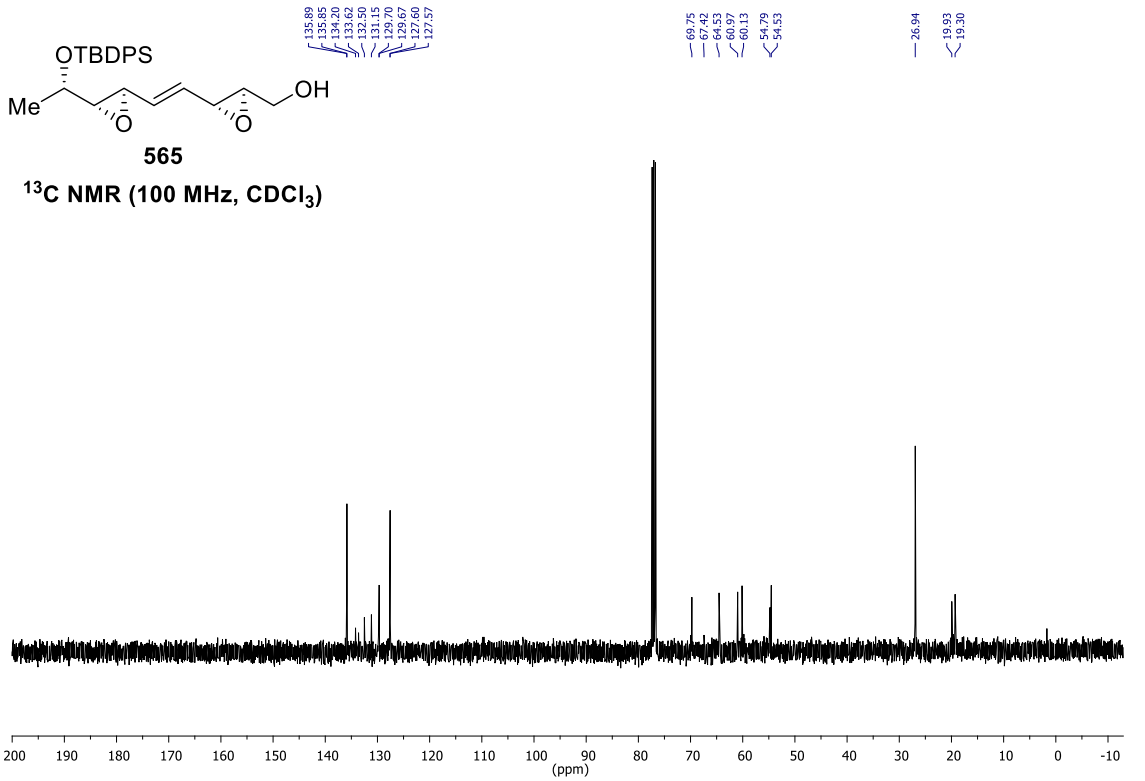
impurified with (+) DET

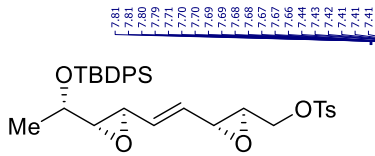
^{13}C NMR (100 MHz, $CDCl_3$)





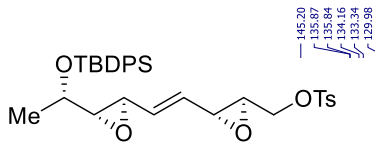






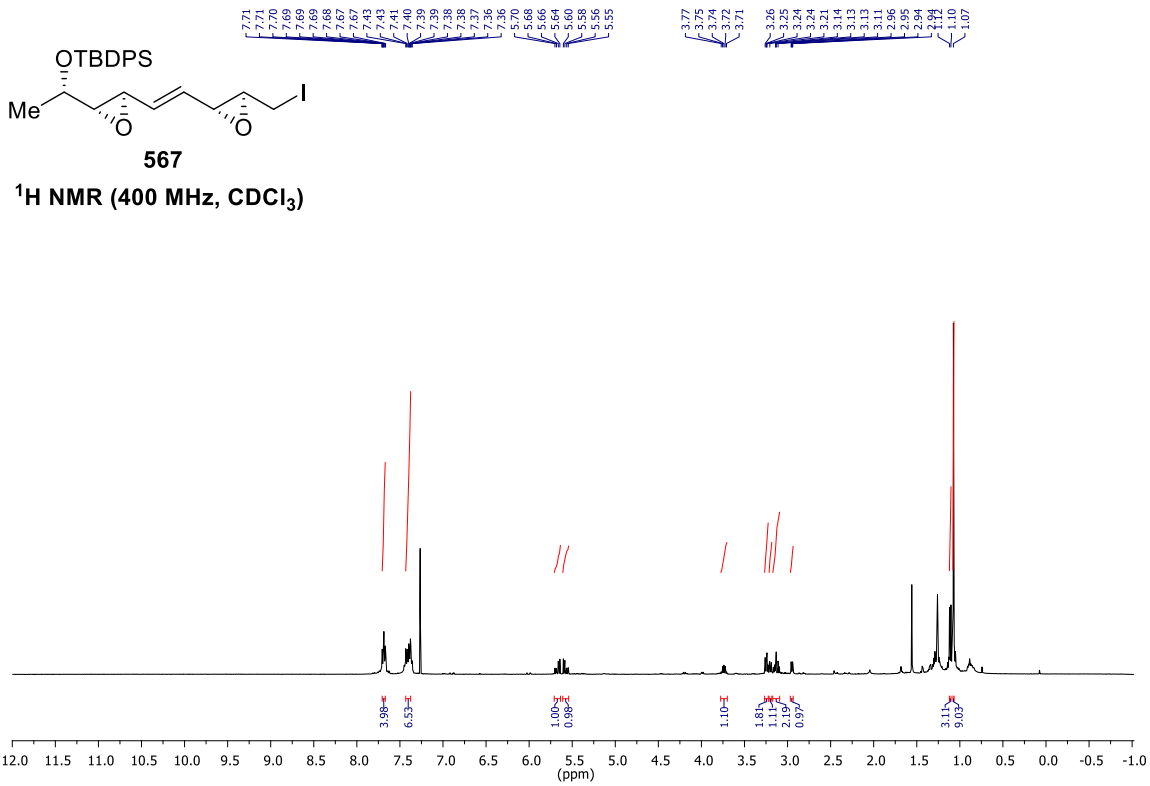
566

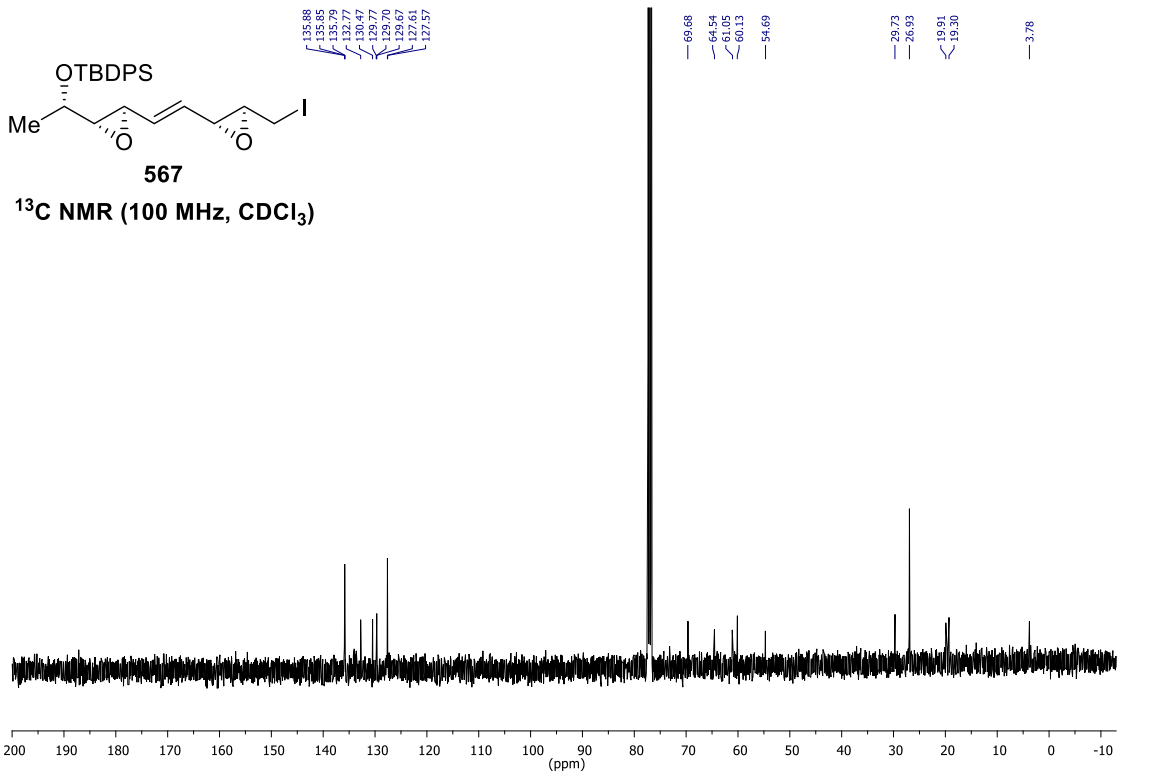
^{1}H NMR (400 MHz, $CDCl_3$)

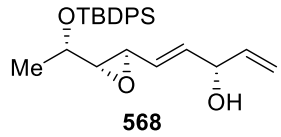


566

^{13}C NMR (100 MHz, $CDCl_3$)

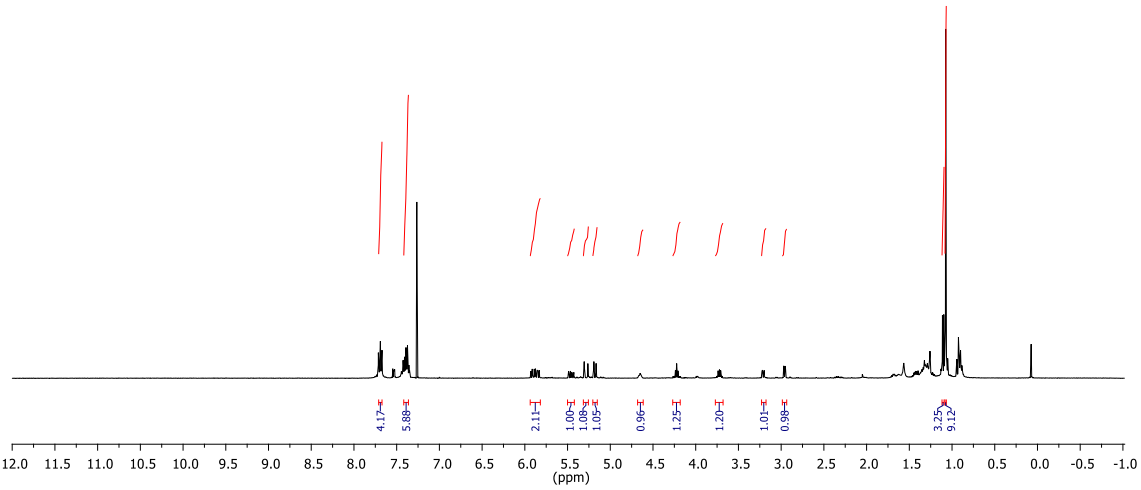


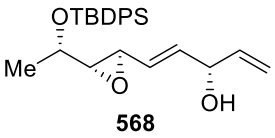




568

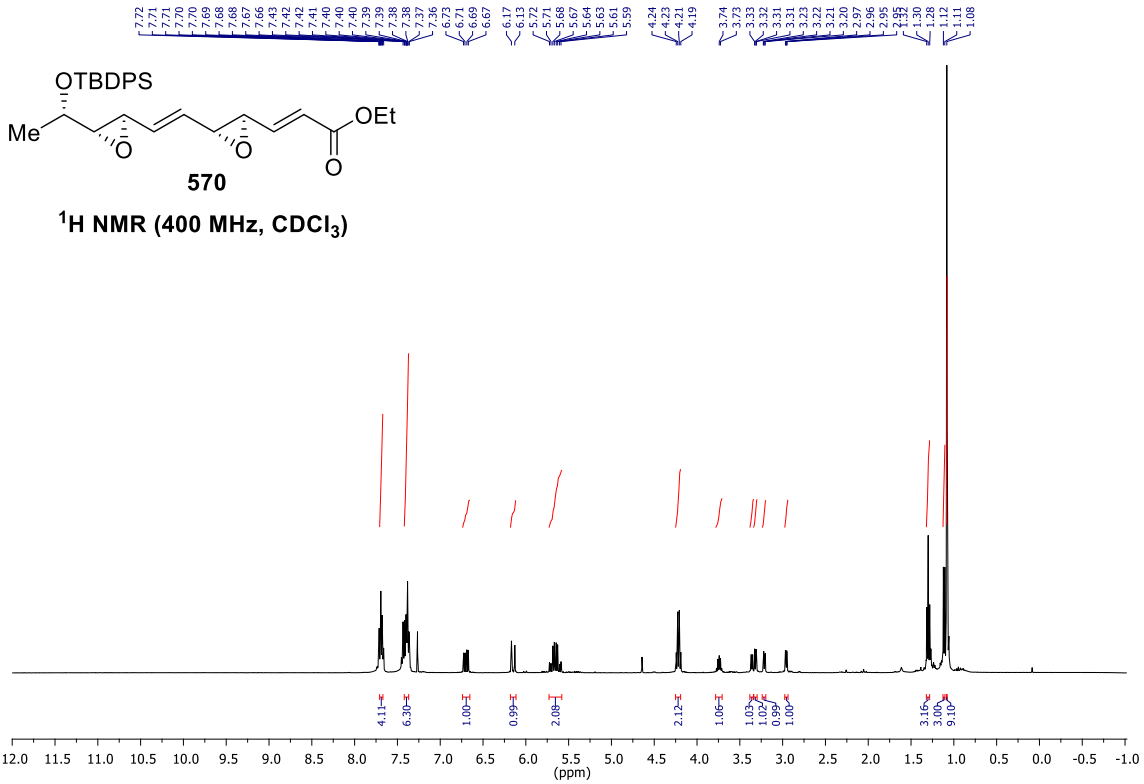
^{1}H NMR (400 MHz, $CDCl_3$)

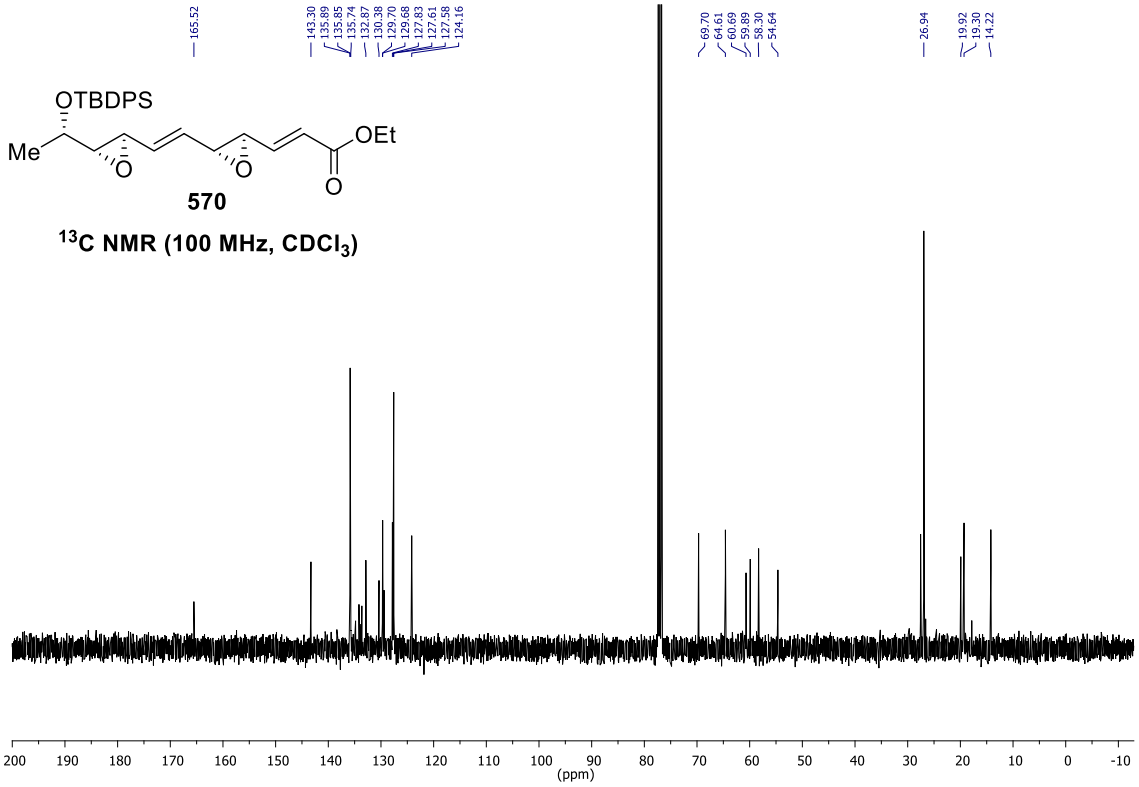


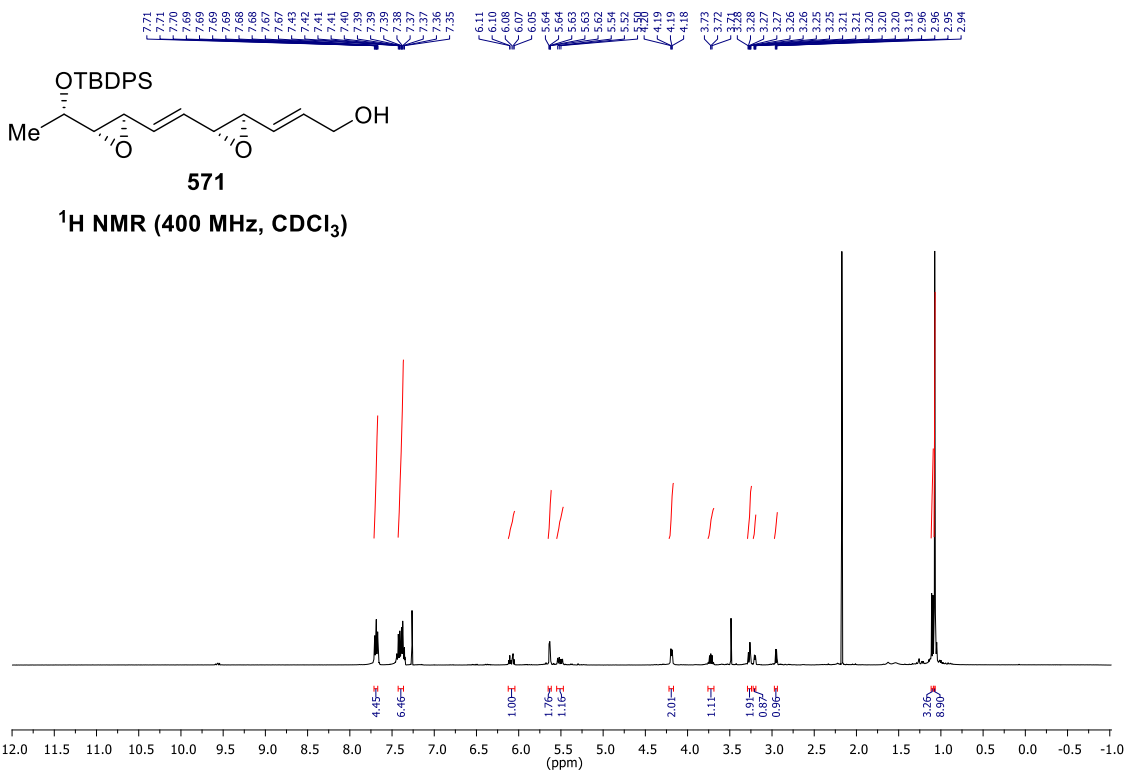


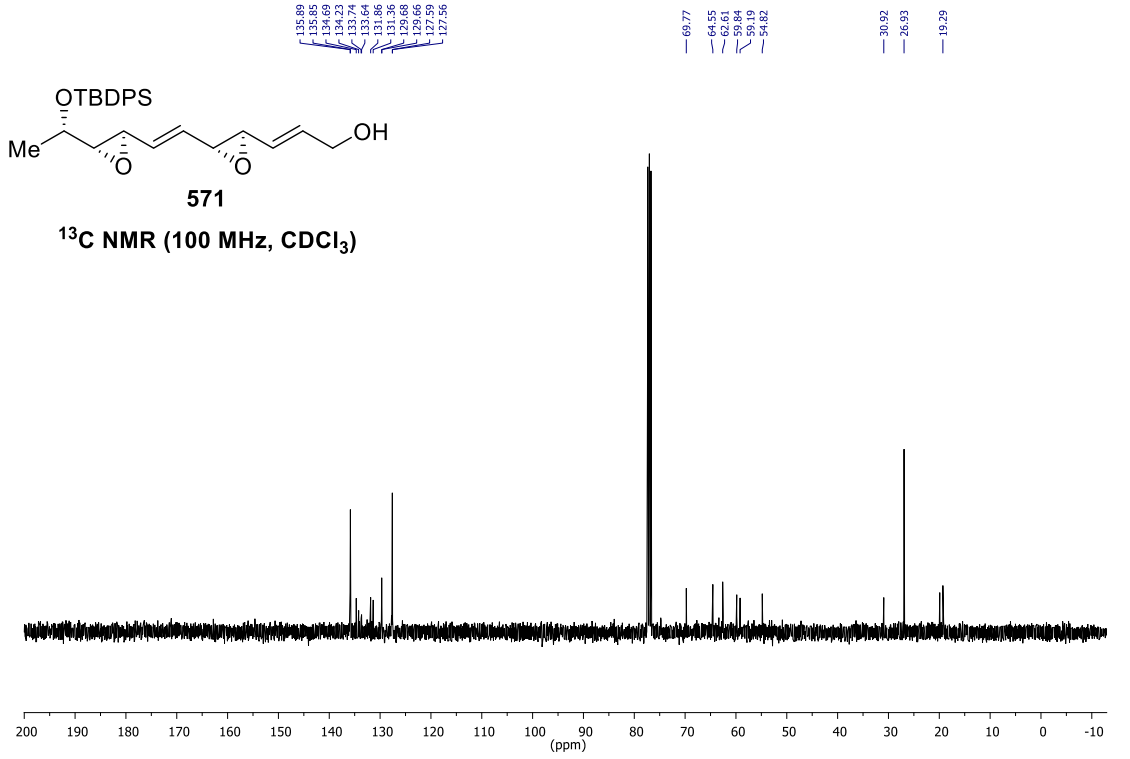
568

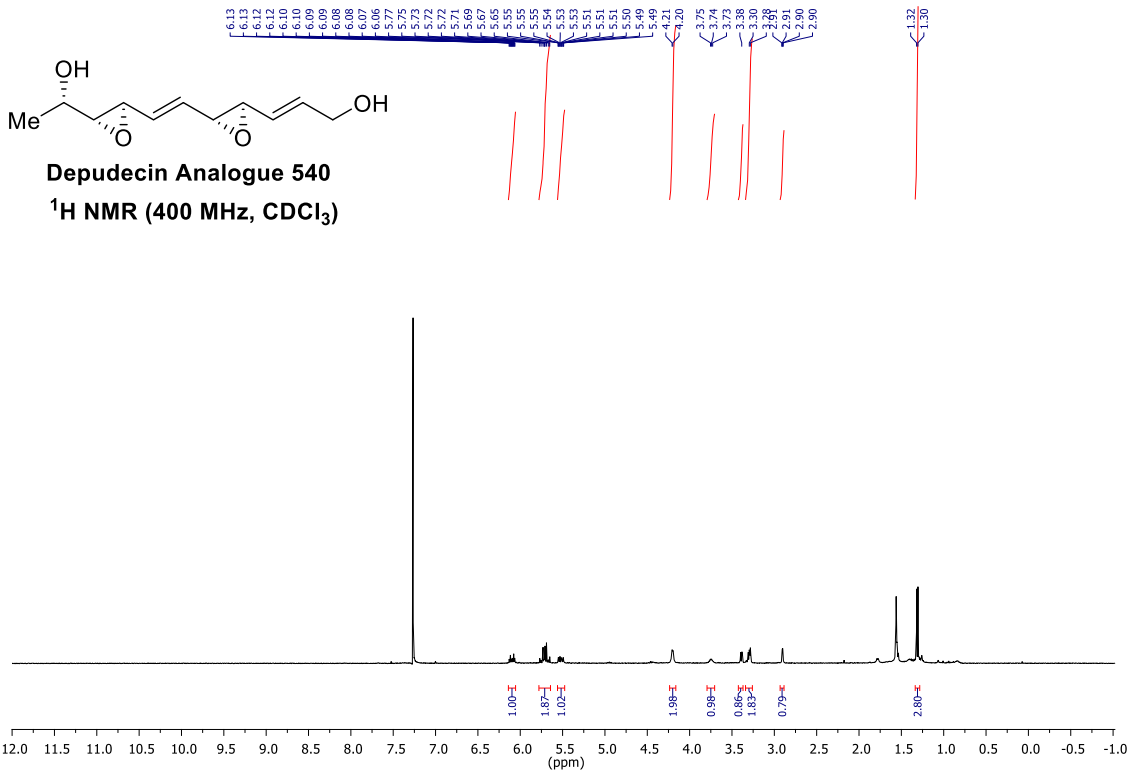
^{13}C NMR (100 MHz, $CDCl_3$)

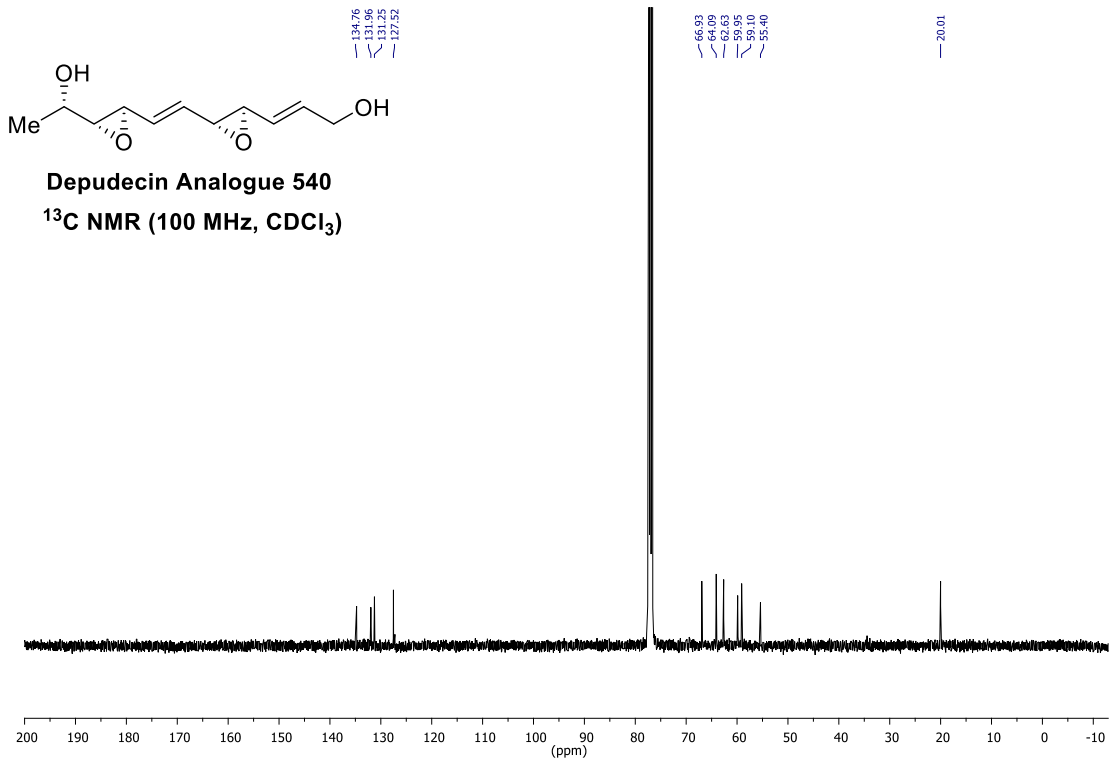


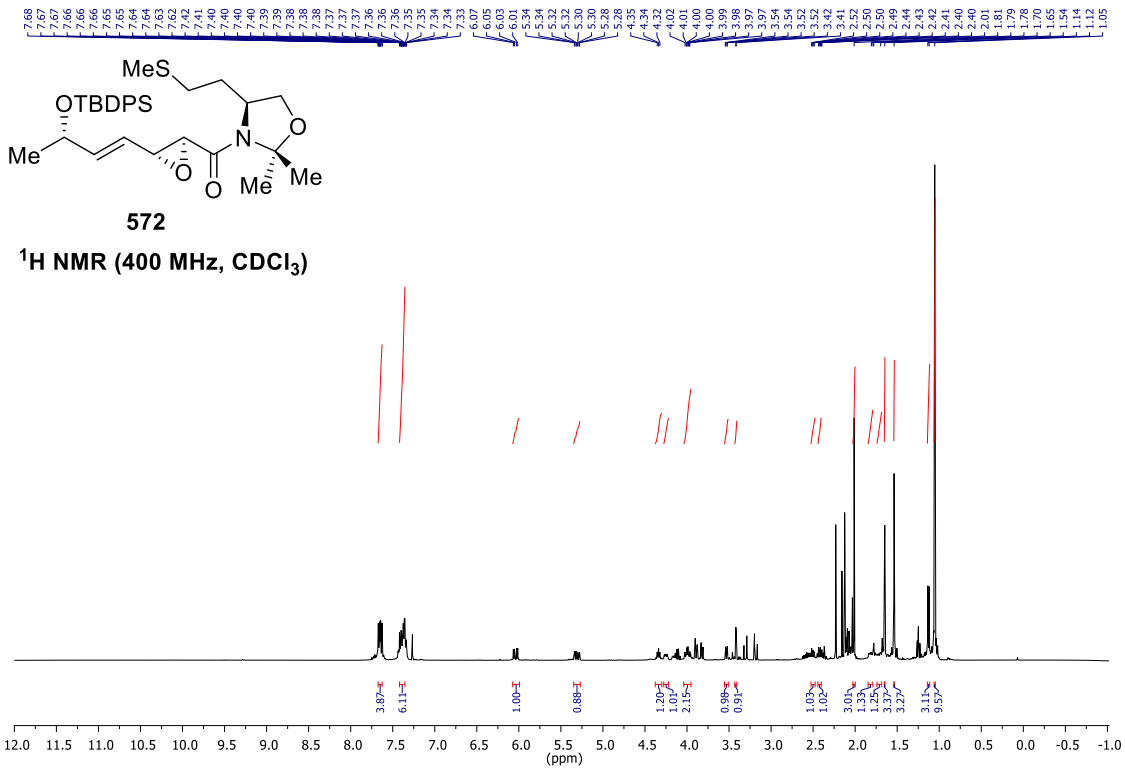






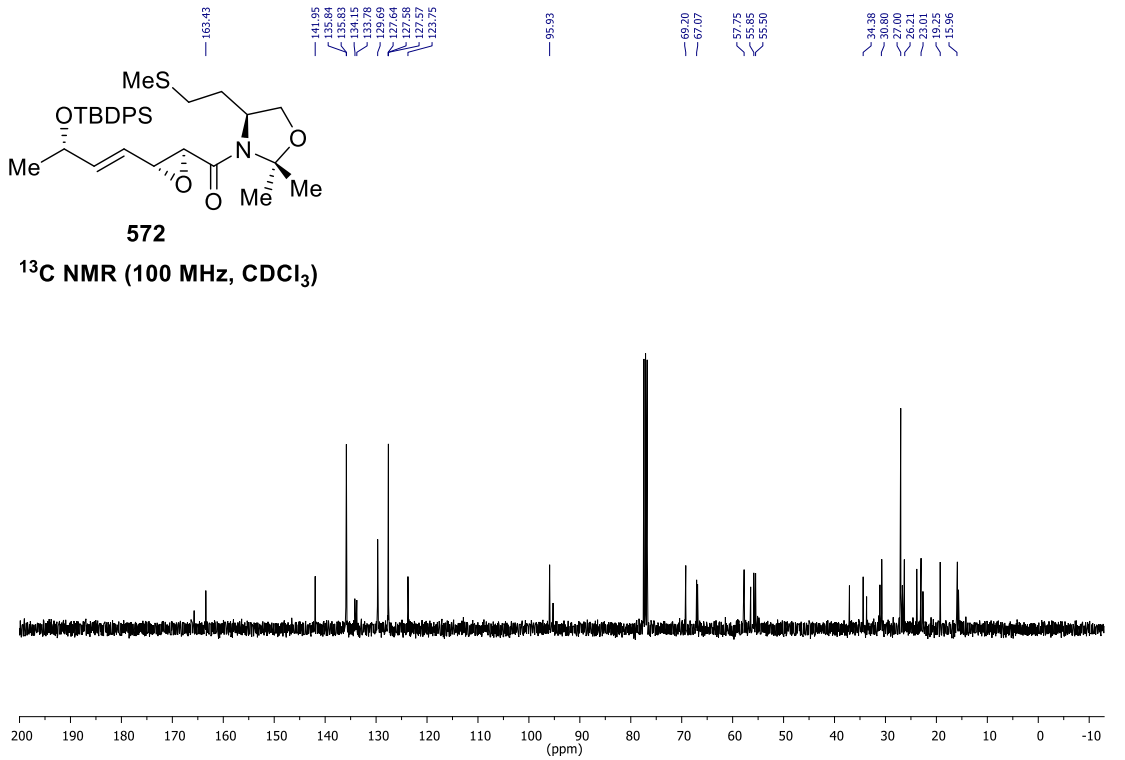






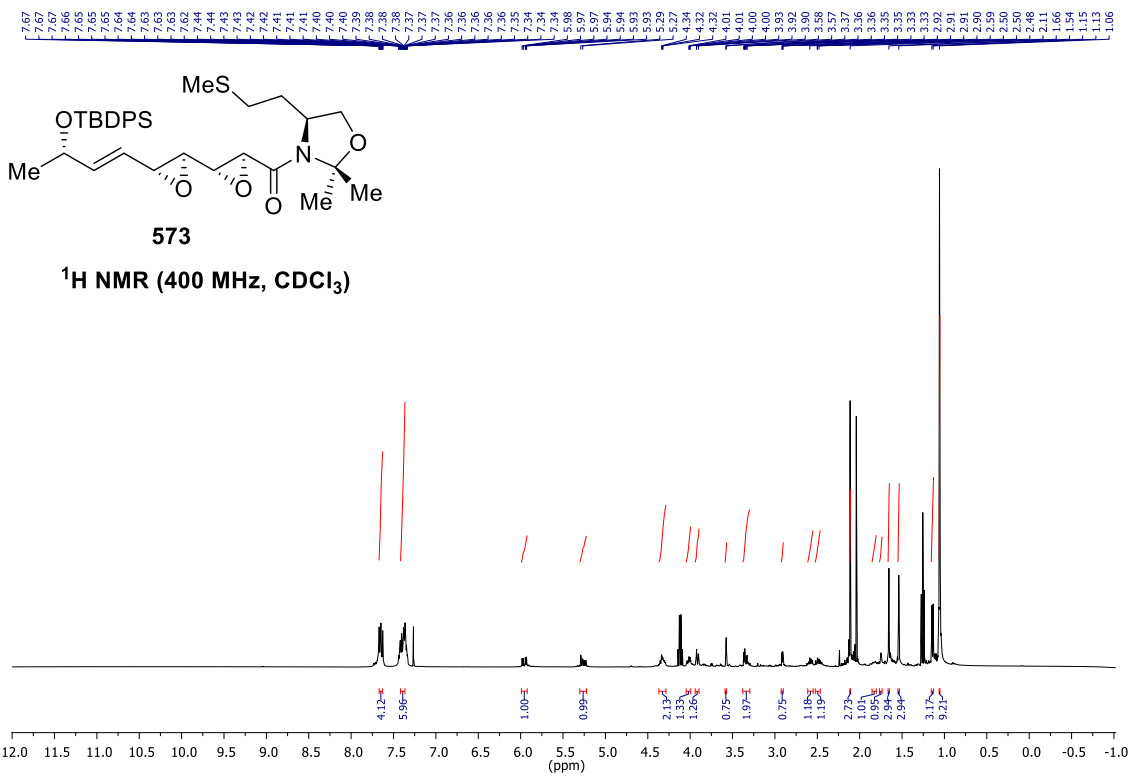
572

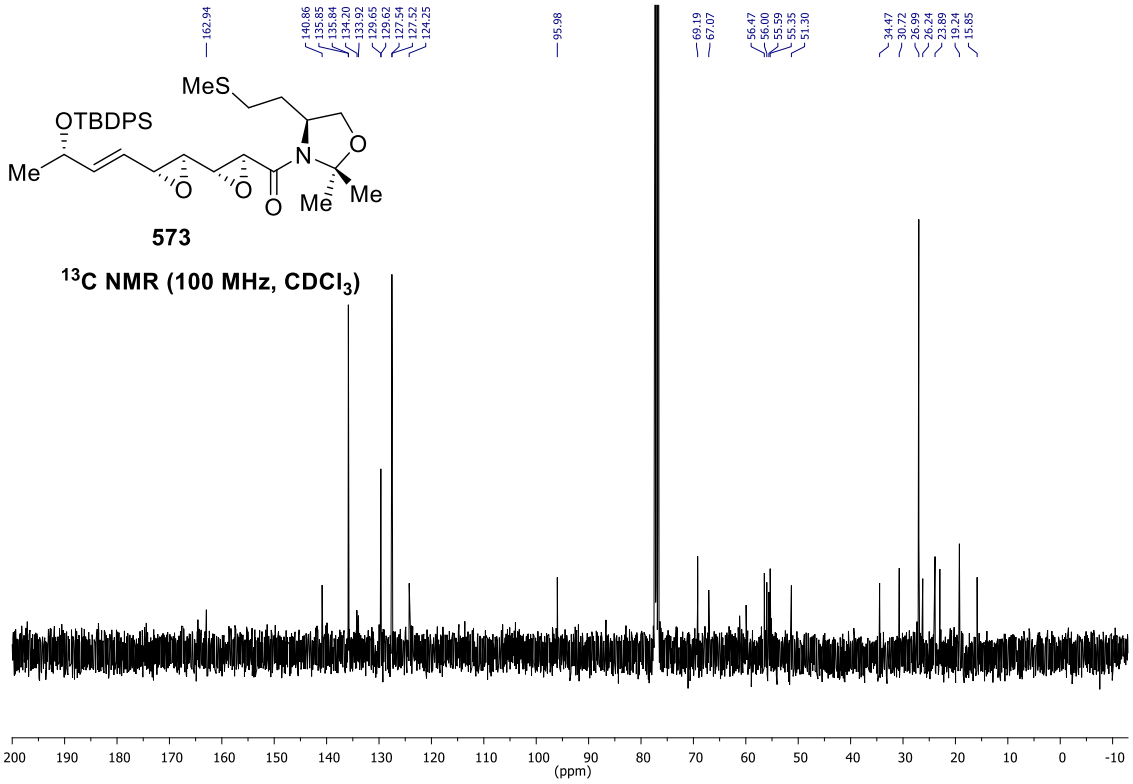
^{1}H NMR (400 MHz, $CDCl_3$)

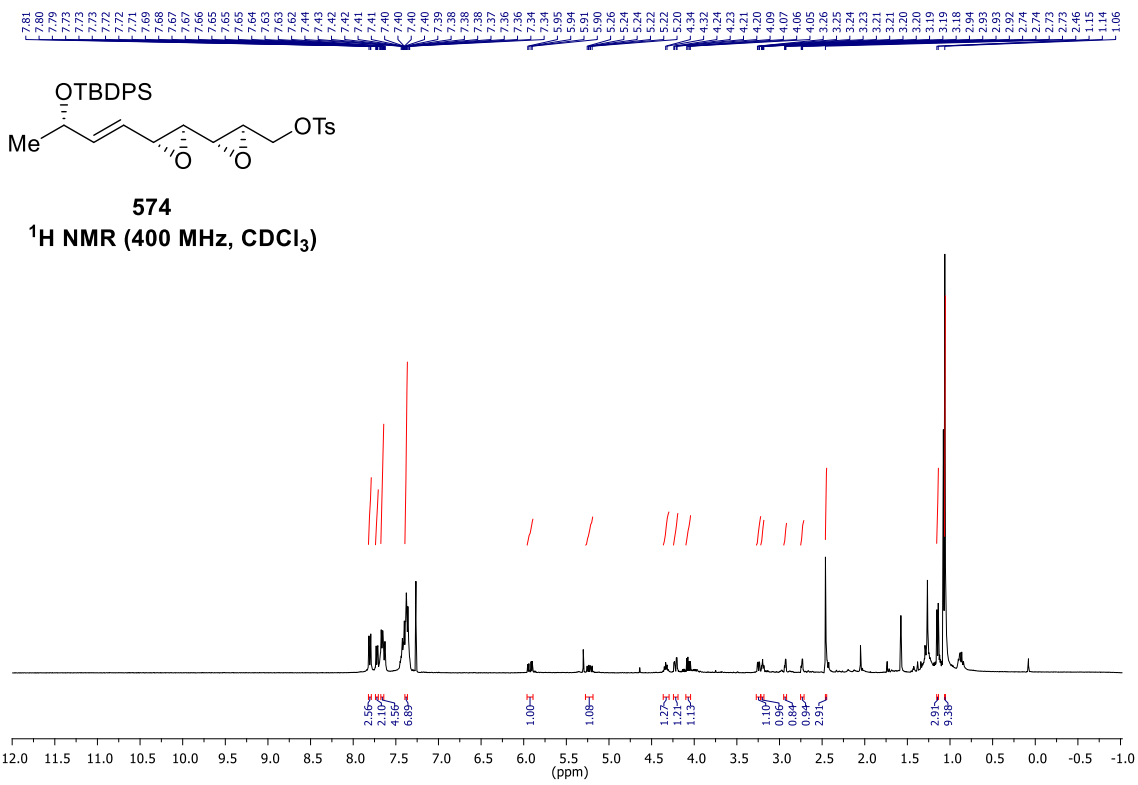


572

^{13}C NMR (100 MHz, $CDCl_3$)

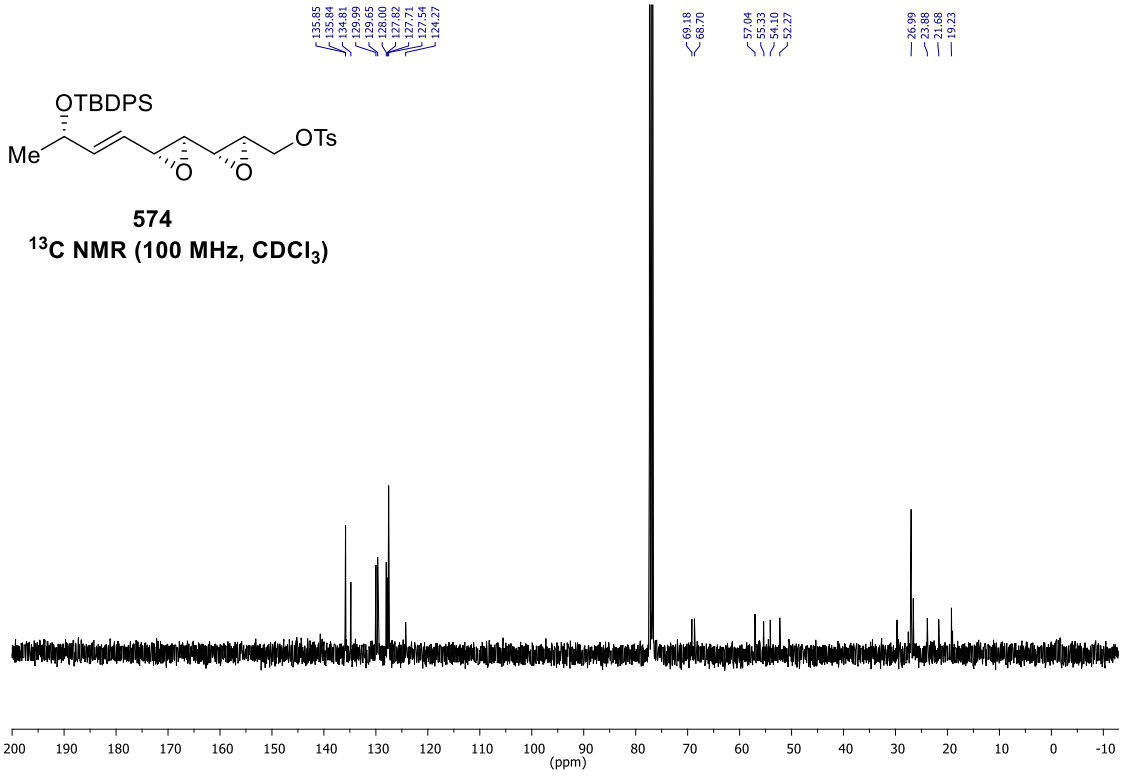






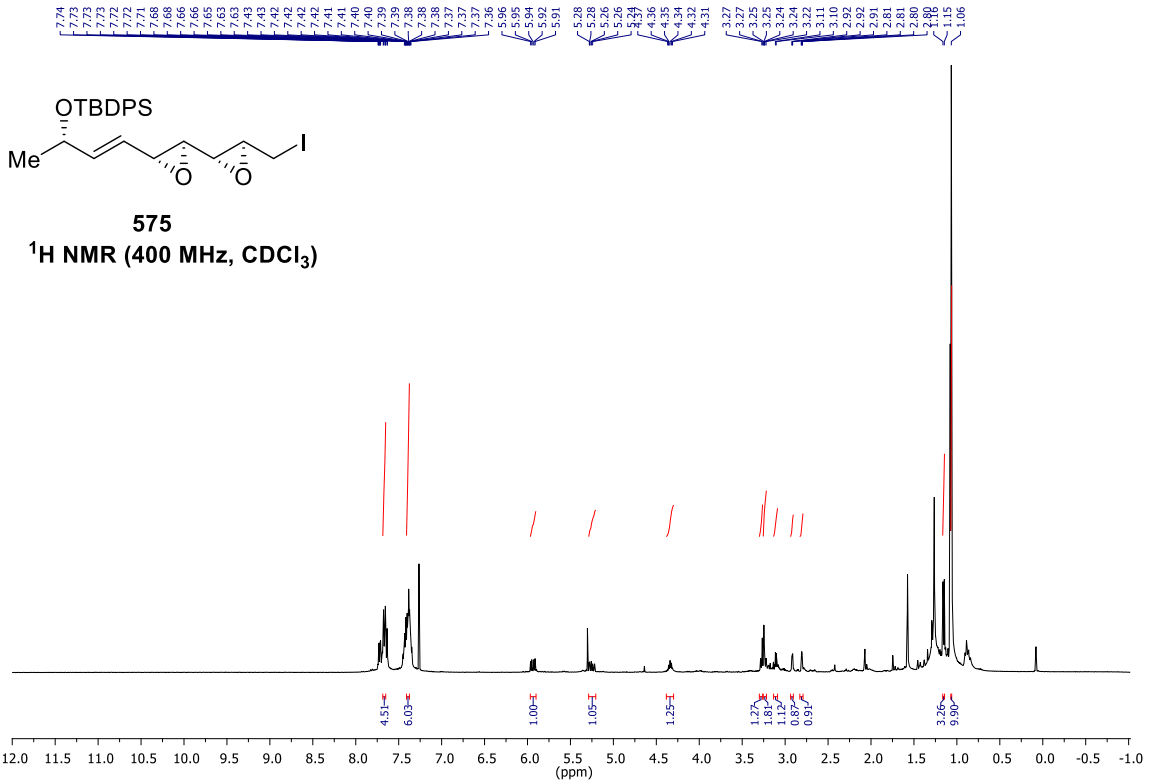
574

^{1}H NMR (400 MHz, $CDCl_3$)



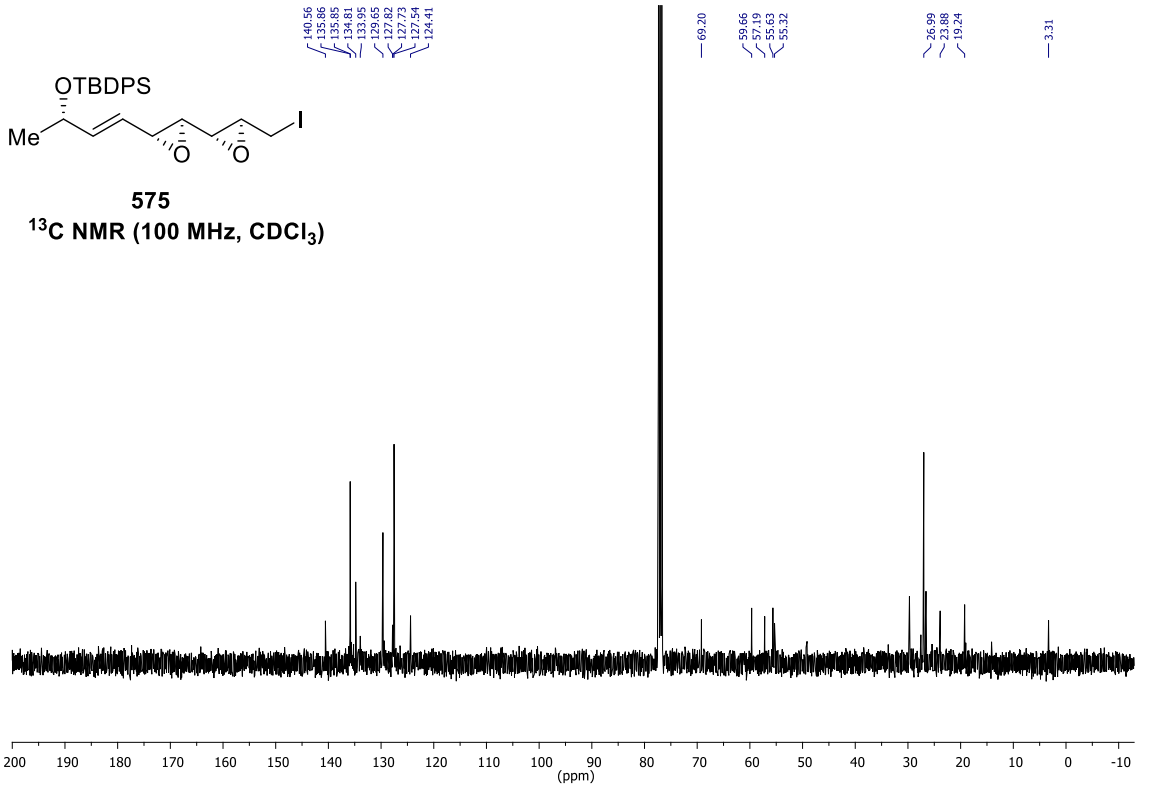
574

^{13}C NMR (100 MHz, $CDCl_3$)



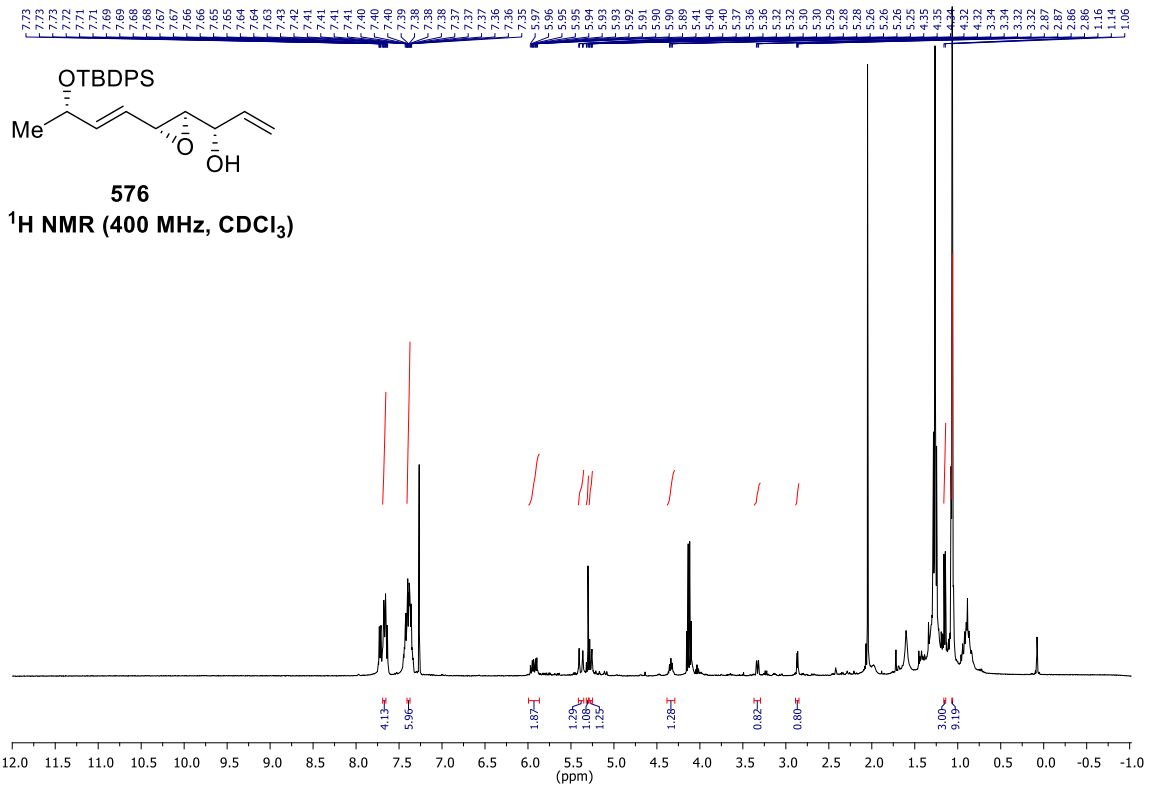
575

^{1}H NMR (400 MHz, $CDCl_3$)



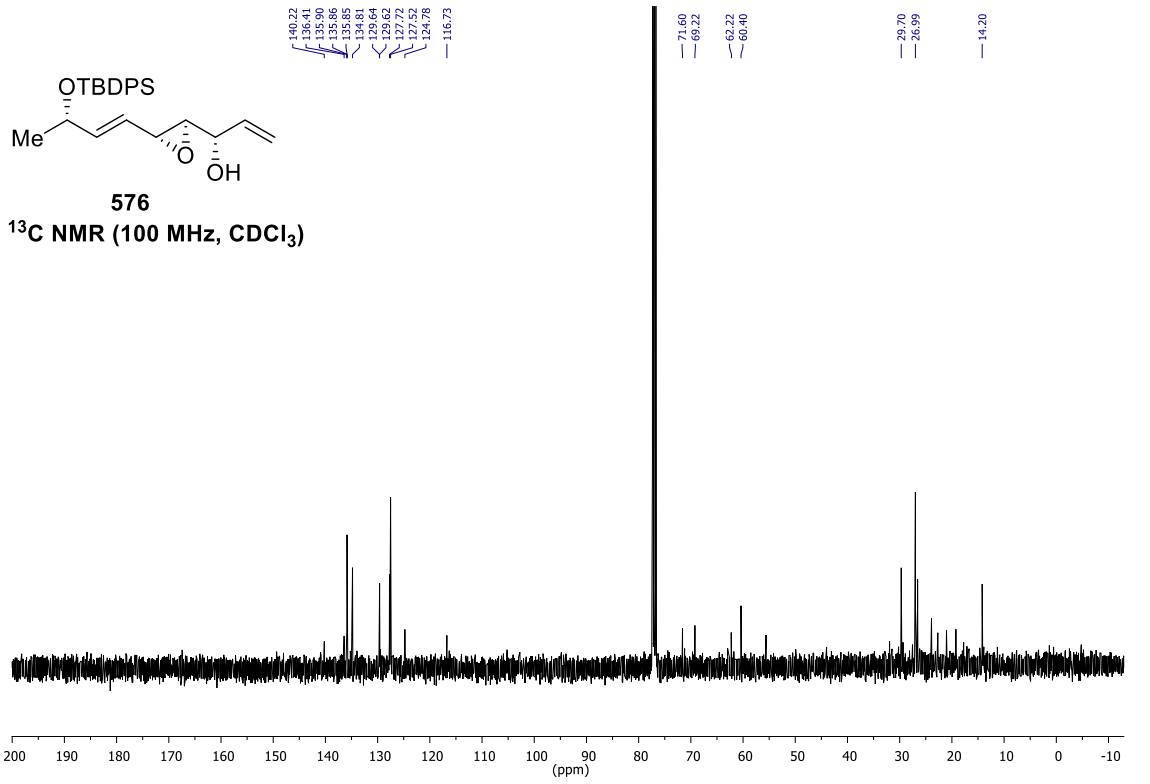
575

^{13}C NMR (100 MHz, $CDCl_3$)



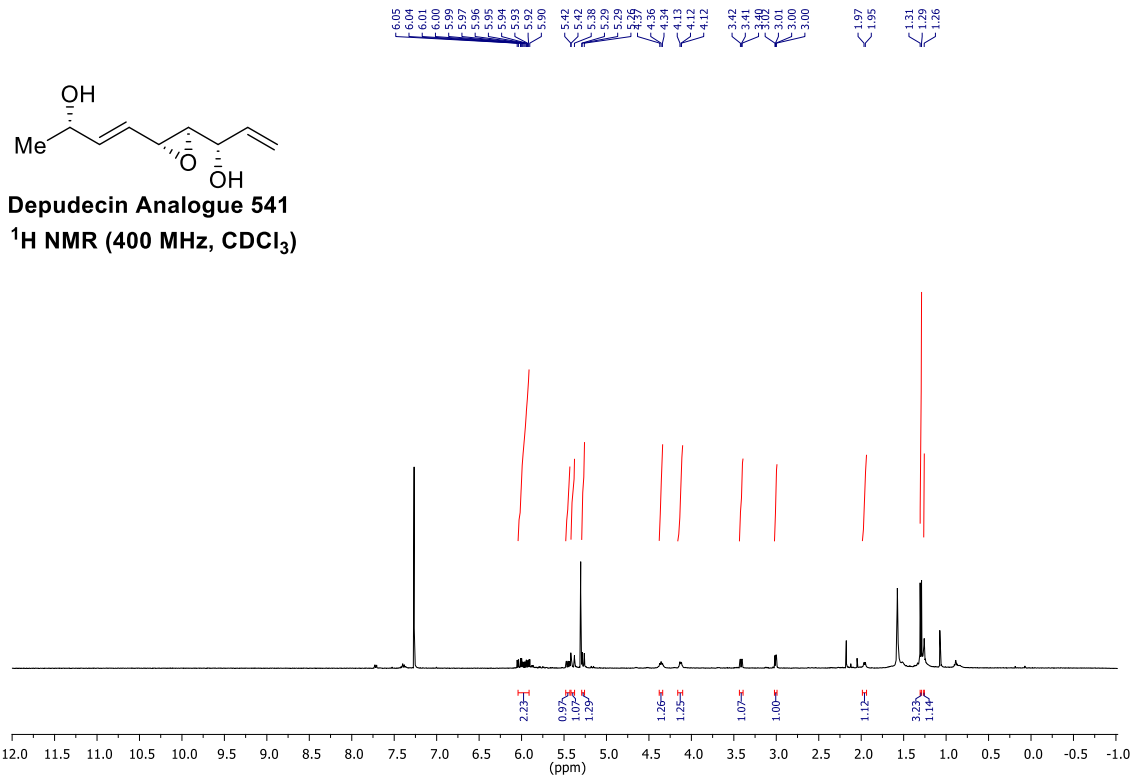
576

^{1}H NMR (400 MHz, $CDCl_3$)



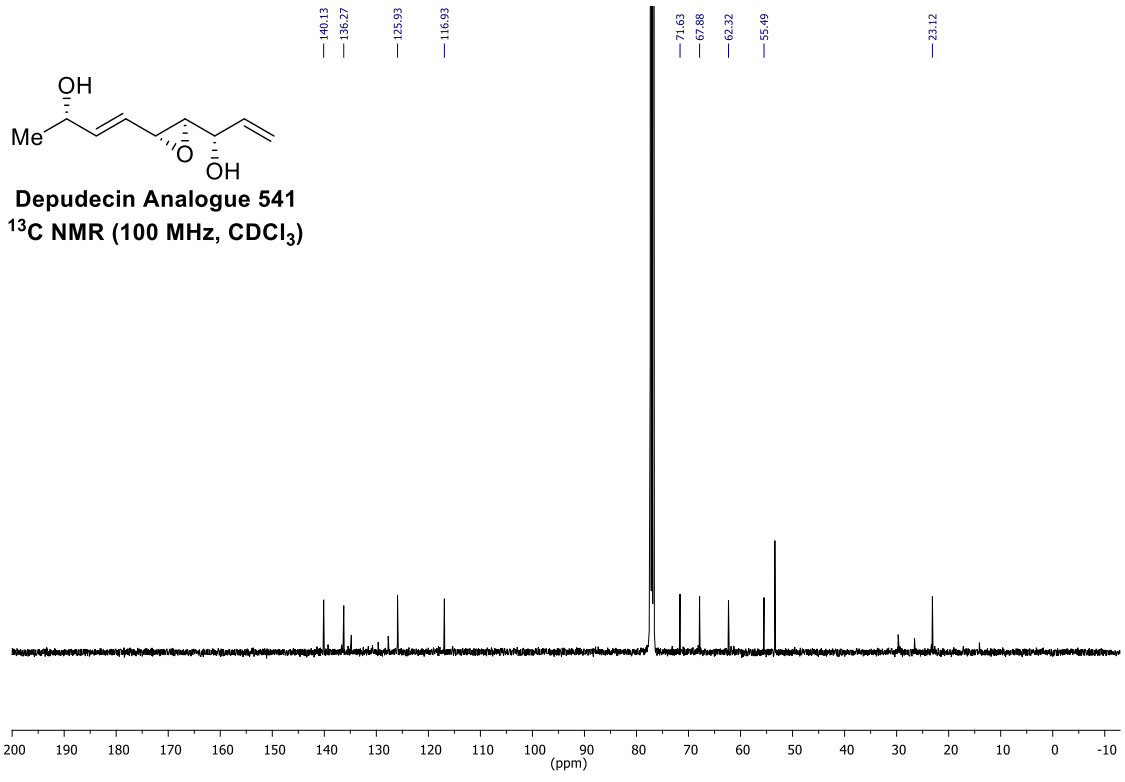
576

^{13}C NMR (100 MHz, $CDCl_3$)



Depudecin Analogue 541

^{1}H NMR (400 MHz, $CDCl_3$)

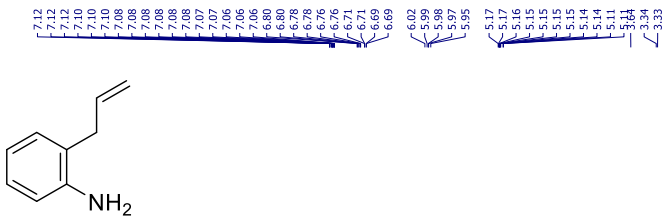


Depudecin Analogue 541

^{13}C NMR (100 MHz, $CDCl_3$)

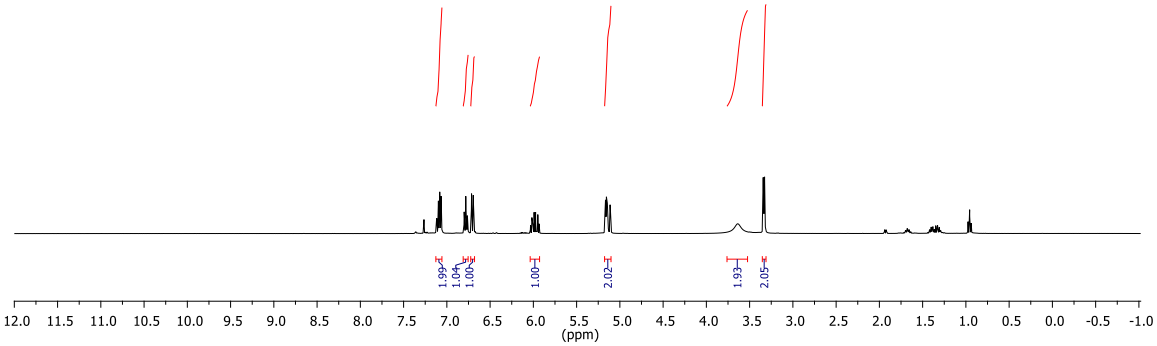
Appendix II

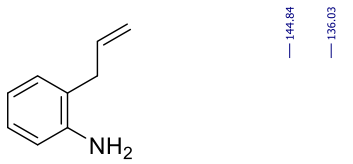
^{1}H and ^{13}C NMR Spectra Related to the Solomonamides



606

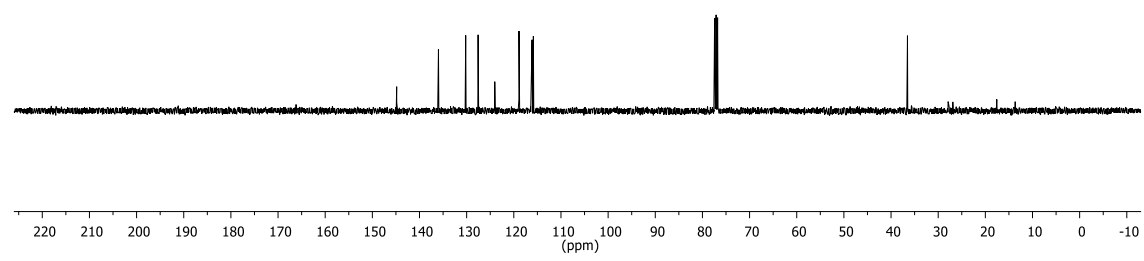
^{1}H NMR (400 MHz, $CDCl_3$)

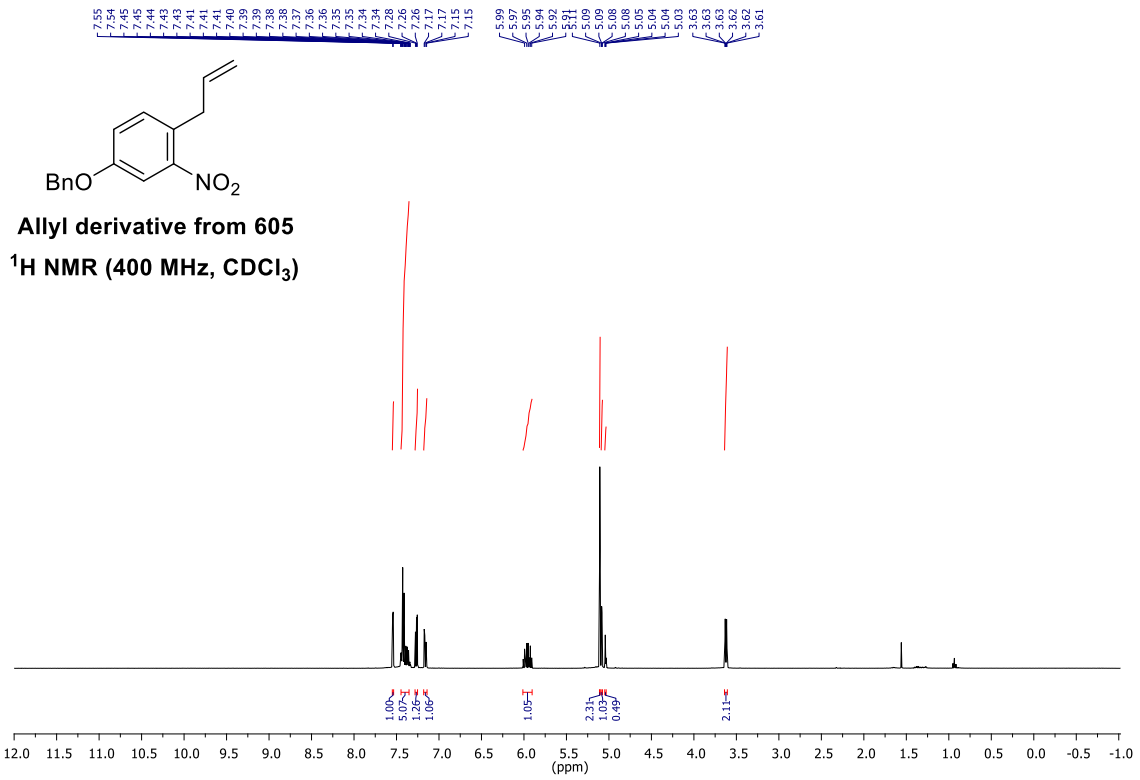




606

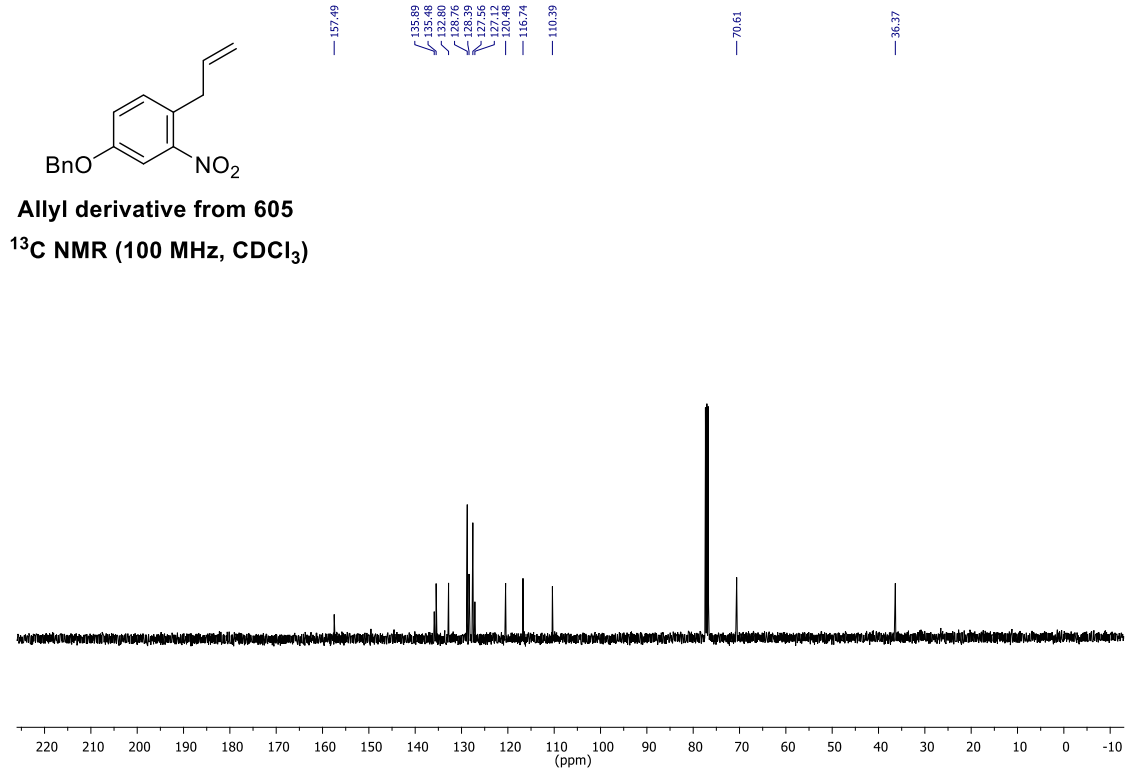
^{13}C NMR (100 MHz, $CDCl_3$)





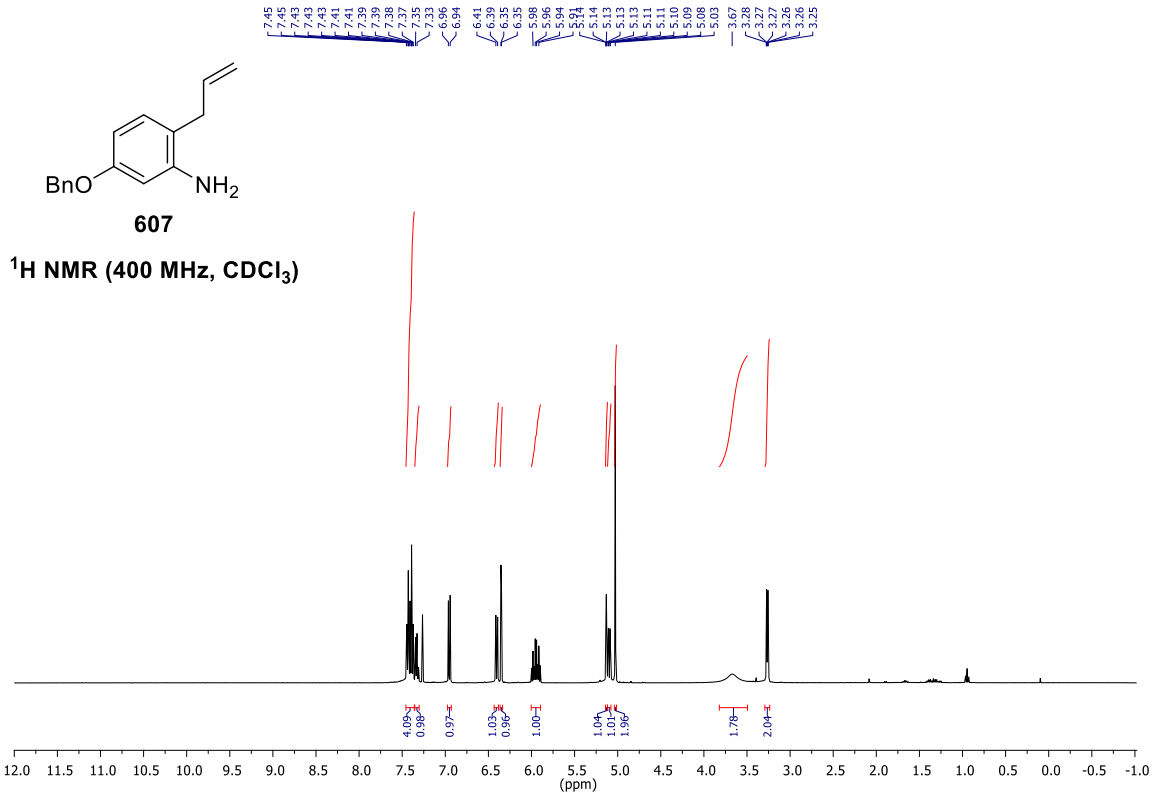
Allyl derivative from 605

^{1}H NMR (400 MHz, $CDCl_3$)



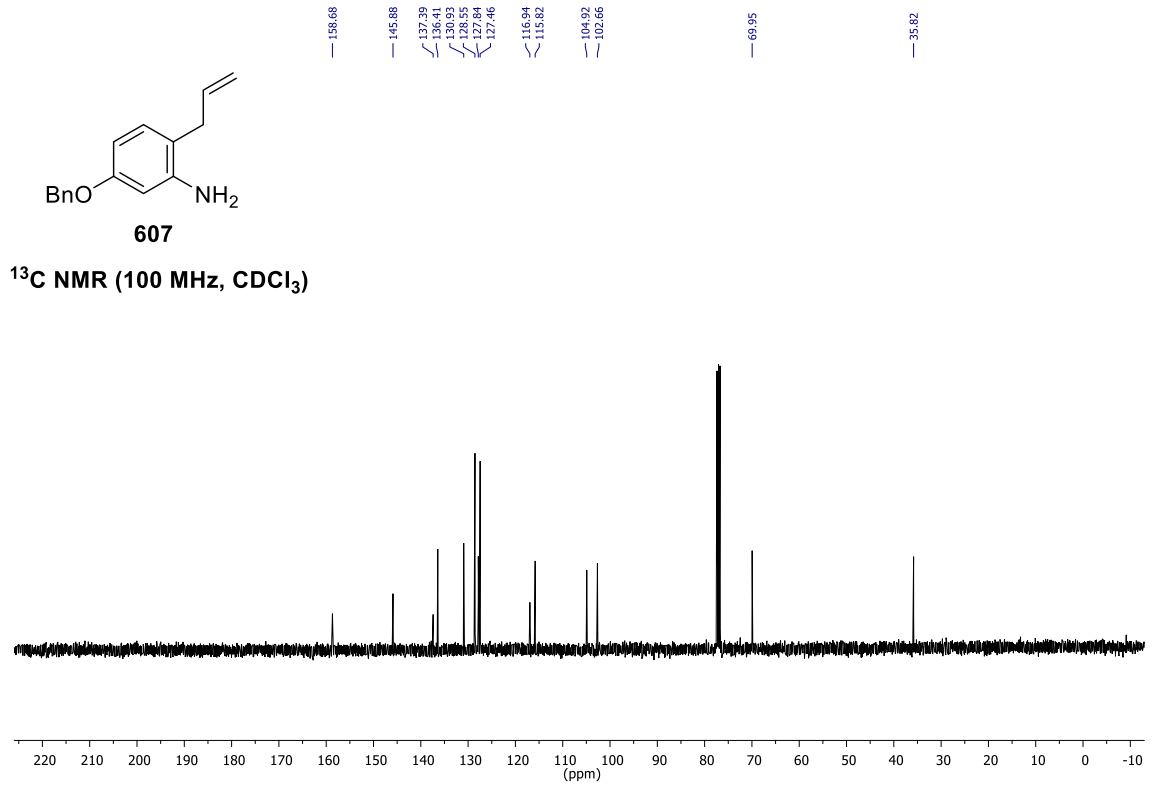
Allyl derivative from 605

^{13}C NMR (100 MHz, $CDCl_3$)



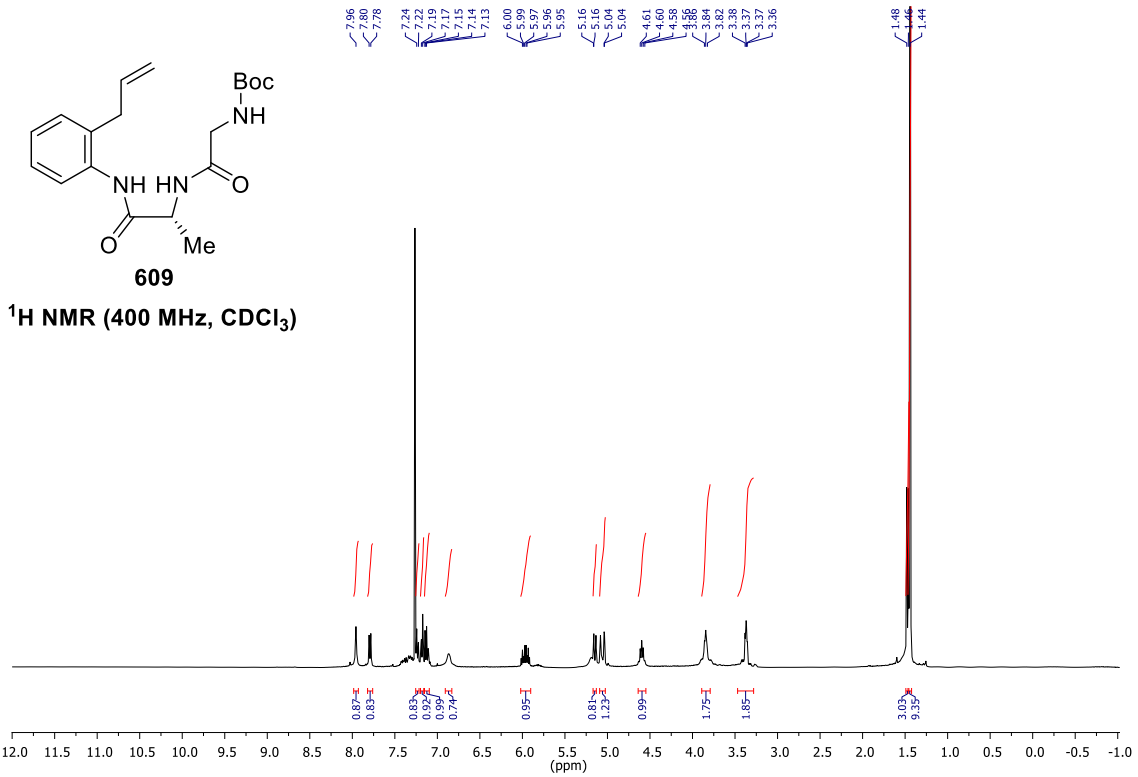
607

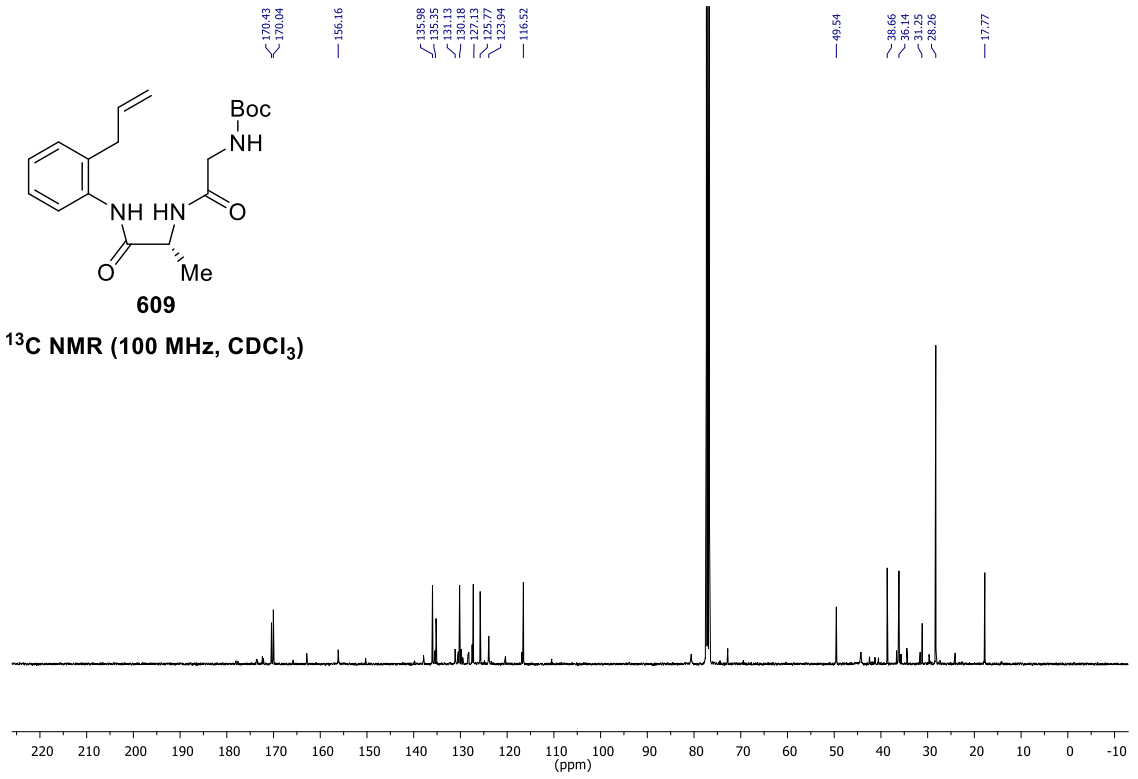
^{1}H NMR (400 MHz, $CDCl_3$)

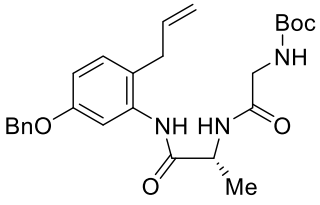


607

^{13}C NMR (100 MHz, $CDCl_3$)

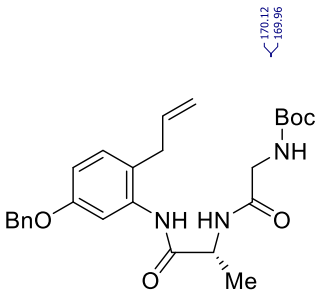






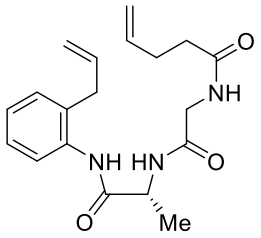
610

^{1}H NMR (400 MHz, $CDCl_3$)



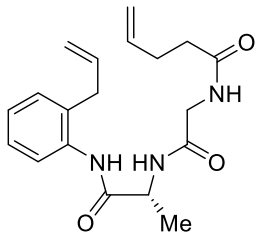
610

^{13}C NMR (100 MHz, $CDCl_3$)



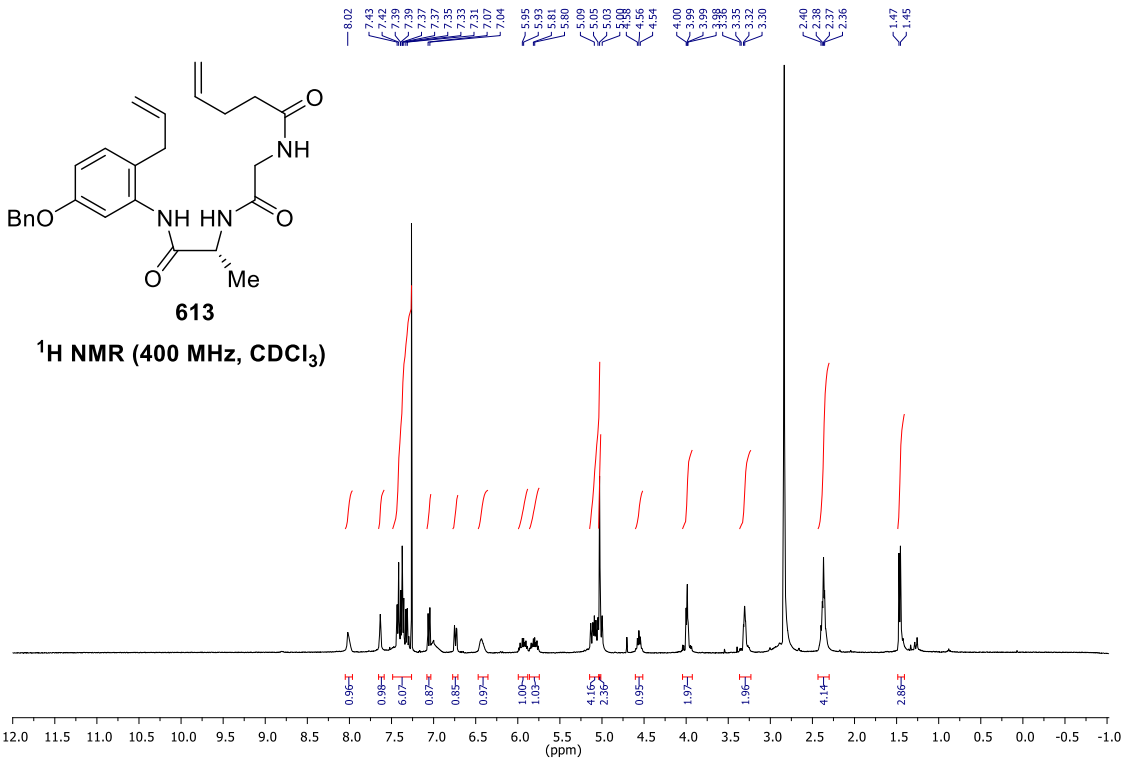
612

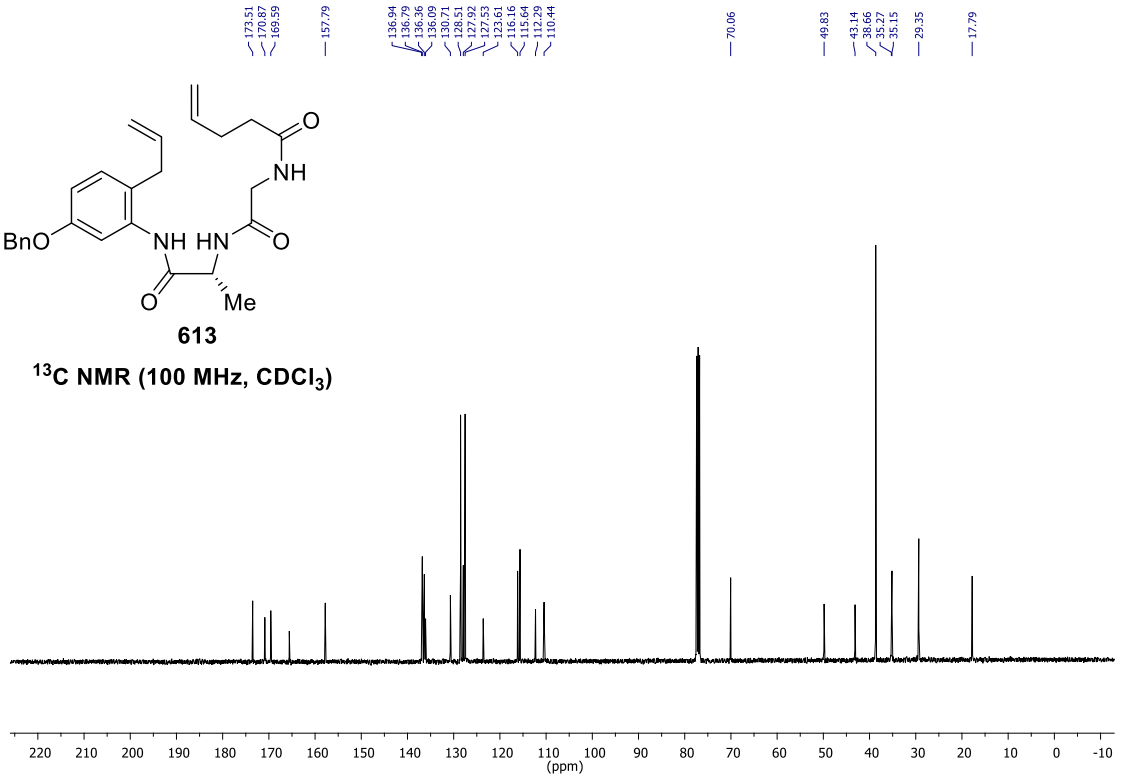
^{1}H NMR (400 MHz, $CDCl_3$)

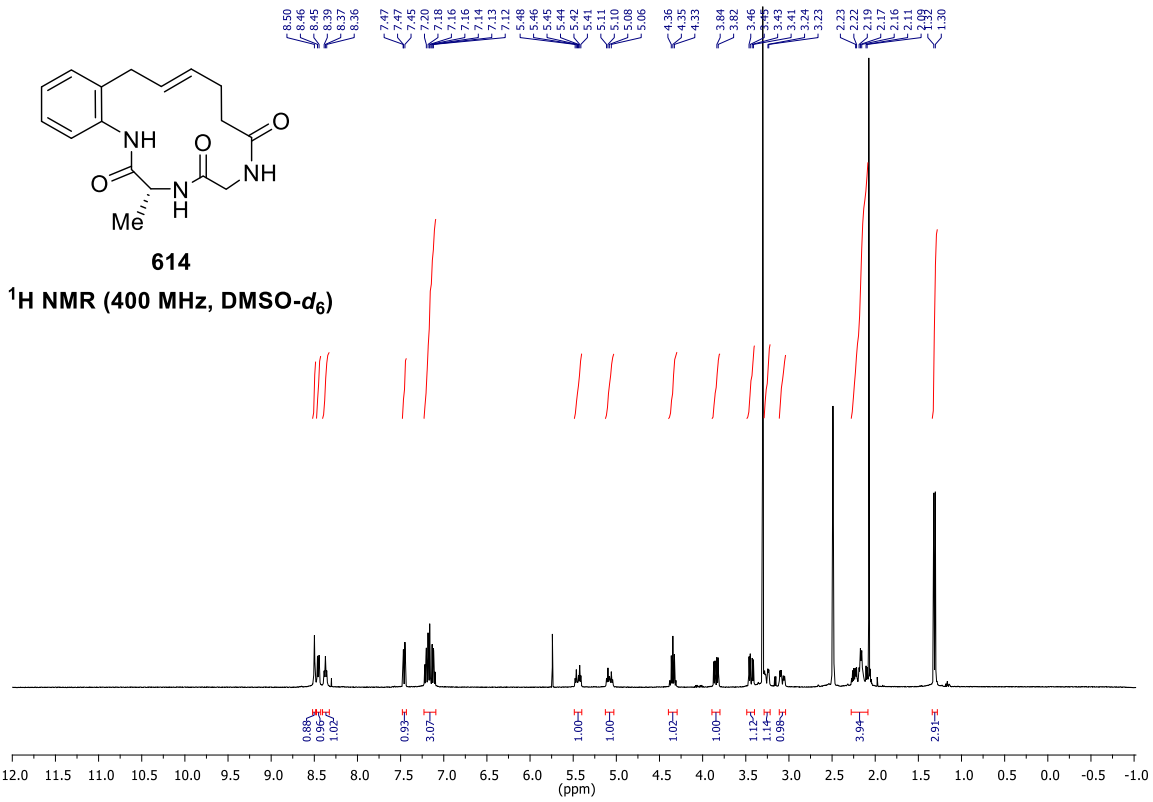


612

^{13}C NMR (100 MHz, $CDCl_3$)

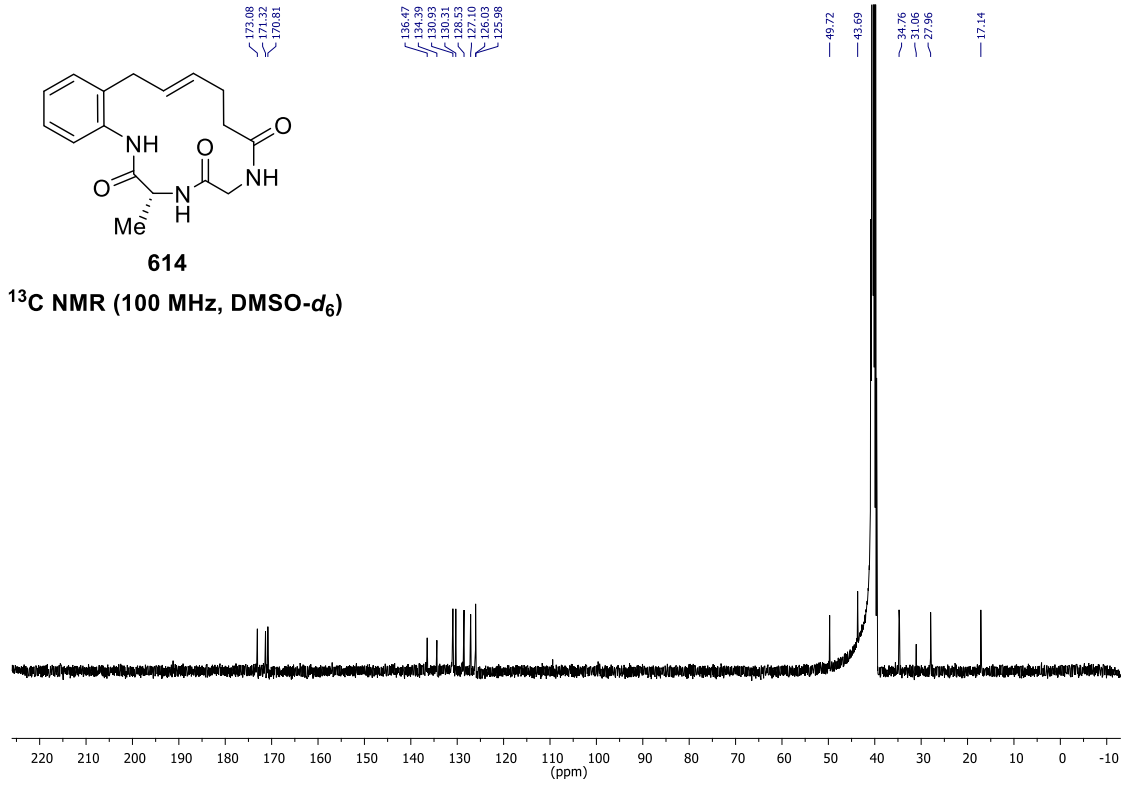






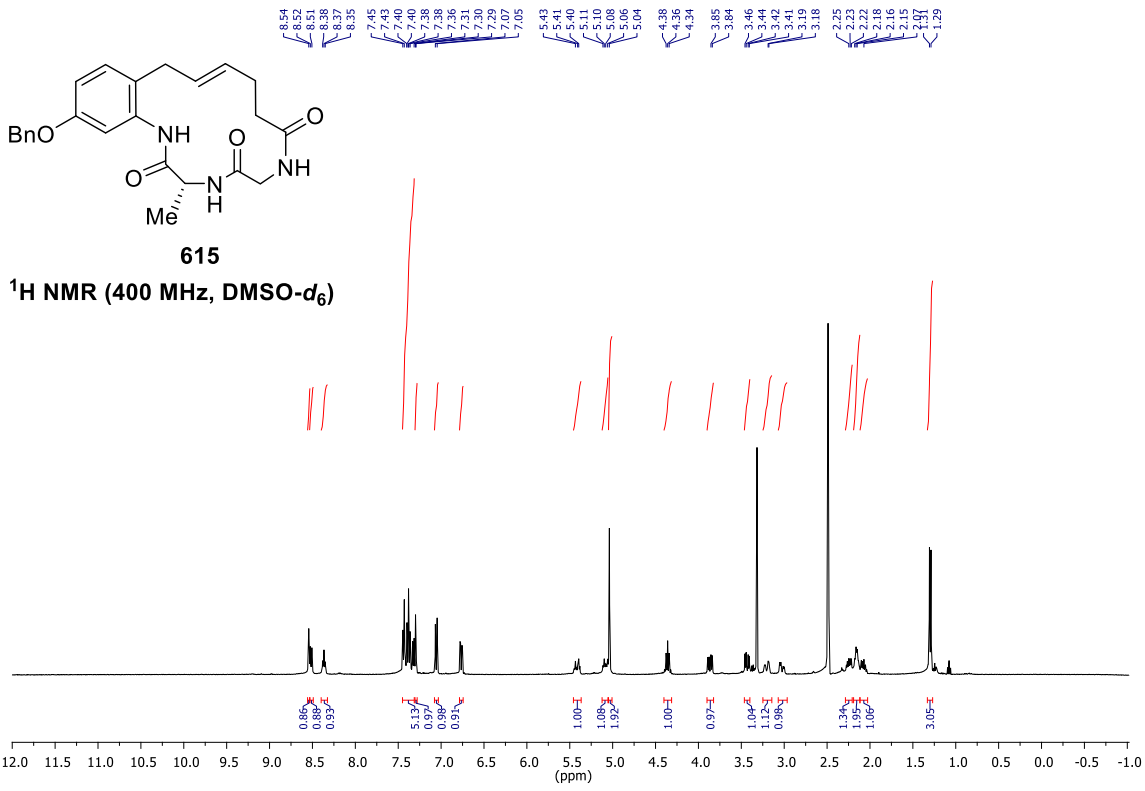
614

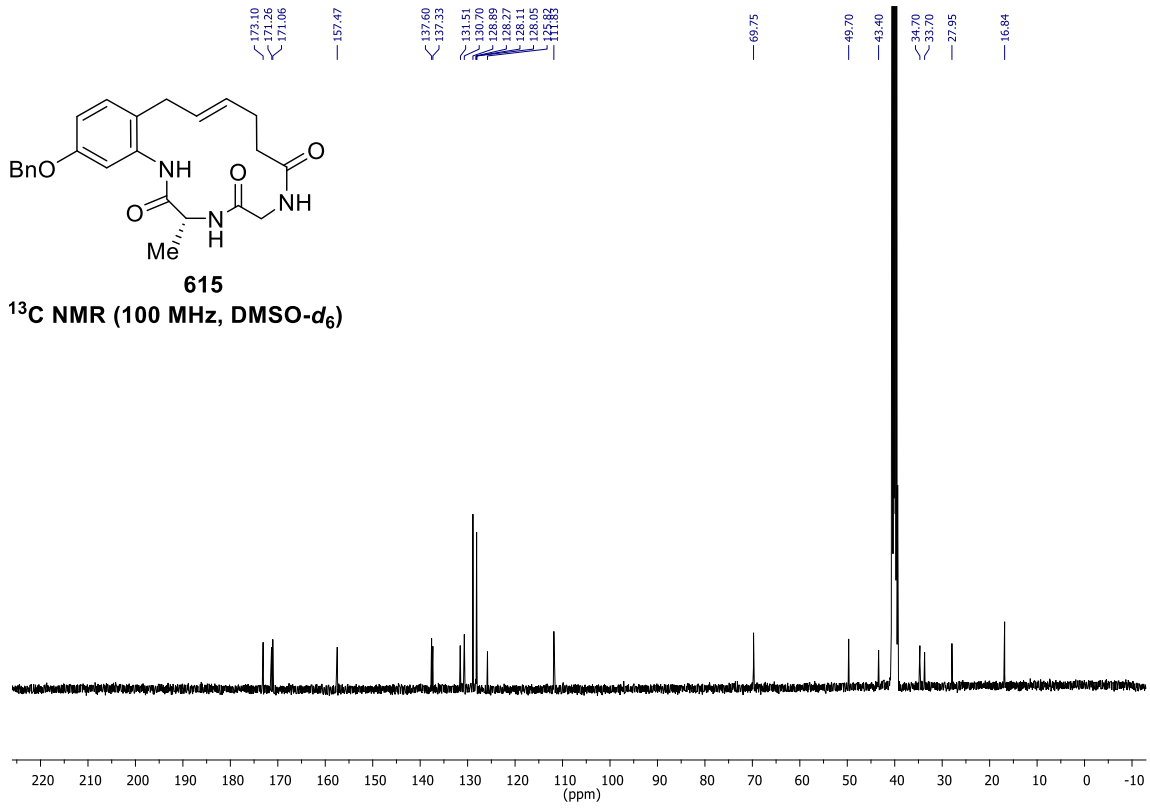
^{1}H NMR (400 MHz, DMSO-d_6)

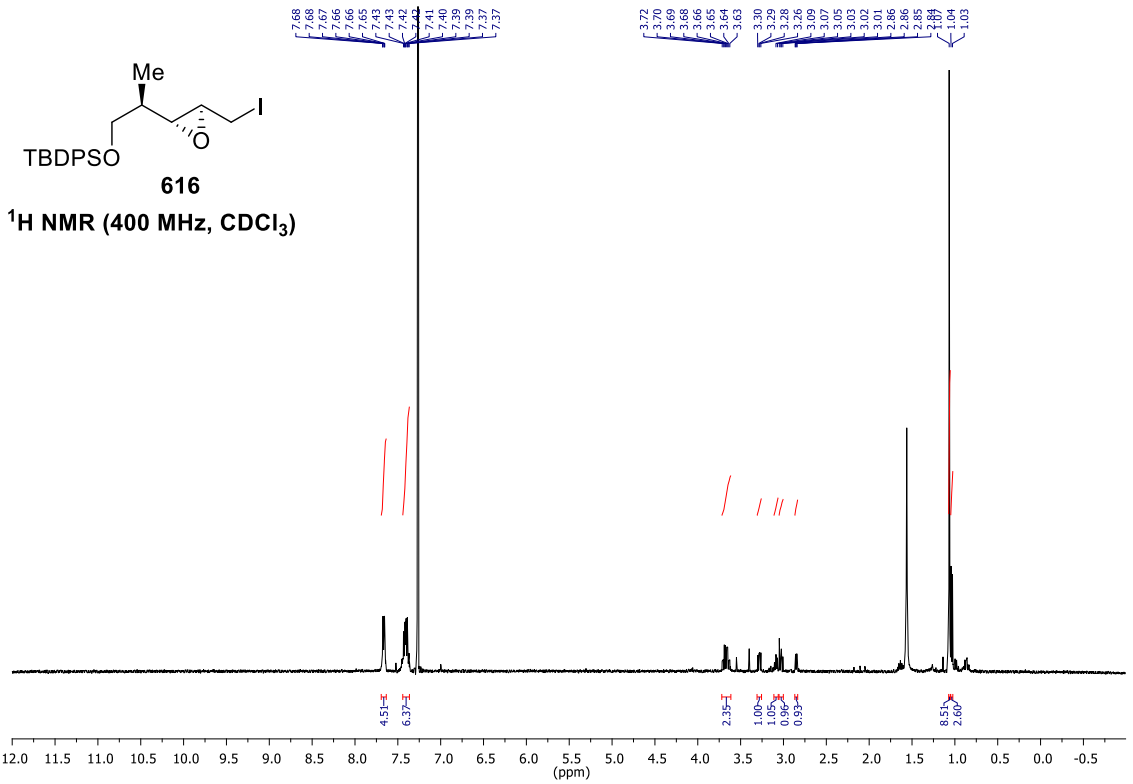


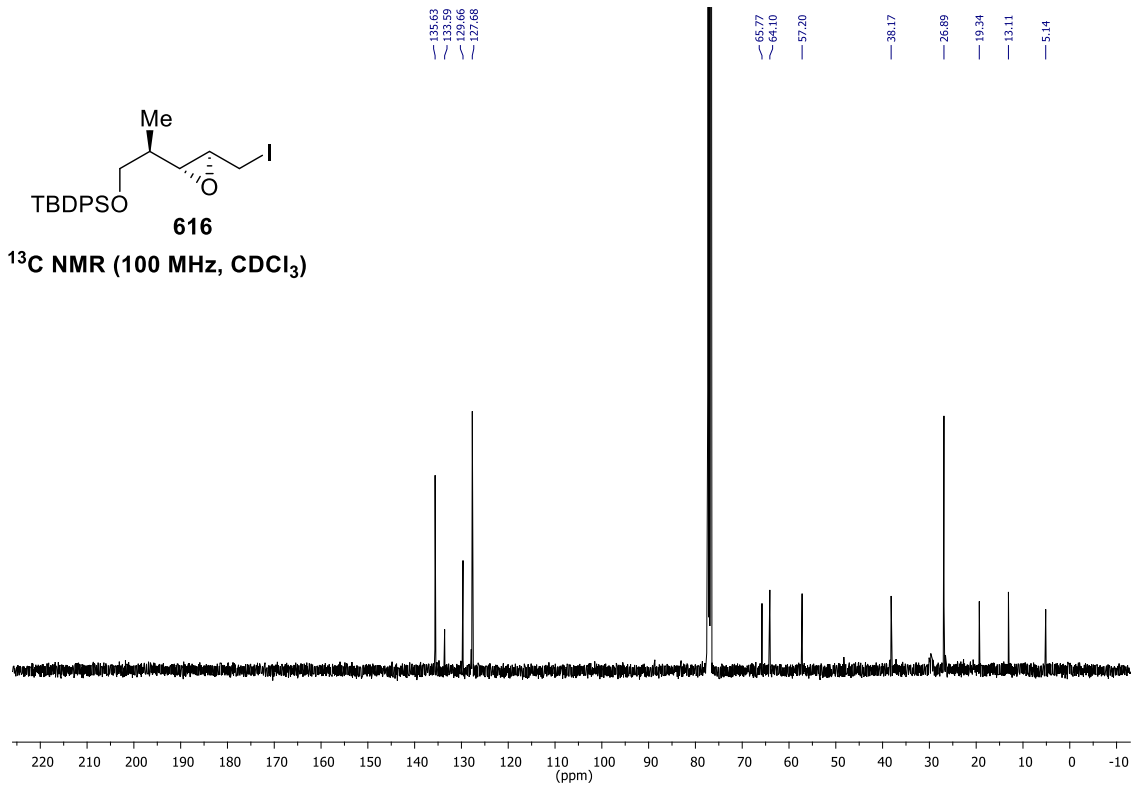
614

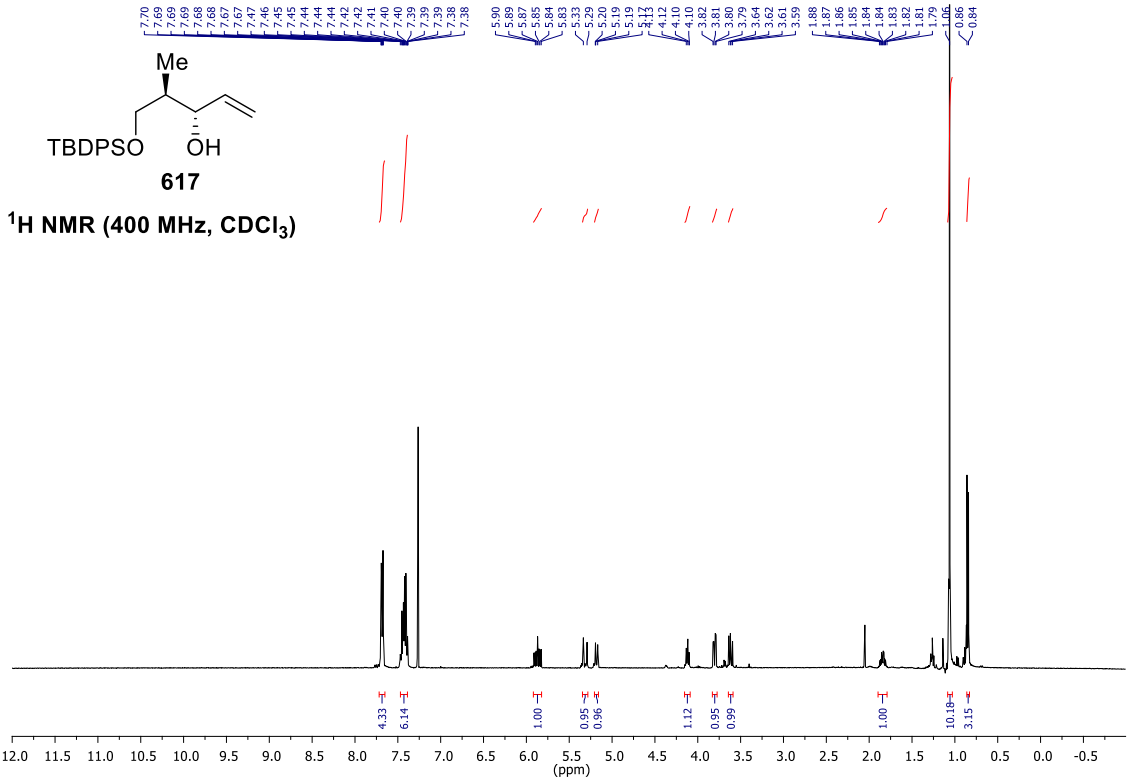
^{13}C NMR (100 MHz, DMSO-d_6)





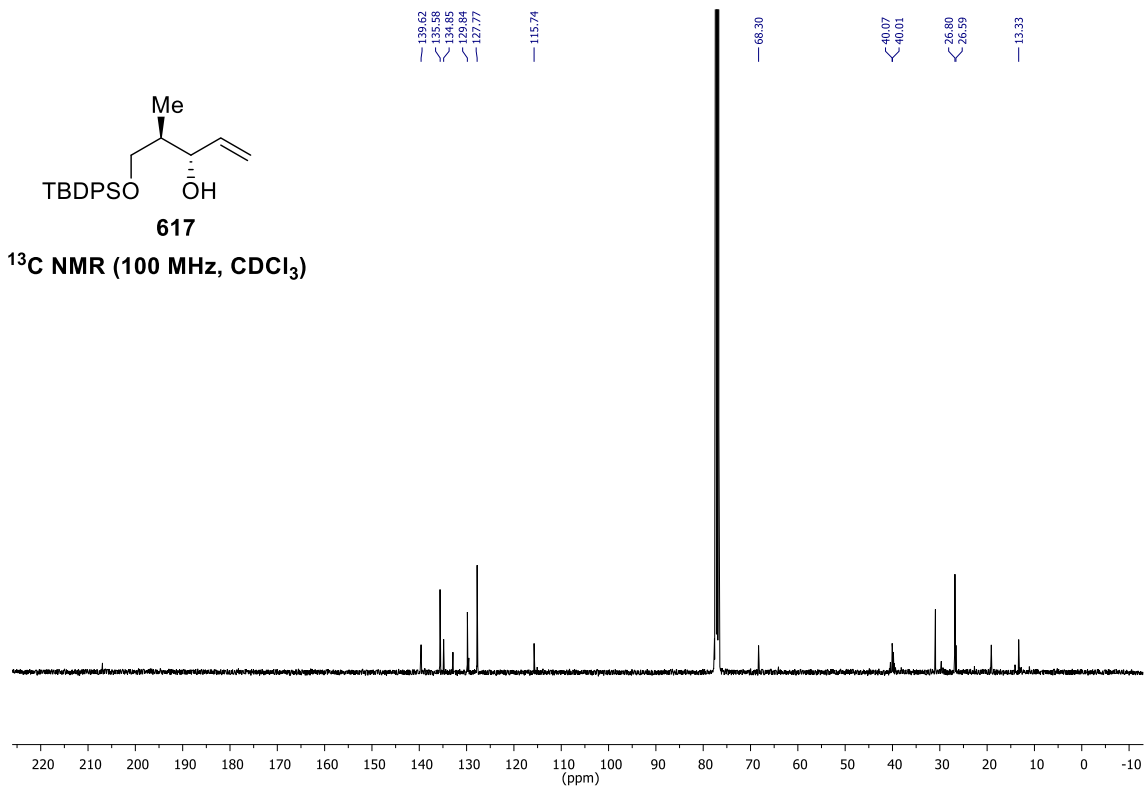






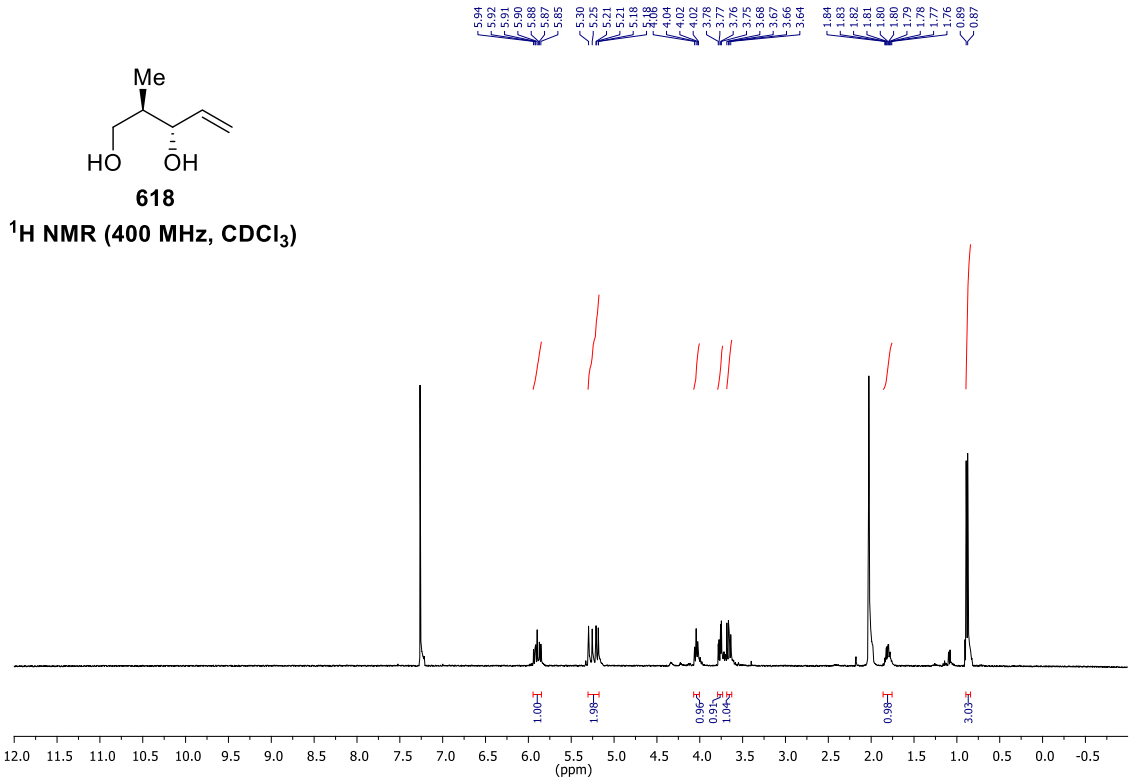
617

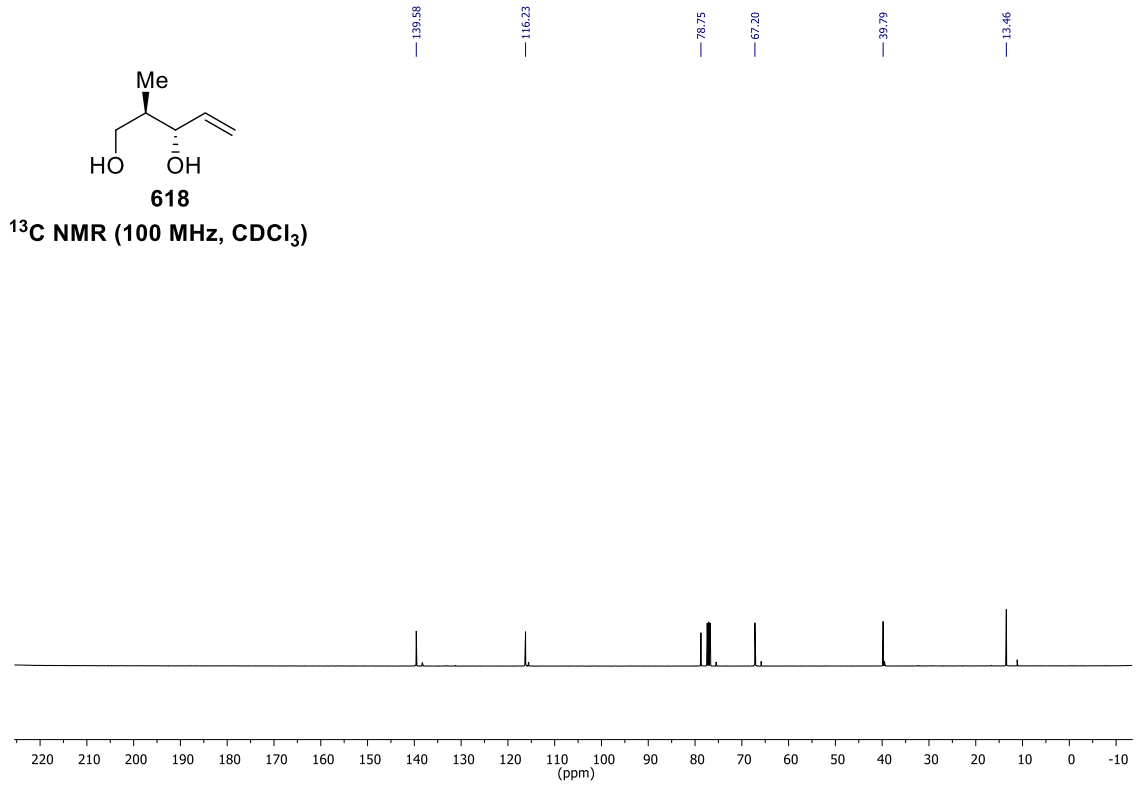
^{1}H NMR (400 MHz, $CDCl_3$)

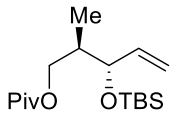


617

^{13}C NMR (100 MHz, $CDCl_3$)

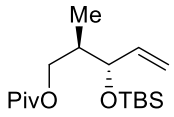






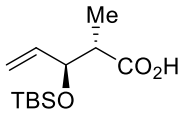
620

^{1}H NMR (400 MHz, $CDCl_3$)



620

^{13}C NMR (100 MHz, $CDCl_3$)



622

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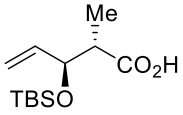
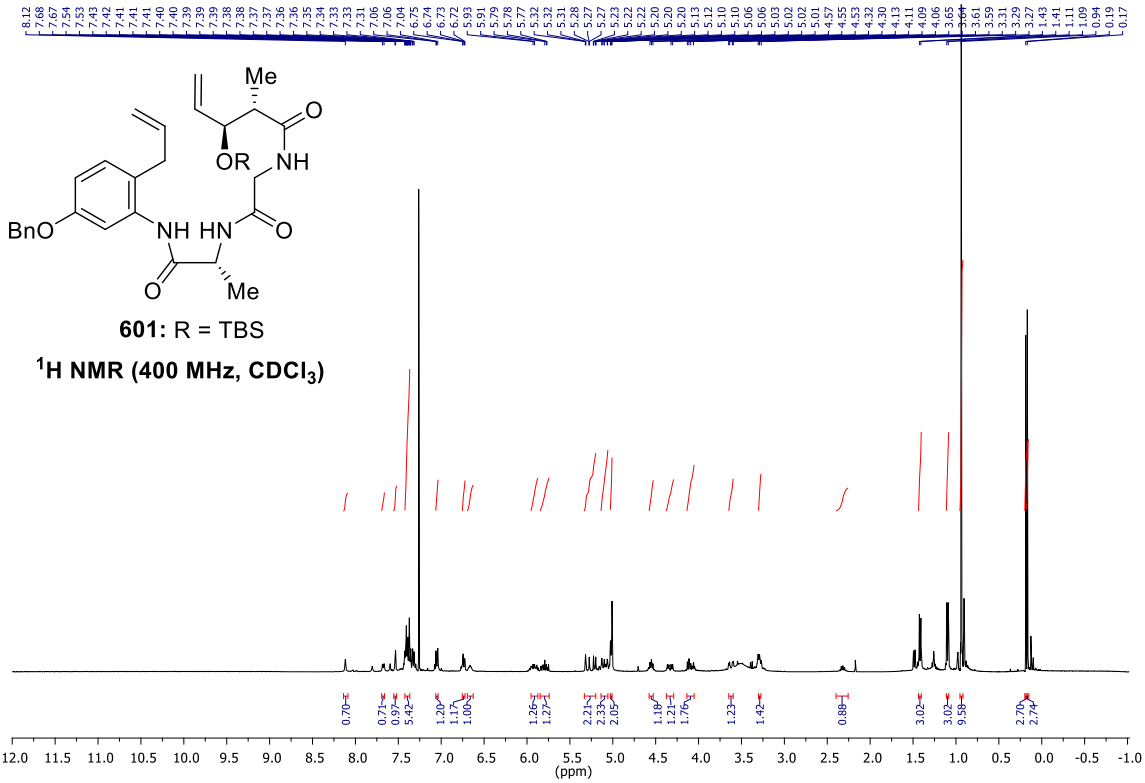


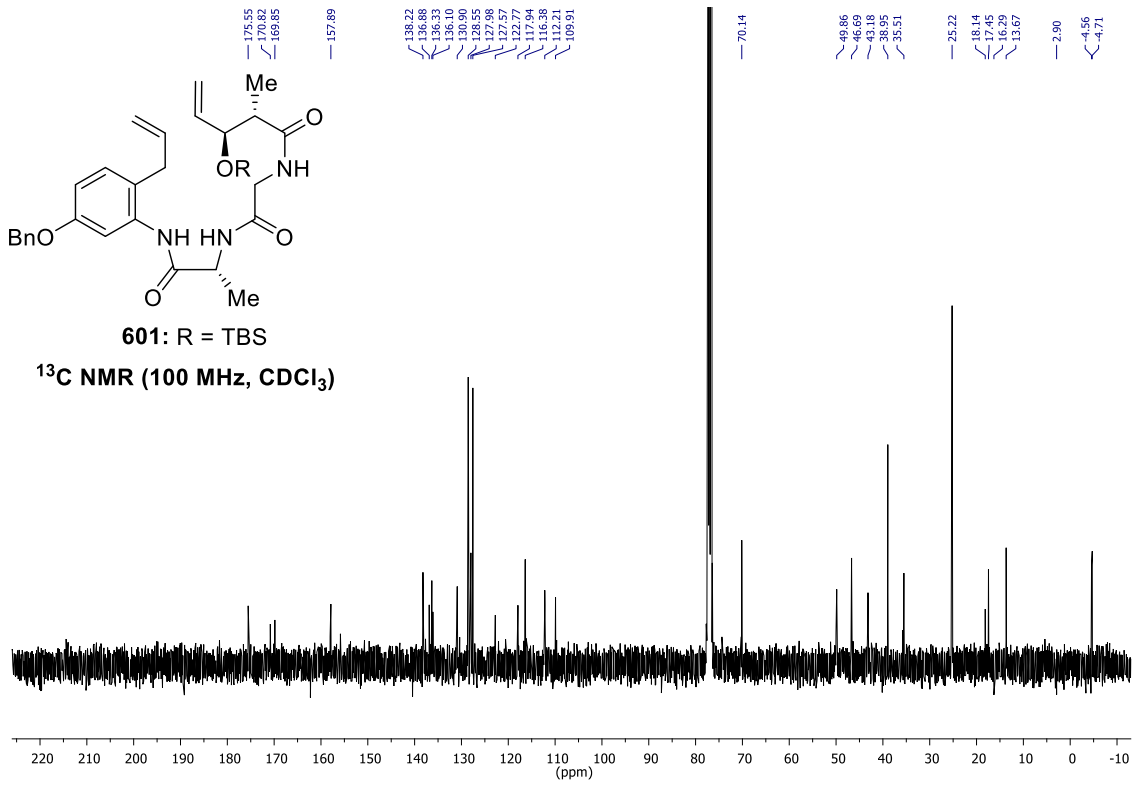
622

^{13}C NMR (100 MHz, $CDCl_3$)



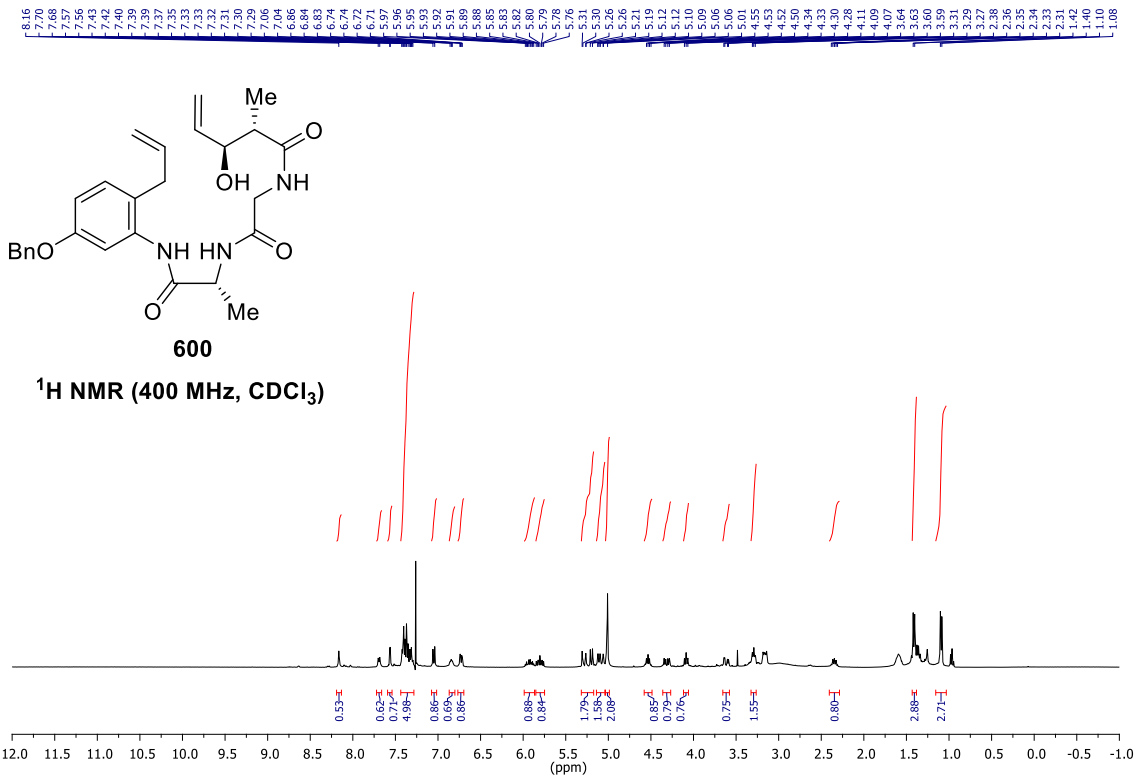
601: R = TBS

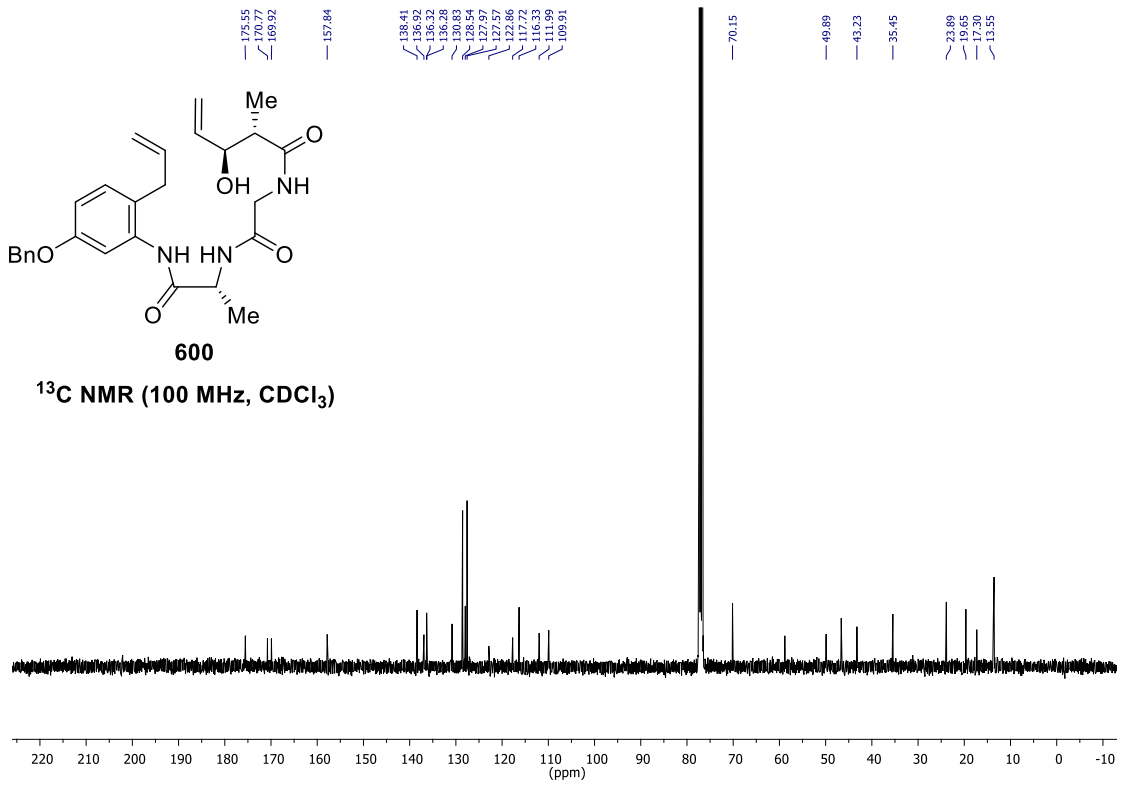
^{1}H NMR (400 MHz, $CDCl_3$)

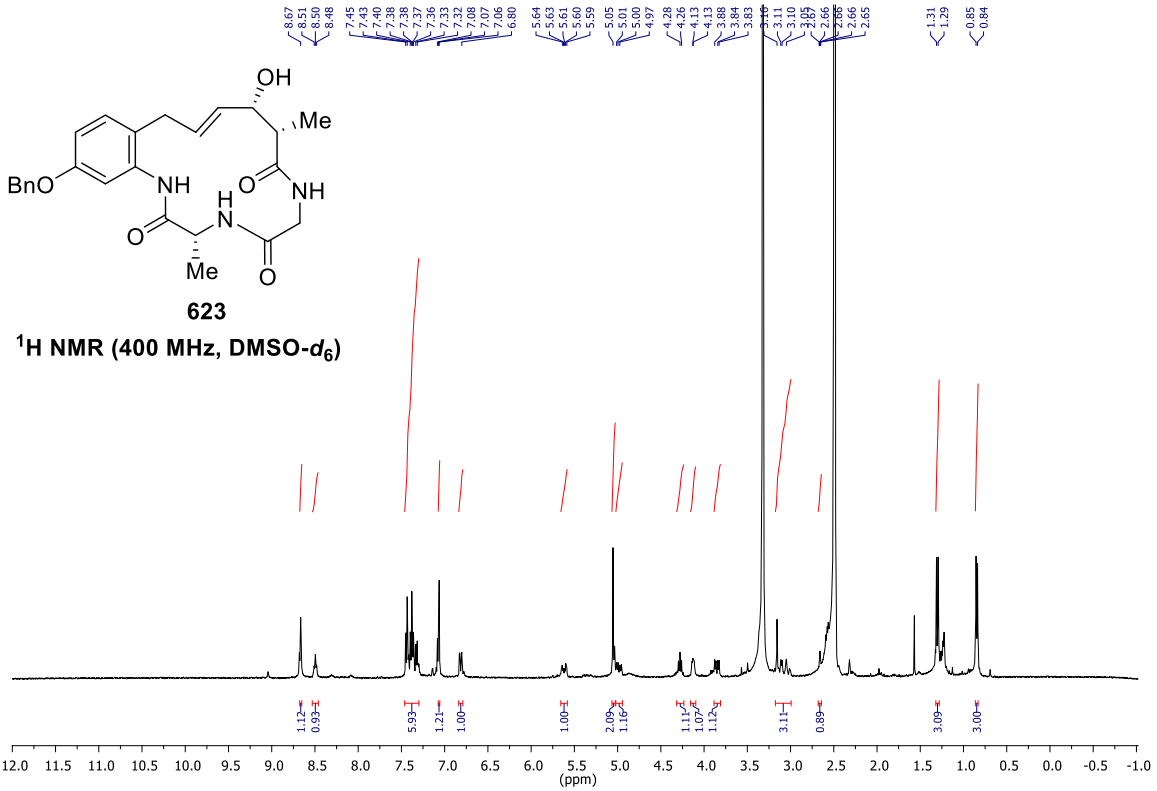


601: R = TBS

^{13}C NMR (100 MHz, $CDCl_3$)

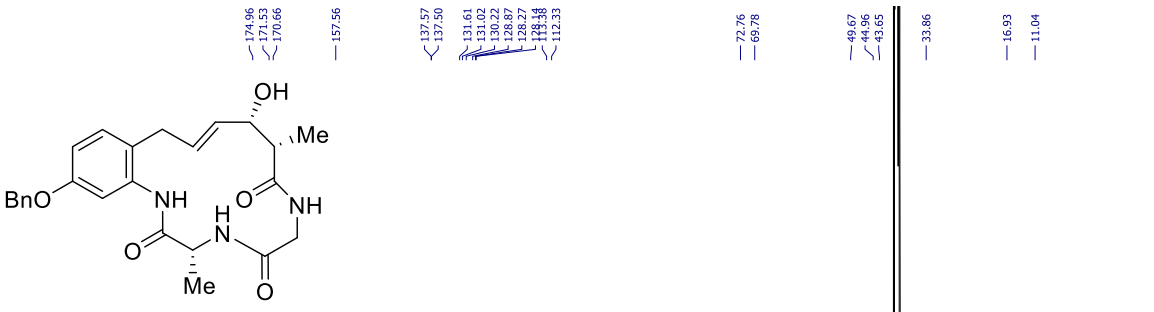






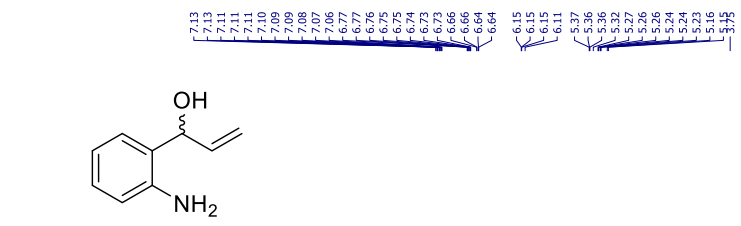
623

^{1}H NMR (400 MHz, DMSO-d_6)



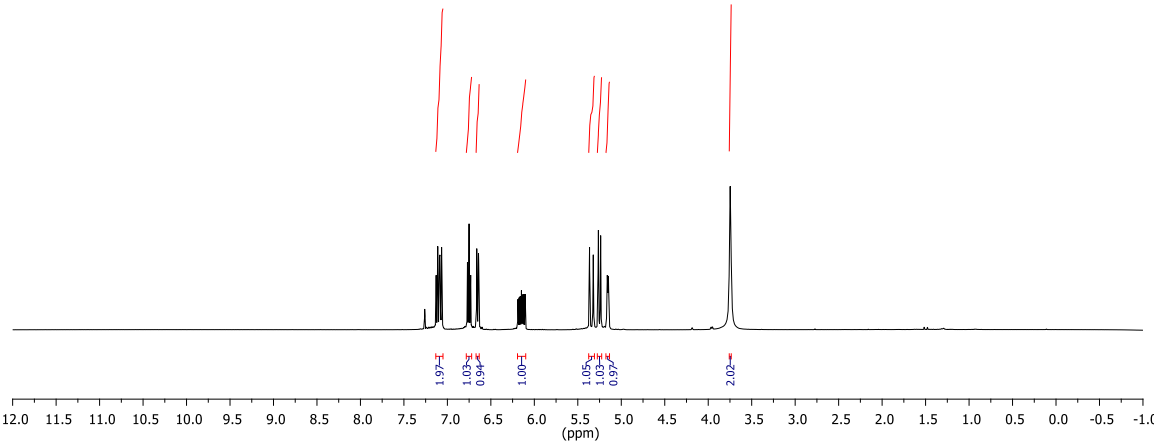
623

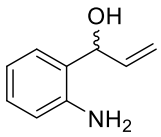
^{13}C NMR (100 MHz, DMSO-d_6)



625

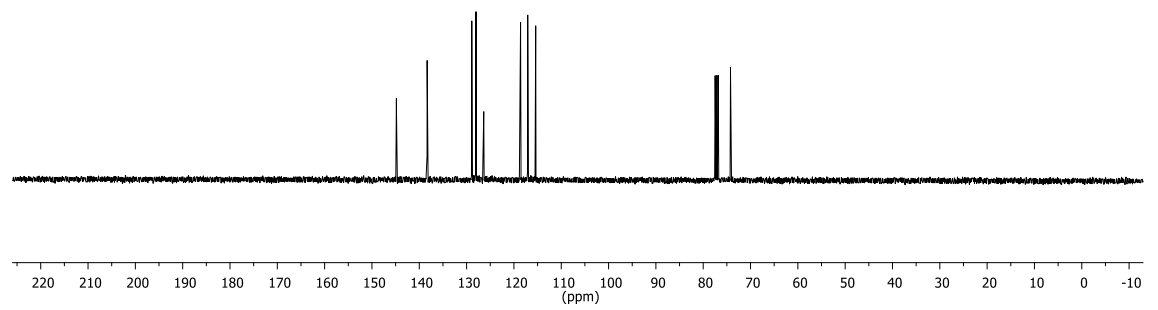
^{1}H NMR (400 MHz, $CDCl_3$)

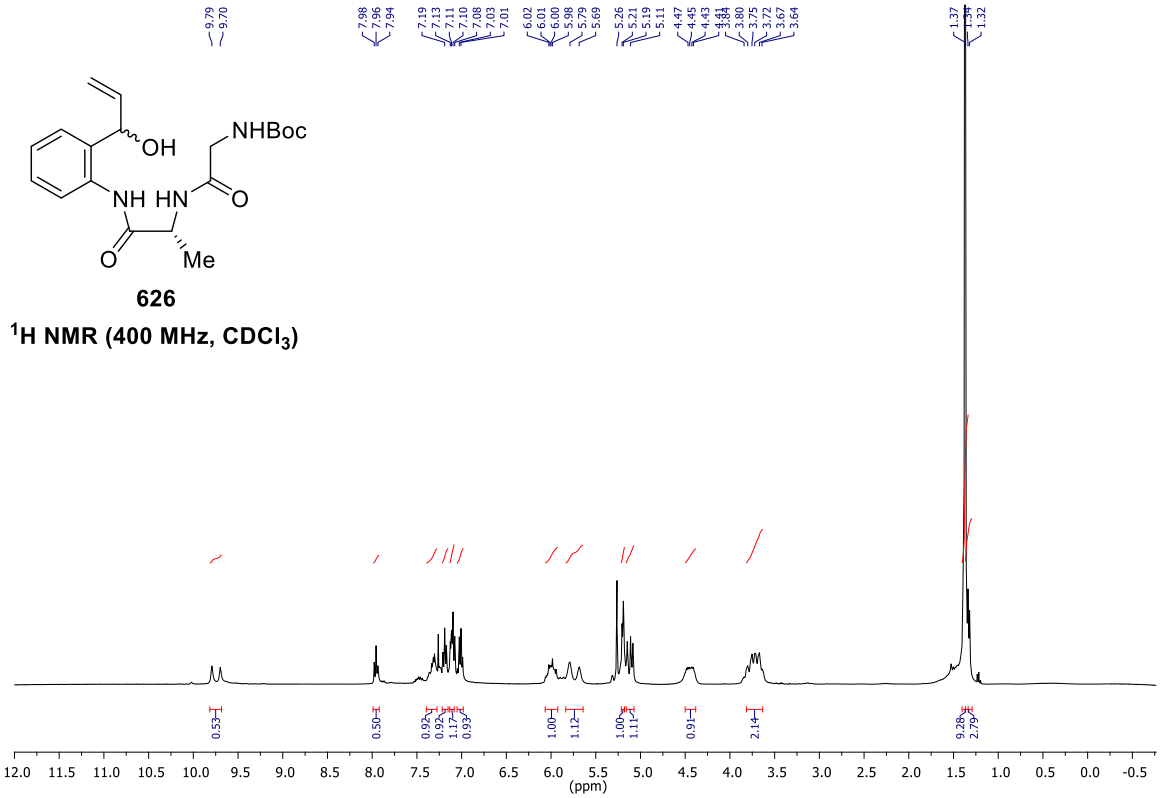




625

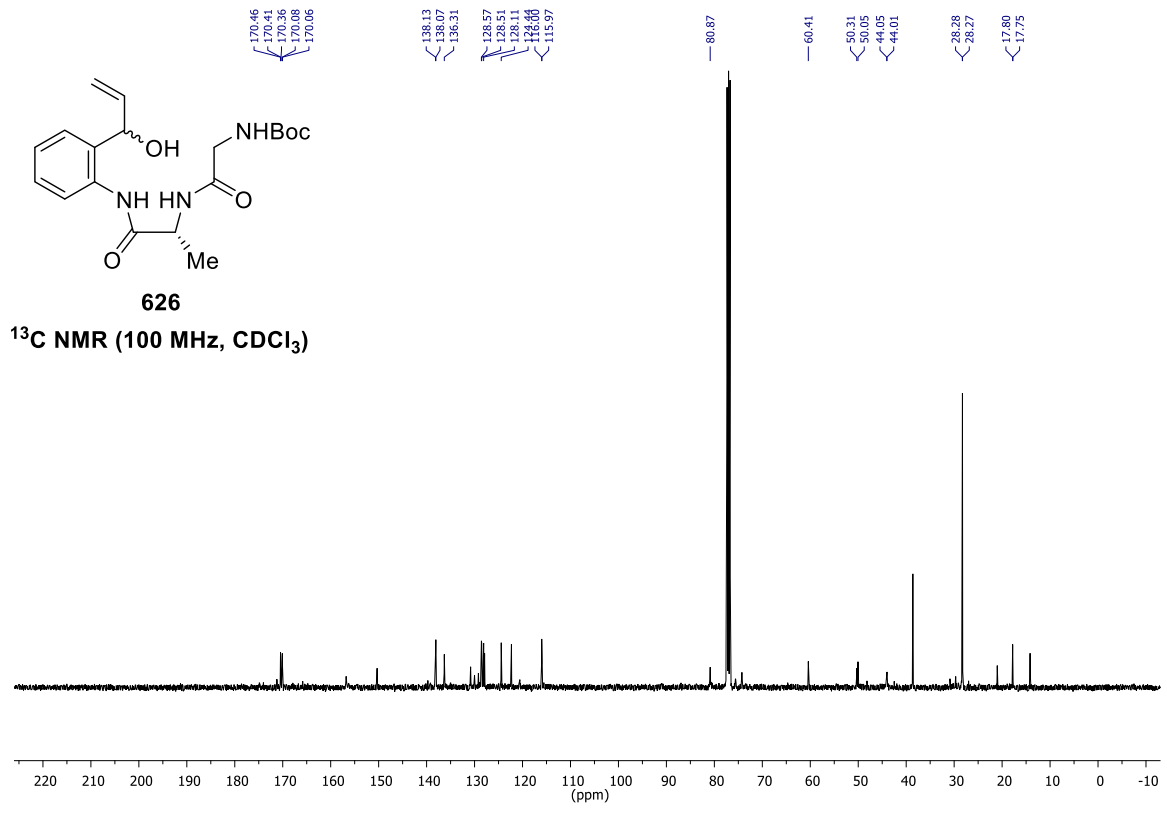
^{13}C NMR (100 MHz, $CDCl_3$)





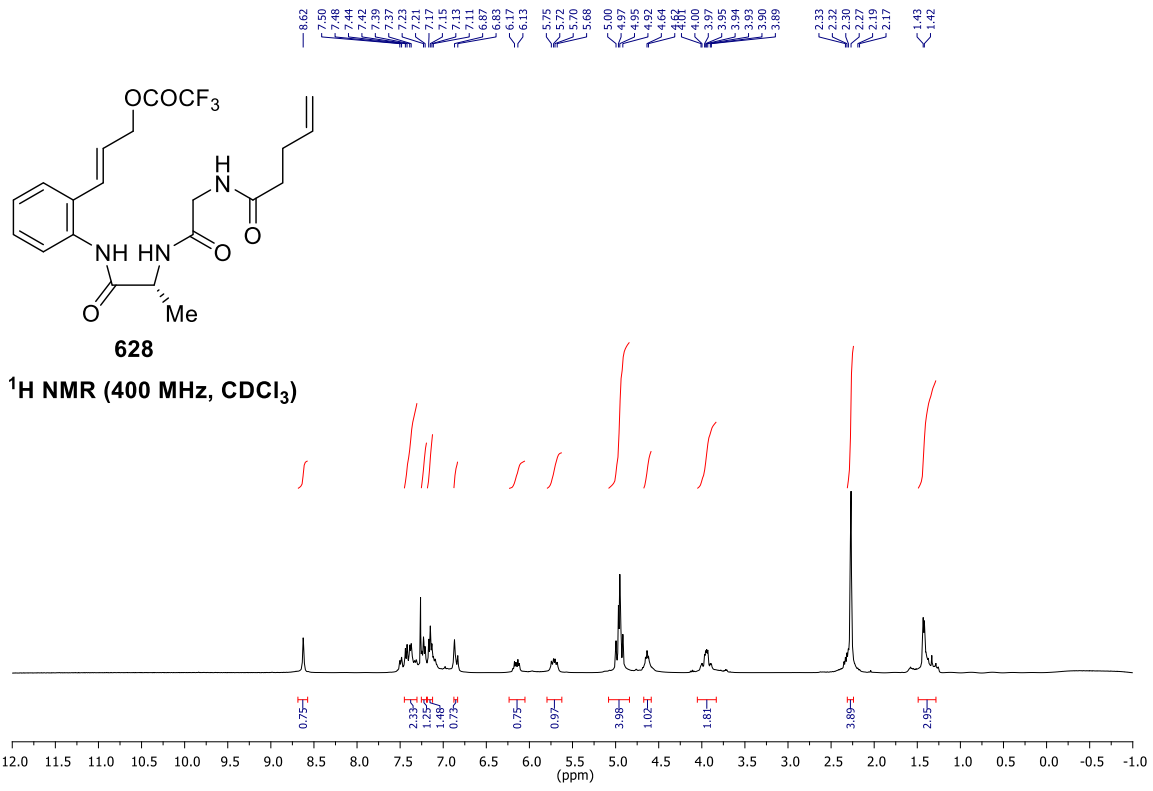
626

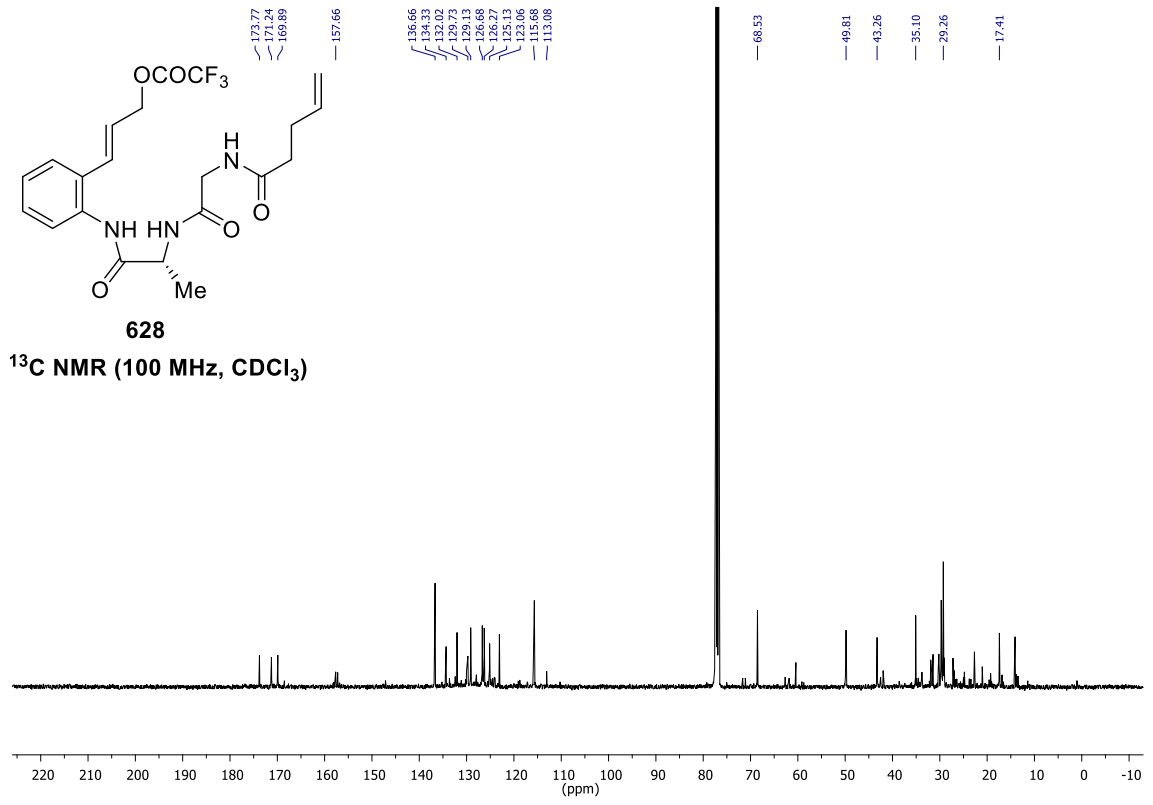
^{1}H NMR (400 MHz, $CDCl_3$)

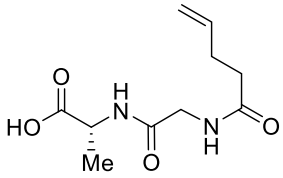


626

^{13}C NMR (100 MHz, $CDCl_3$)

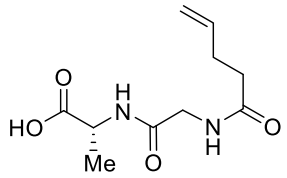






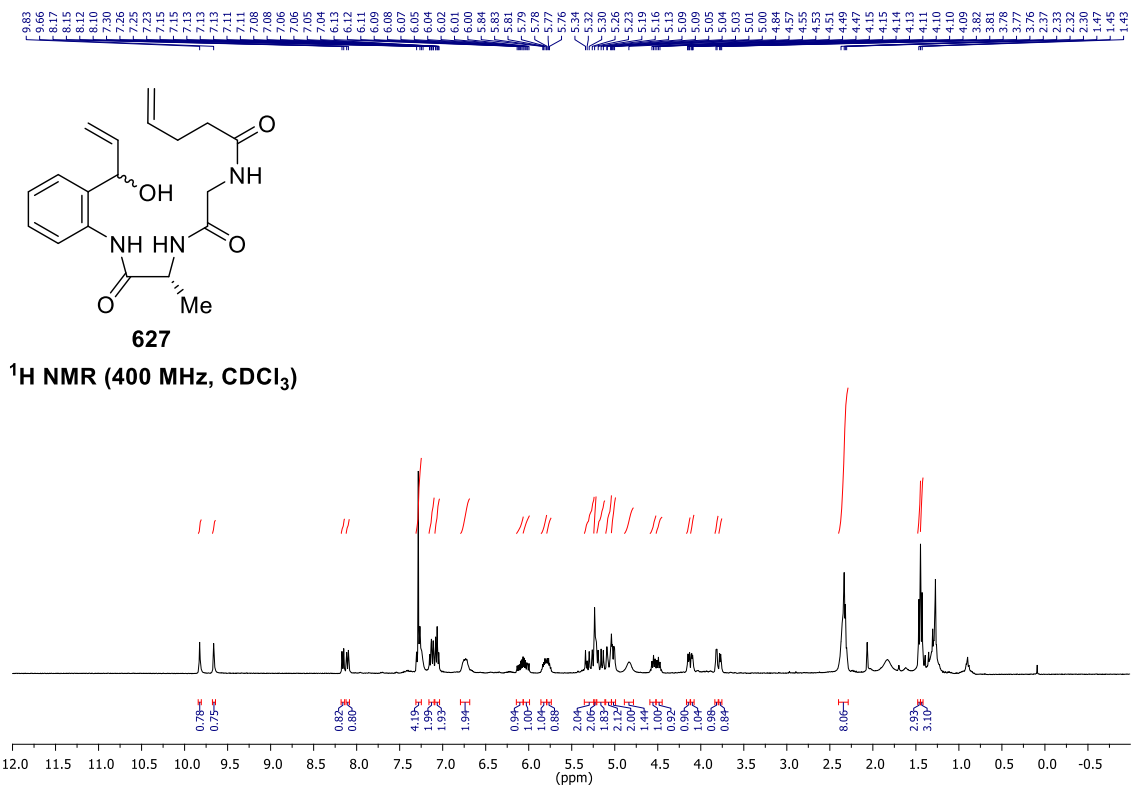
631

^{1}H NMR (400 MHz, $CDCl_3$)



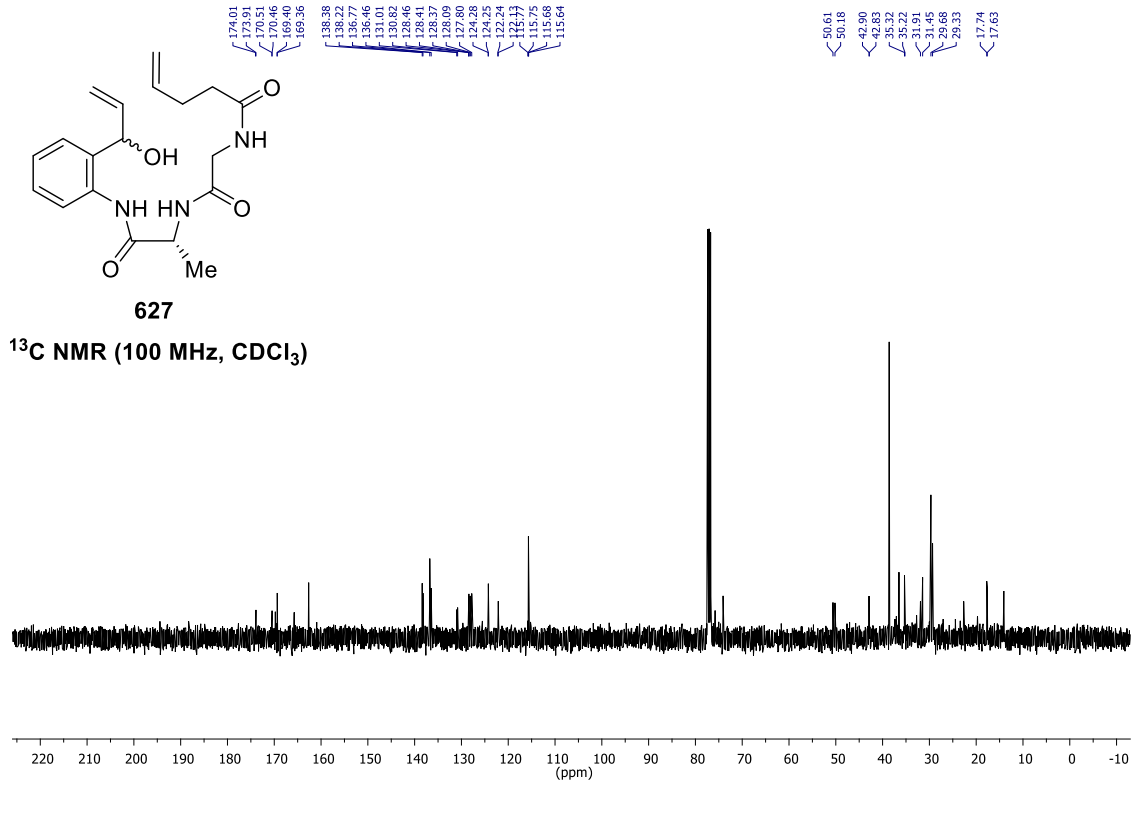
631

^{13}C NMR (100 MHz, $CDCl_3$)



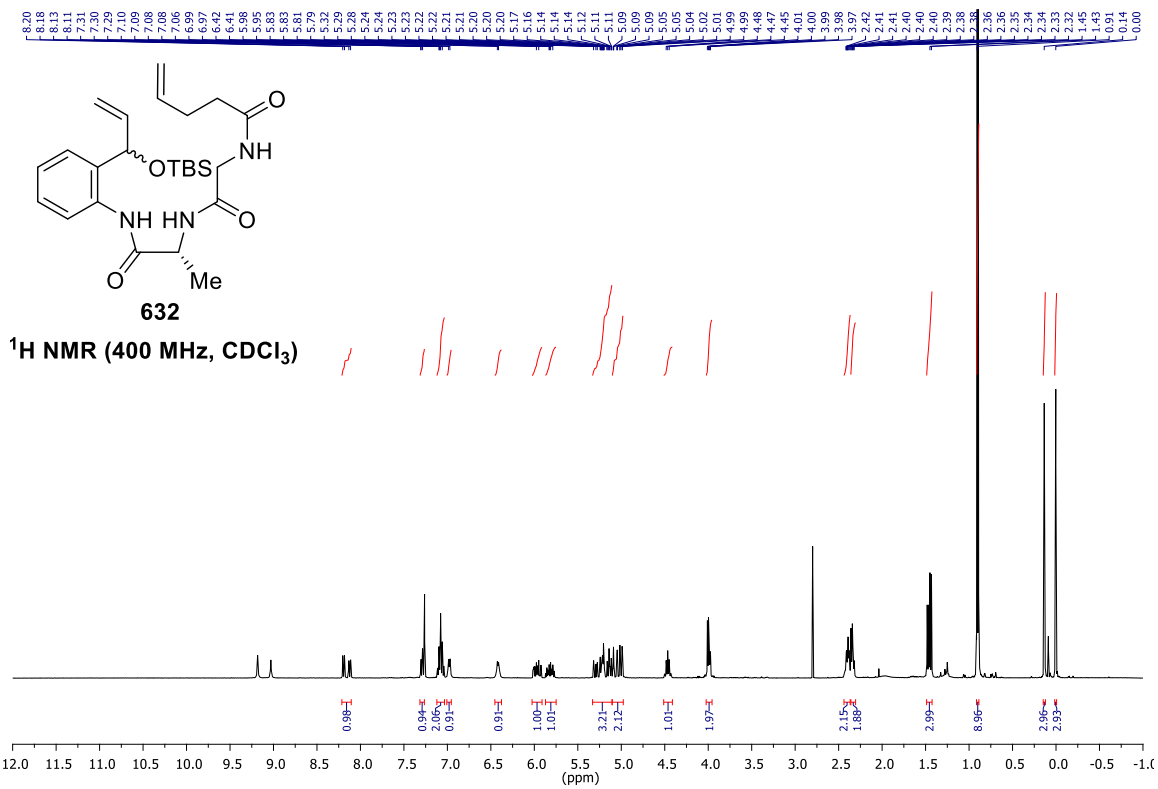
627

^{1}H NMR (400 MHz, $CDCl_3$)



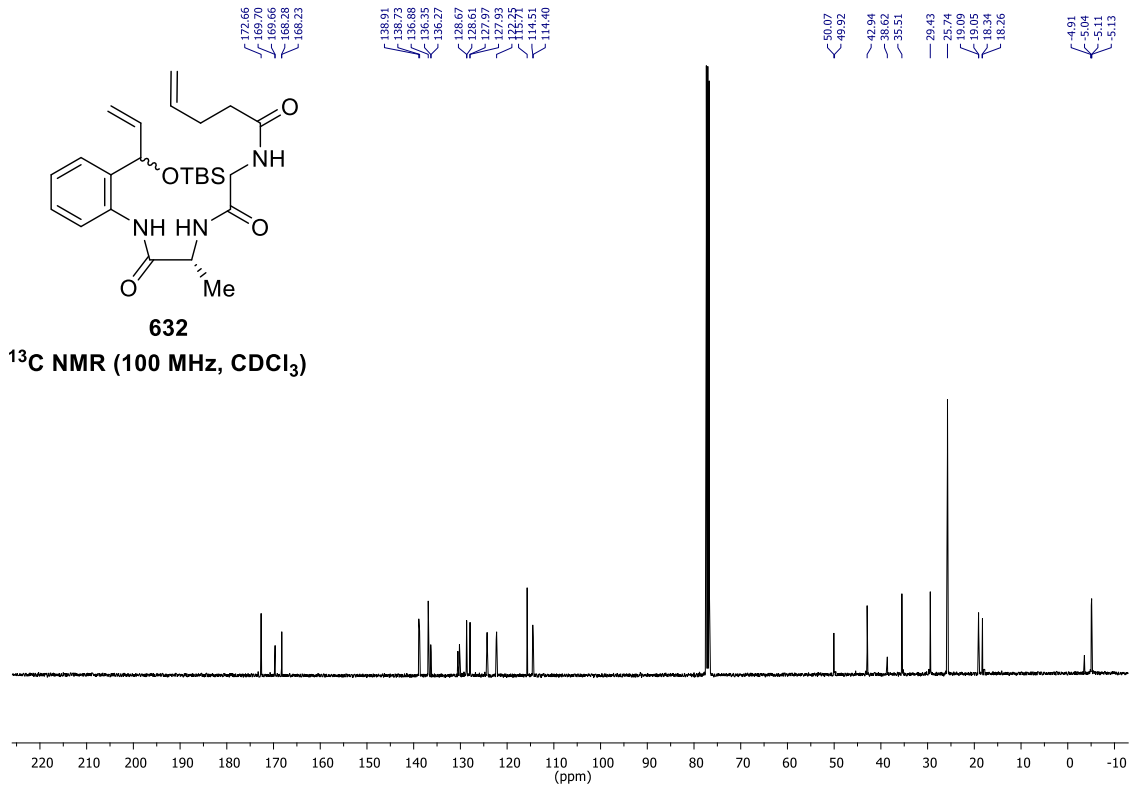
627

^{13}C NMR (100 MHz, $CDCl_3$)



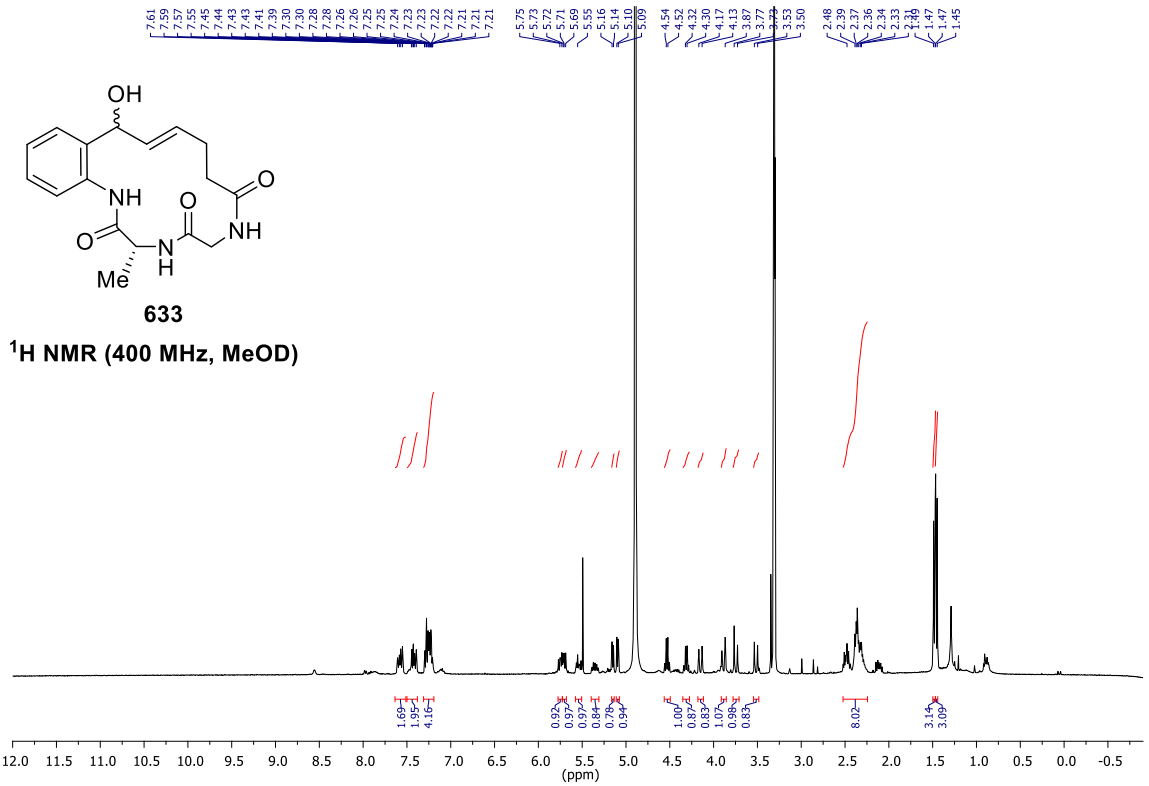
632

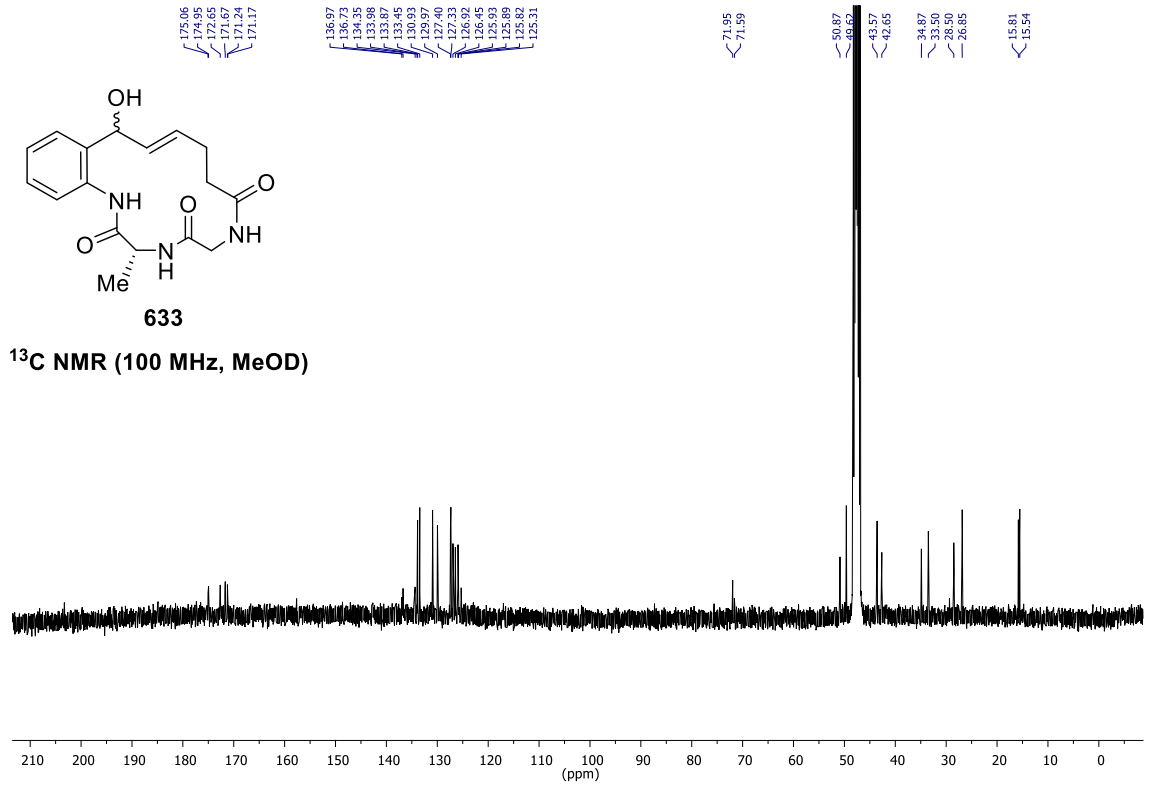
^{1}H NMR (400 MHz, $CDCl_3$)

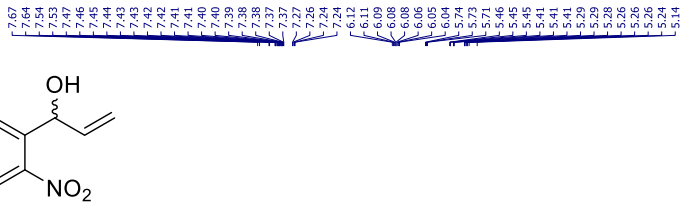


632

^{13}C NMR (100 MHz, $CDCl_3$)

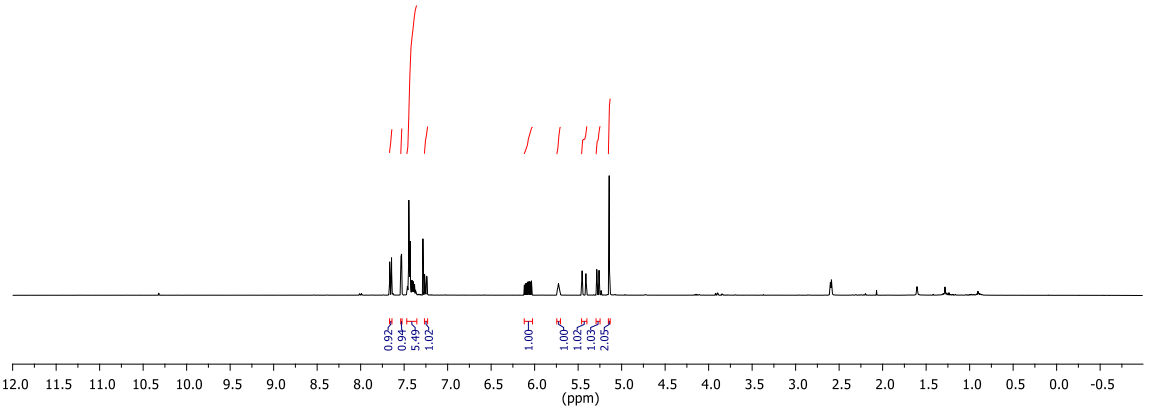


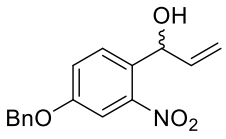




636

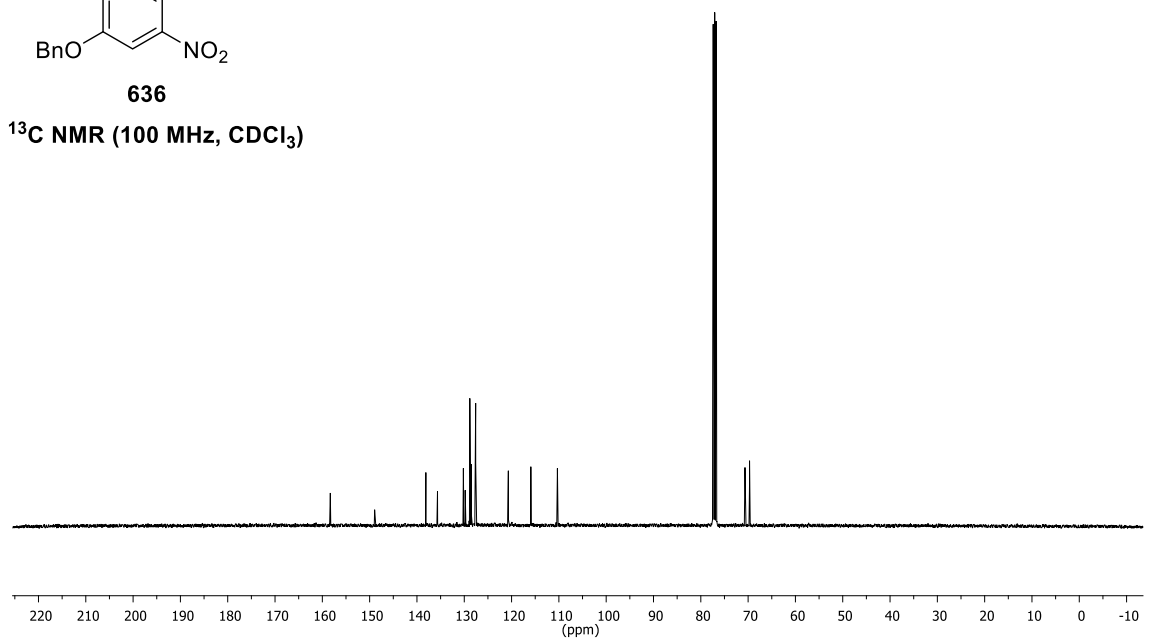
^{1}H NMR (400 MHz, $CDCl_3$)

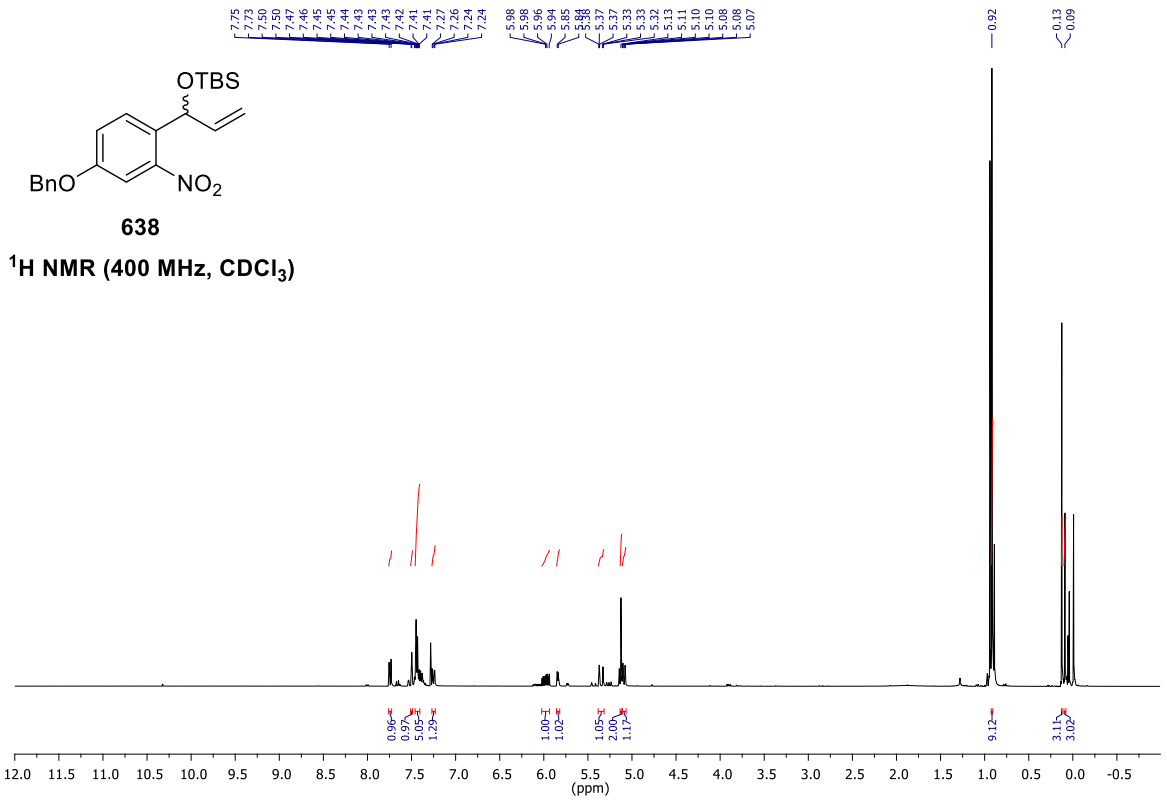


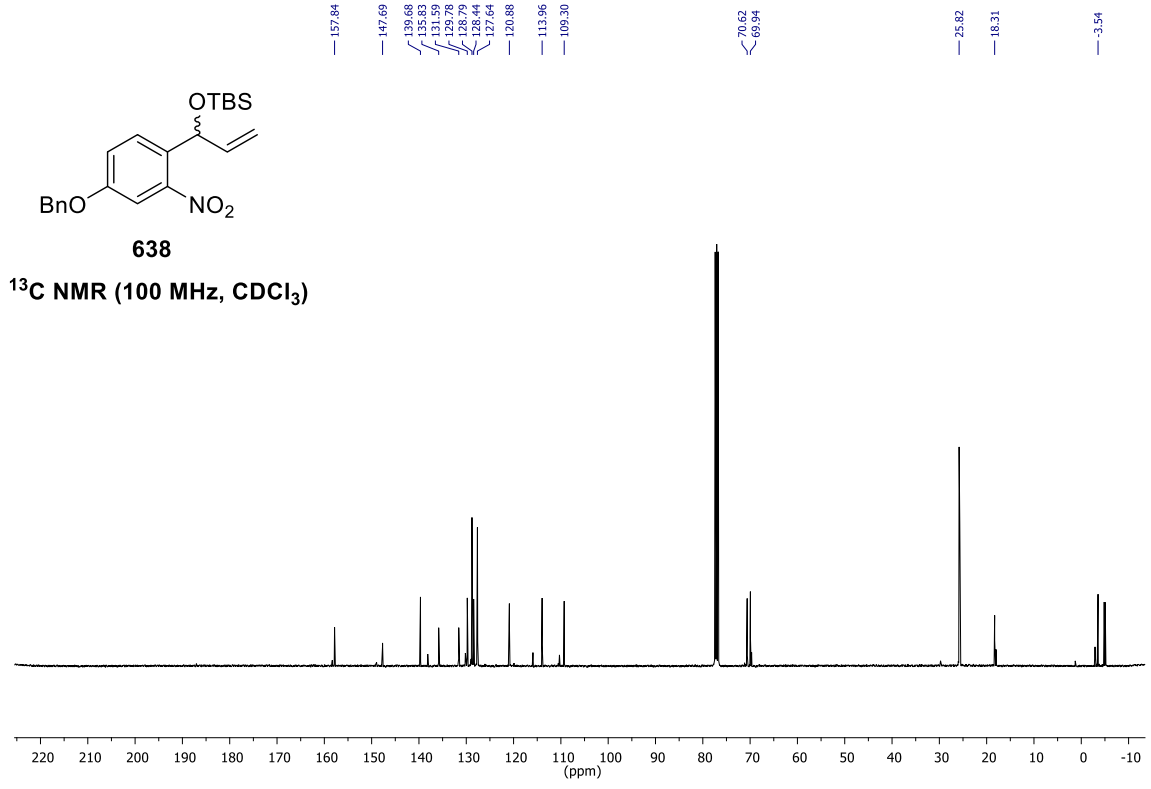


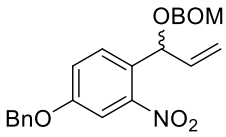
636

^{13}C NMR (100 MHz, $CDCl_3$)



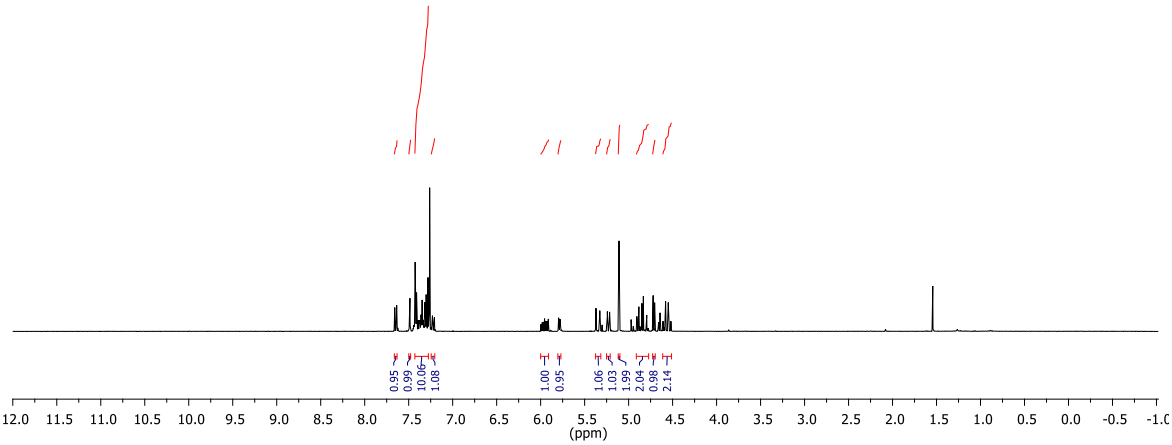


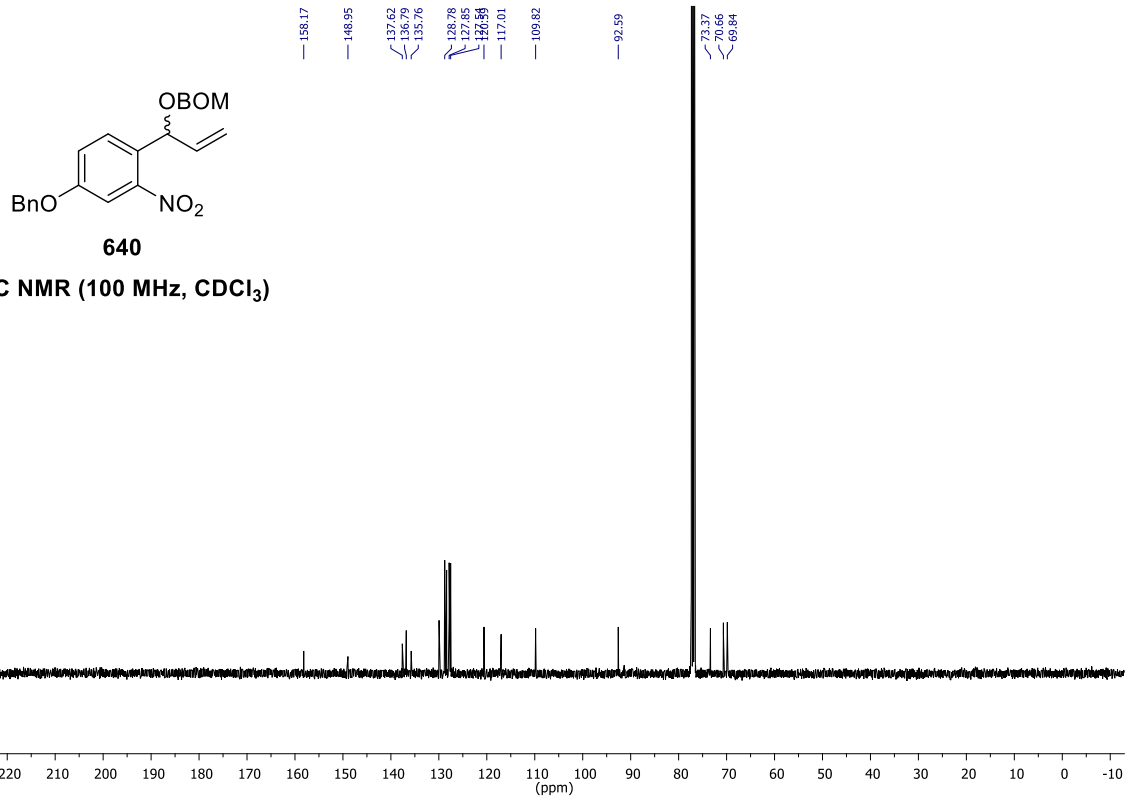




640

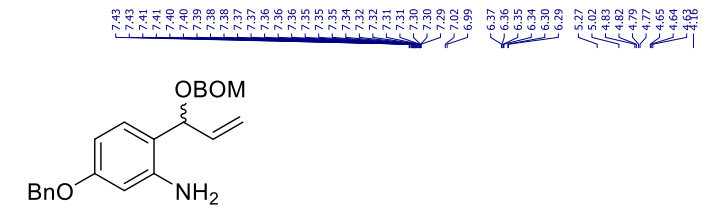
^{1}H NMR (400 MHz, $CDCl_3$)





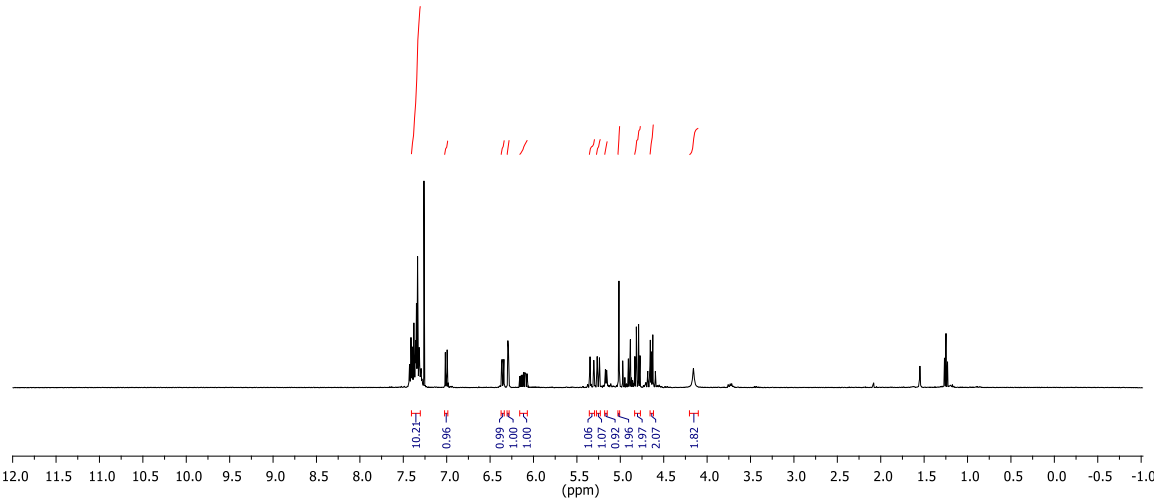
640

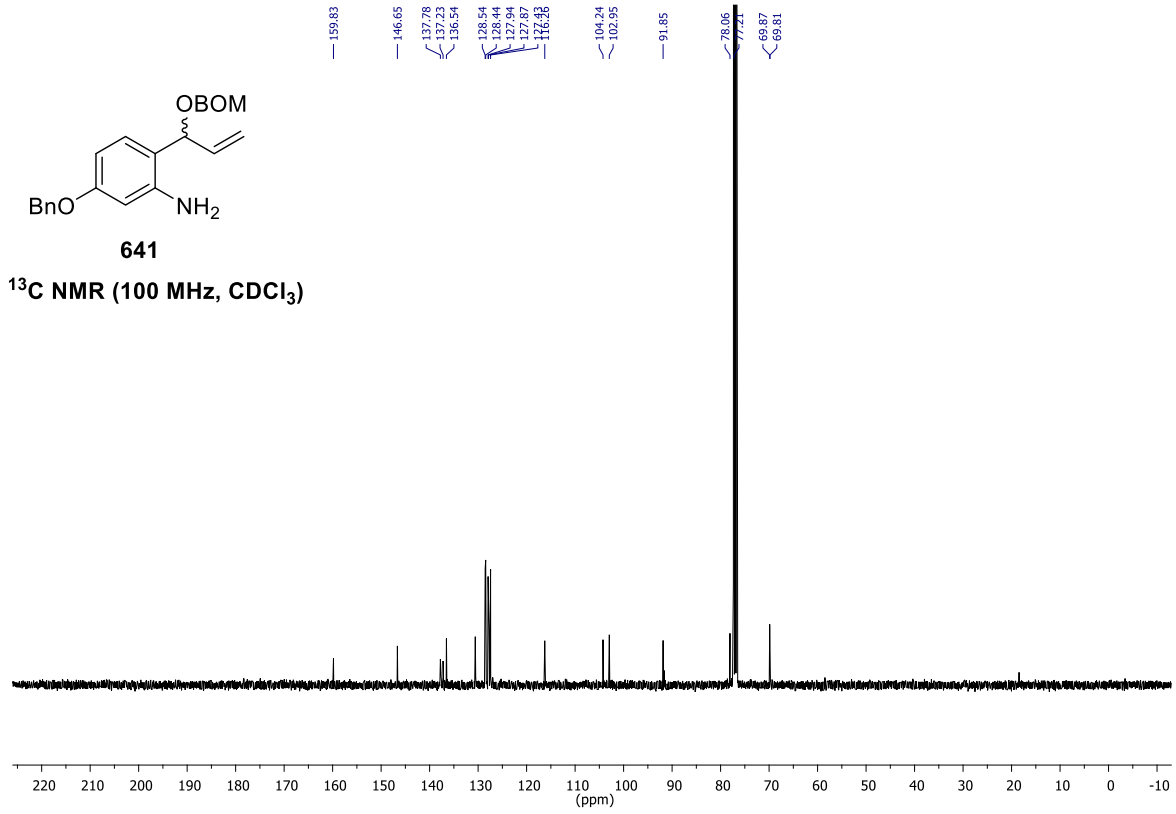
^{13}C NMR (100 MHz, $CDCl_3$)



641

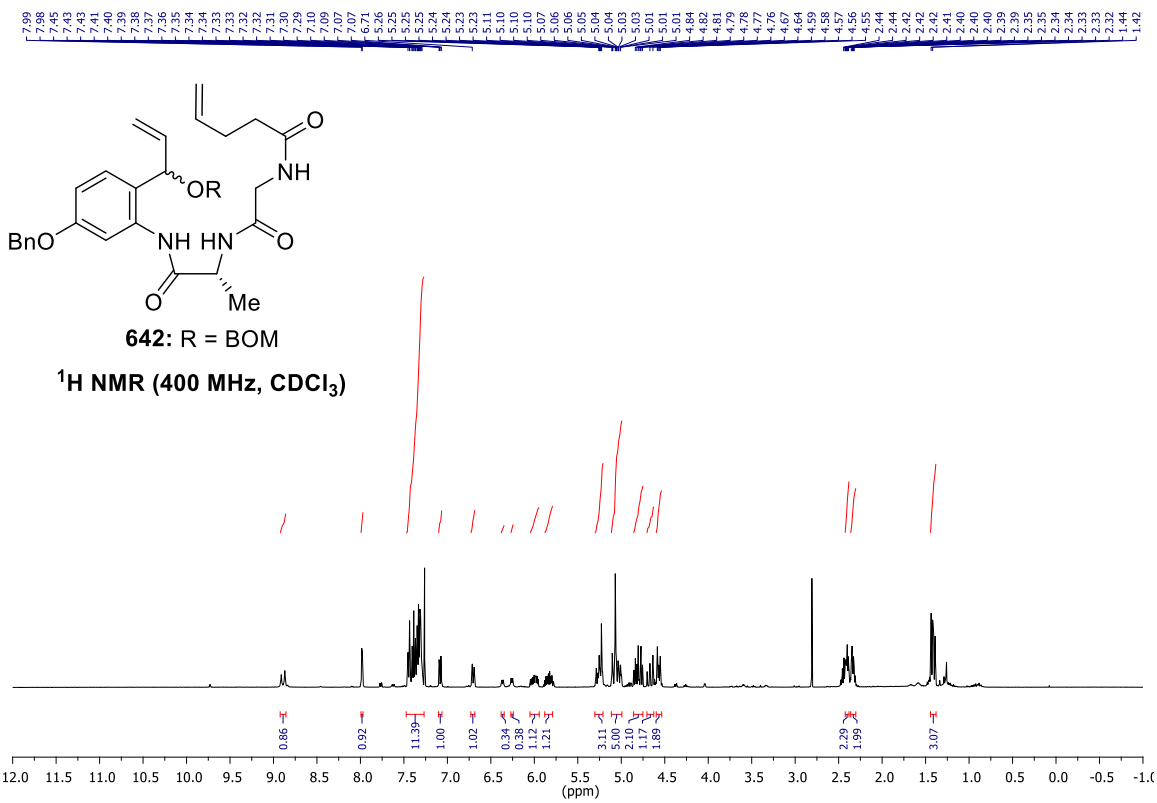
^{1}H NMR (400 MHz, $CDCl_3$)





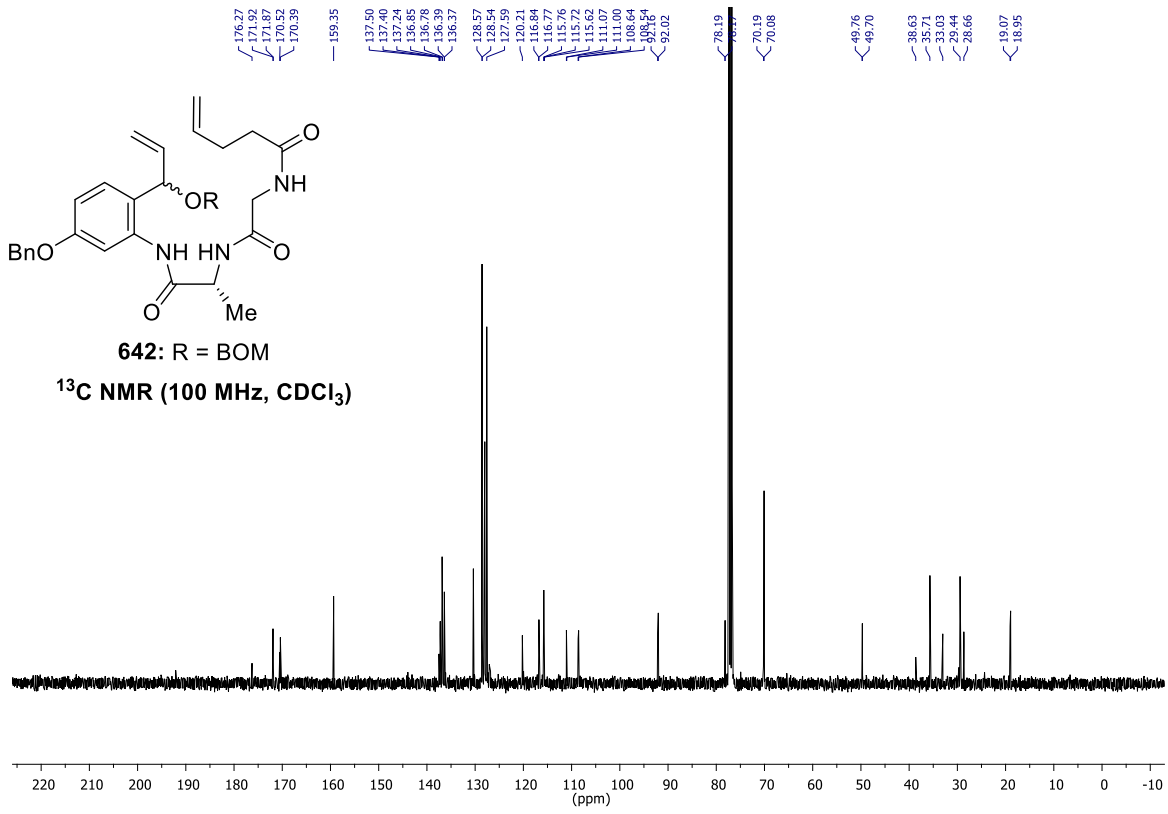
641

^{13}C NMR (100 MHz, $CDCl_3$)



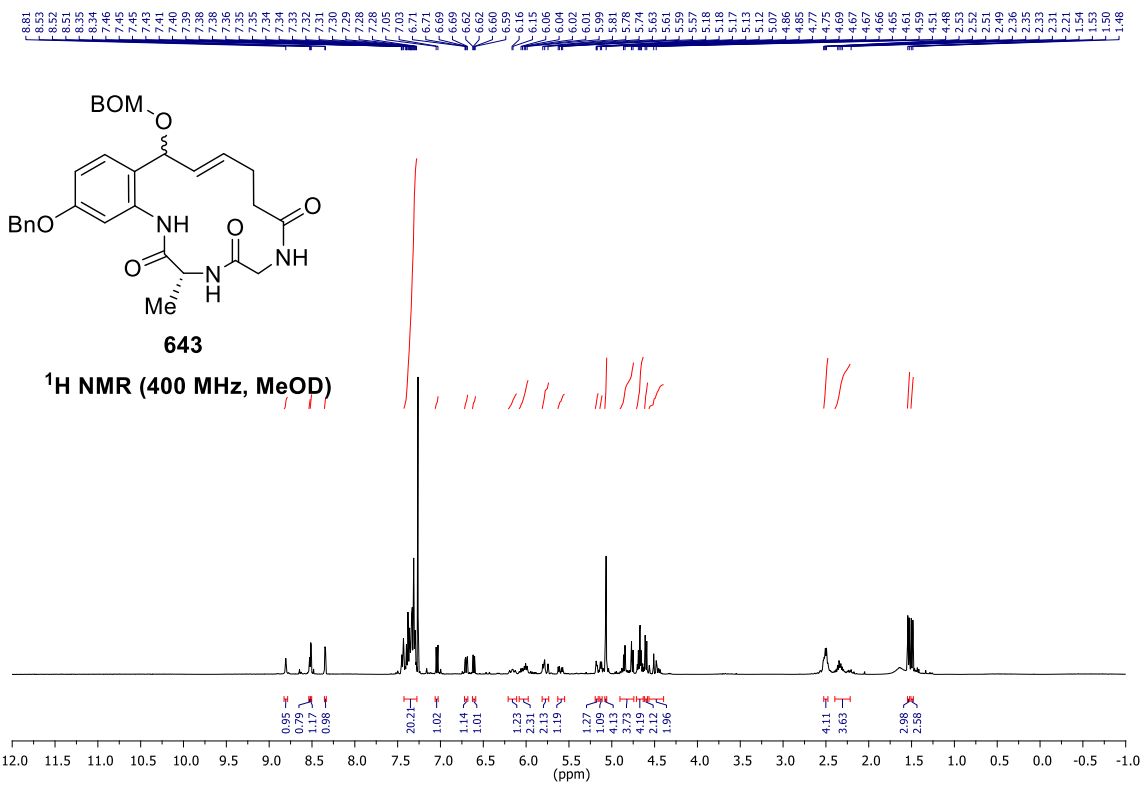
642: R = BOM

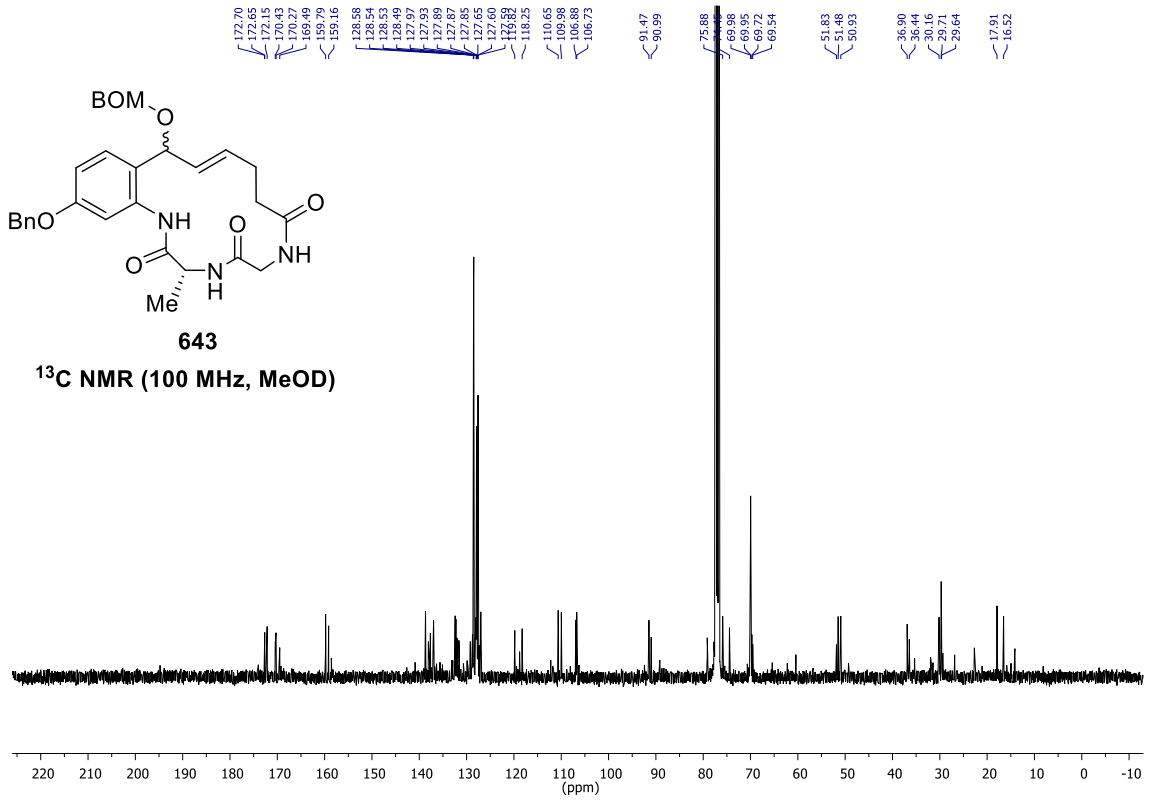
^{1}H NMR (400 MHz, $CDCl_3$)

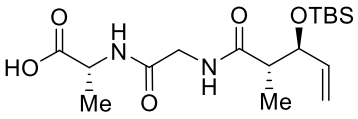


642: R = BOM

^{13}C NMR (100 MHz, $CDCl_3$)

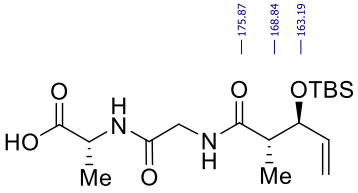






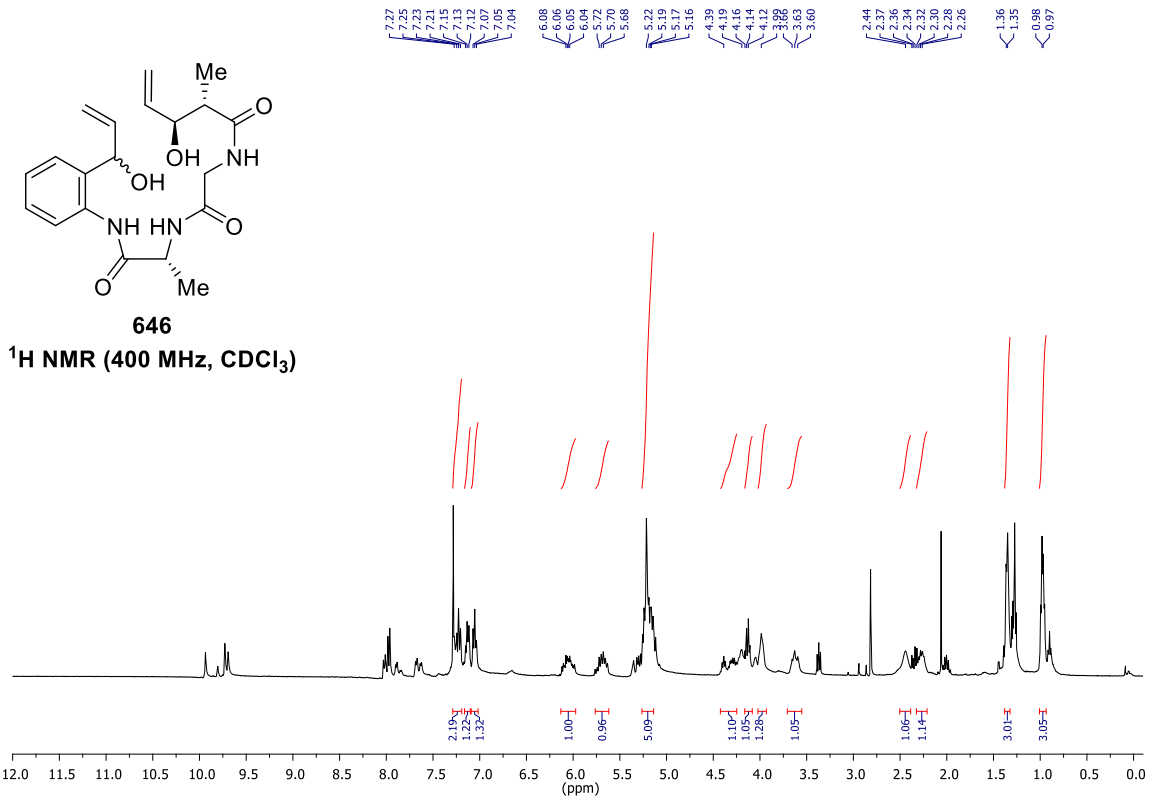
644

^{1}H NMR (400 MHz, $CDCl_3$)



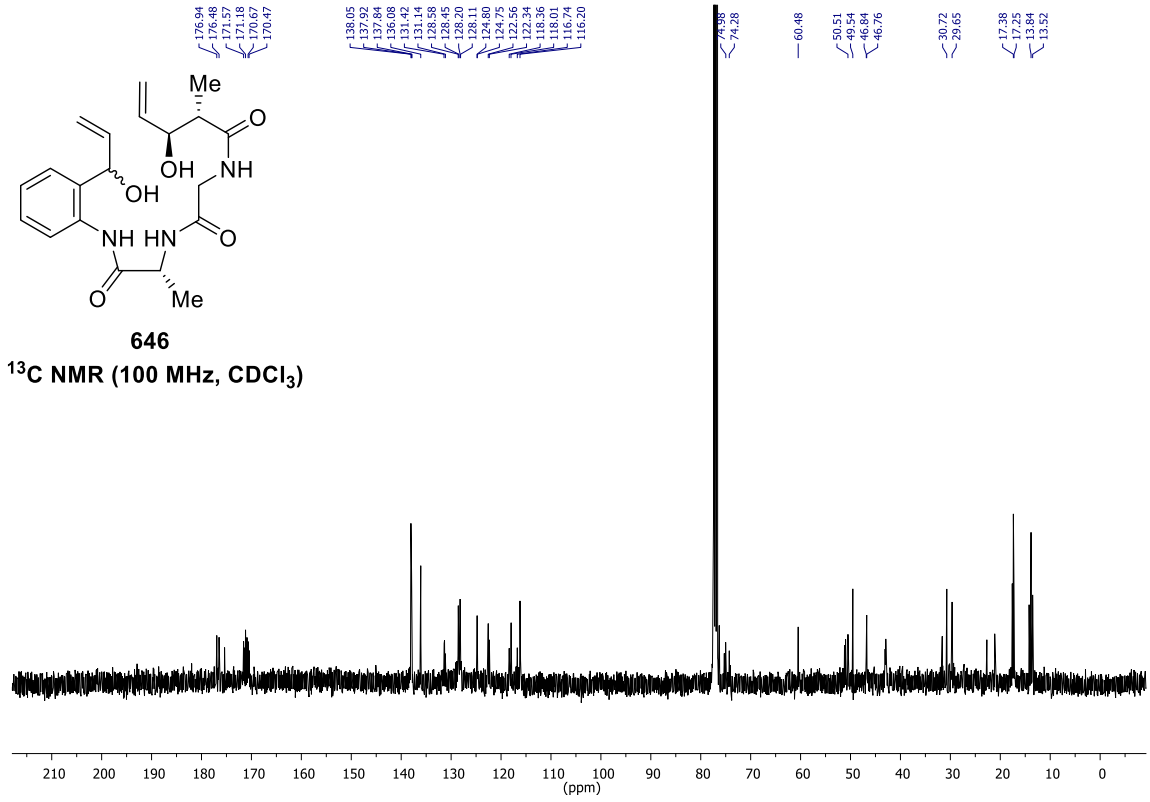
644

^{13}C NMR (100 MHz, $CDCl_3$)



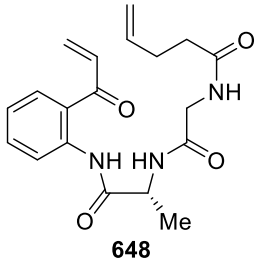
646

^{1}H NMR (400 MHz, $CDCl_3$)



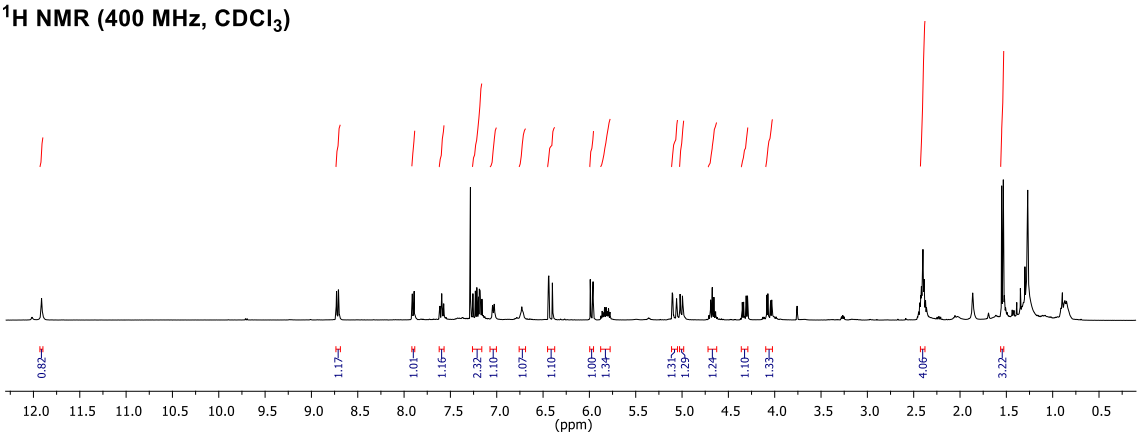
646

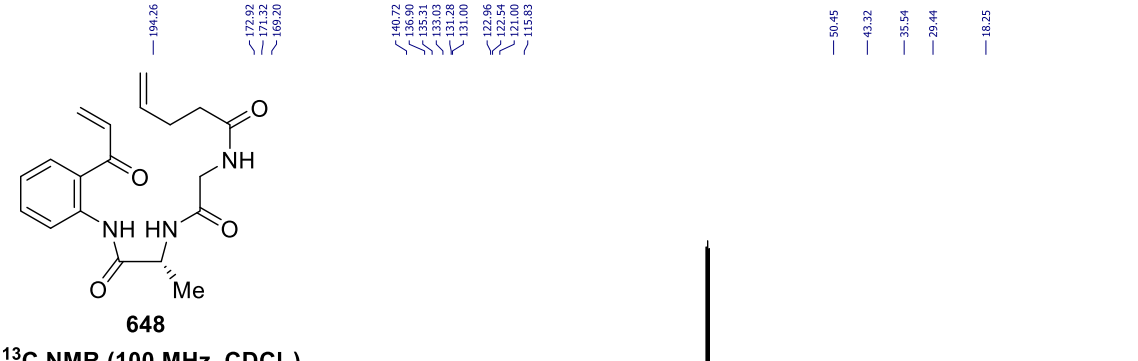
^{13}C NMR (100 MHz, $CDCl_3$)



648

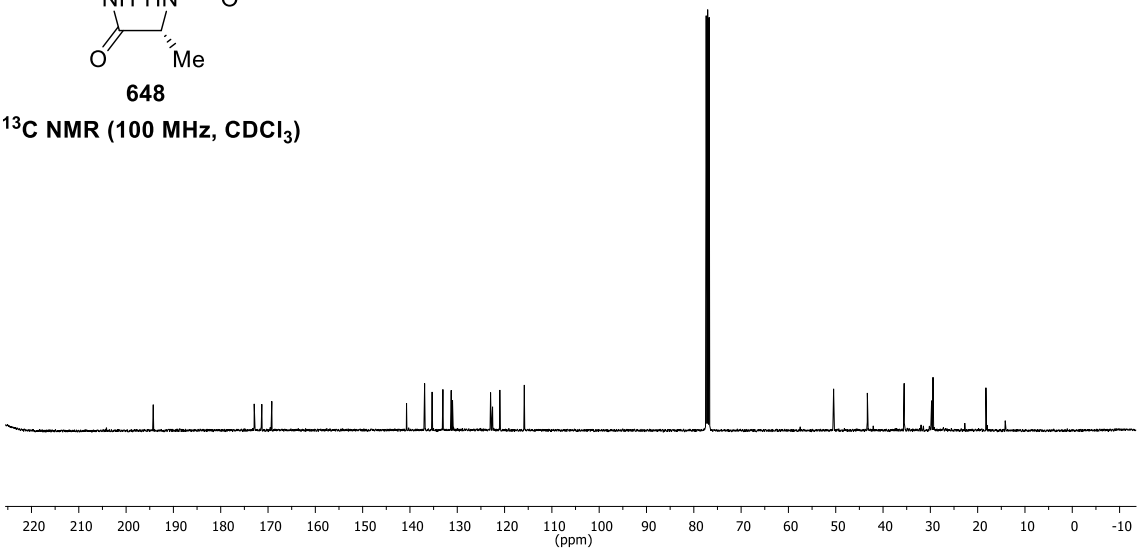
^{1}H NMR (400 MHz, $CDCl_3$)

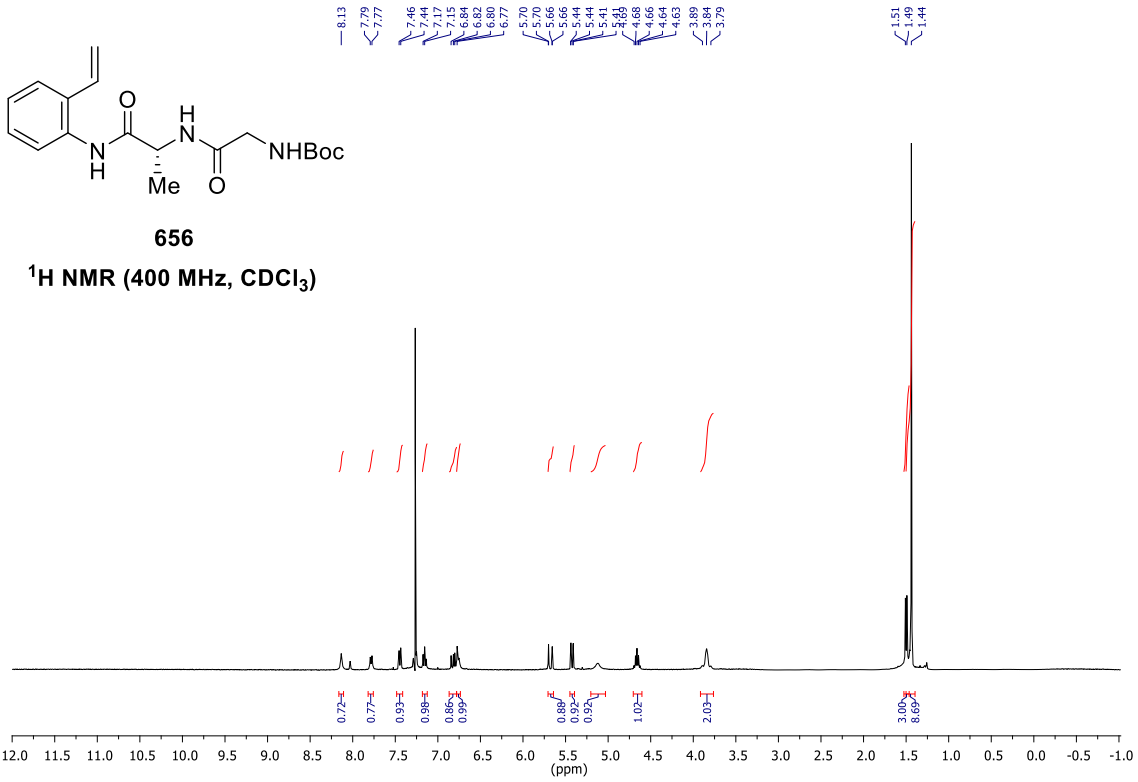


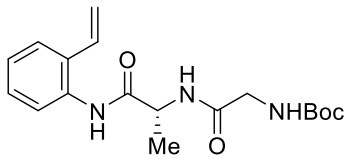


648

^{13}C NMR (100 MHz, $CDCl_3$)





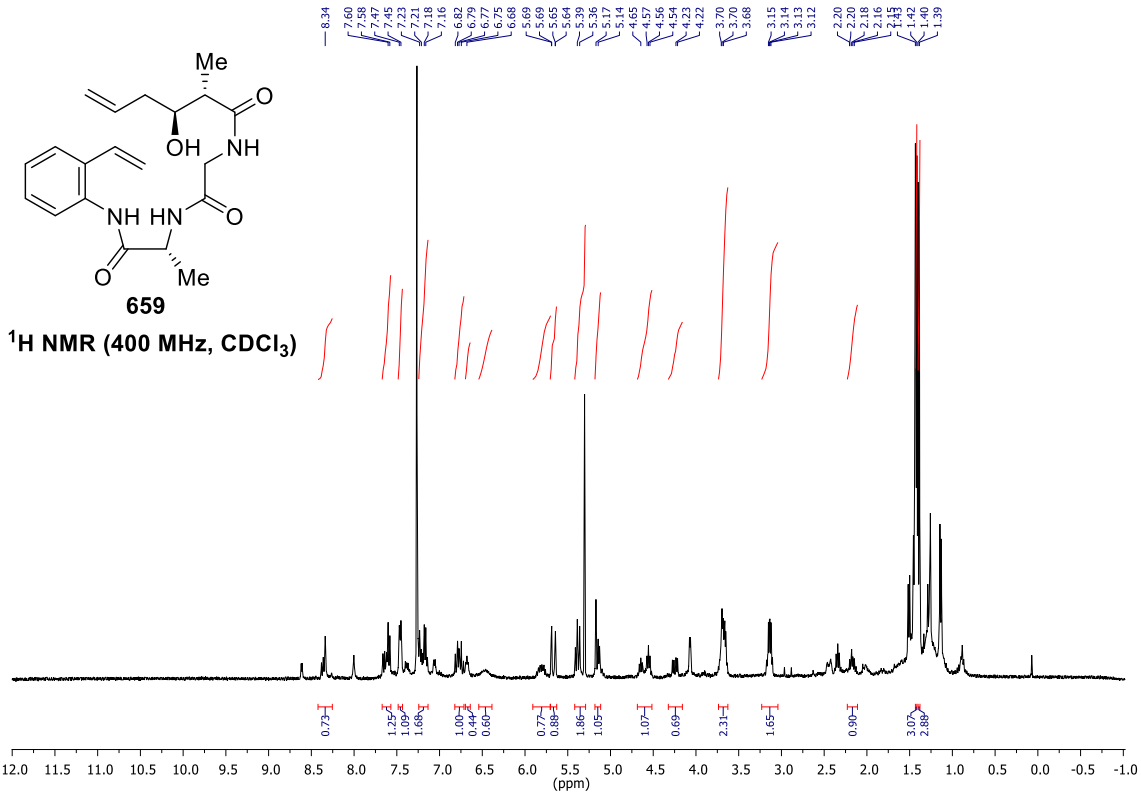


656

^{1}H NMR (400 MHz, $CDCl_3$)

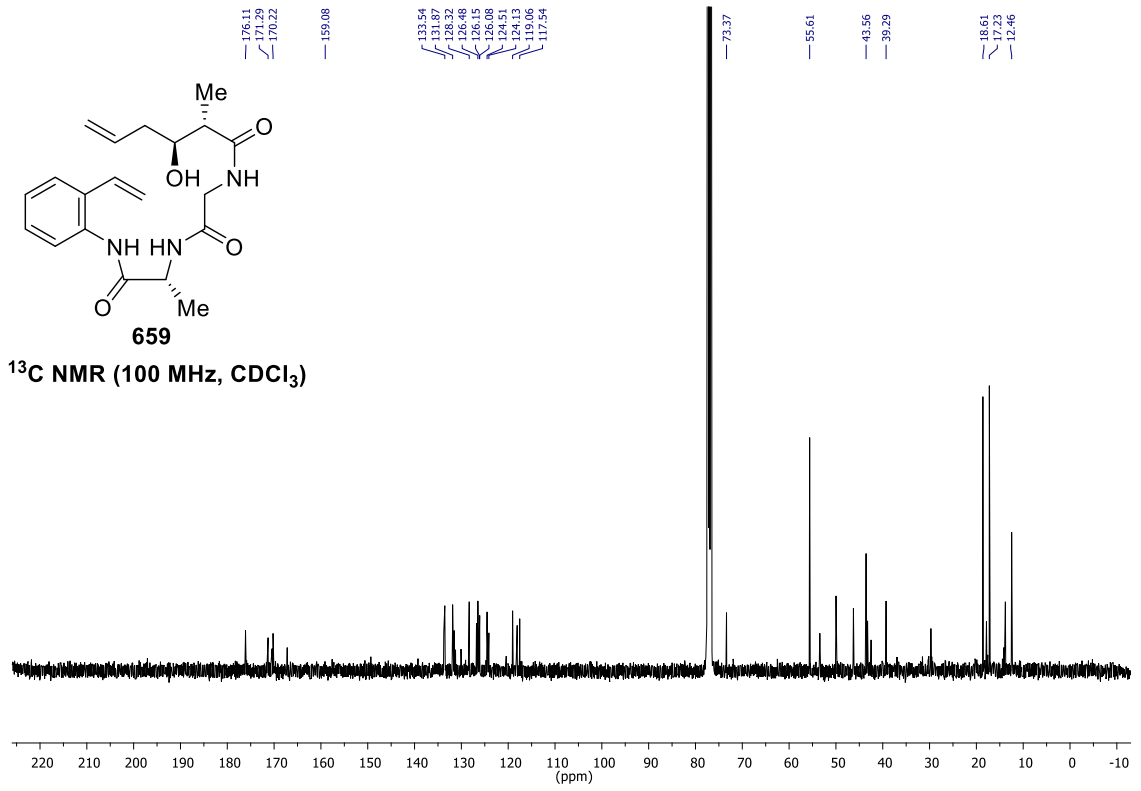
656

^{13}C NMR (100 MHz, $CDCl_3$)



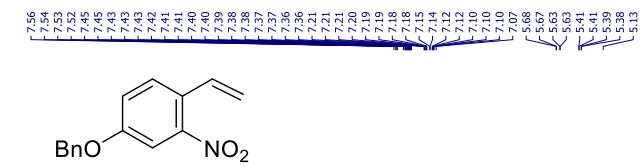
659

^{1}H NMR (400 MHz, $CDCl_3$)



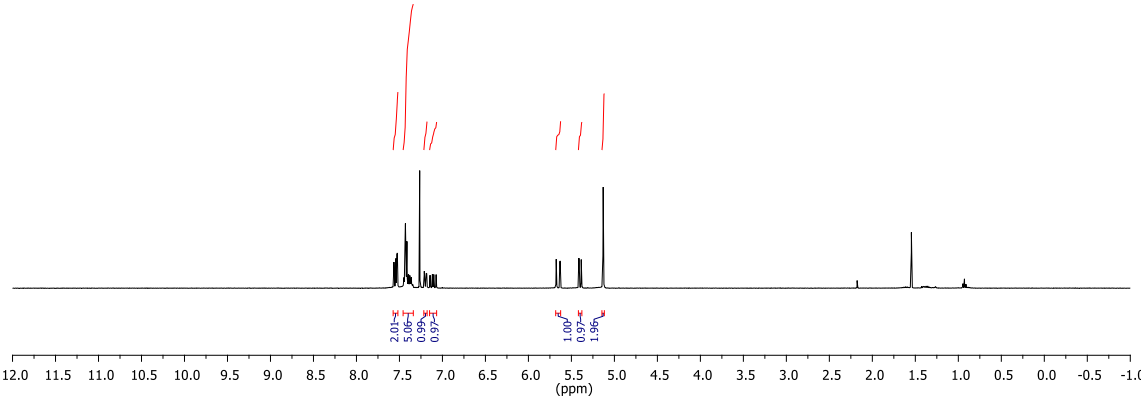
659

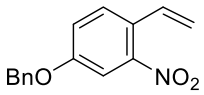
^{13}C NMR (100 MHz, $CDCl_3$)



661

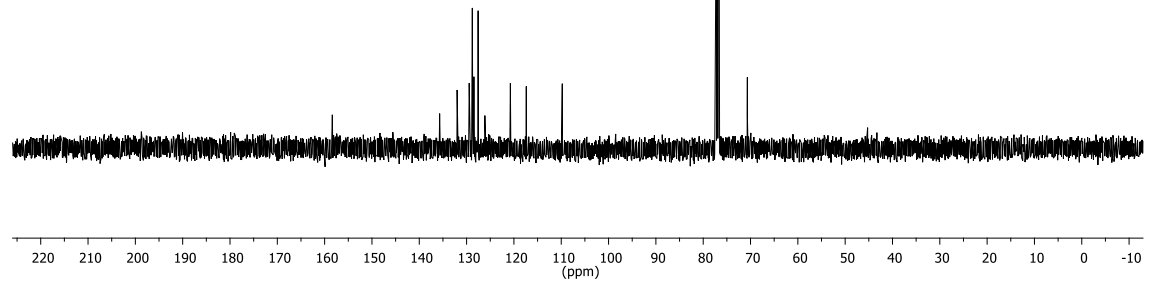
^{1}H NMR (400 MHz, $CDCl_3$)

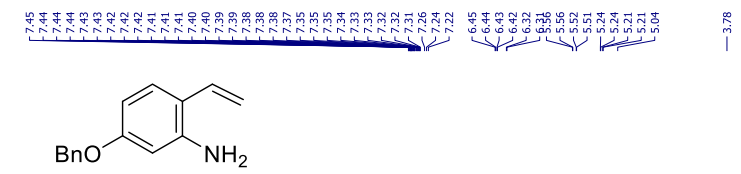




661

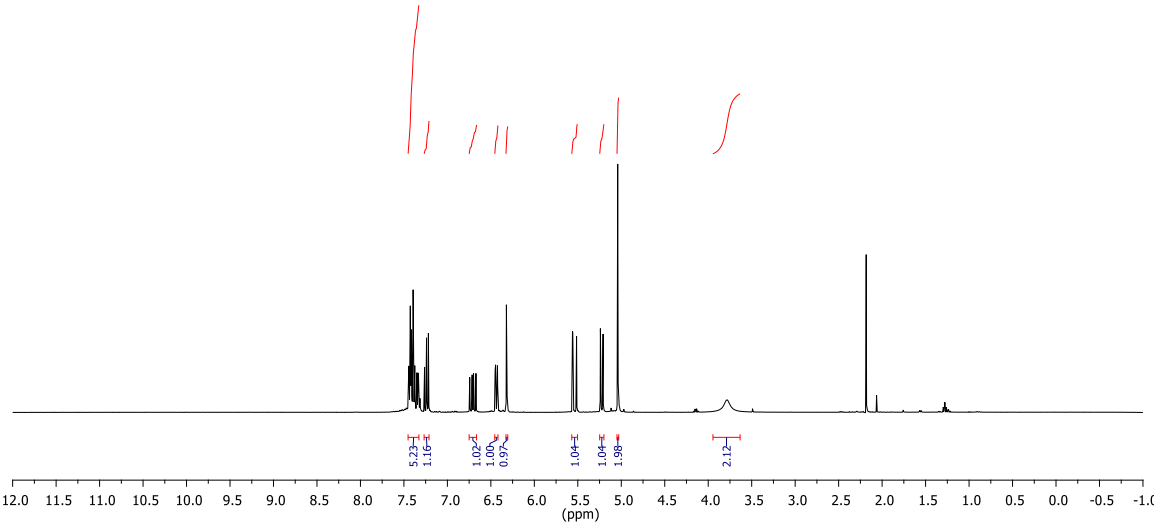
^{13}C NMR (100 MHz, $CDCl_3$)

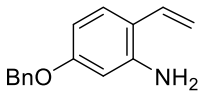




662

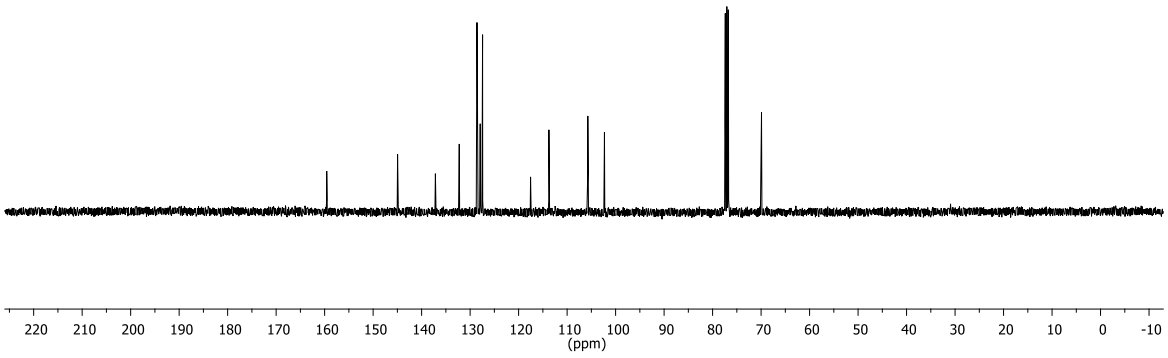
^{1}H NMR (400 MHz, $CDCl_3$)

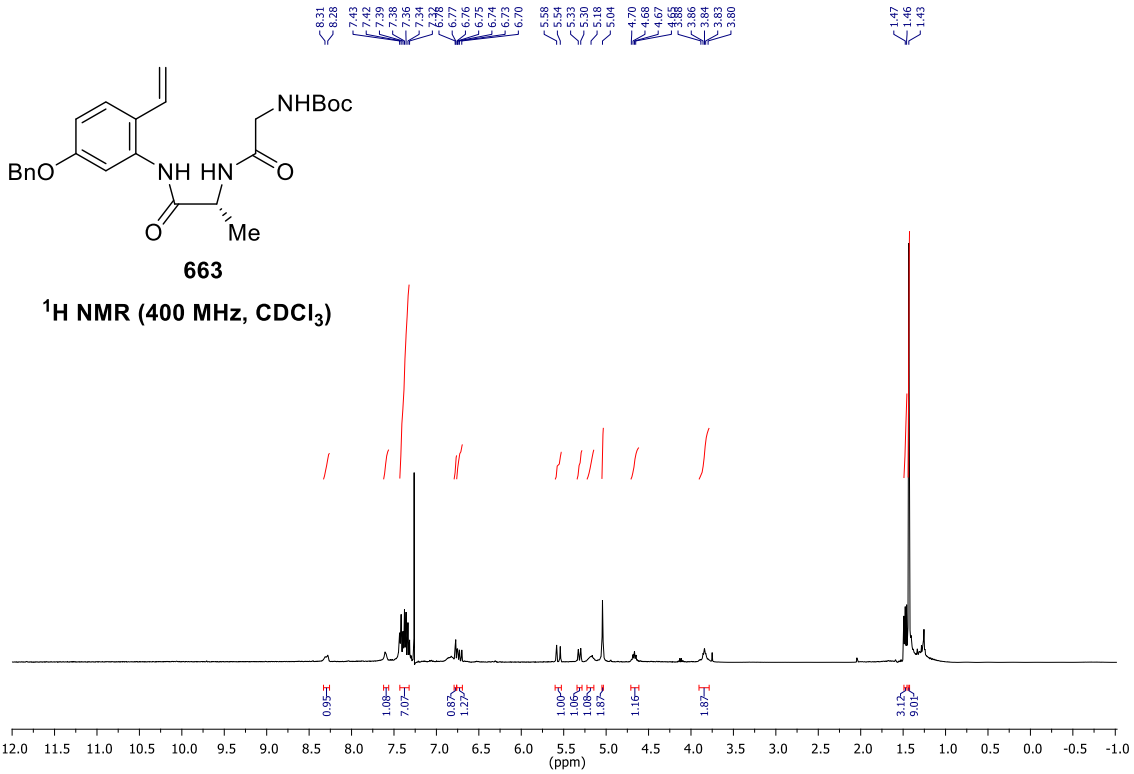


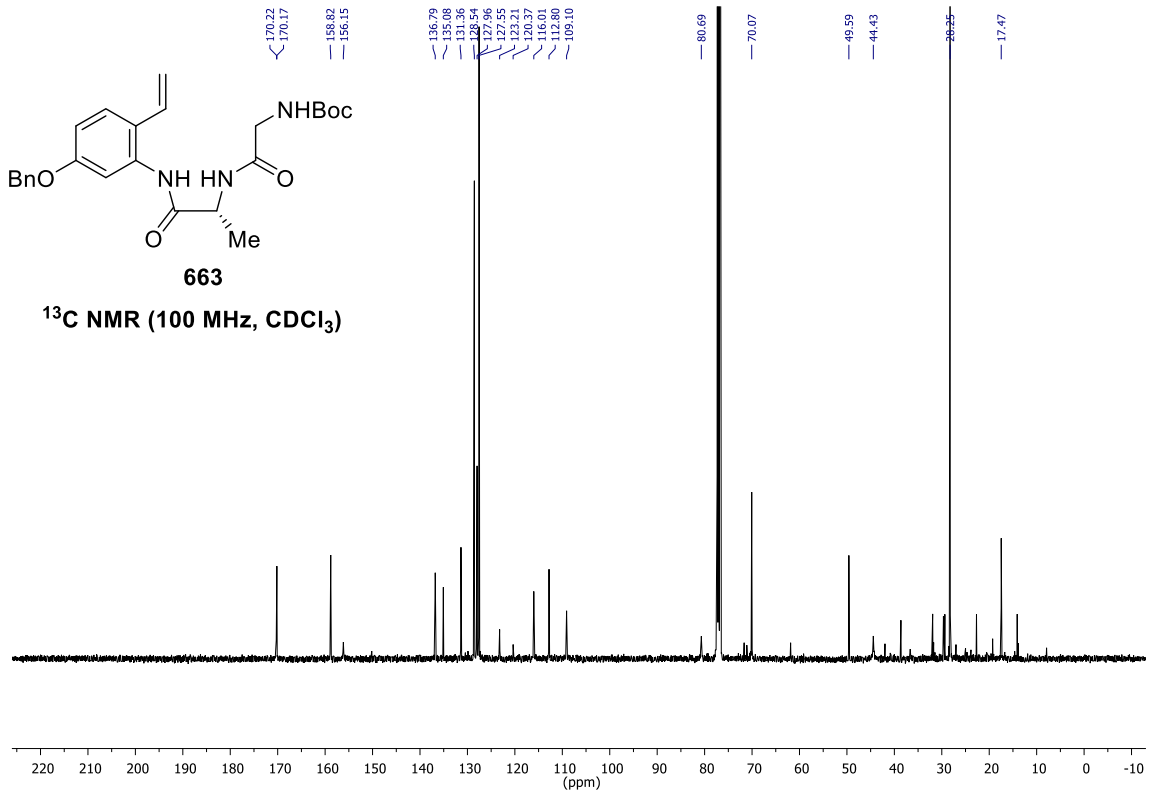


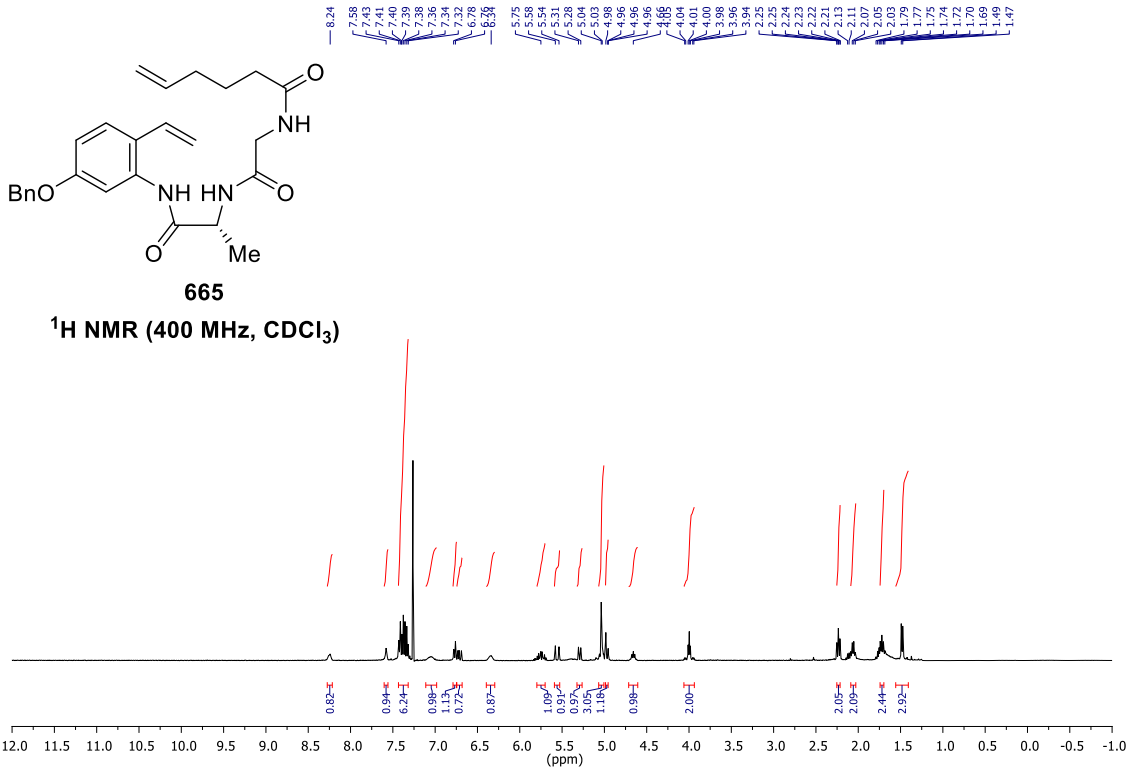
662

^{13}C NMR (100 MHz, $CDCl_3$)



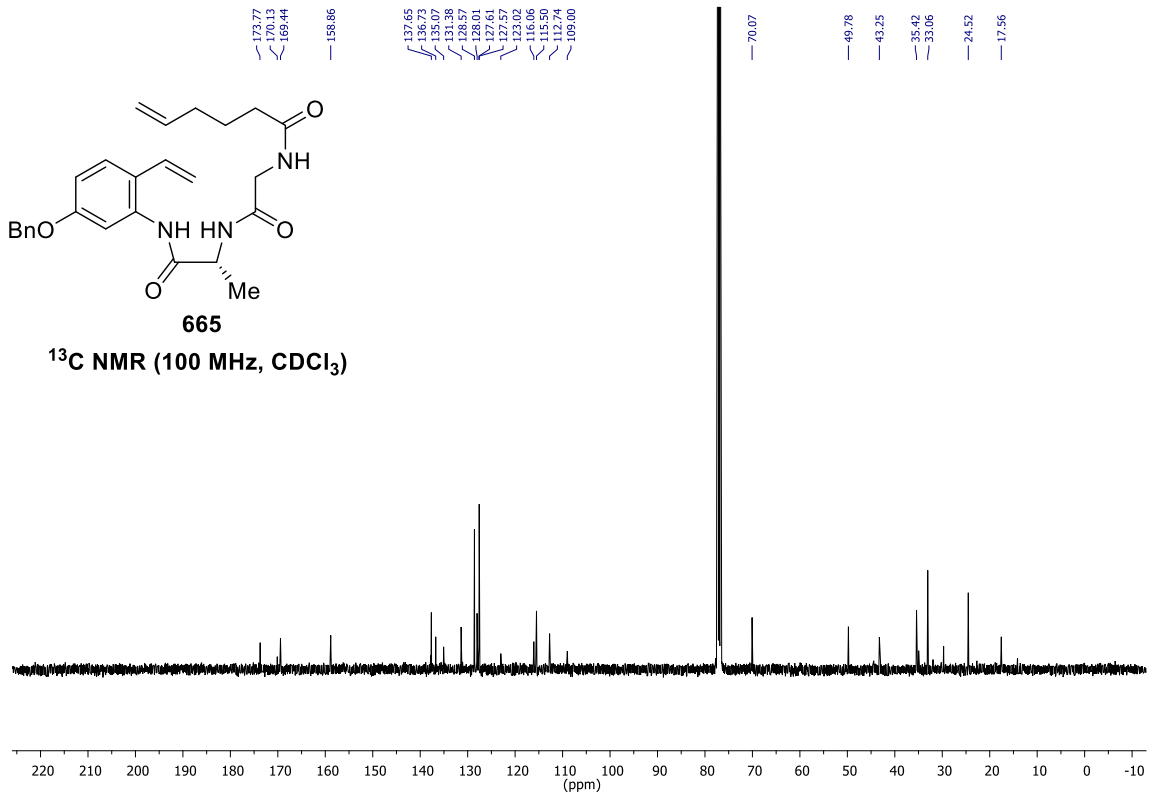






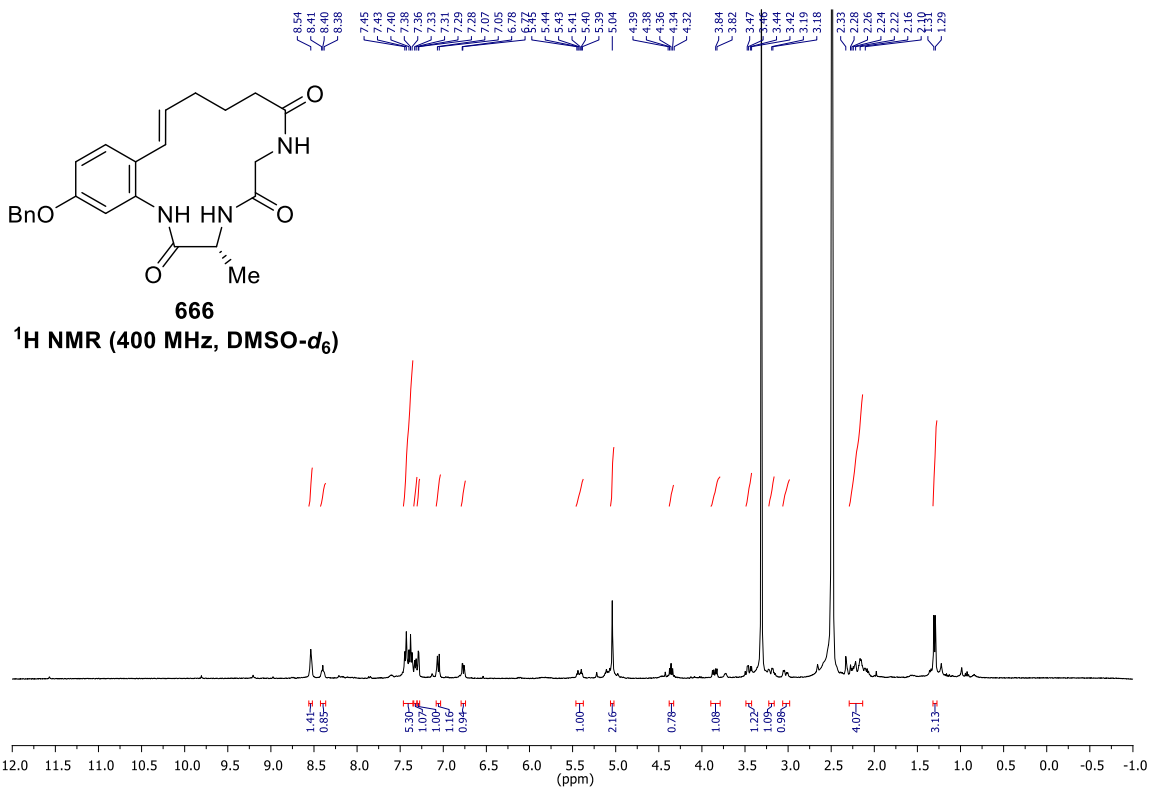
665

^{1}H NMR (400 MHz, $CDCl_3$)



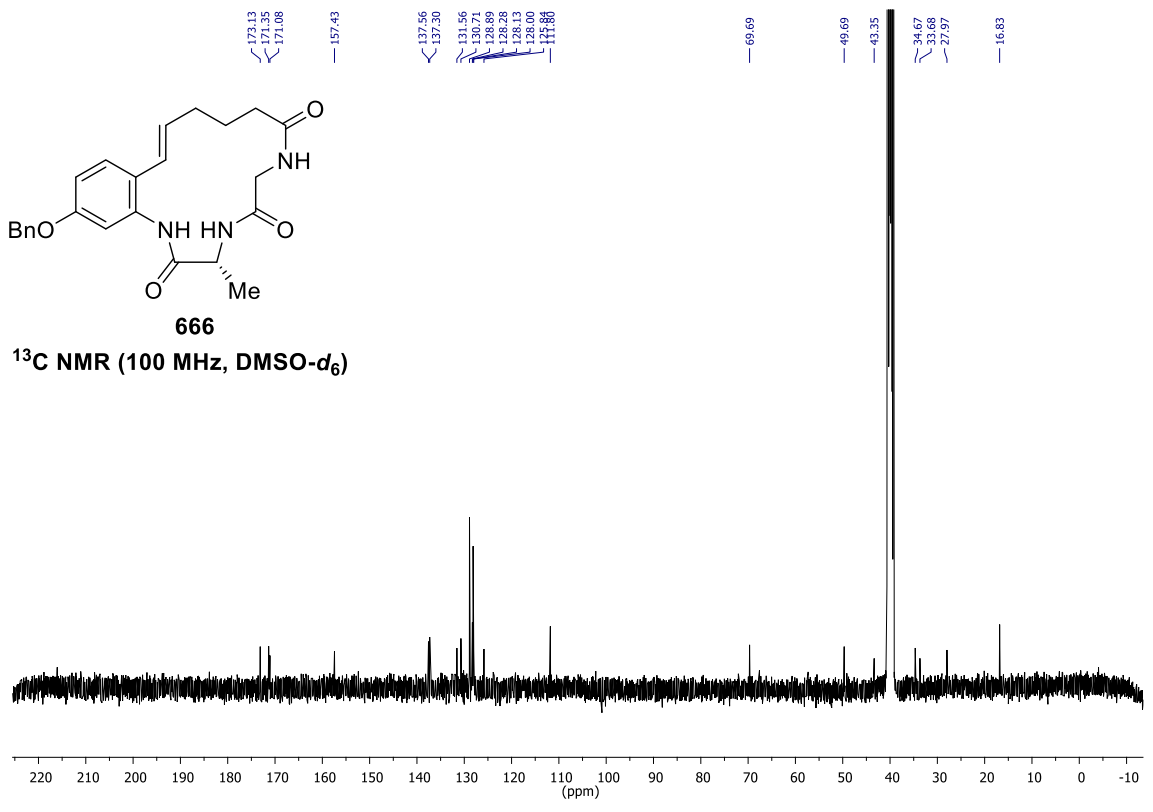
665

^{13}C NMR (100 MHz, $CDCl_3$)



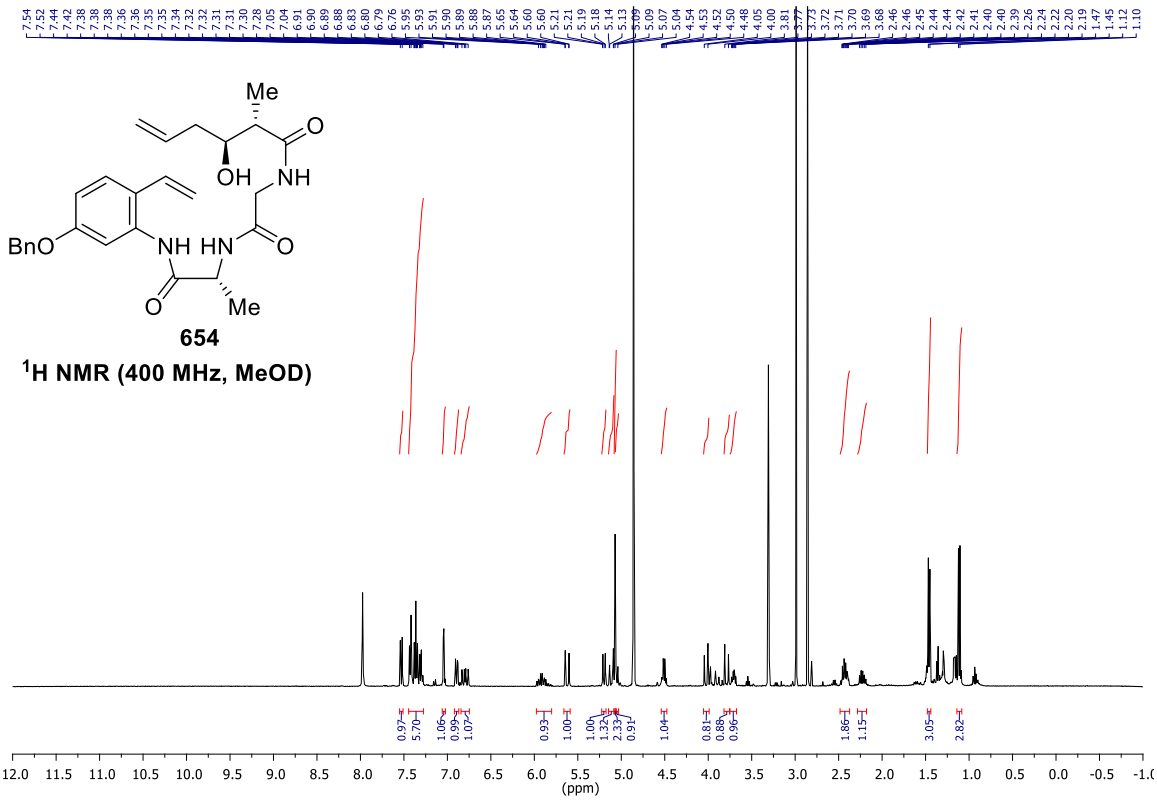
666

^{1}H NMR (400 MHz, DMSO-d_6)



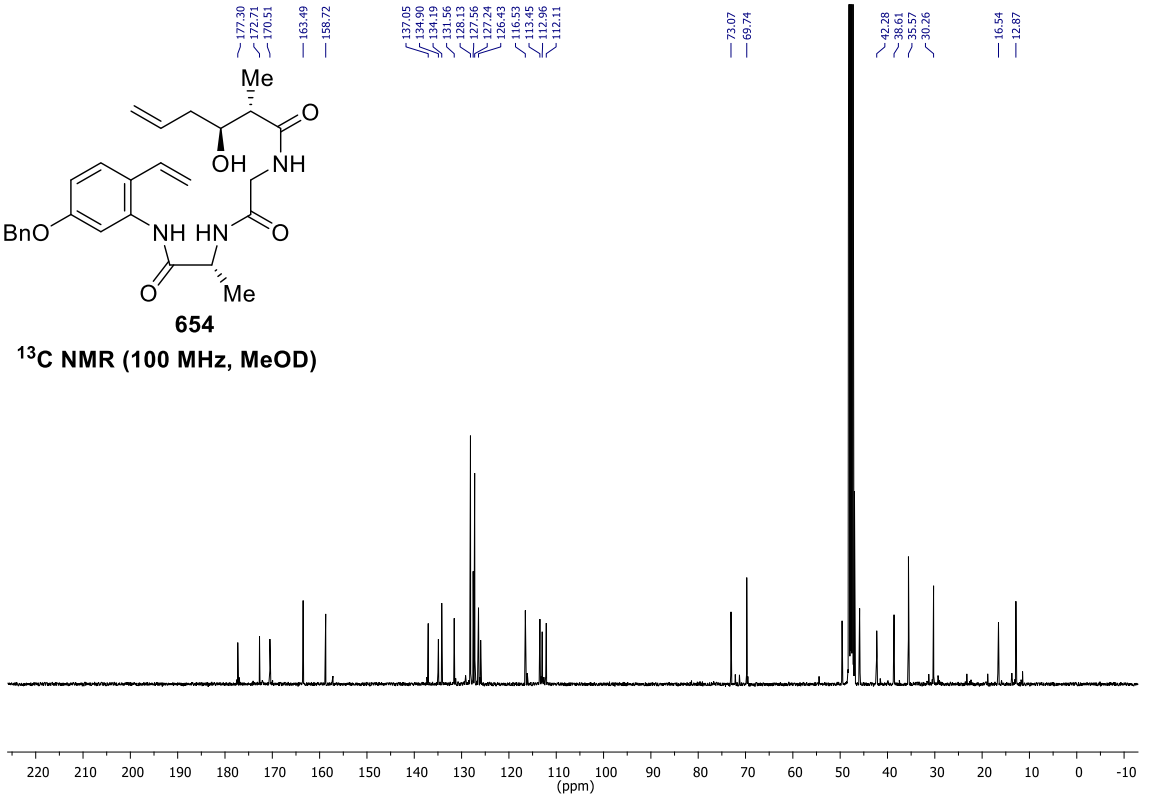
666

^{13}C NMR (100 MHz, DMSO-d_6)



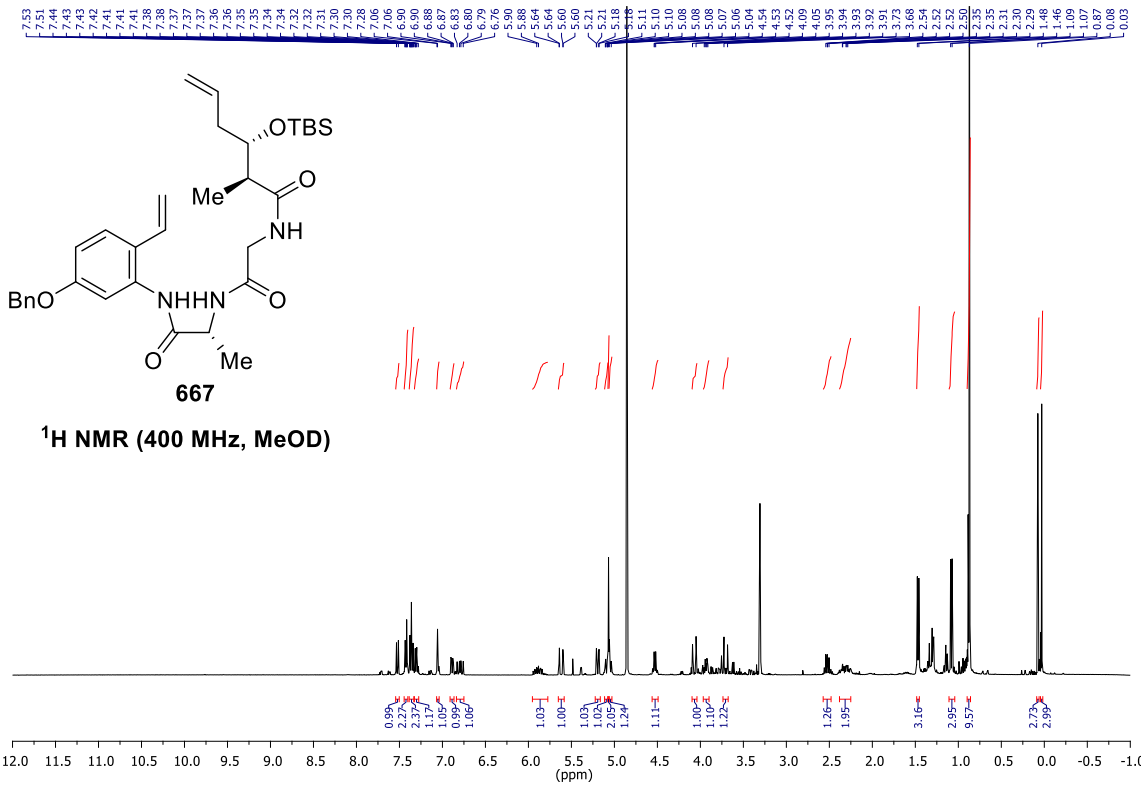
654

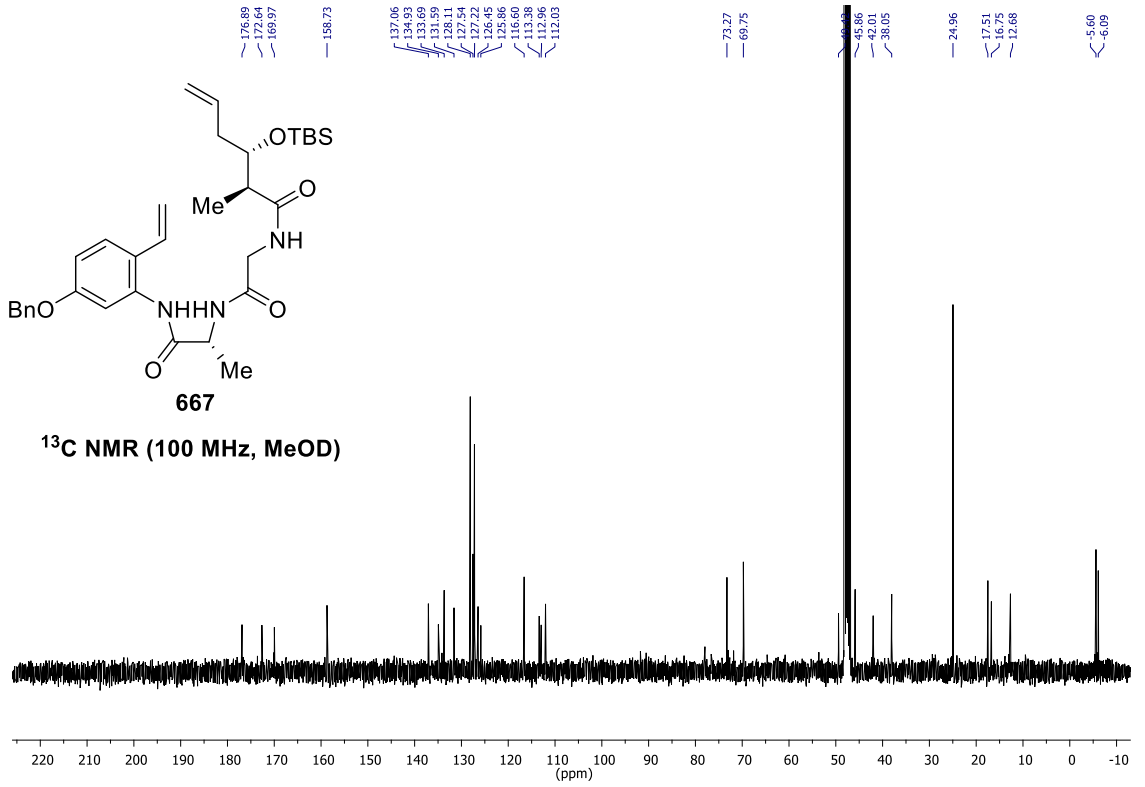
^{1}H NMR (400 MHz, MeOD)

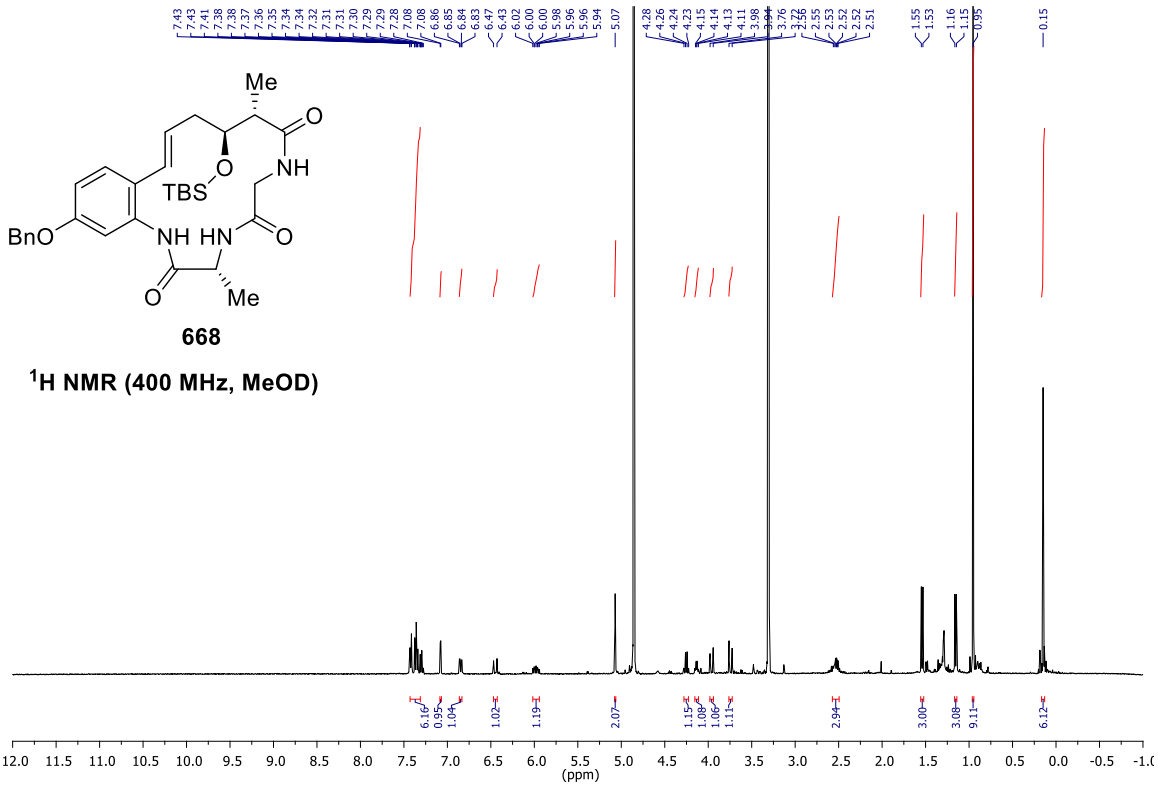


654

^{13}C NMR (100 MHz, MeOD)

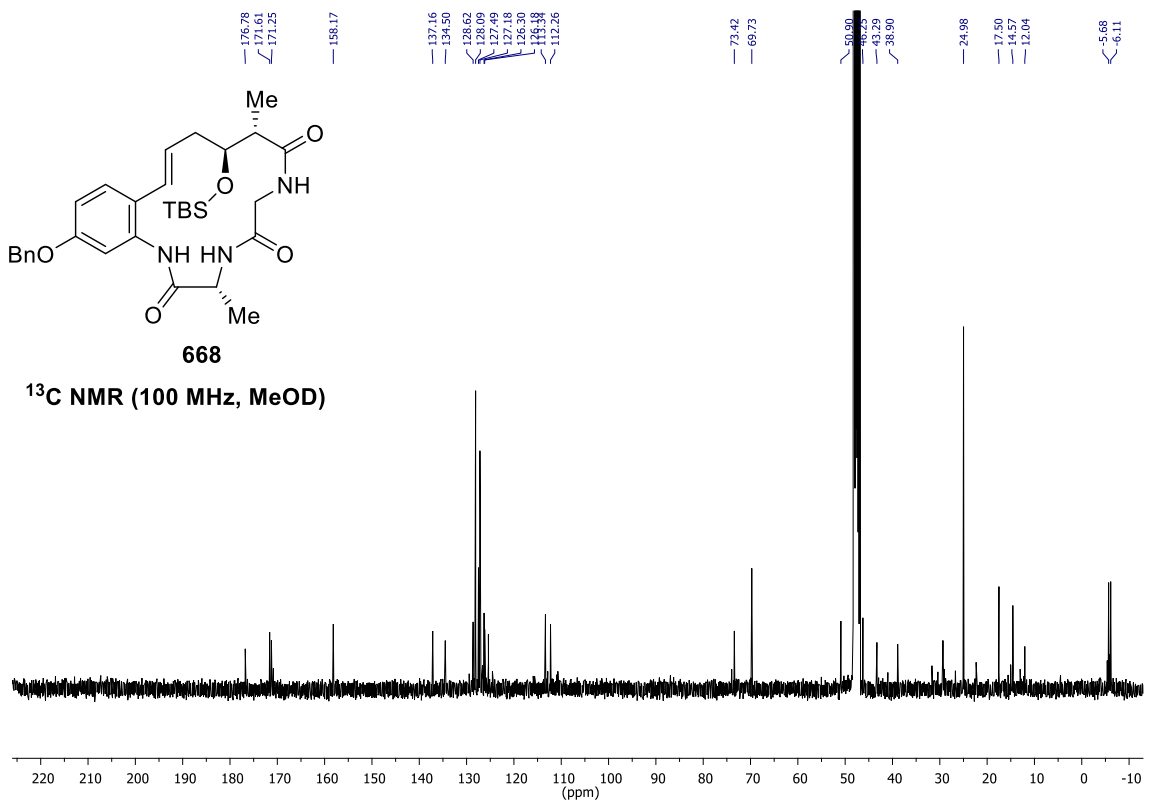






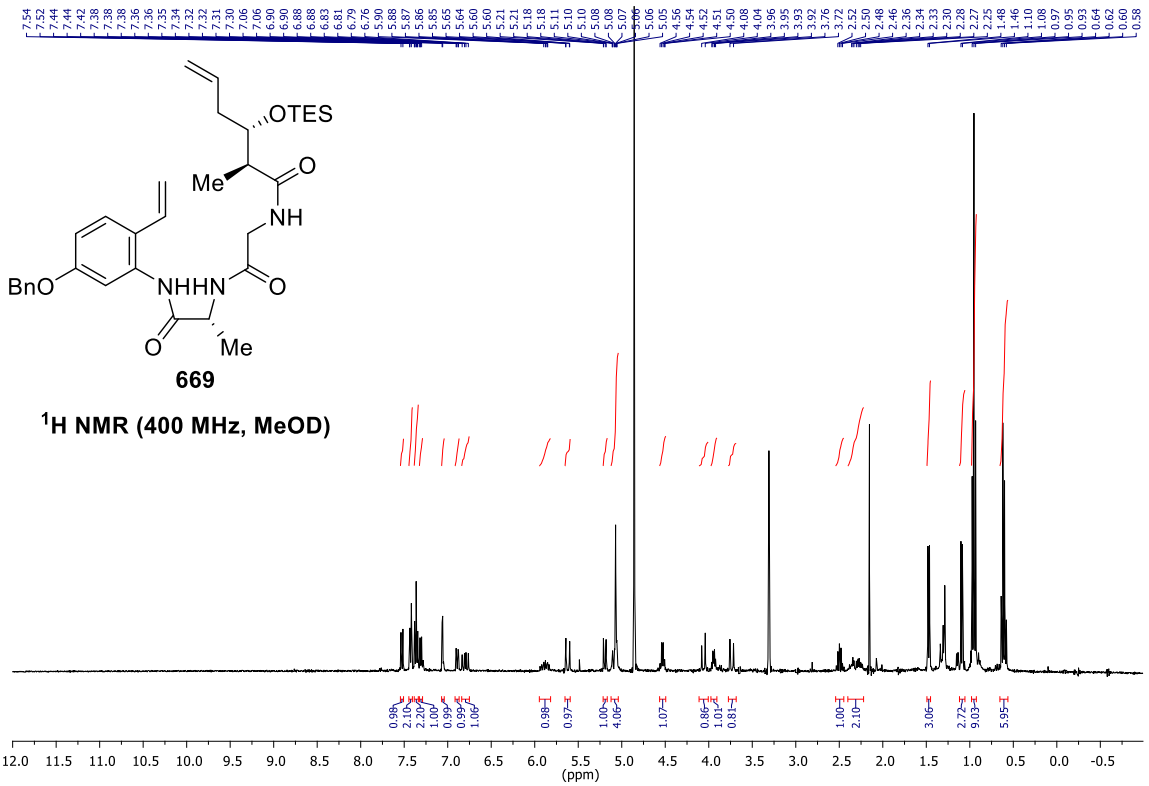
668

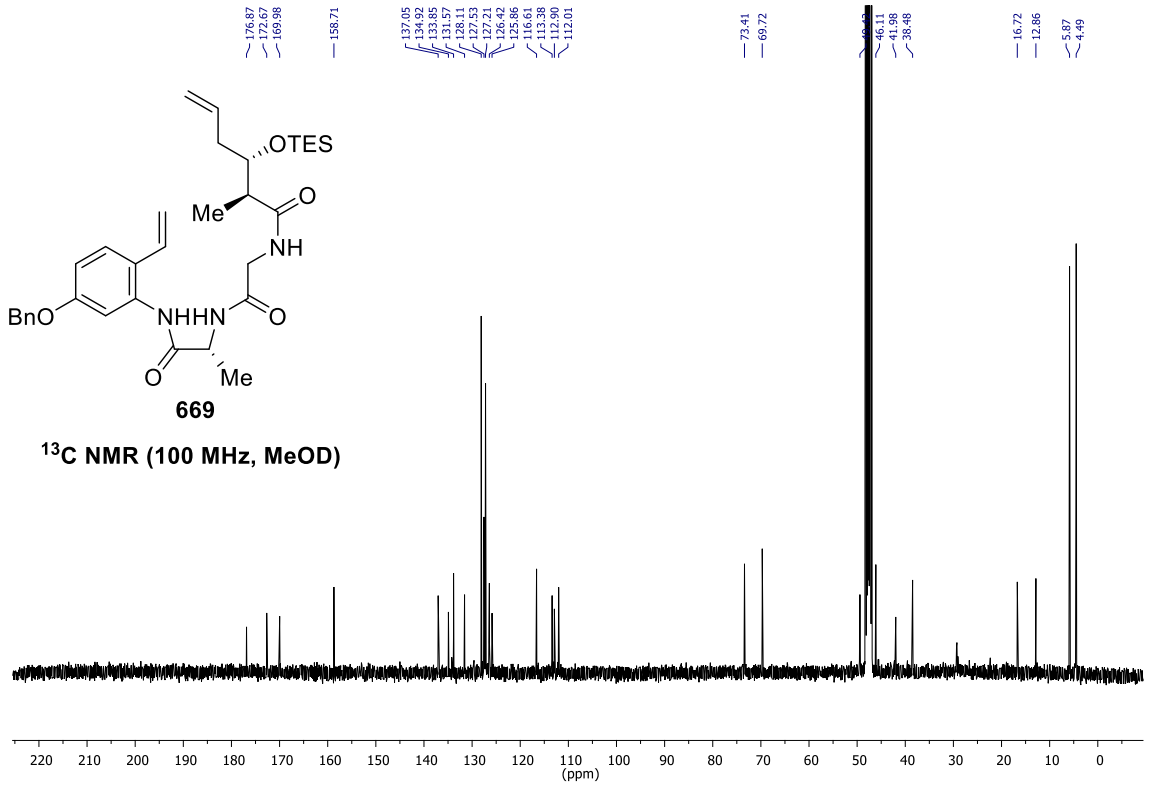
^{1}H NMR (400 MHz, MeOD)

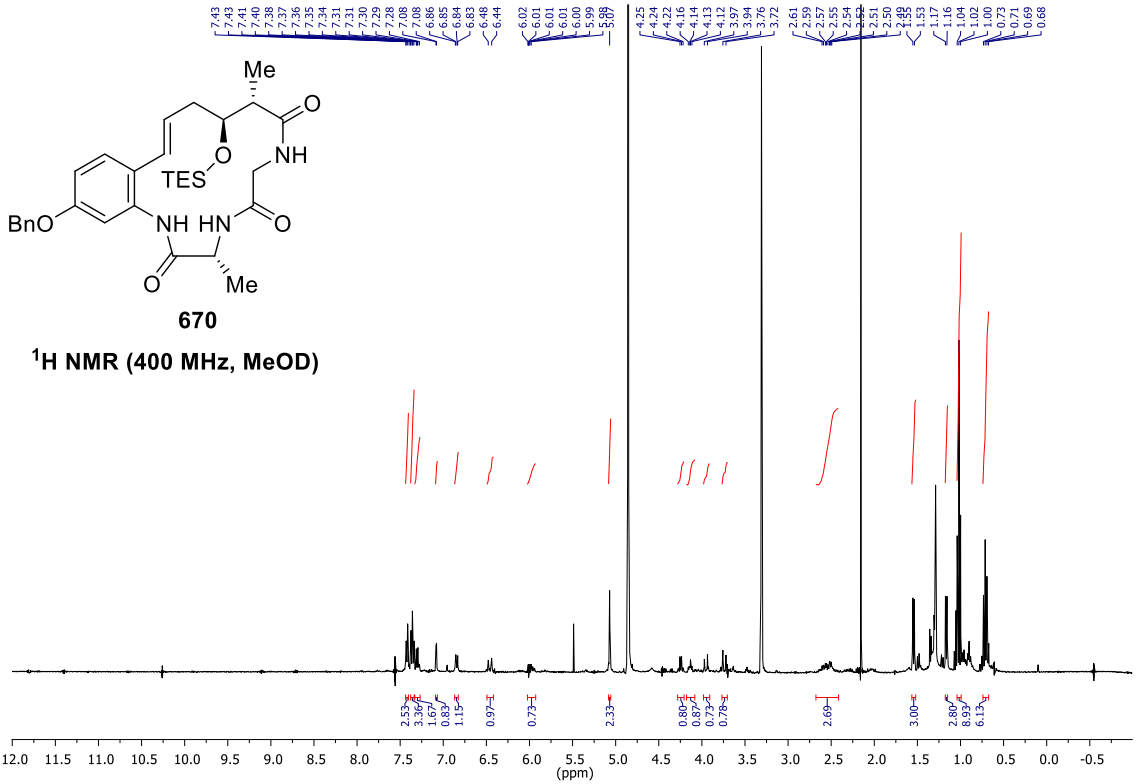


668

^{13}C NMR (100 MHz, MeOD)

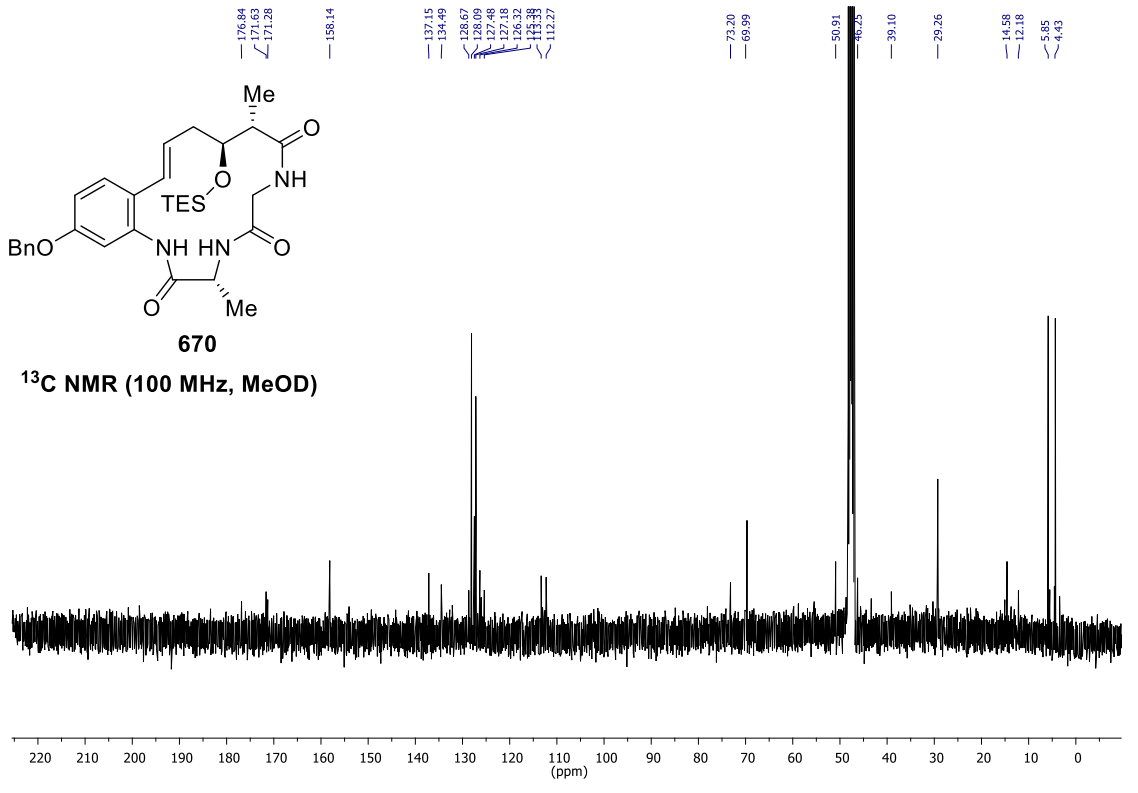






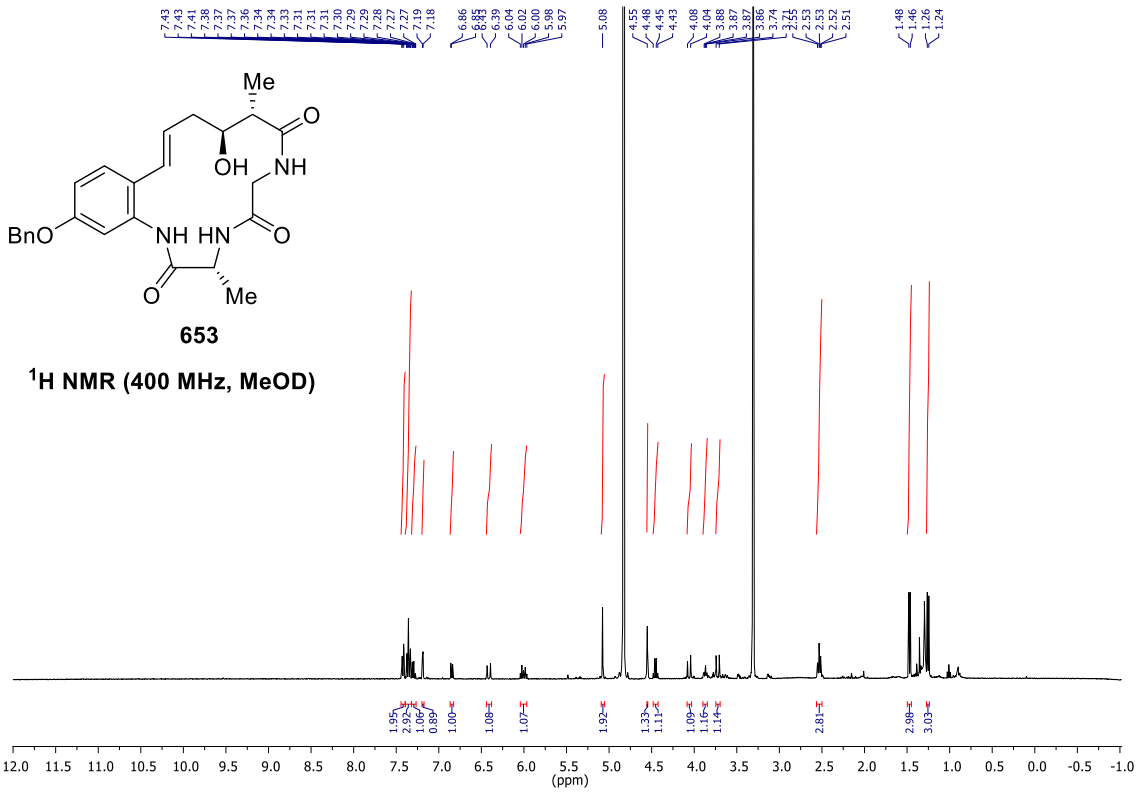
670

^{1}H NMR (400 MHz, MeOD)



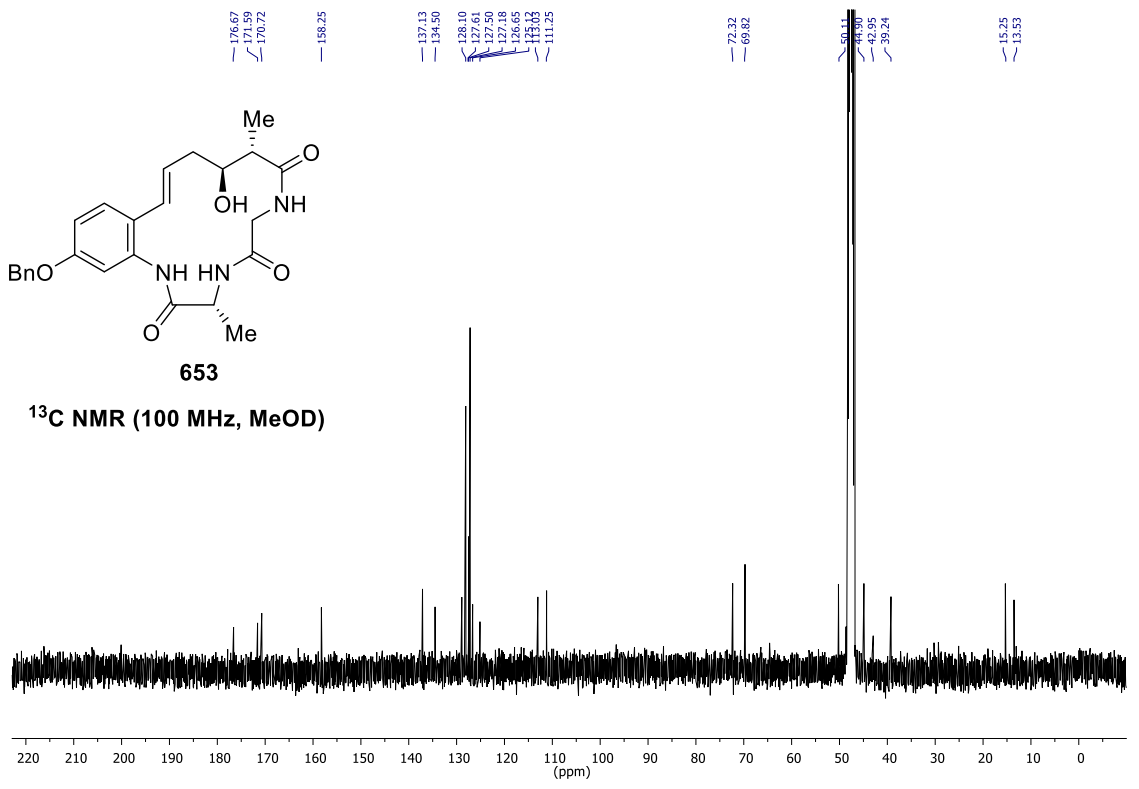
670

^{13}C NMR (100 MHz, MeOD)



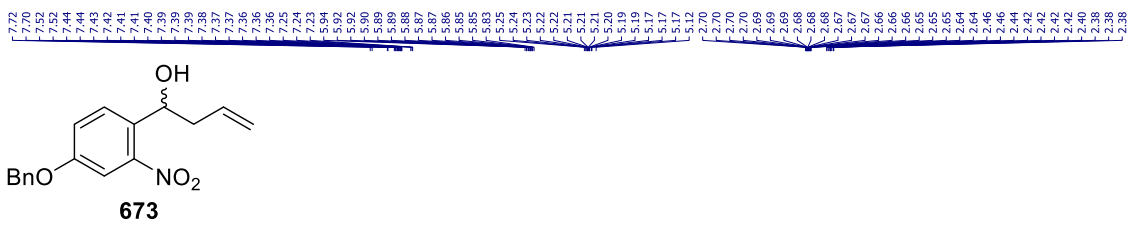
653

^{1}H NMR (400 MHz, MeOD)



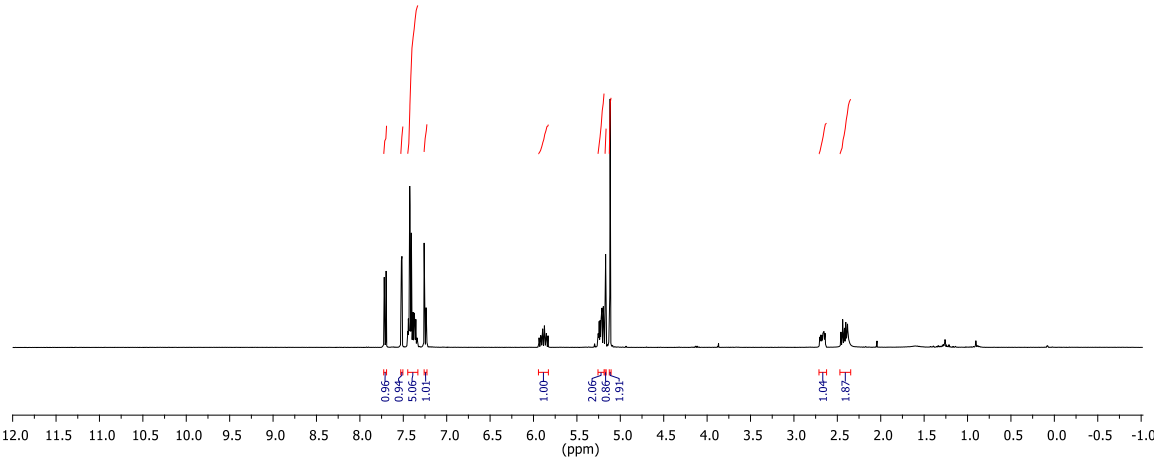
653

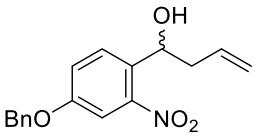
^{13}C NMR (100 MHz, MeOD)



673

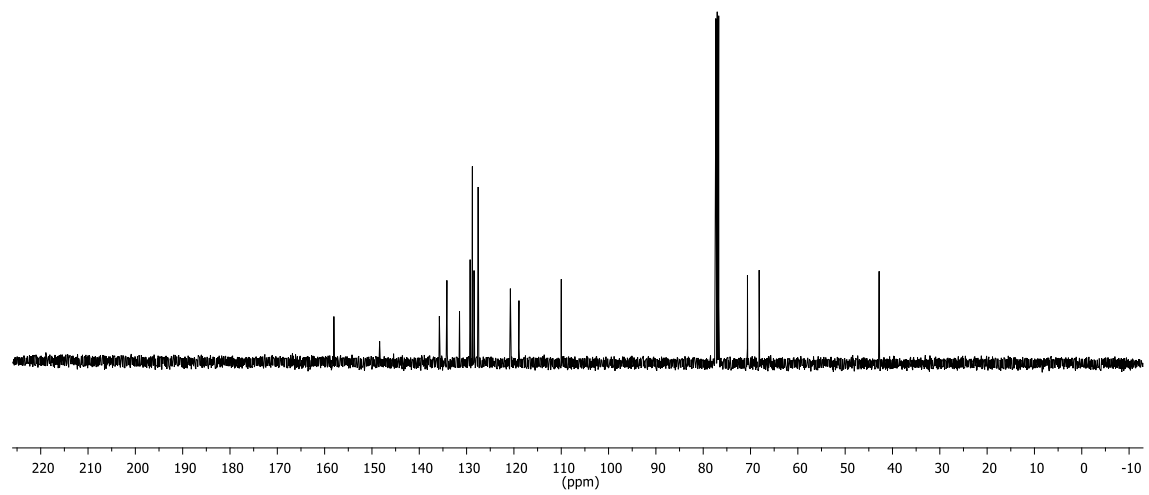
^{1}H NMR (400 MHz, $CDCl_3$)

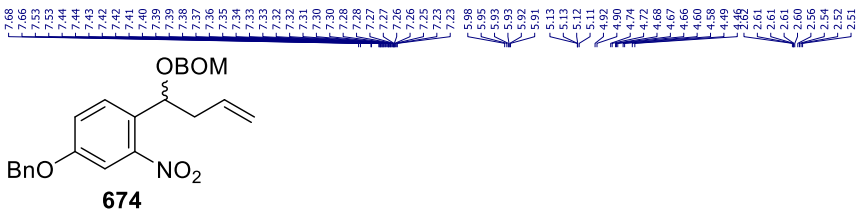




673

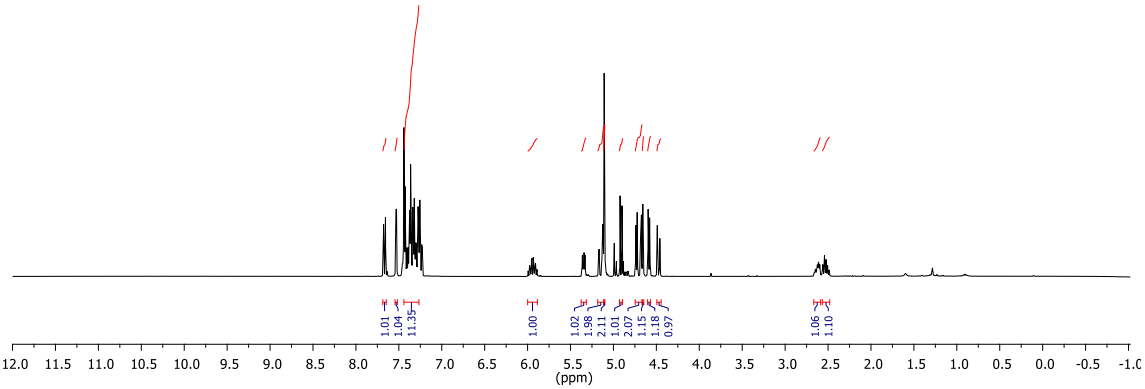
^{13}C NMR (100 MHz, $CDCl_3$)

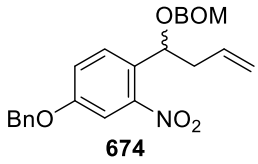




674

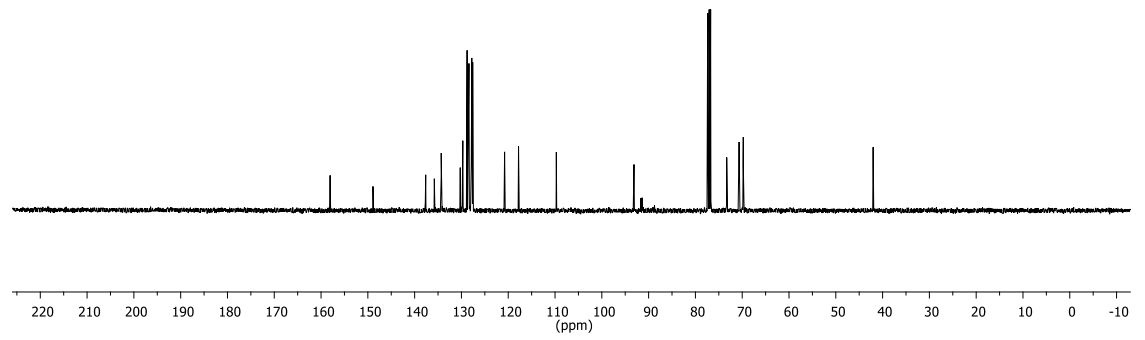
^{1}H NMR (400 MHz, $CDCl_3$)

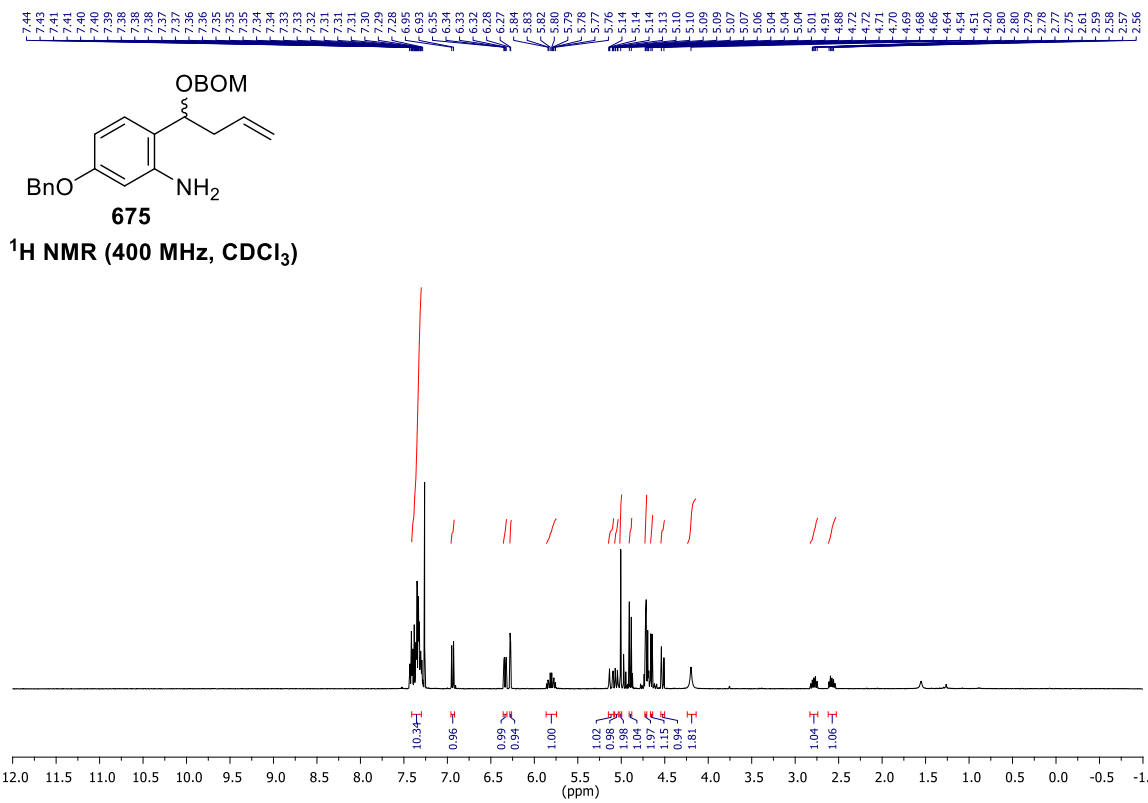


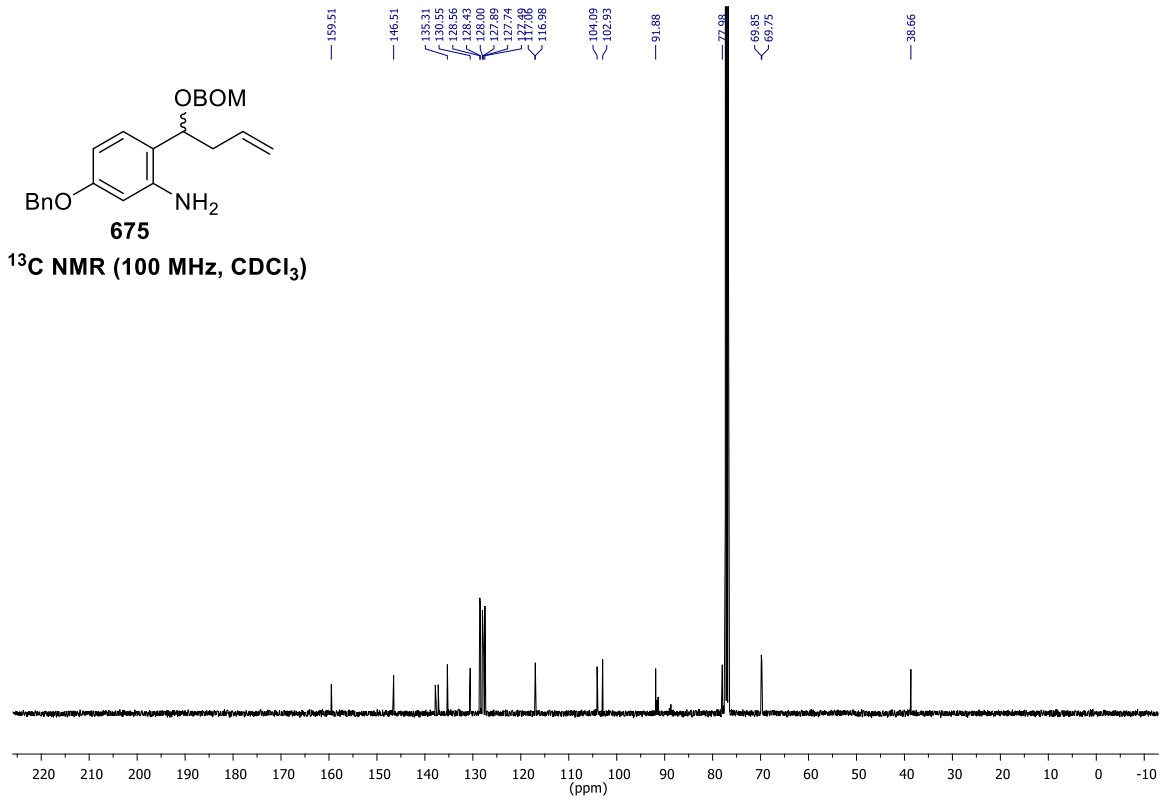


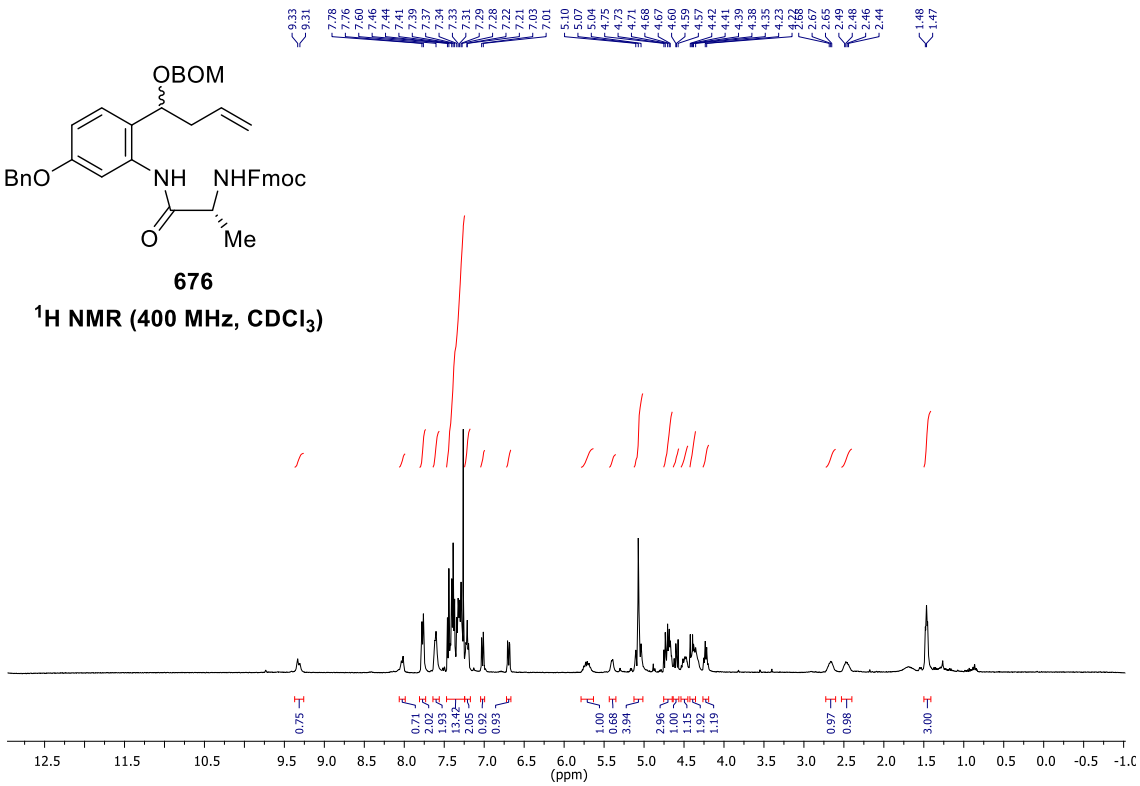
674

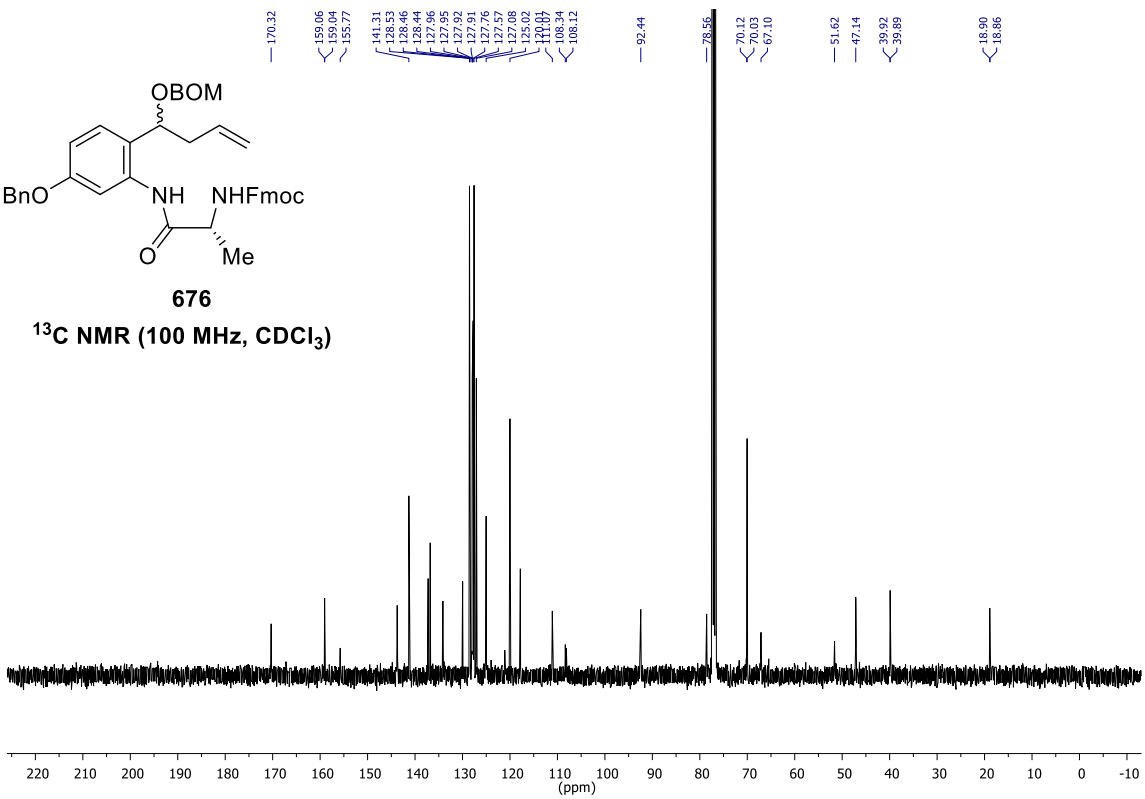
^{13}C NMR (100 MHz, $CDCl_3$)

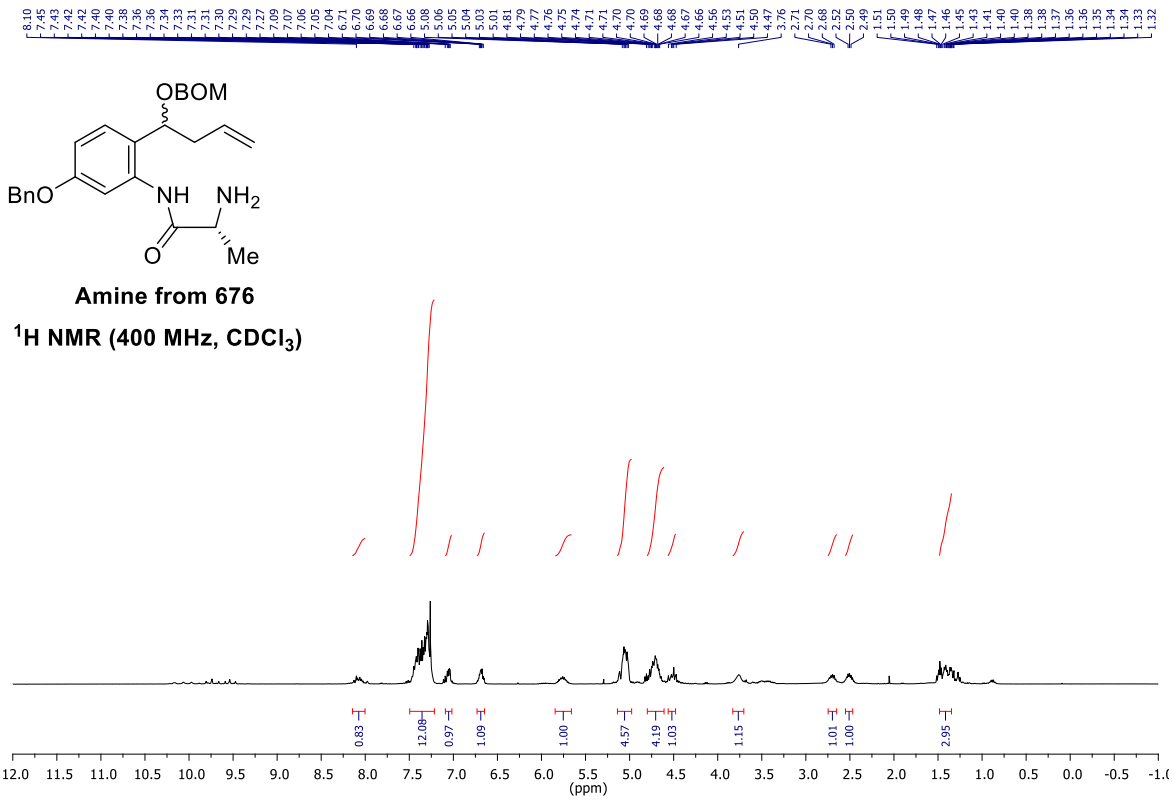






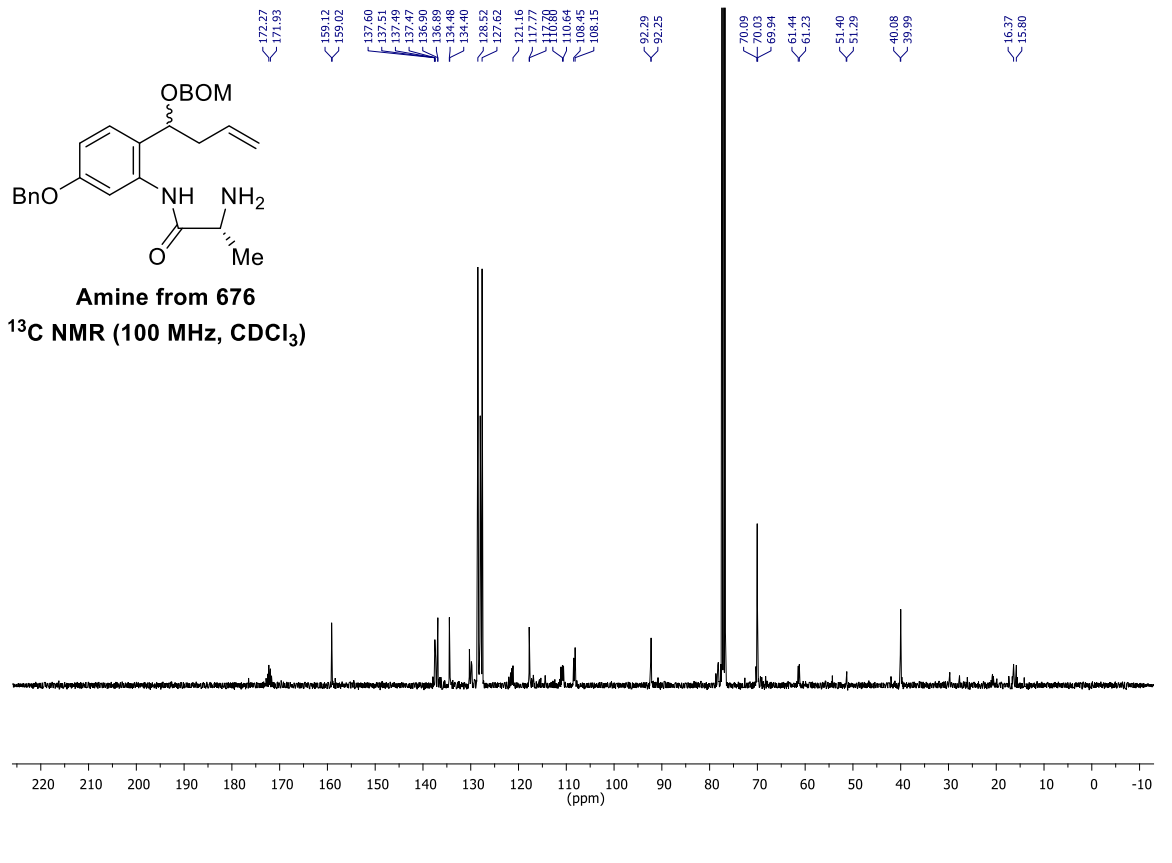






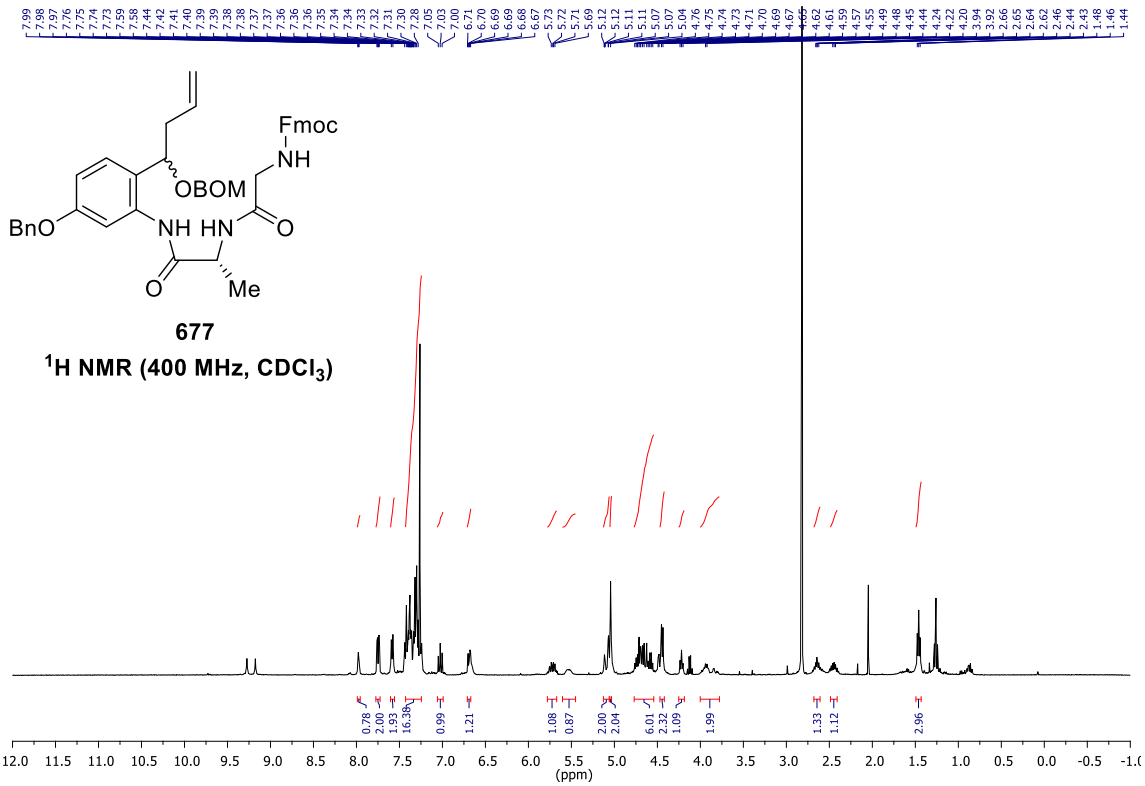
Amine from 676

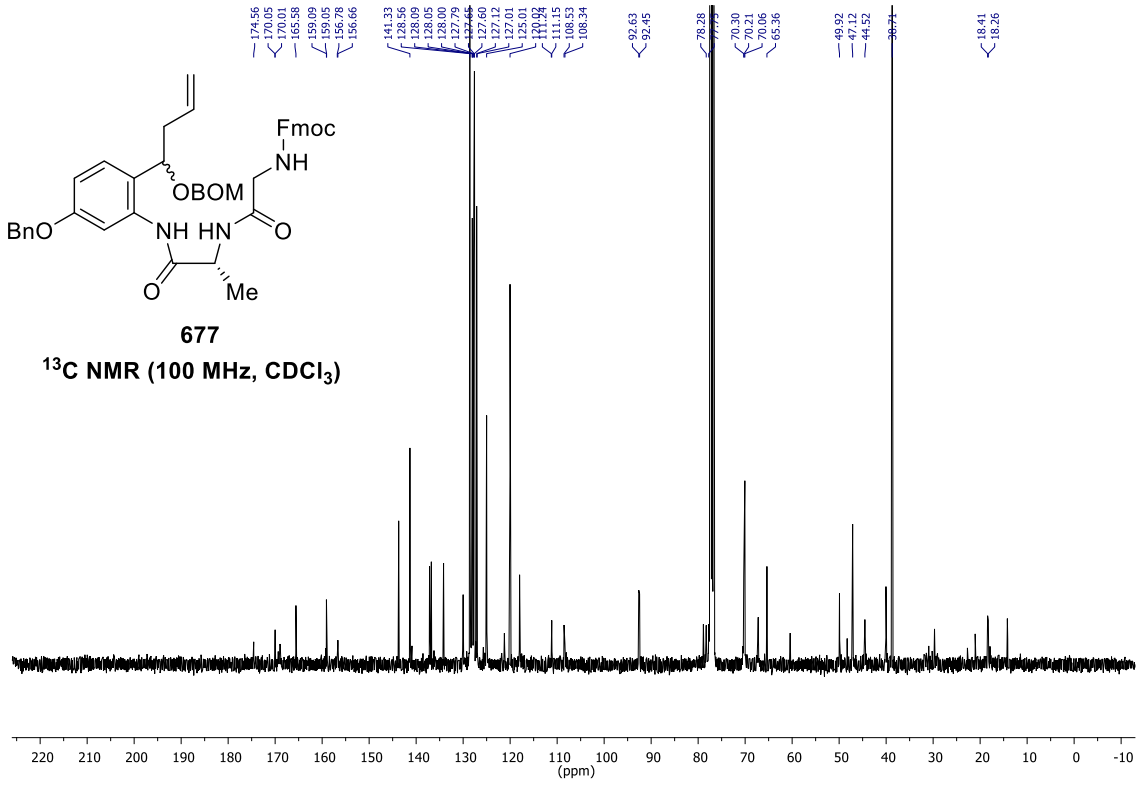
^{1}H NMR (400 MHz, $CDCl_3$)

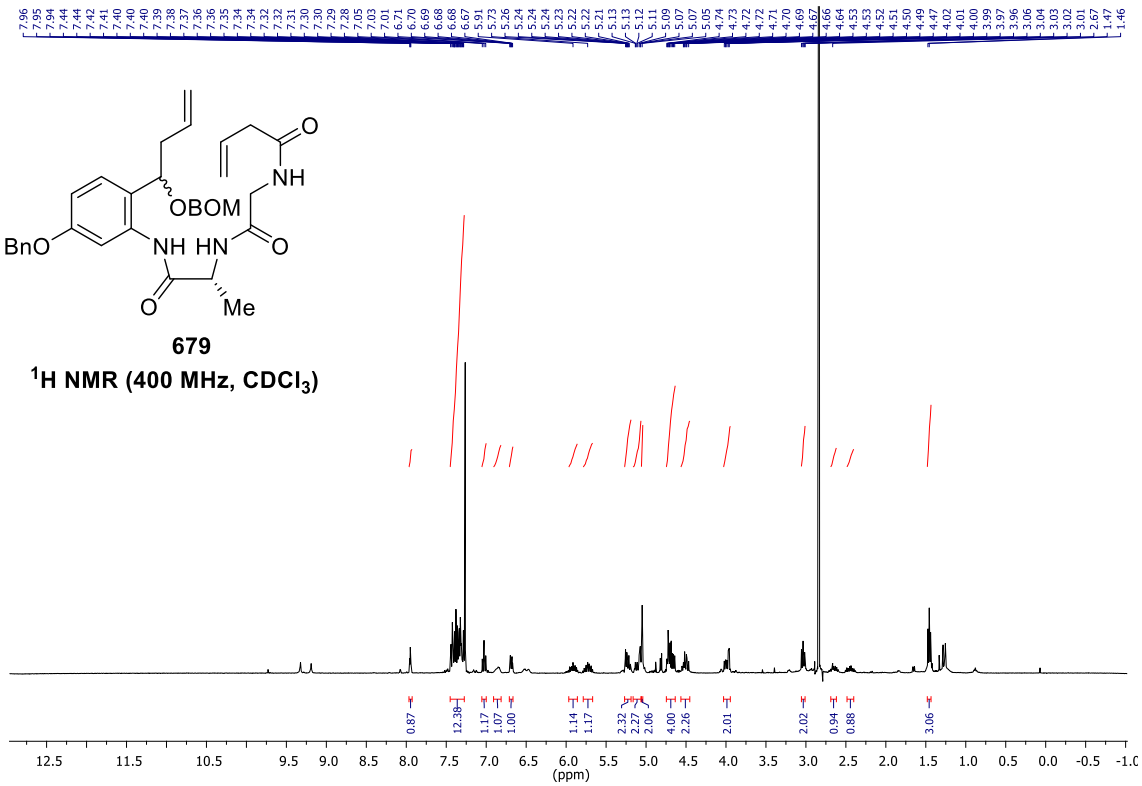


Amine from 676

^{13}C NMR (100 MHz, $CDCl_3$)

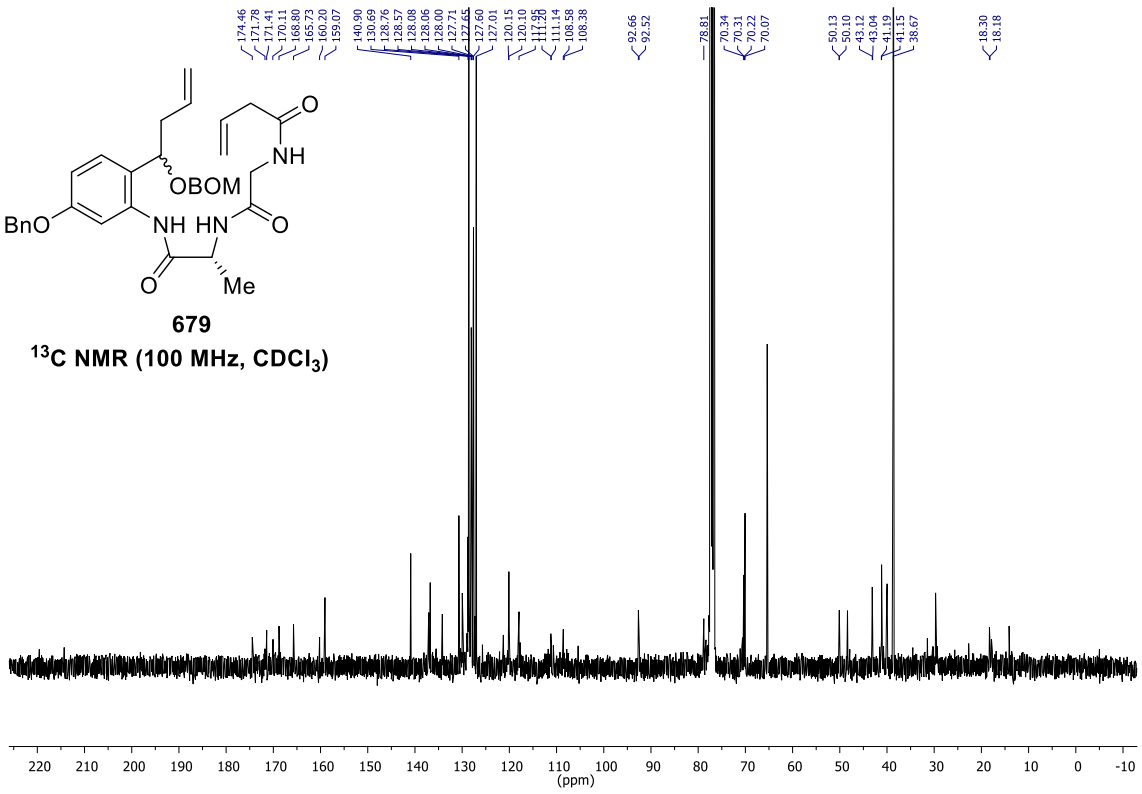






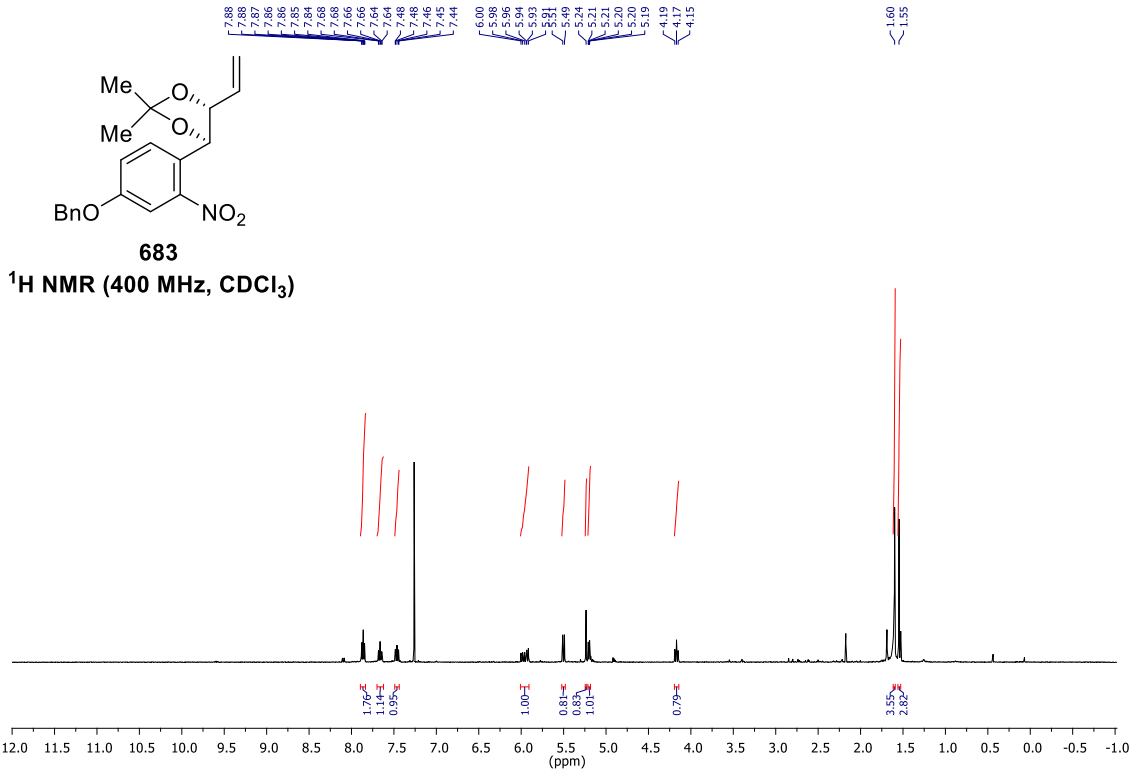
679

^{1}H NMR (400 MHz, $CDCl_3$)



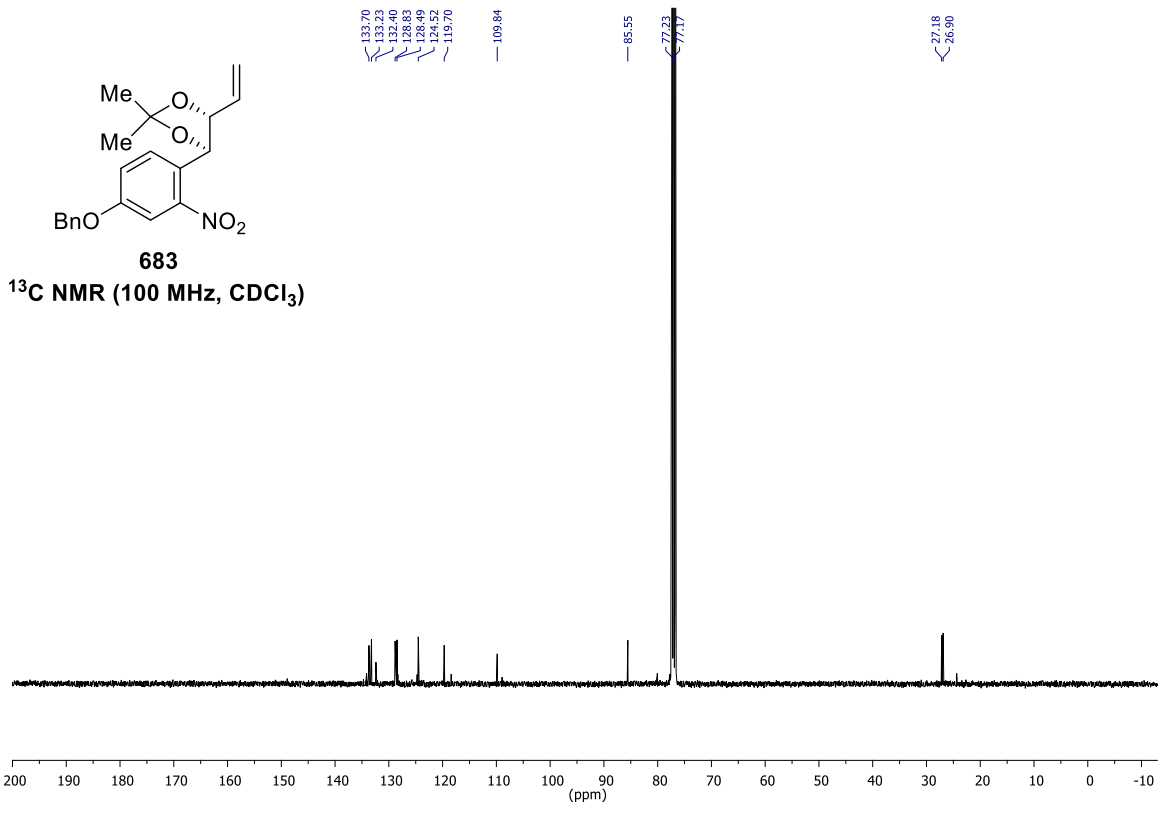
679

^{13}C NMR (100 MHz, $CDCl_3$)



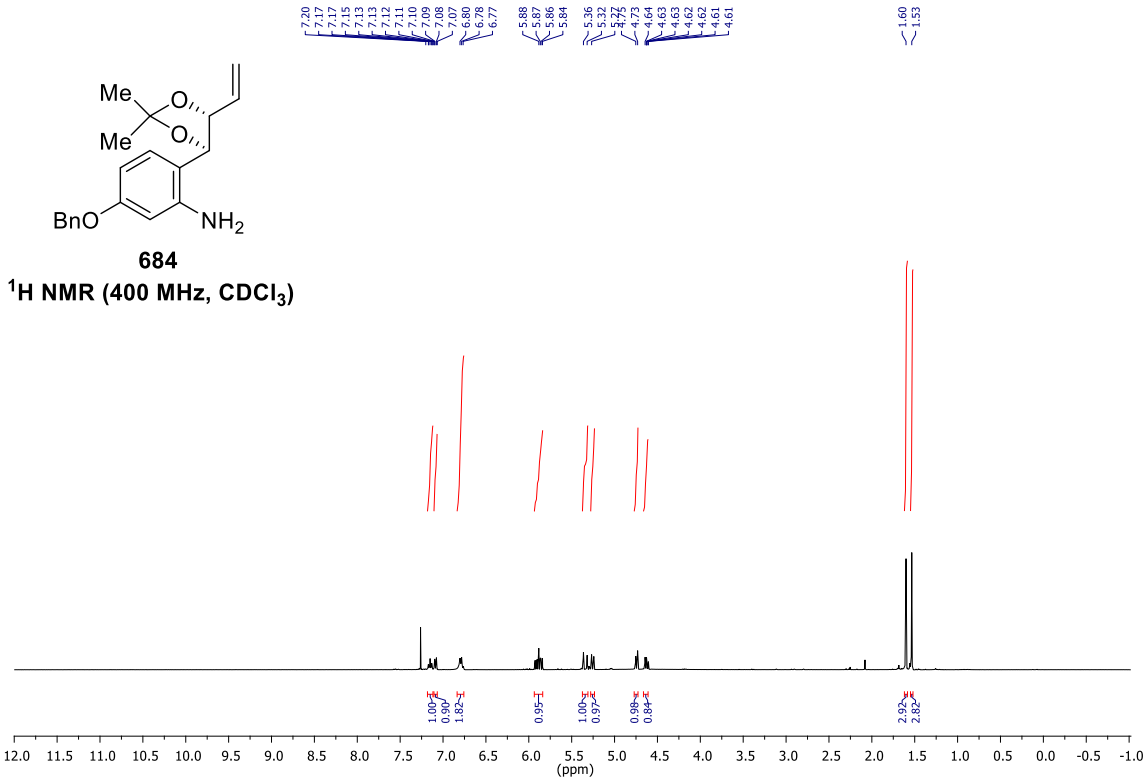
683

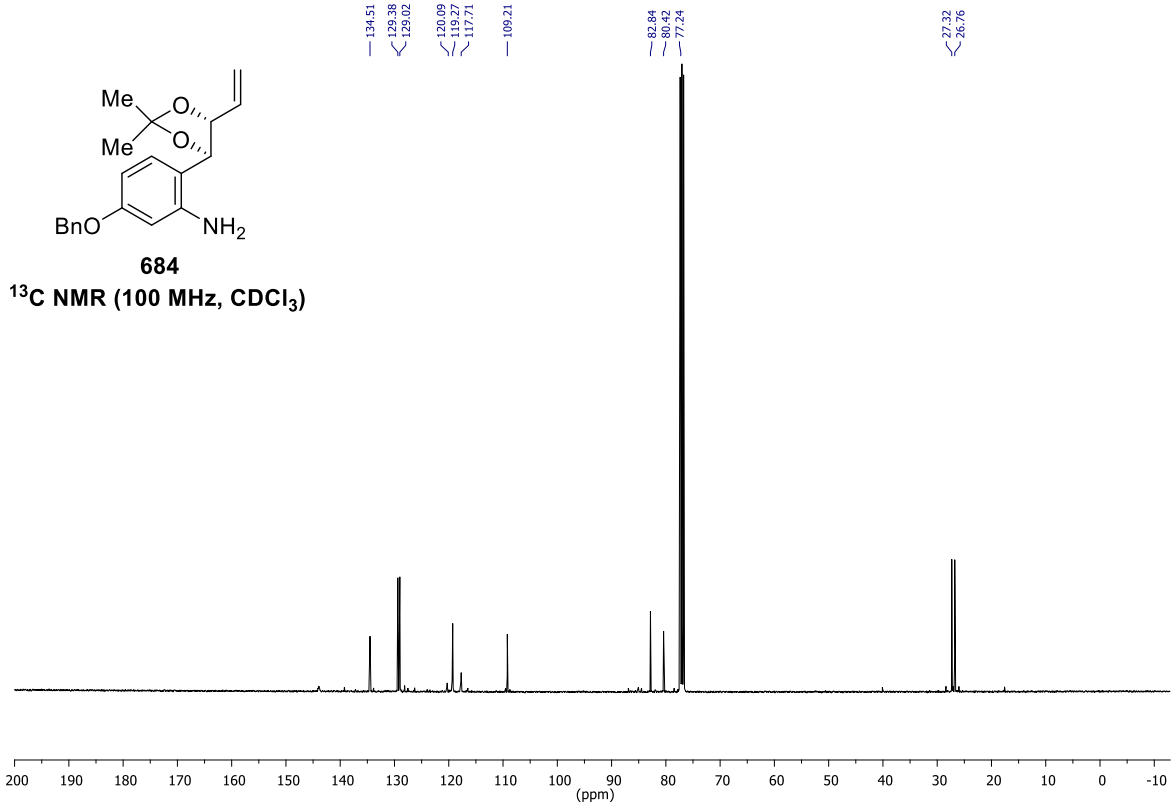
^{1}H NMR (400 MHz, $CDCl_3$)

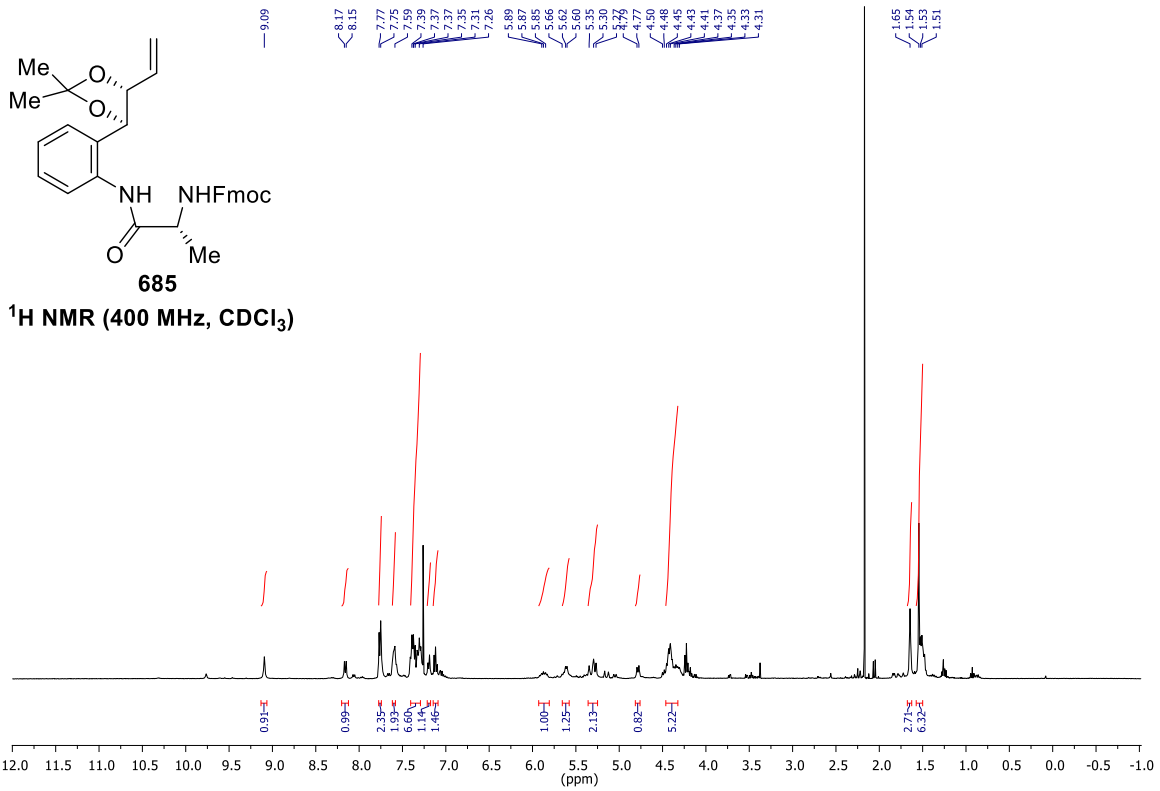


683

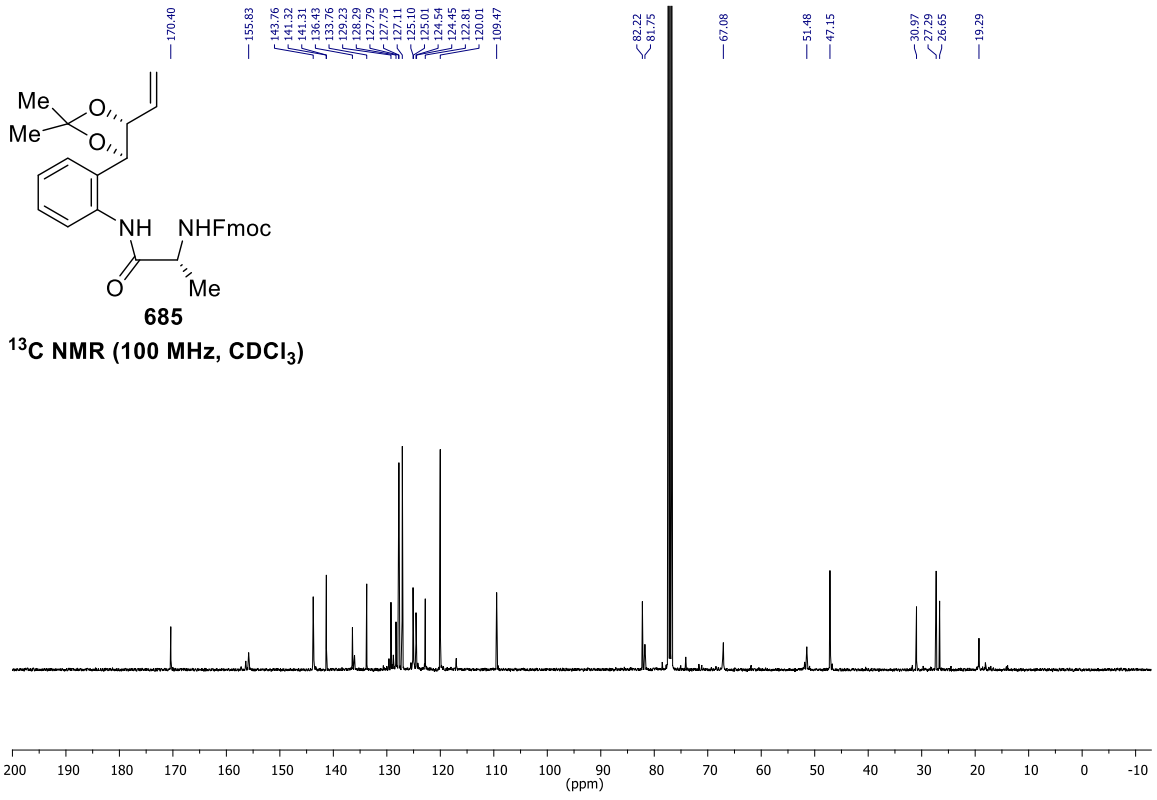
^{13}C NMR (100 MHz, $CDCl_3$)



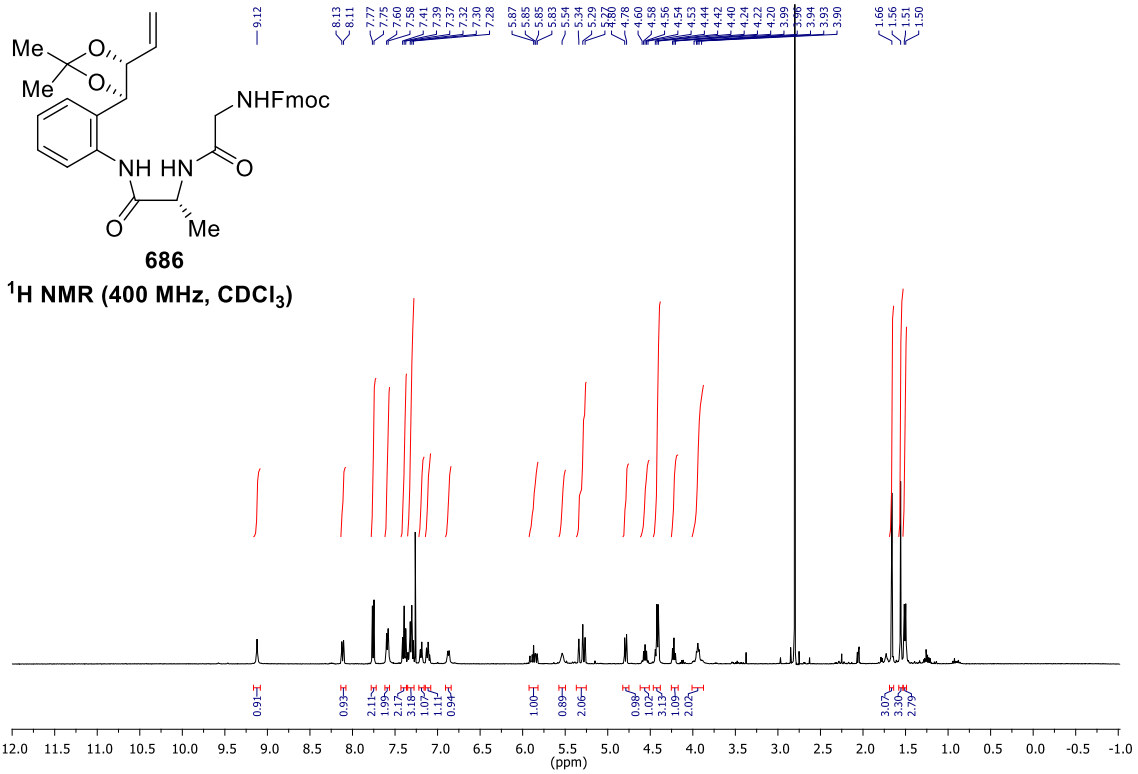




^{1}H NMR (400 MHz, $CDCl_3$)

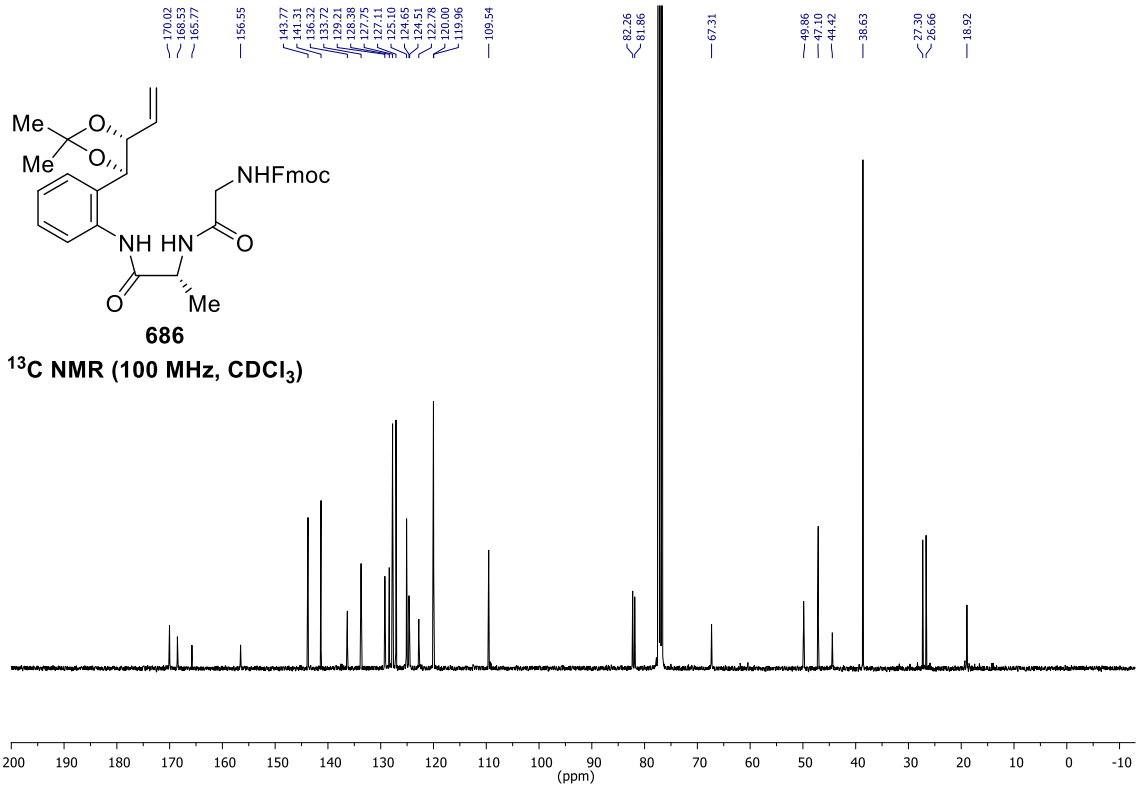


^{13}C NMR (100 MHz, $CDCl_3$)



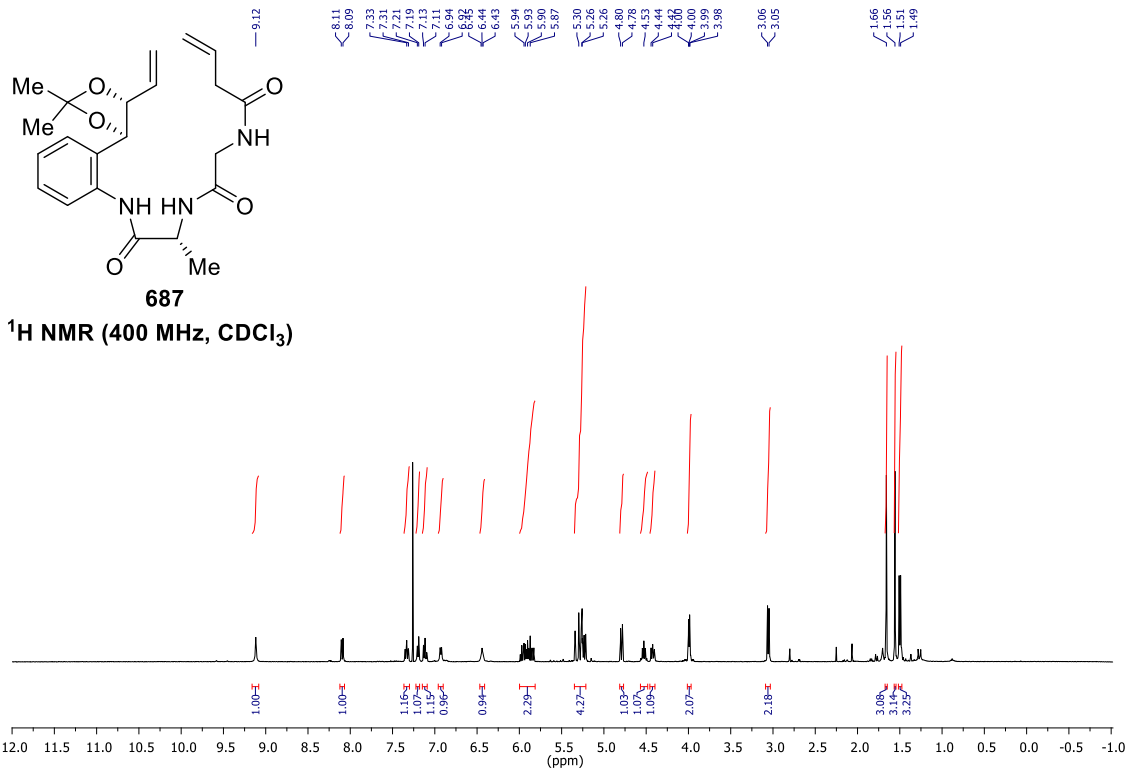
686

^{1}H NMR (400 MHz, $CDCl_3$)



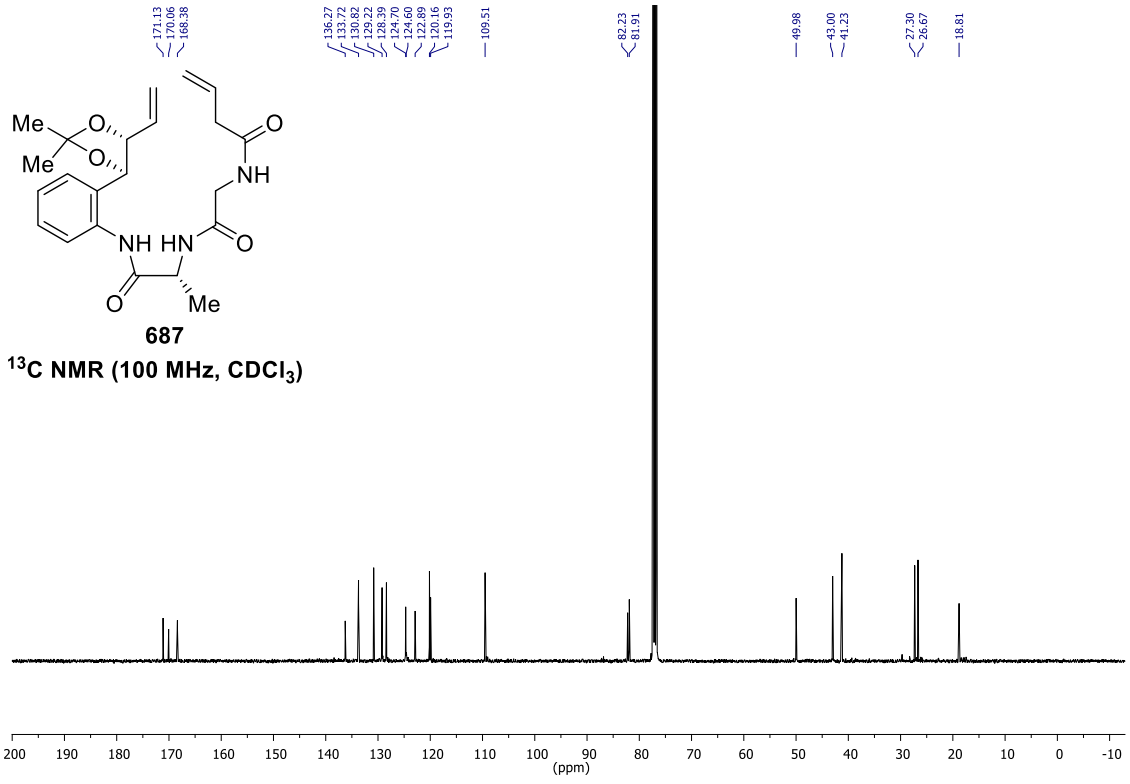
686

^{13}C NMR (100 MHz, $CDCl_3$)



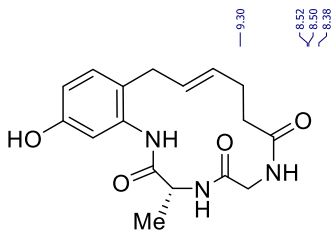
687

^{1}H NMR (400 MHz, $CDCl_3$)



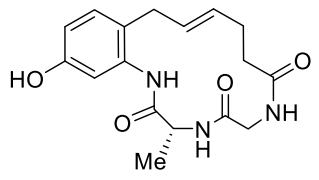
687

^{13}C NMR (100 MHz, $CDCl_3$)



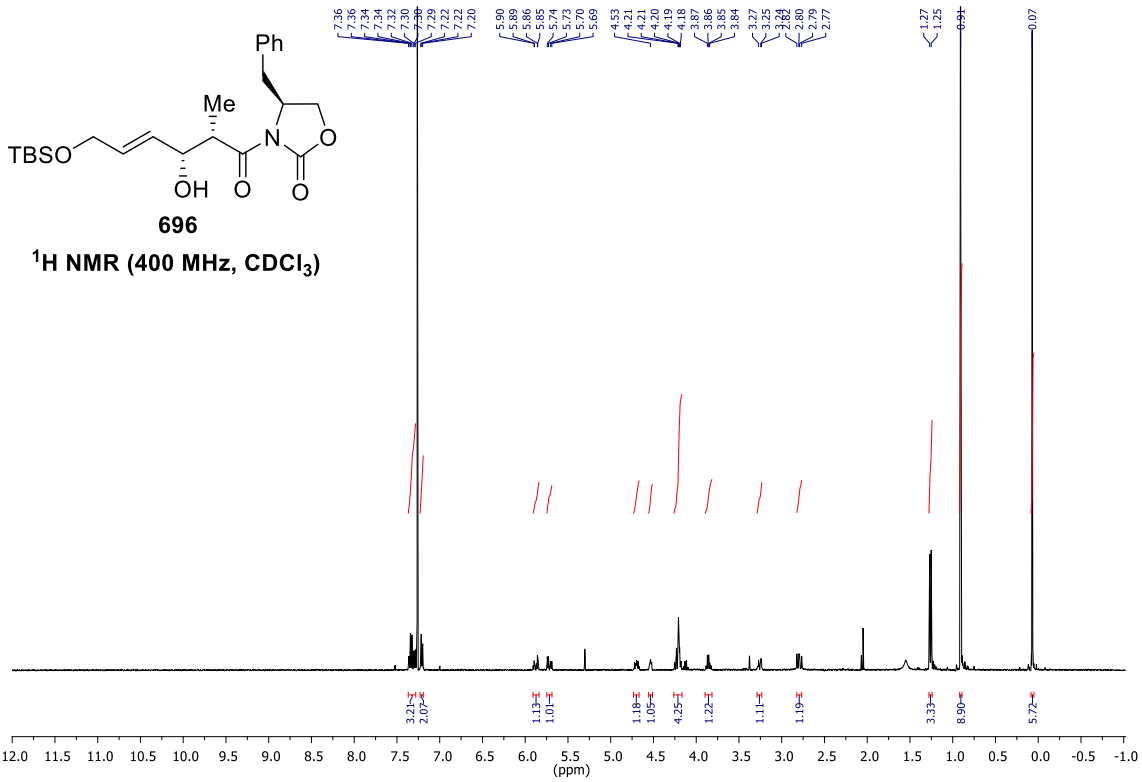
690

^{1}H NMR (400 MHz, DMSO-d_6)



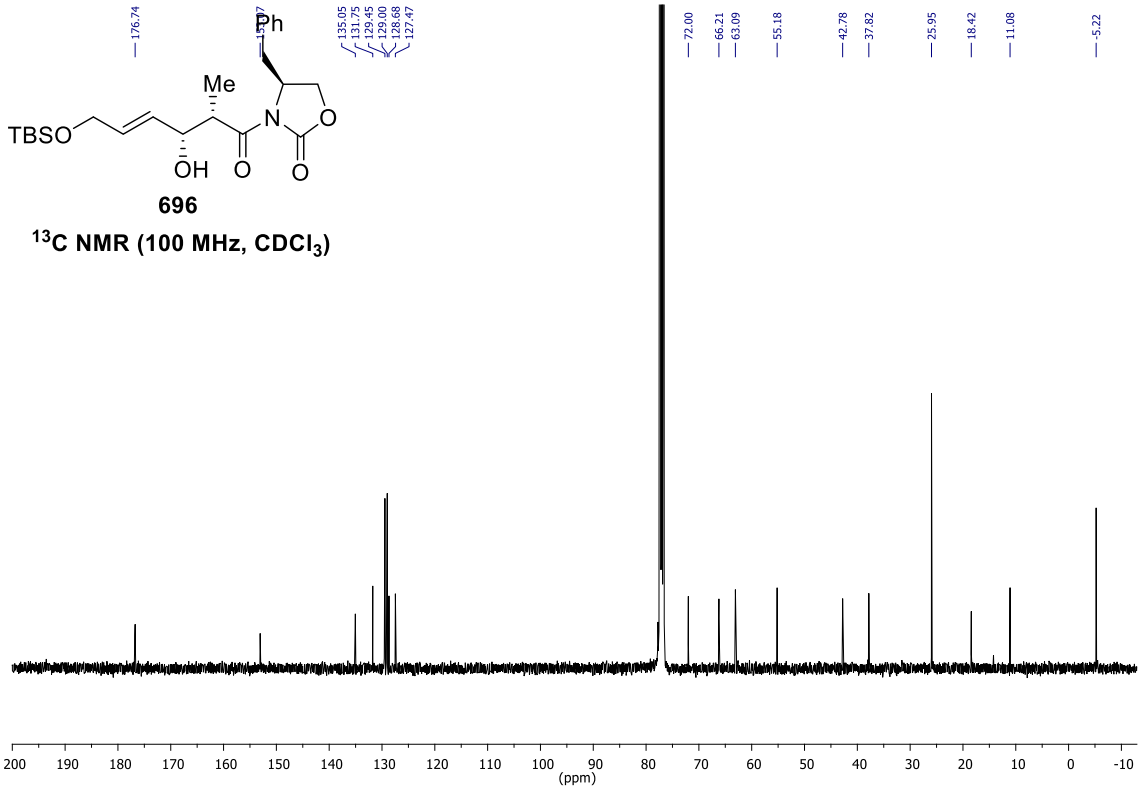
690

^{13}C NMR (100 MHz, DMSO-d_6)



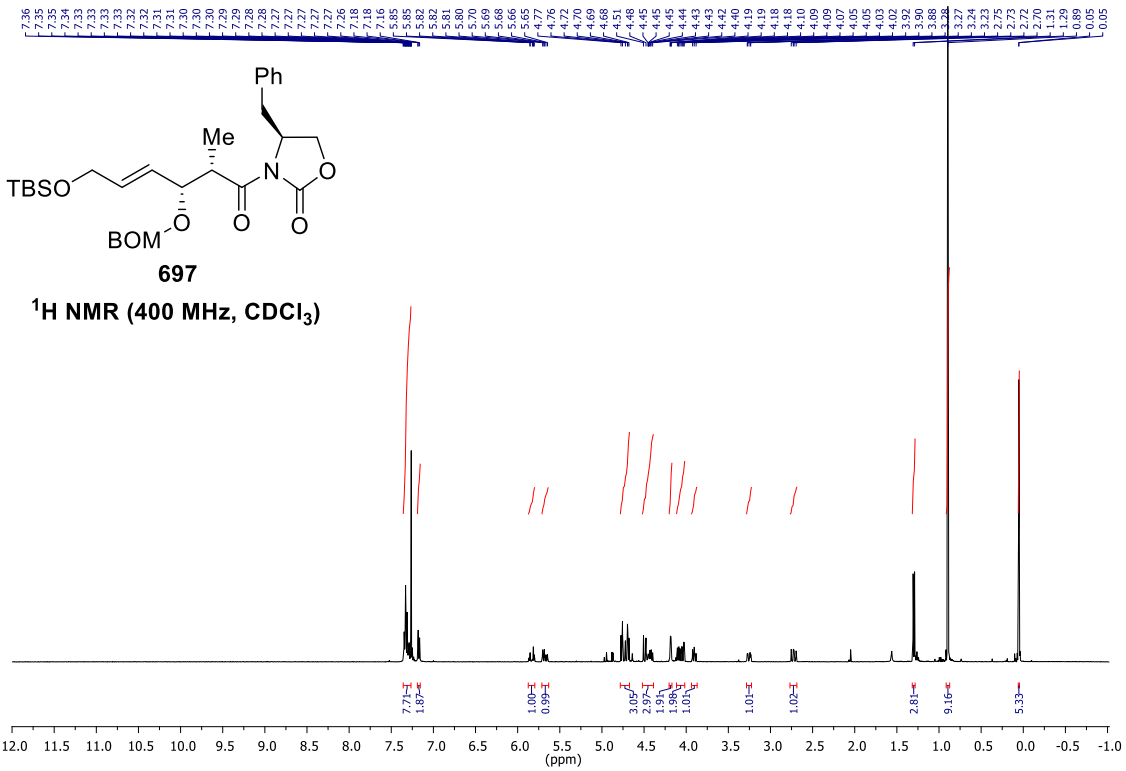
696

^{1}H NMR (400 MHz, $CDCl_3$)



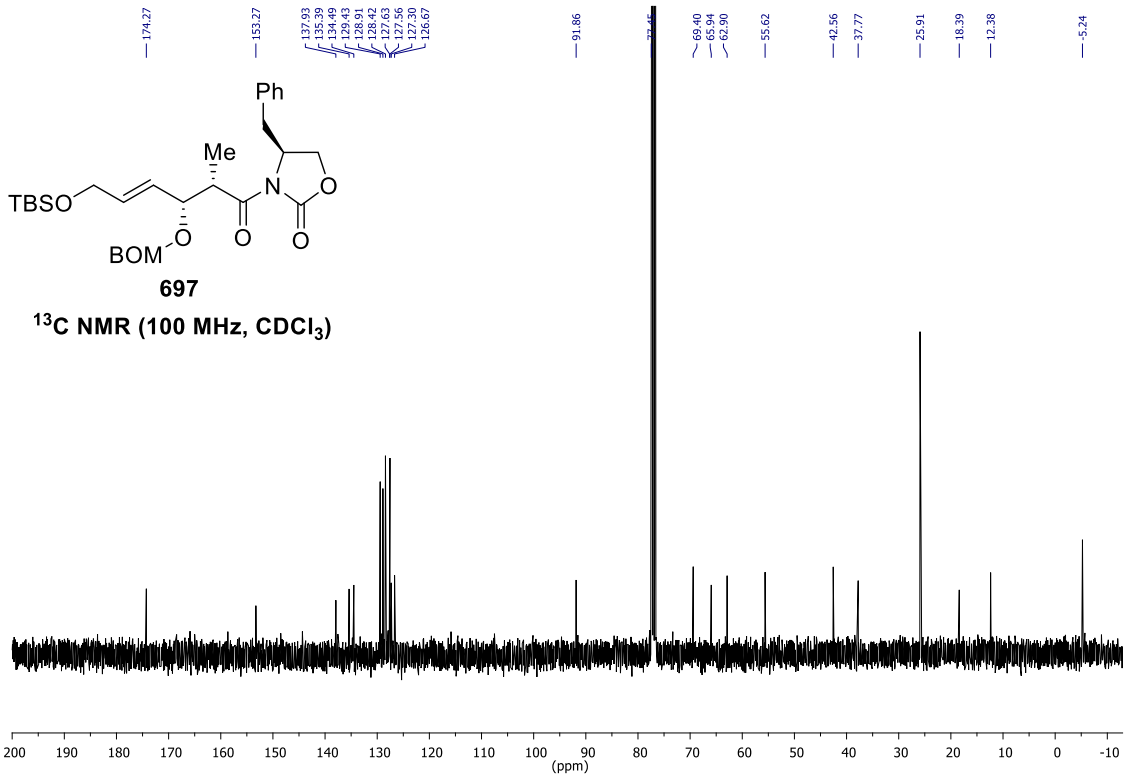
696

^{13}C NMR (100 MHz, $CDCl_3$)



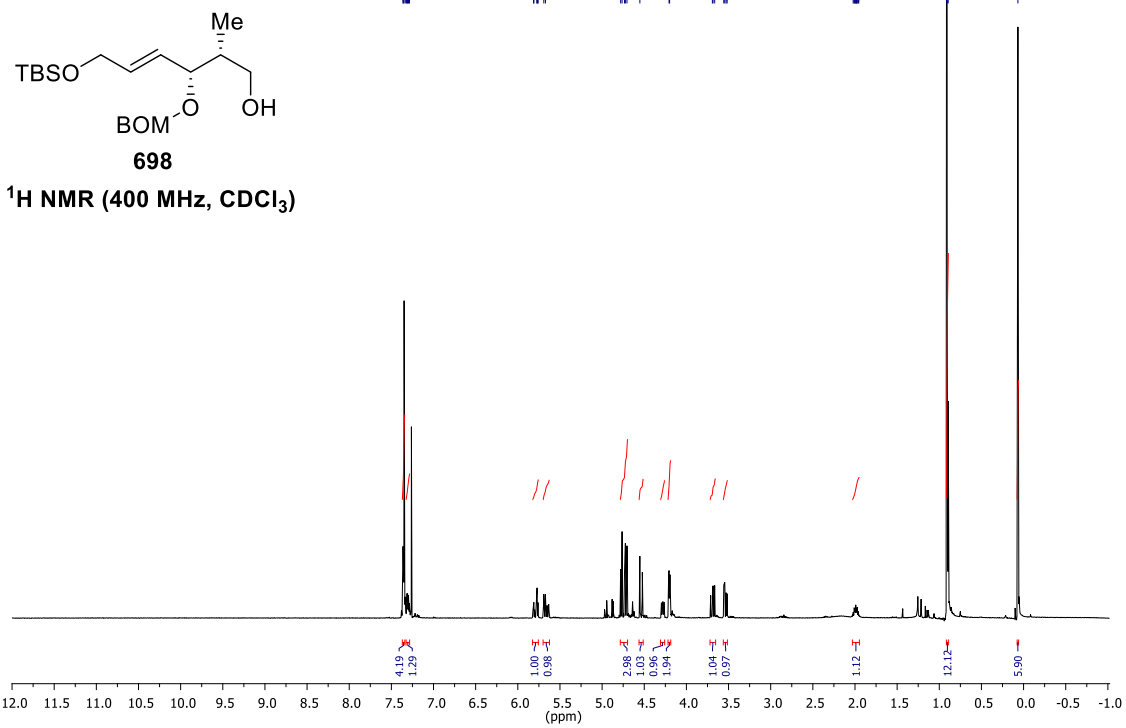
697

^{1}H NMR (400 MHz, $CDCl_3$)



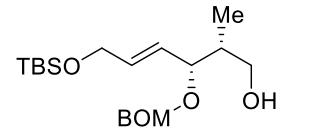
697

^{13}C NMR (100 MHz, $CDCl_3$)



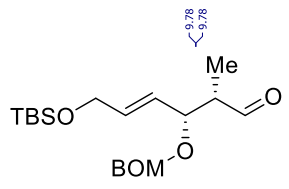
698

^{1}H NMR (400 MHz, $CDCl_3$)



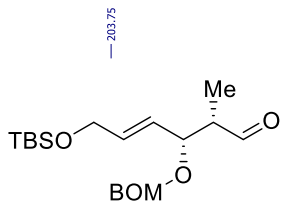
698

^{13}C NMR (100 MHz, $CDCl_3$)



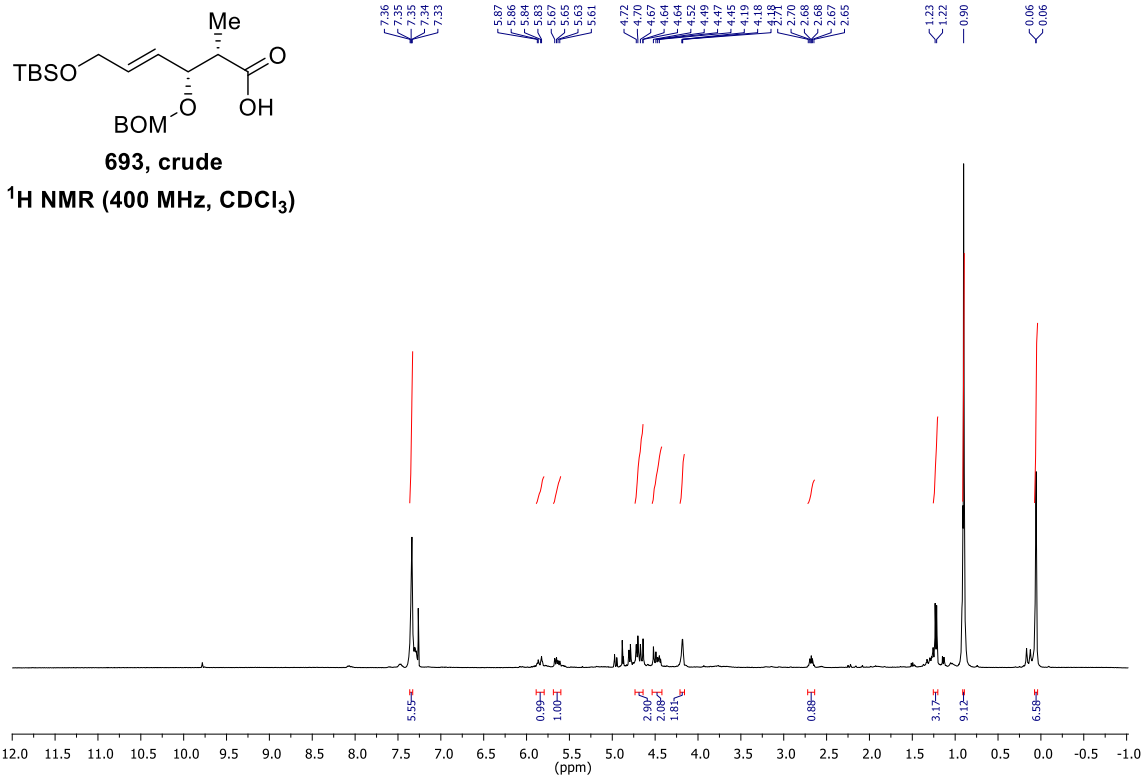
699

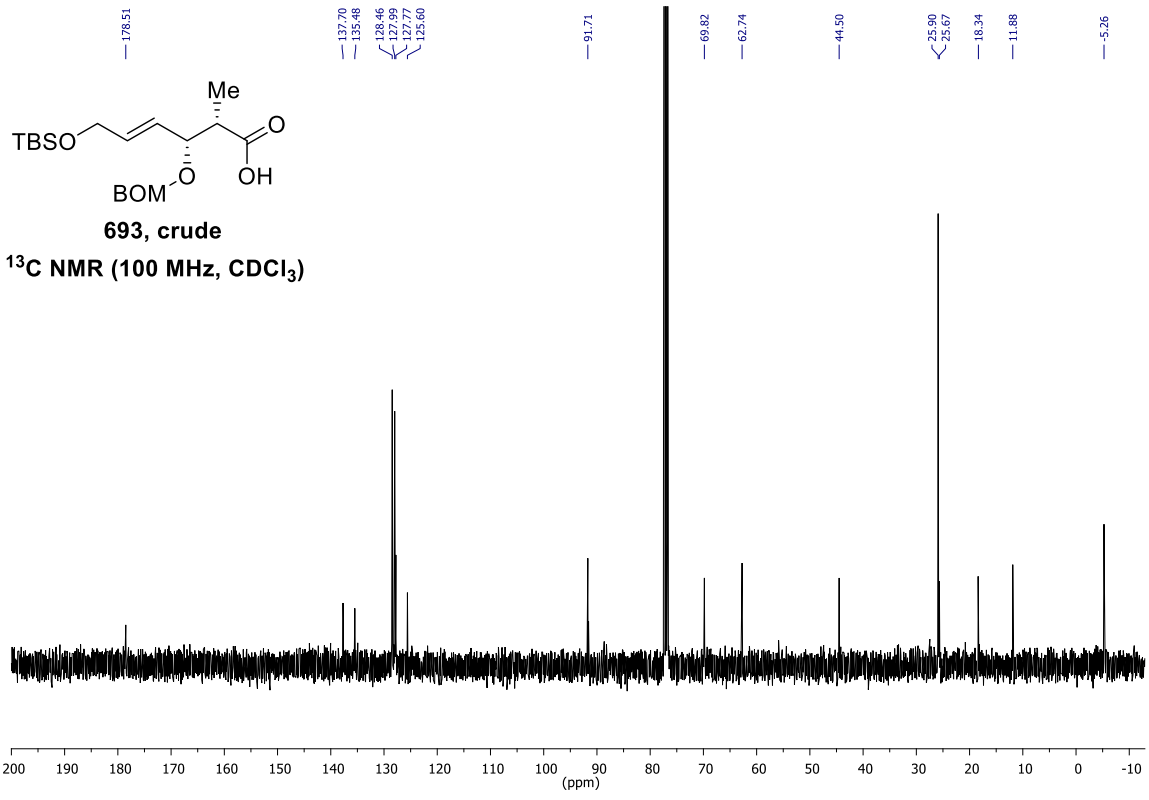
^{1}H NMR (400 MHz, $CDCl_3$)

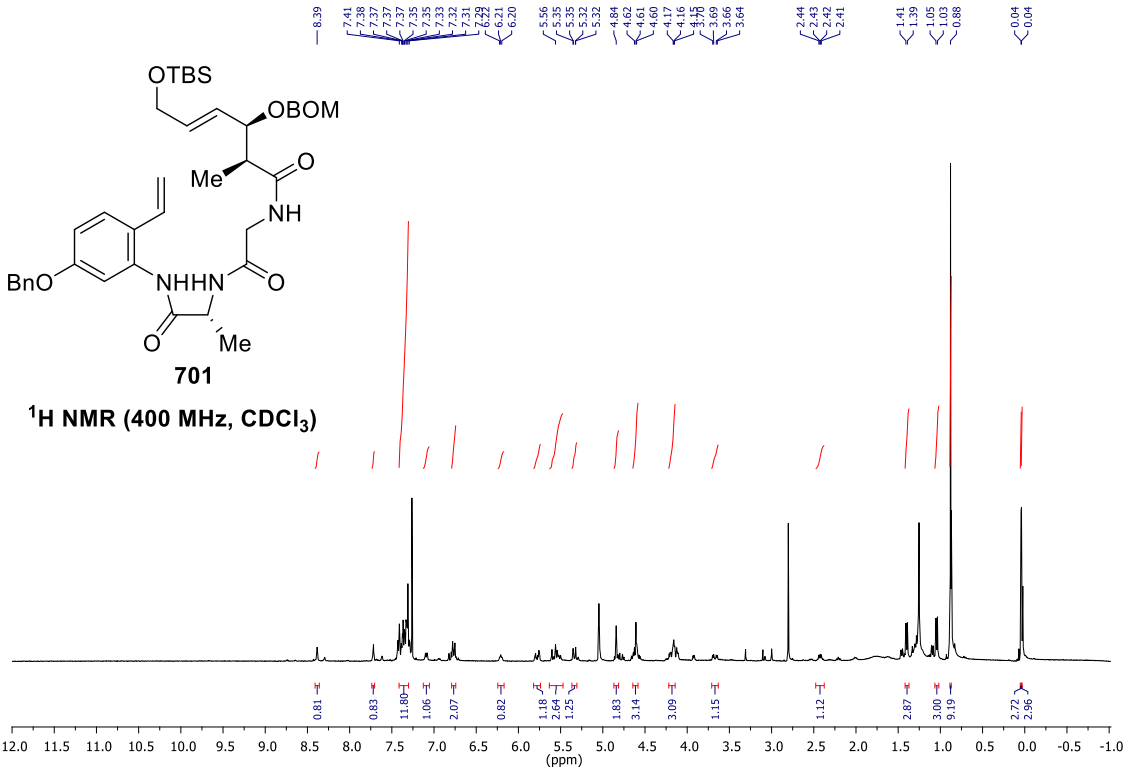


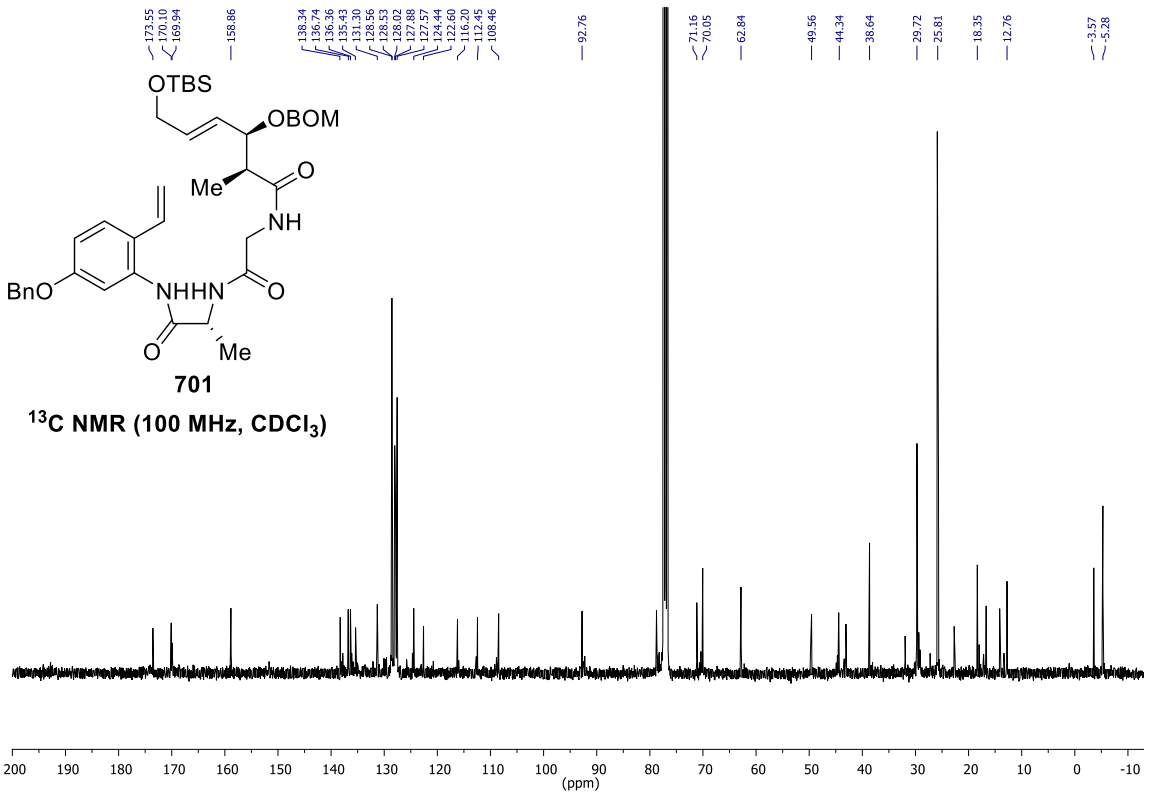
699

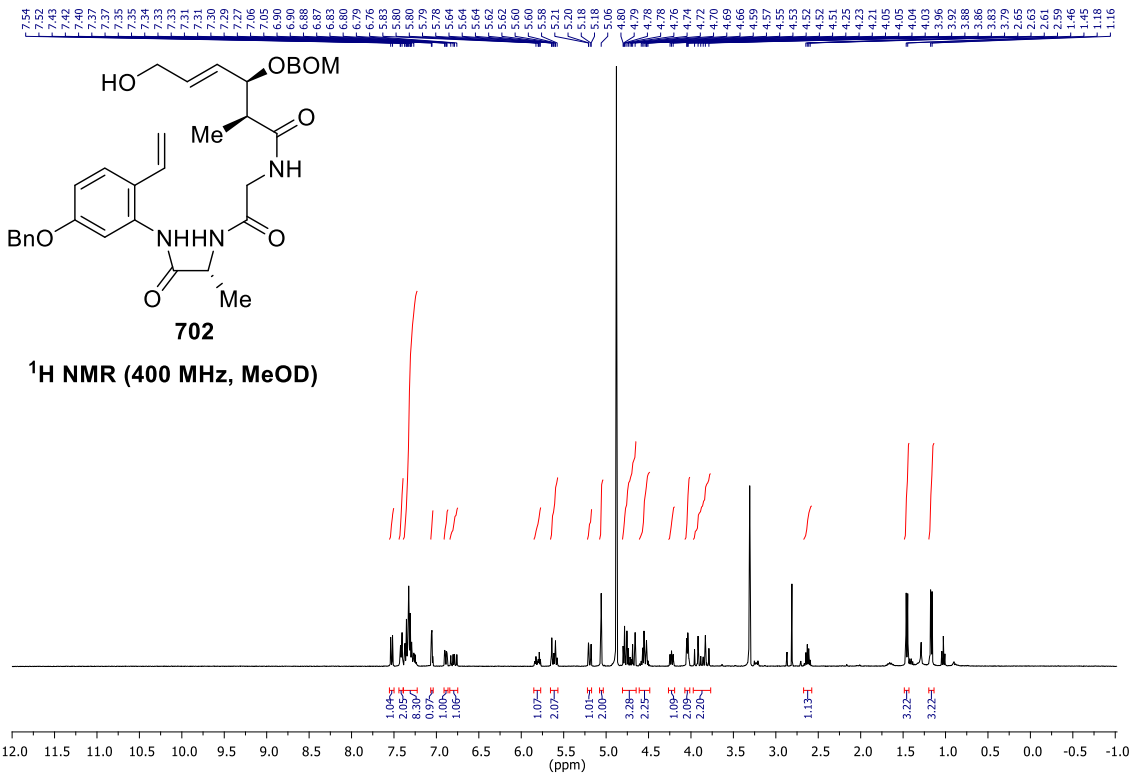
^{13}C NMR (100 MHz, $CDCl_3$)

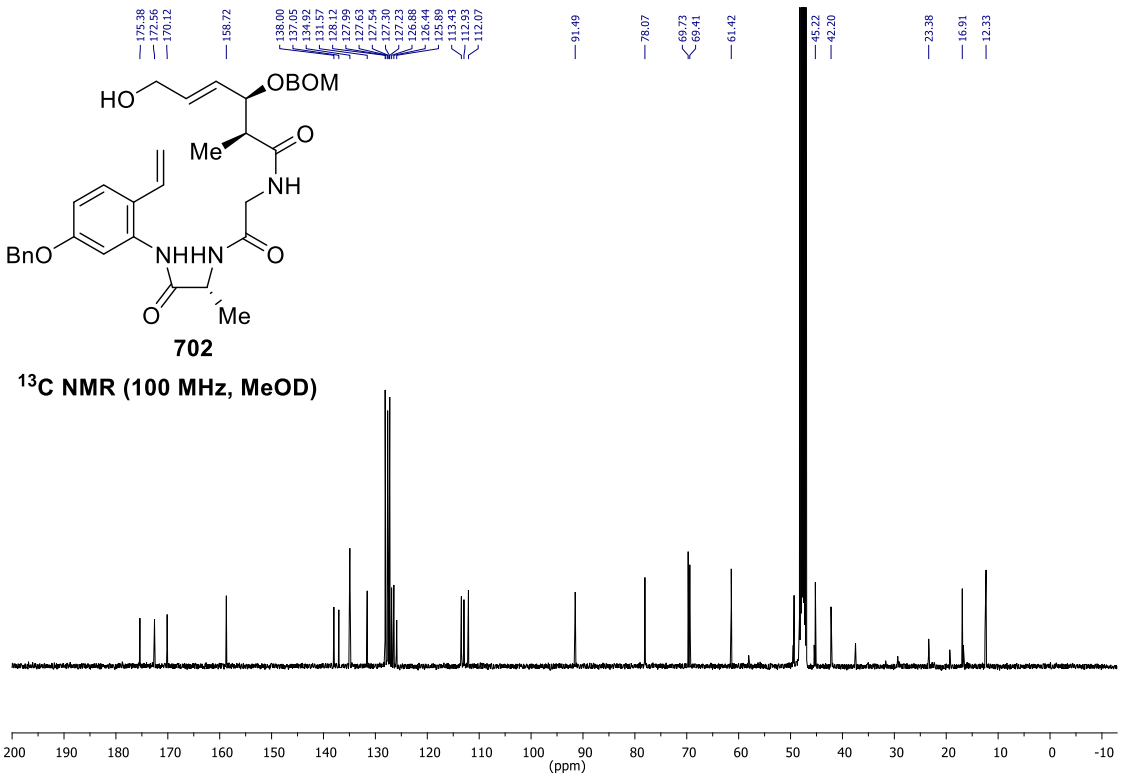


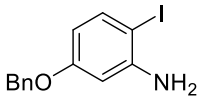






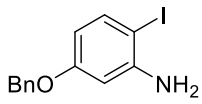






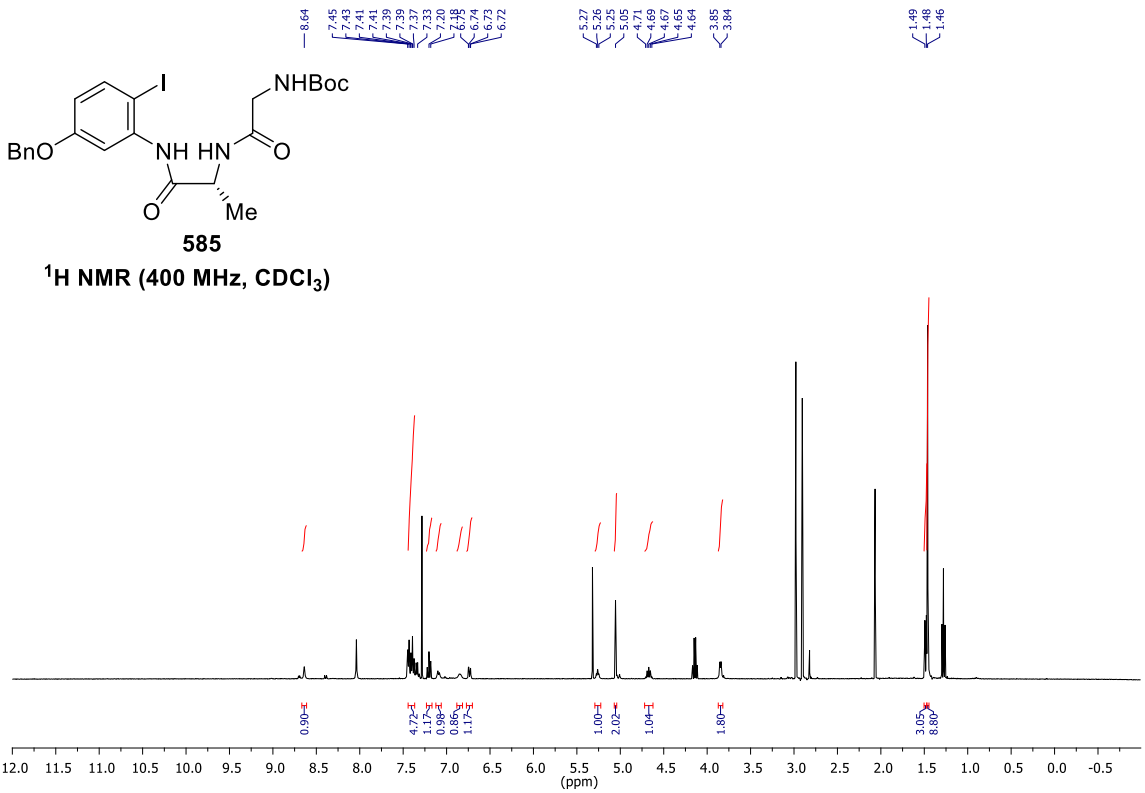
704

^{1}H NMR (400 MHz, $CDCl_3$)



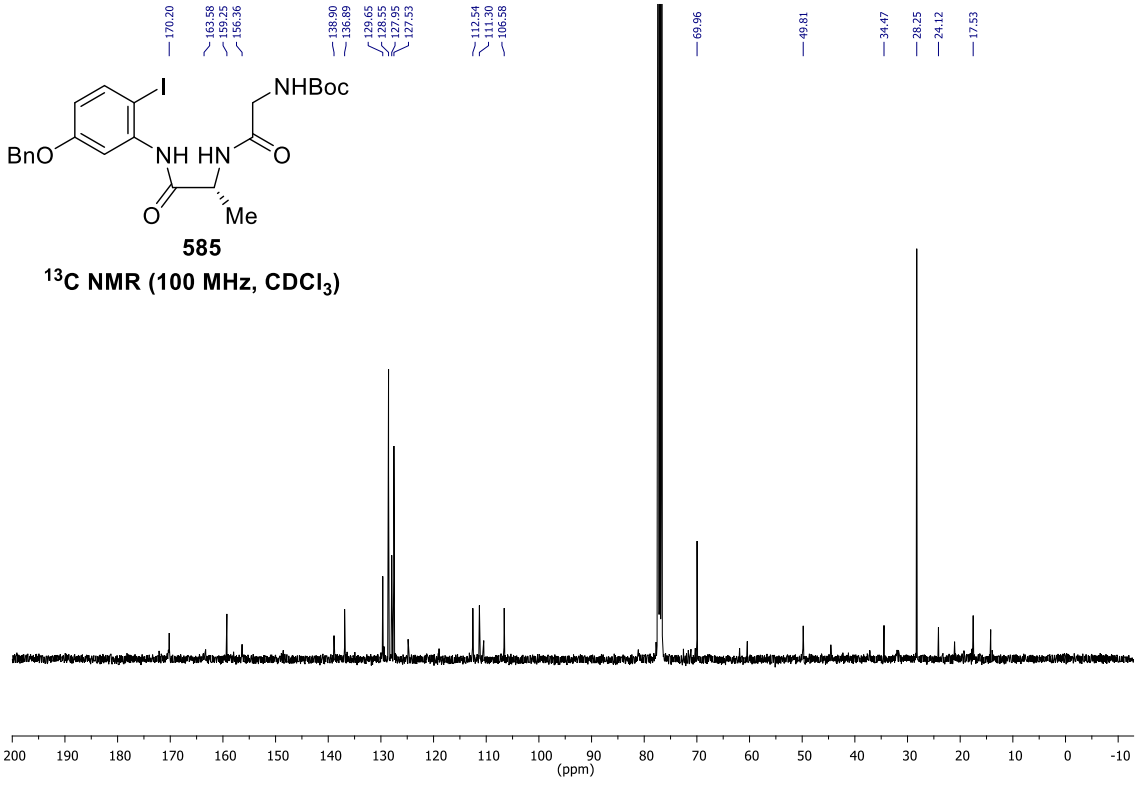
704

^{13}C NMR (100 MHz, $CDCl_3$)



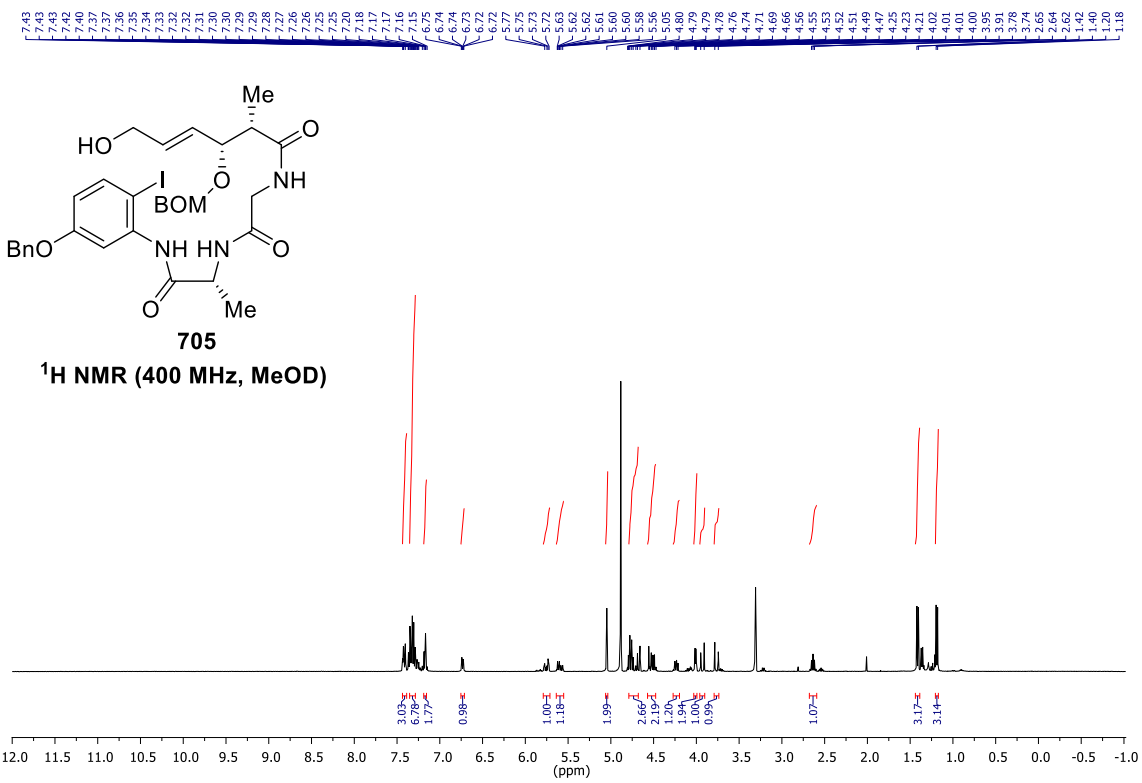
585

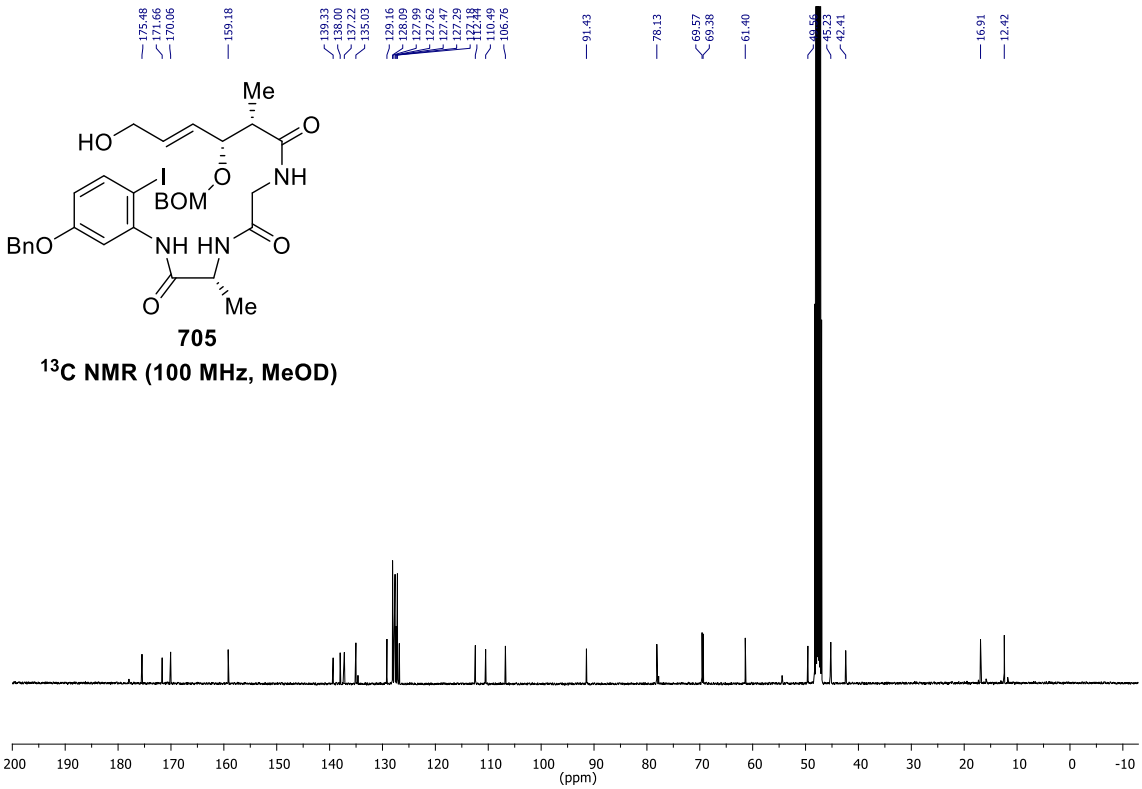
^{1}H NMR (400 MHz, $CDCl_3$)

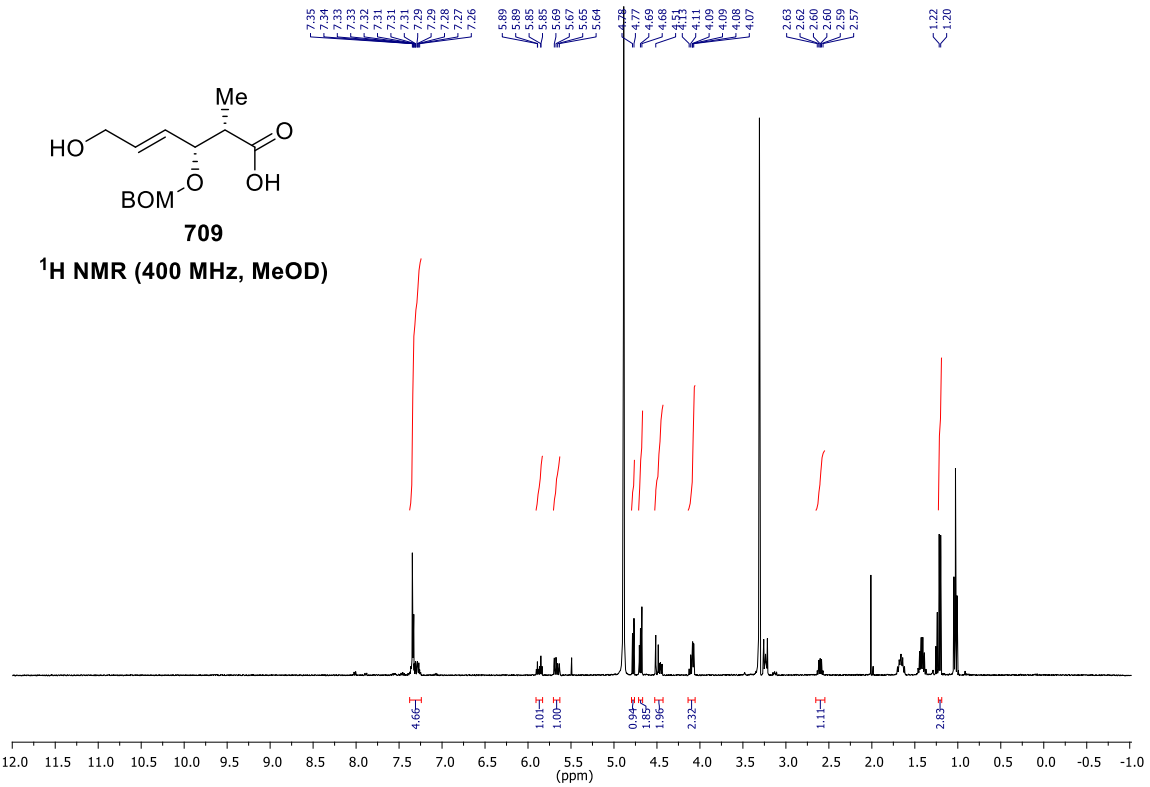


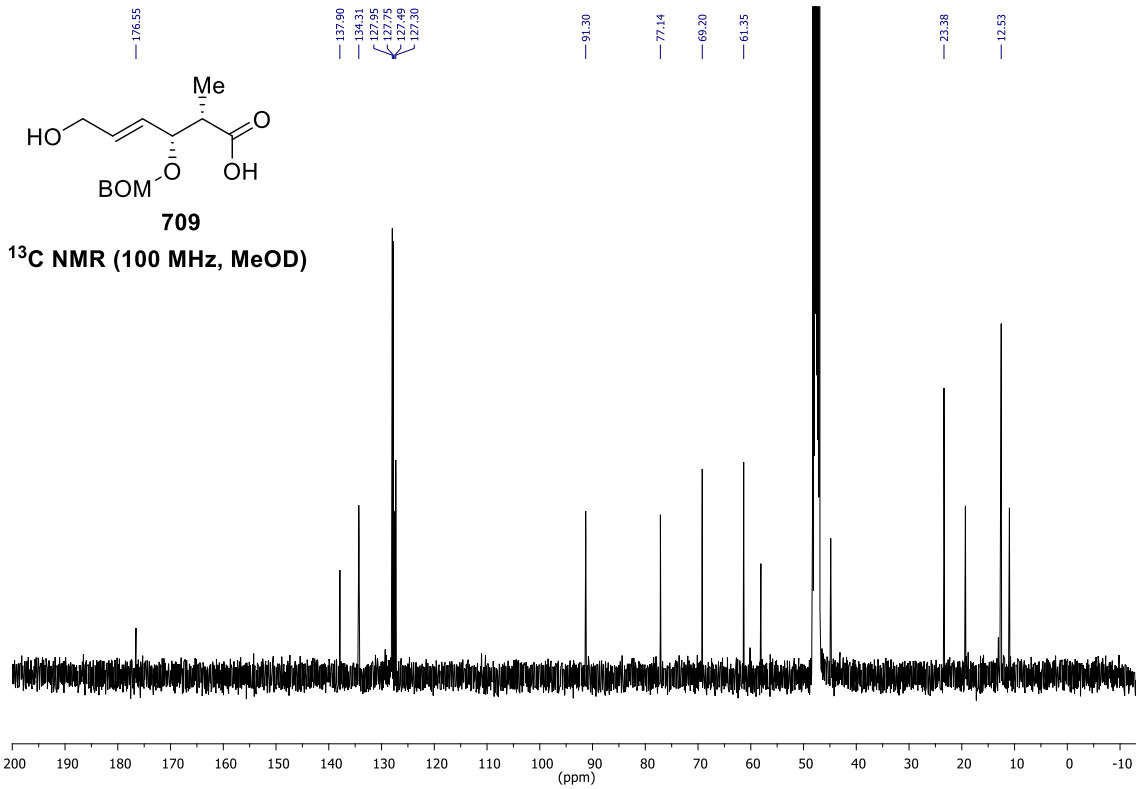
585

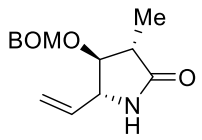
^{13}C NMR (100 MHz, $CDCl_3$)





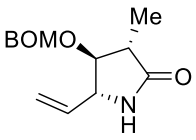






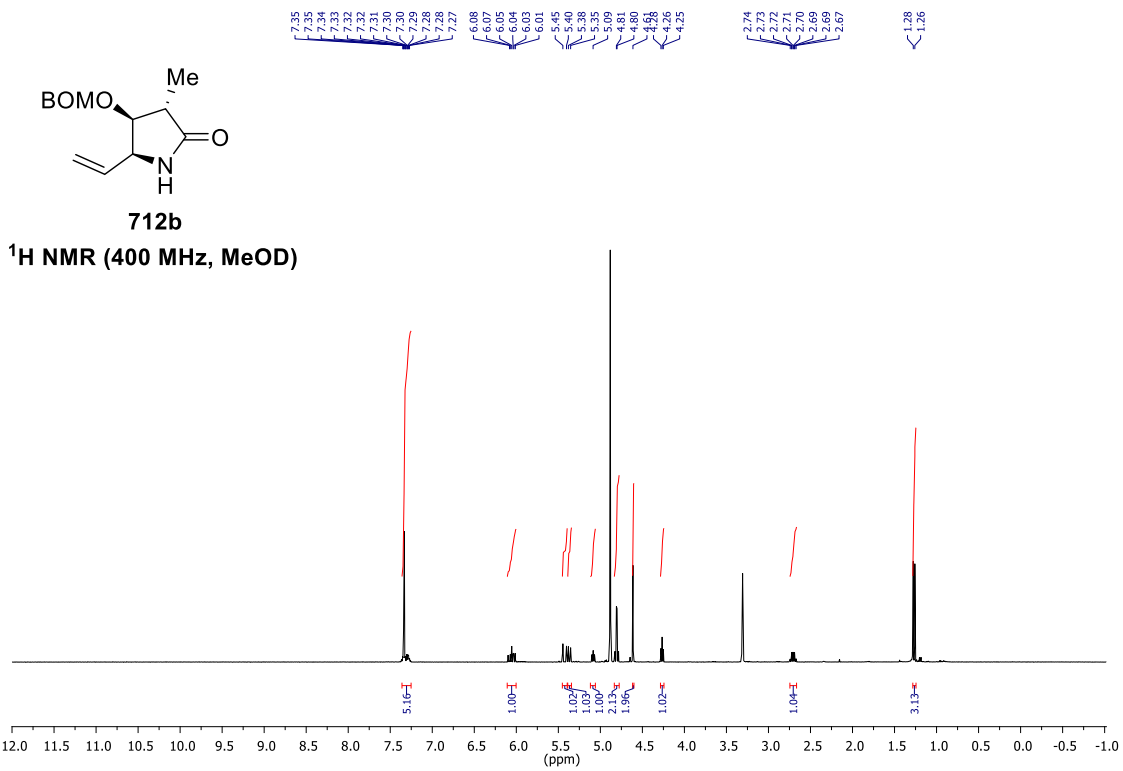
712a

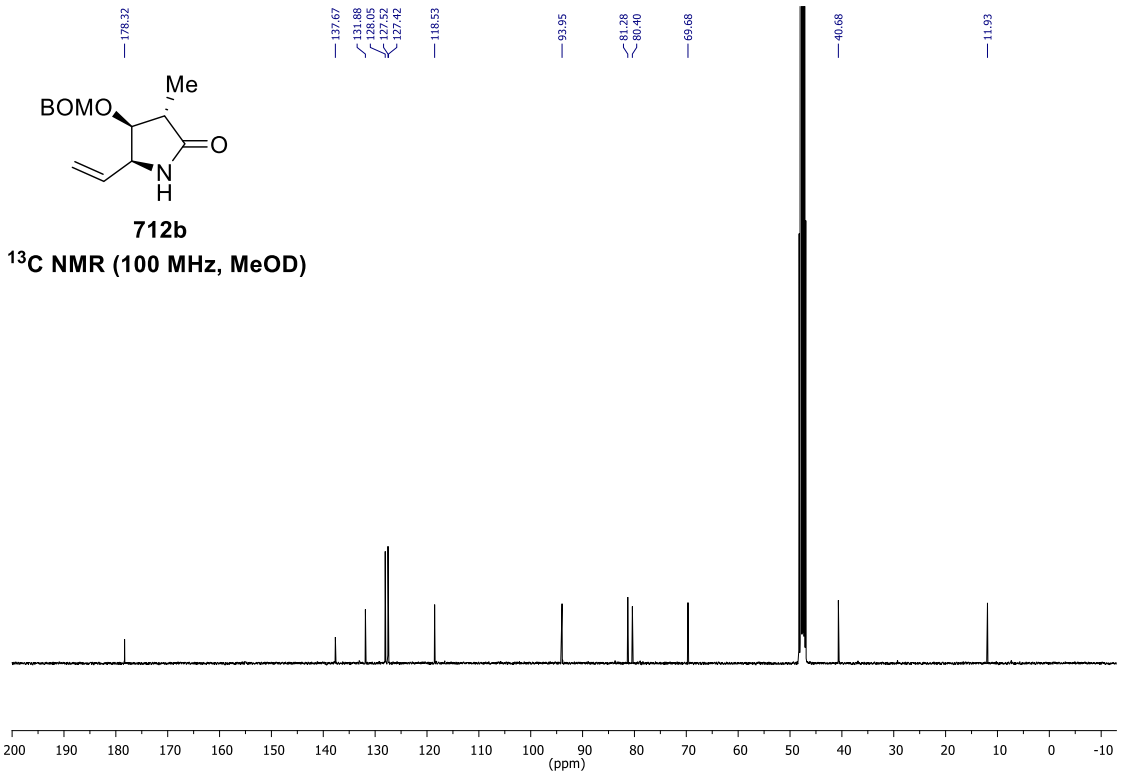
^{1}H NMR (400 MHz, MeOD)

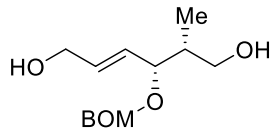


712a

^{13}C NMR (100 MHz, MeOD)

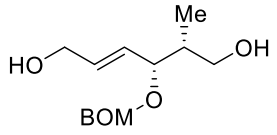






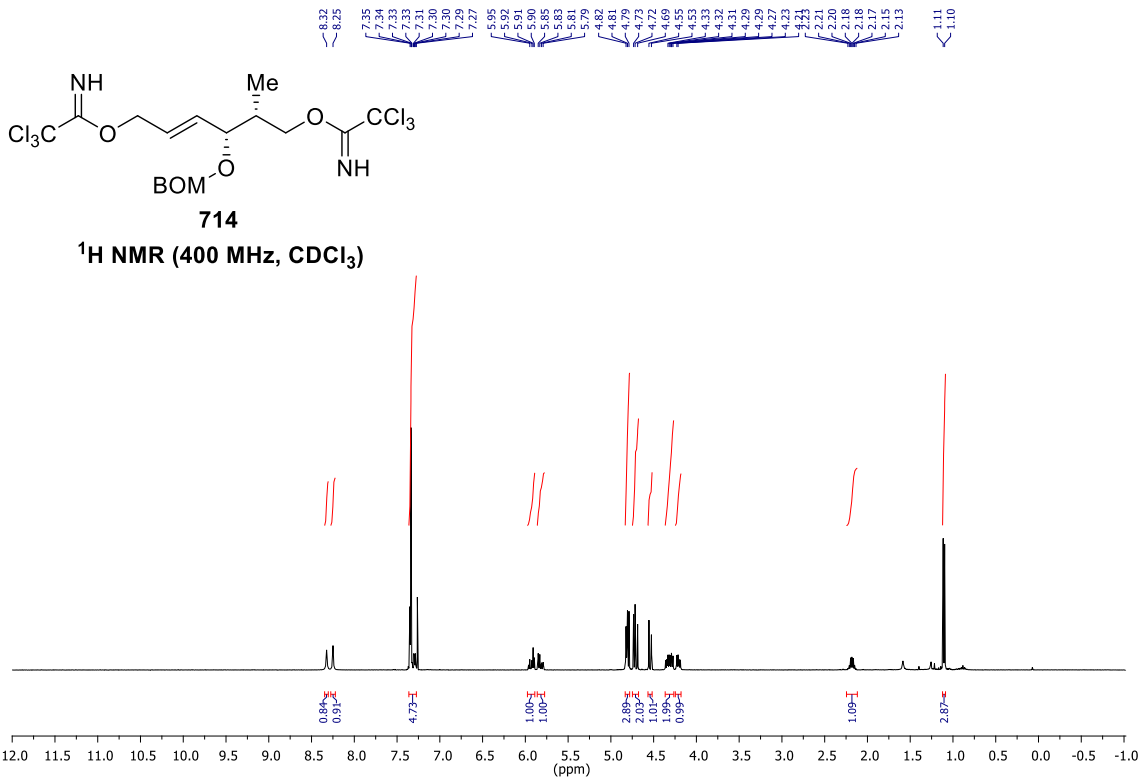
713

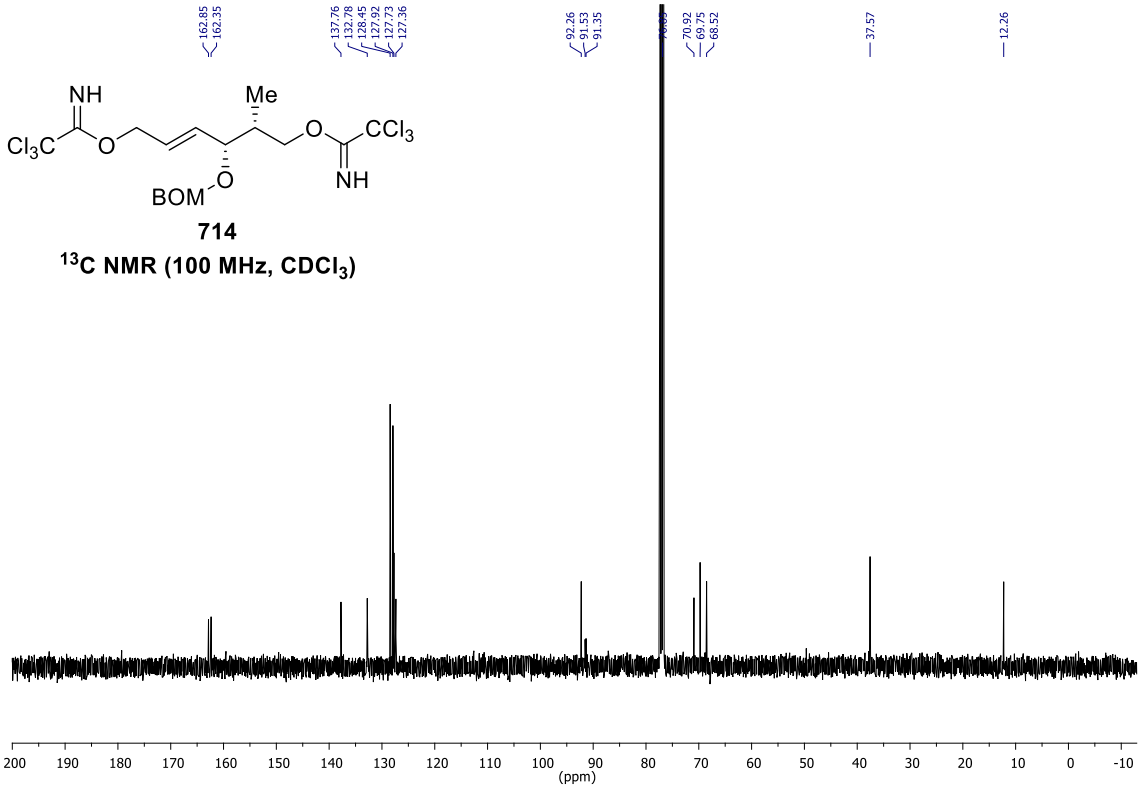
^{1}H NMR (400 MHz, MeOD)



713

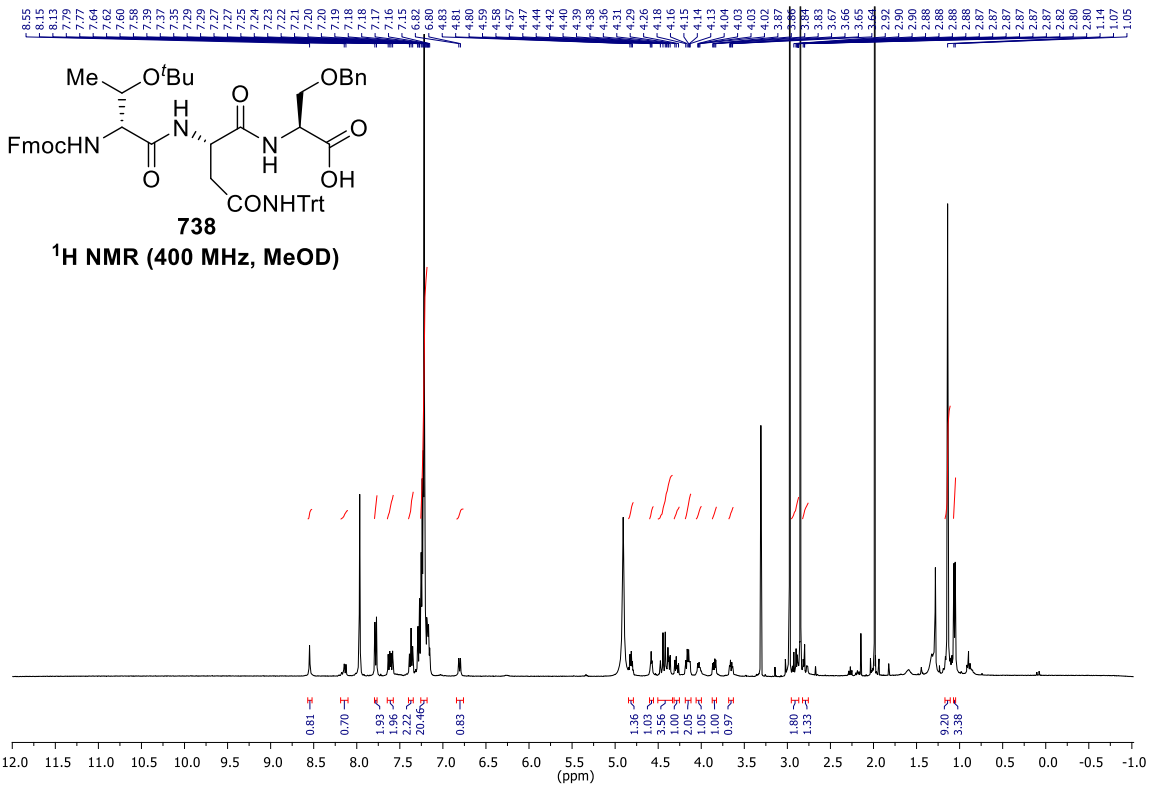
^{13}C NMR (100 MHz, MeOD)

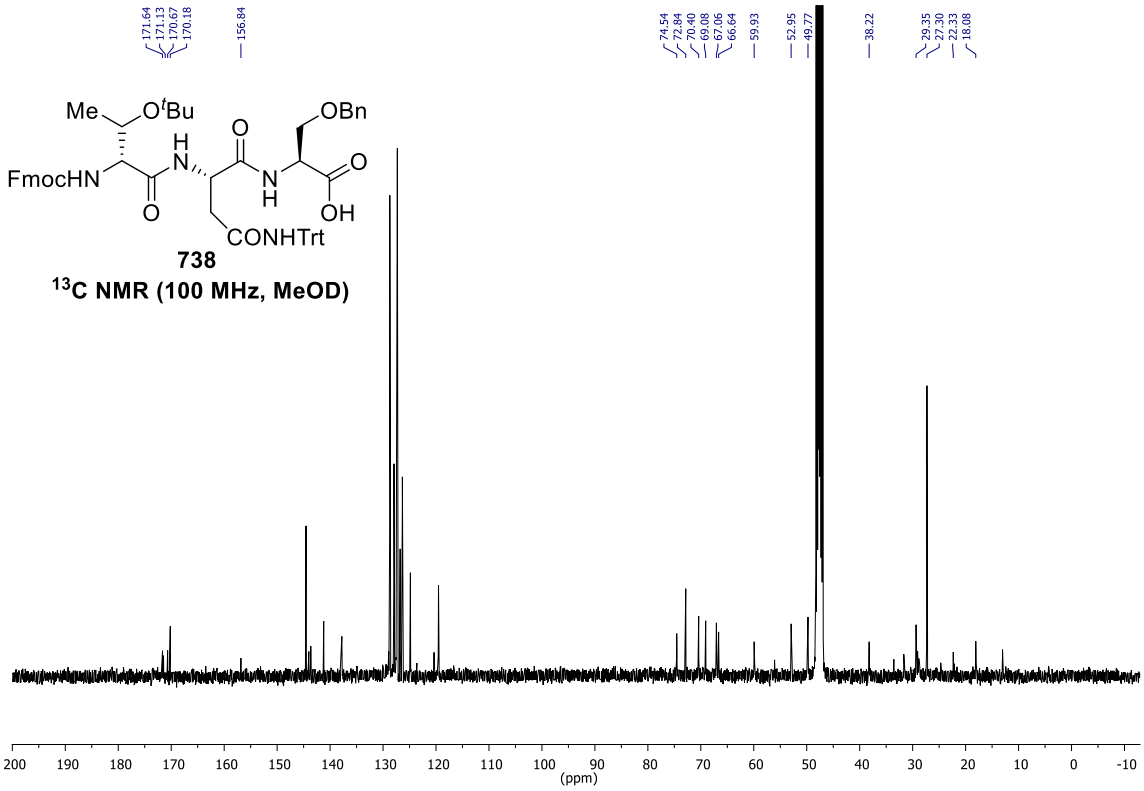


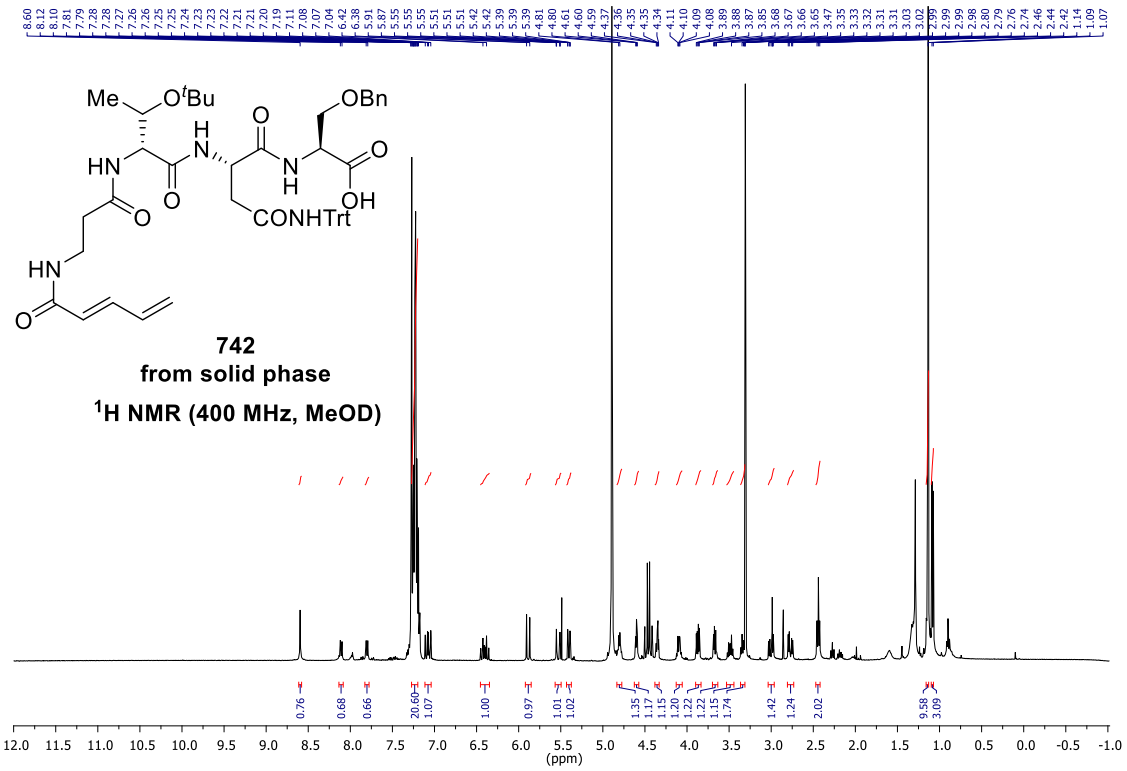


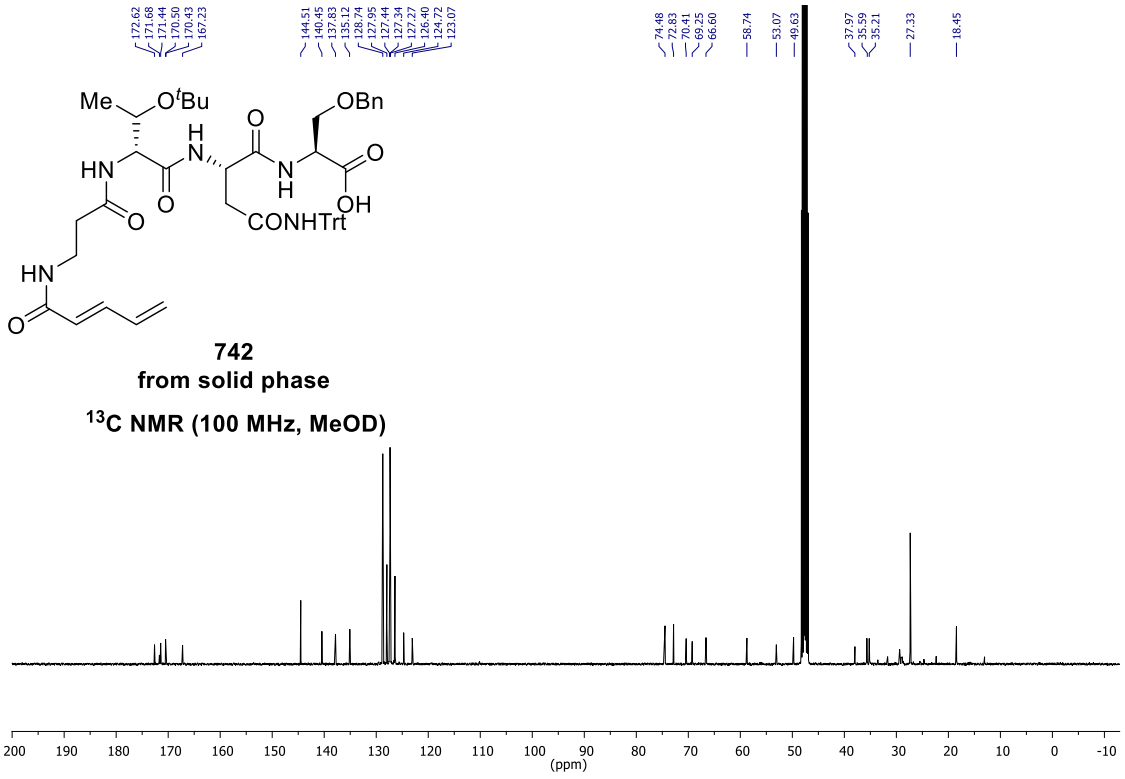
Appendix III

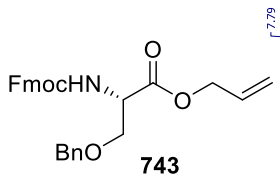
^{1}H and ^{13}C NMR Spectra Related to the Celebesides





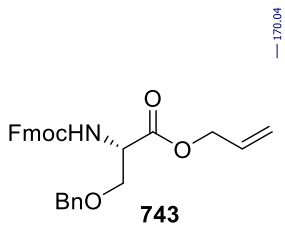






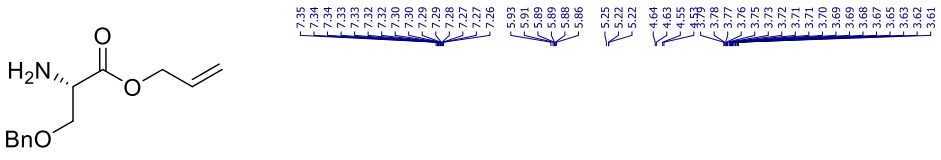
743

^{1}H NMR (400 MHz, $CDCl_3$)



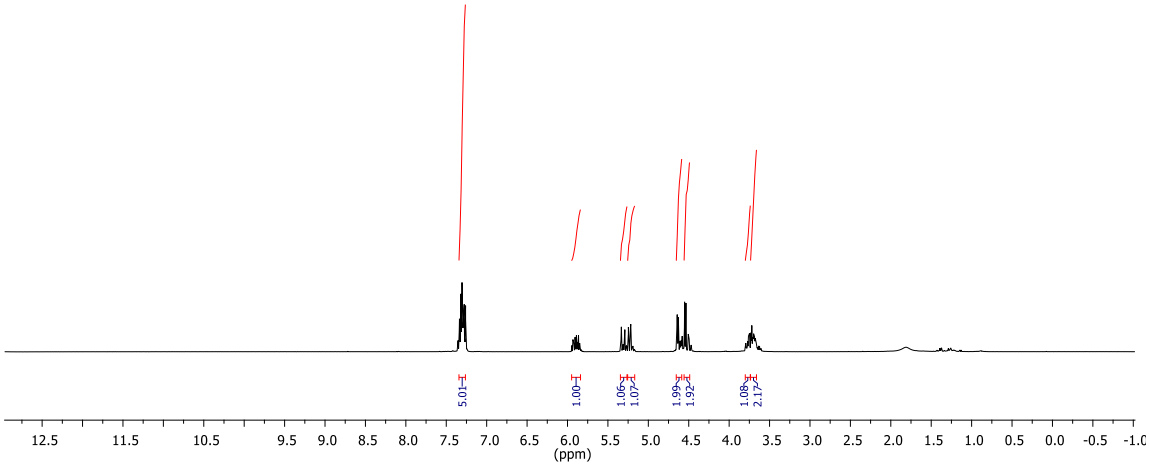
743

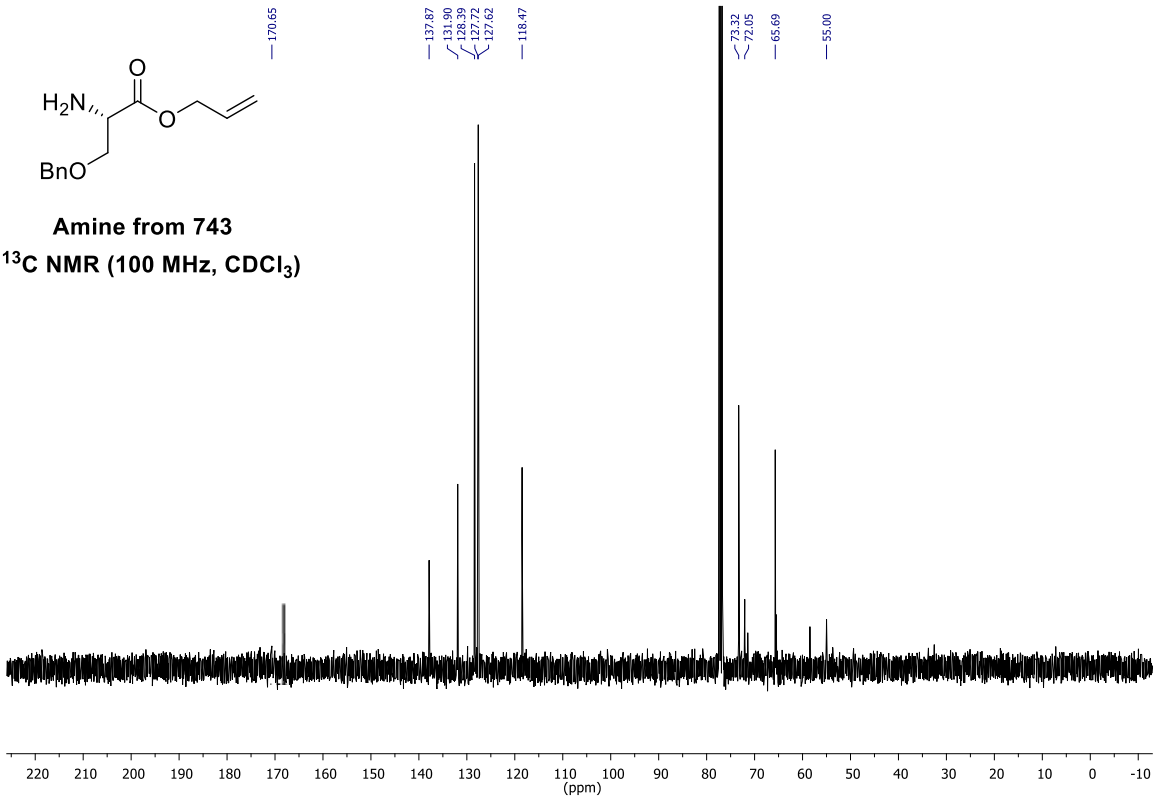
^{13}C NMR (100 MHz, $CDCl_3$)



Amine from 743

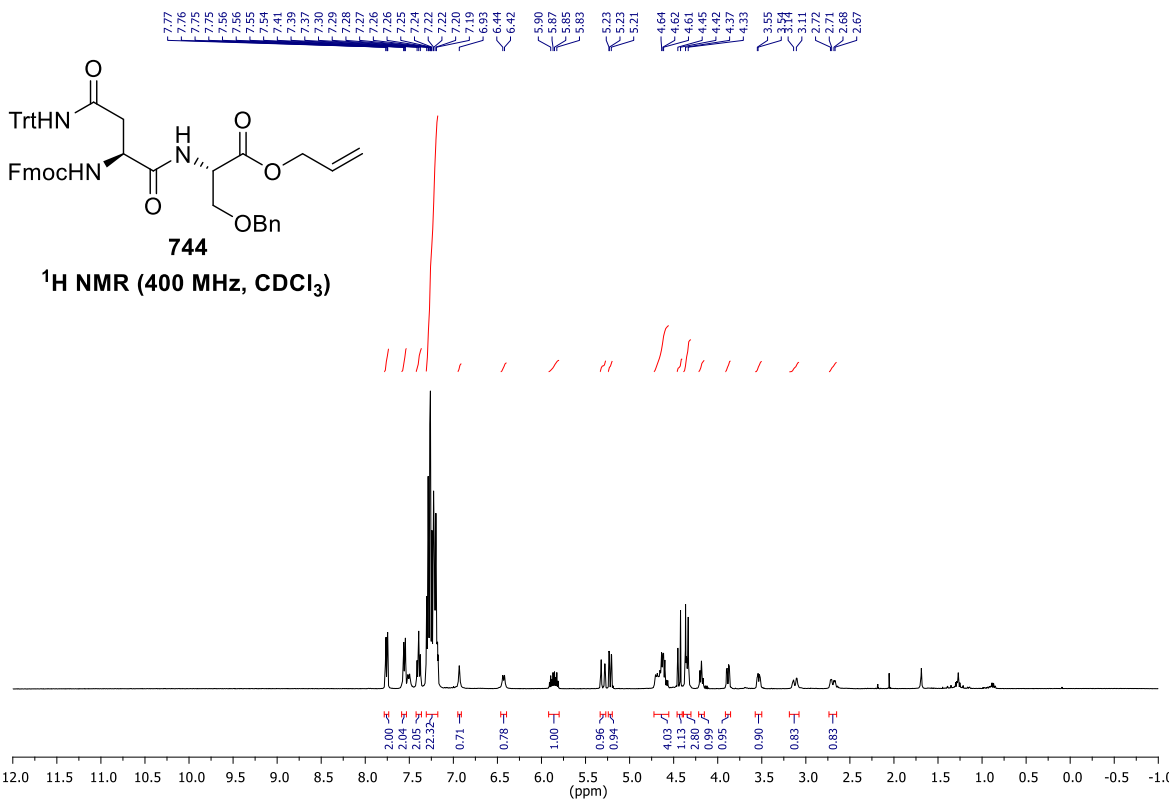
^{1}H NMR (400 MHz, $CDCl_3$)





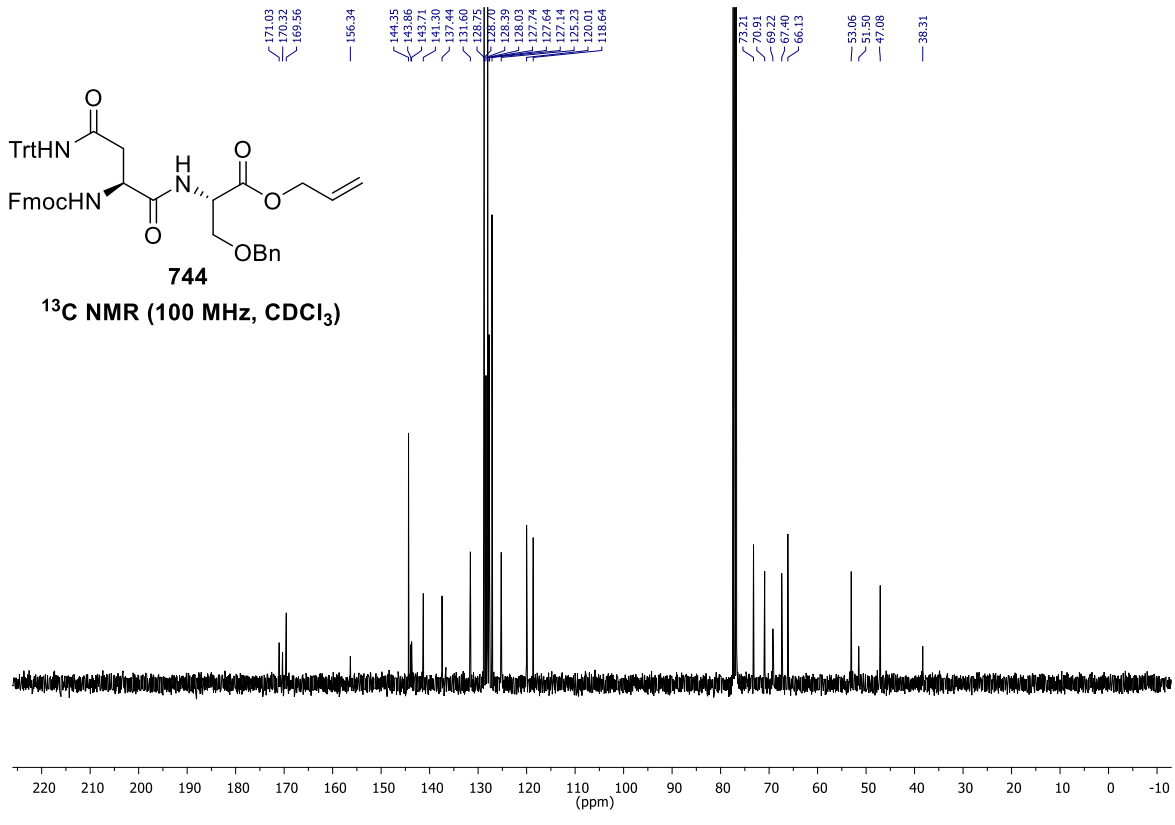
Amine from 743

^{13}C NMR (100 MHz, $CDCl_3$)



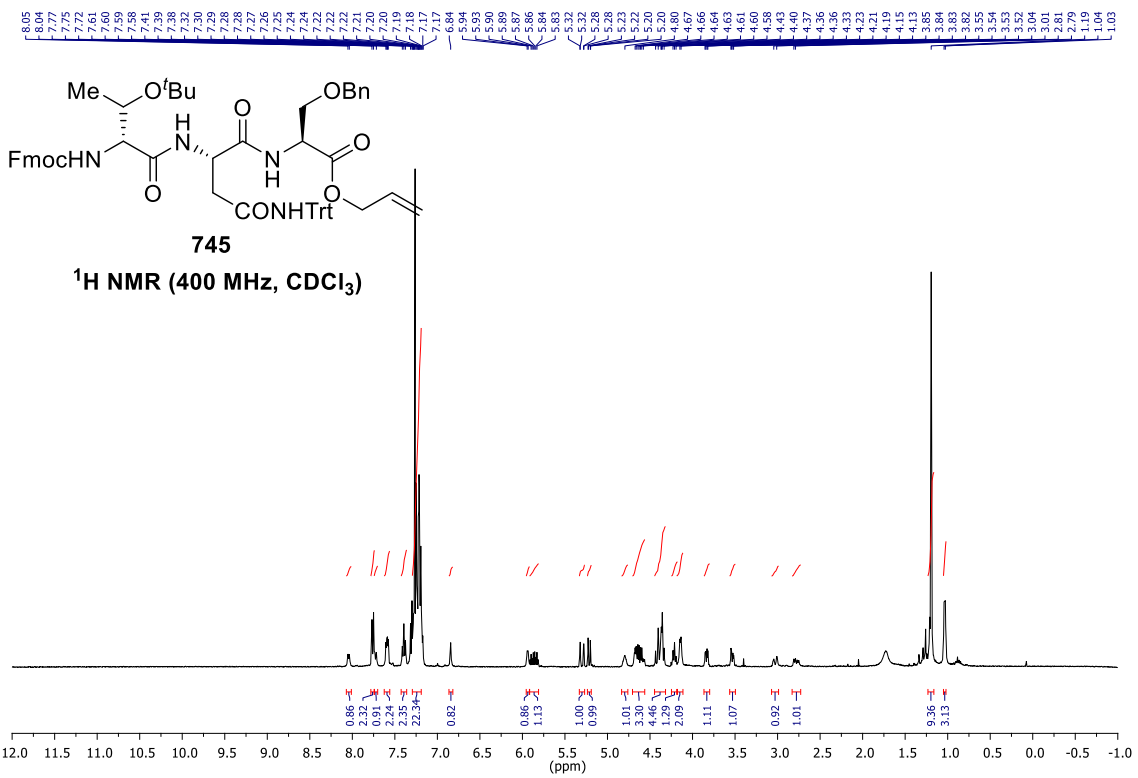
744

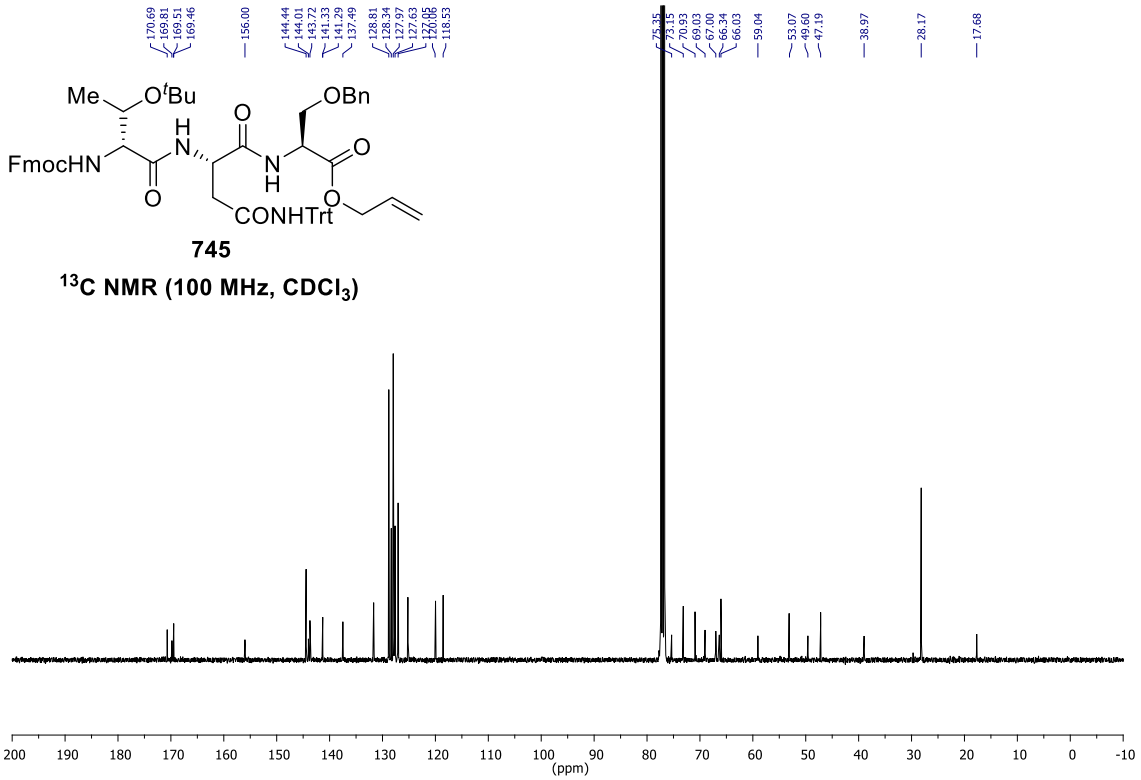
^{1}H NMR (400 MHz, $CDCl_3$)

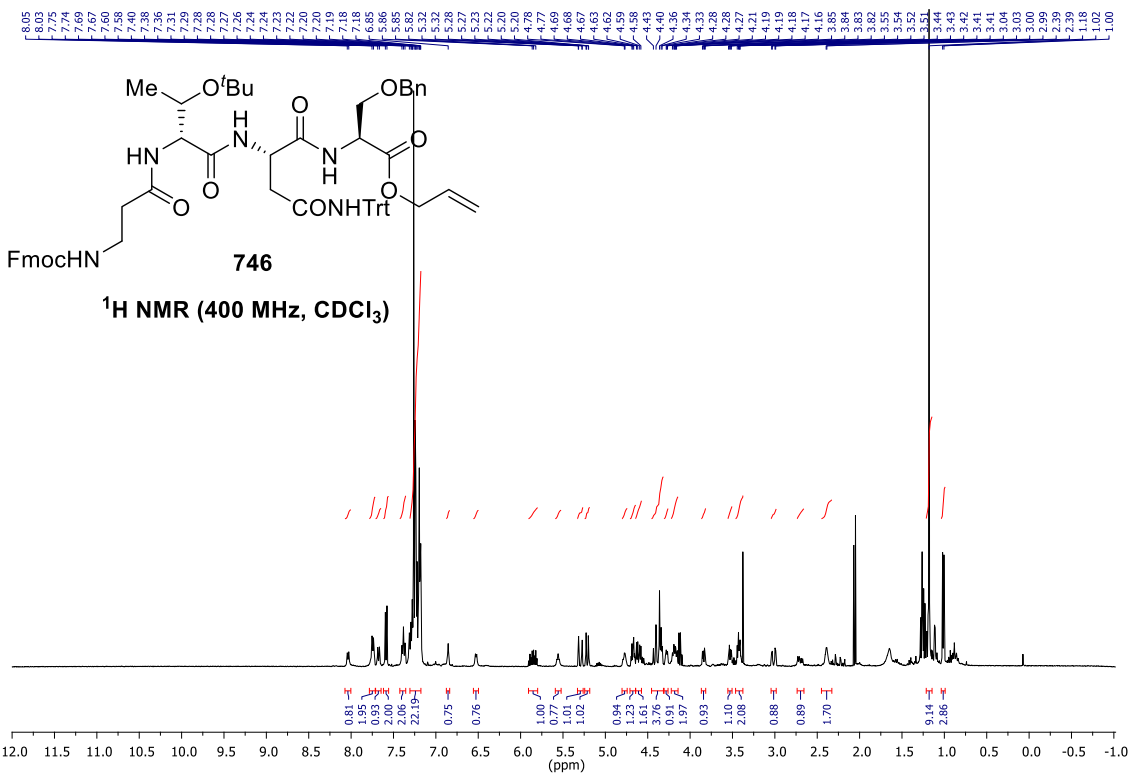


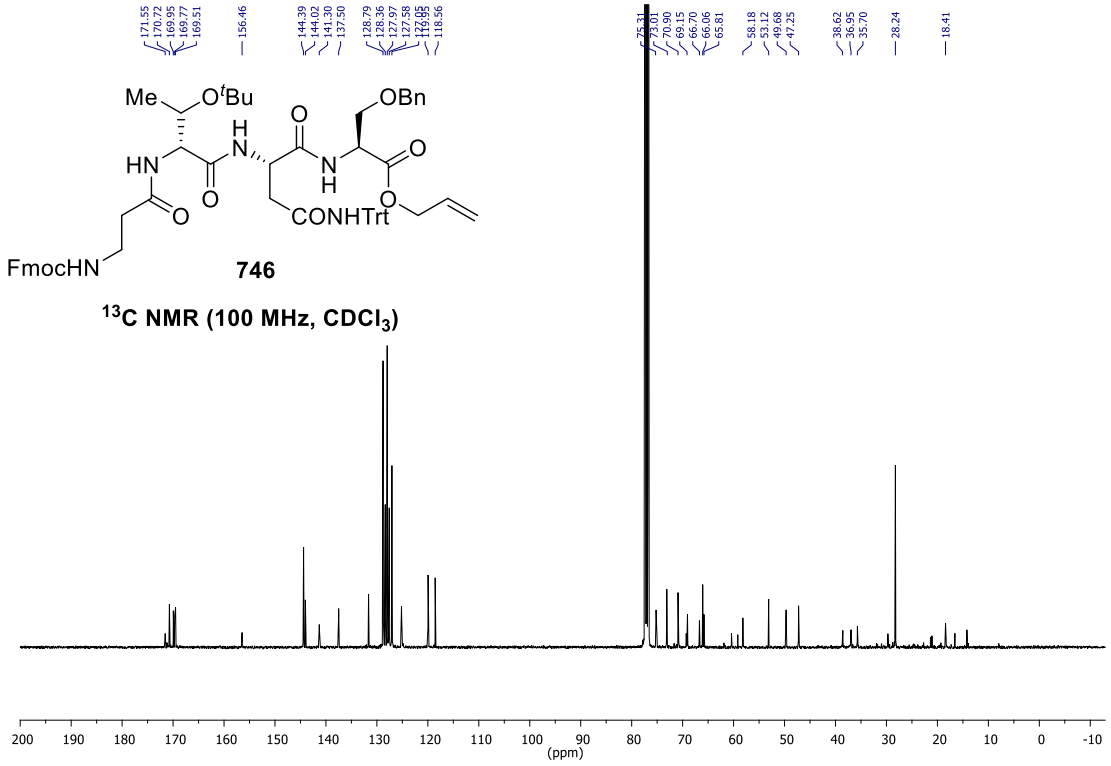
744

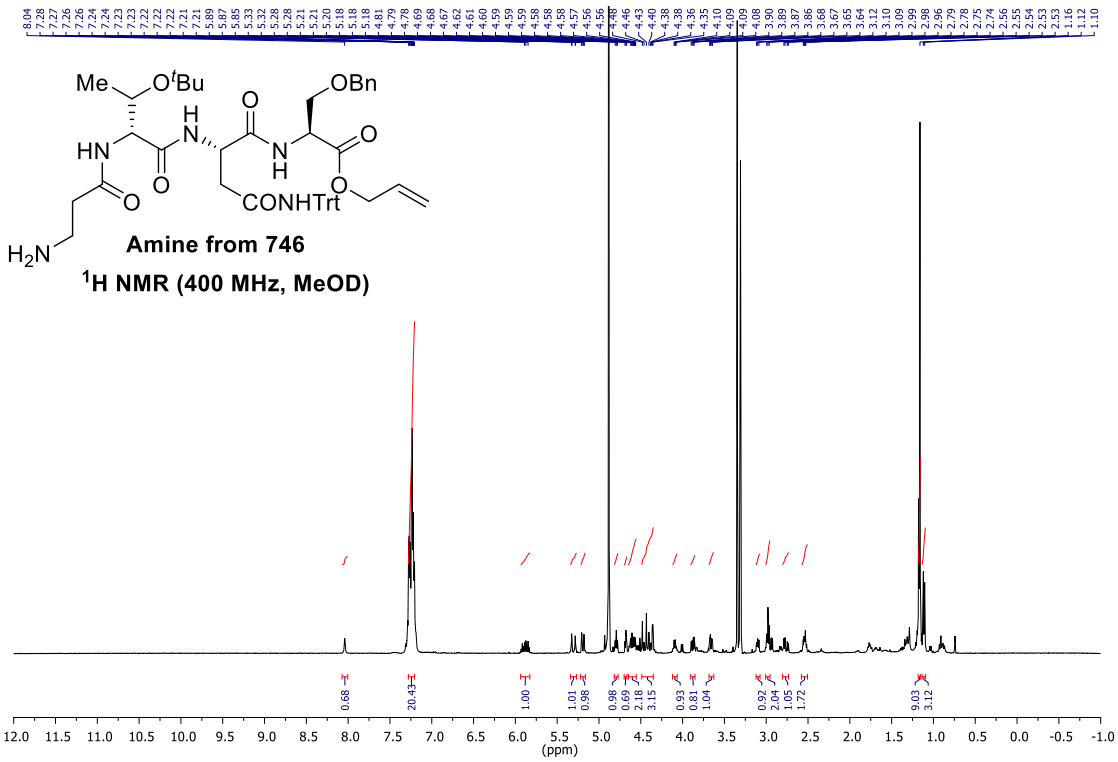
^{13}C NMR (100 MHz, $CDCl_3$)

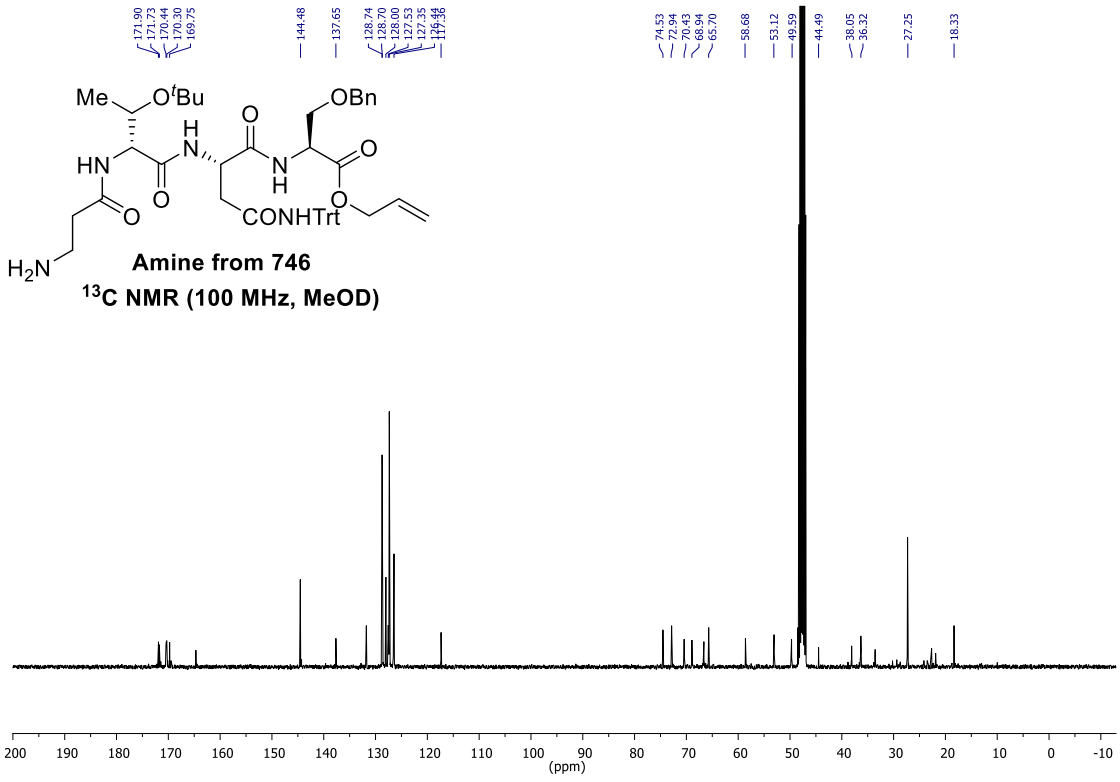


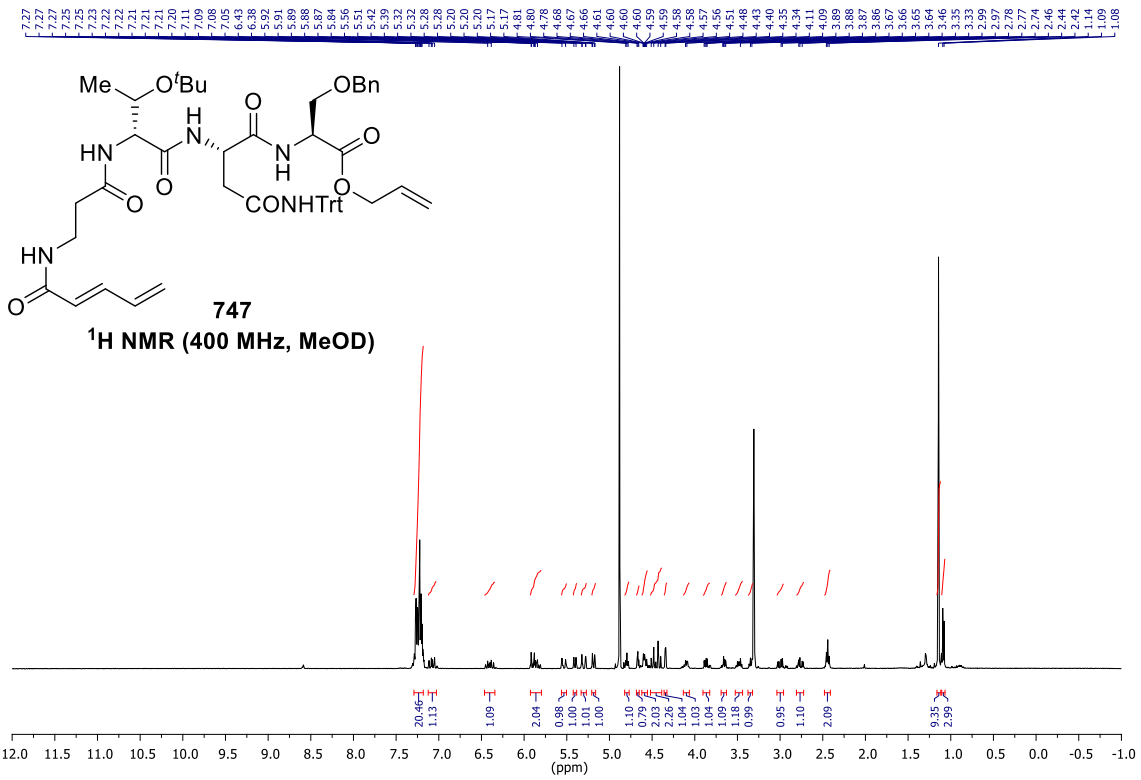


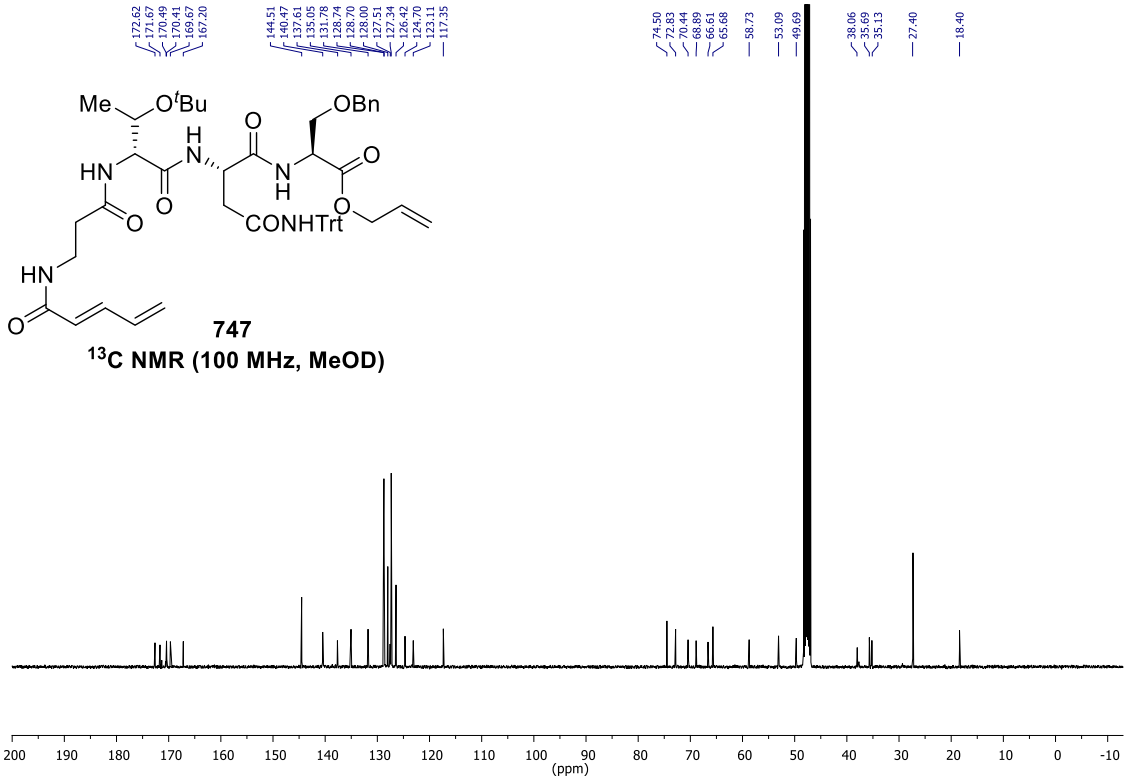


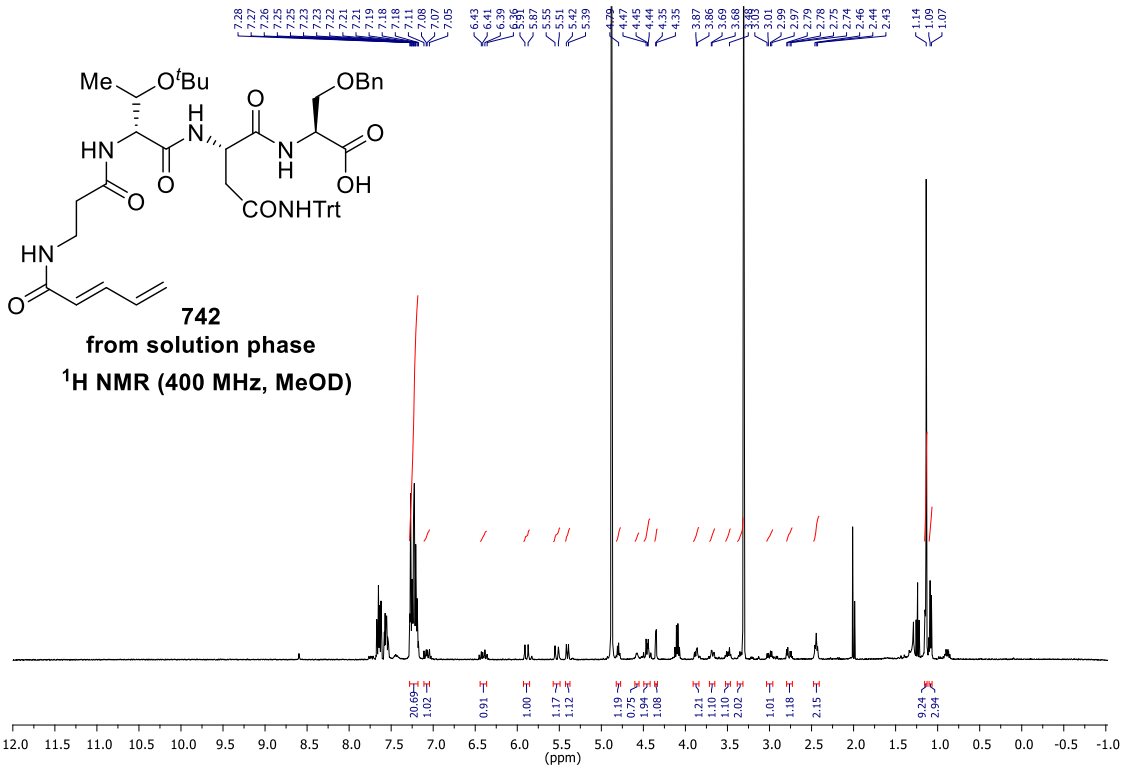


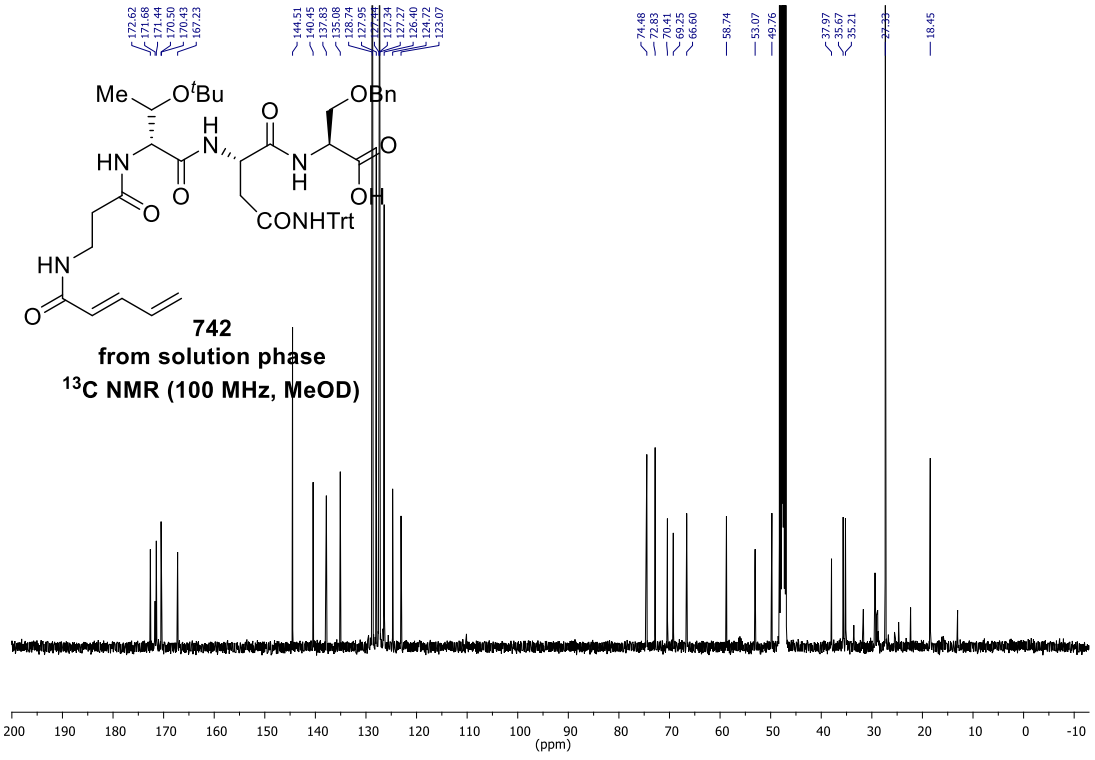


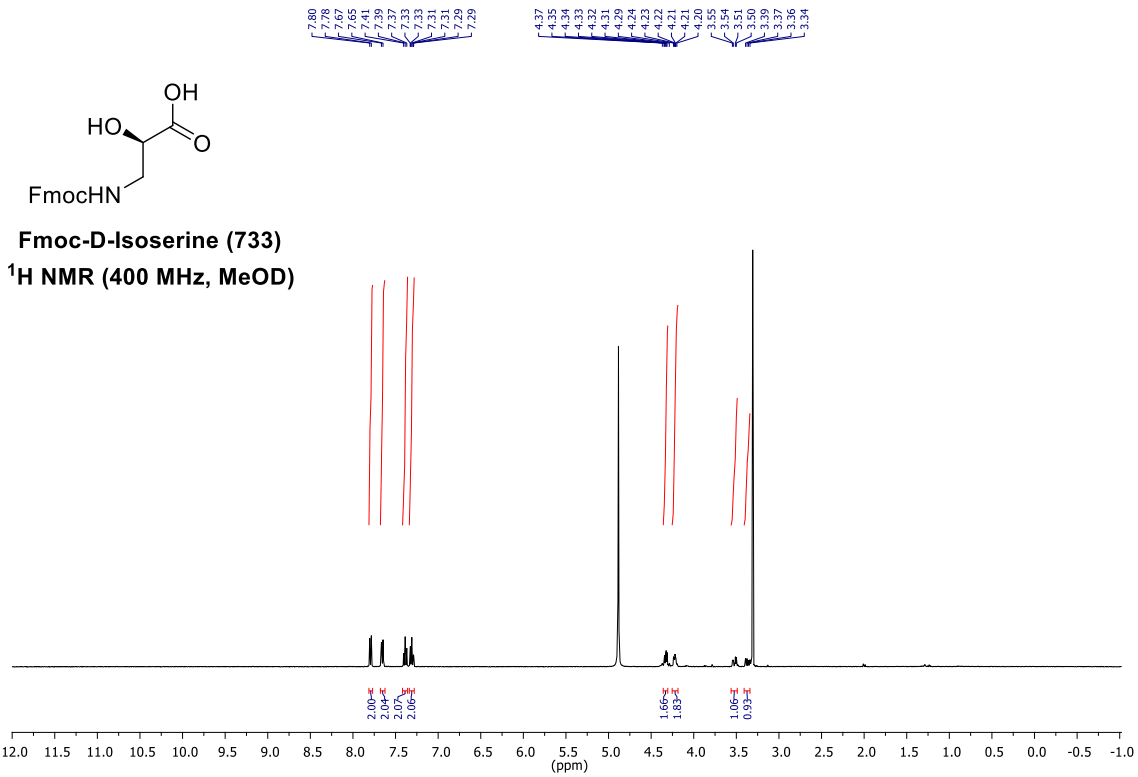




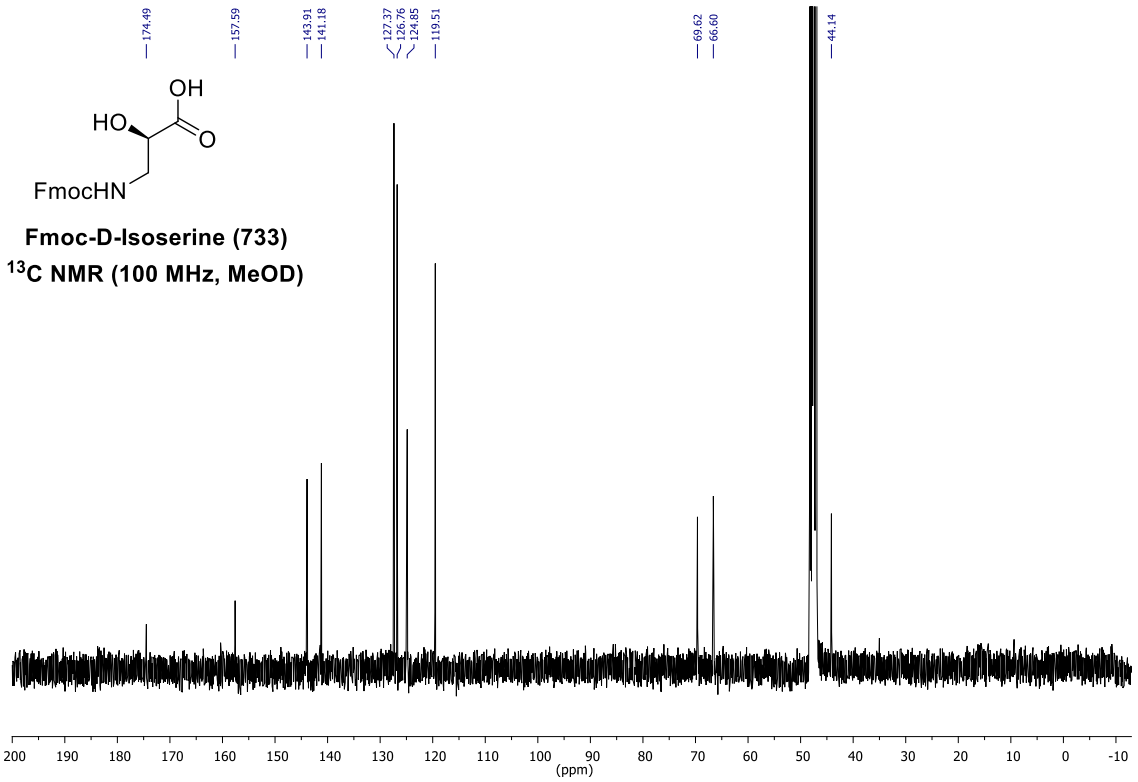




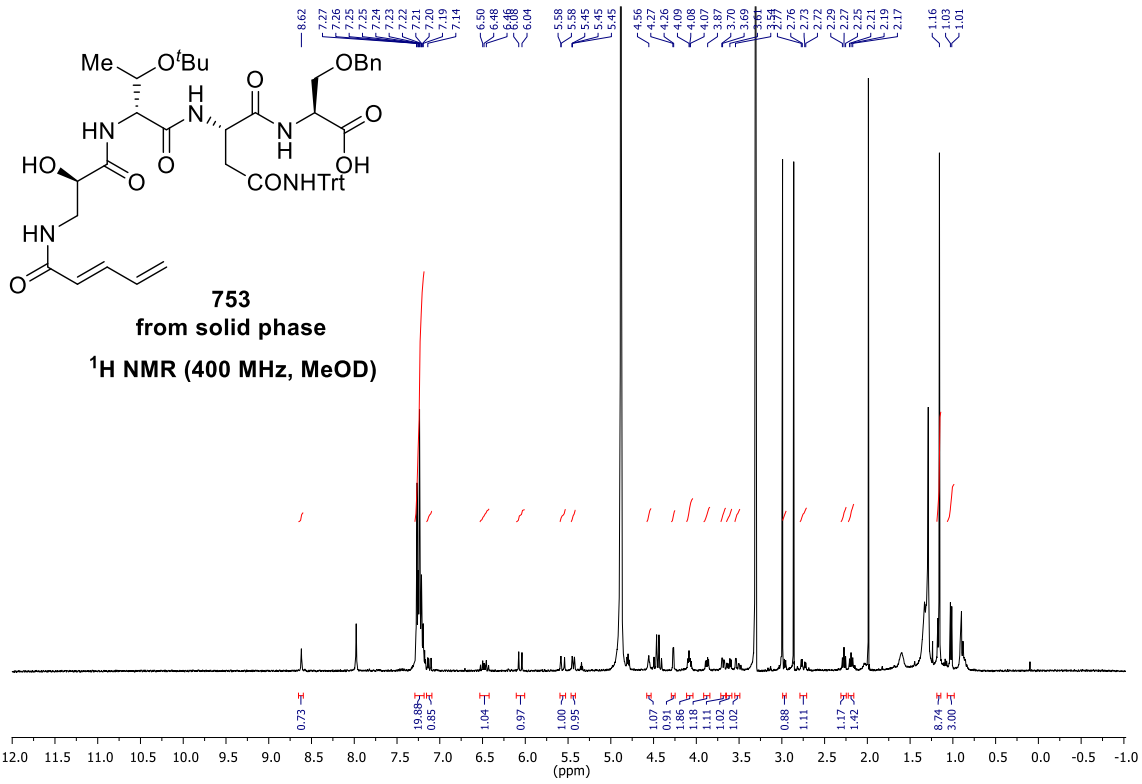


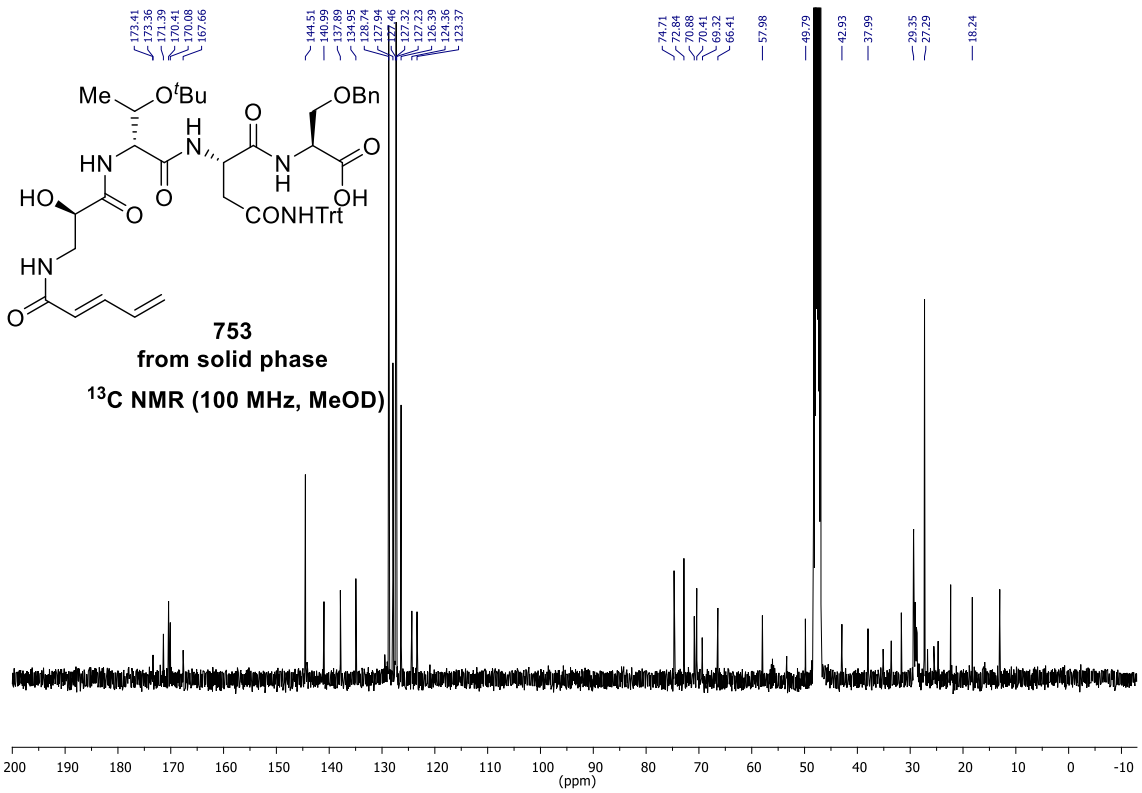


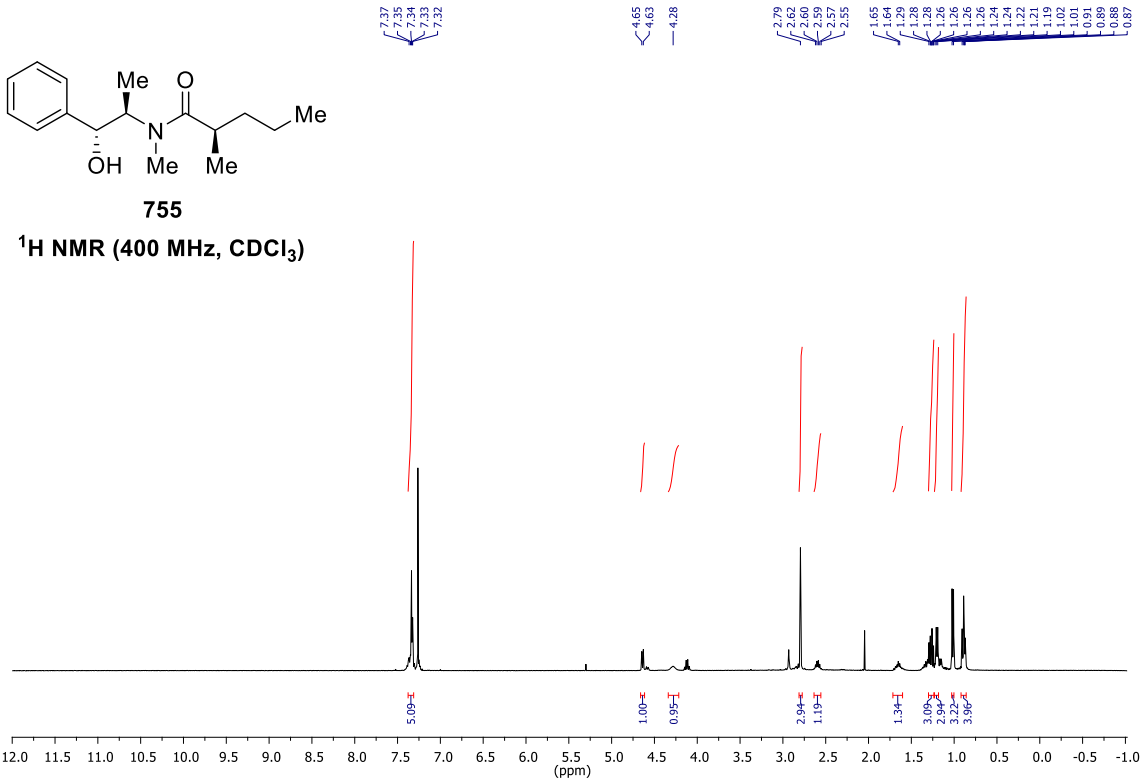
Fmoc-D-Isoserine (733)
^{1}H NMR (400 MHz, MeOD)



Fmoc-D-Isoserine (733)
^{13}C NMR (100 MHz, MeOD)

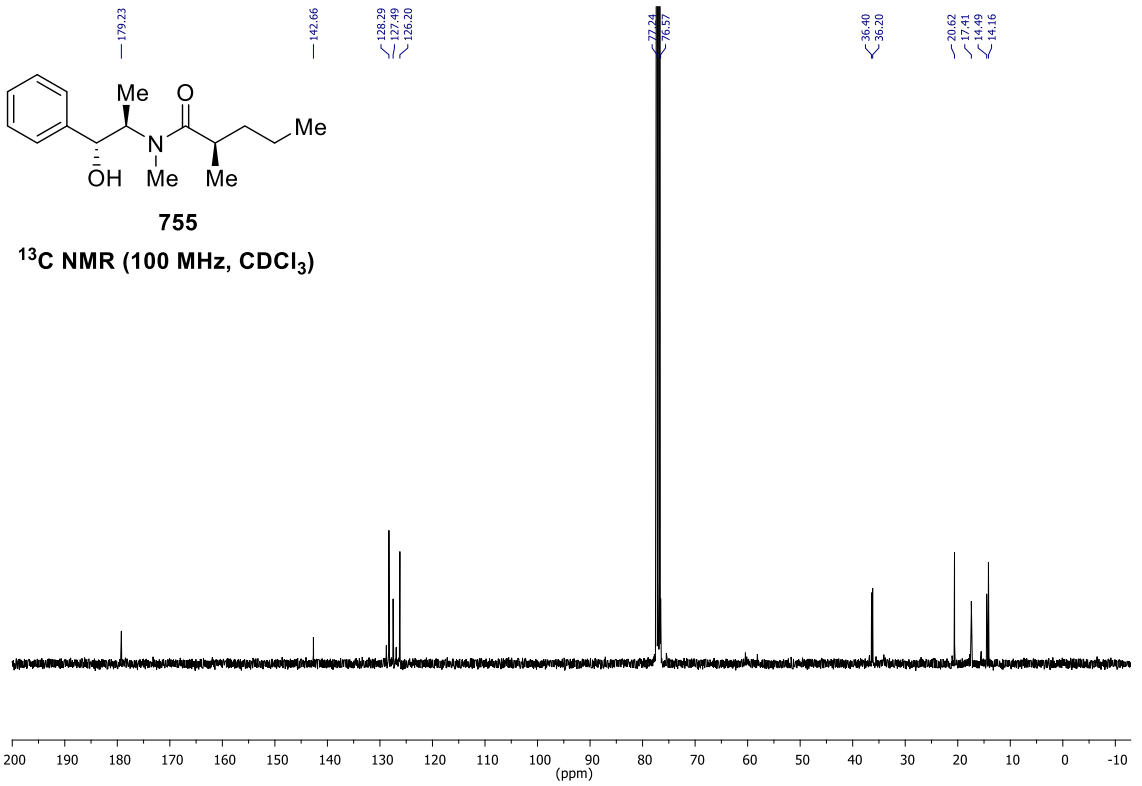






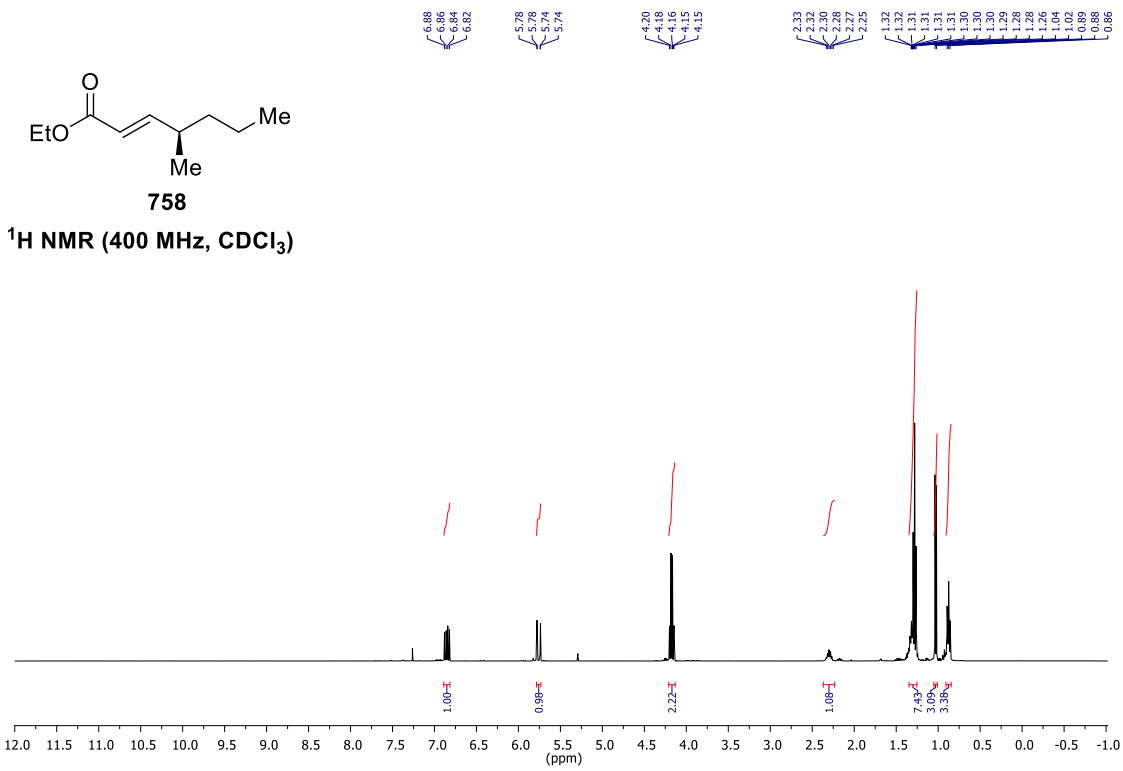
755

^{1}H NMR (400 MHz, $CDCl_3$)



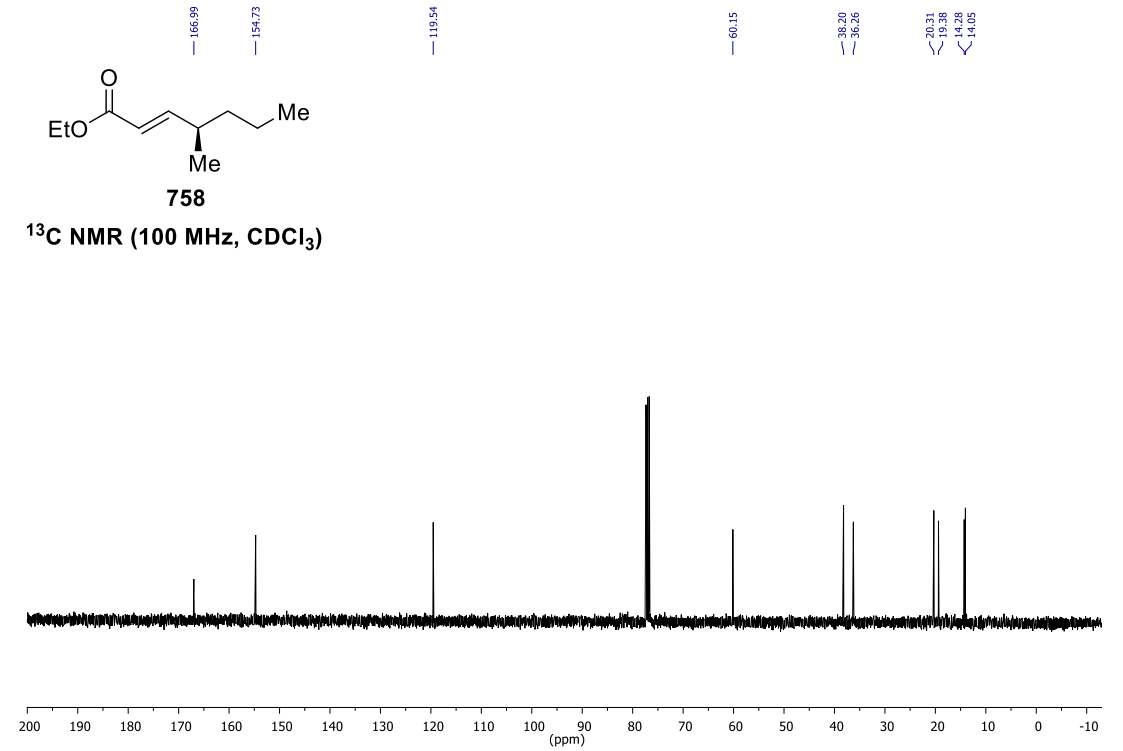
755

^{13}C NMR (100 MHz, $CDCl_3$)



758

^{1}H NMR (400 MHz, $CDCl_3$)



758

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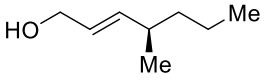

759

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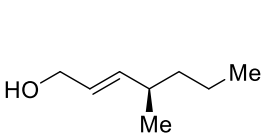

759

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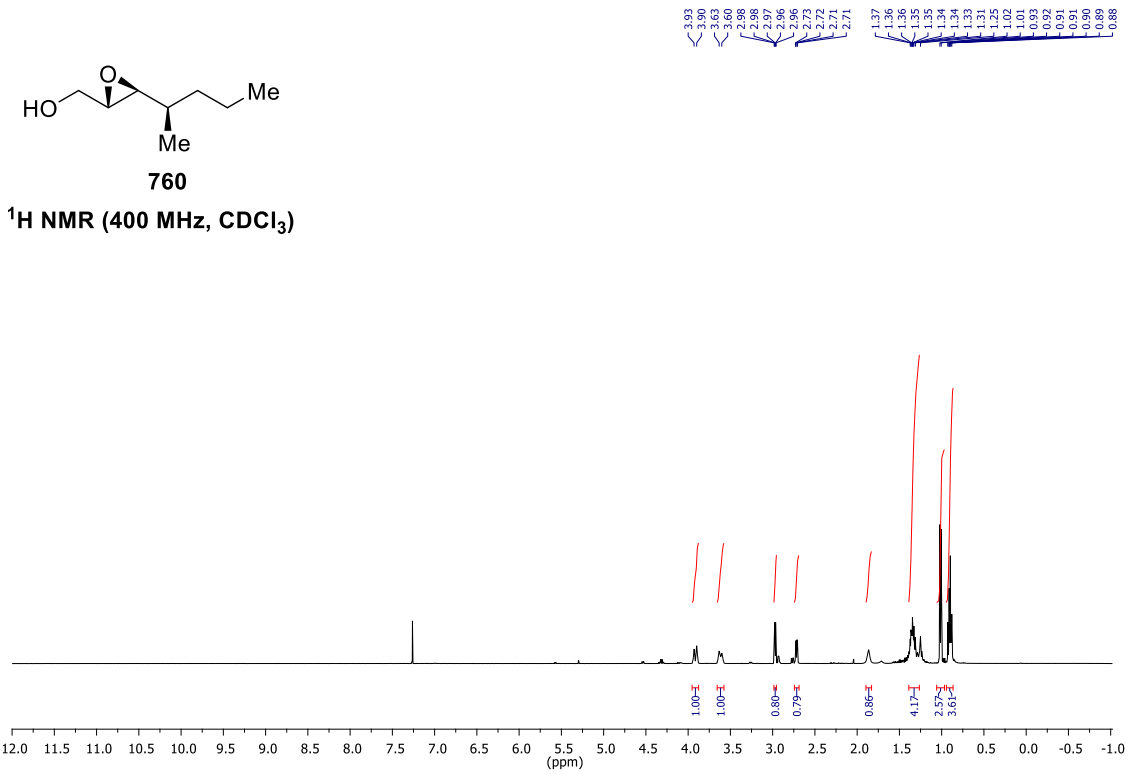

760

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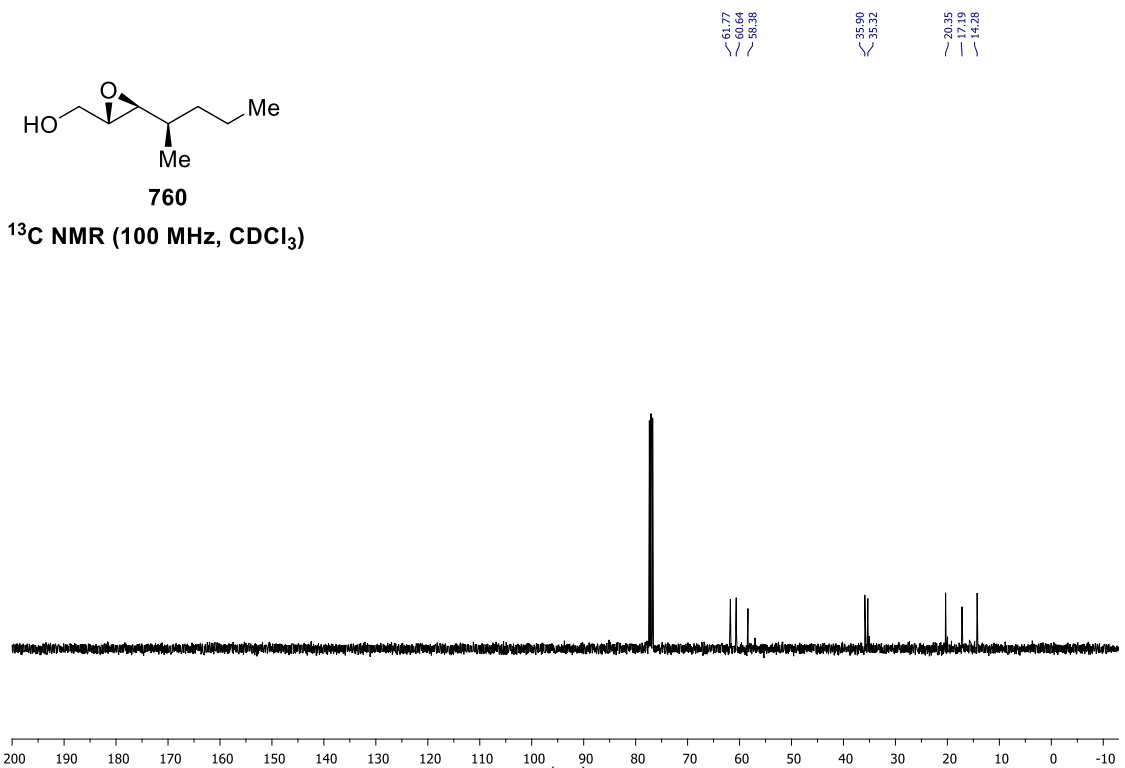

760

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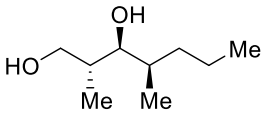

761

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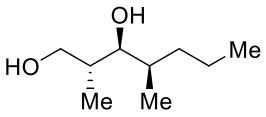

761

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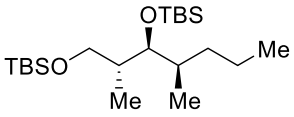

762

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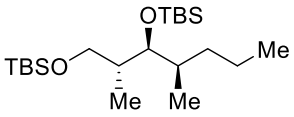

762

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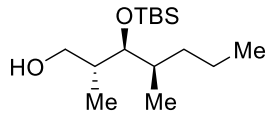

763

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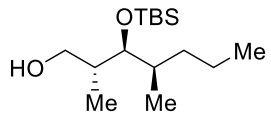

763

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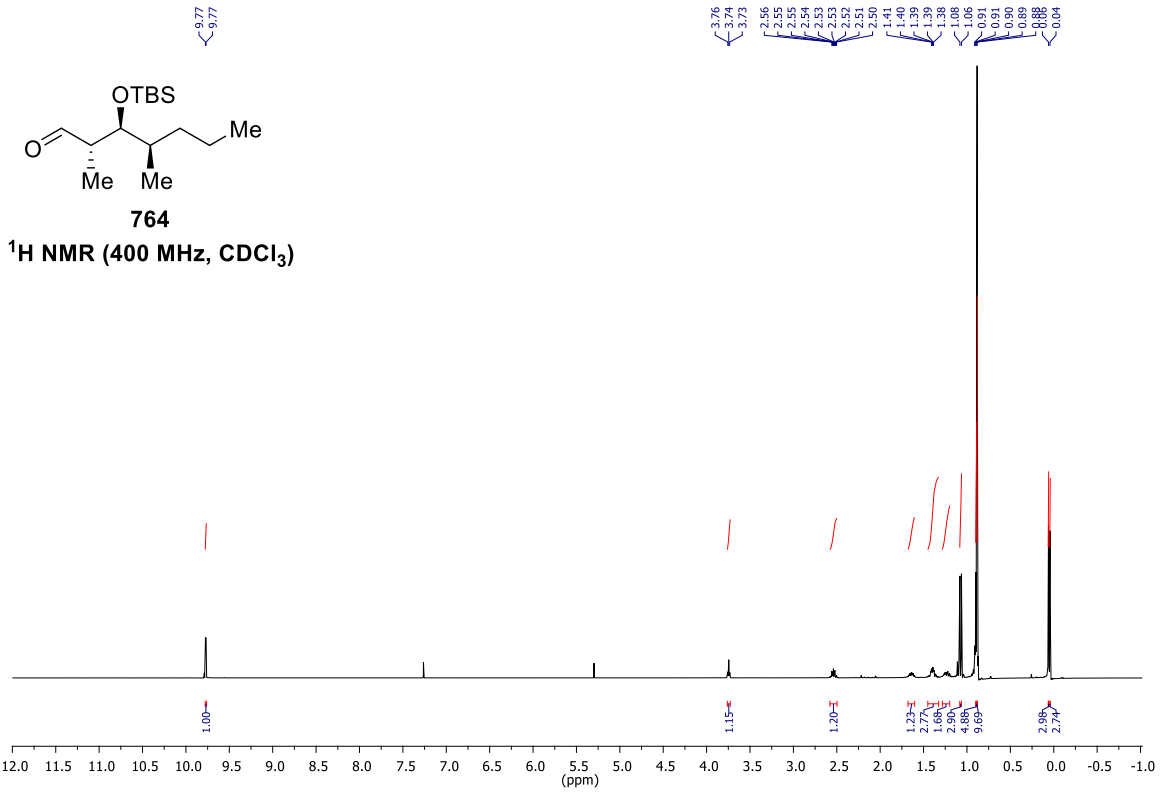

764

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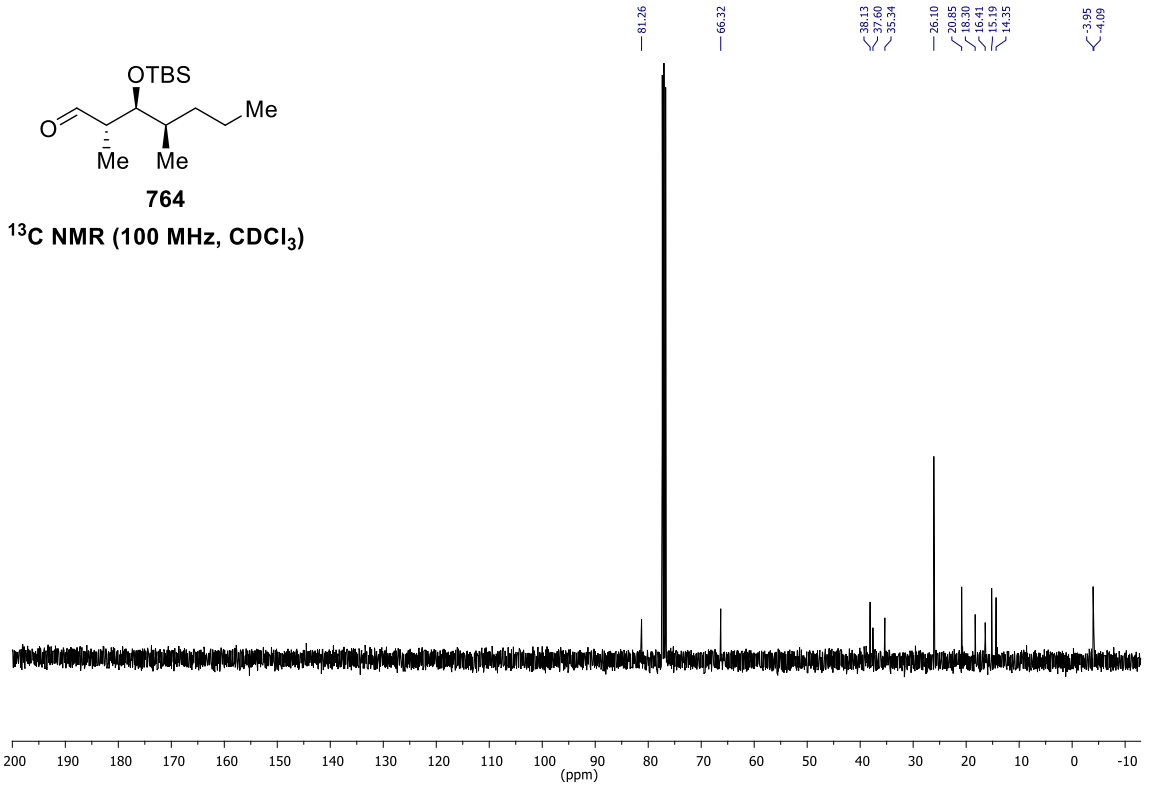

764

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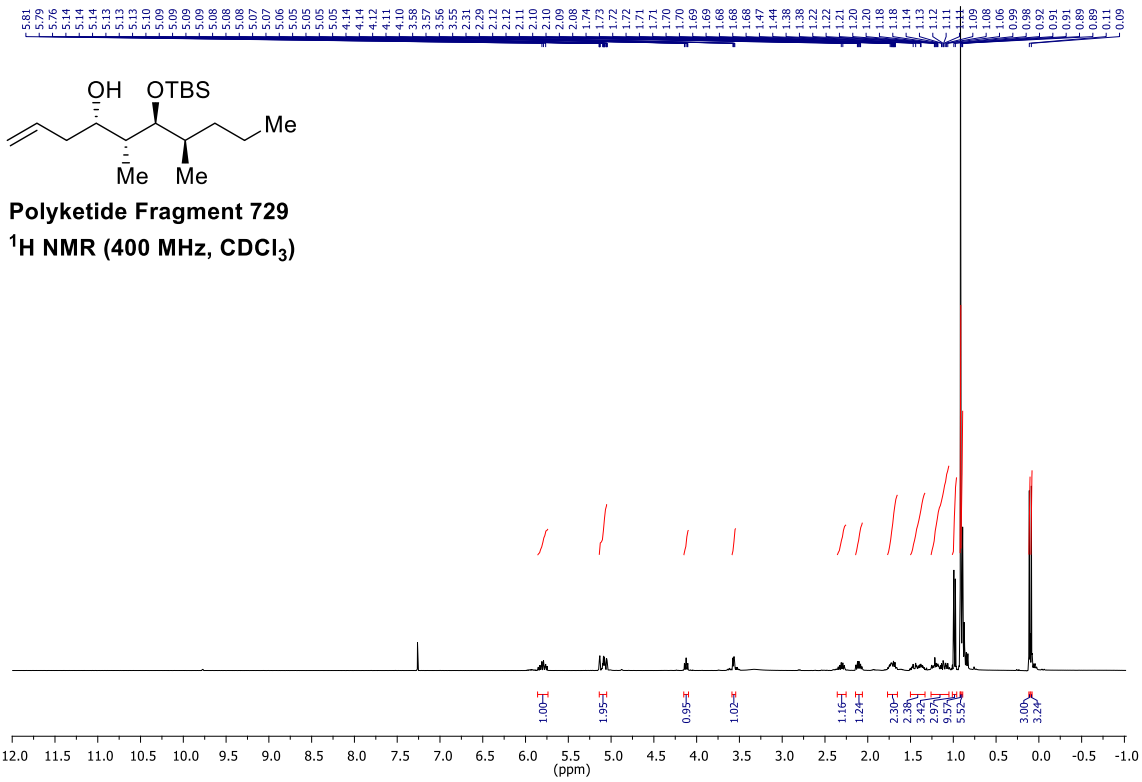
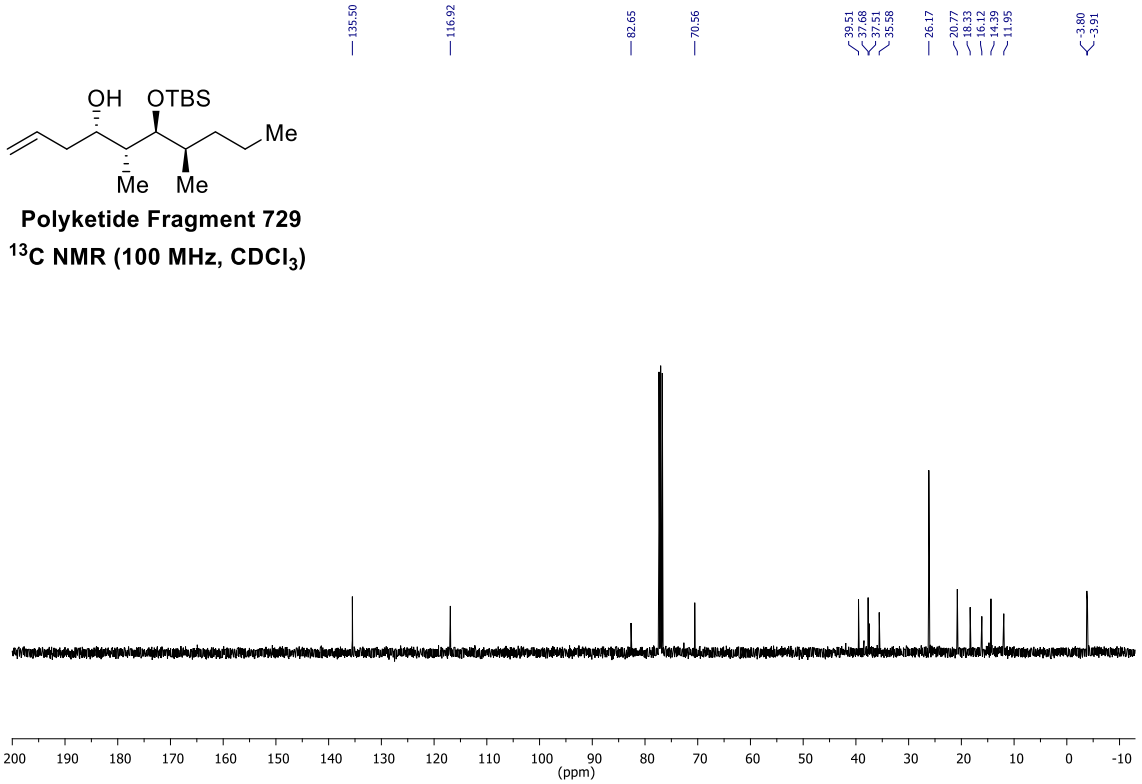


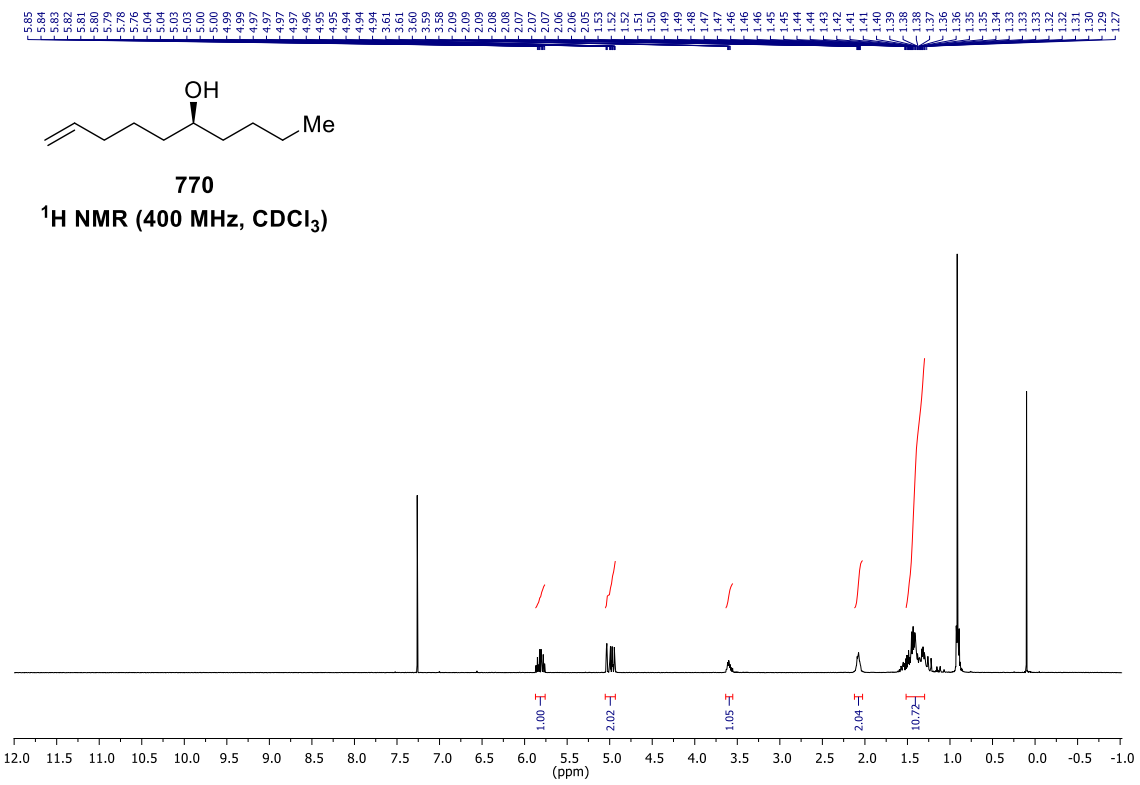
Polyketide Fragment 729

^{1}H NMR (400 MHz, $CDCl_3$)



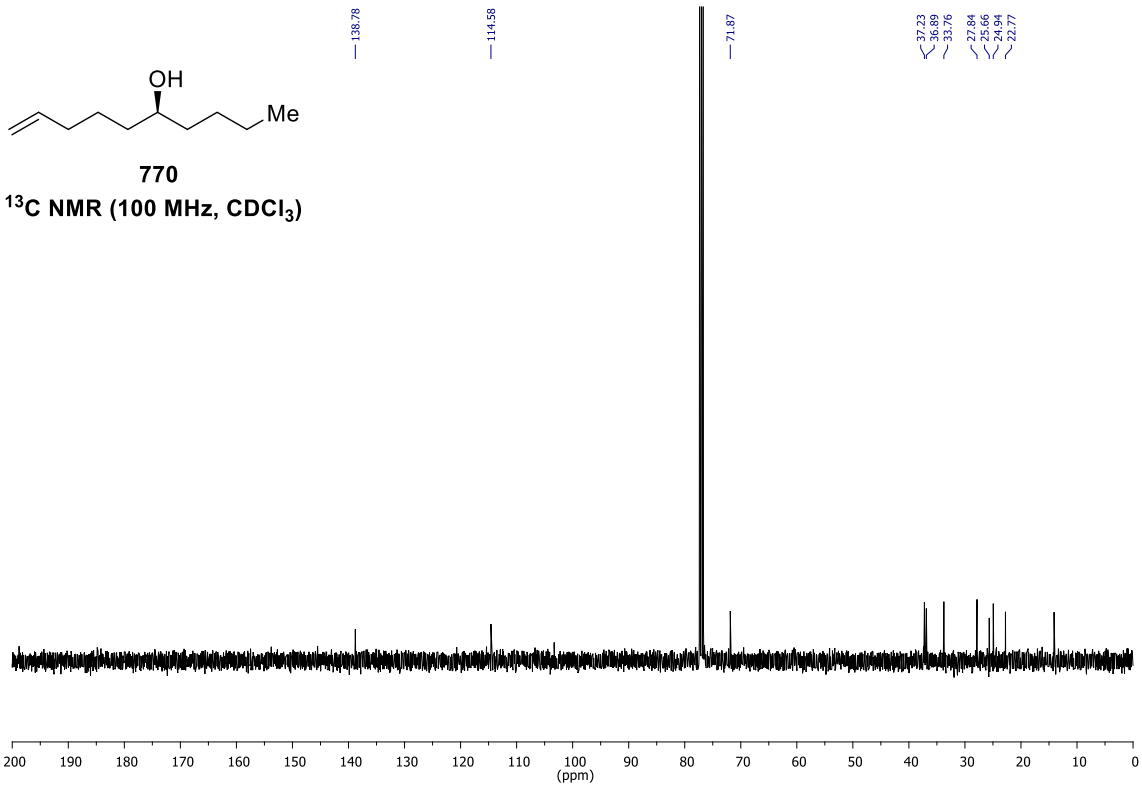
Polyketide Fragment 729

^{13}C NMR (100 MHz, $CDCl_3$)



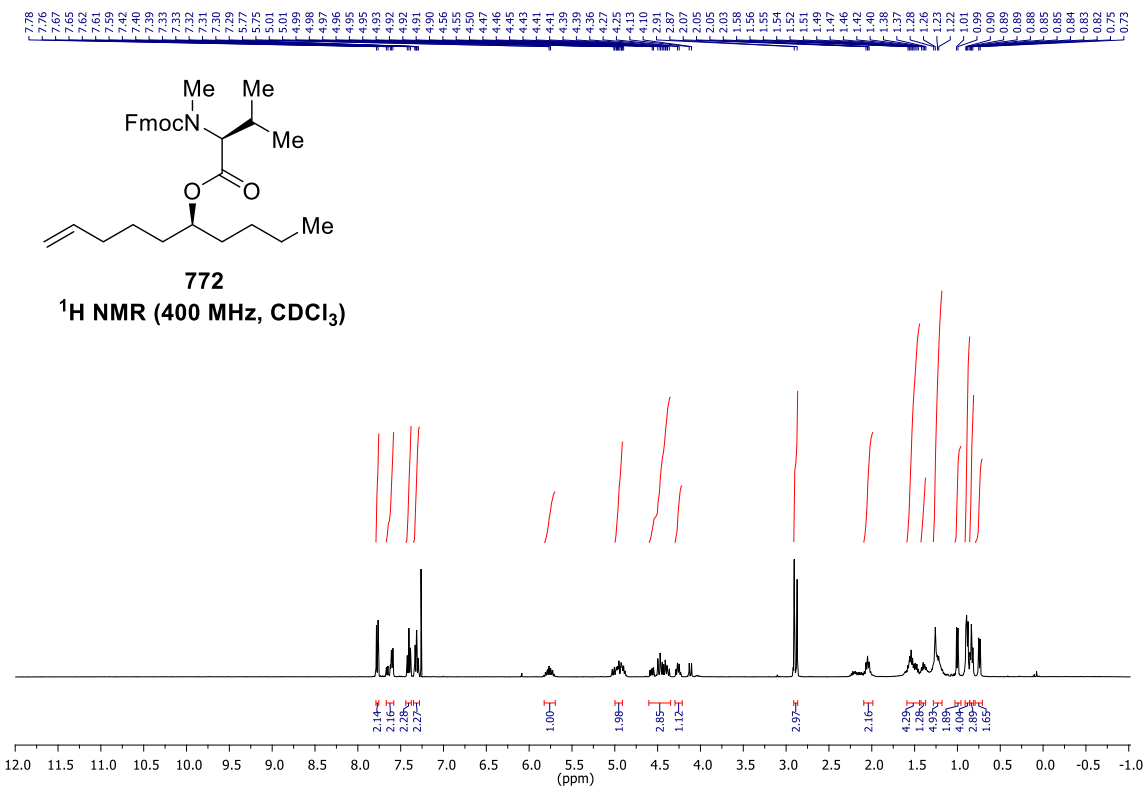
770

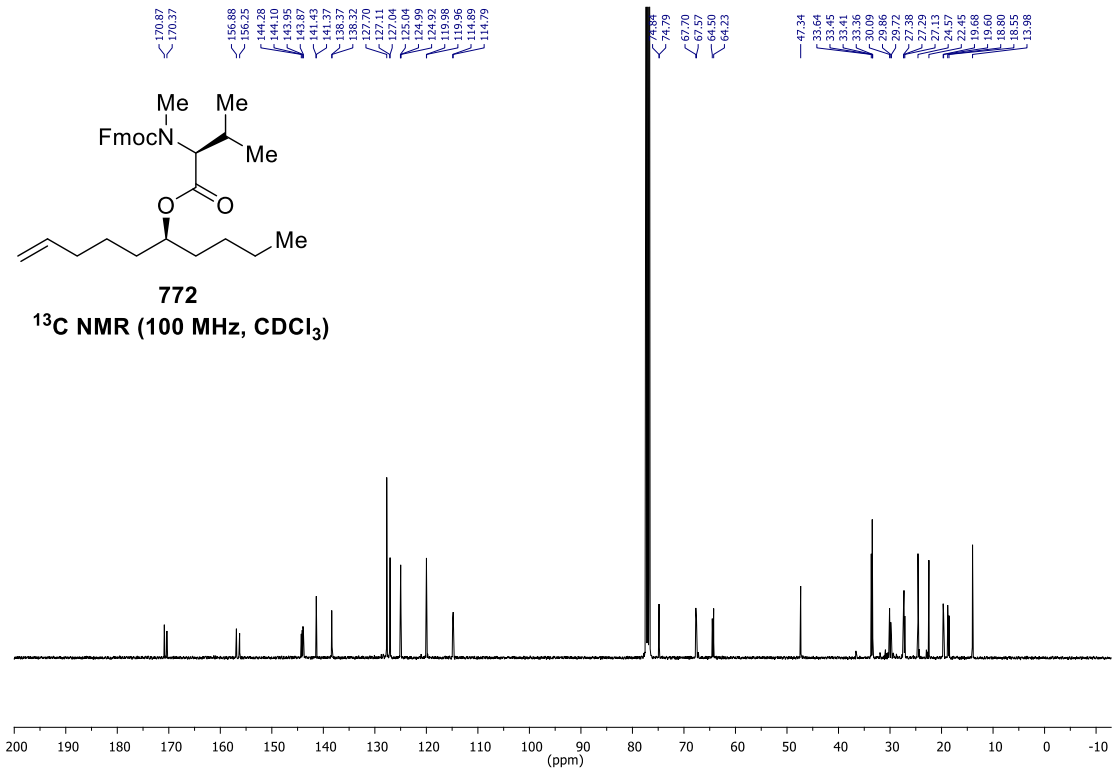
^{1}H NMR (400 MHz, $CDCl_3$)

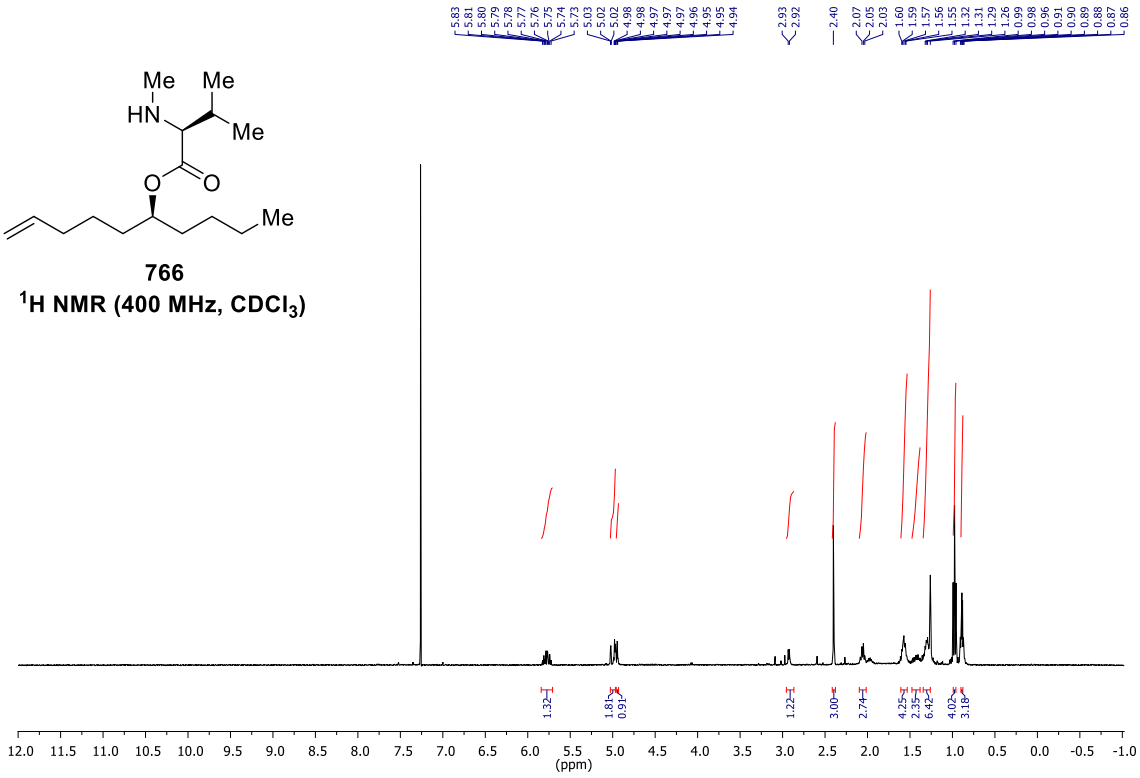


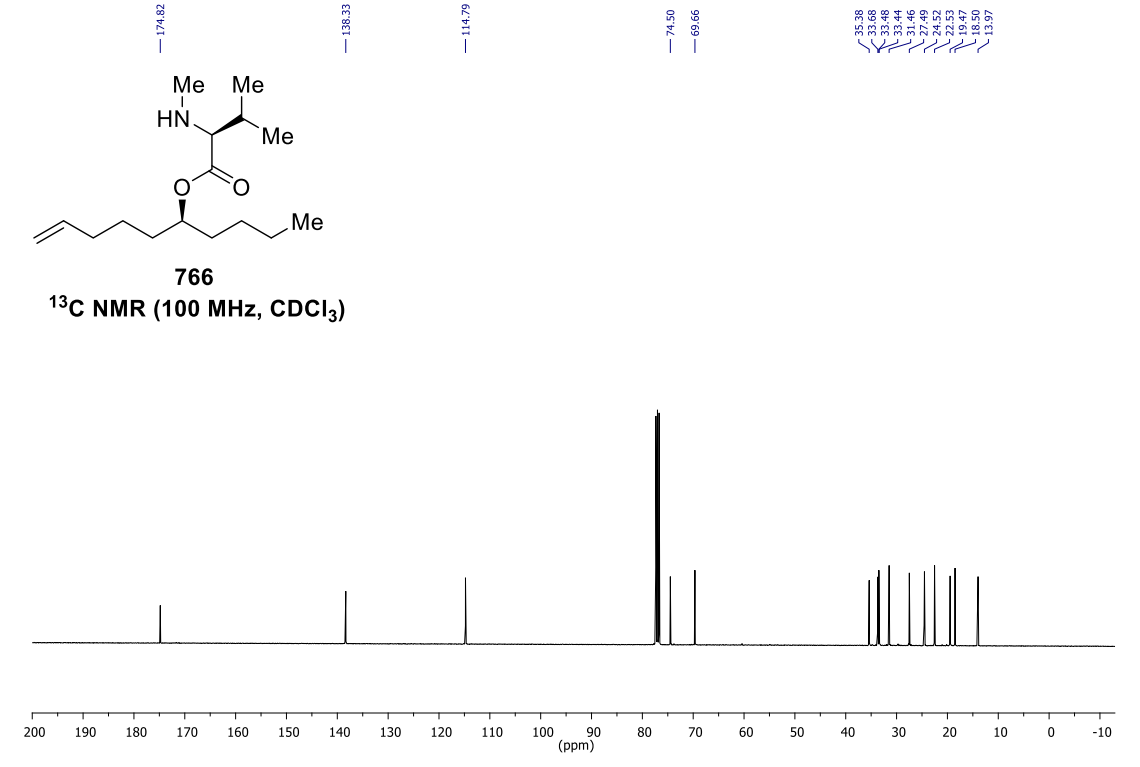
770

^{13}C NMR (100 MHz, $CDCl_3$)









Appendix IV

Theoretical Calculations

Theoretical Calculations

Minimum energy conformations were calculated in vacuo using the PM3 method found in HyperChem 5.0 software. Optimization was performed using Polak-Ribiere algorithm until the RMS gradient reached a value below 0.001 kcal/(Å·mol).

The resulting minimum-energy conformations for compounds **615**, **623**, **666** and **653** are contained in the following .mol files:

Compound 615:

```
 -HYPER- 09141711283D

 58 60  0  0  0  0  0  0  0  0999 V2000
  -0.8613    1.8384    1.0385 C   0  0  0  0  0  0  0  0  0  0  0  0
  -2.1404    1.6973    0.5259 C   0  0  0  0  0  0  0  0  0  0  0  0
  -2.6545    0.3990    0.3587 C   0  0  0  0  0  0  0  0  0  0  0  0
  -1.8962   -0.7217    0.6968 C   0  0  0  0  0  0  0  0  0  0  0  0
  -0.5795   -0.5720    1.1861 C   0  0  0  0  0  0  0  0  0  0  0  0
  -0.0604    0.7376    1.3738 C   0  0  0  0  0  0  0  0  0  0  0  0
  -3.9373    0.3464   -0.1478 O   0  0  0  0  0  0  0  0  0  0  0  0
  -4.4524   -0.9376   -0.5140 C   0  0  0  0  0  0  0  0  0  0  0  0
  -5.0056   -1.6929    0.6490 C   0  0  0  0  0  0  0  0  0  0  0  0
  -4.5813   -2.9996    0.9133 C   0  0  0  0  0  0  0  0  0  0  0  0
  -5.1452   -3.7154    1.9690 C   0  0  0  0  0  0  0  0  0  0  0  0
  -6.1252   -3.1292    2.7697 C   0  0  0  0  0  0  0  0  0  0  0  0
  -6.5412   -1.8220    2.5162 C   0  0  0  0  0  0  0  0  0  0  0  0
  -5.9848   -1.1058    1.4580 C   0  0  0  0  0  0  0  0  0  0  0  0
   1.2792    1.0313    1.9588 C   0  0  0  0  0  0  0  0  0  0  0  0
   2.3733    1.2797    0.9872 C   0  0  0  0  0  0  0  0  0  0  0  0
   2.2484    1.4062   -0.3376 C   0  0  0  0  0  0  0  0  0  0  0  0
   0.2122   -1.6961    1.4842 N   0  0  0  0  0  0  0  0  0  0  0  0
  -0.0402   -3.0147    1.1455 C   0  0  0  0  0  0  0  0  0  0  0  0
  -1.0646   -3.4122    0.5644 O   0  0  0  0  0  0  0  0  0  0  0  0
   1.0894   -4.0270    1.5163 C   0  0  0  0  0  0  0  0  0  0  0  0
   2.2999   -3.7326    0.7887 N   0  0  0  0  0  0  0  0  0  0  0  0
   0.5739   -5.4402    1.2628 C   0  0  0  0  0  0  0  0  0  0  0  0
   3.1866   -2.7756    1.2326 C   0  0  0  0  0  0  0  0  0  0  0  0
   3.1171   -2.3000    2.3838 O   0  0  0  0  0  0  0  0  0  0  0  0
   4.2354   -2.2661    0.2336 C   0  0  0  0  0  0  0  0  0  0  0  0
   3.6151   -1.3107   -0.6458 N   0  0  0  0  0  0  0  0  0  0  0  0
   3.3945    1.7042   -1.2339 C   0  0  0  0  0  0  0  0  0  0  0  0
   3.6872    0.5928   -2.2247 C   0  0  0  0  0  0  0  0  0  0  0  0
   4.3666   -0.5972   -1.5711 C   0  0  0  0  0  0  0  0  0  0  0  0
   5.5185   -0.9542   -1.8786 O   0  0  0  0  0  0  0  0  0  0  0  0
  -0.4546    2.8522    1.1873 H   0  0  0  0  0  0  0  0  0  0  0  0
  -2.7537    2.5685    0.2603 H   0  0  0  0  0  0  0  0  0  0  0  0
  -2.3421   -1.7250    0.5974 H   0  0  0  0  0  0  0  0  0  0  0  0
  -5.2862   -0.6640   -1.2224 H   0  0  0  0  0  0  0  0  0  0  0  0
  -3.6759   -1.5322   -1.0634 H   0  0  0  0  0  0  0  0  0  0  0  0
  -3.7904   -3.4611    0.2990 H   0  0  0  0  0  0  0  0  0  0  0  0
  -4.8108   -4.7434    2.1715 H   0  0  0  0  0  0  0  0  0  0  0  0
  -6.5674   -3.6957    3.6023 H   0  0  0  0  0  0  0  0  0  0  0  0
  -7.3085   -1.3551    3.1508 H   0  0  0  0  0  0  0  0  0  0  0  0
  -6.3031   -0.0719    1.2553 H   0  0  0  0  0  0  0  0  0  0  0  0
   1.6122    0.2232    2.6681 H   0  0  0  0  0  0  0  0  0  0  0  0
```

```
  1.1872    1.9609    2.5957 H   0  0  0  0  0  0  0  0  0  0  0  0
  3.3642    1.3850    1.4669 H   0  0  0  0  0  0  0  0  0  0  0  0
  1.0390   -1.5203    2.0192 H   0  0  0  0  0  0  0  0  0  0  0  0
  1.3078   -3.9125    2.6230 H   0  0  0  0  0  0  0  0  0  0  0  0
  2.3450   -4.0333   -0.1574 H   0  0  0  0  0  0  0  0  0  0  0  0
  0.3133   -5.5862    0.1869 H   0  0  0  0  0  0  0  0  0  0  0  0
  1.3402   -6.1934    1.5637 H   0  0  0  0  0  0  0  0  0  0  0  0
 -0.3521   -5.5948    1.8679 H   0  0  0  0  0  0  0  0  0  0  0  0
  4.6708   -3.1053   -0.3785 H   0  0  0  0  0  0  0  0  0  0  0  0
  5.0760   -1.8014    0.8265 H   0  0  0  0  0  0  0  0  0  0  0  0
  2.7980   -0.8584   -0.2922 H   0  0  0  0  0  0  0  0  0  0  0  0
  4.3215    1.9214   -0.6375 H   0  0  0  0  0  0  0  0  0  0  0  0
  3.1519    2.6361   -1.8166 H   0  0  0  0  0  0  0  0  0  0  0  0
  4.3819    0.9763   -3.0191 H   0  0  0  0  0  0  0  0  0  0  0  0
  2.7412    0.2568   -2.7247 H   0  0  0  0  0  0  0  0  0  0  0  0
  1.2673    1.3100   -0.8330 H   0  0  0  0  0  0  0  0  0  0  0  0
 1  2  4  0  0  0  0
 1  6  4  0  0  0  0
 1 32  1  0  0  0  0
 2  3  4  0  0  0  0
 2 33  1  0  0  0  0
 3  4  4  0  0  0  0
 3  7  1  0  0  0  0
 4  5  4  0  0  0  0
 4 34  1  0  0  0  0
 5  6  4  0  0  0  0
 5 18  1  0  0  0  0
 6 15  1  0  0  0  0
 7  8  1  0  0  0  0
 8  9  1  0  0  0  0
 8 35  1  0  0  0  0
 8 36  1  0  0  0  0
 9 10  4  0  0  0  0
 9 14  4  0  0  0  0
10 11  4  0  0  0  0
10 37  1  0  0  0  0
11 12  4  0  0  0  0
11 38  1  0  0  0  0
12 13  4  0  0  0  0
12 39  1  0  0  0  0
13 14  4  0  0  0  0
13 40  1  0  0  0  0
14 41  1  0  0  0  0
15 16  1  0  0  0  0
15 42  1  0  0  0  0
15 43  1  0  0  0  0
16 17  2  0  0  0  0
16 44  1  0  0  0  0
17 28  1  0  0  0  0
17 58  1  0  0  0  0
18 19  1  0  0  0  0
18 45  1  0  0  0  0
19 20  2  0  0  0  0
19 21  1  0  0  0  0
21 22  1  0  0  0  0
21 23  1  0  0  0  0
21 46  1  0  0  0  0
22 24  1  0  0  0  0
22 47  1  0  0  0  0
23 48  1  0  0  0  0
```

```
 23 49  1  0  0  0  0
 23 50  1  0  0  0  0
 24 25  2  0  0  0  0
 24 26  1  0  0  0  0
 26 27  1  0  0  0  0
 26 51  1  0  0  0  0
 26 52  1  0  0  0  0
 27 30  1  0  0  0  0
 27 53  1  0  0  0  0
 28 29  1  0  0  0  0
 28 54  1  0  0  0  0
 28 55  1  0  0  0  0
 29 30  1  0  0  0  0
 29 56  1  0  0  0  0
 29 57  1  0  0  0  0
 30 31  2  0  0  0  0
M  END
```

Compound 623:

```
  -HYPER- 09141711293D

 62 64  0  0  0  0  0  0  0  0999 V2000
   -1.5482    2.2310    1.1603 C   0  0  0  0  0  0  0  0  0  0  0  0
   -2.7819    1.9721    0.5861 C   0  0  0  0  0  0  0  0  0  0  0  0
   -3.1469    0.6330    0.3587 C   0  0  0  0  0  0  0  0  0  0  0  0
   -2.2897   -0.4123    0.7024 C   0  0  0  0  0  0  0  0  0  0  0  0
   -1.0199   -0.1399    1.2577 C   0  0  0  0  0  0  0  0  0  0  0  0
   -0.6497    1.2103    1.5012 C   0  0  0  0  0  0  0  0  0  0  0  0
   -4.3936    0.4616   -0.2077 O   0  0  0  0  0  0  0  0  0  0  0  0
   -4.7425   -0.8536   -0.6520 C   0  0  0  0  0  0  0  0  0  0  0  0
   -5.2581   -1.7191    0.4498 C   0  0  0  0  0  0  0  0  0  0  0  0
   -4.7079   -2.9860    0.6727 C   0  0  0  0  0  0  0  0  0  0  0  0
   -5.2336   -3.8088    1.6683 C   0  0  0  0  0  0  0  0  0  0  0  0
   -6.3014   -3.3691    2.4505 C   0  0  0  0  0  0  0  0  0  0  0  0
   -6.8439   -2.1014    2.2386 C   0  0  0  0  0  0  0  0  0  0  0  0
   -6.3256   -1.2789    1.2401 C   0  0  0  0  0  0  0  0  0  0  0  0
    0.6296    1.6202    2.1474 C   0  0  0  0  0  0  0  0  0  0  0  0
    1.7335    1.9889    1.2256 C   0  0  0  0  0  0  0  0  0  0  0  0
    1.6259    2.2299   -0.0840 C   0  0  0  0  0  0  0  0  0  0  0  0
   -0.1297   -1.1835    1.5688 N   0  0  0  0  0  0  0  0  0  0  0  0
   -0.2021   -2.5008    1.1481 C   0  0  0  0  0  0  0  0  0  0  0  0
   -1.1308   -2.9761    0.4727 O   0  0  0  0  0  0  0  0  0  0  0  0
    1.0115   -3.3958    1.5529 C   0  0  0  0  0  0  0  0  0  0  0  0
    2.2263   -2.9185    0.9377 N   0  0  0  0  0  0  0  0  0  0  0  0
    0.6895   -4.8412    1.1871 C   0  0  0  0  0  0  0  0  0  0  0  0
    2.9514   -1.8845    1.4890 C   0  0  0  0  0  0  0  0  0  0  0  0
    2.7391   -1.4781    2.6492 O   0  0  0  0  0  0  0  0  0  0  0  0
    4.0011   -1.2050    0.5984 C   0  0  0  0  0  0  0  0  0  0  0  0
    3.3390   -0.3209   -0.3225 N   0  0  0  0  0  0  0  0  0  0  0  0
    2.7873    2.6590   -0.9269 C   0  0  0  0  0  0  0  0  0  0  0  0
    3.2844    1.5872   -1.9123 C   0  0  0  0  0  0  0  0  0  0  0  0
    4.0598    0.5022   -1.1736 C   0  0  0  0  0  0  0  0  0  0  0  0
    5.2794    0.3304   -1.3521 O   0  0  0  0  0  0  0  0  0  0  0  0
   -1.2593    3.2768    1.3552 H   0  0  0  0  0  0  0  0  0  0  0  0
   -3.4728    2.7819    0.3162 H   0  0  0  0  0  0  0  0  0  0  0  0
   -2.6193   -1.4541    0.5539 H   0  0  0  0  0  0  0  0  0  0  0  0
   -5.5690   -0.6420   -1.3895 H   0  0  0  0  0  0  0  0  0  0  0  0
   -3.8790   -1.3314   -1.1853 H   0  0  0  0  0  0  0  0  0  0  0  0
   -3.8493   -3.3309    0.0731 H   0  0  0  0  0  0  0  0  0  0  0  0
```

-4.8002	-4.8053	1.8381	H	0	0	0	0	0	0	0	0	0	0	0
-6.7133	-4.0198	3.2356	H	0	0	0	0	0	0	0	0	0	0	0
-7.6813	-1.7499	2.8588	H	0	0	0	0	0	0	0	0	0	0	0
-6.7442	-0.2751	1.0705	H	0	0	0	0	0	0	0	0	0	0	0
1.0079	0.8353	2.8600	H	0	0	0	0	0	0	0	0	0	0	0
0.4255	2.5270	2.7912	H	0	0	0	0	0	0	0	0	0	0	0
2.7114	2.0864	1.7338	H	0	0	0	0	0	0	0	0	0	0	0
0.6249	-0.9478	2.1816	H	0	0	0	0	0	0	0	0	0	0	0
1.1353	-3.3234	2.6776	H	0	0	0	0	0	0	0	0	0	0	0
2.3837	-3.1696	-0.0108	H	0	0	0	0	0	0	0	0	0	0	0
0.5249	-4.9508	0.0880	H	0	0	0	0	0	0	0	0	0	0	0
1.5177	-5.5171	1.5068	H	0	0	0	0	0	0	0	0	0	0	0
-0.2515	-5.1390	1.7099	H	0	0	0	0	0	0	0	0	0	0	0
4.6054	-1.9604	0.0208	H	0	0	0	0	0	0	0	0	0	0	0
4.7103	-0.6418	1.2723	H	0	0	0	0	0	0	0	0	0	0	0
2.4168	-0.0284	-0.0804	H	0	0	0	0	0	0	0	0	0	0	0
3.6535	2.9663	-0.2689	H	0	0	0	0	0	0	0	0	0	0	0
2.4261	3.7720	-1.7429	O	0	0	0	0	0	0	0	0	0	0	0
4.0258	2.0962	-2.5973	H	0	0	0	0	0	0	0	0	0	0	0
2.1709	1.0149	-2.7571	C	0	0	0	0	0	0	0	0	0	0	0
0.6627	2.1526	-0.6159	H	0	0	0	0	0	0	0	0	0	0	0
2.0175	4.4240	-1.1615	H	0	0	0	0	0	0	0	0	0	0	0
1.6804	1.8457	-3.3228	H	0	0	0	0	0	0	0	0	0	0	0
1.3938	0.5114	-2.1333	H	0	0	0	0	0	0	0	0	0	0	0
2.5803	0.2737	-3.4850	H	0	0	0	0	0	0	0	0	0	0	0

1	2	4	0	0	0	0
1	6	4	0	0	0	0
1	32	1	0	0	0	0
2	3	4	0	0	0	0
2	33	1	0	0	0	0
3	4	4	0	0	0	0
3	7	1	0	0	0	0
4	5	4	0	0	0	0
4	34	1	0	0	0	0
5	6	4	0	0	0	0
5	18	1	0	0	0	0
6	15	1	0	0	0	0
7	8	1	0	0	0	0
8	9	1	0	0	0	0
8	35	1	0	0	0	0
8	36	1	0	0	0	0
9	10	4	0	0	0	0
9	14	4	0	0	0	0
10	11	4	0	0	0	0
10	37	1	0	0	0	0
11	12	4	0	0	0	0
11	38	1	0	0	0	0
12	13	4	0	0	0	0
12	39	1	0	0	0	0
13	14	4	0	0	0	0
13	40	1	0	0	0	0
14	41	1	0	0	0	0
15	16	1	0	0	0	0
15	42	1	0	0	0	0
15	43	1	0	0	0	0
16	17	2	0	0	0	0
16	44	1	0	0	0	0
17	28	1	0	0	0	0
17	58	1	0	0	0	0
18	19	1	0	0	0	0

```
 18 45  1  0  0  0  0
 19 20  2  0  0  0  0
 19 21  1  0  0  0  0
 21 22  1  0  0  0  0
 21 23  1  0  0  0  0
 21 46  1  0  0  0  0
 22 24  1  0  0  0  0
 22 47  1  0  0  0  0
 23 48  1  0  0  0  0
 23 49  1  0  0  0  0
 23 50  1  0  0  0  0
 24 25  2  0  0  0  0
 24 26  1  0  0  0  0
 26 27  1  0  0  0  0
 26 51  1  0  0  0  0
 26 52  1  0  0  0  0
 27 30  1  0  0  0  0
 27 53  1  0  0  0  0
 28 29  1  0  0  0  0
 28 54  1  0  0  0  0
 28 55  1  0  0  0  0
 29 30  1  0  0  0  0
 29 56  1  0  0  0  0
 29 57  1  0  0  0  0
 30 31  2  0  0  0  0
 55 59  1  0  0  0  0
 57 60  1  0  0  0  0
 57 61  1  0  0  0  0
 57 62  1  0  0  0  0
M  END
```

Compound 666:

```
  -HYPER- 09141711303D

 58 60  0  0  0  0  0  0  0  0999 V2000
   -1.2823    1.1922    1.1258 C   0  0  0  0  0  0  0  0  0  0  0  0
   -2.5345    0.8480    1.6112 C   0  0  0  0  0  0  0  0  0  0  0  0
   -3.0193   -0.4521    1.3771 C   0  0  0  0  0  0  0  0  0  0  0  0
   -2.2490   -1.4001    0.6997 C   0  0  0  0  0  0  0  0  0  0  0  0
   -0.9692   -1.0466    0.2246 C   0  0  0  0  0  0  0  0  0  0  0  0
   -0.4950    0.2800    0.4127 C   0  0  0  0  0  0  0  0  0  0  0  0
   -4.2817   -0.6905    1.8815 O   0  0  0  0  0  0  0  0  0  0  0  0
   -4.8265   -1.9926    1.6153 C   0  0  0  0  0  0  0  0  0  0  0  0
   -6.2065   -2.0328    2.1833 C   0  0  0  0  0  0  0  0  0  0  0  0
   -6.7194   -3.2572    2.6283 C   0  0  0  0  0  0  0  0  0  0  0  0
   -8.0187   -3.3294    3.1264 C   0  0  0  0  0  0  0  0  0  0  0  0
   -8.8094   -2.1816    3.1905 C   0  0  0  0  0  0  0  0  0  0  0  0
   -8.2981   -0.9599    2.7539 C   0  0  0  0  0  0  0  0  0  0  0  0
   -7.0004   -0.8839    2.2490 C   0  0  0  0  0  0  0  0  0  0  0  0
    0.7621    0.7141   -0.1786 C   0  0  0  0  0  0  0  0  0  0  0  0
    1.7010    1.4289    0.4533 C   0  0  0  0  0  0  0  0  0  0  0  0
    2.9375    1.8924   -0.2241 C   0  0  0  0  0  0  0  0  0  0  0  0
   -0.1291   -1.9932   -0.3921 N   0  0  0  0  0  0  0  0  0  0  0  0
   -0.5424   -3.0788   -1.1383 C   0  0  0  0  0  0  0  0  0  0  0  0
   -1.7390   -3.3396   -1.3591 O   0  0  0  0  0  0  0  0  0  0  0  0
    0.5699   -4.0293   -1.6672 C   0  0  0  0  0  0  0  0  0  0  0  0
    1.6631   -3.3462   -2.3150 N   0  0  0  0  0  0  0  0  0  0  0  0
   -0.0820   -5.0702   -2.5759 C   0  0  0  0  0  0  0  0  0  0  0  0
```

```
  2.7530   -2.8862   -1.6122 C   0  0  0  0  0  0  0  0  0  0  0  0
  2.7893   -2.9641   -0.3645 O   0  0  0  0  0  0  0  0  0  0  0  0
  3.9343   -2.3043   -2.4088 C   0  0  0  0  0  0  0  0  0  0  0  0
  4.7086   -1.3675   -1.6493 N   0  0  0  0  0  0  0  0  0  0  0  0
  4.1623    1.1301    0.2566 C   0  0  0  0  0  0  0  0  0  0  0  0
  5.1777    0.9417   -0.8538 C   0  0  0  0  0  0  0  0  0  0  0  0
  4.6421   -0.0009   -1.9159 C   0  0  0  0  0  0  0  0  0  0  0  0
  4.1989    0.4184   -3.0020 O   0  0  0  0  0  0  0  0  0  0  0  0
 -0.8978    2.2120    1.2870 H   0  0  0  0  0  0  0  0  0  0  0  0
 -3.1529    1.5680    2.1642 H   0  0  0  0  0  0  0  0  0  0  0  0
 -2.6327   -2.4163    0.5194 H   0  0  0  0  0  0  0  0  0  0  0  0
 -4.8605   -2.1607    0.5039 H   0  0  0  0  0  0  0  0  0  0  0  0
 -4.1717   -2.7689    2.0954 H   0  0  0  0  0  0  0  0  0  0  0  0
 -6.0963   -4.1627    2.5841 H   0  0  0  0  0  0  0  0  0  0  0  0
 -8.4195   -4.2935    3.4721 H   0  0  0  0  0  0  0  0  0  0  0  0
 -9.8336   -2.2407    3.5862 H   0  0  0  0  0  0  0  0  0  0  0  0
 -8.9181   -0.0530    2.8064 H   0  0  0  0  0  0  0  0  0  0  0  0
 -6.5898    0.0791    1.9079 H   0  0  0  0  0  0  0  0  0  0  0  0
  1.5990    1.7088    1.5138 H   0  0  0  0  0  0  0  0  0  0  0  0
  0.8490   -1.8564   -0.2413 H   0  0  0  0  0  0  0  0  0  0  0  0
  0.9828   -4.5524   -0.7473 H   0  0  0  0  0  0  0  0  0  0  0  0
  1.6090   -3.2157   -3.2966 H   0  0  0  0  0  0  0  0  0  0  0  0
 -0.5430   -4.5886   -3.4714 H   0  0  0  0  0  0  0  0  0  0  0  0
  0.6690   -5.8260   -2.9070 H   0  0  0  0  0  0  0  0  0  0  0  0
 -0.8930   -5.5844   -2.0045 H   0  0  0  0  0  0  0  0  0  0  0  0
  3.5784   -1.8123   -3.3594 H   0  0  0  0  0  0  0  0  0  0  0  0
  4.5945   -3.1801   -2.6782 H   0  0  0  0  0  0  0  0  0  0  0  0
  4.8851   -1.6364   -0.7041 H   0  0  0  0  0  0  0  0  0  0  0  0
  4.6489    1.6929    1.0961 H   0  0  0  0  0  0  0  0  0  0  0  0
  3.8588    0.1302    0.6657 H   0  0  0  0  0  0  0  0  0  0  0  0
  6.1388    0.5487   -0.4310 H   0  0  0  0  0  0  0  0  0  0  0  0
  5.3942    1.9249   -1.3496 H   0  0  0  0  0  0  0  0  0  0  0  0
  3.0777    2.9889   -0.0239 H   0  0  0  0  0  0  0  0  0  0  0  0
  2.8361    1.7766   -1.3393 H   0  0  0  0  0  0  0  0  0  0  0  0
  0.8937    0.4376   -1.2414 H   0  0  0  0  0  0  0  0  0  0  0  0
 1  2  4  0  0  0  0
 1  6  4  0  0  0  0
 1 32  1  0  0  0  0
 2  3  4  0  0  0  0
 2 33  1  0  0  0  0
 3  4  4  0  0  0  0
 3  7  1  0  0  0  0
 4  5  4  0  0  0  0
 4 34  1  0  0  0  0
 5  6  4  0  0  0  0
 5 18  1  0  0  0  0
 6 15  1  0  0  0  0
 7  8  1  0  0  0  0
 8  9  1  0  0  0  0
 8 35  1  0  0  0  0
 8 36  1  0  0  0  0
 9 10  4  0  0  0  0
 9 14  4  0  0  0  0
10 11  4  0  0  0  0
10 37  1  0  0  0  0
11 12  4  0  0  0  0
11 38  1  0  0  0  0
12 13  4  0  0  0  0
12 39  1  0  0  0  0
13 14  4  0  0  0  0
```

```
 13 40  1  0  0  0  0
 14 41  1  0  0  0  0
 15 16  2  0  0  0  0
 15 58  1  0  0  0  0
 16 17  1  0  0  0  0
 16 42  1  0  0  0  0
 17 28  1  0  0  0  0
 17 56  1  0  0  0  0
 17 57  1  0  0  0  0
 18 19  1  0  0  0  0
 18 43  1  0  0  0  0
 19 20  2  0  0  0  0
 19 21  1  0  0  0  0
 21 22  1  0  0  0  0
 21 23  1  0  0  0  0
 21 44  1  0  0  0  0
 22 24  1  0  0  0  0
 22 45  1  0  0  0  0
 23 46  1  0  0  0  0
 23 47  1  0  0  0  0
 23 48  1  0  0  0  0
 24 25  2  0  0  0  0
 24 26  1  0  0  0  0
 26 27  1  0  0  0  0
 26 49  1  0  0  0  0
 26 50  1  0  0  0  0
 27 30  1  0  0  0  0
 27 51  1  0  0  0  0
 28 29  1  0  0  0  0
 28 52  1  0  0  0  0
 28 53  1  0  0  0  0
 29 30  1  0  0  0  0
 29 54  1  0  0  0  0
 29 55  1  0  0  0  0
 30 31  2  0  0  0  0
M  END
```

Compound 653:

```
  -HYPER- 09141711293D

 62 64  0  0  0  0  0  0  0  0999 V2000
   -4.2131    1.0331   -0.6592 C   0  0  0  0  0  0  0  0  0  0  0  0
   -5.4161    0.5634   -0.1572 C   0  0  0  0  0  0  0  0  0  0  0  0
   -5.4591   -0.7327    0.3903 C   0  0  0  0  0  0  0  0  0  0  0  0
   -4.3230   -1.5435    0.4160 C   0  0  0  0  0  0  0  0  0  0  0  0
   -3.1018   -1.0645   -0.1022 C   0  0  0  0  0  0  0  0  0  0  0  0
   -3.0480    0.2566   -0.6283 C   0  0  0  0  0  0  0  0  0  0  0  0
   -6.7011   -1.1178    0.8509 O   0  0  0  0  0  0  0  0  0  0  0  0
   -6.8115   -2.3820    1.5124 C   0  0  0  0  0  0  0  0  0  0  0  0
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   -5.2552   -3.1851    3.3169 C   0  0  0  0  0  0  0  0  0  0  0  0
   -4.8239   -3.1740    4.6436 C   0  0  0  0  0  0  0  0  0  0  0  0
   -5.4301   -2.3280    5.5715 C   0  0  0  0  0  0  0  0  0  0  0  0
   -6.4695   -1.4872    5.1721 C   0  0  0  0  0  0  0  0  0  0  0  0
   -6.9056   -1.4984    3.8489 C   0  0  0  0  0  0  0  0  0  0  0  0
   -1.8168    0.8388   -1.1479 C   0  0  0  0  0  0  0  0  0  0  0  0
   -0.6776    0.9161   -0.4478 C   0  0  0  0  0  0  0  0  0  0  0  0
    0.5821    1.4549   -1.0123 C   0  0  0  0  0  0  0  0  0  0  0  0
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-1.9490	-1.8665	-0.1499	N	0	0	0	0	0	0	0	0	0	0	0
-1.7480	-3.0966	0.4490	C	0	0	0	0	0	0	0	0	0	0	0
-2.6096	-3.7010	1.1118	O	0	0	0	0	0	0	0	0	0	0	0
-0.3781	-3.7925	0.2137	C	0	0	0	0	0	0	0	0	0	0	0
0.7622	-2.9290	0.3890	N	0	0	0	0	0	0	0	0	0	0	0
-0.4410	-4.4450	-1.1672	C	0	0	0	0	0	0	0	0	0	0	0
1.6031	-3.0596	1.4774	C	0	0	0	0	0	0	0	0	0	0	0
1.3208	-3.7646	2.4633	O	0	0	0	0	0	0	0	0	0	0	0
2.9511	-2.3170	1.4341	C	0	0	0	0	0	0	0	0	0	0	0
2.8882	-0.9070	1.2156	N	0	0	0	0	0	0	0	0	0	0	0
1.5992	1.8236	0.0689	C	0	0	0	0	0	0	0	0	0	0	0
2.9732	1.1653	-0.1522	C	0	0	0	0	0	0	0	0	0	0	0
2.8390	-0.3499	-0.0478	C	0	0	0	0	0	0	0	0	0	0	0
2.7050	-1.0794	-1.0531	O	0	0	0	0	0	0	0	0	0	0	0
-4.1628	2.0482	-1.0843	H	0	0	0	0	0	0	0	0	0	0	0
-6.3255	1.1787	-0.1753	H	0	0	0	0	0	0	0	0	0	0	0
-4.3765	-2.5489	0.8627	H	0	0	0	0	0	0	0	0	0	0	0
-7.9273	-2.5467	1.5108	H	0	0	0	0	0	0	0	0	0	0	0
-6.3187	-3.1879	0.9083	H	0	0	0	0	0	0	0	0	0	0	0
-4.7525	-3.8419	2.5871	H	0	0	0	0	0	0	0	0	0	0	0
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-5.0870	-2.3206	6.6163	H	0	0	0	0	0	0	0	0	0	0	0
-6.9448	-0.8145	5.9005	H	0	0	0	0	0	0	0	0	0	0	0
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-0.3338	-4.6072	1.0058	H	0	0	0	0	0	0	0	0	0	0	0
1.1094	-2.4625	-0.4218	H	0	0	0	0	0	0	0	0	0	0	0
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0.4511	-5.0961	-1.3300	H	0	0	0	0	0	0	0	0	0	0	0
-1.3606	-5.0766	-1.2257	H	0	0	0	0	0	0	0	0	0	0	0
3.5645	-2.7950	0.6144	H	0	0	0	0	0	0	0	0	0	0	0
3.4521	-2.5085	2.4269	H	0	0	0	0	0	0	0	0	0	0	0
2.8447	-0.3163	2.0114	H	0	0	0	0	0	0	0	0	0	0	0
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1.2221	1.5219	1.0910	H	0	0	0	0	0	0	0	0	0	0	0
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3.6045	1.5336	-1.4766	C	0	0	0	0	0	0	0	0	0	0	0
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1.0242	0.6715	-1.6911	H	0	0	0	0	0	0	0	0	0	0	0
1.9879	3.5738	-0.6818	H	0	0	0	0	0	0	0	0	0	0	0
2.9884	1.1641	-2.3319	H	0	0	0	0	0	0	0	0	0	0	0
3.7114	2.6425	-1.5533	H	0	0	0	0	0	0	0	0	0	0	0
4.6183	1.0716	-1.5577	H	0	0	0	0	0	0	0	0	0	0	0
-1.8853	1.2427	-2.1733	H	0	0	0	0	0	0	0	0	0	0	0

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55 61  1  0  0  0  0
M  END
```

Energies of Computer-generated Conformations for Compounds **615**, **623**, **666** and **653**.

Compound	**Energy (Kcal/mol)**
615	-123.301,142
623	-134.282,212
666	-123.304,239
653	-134.288,315

Appendix V

Biological Material and Methods

Biological Material and Methods

Material. Bovine aortic endothelial cells (BAEC) were isolated by collagenase digestion, and maintained in Dulbecco's modified Eagle's medium (DMEM) containing glucose (1 g/L) supplemented with 10% FBS (DMEM/10% FBS). All the cancer cell lines used in this study were obtained from the American Type Culture Collection (ATCC). Human fibrosarcoma HT-1080, hepatocellular carcinoma HepG2 and glioblastoma U87MG cells were maintained in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% FBS. Human colon adenocarcinoma HT-29 cells and human osteosarcoma U2OS cells were maintained in DMEM containing glucose (4,5 g/L) supplemented with 10% FBS. Human breast cancer carcinoma MDA-MB-231, chronic myelogenous leukemia KU812F and histiocytic lymphoma U937 cells were maintained in RPMI1640 medium supplemented with 10% FBS. Acute promyelocytic leukemia HL-60 cells were maintained in RPMI1640 medium supplemented with 20% FBS. All culture medium contained glutamine (2 mM), penicillin (50 IU/mL), streptomycin (50 μg/mL) and amphotericin (1.25 μg/mL) and all cell lines were grown at 37 °C and humidified 5% CO_2 atmosphere. Cell culture media, penicillin/streptomycin and amphotericin B were purchased from Biowhittaker (Walkersville, MD, USA) and fetal bovine serum (FBS) from BioWest (Kansas, USA). Plastics for cell culture were supplied by NUNC (Roskilde, Denmark). Matrigel was purchased from Corning (NY, USA). Chemicals not listed in this section were obtained from Sigma-Aldrich (MERK) (Darmstadt, Germany). Fertilized chick eggs were purchased from Granja Santa Isabel (Córdoba, Spain). Zebrafish (*Danio rerio*) breeding colony (wild-type AB strain) was maintained at 28°C.

Cell growth assay. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide or MTT dye reduction assay in 96-well microplates was used. This assay is dependent on the reduction of MTT by mitochondrial dehydrogenases of a viable cell to a blue formazan product, which can be measured spectrophotometrically. $2{,}5 \times 10^3$ BAEC, 3×10^3 HL-60 and KU812F and 2×10^3 HepG2, HT-1080, HT-29, MDA-MB-231, U2OS, U937 and U87MG cells in a total volume of 100 μL of their respective growth medium were incubated with serial dilutions 1:1 of the tested compounds. After 3 days of incubation (37 °C and 5% CO_2 in a humid atmosphere), 10 μL of MTT (5 mg/mL in phosphate-buffered saline) were added to each well, and the plate was incubated for a further 4 h at 37 °C. The resulting formazan was dissolved in 150 μL of 0.04 N HCl/2-propanol and read at 550 nm. IC_{50} values were calculated from semi-logarithmic dose-response plots as those concentrations of compound yielding 50% cell survival, taking the values obtained for the control to be 100%. IC_{50} results are expressed as means ±S.D. of at least three independent experiments.

Tubular-like structures formation on Matrigel. Cellular suspensions of $5x10^4$ BAE cells in serum-free DMEM were added to a 96-well plate coated with 50 μL Matrigel (10.5 mg/mL) in the presence of the indicated treatments for 5 hours and photographed with a microscope camera Nikon DS-Ri2 coupled to a Nikon Eclipse Ti microscope (Nikon,

Tokyo, Japan). Each concentration was tested in duplicate and staurosporine 2 μM was used as a routine positive assay control. For the disruption assay, tubular-like structures were formed following the same protocol for the control conditions and then the indicated concentrations of **653** were added. After a further incubation time of 90 min, cultures were observed and photographed. Combretastatin-4-phosphate (CA4P) was used as positive control of disruptor antiangiogenic drug.

Wound healing assay. Confluent BAEC monolayers in 6-well plates were wounded with pipet tips with 2 perpendicular diameters, giving rise to 2 acellular 1 mm-wide lanes per well. Then, complete medium in the absence (controls) or presence of different concentrations of **653** was added. Wounded areas were observed and photographed after 0, 4 and 7 hours of incubation with a microscope camera Nikon DS-Ri2 coupled to a Nikon Eclipse Ti microscope (Nikon, Tokyo, Japan). The migration of BAEC into the cell-free area was quantified by Image J software and represented as the percentage of wounded area in the correspondent time normalized to the initial wounded area (time 0) for each experimental condition.

Cell invasion assay. Invasion of endothelial cells was assayed by using 8.0 μm pore size transwell inserts coated with 100 μL of Matrigel 0,12 mg/mL solution. 10^5 BAE cells, in the absence or presence of the indicated concentrations of **653**, were added to the upper chamber of the transwells in absence of serum, and lower chamber was was filled with 20% FBS DMEM. After 16 hours incubation, invading cells were fixed in 4% paraformaldehide and stained with a 1% crystal violet solution in 2% ethanol. Cells were photographed with a microscope camera Nikon DS-Ri2 coupled to a Nikon Eclipse Ti microscope (Nikon, Tokyo, Japan).

Zymographic assays for MMP-2 and -9 detection. Zymographies for matrix metalloproteinases MMP-2 and MMP-9 activities were performed in both conditioned media and cellular extracts of endothelial (BAEC) and tumoral (HT-1080) cell lines. Briefly, cells seeded in 6-well plates were incubated in serum-free culture medium with 0.1% BSA containing 200 KIU of aprotinin/mL and the correspondent treatment. After 24 h of incubation, conditioned media were collected and cell lysates were obtained. Duplicates were used to determine the cell number and samples were normalized for equal loading. In order to detect the gelatinolytic activity of MMP-9 and MMP-2, samples were loaded in non-reducing SDS/PAGE gels containing gelatine (1 mg/mL). After electrophoresis, gels were incubated overnight at 37 ºC immersed in a substrate buffer (50 mM Tris/HCl, pH 7.4, supplemented with 1% Triton X-100, 5 mM $CaCl_2$, and 0.02% Na_3N) and stained with Commassie blue R-250. The bands of gelatinase activity could be detected as non-stained bands in a dark, stained background. Size and intensity of the bands were quantified using Image J software. A variant of this method was used to obtain complementary information about direct inhibition of tested compound on MMP-2 gelatinase activity: samples of conditioned media of untreated BAEC were submitted to gelatin zymography and, after electrophoresis, 20 μM of **653** was added to the substrate

buffer. Detection of the degrading bands and quantification were performed as described above.

Chick chorioallantoic membrane (CAM) Assay. Fertilized chick eggs were incubated horizontally at 38°C in a humidified incubator, windowed by day 3 of incubation and processed by day 8. **653** was added to a 1.2% solution of methylcellulose in water, and 10 μL drops were dried on a teflon-coated surface under a laminar flow hood. Then, methylcellulose discs were implanted onto the CAM, eggs were sealed with adhesive tape and returned to the incubator for 48 h. Negative controls were always made with DMSO mixed with the methylcellulose and aeroplysinin-1 (3 nmol/CAM) was used as a routine positive control of antiangiogenic compound. After the incubation, the CAM was examined under a stereomicroscope and photographed with a Nikon DS-Ri2 camera. The results were analysed by two different observers, and the assay was scored positive when both of them reported a significant reduction of vessels in the treated area.

FGF-2 induced angiogenesis zebrafish yolk membrane (ZFYM) assay. For the FGF-2 induced angiogenesis zebrafish yolk membrane (ZFYM), 24 hpf embryos were exposed to 1-phenyl-2-thiourea (PTU) to prevent the pigmentation. At 48 hpf, embryos were manually dechorionated with forceps, anaesthetized with tricaine (0.016 %) and injected into the perivitelline space with 2 nL FGF-2 (1 mg/mL). The injection was performed in the proximity of developing subintestinal vessels (SIVs) using borosilicate needles and a Picospritzer microinjector (Eppendorf, Hamburg, Germany). After injection, embryos were incubated for 24 h more in the absence or the presence of **653**. Finally, embryos were fixed in 4% PFA, stained for endogenous alkaline phosphatase (AP) activity and photographed under a Leica MZ16 F stereomicroscope equipped with DFC480 digital camera and ICM50 software (Leica, Wetzlar, Germany). Evaluation of the angiogenic response was performed by assigning negative (-, no response to FGF-2 injection), positive (+, mild response) or very positive (++, strong response) scores to the embryos.

Western-blot analysis. BAE cells were starved in serum-free during 16 hours. After 1 hour treatment with **653** at 10 and 20 μM in the same conditions, cells were induced with 10% of FBS during 10 minutes. Protein lysates were obtained in RIPA buffer (50 mM Tris, pH 7.4, 150 mM NaCl, 1% Triton X-100, 0,25% sodium deoxycholate, 1 mM EDTA) containing phosphatase activity inhibitors (30 mM sodium fluoride, 1 mM sodium orthovanadate, 30 mM β-glycerophosphate) and protease activity inhibitors (Complete mini, Roche, Mannheim, Germany). Protein concentration was determined usinf Lowry method. Samples were subjected to SDS-PAGE electrophoresis and transferred to nitrocellulose membranes. After blocking in TBS-T containing 10% non-fatty dry milk, membranes were hybridized with primary antibodies overnight at 4˚ (Cell Signaling; rabbit anti- Phospho-Akt (Ser473) #9271; rabbit anti-Akt #9272; rabbit anti-Phospho-p44/42 MAPK (ERK1/2) (Thr202/Tyr204) (clon D13.14.4E) #4370; rabbit anti-p44/42 MAPK (ERK1/2) (137F5) #4695; mouse anti-α-Tubulin (DM1A) #3873). Following 1 hour incubation with horseradish peroxidase-conjugated secondary antibodies (MERK; goat anti- rabbit IgG HRP Linked Whole Antibody #NA934V; goat

anti-mouse IgG (whole molecule)–Peroxidase antibody #A4416) at room temperature, immunoreactive bands were detected with SuperSignal West Pico Chemiluminescent Substrate (Pierce, Rockford, USA) and were quantified by ImageJ software. The phosphorilated/total protein ratios were expressed as the percentage of the ratio in serum-stimulated samples in the absence of **653**.

Ethical statement. The animal procedures considered in this project were performed in strict compliance with the European Communities Council Directive 2010/63/EU regulating the use and care of laboratory animals. Experimental procedures with chick embryos were performed at the University of Málaga (Spain) and were conducted in accordance with the Spanish Legislation in compliance with European Community regulation. The protocols were approved by the Ethics Committee for Animal Experiments of the University of Málaga. Zebrafish (Danio rerio) breeding colony (wild-type AB strain) was maintained at the Zebrafish Facilities of the University of Brescia (Italy). Experimental procedures with zebrafish embryos were performed at the University of Brescia and were conducted in accordance with the Italian Legislation for the animal experimentation. Efforts were made to reduce the number of animals used and minimize animal suffering. Furthermore, animals were anaesthetized when it was likely they could be subjected to pain, and they were killed by a method that ensured the least effect on their welfare.

Statistical analysis. Results are expressed as mean ± SD of three independent experiments. Data sets were checked to follow a normal distribution and statistical significance was determined using the two-sided unpaired Student t-test (SPSS software). Values of $P < 0.05$ were considered to be statistically significant. Significance was indicated as follows: ****$P < 0.0001$, ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$.