MIXTURE SYNTHESIS OF A 16-MEMBER MURISOLIN STEREOISOMER LIBRARY & SYNTHESIS OF C1-C20 AND C21-C40 FRAGMENTS OF TETRAFIBRICIN

by

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SYNTHESIS OF A 16-MEMBER MURISOLIN STEREOISOMER LIBRARY & SYNTHESIS OF C1-C20 AND C21-C40 FRAGMENTS OF TETRAFIBRICIN

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Chapter 1 of this thesis describes two new strategies for the solution phase mixture synthesis: OEG-mixture synthesis (OMS) and OEG-fluorous mixture synthesis (OFMS). An OEG-mixture synthesis of four stereoisomers of the hydroxybutenolide unit of murisolin was pursued. A strategy for solution phase stereoisomer synthesis based on orthogonal separation tagging and double demixing was implemented with fluorous (fluoroalkyl) and oligoethylene glycol (OEG, $[OCH_2CH_2]_n$) tags. A mixture of four stereoisomers of a dihydroxytetrahydrofuran subunit encoded by fluorous tags was coupled by a Kocienski-Julia olefination to a mixture of four stereoisomers of the hydroxybutenolide subunit encoded by OEG tags. An orchestrated sequence of reduction (1x), OEG demixing (1x), fluorous demixing (4x) and detagging (16x) provided sixteen stereoisomers of murisolin. Through this double tagging strategy, the configuration of sixteen compounds was encoded with only eight tags.

Chapter 2 describes the synthesis of the C1-C20 and C21-C40 fragments of the natural product tetrafibricin. A convergent synthesis of the proposed structure of tetrafibricin has been explored. In this approach, we envisioned a series of the Kocienski-Julia olefination reactions with appropriate aldehydes and sulfones to afford fragments C35-C40, C31-C35 and C21-C30. The synthesis of the C35-C40 fragment has been achieved in 11 steps starting with the commercially available pent-4-en-1-ol in an overall 25% yield. The synthesis of the C31-C34

fragment commenced with the commercially available (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol in 5 steps in an overall 46% yield. 16 steps are implemented in the synthesis of the C21-C30 fragment in a 4.5% overall yield. The synthesis of the C14-C20 fragment was achieved in 10 steps in an overall 23% yield. A synthesis of the C9-C13 fragment was established in 5 steps in 37% overall yield. The synthesis of the C1-C8 fragment was pursued in 8 steps in an overall 22% yield. The assembly of the C1-C8, C9-C13 and C14-C20 fragments was performed to afford the C1-C20 fragment. The C21-C30, C31-C34 and C35-C40 fragments were assembled by a Kocienski-Julia olefination to form the C21-C40 fragment of tetrafibricin.

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LIST OF ABBREVIATIONS

Ac	Acetyl
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
COSY	Correlation spectroscopy
CSA	10-Camphorsulfonic acid
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethylazodicarboxylate
DIAD	Diisopropylazodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DMAP	Dimethylaminopyridine
DMB	3,4-Dimethoxybenzyl
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
GC	Gas chromatography
Et	Ethyl
EtOAc	Ethyl acetate

FMS	Fluorous mixture synthesis
HKR	Hydrolytic kinetic resolution
HMBC	Heteronuclear multiple bond coherence
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear multiple quantum coherance
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IR	Infrared spectrometry
IBX	*o*-Iodobenzoic acid
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LiHMDS	Lithium bis(trimethylsilyl)amide
MS	Low resolution mass spectrometry
***m*CPBA**	*m*-chloroperbenzoic acid
Me	Methyl
Ms	Methanesulfonyl
NaHMDS	Sodium bis(trimethylsilyl)amide
NMR	Nuclear Magnetic resonance
OEG	Oligoethyleneglycol
OMS	OEG-mixture synthesis
OFMS	OEG-fluorous mixture synthesis
Ph	Phenyl
PMB	*p*-Methoxybenzyl

Pr	Propyl
PTSH	1-Phenyl-1*H*-tetrazole-5-thiol
Pyr	Pyridine
R_f	Retention factor
R_F	Perfluoroalkyl
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium Iodide
TBS	*t*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	4-Toluenesulfonyl

PREFACE

I would like to sincerely thank Prof. Dennis Curran for providing me such a wonderful opportunity to pursue graduate studies in his research group. It's been a great joy and experience working under your guidance. I am indebted to you for your support, encouragement and understanding during the critical times in my graduate studies. Thank you very much Prof. Curran for everything.

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I take this opportunity to thank my parents (Sri G. Seshagiri Rao and Smt. G. Vijayalaxmi) for their encouragement, love and support in several ways. My special thanks are also due to my elder brother (G. Nagabushanam), who always guided me when I needed. Thank you Subrahmanyam for your friendly discussions during my stay in Pittsburgh. Finally I would like to thank my Wife, Sumalata and my son Sriramsuhas for always being there for me and your understanding during my late work hours in the lab. Thank all you again.

1. CHAPTER 1

An orthogonal tagging technique for the synthesis of stereoisomer libraries: Total synthesis of (+)-murisolin and fifteen diastereoisomers

1.1. INTRODUCTION

In early days, the structural elucidation of natural products involved the near exclusive use of chemical synthesis, degradation or derivatization processes. However, in most cases, the assignment of the relative or absolute configuration was not possible by these methods. By the late 1960s, the "classical" chemical approach was gradually replaced by advanced, non-destructive methods such as NMR, UV spectroscopy, IR spectroscopy, mass spectrometry and X-ray crystallography. These methods allow the structure elucidation of highly challenging, complex natural products in far less time even when the compounds are available in miniscule amounts. However, there are numerous examples available in the literature where natural products were assigned an incorrect structure.[1] In those cases, the chemical synthesis of candidate structures coupled with comparison of various physical and spectral data is generally pursued to uncover and fix the errors in structural assignments. In order to establish a rigorous structural proof for molecules with several structure possibilities, it must be shown that all structures but one are different from the proposed structure in one or more ways. This requires the synthesis of a library of stereoisomers.

One major challenge in the traditional "one at a time" synthesis of stereoisomers is the huge amount of work involved. This has recently been supplemented by the solid-phase and solution-phase mixture synthesis techniques. However, identification and isolation of compounds from the mixture are the common problems in the mixture synthesis.[2] Fluorous mixture synthesis $(FMS)^3$ is the first solution phase mixture synthesis that provides a predictable separation of compounds from a mixture at the end of the synthesis.

1.1.1. Fluorous mixture synthesis

Fluorous mixture synthesis typically involves five stages: tagging, mixing, synthesis, demixing, and detagging (figure 1.1). In the first stage, a series of organic substrates (S^1-S^n) are tagged with a series of different fluorous tags (F^1-F^n). Fluorous tags contain short perfluoroalkyl chains[4] (C_3F_7 to $C_{10}F_{21}$), which allow the separation of tagged components at the end of mixture synthesis. In the second stage, the tagged substrates (S^1F^1-S^nF^n) are mixed to give a starting mixture M^S. The resulting mixture M^S is subjected to a serious of reactions to yield an intermediate mixture M^I, which can further be split into n components ($M_1{}^E$-$M_x{}^E$) and carried through another series of reactions. The resulting final mixtures are separated (demixed) by chromatography on fluorous silica gel.[5] Fluorous silica gel separates the fluorous tagged compounds based on their different fluorine content. Finally, the demixed compounds ($F^1P_1{}^1$) are individually subjected to detagging (removal of tag) to yield the final products ($P_1{}^1$-$P_x{}^n$).

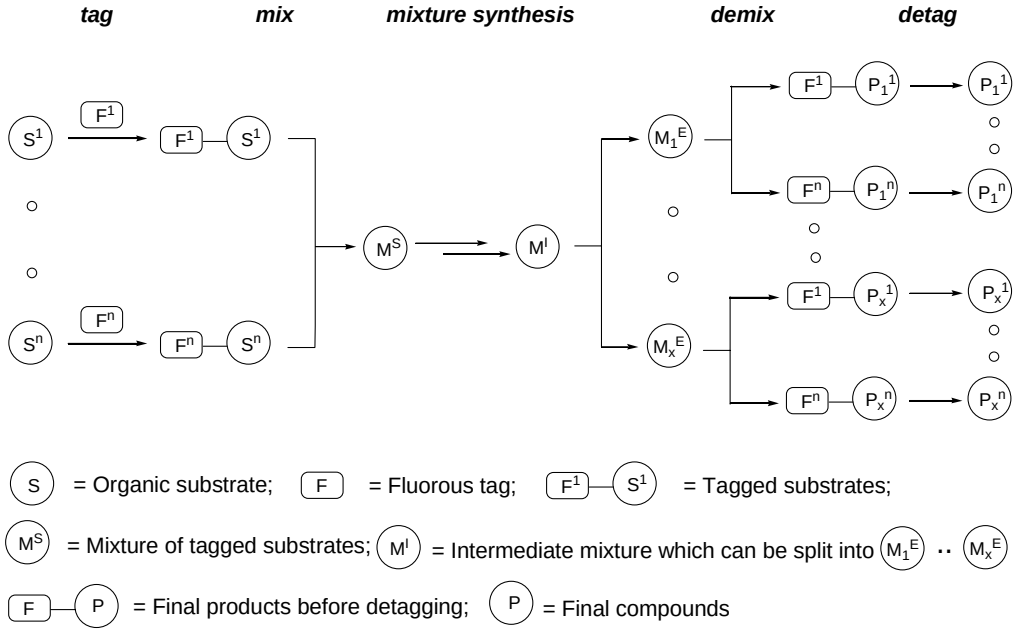
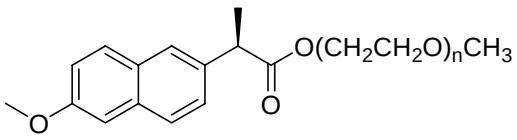


Figure 1.1 Schematic representation of fluorous mixture synthesis

The viability of the concept of fluorous mixture synthesis was efficiently demonstrated by Curran and coworkers in the synthesis of a 560-compound library of mappicine analogues, four analogues of discodermolide,[6] sixteen stereoisomers of murisolin,[7] a sixteen stereoisomer library of pine sawfly sex pheromone[8] and eight stereoisomers of passifloricin A.[9]

1.1.2. Oligoethylene glycols as new class of sorting tags

In an effort to further empower the concept of chromatographic tagging strategies and to extend the concept of mixture synthesis, Wilcox and Turkyilmaz have introduced oligoethylene glycols[10] (OEG, $-[OCH_2CH_2]_nOCH_3$, n = 1, 2...) as a new class of separation tags that can be used in solution phase mixture synthesis and polarity-based demixing. OEG derivatives containing five or fewer ethylene glycol subunits elute on regular silica-flash column or TLC in the order of increasing number of the ethylene glycol units. The trend was demonstrated by separating a mixture **M1** of four esters **1a-d,** on a standard analytical silica-TLC plate (100% ethyl acetate) (figure 1.2). The four esters were well separated in the order of number of ethylene glycol units. The ester **1a** has the fewest ethylene glycol units and hence it is the least polar among the esters **1a-d** with an R_f of 0.7 (100% ethyl acetate). Ester **1d** has the most ethylene glycol units and hence it is the most polar among **1a-d** with an R_f = 0.3. The remarkable difference in the polarity of OEG-tags can facilitate the mixture synthesis by providing an easy separation of compounds from the mixture.



M1

	n	R_f
1a	1	0.70
1b	2	0.60
1c	3	0.48
1d	4	0.33

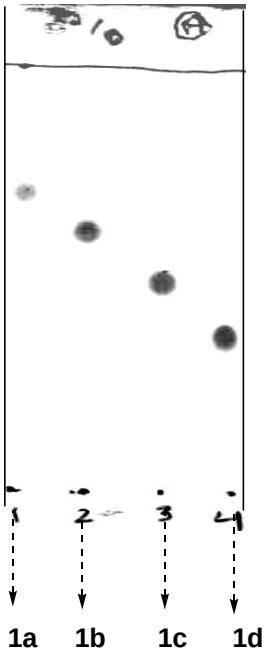


Figure 1.2 Simple proof of concept experiment demonstrate the predictable separation of OEG-tagged compounds on a silica-TLC plate (100% ethyl acetate): Figure courtesy of Prof. Wilcox.

1.1.3. OEG-mixture synthesis (OMS)

The availability of OEG-tags opens the possibility for "OEG mixture synthesis" (OMS), a new class of solution phase mixture synthesis. The envisioned OEG-mixture synthesis, similar to FMS, can be carried in five steps- tagging, mixing, mixture synthesis, demixing and detagging. The OEG tags, similar to the fluorous tags, can be used in combination with a variety of protecting groups. For example the analogs **2** or **3** of the *p*-methoxybenzyl (PMB) protecting group as well as the analogs **4** or **5** of the 3,4-dimethoxy benzyl (DMB) protecting group (figure 1.3) can be used to tether the OEG-tags to hydroxy functionality. The identity of each of the final compounds can be encoded from the OEG tag attached to it. However, OEG tags have an NMR finger print (4.2-3.0 ppm in ^{1}H NMR), which might interfere in the characterization of some OEG-bound compounds. On the other hand, the OEG-finger print region in ^{1}H-NMR spectrum

sometimes facilitates in identifying the OEG-bound compound based on the corresponding integral values.

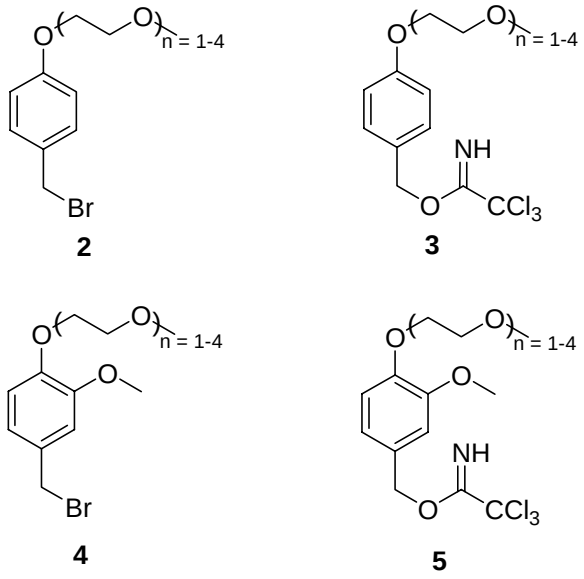


Figure 1.3 Proposed analogs of PMB and DMB protecting group reagents for tethering OEG tags to a hydroxy group

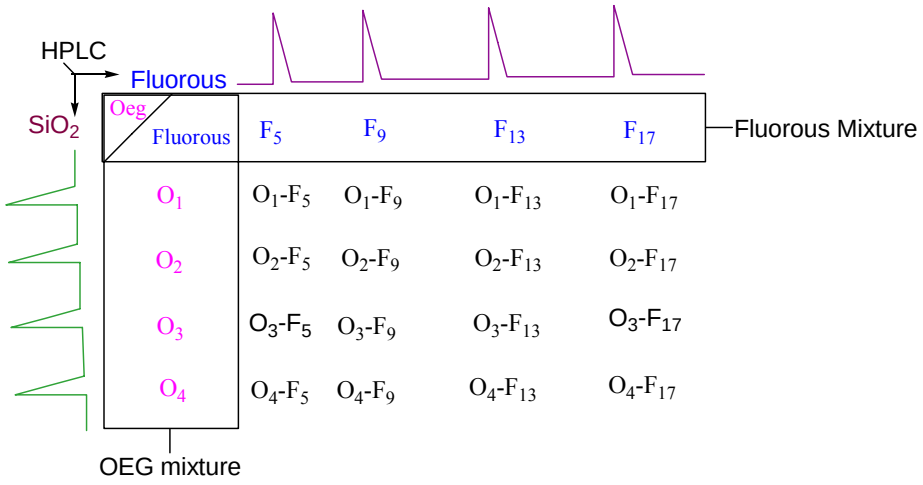
The proposed OEG-mixture synthesis is a complementary type of liquid-phase synthesis that is very similar to fluorous mixture synthesis strategically, but very different in practice. In FMS, purification of the fluorous mixtures (mixture of compounds tagged with fluorous tags) can often be achieved on the regular silica gel without demixing the compounds since the fluorous demixing is tag- based instead of polarity-controlled process. On the other hand, in OMS, purification of the OEG mixtures (a mixture of compounds tethered with OEG tags) on silica gel will lead to simultaneous demixing since the OEG-tags are meant for polarity based demixing. In other words, each chromatographic step on the silica gel in OEG mixture synthesis can potentially turn out to be a demixing exercise. Despite this difference, OMS brings in the

main advantage typical of FMS: a series of reactions, workups and purifications can be carried on a mixture of compounds in solution phase.

1.1.4. OEG-fluorous mixture synthesis (OFMS)

The availability of two different classes of separation tags (fluorous and OEG) opens the door for double tagging strategies. Tagging of 'n' precursors with a first class of tag and 'm' precursors with a complementary second class provides 'n+m' precursors. However, reaction of these two orthogonally tagged mixtures provides a new mixture of 'n•m' products, wherein each product has a unique pair of tags. Isolation of the final products can be achieved by a double demixing exercise wherein each demixing targets a separate tag class.

Our envisioned double tagging strategy where four OEG and four fluorous tags are employed is illustrated in Figure 1.4. During the premix stage, a four-compound OEG mixture will be made by tethering four precursors with OEG tags (n = 1-4) and a four-compound fluorous mixture will be made by tethering another set of four precursors with fluorous tags (R_F = C_2F_5-C_8F_{17}). Reaction of the two orthogonally tagged mixtures will give a sixteen-compound mixture, wherein the identity of each compound is encoded from the unique pair of tags bound to them. We hypothesized that an initial OEG demixing (polarity based demixing) followed by fluorous demixing or vice versa will give sixteen individual doubly tagged compounds. This approach, called double demixing, is shown in Figure 1.4.



O_1, O_2, O_3 and O_4 = OEG-tagged precursors

F_5, F_9, F_{13} and F_{17} = Fluorous tagged precursors

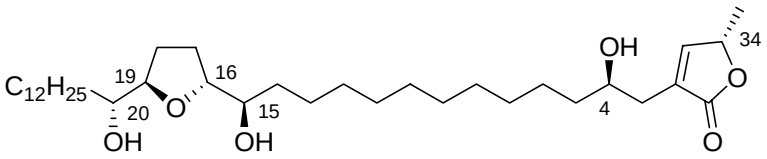
O_1-F_5.... O_4-F_{17} = Orthogonally-tagged products resulting from the reaction of two orthogonally tagged compounds

Figure 1.4 Schematic representation of OFMS by applying double tagging-double demixing strategy

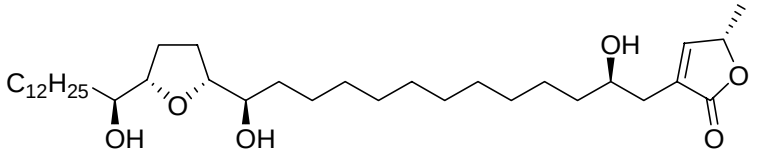
1.1.5. Murisolin and its stereoisomers

Murisolin, a member of the mono-THF class of acetogenins, was isolated by Cave´ and co-workers from the seeds of *Annona muricata*.[11] It was characterized by mass spectrometry and 2D homonuclear and heteronuclear correlations NMR spectroscopy. The relative stereochemistry of the dihydroxy-THF ring was established by ^{1}H-NMR comparative spectral studies. Murisolin was also isolated by McLaughlin and co-workers[12] from *Asmina triloba*, along with 16, 19-*cis*-murisolin and murisolin A. They have assigned the structure of 16,19-*cis*-murisolin as **7** by a combination of ^{1}H NMR studies on the natural product to establish the relative configuration of the dihydroxy-THF ring and Mosher ester studies to establish the absolute configuration. With similar methods, the structure of murisolin was refined to **6** and the structure of murisolin A was narrowed to two candidates, **8** and **9**. These compounds show potent cytotoxic activities against

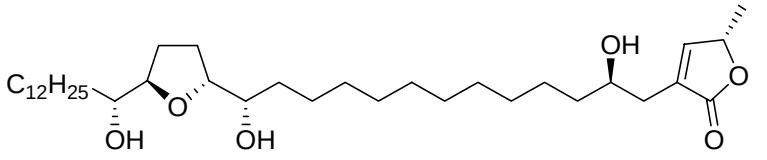
several human cancer cell lines and act by inhibition of complex I (NADH/ubiquinone oxidoreductase) in mitochondrial electron transport systems.[13] Recently, two independent groups (the Curran group at the University of Pittsburgh and the Tanaka group[14] at Osaka University) have achieved the total synthesis of murisolin. The Curran group has applied fluorous mixture synthesis for the synthesis of murisolin and fifteen of its stereoisomers. Two compounds in the obtained stereoisomer library, 15*R*,16*R*,19*R*,20*R*-**6** and 15*S*,15*S*,19*S*,20*S*-**6** showed identical spectra to that of natural product murisolin. However, 15*R*,16*R*,19*R*,20*R*-**6** was identical to the natural product murisolin by co-injection on a Chiracel OD column, while 15*S*,15*S*,19*S*,20*S*-**6** was different. This work conformed that the original stereochemical assignment of murisolin was correct.



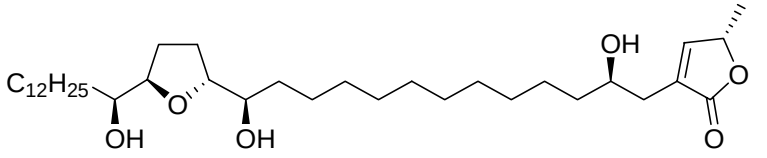
6 murisolin, (15*R*,16*R*,19*R*,20*R*)



7 16,19-*cis*-murisolin (15*R*,16*R*,19*S*,20*S*)



8 murisolin A (15*S*,16*R*,19*R*,20*R*)



9 (15*R*,16*R*,19*R*,20*S*)

Figure 1.5 Proposed structure of murisolin (**6**), 16,19-cis murisolin (**7**), and murisolin A (**8** or **9**)

Encouraged by the fruitful results of the fluorous mixture synthesis of the 16-isomer library of murisolin by a 4mix/4split strategy, we aimed at advancing the solution phase mixture synthesis to the 16mix level by applying a double tagging technique. In a 4mix/4split strategy, a mixture of four compounds is split into four mixtures of four compounds to increase the diversity of mixture synthesis. However, in a 16mix strategy, a similar diversity can be made without the need to split the intermediate mixture. To this end, we planned to explore the envisioned double tagging strategy by initially studying the complementarities of OEG and fluorous tags; will the fluorous tags interfere in the OEG demixing or vice versa? The complementarity of the tags is crucial for the success of our envisioned double tagging strategy. Our next goal was to examine the viability of our envisioned OEG-mixture synthesis (OMS) and OEG-fluorous mixture synthesis (OFMS) for syntheses of a sixteen isomer library of murisolin.

The proposed strategy for the synthesis of murisolin and its isomers by OFMS is shown in Figure 1.6. All sixteen isomers of **10**, with C15, C16 stereocenters fixed, can be obtained by demixing the sixteen-compound mixture **M11**. Mixture **M11** can be obtained by coupling two orthogonally tagged four-compound mixtures **M12** and **M13**. The aldehyde mixture **M12** can be synthesized by applying the newly envisioned OMS while the sulfone mixture **M13** can be synthesized by FMS using the previously reported strategy.

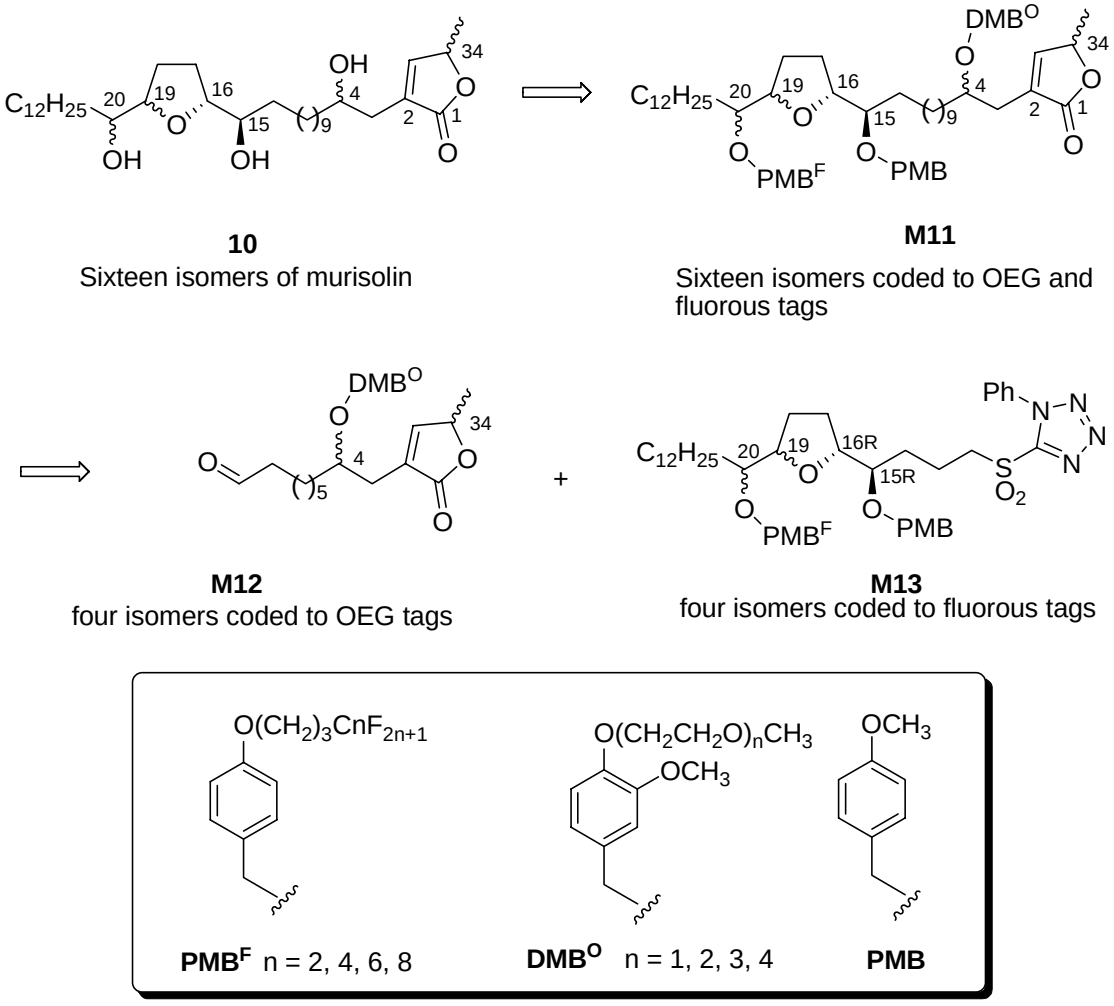


Figure 1.6 Double tagging strategy for the synthesis of murisolin and fifteen of its stereoisomers

The OEG-mixture synthesis strategy for accessing aldehyde mixture M**12** is shown in Figure 1.7. The aldehyde **M12** has two stereocenters (C4 and C34) and hence four stereoisomers are possible. In the pre-mix stage, the four tagged precursors (*S*)-**14a**, (*S*)-**14b**, (*R*)-**14c** and (*R*)-**14d** can be made and grouped into two quasi-racemic mixtures **M14a** and **M14b**. The initial coding of each stereocenter (C4) with two tags permits the coding of the C34 butenolide center without the need for additional tags. The mixtures **M14a** and **M14b** can be advanced to a pair of two-compound mixtures **M15a** and **M15b**, respectively, followed by mixing them together to

give a four-compound mixture **M15**. The mixture **M15** can be advanced to **M12**, which is the aldehyde component for the proposed OEG-fluorous mixture synthesis. At this stage, the OMS and FMS can be advanced to OFMS by the reaction of two orthogonally tagged mixtures **M12** and **M13** affording a sixteen-compound mixture **M11**. The sixteen-compound mixture can be subjected to double demixing to give sixteen doubly tagged final compounds wherein the identity of each isomer can be encoded from the unique pair of tags attached to it. Detagging of the final compounds gives individual isomers of murisolin.

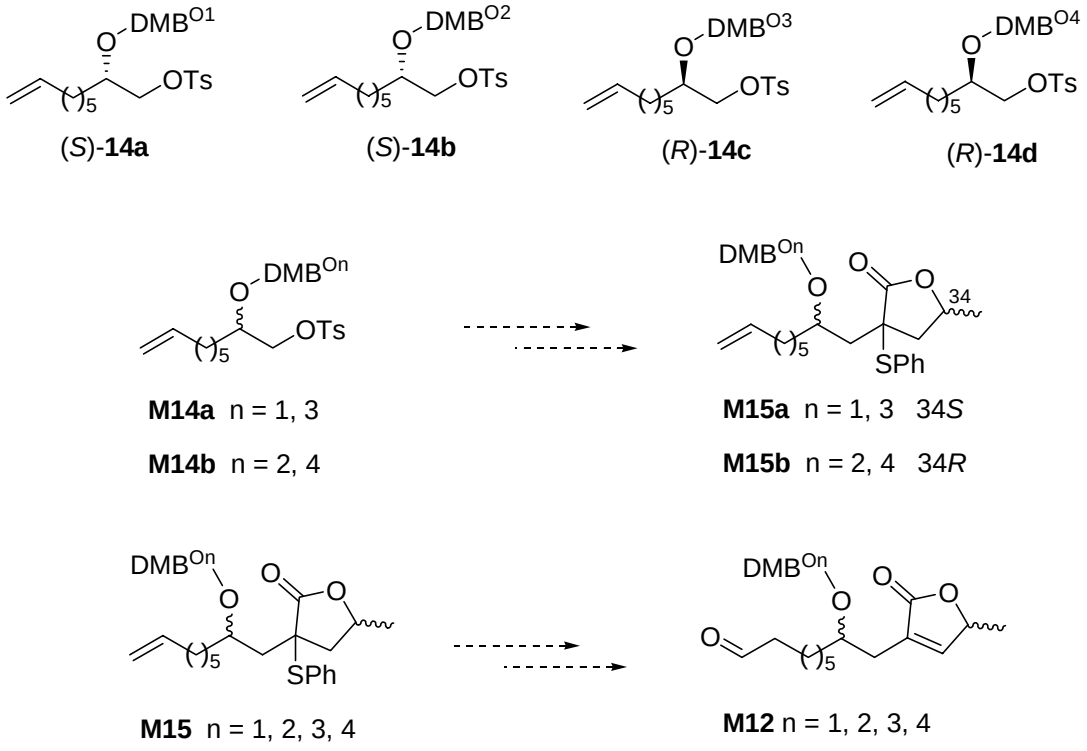
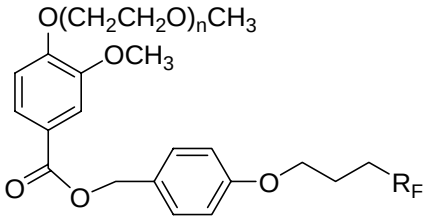


Figure 1.7 OEG-mixture synthesis strategy for the synthesis of four-compound mixture **M12**

1.2. RESULTS AND DISCUSSION

1.2.1. Model double demixing experiments

To address the vital issue of complementarity of OEG and fluorous tags, we decided to perform a model study with a mixture **M16** (Figure 1.8).[15] This mixture contains sixteen doubly tagged vanillic esters wherein each compound had one of a series of four OEG tags on the phenolic hydroxyl group (n = 1-4) and one of a series of four homologous fluorous tags on the carboxylate group (R_F = C_2F_5, C_4F_9, C_6F_{13}, C_8F_{17}). The mixture **M16** was readily prepared, as summarized below.

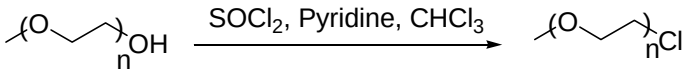


M16 n = 1, 2, 3, 4;

R_F = C_2F_5, C_4F_9, C_6F_{13}, C_8F_{17}

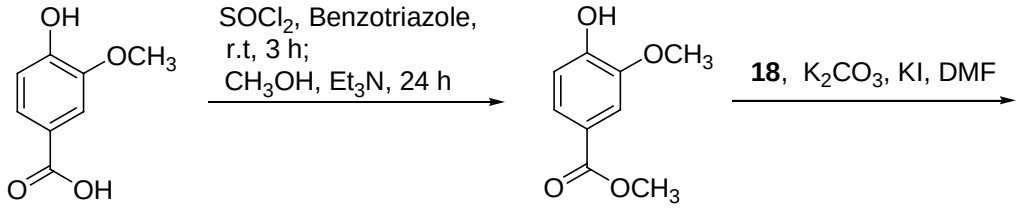
Figure 1.8 Four-compound mixture **M16** for model double demixing experiments

Alkyl halide **18b** was prepared by reaction of alcohol **17b** with thionyl chloride in 92% yield. Similarly alkyl halides **18c** (94% yield) and **18d** (93%) were prepared from the corresponding alcohols **17c** and **17d**, respectively, while 1-chloro-2-methoxyethane **18a** was obtained from commercial sources. Vanillic acid **19** was converted to methyl vanillate **20**[16] in 80% yield by a standard esterification procedure ($SOCl_2$, benzotriazole, CH_3OH). *O*-Alkylation of methyl vanillate **20** with 1-chloro-2-methoxyethane **18a**, employing K_2CO_3, KI in DMF, provided ester **21a** in 93% yield. Similarly, OEG^2-analog **22b** (96% yield), OEG^3 analog **21c** (95% yield) and OEG^4 analog **21d** (91% yield) were prepared (Scheme 1.1).

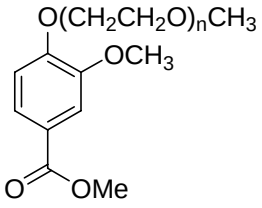


	n
17b	2
17c	3
17d	4

	n	
18a	1	(commercial)
18b	2	(92%)
18c	3	(94%)
18d	4	(93%)



19 **20** (80%)

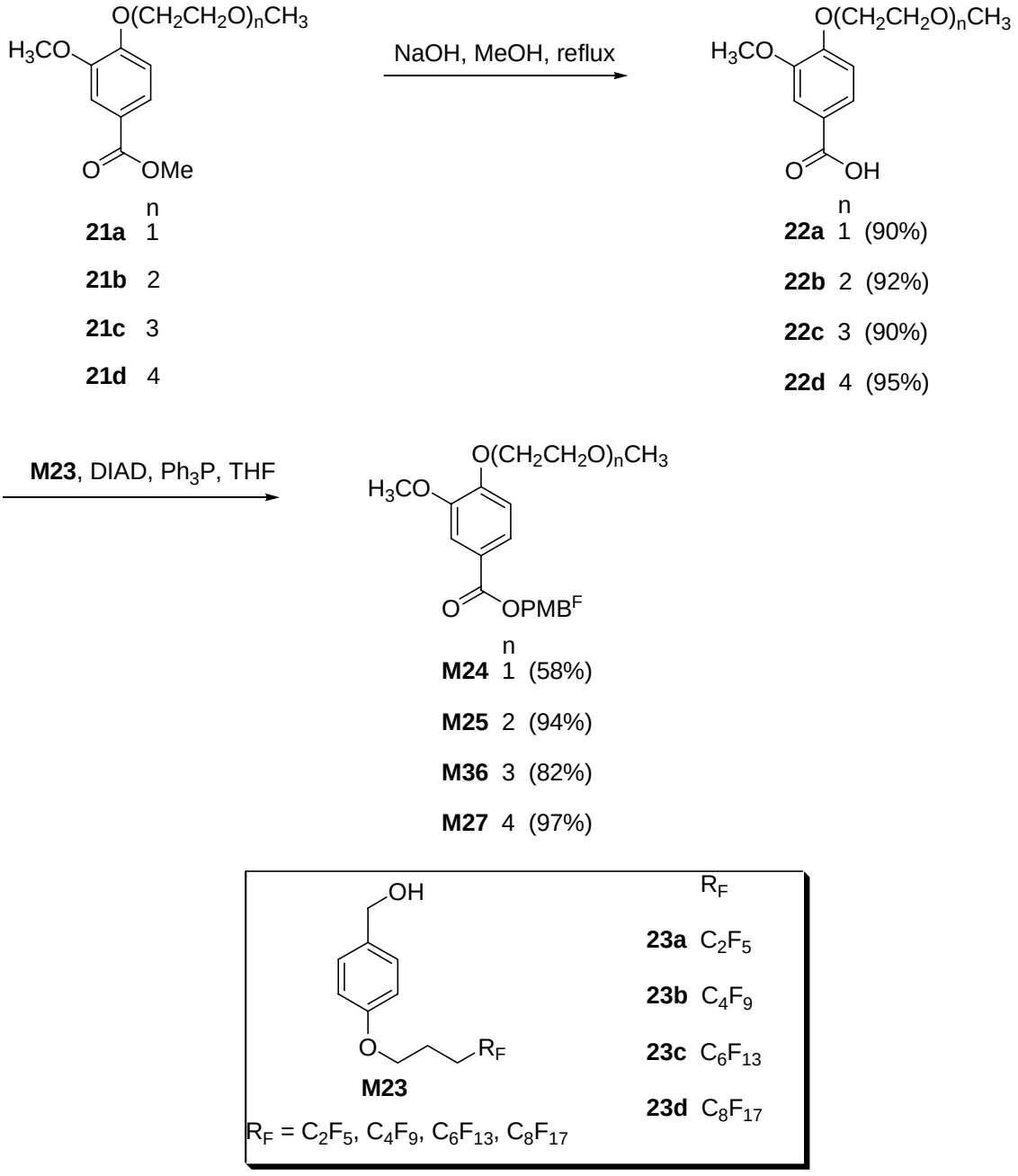


	n	
21a	1	(93%)
21b	2	(96%)
21c	3	(95%)
21d	4	(91%)

Scheme 1.1 Synthesis of Vanillic esters **21a-21d**

The rest of the experiments in this model study were carried out by Dr. Hejun Lu as described below (Scheme 1.2). The esters **21a**, **21b**, **21c** and **21d** were independently subjected to saponification (NaOH, CH_3OH, reflux) to give the corresponding acids **22a** (90%)**, 22b** (92%)**, 22c** (90%) and **22d** (95%). The fluorous alcohol mixture **M23** was prepared by mixing equimolar amounts of the commercially available[17] *p*-perfluoroalkoxy benzyl alcohols **23a**, **23b**,

23c and **23d**. Acid **22a** was subjected to esterification with the fluorous alcohol mixture **M23** to give a mixture of four doubly tagged analogs **M24** (58% yield), wherein each compound had an OEG[1] tag on the phenolic hydroxy group and one of a series of four homologous fluorous tags on the carboxylate group (R_F = C_2F_5, C_4F_9, C_6F_{13} and C_8F_{17}). Similarly, mixtures **M25** (94% yield)**, M26** (82% yield) and **M27** (97% yield) were prepared**.**



Scheme 1.2 Synthesis of Doubly-tagged Mixtures **M24**, **M25**, **M26** and **M27**

TLC analysis of **M24** (SiO_2, 1:1 pentane/ethyl acetate) showed only one spot (R_f: 0.87). Similarly TLC analysis (SiO_2, 1:1 pentane/ethyl acetate) of the mixtures **M25** (R_f: 0.55), **M26** (R_f: 0.27) and **M27** (R_f: 0.09) showed a single spot for each mixture. It is well known that

addition of CF_2 groups decreases the polarity of molecules,[18] yet this effect is masked by the large polarity effects of the OEG tag as indicated by the single spot on TLC for the mixtures **M24**-**M27**. Then, an HPLC analysis of the mixture **M24** was performed with an analytical Fluoroflash PF-C8 column (Figure 1.9). As expected, the products in this chromatography eluted in the order of the fluorous tag from C_2F_5 to C_8F_{17}. Similar results were obtained with mixtures **M25**, **M26** and **M27** under the same HPLC analytical conditions (Table 1.1). The huge polarity effects of OEG tags are largely masked on the fluorous column by the fluorine content as indicated by four well separated peaks in analytical fluorous HPLC studies of the mixtures **M24**-**M27**.

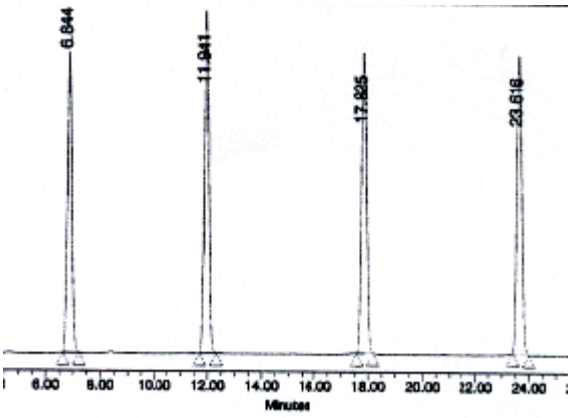


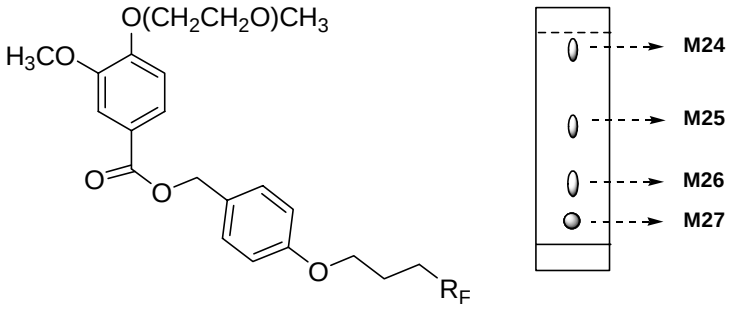
Figure 1.9 HPLC analysis of the mixture **M22**: HPLC analysis was carried out with a fluorous PF-C8 5-micron 150 x 4.6 mm HPLC column, 60% acetonitrile/water to 90% acetonitrile/water for 20 min then 90% acetonitrile/water for 10 min

Entry	Mixture	Retention times (min)			
		Peak 1 (C_2F_5)	Peak 2 (C_4F_9)	Peak 3 (C_6F_{13})	Peak 4 (C_4F_{17})
1	**M24** (OEG[1])	6.84	11.94	17.82	23.61
2	**M25** (OEG[2])	6.48	11.52	17.5	23.49

3	**M26** (OEG^3)	6.20	11.17	17.17	23.30
4	**M27** (OEG^4)	5.94	10.82	16.81	23.08

Table 1.1 HPLC analysis of mixtures **M24, M25**, **M26** and **M27** on an analytical fluorous PF-C8 (150 x 4.6 mm) column.

A mixture of sixteen doubly tagged analogs **M16** of vanillic acid was obtained by mixing together the four doubly-tagged vanillic acid analog mixtures **M24**, **M25**, **M26** and **M27**. TLC analysis (SiO_2**,** 1:1 pentane/ethyl acetate) of the mixture **M16** showed four spots (Figure 1.10) wherein each spot represented a different OEG analog mixture. The identity of each spot was confirmed by co-analysis of individual mixtures on the TLC. The mixture **M16** was separated by flash chromatography (SiO_2, pentane/EtOAc gradient) into four fractions **M24**-**M27** based on the properties of the OEG tags. This simple proof-of-concept experiment demonstrates the viability of OEG-demixing (separation of OEG-tagged molecules on regular silica gel) of doubly tagged compounds.



M16 n = 1, 2, 3, 4;

$R_F = C_2F_5, C_4F_9, C_6F_{13}, C_8F_{17}$

Figure 1.10 Analyses of sixteen vanillic acid esters **M16** on standard silica gel TLC (1:1 pentane/ethyl acetate)

An analytical HPLC trace of the 16 compound mixture **M16** on a FluoroFlash PF-C8 column (CH_3CN/H_2O, 40/60 to 90/10) is shown in Figure 1.11. The identity of each peak was determined by LC-MS analysis of the sixteen-compound mixture **M14**. The compounds emerge

as four groups of four peaks. The larger separations correspond to the fluorous tag, with the four compounds bearing the C_2F_5 tag eluting well before the four compounds bearing the C_4F_9 tag, etc. The smaller separations within the groups of peaks correspond to OEG separation from the more polar n = 4 tag to the less polar n = 1 tag.

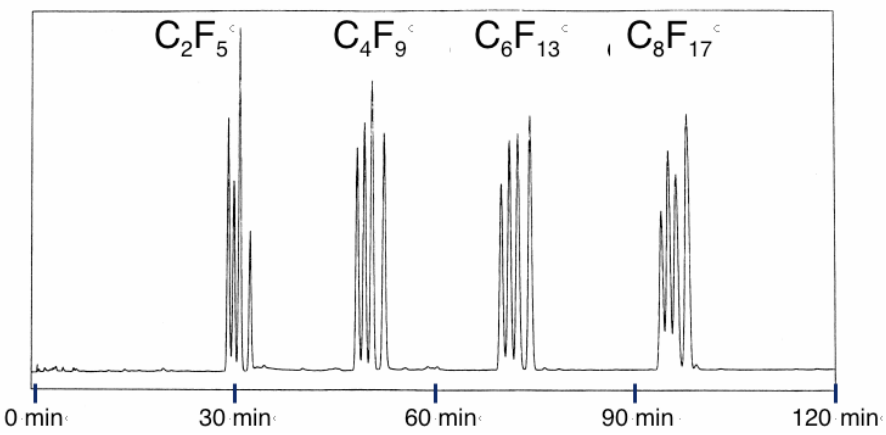


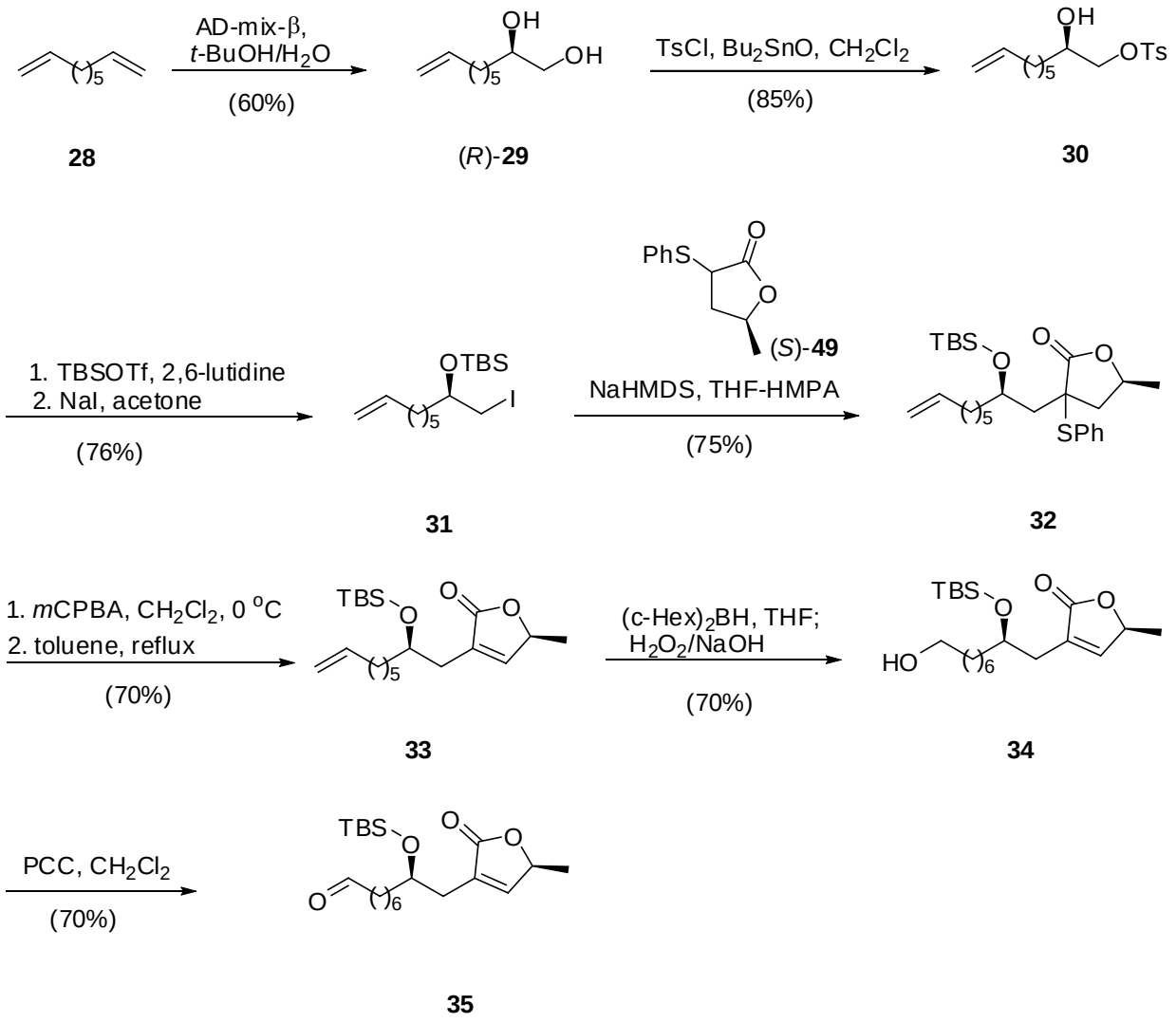
Figure 1.11 Analytical HPLC trace of M16 on a FluoroFlash PF-C8 column (CH_3CN/H_2O, 40/60 to 90/10)

These simple proof-of-concept experiments are remarkable and show that fluorous and OEG tags are complementary in double demixing. Initial preparative separation of the doubly tagged analog mixture **M16** (20 mg of **M16** was used for this study) by silica-column chromatography (OEG-demixing) followed by subjecting each of the resulting four fractions **M24** (4.5 mg), **M25** (5.8 mg), **M26** (2.0 mg) and **M27** (6.8 mg) to fluorous HPLC (fluorous demixing) provided all sixteen individual compounds in an average of 1 mg quantity. The order of demixing can also be reversed by initially carrying out a fluorous demixing followed by an OEG demixing. To verify the applicability of the above demonstrated double tagging-double demixing strategy, we proceeded to prepare 16 stereoisomers of the acetogenin murisolin in a single reaction flask.

1.2.2. Synthesis of Hydroxybutenolide (4*R*,34*S*)-35

In the initial 16-member murisolin library, hydroxybutenolide **35** was synthesized by Dr. Cyrille Richard as summarized in Scheme 1.3. Sharpless dihydroxylation[19] of 1,8-nonadiene **28** with the commercially available AD-mix-β catalyst afforded diol (*R*)-**29** in 60% yield with an enantiomeric ratio of 91/9. The primary hydroxylic group was selectively converted to tosylate **30** in 85% yiled by treatment with *p*-TsCl/Bu_2SnO. Protection of the seconday alcohol as TBS ether (85% yield) followed by displacement of the tosylate by iodide (NaI, acetone, reflux) provided **31** in 90% yield. The sodium enolate of lactone (*S*)-**49** was alkylated[20] with iodide **31** to afford **32** in 75% yield. Oxidation of the sulfide **32** with *m*CPBA followed by thermal elimination gave butenolide **33** in 70% yield. The terminal olefin **33** was subjected to hydroboration-oxidation to afford the primary alcohol **34** in 70% yield. Finally, oxidation of **34** with PCC[21] gave aldehyde (4*R*,34*S*)-**35** in 70% yield.

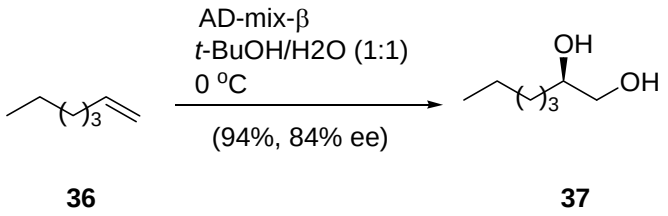
The minor (4*S*) enantiomer of alcohol **29** resulted in a diastereomeric impurity in lactone **35**, which was an inseperable ~9/1 mixture of epimers (C4) as assayed by ^{13}C NMR spectroscopy. The diastereomeric impurity in **35** was carried through the rest of the synthesis resulting in minor diastereomeric impurities in each of the sixteen final murisolins. In the current murisolin library synthesis, we explored Jacobsen hydrolytic kinetic resolution method to access enantiopure **29** as described below.



Scheme 1.3 Synthesis of aldehyde **35** (by Dr. Cyrille Richard, Curran labs)

1.2.3. Synthesis of enantiomerically pure diol 29

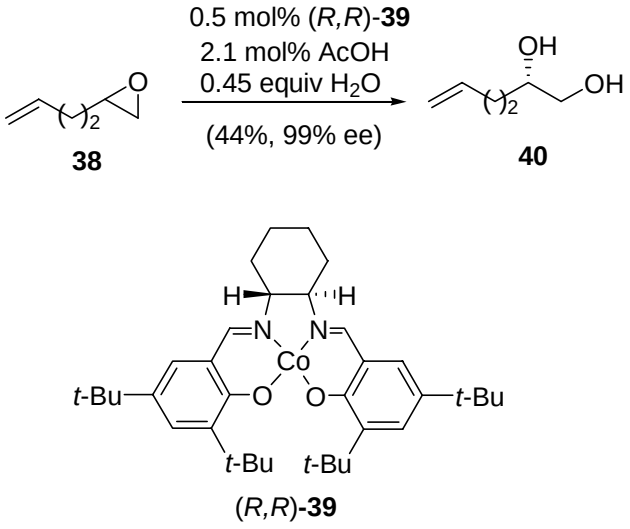
Terminal olefins are known to furnish the diols in relatively lower ee's (80-90%) in the Os-catalyzed asymmetric dihydroxylation reactions.[22] This trend is apparent in the literature results wherein conversion of terminal olefin **36** to (*R*)-diol **37** (Scheme 1.4) occurred in 94% yield and in 84% enantiomeric excess (ee).[23]



36 **37**

Scheme 1.4 Asymmetric dihydroxylation of terminal olefin **29**

Hydrolytic kinetic resolution of terminal racemic epoxides with Chiral Co(Salen) Complexes was proven to provide terminal diols in good to excellent enantiomeric excess.[24] The Jacobsen group reported that **38** was treated with the (*R,R*)-Jacobsen catalyst (*R,R*)-**39** to give (*S*)-5-hexane-1,2-diol **40** (44% yield) in 99% enantiomeric excess (Scheme 1.5). Hence, we plan to examine the hydrolytic kinetic resolution method for accessing diols (*R*)-**29** and (*S*)-**29** in high enantiomeric purity.

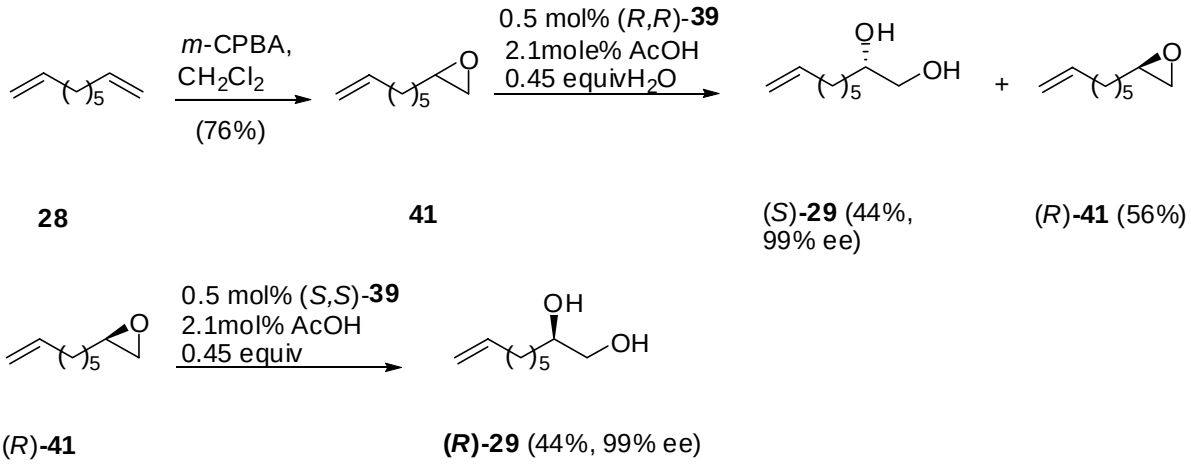


38 **40**

(*R,R*)-**39**

Scheme 1.5 Jacobsen hydrolytic kinetic resolution of terminal epoxides

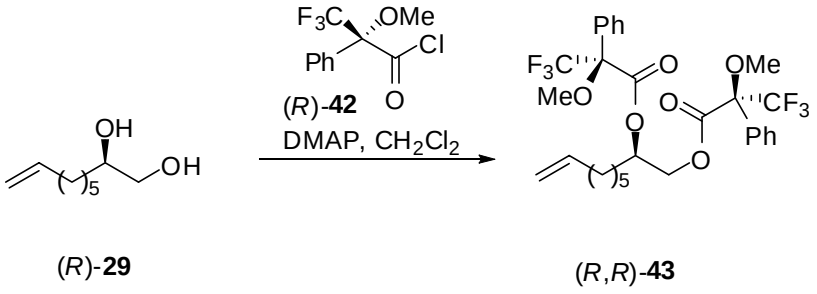
Our initial efforts on mono-epoxidation of the terminal diene **28** with *m*-CPBA or with oxone[25] were low yielding due to the competing bis-epoxidation reaction. However, the epoxidation of diene **28** with *m*-CPBA as the limiting reagent (1 equiv) and use of an excess of olefin **28** (2.5 equiv) afforded the mono-epoxide **41** in 76% yield (based on *m*-CPBA). The racemic epoxide **41** was subjected to hydrolytic kinetic resolution (HKR) with the (*R*,*R*)-Jacobsen catalyst (*R*,*R*)-**39** to give the corresponding diol (*S*)-**29** in 43% yield and in 99% enantiomeric excess (ee) along with the enantiomerically enriched epoxide (*R*)-**41** (see experimental section for details). Epoxide (*R*)-**41** was than subjected to Jacobsen HKR with the Jacobsen catalyst (*S*,*S*)-**39** to yield (*R)*-diol (*R*)-**29** in 44% yield (based on the quantity of racemic epoxide) and 99% enantiomeric excess.



Scheme 1.6 Hydrolytic kinetic resolution of racemic epoxide **41**

The enantiomeric purity of diols (*R*)-**29** and (*S*)-**29** was assayed by ^{1}H NMR spectroscopy by applying the Mosher method.[26] Alcohol (*R*)-**29** was *bis*-acylated with (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (*R*)-**42** to give the Mosher ester (*R*,*R*)-**43** (Scheme 1.7).

Alcohol (*R*)-**29** was spiked with (*S*)-**29** to give a sample **29a**. Alcohol **29a** was *bis*-acylated to give **43a** (not shown in scheme). The ^{1}H NMR spectrum of **43a** obtained at 500 MHz showed a doublet of doublet (dd) centered at δ 4.56 and another *dd* centered at δ 4.62. The ^{1}H NMR spectrum of (*R*,*R*)-**43** showed a doublet of doublet at centered at δ 4.56 but none of the peak for the other diastereomer could be detected (figure 1.12). Hence, the enantiomeric excess of the alcohol (*R*)-**29** must be higher than 99%. Similarly, the enantiomeric excess of (*S*)-**29** was determined to be > 99%.



(*R*)-**29** (*R*,*R*)-**43**

Scheme 1.7 Determination of enantiomeric purity by Mosher method

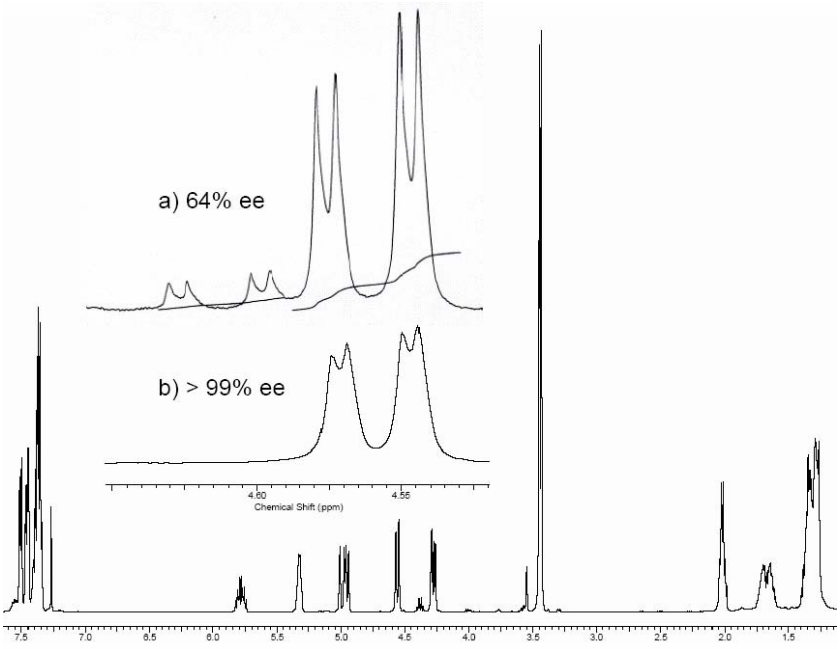
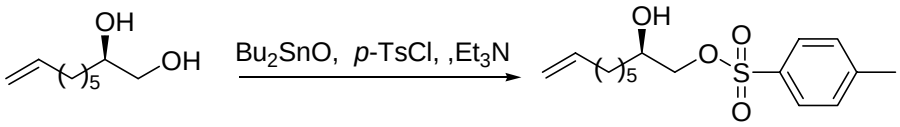


Figure 1.12 500 MHz 1H NMR spectra of (*R*,*R*)-**43**; insert (a) expansion of **43a** (spiked sample); insert (b) expansion of (*R*,*R*)-**43** (from HKR)

The primary hydroxy group of diol (*R*)-**29** was selectively functionalized as tosylate (*R*)-**30** in 74% yield by the reaction of diol (*R*)-**29** with *p*-toluenesulfonyl chloride in presence of catalytic amount (0.2 equiv) of dibutyltin oxide[77,27] Similarly, primary alcohol of diol (*S*)-**29** was selectively tosylated to give(*S*)-**30** in 76% yield (Scheme 1.8).



(*R*)-**29** (*R*)-**30** (74%)

(*S*)-**29** (*S*)-**30** (76%)

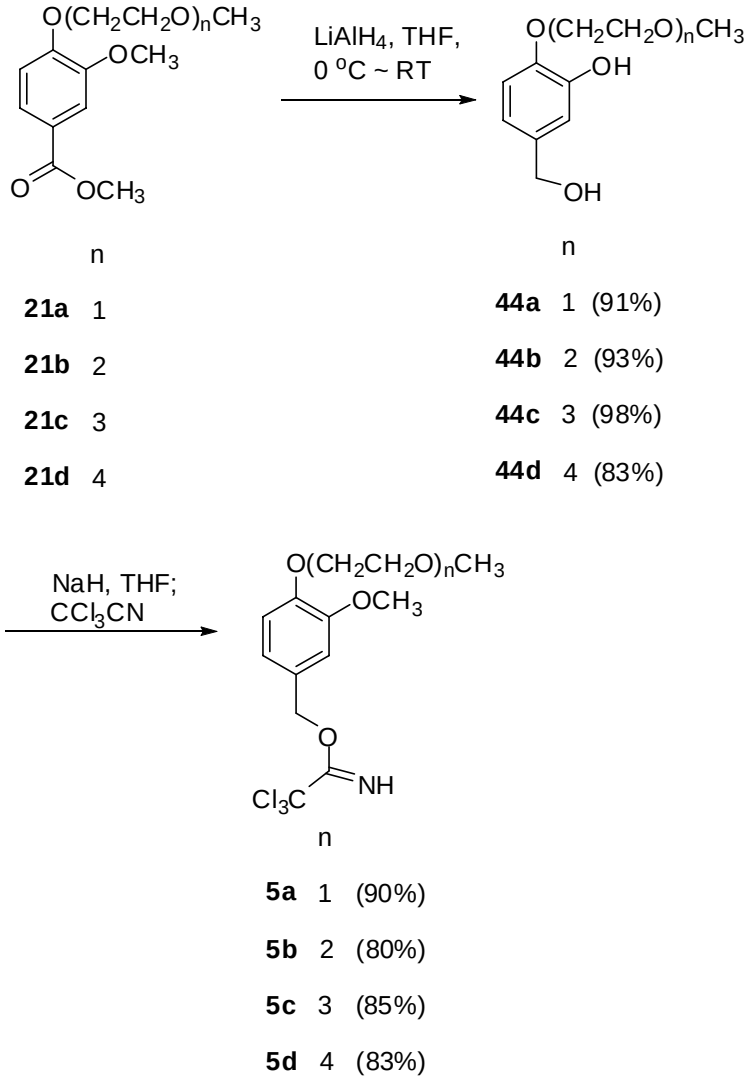
Scheme 1.8 Synthesis of sulfones (*R*)-**30** and (*S*)-**30**

Attempts to protect the *sec*-alcohol (*R*)-**30** with DMB^{O1}-bromide **4a** (n = 1) under basic conditions were unsuccessful due to the competing displacement of the tosylate to give back epoxide (*R*)-**41**. Hence, we decided to examine the utility of imidate **5** under acidic conditions for the protection of alcohols with PMB or benzyl imidates.

1.2.4. Synthesis of DMB^{O} imidate 5

The DMB^{O} imidates **5,** OEG-tagged DMB protecting reagent, were readily synthesized as summarized in Scheme 1.9. Ester **21a** was reduced with lithium aluminum hydride ($LiAlH_4$) to yield alcohol **44a** in 91% yield. Similarly, esters **21b**, **21c** and **21d** were reduced to give the corresponding alcohols **44b** (93% yield), **44c** (98% yield) and **44d** (95% yield) respectively. Alcohol **44a** was converted to imidate **5a** in 90% yield by treatment with NaH in THF followed by the addition of trichloroacetonitrile.[28] Similarly the imidates **5b** (80%), **5c** (85%) and **5d**

(83%) were prepared from the corresponding alcohols **44b**, **44c** and **44d** respectively. The resulting imidates were stored under argon at 0 ^{o}C for more than a month without any deterioration.



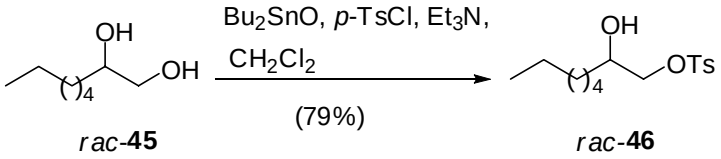
	n		n	
21a	1	**44a**	1	(91%)
21b	2	**44b**	2	(93%)
21c	3	**44c**	3	(98%)
21d	4	**44d**	4	(83%)

	n	
5a	1	(90%)
5b	2	(80%)
5c	3	(85%)
5d	4	(83%)

Scheme 1.9 Synthesis of imidates **5a-5d**

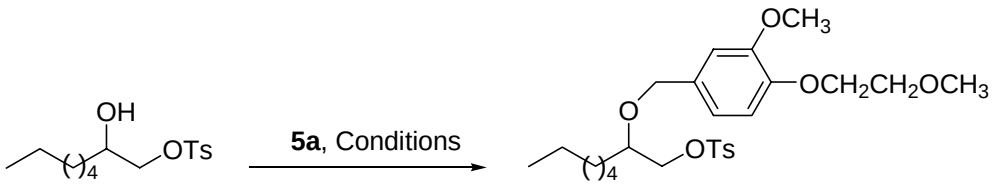
Next our efforts were focused on identifying the conditions for tethering the OEG-tags to alcohols (*R*)-**30** and (*S*)-**30**. The secondary alcohol *rac*-**46** was made from the commercially available octane-1,2-diol *rac*-**45** in 79% yield (Scheme 1.10). Reaction of alcohol *rac*-**46** with

DMB^{O1} imidate **5a** under standard Bundle or Yonemitsu[29] conditions with catalytic amount of trifluoromethanesulfonic acid (TFA) (0.3-10 mole%) was unsuccessful. However, the reaction of alcohol *rac*-**46** with imidate **5a** in presence of catalytic amount (0.1 equiv) of camphorsulphonic acid[30] afforded **47** in 72% yield (Table 1.2).



rac-**45** *rac*-**46**

Scheme 1.10 Synthesis of rac-**46**



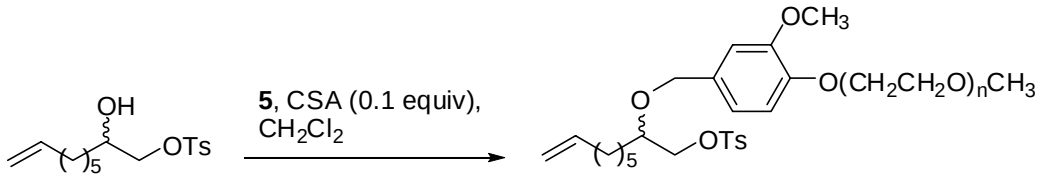
rac-**46** *rac*-**47**

Entry	Conditions	Yield
1	**5a** (1.2 equiv), TFA (0.3 mole%), ether	trace
2	**5a** (2.0 equiv), TFA (0.3 mole%), ether	trace
3	**5a** (2.0 equiv), TFA (10 mole%), ether	trace
4	**5a** (2.0 equiv), TFA (10 mole%), CH_2Cl_2	15%
5	**5a** (2.0 equiv), camphor sulfonic acid, CH_2Cl_2	72%

Table 1.2 Acid catalyzed DMB^{O} protection of alcohol rac-**46** with imidate **5a**

In our efforts to access the four tagged precursors **14a-14d** for OEG mixture synthesis, the secondary alcohol (*S*)-**29** was reacted independently with imidates **5a** and **5b** in presence of

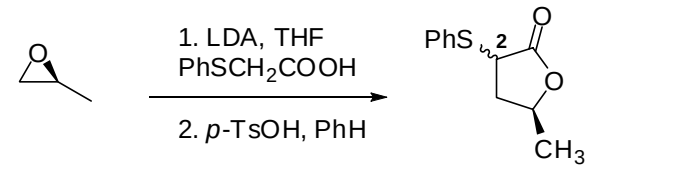
catalytic amount of camphorsulfonic acid (0.1 equiv) to afford **14a** (68% yield) and **14b** (66% yield), respectively. Similarly, **14c** (70% yield) and **14d** (64% yield) were obtained by the reaction of alcohol (*R*)-**29** with **5c** and **5d** (Scheme 1.11).



		n	
(*S*)-**29**	**5a**	**14a** 1	(68%)
(*S*)-**29**	**5b**	**14b** 2	(66%)
(*R*)-**29**	**5c**	**14c** 3	(70%)
(*R*)-**29**	**5d**	**14d** 4	(64%)

Scheme 1.11 Acid catalyzed DMB^{O} protection of alcohols (*R*)-**46** and (*S*)-**46**

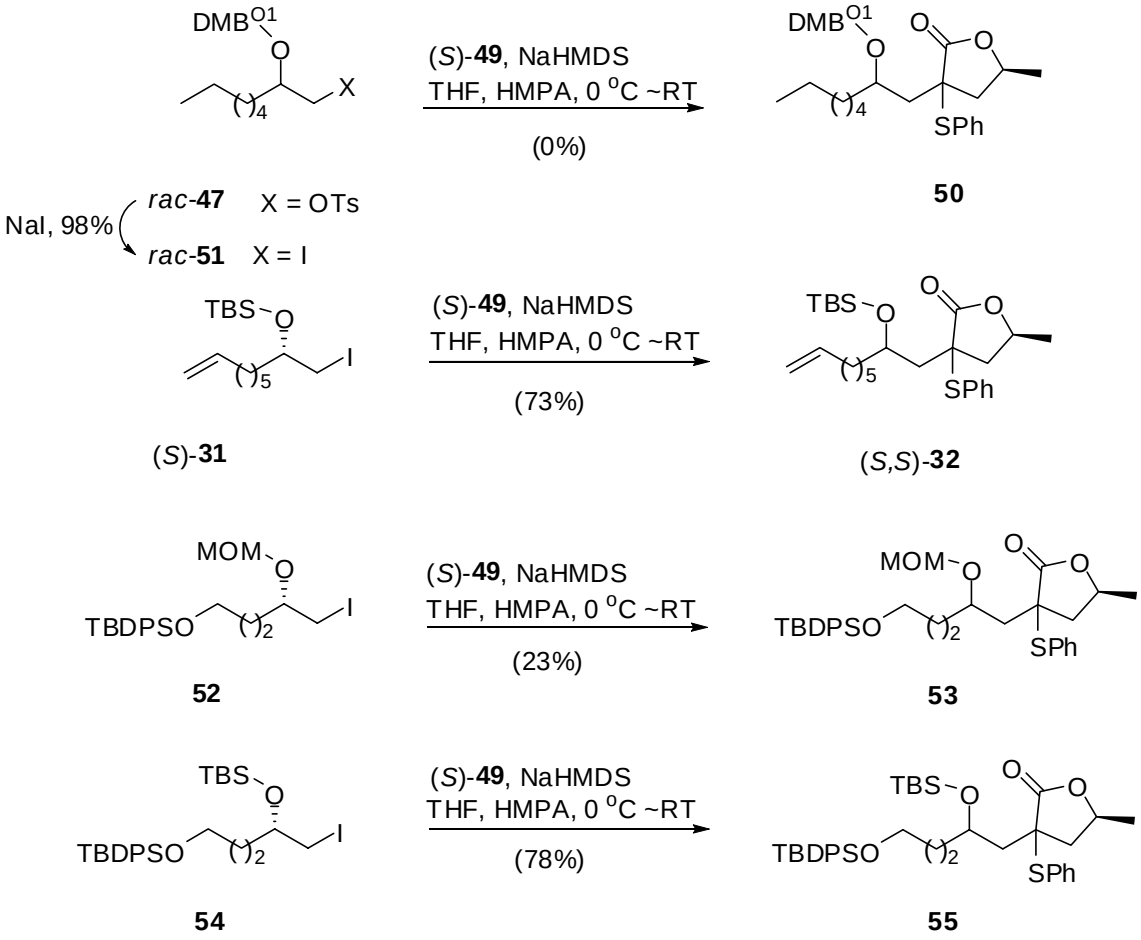
Lactones (*S*)-**49** (96% yield) and (*R*)-**49** (98% yield) were readily synthesized according to standard literature procedure from phenylthioacetic acid and the corresponding 2-methyloxiranes (*S*)-**48** and (*R*)-**48** (not shown in the Scheme), as illustrated in Scheme 1.12.[31,32] The lactones (*S*)-**49** and (*R*)-**49** were obtained as a 1:1 mixture of stereoisomers at C(2) (Scheme 1.12).

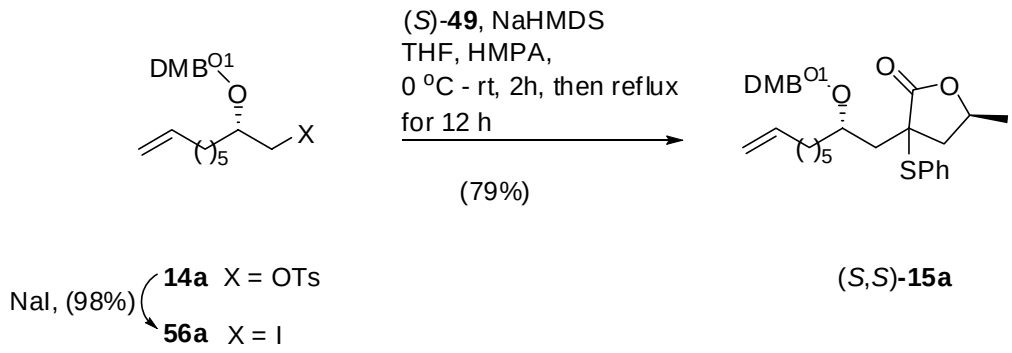


(*S*)-**48** (*S*)-**49** (96%)

Scheme 1.12 Synthesis of lactone (*S*)-**49**

Our efforts in alkylation of the sodium enolate derived from (*S*)-**49** with the tosylate *rac*-**46** and iodide *rac*-**51** were unsuccessful. However, the alkylation of the enolate was feasible (73% yield) with (*S*)-**31** (TBS protecting group on the hydroxy functionality) that was synthesized by following Richard's procedure (Scheme 1.3). This scenario parallels the literature results[33] wherein alkylation of the sodium enolate of (*S*)-**49** with **52** (MOM protecting group on hydroxy group) was low yielding while alkylation with **53** (TBS protecting group on the hydroxy group) gave 78% yield. However, we were delighted to achieve the alkylation of the sodium enolate of (*S*)-**49** with iodide **56a** by simply refluxing the reaction mixture for 12 h. The lactone (*S*,*S*)-**15a** was obtained in 79% yield as a 1: 6 stereoisomeric mixture at C2 (Scheme 1.13).



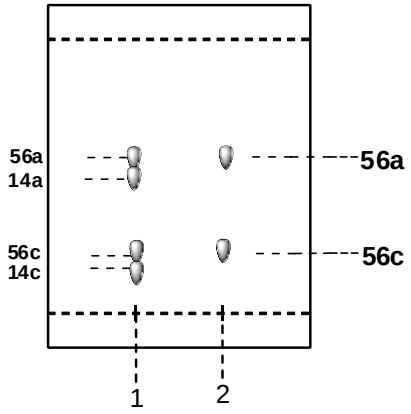


Scheme 1.13 Synthesis of (*S*,*S*)-**15a**

In order to begin the first application of OEG-tags in quasi-racemic synthesis,[34] a starting mixture **M14a** was obtained by mixing tosylates **14a** (DMB^{O1}-tagged) and **14c** (DMB^{O3}-tagged). The quasiracemic mixture **M14a** was treated with NaI in acetone and refluxed for 20 h to afford the iodide mixture **M56a** in 98% yield (Scheme 1.14). TLC analysis (SiO_2, ethyl acetate/hexanes) of the reaction mixture after 8 h (Figure 1.13) showed two closely positioned spots at R_f = 0.53 and another set of two closely positioned spots at R_f = 0.20. The larger separation of the spots is due to the polarity difference between the OEG1 (less polar) and OEG3 (more polar) tags while the smaller separation is due to the polarity difference between the tosylate **14a** (slightly more polar) and the iodide **56a** (slightly less polar). The Finkelstein reaction went to completion in 20 h as evidenced by the disappearance of the pair of slightly more polar spots.

^{1}H NMR analysis of the crude product **M56a** indicated complete conversion of reactants **M14a** to products **M56a**; hence no purification was necessary. However, a small sample (100 mg) of the above mixture **M56a** was separated by flash column chromatography on silica gel for

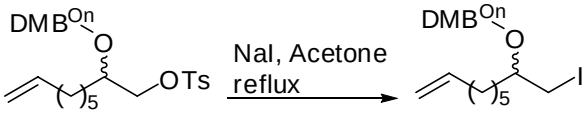
characterization purposes and to study the ease of separation of the components from each mixture. The DMB^{O1} and DMB^{O3} analogs **56a** and **56c** were easily separated from the mixture **M56a** in spectroscopically pure form in a gradient elution wherein **56a** was eluted (25% ethyl acetate/hexanes) followed by **56c** (50% ethyl acetate/hexanes).



1 = TLC analysis of reaction mixture after 8 h

2 = TLC analysis of the reaction mixture after 20 h

Figure 1.13 TLC analysis (SiO_2, 50% ethyl acetate/hexanes) in conversion of tosylate **M14a** to iodide **M56a**



M14a n = 1, 3 **M56a** n = 1, 3 (98%)

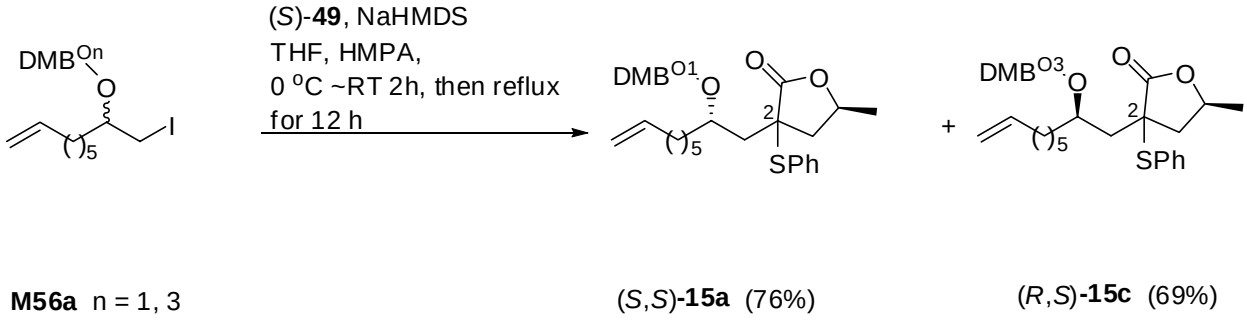
M14b n = 2, 4 **M56b** n = 2, 4 (99%)

Scheme 1.14 Synthesis of iodides **M56a** and **M56b**

Similarly, a second quasi-racemate **M14b** was obtained by mixing tosylate **10b** (DMB^{O2}-tagged) and **10d** (DMB^{O4}-tagged). The mixture **M14b** (n = 2, 4) was subjected to Finkelstein reaction with NaI in acetone to give the iodide quasi-racemate **M56b** (n = 2, 4) in 99% yield

(Scheme 1.14). The mixture **M56b** was spectroscopically pure and hence it was taken to the next step without further purification.

The sodium enolate of (*S*)-**49**, generated by treating (*S*)-**49** with NaHMDS, was reacted with the iodide mixture **M56a** (n = 1, 3) to afford a mixture **M15a** (n = 1, 3) of diastereomers (*S*,*S*)-**15a** and (*R*,*S*)-**15c** (Scheme 1.15). TLC analysis (SiO_2, ethyl acetate/hexanes 1:1 v/v) of the crude reaction mixture showed a spot at R_f = 0.51 corresponding to (*S*,*S*)-**15a**, and another spot at R_f = 0.20 corresponding to (*R*,*S*)-**15c**. The crude reaction product was subjected to flash chromatography on silica gel under gradient conditions. Initial elution with 25% ethyl acetate/hexanes gave (*S*,*S*)-**15a** (76% yield) as a stereoisomeric mixture at C2. A second elution with 50% ethyl acetate/hexanes gave (*R*,*S*)-**15c** (69% yield) as a stereoisomeric mixture at C2 (Scheme 1.15).

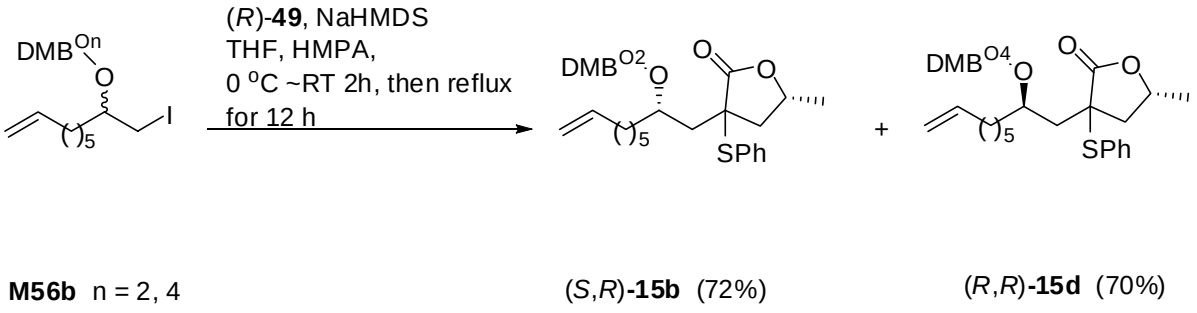


M56a n = 1, 3 (*S*,*S*)-**15a** (76%) (*R*,*S*)-**15c** (69%)

Scheme 1.15 Alkylation of (*S*)-**49**

Sodium enolate of (*R*)-**49**, generated by treating (*R*)-**49** with NaHMDS, was reacted with the iodide mixture **M15b** (n = 2, 4) to afford a mixture **M15b** (n = 2, 4) of alkylated products (*S*,*R*)-**15b** and (*R*,*R*)-**15d** (Scheme 1.16). TLC analysis (SiO_2, 65% ethyl acetate/hexanes) of the crude reaction mixture showed a spot at R_f = 0.54 corresponding to (*S*,*R*)-**15b**, and another spot

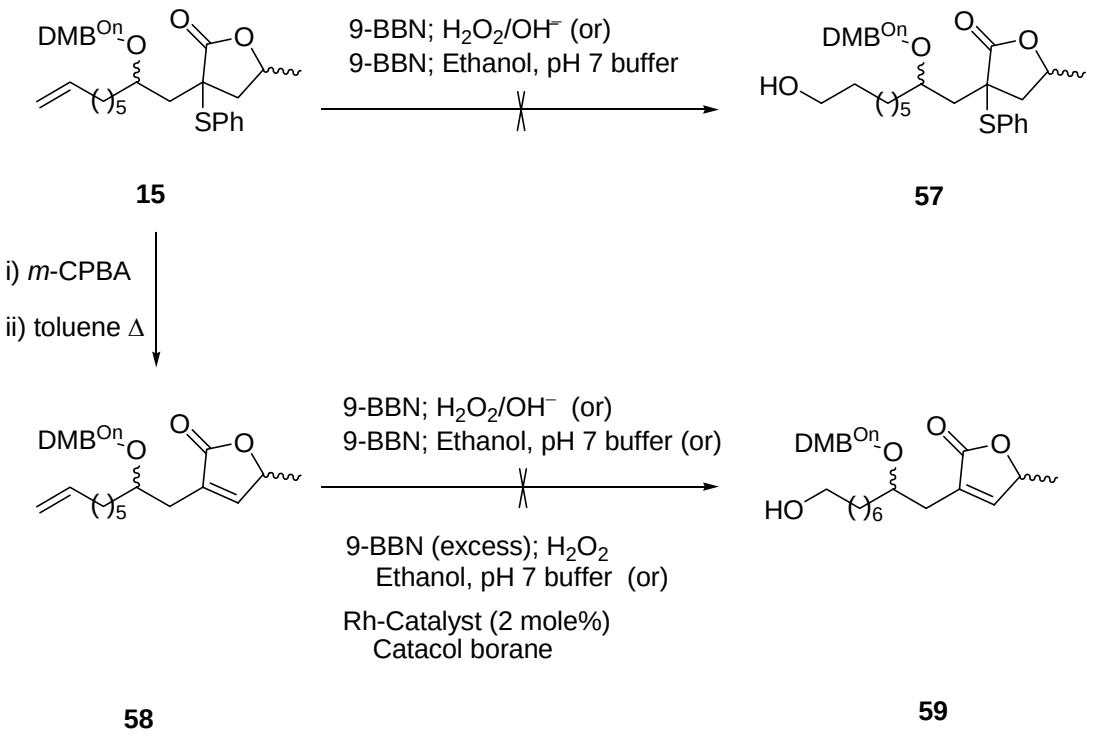
at R_f = 0.25.corresponding to (*R*,*R*)-**15d**. The crude reaction product was subjected to flash chromatography on silica gel under gradient conditions. Initial elution with 35% ethyl acetate/hexanes gave (*S*,*R*)-**15b** (72% yield) as a stereoisomeric mixture at C2. A second elution with 60% ethyl acetate/hexanes gave (*R*,*R*)-**15c** (69% yield) as a stereoisomeric mixture at C2 (Scheme 1.16).



M56b n = 2, 4 (*S*,*R*)-**15b** (72%) (*R*,*R*)-**15d** (70%)

Scheme 1.16 Alkylation of (*R*)-**49**

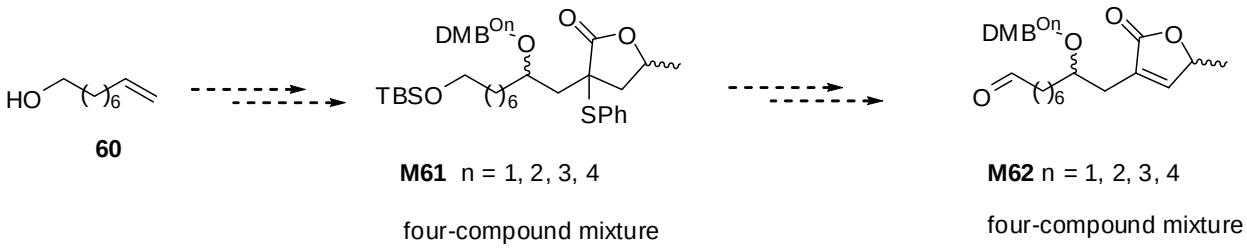
Attempts at hydroboration-oxidation of the terminal double bond either in **15** or **58** were unfruitful under various conditions (Scheme 1.17). Employing 1 equiv of 9-BBN[35] resulted in recovery of starting material, while use of excess 9-BBN or catecholborane[36] resulted in complex crude reaction product. In light of unsatisfactory results of hydroboration-oxidation of the terminal olefin **15** or **58**, an alternative synthesis was planned wherein the terminal alkene is replaced with terminal alcohol.



Scheme 1.17 Attempted hydroboration-oxidations

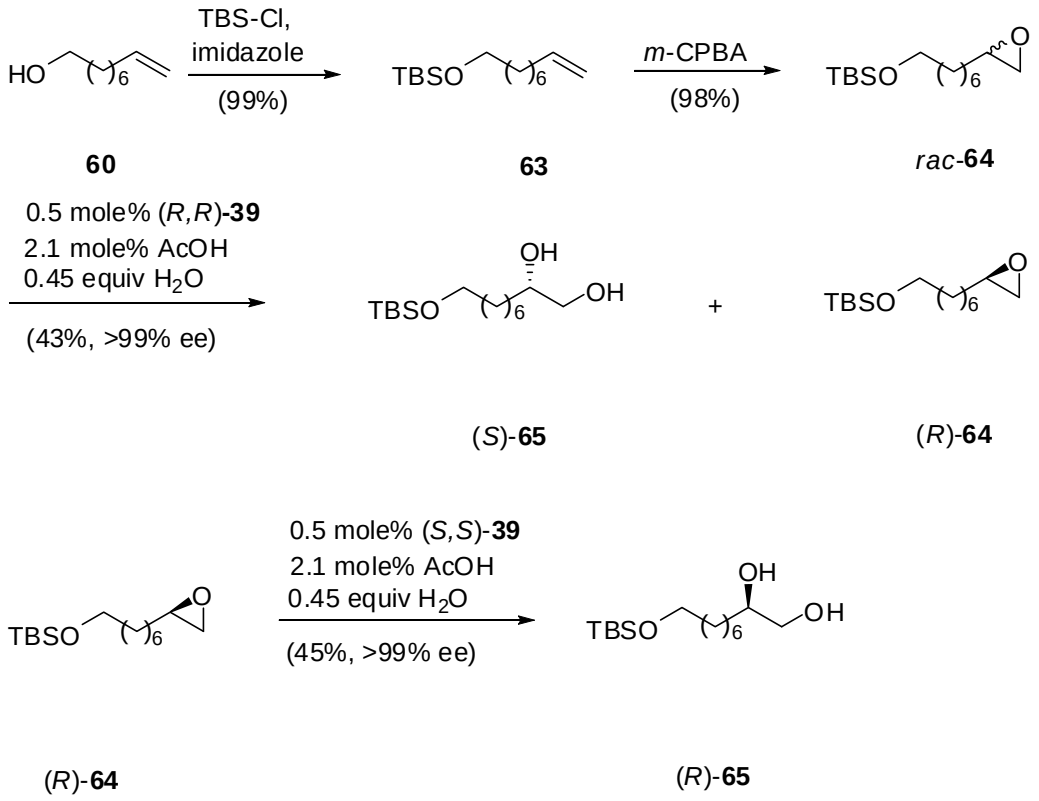
1.2.5. Re-designed protocol for the synthesis of four-compound aldehyde mixture **M62**

The protocol for the re-designed synthesis to access the aldehyde mixture **M62** is shown in Scheme 1.18. The commercially available alcohol **60** can be advanced to a four-compound mixture **M61** without having to pursue the difficult hydroboration reaction. A few transformations on the four-compound mixture **M61** can give the desired aldehyde **M12**.



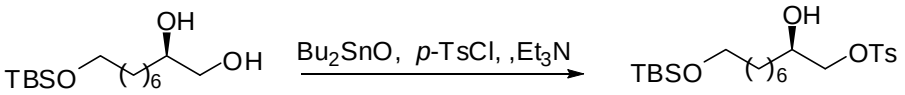
Scheme 1.18 Re-designed strategy for the synthesis of aldehyde **M62**

Silylation of 8-nonen-1-ol **60** with TBS-Cl give silyl ether **63** in 99% yield (Scheme 1.19). Epoxidation of the alkene **63** with *m*-chloroperbenzoic acid gave the recemic epoxide *rac*-**64** in 98% yield. The racemic epoxide was subjected to Jacobsen hydrolytic kinetic resolution[37] with **(*R*,*R*)-39** to give (*S*)-**65** in 43% yield along with 56% of enantiomerically enriched (*R*)-epoxide (*R*)-**64**. The epoxide (*R*)-**64** was subjected to Jacobsen hydrolytic kinetic resolution with **(*S*,*S*)-39** to give *R*-diol (*R*)-**65** in 45% yield. The enantiomeric excesses of (*S*)-**65** and (*R*)-**65** were determined to be greater than 98% by Mosher ester method as previously described for (*R*)-**29**.



Scheme 1.19 Synthesis of (*R*)-**64** and (*S*)-**64**

The primary hydroxy group of diol (*R*)-**65** was selectively functionalized as tosylate (*R*)-**66** (72% yield) by the reaction of diol **65** with *p*-toluenesulfonyl chloride in the presence of catalytic amount of dibutyltin oxide. Similarly, primary alcohol of the diol (*S*)-**60** was selectively tosylated (76% yield) (Scheme 1.20).



(*R*)-**65**

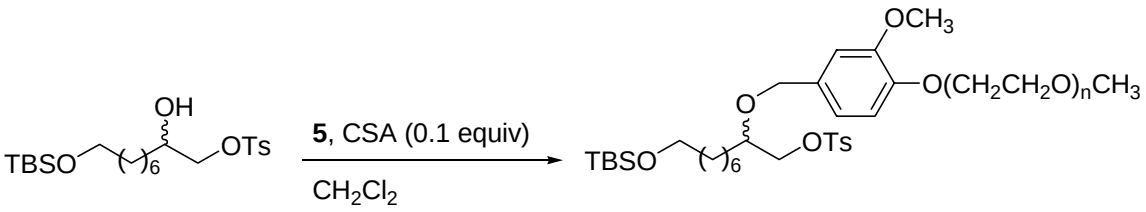
(*S*)-**65**

(*R*)-**66** (72%)

(*S*)-**66** (76%)

Scheme 1.20 Synthesis of sulfonates (*R*)-**66** and (*S*)-**66**

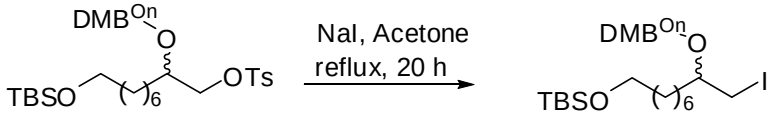
In our efforts to access four tagged precursors for OEG-mixture synthesis, the secondary alcohol (*R*)-**66** was reacted with imidates **5a** and **5b** independently in presence of catalytic amount of camphorsulfonic acid (0.1 equiv) to afford **67a** (60% yield) and **67b** (62% yield), respectively. Similarly **67c** (63% yield) and **67d** (61% yield) were obtained by the reaction of alcohol (*S*)-**66** with imidates **5c** and **5d** respectively (Scheme 1.21).



		n	
(*R*)-**66**	**5a**	**67a** 1	(60%)
(*R*)-**66**	**5b**	**67b** 2	(62%)
(*S*)-**66**	**5c**	**67c** 3	(63%)
(*S*)-**66**	**5d**	**67d** 4	(61%)

Scheme 1.21 Synthesis of OEG-tagged precursors 67a-67d

The tosylates **67a** and **67c** were mixed together to give a quasi-racemate **M67a**. The quasi racemate **M67a** was subjected to Finkelstein reaction with NaI in refluxing acetone to give the corresponding iodide **M68a** in 98% yield (Scheme 1.22). The crude iodide **M68a** was pure by both TLC (SiO_2 50% ethyl acetate/hexanes) and ^{1}H NMR spectral analysis and hence it was taken to the next step with out further purification. Similarly, a quasi racemic mixture **M67b** was obtained by mixing tosylates **67b** and **67d** and the mixture was subjected to Finkelstein reaction in refluxing acetone to give the corresponding iodide mixture **M68b** in 99% yield.

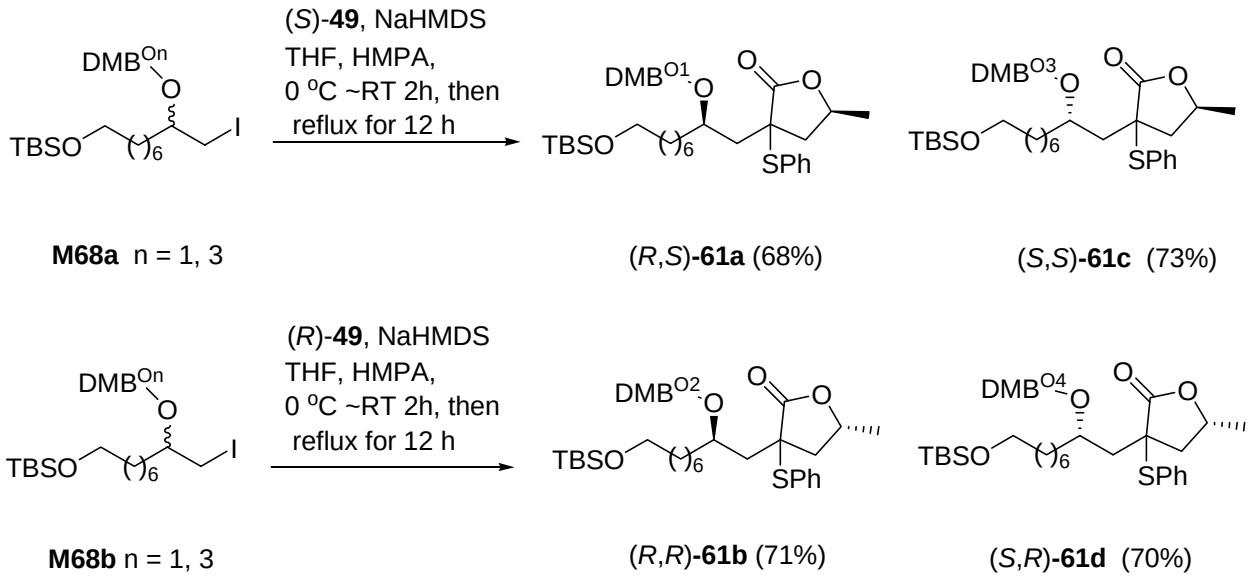


M67a n = 1, 3 **M68a** n = 1, 3 (98%)

M67b n = 2, 4 **M68b** n = 2, 4 (99%)

Scheme 1.22 Synthesis of iodides **M68a** and **M68b**

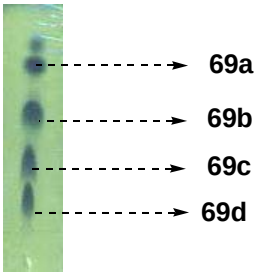
The sodium enolate of (S)-**49**, which was generated by treating (S)-**49** with NaHMDS, was reacted with the iodide mixture **M68a** to afford the alkylated products (*R*,*S*)-**61a** (68% yield) and (*S*,*S*)-**61c** (73% yield) as stereoisomeric mixture at C2 (Scheme 1.23). Similarly, the sodium enolate of (R)-**49** was alkylated with the quasi-racemic iodide mixture **M68b** to give the corresponding alkylated products (*R*,*R*)-**61b** (71% yield) and (*S*,*R*)-**61d** (70% yield) as stereoisomeric mixtures at C2.

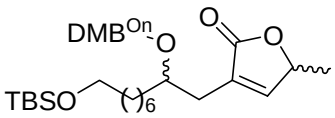


Scheme 1.23 OEG-mixture synthesis

The resulting four compounds **61a-61d** were mixed together to give a mixture **M61**. The sulfide **M61** was oxidized with *m*-CPBA to sulfoxide at 0 °C and the obtained crude product in DMF was heated in microwave[38] (150W power) at 160 °C for 5 min. TLC analysis (SiO_2, 70% ethyl acetate/hexanes) of the above crude reaction mixture showed four major spots (Figure 1.14). The crude reaction mixture was separated by flash column chromatography on silica gel

under step gradient conditions (25%, 40%, 60% and 80% ethyl acetate/hexanes) into four fraction based on the polarity of OEG tags. The least polar fraction (eluted with 1:4 ethyl acetate/hexanes) contained OEG1-tagged butenolide **69a** (88% yield). Succeeding fractions contained OEG_2-, OEG_3- and OEG_4-tagged molecules **69b** (85% yield), **69c** (89% yield) and **69d** (85% yield), respectively (Scheme 1.24).

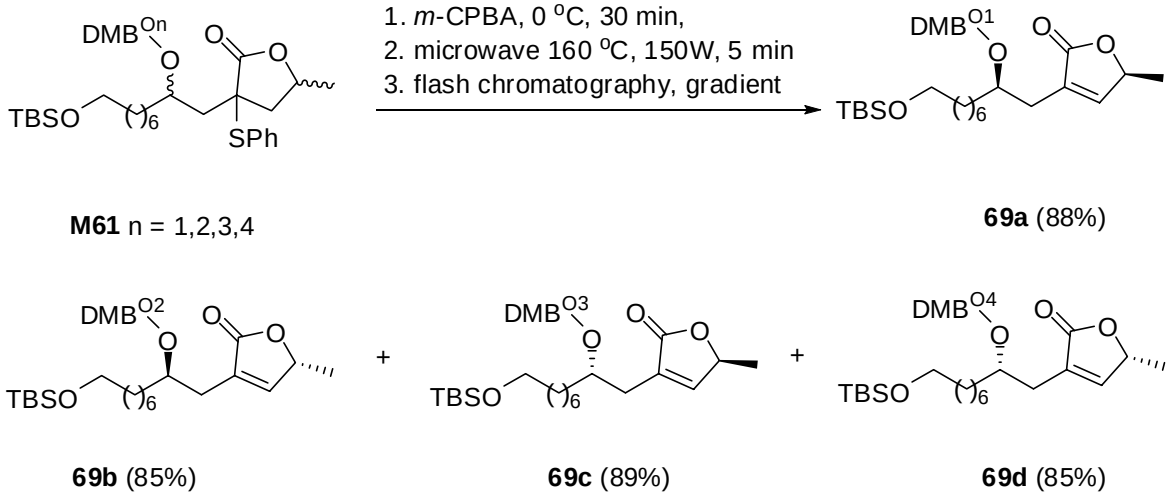




M69 n = 1, 2, 3, 4

SiO_2, 70% ethyl acetate/hexanes

Figure 1.14 TLC analysis of crude product **M69**



M61 n = 1,2,3,4

69a (88%)

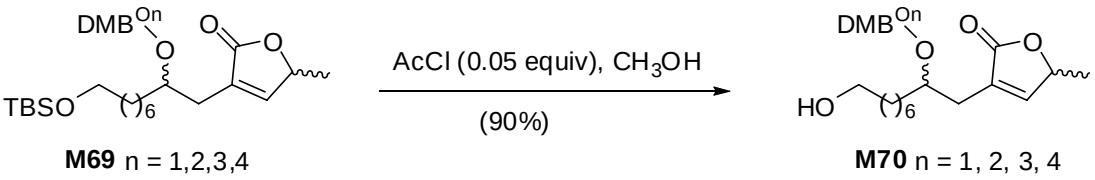
69b (85%)

69c (89%)

69d (85%)

Scheme 1.24 Conversion of **M61** to **M69**

The compounds **64a-d** were mixed together to give a four-compound mixture **M69**. The mixture **M69** was treated with methanolic HCl (AcCl, CH_3OH) to afford the primary alcohol[39] mixture **M70**. Crude product **M70** was carried to the next step without any further purification.



M69 n = 1,2,3,4 **M70** n = 1, 2, 3, 4

Scheme 1.25 Synthesis of four-compound mixture M70

The alcohol mixture **M70** was oxidized to aldehyde **M62** by treating it with *o*-iodoxybenzoic acid (IBX) until TLC indicated complete conversion of alcohol to aldehyde **M62**. The crude reaction mixture was separated by flash column chromatography (SiO_2, ethyl acetate/hexanes, gradient) based on the properties of OEG tag (Figure 1.15). The pure aldehydes **62a - 62d** were recombined to give the four-compound mixture **M62** (Scheme 1.26).

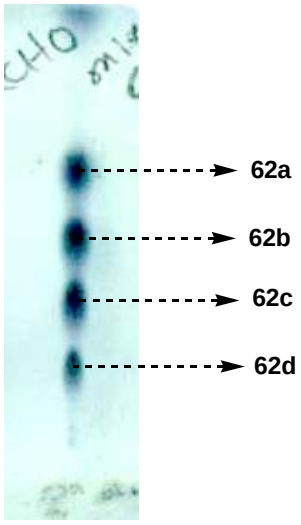
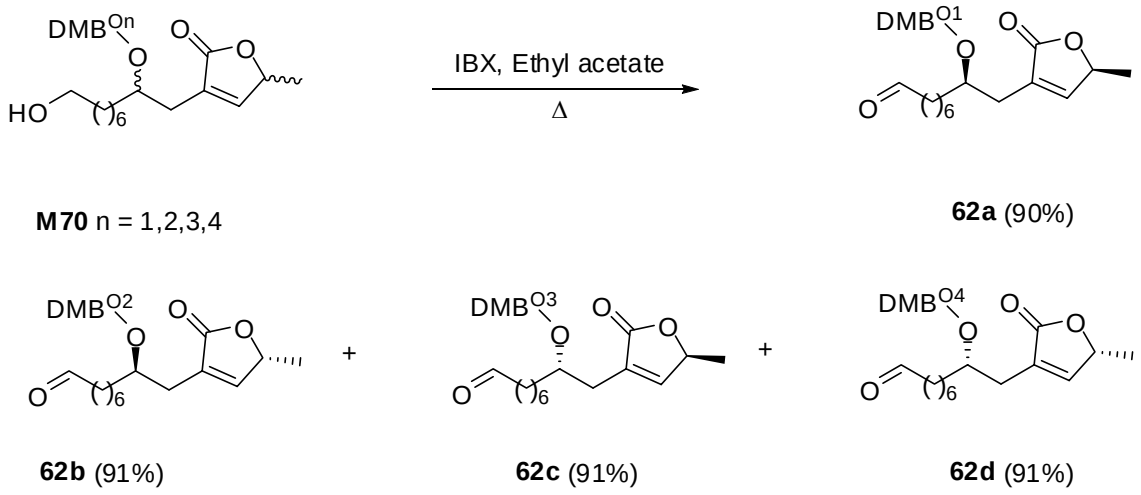


Figure 1.15 TLC analysis of **M62** (SiO_2, 100% ethyl acetate)

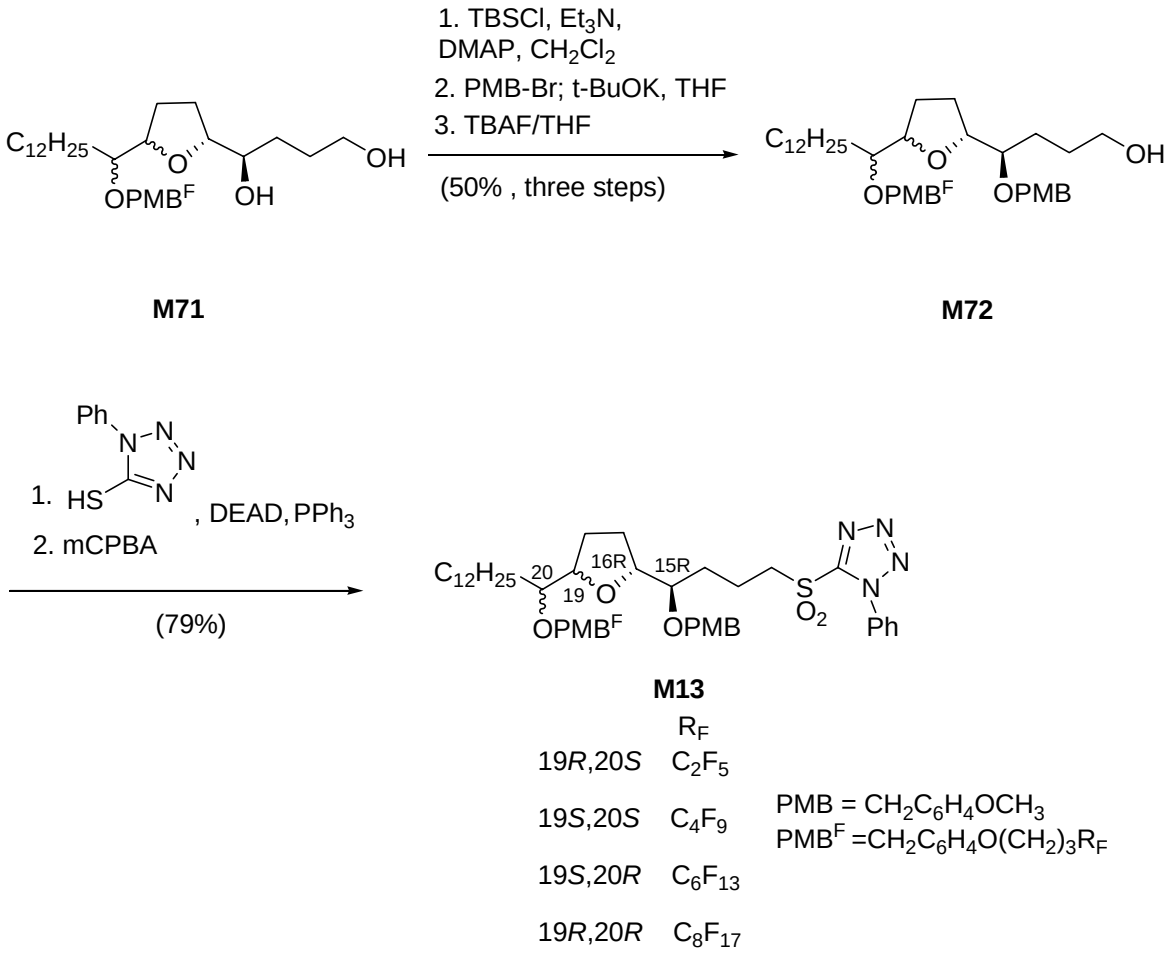


Scheme 1.26 Oxidation of **M70** with IBX

The value of the OEG-mixture synthesis is evident from this exercise: four analogues **62a-62d** of aldehyde **62** were prepared in a single synthetic sequence with only a little more effort than that required for one. Overall, 16 steps were saved by the mixing (multi-step conversion of **M67** to **M62**). The first step (conversion of **M67** to **M68**) demonstrated the application of OEG-tags in quasi-racemic synthesis. We envision that OEG-tags, similar to fluorous tags,[40] have potential applications in multi-step quasi racemic synthesis. All mixtures in the synthesis that were separated during purification were characterized by NMR (^{1}H NMR and ^{13}C NMR) IR and MS data.[41]

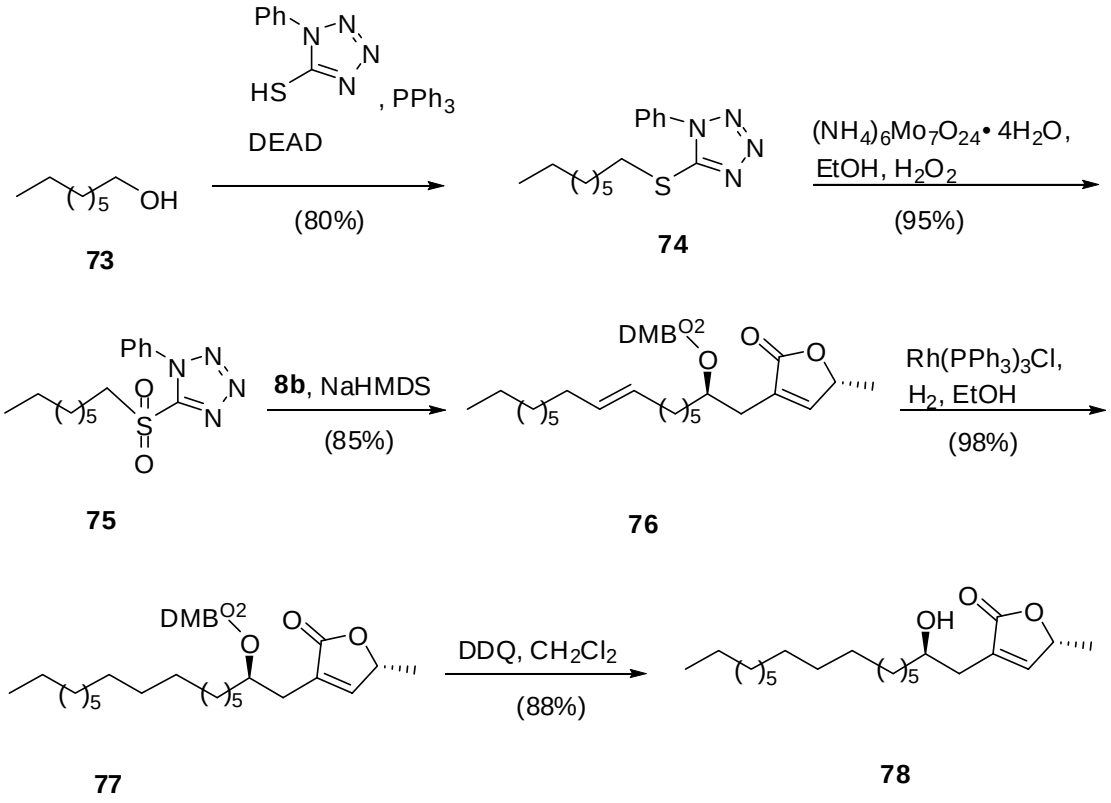
The four-compound mixture of fluorous tagged sulfones **M13** was synthesized by Dr. Hejun Lu as summarized in Scheme 1.27.[42] The four compound diol mixture **M71** was synthesized using the previously pursued protocol for the synthesis of murisolin.[7] TBS protection of primary alcohol in **M71** followed by PMB protection of secondary alcohol and desilylation of primary alcohol with TBAF gave **M72** 50% yield (three steps). A Mitsunobu/oxidation sequence of the mixture **M72** afforded sulfone **M13**.

The OEG-mixture synthesis of aldehyde **M62** afforded its precursor **M69** in 1.4 mmol (equivmolar mixture of **69a**, **69b**, **69c** and **69d**) quantity. However, the conversion of fluorous mixture **M71** to **M72** resulted in considerable loss of the mixture and ultimately afforded 0.26 mmol of sulfone **M13** wherein the C_2F_5, C_4F_9, C_6F_{13} and C_8F_{17}-tagged compounds were present in 1 : 1.28 : 1.25 : 4.59 mole ratio. Hence sulfone mixture **M13** was limiting reagent for the scale of upcoming OEG-Fluorous mixture synthesis. We estimated that 0.26 mmol of sulfone mixture **M13** in OFMS would result the murisolin and its isomers in an average of 1-2 mg quantity and proceeded to pursue the OFMS.



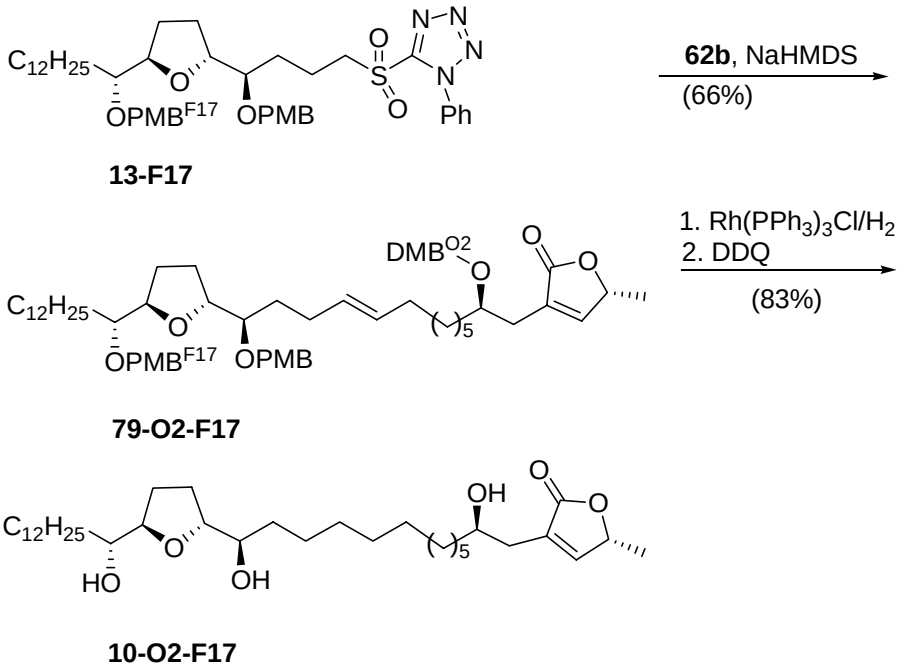
Scheme 1.27 Synthesis of sulfone mixture M13

A model study was carried out to test the Julia olefination and the selective reduction of the internal double bond in the presence of an unsaturated lactone before coupling the dihydroxy-THF fragment **M13** with the hydroxybutenolide unit **M62**. The sulfone **75** was synthesized from 1-octanol **73** in 76% yield (two steps) (Scheme 1.28). The anion of the sulfone **75** was generated by treatment with NaHMDS in THF at −78 ^{o}C for 30 min and reacted with the aldehyde **62b** to give the olefin **76** as a mixture of (*E*)- and (*Z*)- isomers in 85% yield (ratio was not determined). Attempts at selective reduction of internal double bond by hydrogenation with Wilkinson's catalyst in benzene resulted recovery of starting materials. However, carrying the reduction in ethanol gave **77** in 98% yield. Treatment of **77** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[43] (1.1 equiv) gave the detagged product **78** in 88% yield (Scheme 1.28).



Scheme 1.28 Synthesis of alcohol **78**

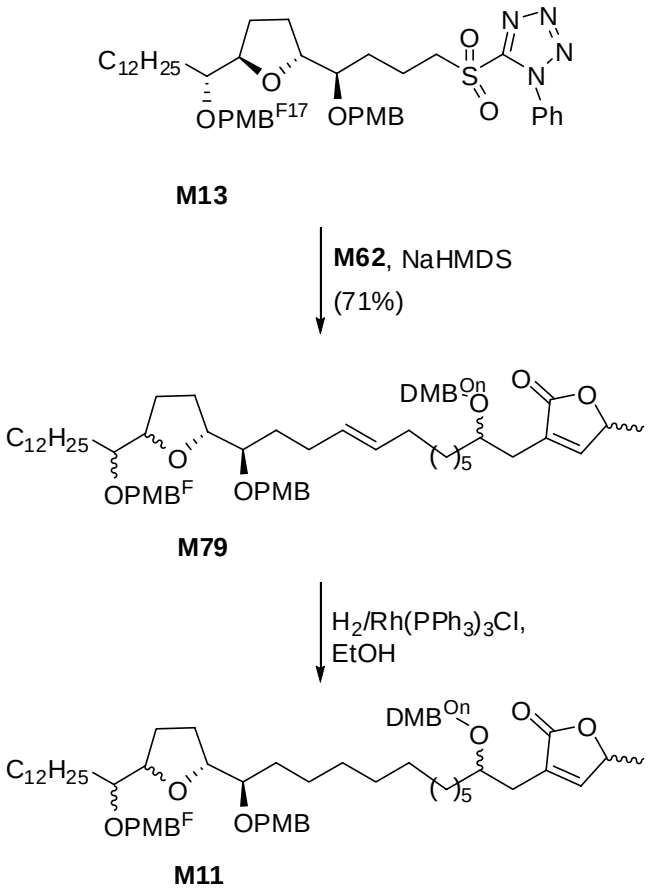
In a second model reaction, Julia olefination reaction between the aldehyde **62b** and **13-F17** was carried out in similar manner to afford **79-O2-F17** in 66 % yield. The compound numbers were given based on the tags bound to them. For example, **79-O2-F17** denotes a compound bearing DMB^{O2} and PMB^{F17} tags. The internal double bond (alkene introduced in coupling) in **79-O2-F17** was selectively reduced by hydrogenation in ethanol in presence of catalytic amount of Wilkinson's catalyst followed by global deprotection of three protecting groups (PMB^{F17}, and DMB^{O2} and PMB) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3.2 equiv) (DDQ) in CH_2Cl_2/H_2O (19:1) gave **10-O2-F17** in 83% (two steps) isolated yield (Scheme 1.29).



Scheme 1.29 Synthesis of compound 10-O2-F17

1.2.6. OEG-Fluorous mixture synthesis of murisolin isomers

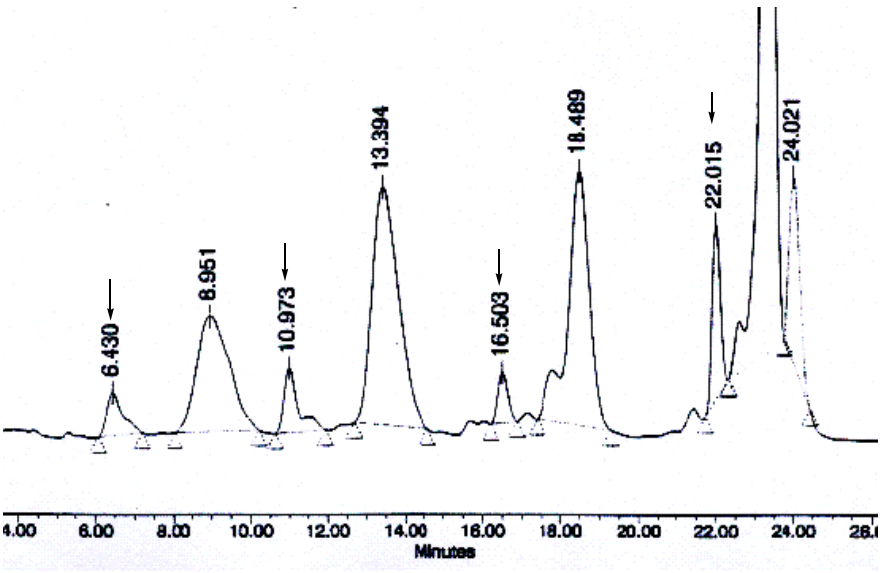
Kocienski-Julia olefination of the four-component fluorous-tagged mixture **M13** with the four-componet OEG-mixture **M62** is illustrated in scheme 1.30. Deprotonation of sulfone **M13** (0.26 mmol) with NaHMDS generated the corresponding anion, which was reacted with aldehyde **M62** (0.28 mmol) to furnish alkene **M79**.



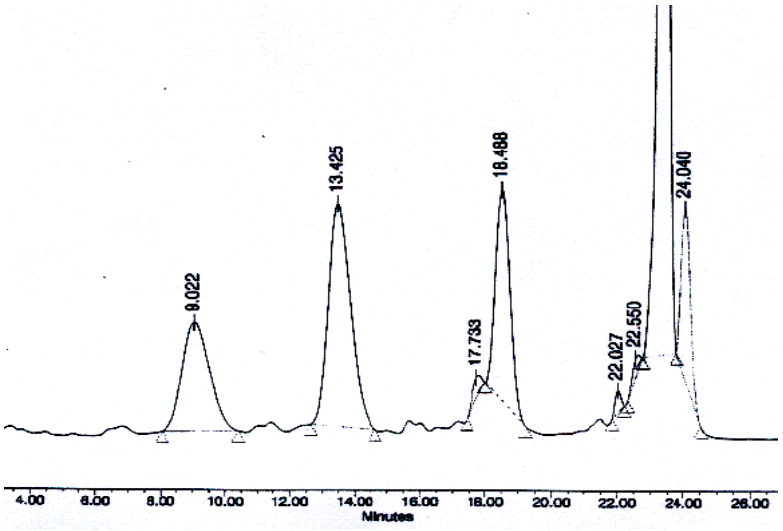
Scheme 1.30 First example of OEG-fluorous mixture synthesis for the synthesis of stereoisomers

Fluorous HPLC analysis of the crude reaction mixture **M79** occurred with fluorous demixing but not OEG demixing to provide four pairs of peaks, each pair with a ratio of about 85/15 (Figure 1.16a). Both fluorous HPLC analysis and standard TLC analysis showed that the minor peaks

belonged to the starting sulfones in **M13**. The crude mixture **M79** was purified by flash column chromatography on silica gel with gradient elution. First step elution with with 25% ethyl acetate/hexanes provided unreacted sulfone **M13** followed by a fraction **79a** containing four DMB^{O1}-tagged molecules. The succeeding steps of the gradient elution provided fractions **79b**, **79c** and **79d** that contained DMB^{O2}-, DMB^{O3}-, and DMB^{O4}-tagged molecules, respectively. The identity of the fractions **79a**-**79d** was conflrmed by LCMS (APCI) analysis. The fractions **79a** - **79d** were mixed together to give the purified sixteen-compound mixture **M79**. Fluorous HPLC analysis of the mixture **M79** indicated the disappearance of minor peaks (Figure 1.16b).



a: Analytical Fluorous HPLC chromatogram of crude **M79**; arrows show unreacted sulfones



b: Analytical HPLC trace after purification of mixture M79 by flash column

Figure 1.16 HPLC trace of analysis of **M79** on a FluoroFlash PF-C8 column (CH_3CN/H_2O, 80/20 to 100% CH_3CN in 20 min then 100% CH3CN for 10 min. a: before purification of mixture **M79** by flash column chromatography b: after purification by flash chromatography.

The internal double bond in **M79** was selectively hydrogenated in ethanol with Wilkinson's catalyst (Scheme 1.30). Once the reaction was complete as indicated by ^{1}H NMR spectroscopy, the crude reaction product **M11** (320 mg) was subjected to a simultaneous purification and OEG-demixing with a silica-flash chromatography with step-gradient elution (25%, 50%, 65% and 80% ethyl acetate/hexanes). The product **M11** separated into four fractions **11-O1**, **11-O2**, **11-O3** and **11-O4**, based on the properties of OEG- tags (n = 1 – 4). The least polar fraction **11-O1** contained all four molecules bearing OEG^1-tag. The succeeding fractions **11-O2**, **11-O3** and **11-O4** contained OEG^2-, OEG^3- and OEG^4-tagged molecules, respectively. The identity of each fraction was confirmed by LCMS analysis of each fraction (see the experimental section for the LCMS data). Mixtures **11-O2** and **11-O3** showed two closely positioned spots by TLC on silica gel (Figure 1.17) suggesting some separation of fluorous-tagged diastereomers; however, these were collected togather. The most polar fraction **11-O4** co-

eluted with traces of unidentified impurities (Scheme 1.31). A combined yield of 84% for Wilkinson's hydrogenation and OEG-demixing was obtained.

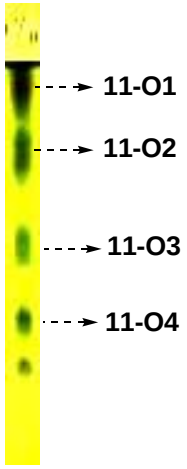
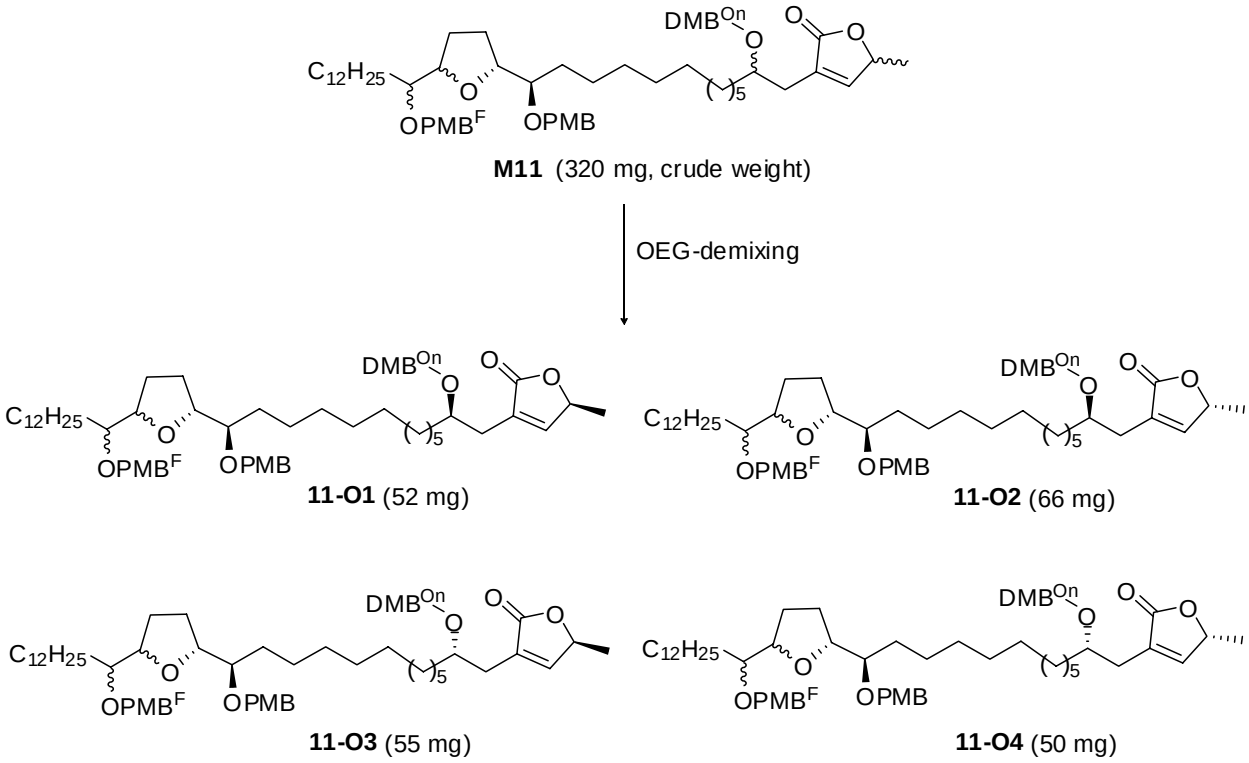


Figure 1.17 TLC analysis (SiO_2, 80% ethyl acetate/hexanes) of Mixture **M11**



Scheme 1.31 Demixing of mixture **M11** on silica-flash column (ethyl acetate/hexanes, gradient)

The mixture **11-O2** was subjected to preparative separation over a FluoroFlash semi prep HPLC column (20 x 250 mm) under gradient conditions. The gradient started from 85% CH_3CN/15% H_2O and changed to 100% CH_3CN over 25 min. Following this was isocratic elution with 100% CH_3CN for 10 min. The flow rate was 15 mL/min through out the elution. Under these conditions, the four components **11-2-F5**, **11-2-F9**, **11-2-F13** and **11-2-F17** were eluted at 10.0, 14.2, 19.0 and 23.4 min, respectively (Figure 1.18). About 20 mg of the mixture was injected each time. After 3 injections, the amounts of **11-2-F5**, **11-2-F9**, **11-2-F13** and **11-2-F17** obtained were 6.3 (5.2 μmol), 7.4 (5.7 μmol), 9.5 (6.8 μmol) and 33.0 (21.9 μmol) mg respectively. The overall recovery of the preparative separation was 86% (Scheme 1.32).

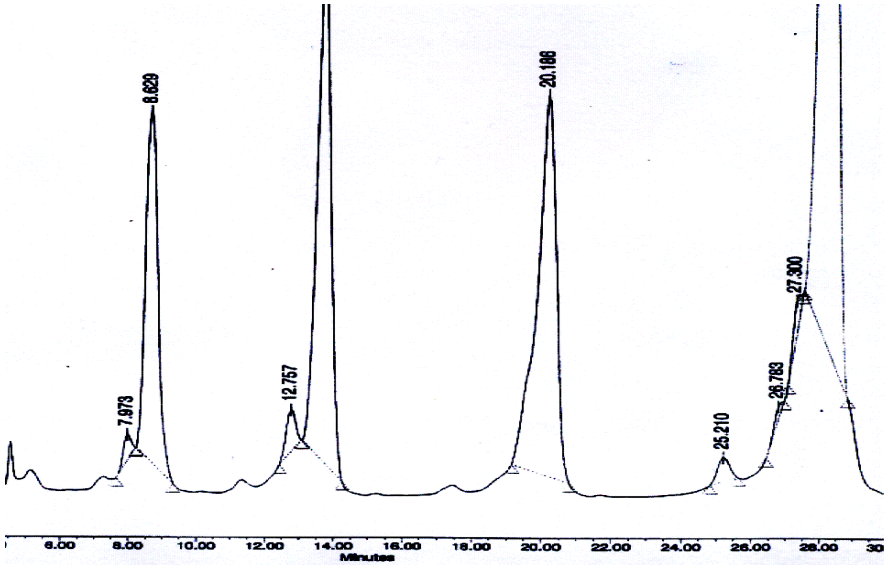
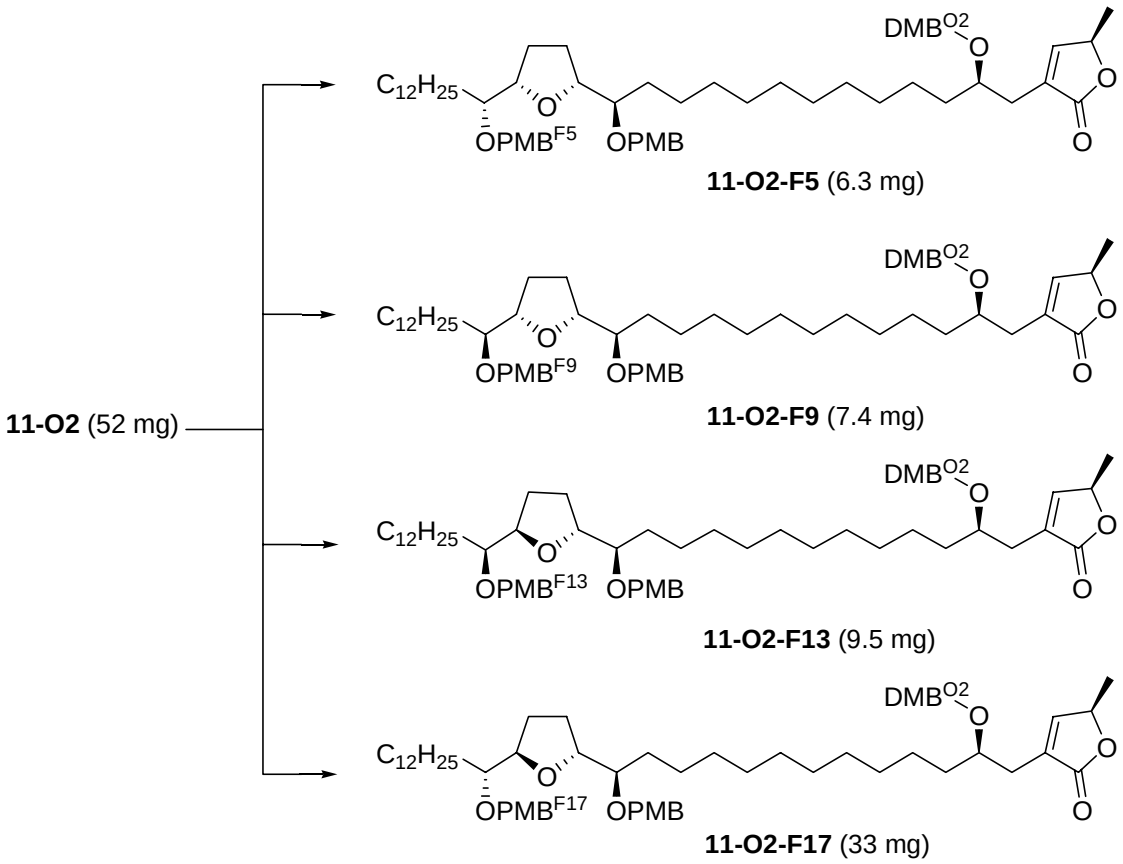


Figure 1.18 A typical chromatogram of semi-prep demixing of **11-O2**



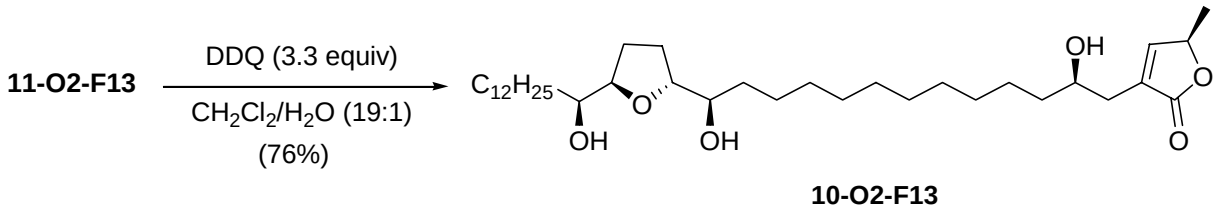
Scheme 1.32 Fluorous Demixing of the mixture **11-O2**

The mixtures **11-O1** (52 mg) was demixed on FluoroFlash semi-prep HPLC column in similar manner to the mixture **11-O2** to give **11-O1-F5** (2.5 mg, 2.2 μmole), **11-O1-F9** (4.7 mg, 3.7 μmole), **11-O1-F13** (8.8 mg, 6.5 μmole) and **11-O1-F17** (22.5 mg, 15.4 μmole) with a 74% overall recovery of preparative separation (structures shown in appendix 1).

The mixtures **11-O3** (55 mg) was demixed on FluoroFlash semi-prep HPLC column in similar manner to the mixture **11-O2** to give **11-O3-F5** (3.8 mg, 3.0 μmole), **11-O3-F9** (5.9 mg, 4.4 μmole), **11-O3-F13** (6 .6mg, 4.6 μmole) and **11-O3-F17** (14.8 mg, 9.6 μmole) with a 57% overall recovery after fluorous demixing (structures shown in appendix 1).

The mixtures **11-O4** (44 mg) was demixed on FluoroFlash semi-prep HPLC column in similar manner to the mixture **11-O2** to give **11-O4-F5** (3.8 mg, 2.9 μmole), **11-O4-F9** (6.1 mg, 4.4 μmole), **11-O4-F13** (5.4 mg, 3.6 μmole) and **11-O4-F17** (13 mg, 8.2 μmole) with a 64% overall recovery after fluorous demixing (structures shown in appendix 1).

The fluorous PMB group, the standard PMB group and the DMB^{O2} group in **11-O2-F13** were removed by treating **11-O2-F13** (9.5 mg, 6.8 μmole) with DDQ (3.3 equiv) in CH_2Cl_2/H_2O (19:1). The crude reaction mixture was purified by prep-TLC (SiO_2, 70% ethyl acetate/hexanes affording the crude detagged product **11-O2-F13** in 76% yield (Scheme 1.33). Similarly the other fifteen isomers were subjected to detagging (structures given in appendix 2). Of the sixteen tagged compounds, **11-O1-F13**, **11-O1-F17**, **11-O4-F5**, **11-O4-F9**, **11-O4-F13** and **11-O4-F17** were detagged and purified by Dr. Hejun Lu.



Scheme 1.33 Global deprotection of doubly tagged murisolin

The 500 MHz ^1H NMR spectrum of **11-O3-F13** showed signals for unidentified diastereomeric impurities although TLC analysis showed single spot for the product. This suggests the diastereomeric impurities were co-eluting with the desired product. Hence all the sixteen isomers were subjected to purification with semi-prep HPLC Chiralcel OD column (2 x 20 cm). The column was eluted under a linear gradient plus an isocratic condition for 45 min. The gradient started with hexanes/2-propanol (94/6) and ended with hexanes/2-propanol (90/10)

in 30 min followed by isocratic elution with hexanes/2-propanol for (90/10) for 15 min. The flow rates in both are 10 mL/min.

The sixteen isomers purified by Chiralcel OD column were then analyzed on analytical Chiralcel OD (4.6 x 250 mm) column and symmetry C18 (3.9 x 160 mm) column. The purity of each isomer by this analysis and their retention times on analytical Chiralcel OD column were shown in Table 1.3.

Murisolin isomers		F5	F9	F13	F17
OEG1	Compd.	**10-O1-F5**	**10-O1-F9**	**10-O1-F13**	**10-O1-F17**
	C18	99%	96%	100%	92%
	chiral	100%	100%	100%	100%
	RT	16.0min	17.2min	22.0min	24.6min
OEG2	Compd.	**10-O2-F5**	**10-O2-F9**	**10-O2-F13**	**10-O2-F17**
	C18	99%	93%	**67%**	100%
	Chiral	100%	100%	100%	100%
	RT	17.5min	17.9min	23.8min	26.3min
OEG3	Compd.	**10-O3-F5**	**10-O3-F9**	**10-O3-F13**	**10-O3-F17**
	C18	100%	96%	**74%**	93%
	Chiral	100%	100%	95%	100%
	RT	15.8min	16.6min	22.1min	24.5min
OEG4	Compd.	**10-O4-F5**	**10-O4-F9**	**10-O4-F13**	**10-O4-F17**
	C18	100%	**95%**	98%	**83%**
	chiral	100%	100%	100%	100%
	RT	15.6min	16.3min	21.9min	25.1min

Table 1.3 Purity of sixteen murisolin isomers synthesized by double tagging strategy. C18 = Purity of compounds by symmetry C18 column; Chiral = Purity of compounds by Chiralcel OD analysis;

The isomers **10-2-F13**, **10-3-F13** and **10-4-F17** were then purified over Symmetry C18 column (19 x 300 mm). The column was eluted under a linear gradient plus an isocratic for 45min. The gradient started with 80% CH_3OH/20% H_2O and ended with 100% CH_3OH in 30min. The isocratic was a 100% CH_3OH 15 min elution. The flow rates in both are 12mL/min. Optical rotation data and the individual yields of murisolin isomers are given in table 1.4.

Murisolin isomers $[\alpha]_D^{25}$ (c, $CHCl_3$)	F5	F9	F13	F17
OEG1	**10-O1-F5** +4.1 (0.05)	**10-O1-F9** +9.8 (0.1)	**10-O1-F13** +10.3 (0.2)	**10-O1-F17** +6.6 (0.27)
Yield*	*37%*	*59%*	*50%*	*33%*
OEG2	**10-O2-F5** -5.0 (0.07)	**10-O2-F9** +4.1 (0.1)	**10-O2-F13** -1.4 (0.09) -2.5 (0.05)	**10-O2-F17** +5.2 (0.18)
Yield*	*13%*	*18%*	*18%*	*16%*
OEG3	**10-O3-F5** -11.9 (0.1)	**10-O3-F9** -1.4 (0.18)	**10-O3-F13** +3.4 (0.14) +5.9 (0.09)	1**0-O3-F17** -1.9 (0.12)
Yield*	*57%*	*66%*	*46%*	*19%*
OEG4	**10-O4-F5** +1.5 (0.05)	**10-O4-F9** -0.3 (0.08)	**10-O4-F13** +4.3 (0.05)	**10-O4-F17** -1.2 (0.09)

Yield*	*30%*	*31%*	*24%*	-0.3 (0.05) *21%*

***** Combined yield for global deprotection and purifications by Chiralcel OD column and Symmetry C18 column

Table 1.4 Optical rotation data and yields of individual murisolin isomers

The stereoisomer library was designed with four control compounds (OEG1 series, 4*R*,34*S*) which were present in previous synthesis of murisolin isomers by fluorous mixture synthesis. The compounds **10-1-F5**, **10-1-F9**, **10-1-F13** and **10-1-F17** were shown to be identical with first library samples (FMS) by chiral HPLC analysis, and this proves that double demixing worked as anticipated.

Combining this and the prior library synthesis, the Curran group has achieved the synthesis of two 16-member stereoisomer libraries of murisolin isomers. Among the 32 murisolins, 28 are unique and four compounds are same in the two libraries (*4R,34S* series). Among these 28, four of the compounds of *4S,34R* series from the double mixture synthesis (OFMS) are enantiomers of four compounds in the first library (FMS). Therefore a total of 24 of the 32 possible diastereomers of murisolin are made. Configurations, optical rotations, and retention times for the 28 murisolin isomers are shown in table 1.5. Compound numbers parallel with the numbers in our published work for consistency.[44]

number	abs configuration (C4,15,16,19,20,34)	α_D (c = 0.05-0.27)	$T_R{}^f$
1.1	RRSSRS	1.1	27.8
1.2	RRSSSS	0.7	20.3
1.3	RRSRSS	9.9	20.6
1.4	RRSRRS	8.2	18

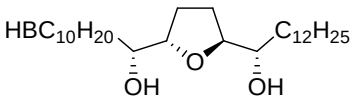
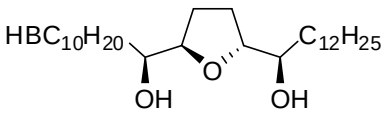
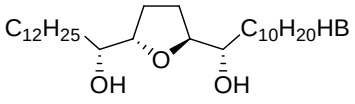
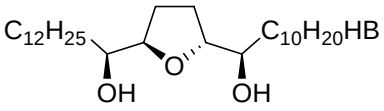
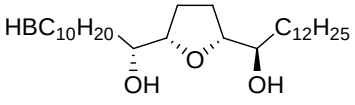
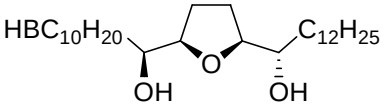
1.5	RSSSRS	1.9	22.6
1.6	RSSSSS	2.1	20.7
1.7	RSSRSS	7.5	14
1.8	RSSRRS	4.5	15.9
1.9	RSRRSS	13.5	25.3
1.1	RSRRRS	9.5	22.1
1.11	RSRSRS	3.1	21.6
1.12[a]	RSRSSS	6.9	14.3
1.13[a]	RRRRSS	14.0	21.6
1.14[a]	RRRRRS	16.1	23.2
1.15[a]	RRRSRS	3.0	15.9
1.16	RRRSSS	8.1	16.4
1.17	RRRRSR	–2.5	23.8
1.18	RRRRRR	5.2	26.3
1.19	RRRSRR	–5.0	17.5
1.20	RRRSSR	4.1	17.9
1.21[b]	SRRRSR	4.3	21.9
1.22[b]	SRRRRR	–1.2	25.1
1.23[b]	SRRSRR	1.5	15.6
1.24[b]	SRRSSR	–0.3	16.3
1.25	SRRRSS	3.4	22.1
1.26	SRRRRS	–1.9	24.5
1.27	SRRSRS	–11.9	15.8
1.28	SRRSSS	–1.4	16.6

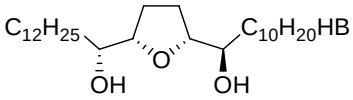
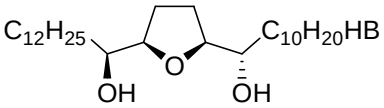
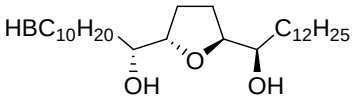
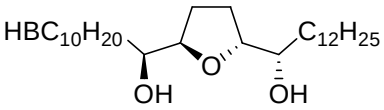
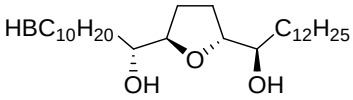
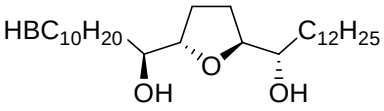
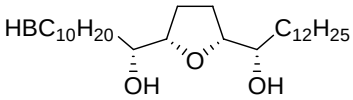
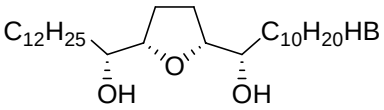
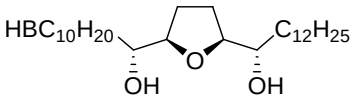
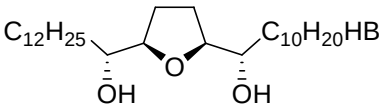
[a] Made in both first library (FMS) and second library (OFMS); [b] **1.21-1.24** are enantiomers of **1.5-1.8**

Table 1.5 28 Member stereoisomer library of murisolin

Remarkably, each of the 28 murisolins exhibit one of only six sets of substantially identical ^{1}H NMR spectra under standard conditions ($CDCl_3$, ambient temberature, 600 MHz). These spectra follow directly from a local symmetry analysis of the dihydroxy-THF fragment of the molecule and provide no information about the configuration of the hydroxybutenolide.[44] Starting with the relative configuration, the C15 and C20 hydroxy groups can be *threo* (th) or *erythro* (er) with respect to adjacent stereocenter on the THF ring, and the two substituents on the THF ring can be *cis* (c) or *trans* (t). Making the two side chains of dihydroxybutenolide same

in murisolins will grouping them into six classes based on local symmetry as indicated in Table 1.6. Molecules with relative configuration er-t-th, th-t-er, er-c-th and th-c-er (group 1 and 2) have no local symmetry. Compound with relative configuration er-t-er (group 3) and th-t-th (group 4) are C2-local-symmetric while the compounds with relative configuration er-c-er (group 5) and th-c-th (group 6) fall into meso category. Spectra of compounds in each group are substancially identical (no difference in chemical shift or peak shape). There are two groups of four compounds (group 1 and 2) that share identical spectra, and four groups of two compounds (group 3-6) that cannot be differentiated either.

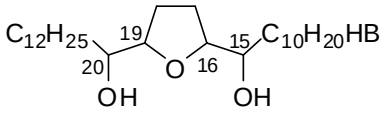
Group # Symmetry	Relative configuration[a]	Murisolin group numbers[b]	
1 No symmetry	er-t-th	 **1.2** RSSS	 **1.10** SRRR
	th-t-er	 **1.5** SSSR	 **1.13** RRRS
2 No Symmetry	er-c-th	 **1.4** RSRR	 **1.12** SRSS

	th-c-er		
		1.15 RRSR	**1.7** SSRS
3 *C*2	er-t-er		
		1.1 RSSR	**1.9** SRRS
4 *C*2	th-t-th		
		1.14 RRRR	**1.6** SSSS
5 meso	er-c-er		
		1.3 RSRS	**1.11** SRSR
6 meso	th-c-th		
		1.16 RRSS	**1.8** SSRR

[a] er, *erythro*; th, *threo*; c, *cis*; t, *trans*
[b] HB, the hydroxybutenolide fragment, 4*R*,34*S*
Table 1.6 Group classification of murisolin isomers on the bases of local symmetry of dihydroxy-THF fragment

A complete set of ^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) have been recorded for first library of compounds with *4R,*34*S* configurations fixed with all possible configurations at the remaining stereocenters in the dihydroxy-THF fragment by Drs Qisheng Zhang and Hejun

Lu. This allowed putting forth a set of guidelines to assign the relative configuration of the dihydroxy-THF fragment stereocenters as summarized in Table 1.7. The six carbons (C4, C15, C16, C19, C20, C34) bearing oxygen resonate in region δ 70-84. Peaks at 70.09 and 78.05 (±0.02 ppm), which belong to C4 and C34 respectively, are ignored. If there are two resonances remaining in this region, then the compound belongs to one of the four groups with local symmetry (groups 3, 4, 5 or 6). A characteristic pattern has been observed for these two resonances, which allows classing an unknown murisolin isomer to a particular group as illustrated in Table 1.7. If there are four resonances, then it belongs to one of the two groups lacking local symmetry (group 1 or 2). In group 1, the most down field resonance was observed at 83.3 ppm and in group 2 at 82.8 ppm. However, since the spectra within the groups are substantially identical, no further guidelines could be elicited to identify a compound within a group based on the spectral data.

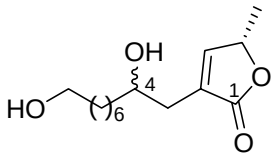


Group # Configuration	δC15,C20	δC16,19
1 er-t-th or th-t-er		83.3
2 er-c-th or th-c-er		82.8
3 er-t-er	72.0	83.0
4 eh-t-th	74.1	82.7

5 er-c-er	72.8	82.4
6 th-c-th	74.1	82.7

Table 1.7 Assignment of the relative configuration of the dihydroxy-THF fragment of murisolins by comparing ^{13}C NMR resonances

The syn/anti relative configuration of the hydroxybutenolide has been determined in the literature either by derivativatization or Mosher ester analysis[45] and no direct method has been reported till date. The second 16 member murisolin library (from OFMS) contains 8 diastereomers with *syn* relative configuration of C4 and C34 in the hydroxybutenolide. ^{1}H NMR spectra of these compounds are substantially identical to the isomers with *anti* configuration. However, we were able to identify small yet reliable differences in ^{13}C NMR of *syn* and *anti* isomers as illustrated with hydroxybutenolide fragment shown in figure 1.19. Compounds (*4R*,34*S*)-**80** and (4*S*,34*S*)-**80** were obtained from **69a**, **69c** respectively by removal of both TBS (AcCl, MeOH) and DMB (DDQ, CH_2Cl_2) protecting groups. Both compounds exhibited very similar ^{1}H and ^{13}C NMR spectra. However, upon mixing the samples in a 2/1 ratio, doubling of five resonances was observed in ^{13}C NMR spectrum. The differences in chemical shifts ranged from 0.03 ppm to 0.1 ppm. Enhansed $\Delta\delta$ were obtained by subtraction of chemical shift of a peak at around 70 ppm (C4) from a peak at about 152 ppm (C34). $\Delta\delta$ for the syn isomer was 82.0 while it was 81.8 for the anti isomer. This trend ($\Delta\delta$ = 81.8 for anti isomer) was observed in ^{13}C NMR spectra of all compounds in the first library (FMS: *4R,34S*) without exception.



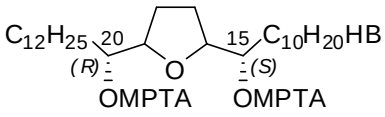
80

	C1	C2	C4
4*R*,34*S*, anti	174.60	151.82	70.00
4*S*,34*S*, syn	174.57	151.89	69.90

anti, $\Delta\delta$C2–C4 = 81.8
syn, $\Delta\delta$C2–C4 = 82.0

Figure 1.19 Assignment of the relative configuration of the hydroxybutenolide fragment by ^{13}C NMR data

The stereochemistry of secondary alcohol stereocenters in acetogenins is commonly pursued by using "advanced Mosher analysis".[46] During this exercise, a secondary alcohol of unknown stereochemistry is reacted with both (*R*)- and (*S*)- Moscher acid chlorides [α-methoxy-α-(trifluoromethyl)phenylacetyl chloride] to generate the corresponding (*S*)- and (*R*)-Mosher esters. The signs of Δδ, calculated by subtraction of the chemical shifts of the protons of the (*R*)-Moscher ester from the (*S*)-Mosher ester, is to assign the configuration of the stereocenter. This method was validated for the first murisolin library as shown in figure 1.20. Two murisolin isomers **1.15** and **1.17** were converted to their tris-(*S*)- and tris-(*R*)-Mosher esters **3.15**/**4.15** and **3.7**/**4.7**. The signs of Δδ are consistent with the known configuration of **1.15** (15*R*,20*R*) and **1.17** (15*S*,20*S*).



Δδ (*S* − *R*) is positive (+) or negative (−)

configs	14H	16/17H	18/19H	21H
15*R*,20*R*	+	−	−	+
15*S*,20*R*	−	+	−	+
15*S*,20*S*	−	+	+	−
15*R*,20*S*	+	−	+	−

Δδ (*S* − *R*) + − + −

MTPA = COC(OMe)(CF_3)Ph

3.7, *SSRS*, *tris*-(*S*)-ester
4.7, *SSRS*, *tris*-(*R*)-ester

	21H	19H	16H	14H
Δδ (*S* − *R*)	−0.11	+0.02	+0.14	−0.01

All four values are consistent with Mosher guidelines

3.15, *RRSR*, *tris*-(*S*)-ester
4.15, *RRSR*, *tris*-(*R*)-ester

	21H	19H	16H	14H
Δδ (*S* − *R*)	+0.11	−0.03	−0.14	+0.01

All four values are consistent with Mosher guidelines

Figure 1.20 Assignment of absolute configurations by "advanced Mosher method"

A "shortcut" Mosher method is derived wherein a single Mosher ester [tris-(*S*) or tris-(*R*)] for each of the 16 murisolin isomers is made and resonances of that are subtracted from its appropriate diastereomer with the locally enantiomeric configuration in the dihydroxy-THF fragment (quasienantiomeric relationship in the dihydroxy-THF fragment). To test the "shortcut" method, resonances of **3.15** (15*R*,20*R*) are subtracted from **3.7** (15*S*,20*S*). This resulted in identical signs and magnitudes of the differences in chemical shifts (figure 1.21) to the subtraction the appropriate tris-(*R*)- and tris-(*S*)-Mosher esters. This demonstrates that making a pair of tris-(*R*)/(*S*)-Mosher esters for each murisolin isomer provides redundant information. (*S*)-

Mosher ester derivatives were prepared for the other 14 murisolin isomers and then chemical shifts of the relevant resonances are subtracted to provide signs and magnitude for each Δδ. However, the two pairs of spectra corresponding to groups 5 and 6 (**3.8** and **3.16**; **3.3** and **3.11**) were substantially identical and hence it is pointless to subtract resonances of these pairs of spectra. Four additional pairs of spectra (**3.2** and **3.5**; **3.10** and **3.13**; **3.4** and **3.15**; **3.7** and **3.12**) were also identical to each other. These compounds share a common feature that one can be converted to the other by interchanging the two side chains on C15 and C20. As a result, each of the 16 tris-(*S*)-Mosher esters of murisolin isomers exhibit only 10 sets of ^{1}H NMR. There are four compounds with unique spectra; whereas six pairs of compounds have identical spectra.

3.7, *SSRS*, *tris*-(*S*)-ester
3.15, *RRSR*, *tris*-(*S*)-ester

	21H	19H	16H	14H
Δδ (***3.7*** − ***3.15***)	+0.11	−0.03	−0.14	+0.01

All four values are consistent with Mosher guidelines
All four values have equal signs as Δδ (***3.7*** − ***4.7***)

Figure 0.21 "Short-cut" Mosher assignment

With well characterized 28-murisolin isomers in hand, structural assignment of three murisolin natural products (murisolin, 16,19-*cis*-murisolin and murisolin A) were assessed. Unambiguous structure assignment requires disproving all possible candidates but one. Comparison of ^{1}H NMR data of natural product murisolin with each of the six groups of compounds from the current work places it in group 4 and confirms the *threo-trans-threo* relative stereochemistry originally assigned by cave and co-workers.[47] Hoye's application of the Mosher method conforms the relative and absolute stereochemistry (4*R*,34*S*) of the hydroxybutenolide

fragment. This reduces the number of possible murisolin candidates from eight to two, **1.6** and **1.14**. Application of Mosher method eliminates **1.6** and puts **1.14** as the sole possible structure for murisolin. To further confirm the structure, a sample of natural murisolin (provided by Dr. Bruno Figadere) was compared with two key candidate isomers **1.6** and **1.14** as well as three other isomers in group 4 with differing configuration at C4 and C34 (**1.18**, **1.22** and **1.26**). In this experiment, only **1.14** co-eluted with natural murisolin.

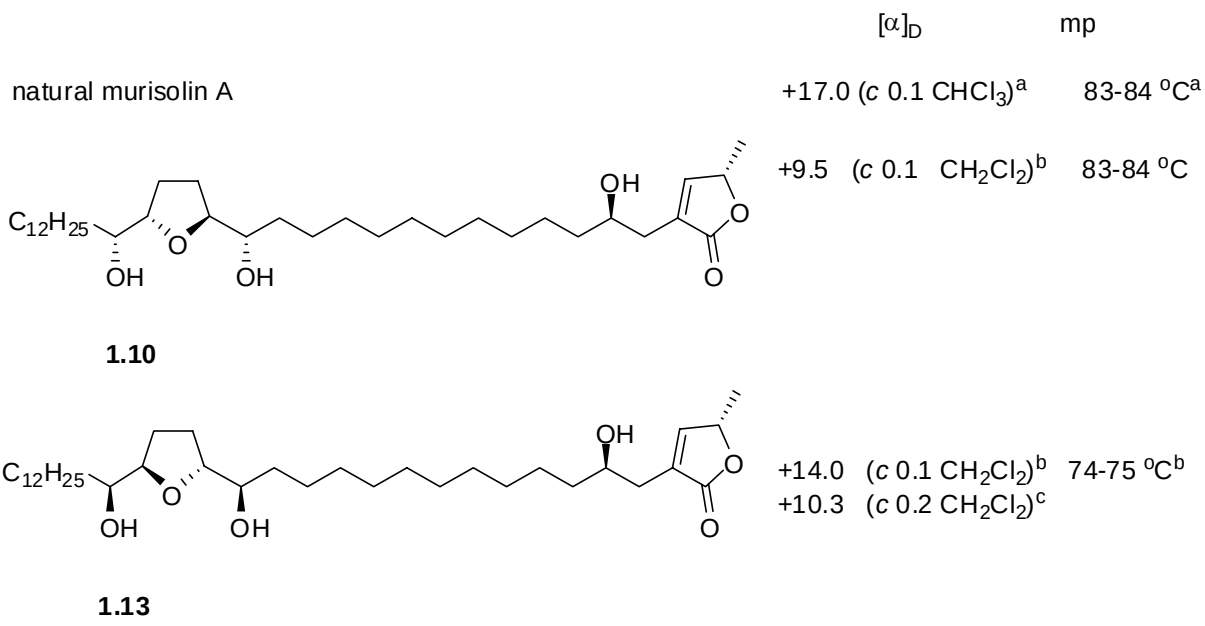
Comparison of the published NMR spectra of 16,19-cis-murisolin[48] with spectra of each of the six groups of compounds from the current work places it in group 6 and confirms relative stereochemistry (th-c-th) in dihydroxy-THF fragment. The relative stereochemistry of hydroxybutenolide fragment is conformed as C*4*,C*34-anti*, since Δδ C2-C4 is 81.8. McLaughlin and co-workers made tris-(*R*)- and tris-(*S*)-Mosher esters and showed that the absolute configuration is C4*R*,C34*S*. This narrowed that candidate structures to **1.8** and **1.16**. McLaughlin proposed the structure of 16,19-cis-murisolin as **1.16** based on subtraction of resonances in pairs of Mosher esters. However, as described earlier, the spectra of **3.8** and **3.16** are identical and hence it is meaningless to perform advanced Mosher ester analysis on these molecules. Since the available spectral data is not useful in determining the correct structure, we resorted to compare available physical data. A comparison of the optical rotation and melting points of natural 16,19-cis-murisolin, candidate structures (**1.8** and **1.16**) from our work (Curran and co-workers) and Tanaka's work is shown in figure 1.22. Although the optical rotation data provides no clue in determining the structure, we can tentatively assign structure **1.8** to 16,19-cis-murisolin based on melting points.

	$[\alpha]_D$	mp
natural 16,19-*cis*-murisolin	+11.0 (*c* 0.1 CH_2Cl_2)[a]	67-68 °C[a]
1.8	+4.5 (*c* 0.1 CH_3OH)[b] +9.1 (*c* 0.5 CH_2Cl_2)[c]	63-64 °C[b] 65-66 °C[b]
1.16	+8.1 (*c* 0.1 CH_3OH)[b] +9.8 (*c* 0.11 CH_3OH)[c] +11.3 (*c* 0.62 CH_2Cl_2)[d]	72-73 °C 76.5-77.5 °C

a) From McLaughlin; b) Curran group first library sample; c) Curran group second library sample; d) from Tanaka

Figure 1.22: Comparison of optical rotation and melting point data for natural 16,19-*cis*-murisolin and synthetic **1.8** and **1.16.**

McLaughlin proposed structures **1.10** and **1.13** as probable candidates for murisolin A. These two compounds are end-switched isomers and hence chiral derivative method is not suitable for structure assignment. A comparison of melting points and optical rotation data for synthetic and natural samples is shown in figure 1.23. Again, optical rotation data is not conclusive and structure **1.10** was tentatively assigned to murisolin A based on the melting points.



a) From McLaughlin; b) Curran group first library sample; c) Curran group second library sample

Figure 1.23 Comparison of optical rotation and melting point data for natural murisolin A and synthetic **1.10** and **1.13.**

1.3. CONCLUSIONS

Two new solution phase mixture synthetic methods (OEG mixture synthesis, OEG-Fluorous mixture synthesis) have been explored. Three powerful synthetic tools in solution phase mixture synthesis (fluorous mixture synthesis, OEG-mixture synthesis and OEG-fluorous mixture synthesis) have been evaluated and applied for the synthesis of sixteen stereoisomer library of murisolin. The principles of the oligoethylene glycol (OEG) mixture synthesis are illustrated with the synthesis of all four possible stereoisomers of a hydroxyl butenolide fragment common to murisolin and many other acetogenins. Modified dimethoxybenzyl groups with varying number of OEG units (-CH_2CH_2O-) are used to protect alcohols and serve as code of configuration at two stereocenters. The encoded isomers are carried through several steps in a sequence of mixing prior to the reaction and then demixing during the separation to give

individual pure products. A new tagging scheme is introduced in which a stereocenter bearing a hydroxyl group is given two different tags. These initially redundant tags subsequentsly serve to encode the configuration of another untagged stereocenter. Double mixture synthesis (OEG-fluorous mixture synthesis) was pursued by the Kocienski-Julia olefination of sulfone mixture **M13** (fluorous tagged) with the aldehyde mixture **M62** (OEG-tagged). Double demixing, and detagging of the final sixteen compound mixture provided the 16 individual murisolins. Twelve of these isomers are new, while four match samples from the first library. The structure of murisolin was proved to be the 4*R*,15*R*,16*R*,19*R*,20*R*,34*S* isomer, where as the assignment of the 16,19-*cis*-murisolin was corrected to the *RSSRRS* diastereomer and murisolin A is suggested to be *RSRRRS*.

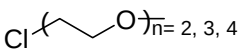
1.4. EXPERIMENTAL SECTION

Proton nuclear magnetic resonance (^{1}H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR) spectra and fluorine magnetic resonance spectra (^{19}F) were recorded on a Bruker WH-300 MHz, an IBM AF-300, an AM-500 or a Bruker Avance^{TM} 600 NMR spectrometer using deuteriated chloroform as the solvent. Signal positions are given in parts per million (δ) and were determined relative to the residual proton signal for $CHCl_3$ (7.27) and the carbon signal for $CDCl_3$ (77.09). The ^{1}H NMR coupling constants (*J*-values) are given in Hz. Spectral content is listed in the following order: chemical shift (δ), multiplicity, coupling constants (Hz), number of protons. Spectra were recorded at room temperature unless otherwise indicated.

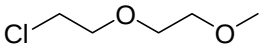
Infrared (IR) spectra were recorded on an IBM IR/32 spectrometer and run as neat films or chloroform solutions on sodium chloride plates. Low-resolution mass spectra were obtained on a Hewlett Packard-9000 GC-MS, and high-resolution spectra were recorded on a Varian MATCH-5DF instrument. HPLC analysis was performed on a Waters 600E system with UV detector using a Fluoflash column. LC-MS spectra were obtained on a Hewlett Packard-1100 LC-MS using APCI mode.

Preparative silica gel thin layer chromatography was performed on commercially available (PF-254), glass backed plates (25 x 25 cm), precoated with silica gel 60 to a thickness of 0.5 mm. Visualization of the chromatograms was accomplished with an ultraviolet light (254 nm), heating the chromatogram after staining with commercially available (Aldrich Chemical Co., Inc.) phosphomolybdic acid in ethanol (1:4 ratio), a 5% aqueous solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v), or with an aqueous 5% potassium permanganate solution. Conventional flash chromatography was performed with 230-400 mesh silica gel (E. Merck, Silica gel 60).

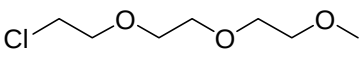
All dry solvents were obtained by refluxing over an appropriate drying agent. Distilled solvents were used immediately or stored over molecular sieves where appropriate. Diethyl ether and tetrahydrofuran were dried over sodium benzophenone ketyl. Unless stated otherwise, all reactions were carried out under an atmosphere of dry argon using glassware that had been thoroughly dried under vacuum.



General procedure 1: synthesis of alkyl chlorides (18): A solution of thionyl chloride (92 mmol) in $CHCl_3$ (15 mL) was added slowly over 15 min to a stirred solution of oligoethyleneglycol monomethyl ether (72 mmol) and pyridine (72 mmol) in $CHCl_3$ (60 mL) under argon followed by refluxing the above reaction mixture for 3 h. The above reaction mixture was washed with 300 mL of water, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product (yellow to brown colored) was spectroscopically pure and can be used in next step without further purification. However, bulb-to-bulb (Kugelrohr distillation) distillation into a cold receiving flask (−78 ^oC) under reduced pressure gave the desired alkyl chloride as colorless to pale yellow oils.

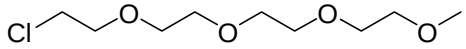


1-Chloro-2-(2-methoxyethoxy)ethane (18b):[1] Performing the general procedure 1 with 2-(2-methoxyethoxy)ethanol **17b** (8.7 g, 72 mmol) gave 1-chloro-2-(2-methoxyethoxy)ethane (**18b**) (9.2 g, 92 %) as colorless oil.

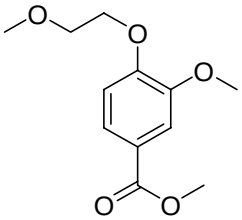


[1] CAS Reg # 52808-36-3

1-Chloro-2-[2-(2-methoxyethoxy)ethoxy]ethane (18c):[2] Performing the general procedure 1 with 2-[2-(2-methoxyethoxy)ethoxy]ethanol **17c** (12 g, 72 mmol) gave 1-chloro-2-[2-(2-methoxyethoxy)ethoxy]ethane **18c** (12 g, 94%) as pale yellow oil.



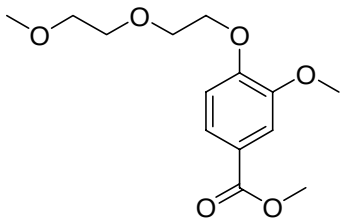
1-Chloro-2-{2-[2-(2-methoxy ethoxy)ethoxy]ethoxy}ethane (18d):[3] Performing the general procedure 1 with 2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethanol **17d** (15 g, 72 mmol) gave 1-chloro-2-{2-[2-(2-methoxy ethoxy)ethoxy]ethoxy}ethane **18d** (15 g, 93%) as pale yellow oil.



3-Methoxy-4-(2-methoxyethoxy)benzoic acid methyl ester (21a): Potassium carbonate (10 g, 72 mmol) and potassium iodide (1.5 g, 9.0 mmol) were added to a solution of methyl vanillate **20** (5.0 g, 27 mmol) and 1-chloro-2-methoxyethane **18a** (3.4 g, 36 mmol) in dry DMF and the reaction mixture was stirred for 24 h under argon. The DMF was removed by concentrating the reaction mixture with a rotovap equipped with dry-ice/acetone bath (−78 ^{o}C condenser). Dichloromethane (15 mL) was added to the above crude product and the resulting solution was filtered to remove the potassium salts. The filtrate was concentrated and the traces of solvents (CH_2Cl_2 and DMF) present in it were removed in *vacuo* (0.08 mm Hg, 45 ^{o}C) into a cold receiving flask (−78 ^{o}C) by bulb-to-bulb (Kugelrohr) distillation. The resulting residue was

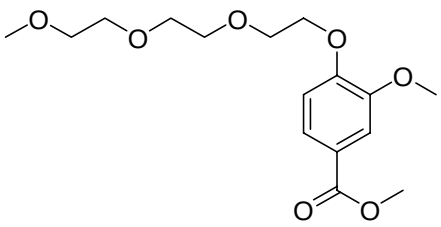
[2] CAS Reg # 52996-76-3
[3] CAS Reg # 57722-04-0

distilled bulb-to-bulb (0.08 mm Hg, 55-60 ^{o}C) into a cold receiving flask (−78 ^{o}C) to yield 3-methoxy-4-(2-methoxyethoxy)benzoic acid methyl ester **21a** (6.1 g, 93%) as pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (s, 3H), 3.77-3.80 (m, 2H), 3.87 (s, 3H), 3.89 (s, 3H), 4.19-4.22 (m, 2H), 6.89 (d, *J* = 8.2 Hz, 1H), 7.52 (d, *J* = 1.6Hz, 1H), 7.63 (dd *J* = 8.5 Hz, 1.9Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7, 55.7, 58.9, 67.9, 70.5, 111.6, 112.0, 122.6, 123.1, 148.7, 152.0, 166.5; IR (neat) 1720, 1600, 1513; EIMS *m/z* 240 (M^{+}); HRMS for $C_{12}H_{16}O_5$: calcd 240.0998; found 240.0985.



3-Methoxy-4-[2-(2-methoxyethoxy)ethoxy]benzoic acid methyl ester (21b): Potassium carbonate (10 g, 72 mmol) and potassium iodide (1.5 g, 9.0 mmol) were added to a solution of methyl vanillate **20** (5.0 g, 27 mmol) and 1-(2-chloroethoxy)-2-methoxyethane **18b** (4.9 g, 36 mmol) in dry DMF (125 mL) and the reaction mixture was stirred at 60 ^{o}C for 24 h under argon. The DMF was removed from the reaction mixture by concentrating it with a rotovap equipped with a dry-ice/acetone bath (−78 ^{o}C condenser). Dichloromethane (15 mL) was added to the above crude product and the resulting solution was filtered to remove the potassium salts. The filtrate was concentrated and the traces of solvents (CH_2Cl_2, DMF) and excess of alkyl halide present in it were removed in *vacuo* (0.08 mm Hg, 50-55 ^{o}C) into a cold receiving flask (−78 ^{o}C) by bulb-to bulb distillation. The resulting residue was distilled bulb-to-bulb (0.08 mm Hg, 68-72 ^{o}C) into a cold (−78 ^{o}C) receiving flask to yield 3-methoxy-4-[2-(2-methoxyethoxy)ethoxy] benzoic acid methyl ester **21b** (7.5 g, 96%) as yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (s,

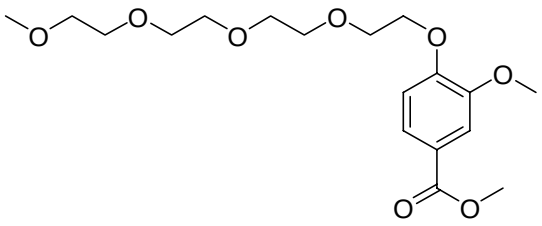
3H), 3.56-3.59 (m, 2H), 3.72-3.75 (m, 2H), 3.90-3.94 (m, 8H), 4.94 (t, *J* = 5.0Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.65 (dd, *J* = 8.5, 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8, 55.8, 58.9, 68.2, 69.3, 70.7, 71.8, 111.8, 112.2, 122.7, 123.3, 148.8, 152.1, 166.7; IR (neat) 2928, 2888, 1714, 1599; EIMS *m/z* 284 (M^+); HRMS for $C_{14}H_{20}O_6$: calcd 284.1260; found 284.1265.



3-Methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}benzoic acid methyl ester (21c):

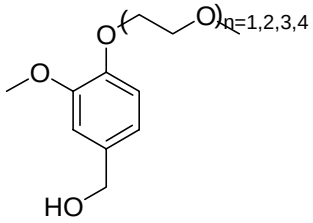
Potassium carbonate (10 g, 72 mmol) and potassium iodide (1.5 g, 9.0 mmol) were added to a solution of methyl vanillate **20** (5.0 g, 27 mmol) and 1-[2-(2-chloroethoxy)ethoxy]-2-methoxyethane **18c** (6.6 g, 36 mmol) in dry DMF (125 mL) and the reaction mixture was stirred at 60 ^{o}C for 24 h under argon. The DMF was removed from the reaction mixture by concentrating it with a rotovap equipped with a dry-ice/acetone bath (−78 ^{o}C condenser). Dichloromethane (15 mL) was added to the above crude product and the resulting solution was filtered to remove the potassium salts. The filtrate was concentrated and the traces of solvents (CH_2Cl_2, DMF) and excess of alkyl halide present in it were removed in *vacuo* (0.08 mm Hg, 65 ^{o}C) into a cold receiving flask (−78 ^{o}C) by bulb-to-bulb distillation. The resulting residue was distilled bulb-to-bulb (0.08 mm Hg, 85-90 ^{o}C) to yield 3-methoxy-4-{2-[2-(2-methoxyethoxy) ethoxy]ethoxy}benzoic acid methyl ester (8.5 g, 95%) **21c** as yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.24 (s, 3H), 3.39-3.42 (m, 2H), 3.48-3.56 (m, 4H), 3.60-3.63 (m, 2H), 3.76-3.80 (m, 8H), 4.11 (t, *J* = 5.0 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 1.8 Hz, 1H), 7.51 (dd, *J* = 8.4,

2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.5, 55.5, 58.6, 68.0, 69.0, 70.1, 70.2, 70.5, 71.5, 111.6, 111.9, 122.4, 123.0, 148.6, 152.0, 166.4; IR (neat) 3085, 2870, 1716, 1508; EIMS *m/z* 328 (M^+); HRMS for $C_{16}H_{24}O_7$: calcd 328.1522; found 328.1523.

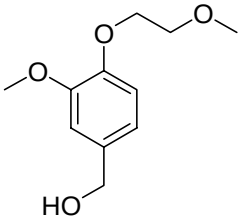


3-Methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)benzoic acid methyl ester (21d): Potassium carbonate (10 g, 72 mmol) and potassium iodide (1.5 g, 9.0 mmol) were added to a solution of methyl vanillate **20** (5.0 g, 27 mmol) and 1-[2-(2-chloroethoxy) ethoxy]-2-(2-methoxyethoxy)ethane **18d** (8.1 g, 36 mmol) in dry DMF (125 mL) and the reaction mixture was stirred at 60 ^{o}C for 24 h under argon. The DMF was removed from the reaction mixture by concentrating it with a rotovap equipped with a dry-ice/acetone bath. Dichloromethane (15 mL) was added to the above crude product and the resulting solution was filtered to remove the potassium salts. The filtrate was concentrated and the traces of solvents (CH_2Cl_2, DMF) and excess alkyl halide present in it were removed in *vacuo* (0.08 mm Hg, 65 ^{o}C) into a cold receiving flask (−78 ^{o}C) by bulb-to-bulb distillation. The resulting residue was distilled bulb-to-bulb (0.08 mm Hg, 85-90 ^{o}C) into a cold receiving flask (−78 ^{o}C) to yield 3-methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy) benzoic acid methyl ester **21d** (9.3 g, 91%) as yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.19 (s, 3H), 3.35-3.38 (m, 2H), 3.46-3.51 (m, 8H), 3.55-3.59 (m, 2H), 3.71-3.75 (m, 8H), 4.06 (t, *J* = 5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 1.5Hz, 1H), 7.46 (dd, *J* = 8.5, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.4, 55.5, 58.5, 67.9, 69.0,

70.0, 70.1, 70.4, 71.4, 111.6, 111.9, 122.4, 122.9, 148.5, 151.9, 166.24; IR (neat) 2941, 2873, 1716, 1598, 1509; EIMS *m/z* 372 (M^+); HRMS for $C_{18}H_{28}O_8$: calcd 372.1784; found 372.1796.

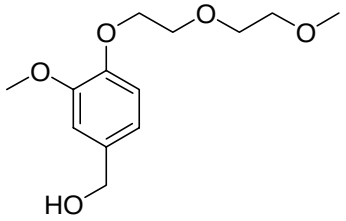


General procedure 2: Reduction of esters 21 to alcohols 44 with $LiAlH_4$: A solution of ester **21** (1.0 equiv) in THF was added slowly to a suspension of $LiAlH_4$ (0.55 equiv) in THF at 0 ^oC and the resulting reaction mixture was stirred at 0 ^oC for 15 min followed by 30 min at room temperature. The reaction mixture was quenched with methanol and diluted with ethyl acetate and saturated sodium potassium tartarate (1:1) followed by vigorous stirring for 3.5 h. Organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure to yield the alcohol **44** as an oil.

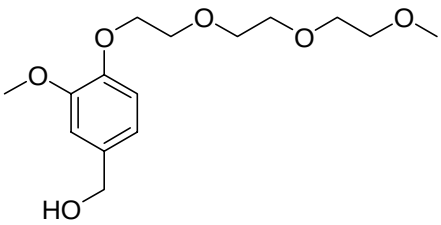


[3-Methoxy-4-(2-methoxyethoxy)phenyl]methanol 44a: Performing the general procedure 2 with 3-methoxy-4-(2-methoxyethoxy)benzoic acid methyl ester (5.9 g, 24 mmol) gave [3-methoxy-4-(2-methoxyethoxy)phenyl]methanol (4.7 g, 91%) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 3.50 (s, 3H), 3.78 (t, J = 5.1 Hz, 2H), 3.87 (s, 3H), 4.15 (t, J = 3.1 Hz, 2H), 4.62 (s,

2H), 6.87-6.93 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.9, 59.2, 65.1, 68.5, 71.1, 110.8, 113.6, 119.2, 134.3, 147.7; IR (neat) 3400, 2940, 2868, 1588, 1516.

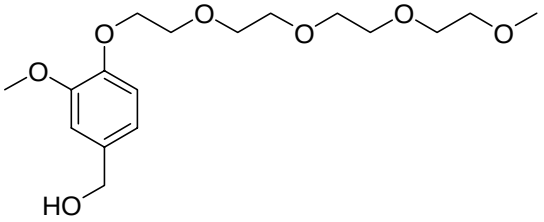


{3-Methoxy-4-[2-(2-methoxyethoxy)ethoxy]phenyl}methanol 44b: Following the general procedure 2 with 3-methoxy-4-[2-(2-methoxyethoxy)ethoxy]benzoic acid methyl ester (7.1 g, 25 mmol) gave {3-methoxy-4-[2-(2-methoxyethoxy)ethoxy]phenyl}methanol (6.0 g, 93%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.57-3.60 (m, 2H), 3.72-3.75 (m, 2H), 3.88 (s, 3H), 3.90 (t, *J* = 5.5 Hz, 2H), 4.20 (t, *J* = 5.0 Hz, 2H), 4.63 (s, 2H), 6.87-6.93 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.0, 59.2, 65.4, 68.7, 69.8, 70.9, 72.0, 110.0, 113.7, 119.5, 134.3, 147.9, 149.8; IR (neat) 3390, 2930, 2878, 1588, 1511; EIMS *m/z* 256 (M^+); HRMS for $C_{13}H_{20}O_5$: calcd 256.1311; found 256.1308.



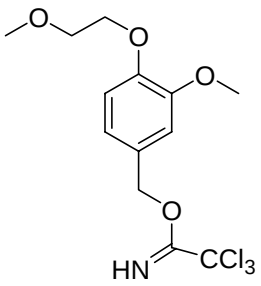
(3-Methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}phenyl)methanol 44c: Following the general procedure 2 with 3-methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}benzoic acid methyl ester (8.4 g, 26 mmol) gave (3-methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy] ethoxy}phenyl)methanol (7.5 g, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.53-3.56 (m,

2H), 3.64-3.70 (m, 4H), 3.72-3.79 (m, 2H), 3.87 (s, 3H), 3.88-3.90 (m, 2H), 4.17-4.21 (m, 2H), 4.62 (s, 2H), 6.85-6.93 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.0, 59.1, 65.2, 68.6, 69.7, 70.6, 70.7, 70.9, 72.0, 111.0, 113.7, 119.4, 134.4, 147.8, 149.7; IR (neat) 3426, 2929, 3868, 1593, 1516, 1455; EIMS *m/z* 300 (M^+); HRMS for $C_{15}H_{24}O_6$: calcd 300.1573; found 300.1564.

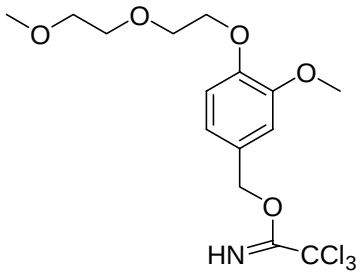


[3-Methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)phenyl]methanol 44d:

Following the general procedure 2 with 3-methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy] ethoxy}ethoxy) benzoic acid methyl ester (8.6 g, 23 mmol) gave [3-methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)phenyl]methanol (7.6 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.53-3.57 (m, 2H), 3.62-3.74 (m, 10H), 3.87 (s, 3H), 3.88-3.93 (m, 2H), 4.18 (t, *J* = 5.3 Hz, 2H), 4.63 (s, 2H), 6.87-6.93 (m, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 55.9, 59.1, 65.2, 68.7, 69.8, 70.6, 70.9, 71.0, 72.0, 111.0, 113.7, 119.4, 134.4, 147.8, 149.7; IR (neat) 3462, 2935, 2873, 1588, 1516.



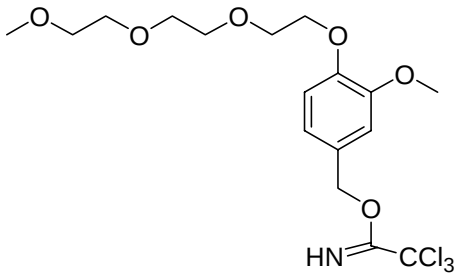
General procedure 3: 2,2,2-Trichloroacetimidic acid 3-methoxy-4-(2-methoxyethoxy)benzyl ester 5a: [3-Methoxy-4-(2-methoxyethoxy)phenyl]methanol (4.5 g, 21 mmol) was added slowly to a suspension of sodium hydride (51 mg, 2.1 mmol) in THF (25 mL) under argon. The reaction mixture was stirred at room temperature for 20 min and then cooled to 0 ^{o}C followed by slow addition of trichloroacetonitrile (2.1 mL, 21 mmol) over 15 min. The reaction mixture was allowed to warm to room temperature over 1 h followed by concentration under reduced pressure. To the concentrate was added a mixture of pentane/methanol (49:1, 50 mL) followed by vigorous shaking, filtration, and concentration of filtrate and pentane washings[4] (3 x 30 mL) resulting 2,2,2-trichloroacetimidic acid 3-methoxy-4-(2-methoxyethoxy)benzyl ester (6.8 g, 90%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (s, 3H), 3.79 (t, *J* = 4.9 Hz, 2H), 3.87 (s, 3H), 4.18 (t, *J* = 4.9 Hz, 2H), 5.29 (s, 2H), 6.90-6.98 (m, 3H), 8.38 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.7, 59.0, 68.3, 70.6, 70.8, 91.3, 111.5, 113.3, 120.4, 128.4, 148.2, 149.4, 162.3; IR (neat) 3320, 2939, 1665, 1594, 1513; EIMS *m/z* 355 (M^+); HRMS for $C_{13}H_{16}NO_4Cl_3$: calcd 355.0145; found 355.0127.



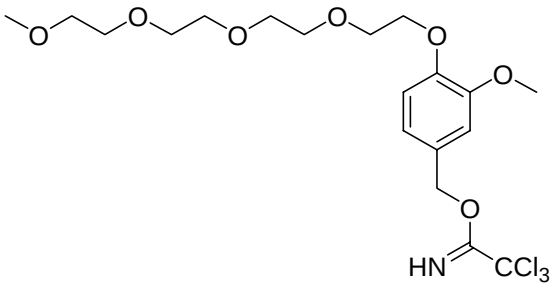
2,2,2-Trichloroacetimidic acid 3-methoxy-4-[2-(2-methoxyethoxy)ethoxy]benzyl ester 5b: Following the general procedure 3 with {3-methoxy-4-[2-(2-methoxyethoxy) ethoxy]phenyl} methanol (4.2 g, 16 mmol) gave 2,2,2-trichloroacetimidic acid 3-methoxy-4-[2-(2-

[4] Wessel, H-P; Iversen, T.; Bundle, D. R. *J. Chem. Soc. Perkin. Trans. I*, **1985**, 2247.

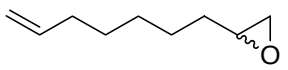
methoxyethoxy)ethoxy]benzyl ester (5.2 g, 80%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.35 (s, 3H), 3.53 (m, 2H), 3.68 (m, 2H), 3.82 (s, 3H), 3.85 (t, *J* = 5.0 Hz, 2H), 4.16 (t, *J* = 5.0 Hz, 2H), 5.24 (s, 2H), 6.86 (m, 3H), 8.36 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.8, 58.9, 68.4, 69.5, 70.6, 71.8, 91.4, 111.7, 113.4, 120.5, 128.4, 148.3, 149.5, 162.3; IR (neat) 3333, 2931, 2881, 1665, 1593, 1517; HRMS for $(M + Na)^+$ $C_{15}H_{20}O_5NCl_3Na$: calcd 422.0305; found 422.0309.



2,2,2-Trichloroacetimidic acid 3-methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}benzyl ester 5c: Following the general procedure 3 with (3-methoxy-4-{2-[2-(2-methoxyethoxy) ethoxy]ethoxy}phenyl)methanol (6.5 g, 22 mmol) gave 2,2,2-trichloroacetimidic acid 3-methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}benzyl ester (8.2 g, 85%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.35 (s, 3H), 3.50-3.54 (m, 2H), 3.62-3.66 (m, 4H), 3.70-3.73 (m, 2H), 3.83 (s, 3H), 3.86 (t, *J* = 5.0 Hz, 2H), 4.17 (t, *J* = 5.3 Hz, 2H), 5.25 (s, 2H), 6.87-6.96 (m, 3H), 8.36 (br s, 1H);); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.8, 59.0, 68.5, 69.5, 70.5, 70.6, 70.7, 70.8, 71.9, 91.4, 111.7, 113.4, 120.6, 128.4, 148.3, 149.5, 162.4; IR (neat) 3332, 2931, 1665, 1593, 1517; EIMS *m/z* 445 (M^+).

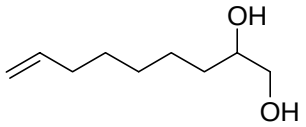


2,2,2-Trichloroacetimidic acid 3-methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)benzyl ester 5d: Following the general procedure 3 with [3-methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)phenyl]methanol (7.5 g, 22 mmol) gave 2,2,2-trichloroacetimidic acid 3-methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)benzyl ester (8.8 g, 83%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.48-3.51 (m, 2H), 3.58-3.64 (m, 8H), 3.66-3.70 (m, 2H), 3.81 (s, 3H), 3.83 (t, *J* = 5.3 Hz, 2H), 4.14 (t, *J* = 5.0 Hz, 2H), 5.23 (s, 2H), 6.85-6.94 (m, 3H), 8.35 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.8, 58.9, 68.4, 69.4, 70.4, 70.5, 70.6, 70.7, 71.8, 91.3, 111.6, 113.3, 120.5, 128.3, 148.3, 149.4, 162.3; IR (neat) 3332, 2937, 2872, 1663, 1518; EIMS *m/z* 487 (M^+).



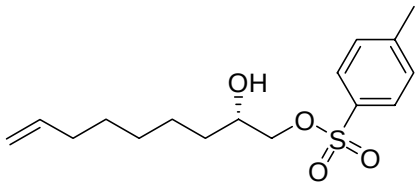
2-(Hept-6-enyl)oxirane 41: *m*-Chloroperbenzoic acid (36 g, 0.21 mol, 75% w/w in H_2O) was added to a solution of nona-1,8-diene (44 g, 0.32 mol) in dichloromethane (325 mL) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 20 min, room temperature for 20 min and treated with saturated $NaHCO_3$. The layers were separated and the aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 15% ethyl acetate/hexanes) to give 2-(hept-6-enyl)oxirane (22 g, 76%) as colorless oil: ^{1}NMR (300

MHz, $CDCl_3$) δ 1.38-1.56 (m, 10H), 2.02-2.06 (m, 2H), 2.46 (dd, *J* = 5.0, 3.0 Hz, 1H), 2.73-2.76 (m, 1H), 2.87-2.91 (m, 1H), 4.91-5.03 (m, 2H), 5.80 (ddt, *J* = 16.9, 10.0, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 28.7, 28.8, 32.4, 33.6, 47.0, 57.3, 114.3, 138.9.

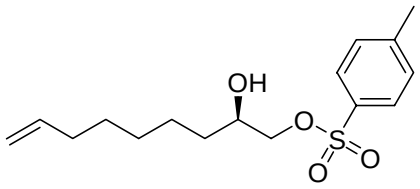


Non-8-ene-1,2-diol 29: The (*R*,*R*)-Jacobson catalyst[5] (*R*,*R*)-**39** (0.43g, 0.70 mmol) was dissolved in 2-(hept-6-enyl)oxirane (20 g, 0.14 mol), AcOH (172 μL, 2.9 mmol) and 1.4 mL THF. The solution was cooled to 0 ^oC, treated with H_2O (1.16 mL, 64.5 mmol) and stirred for 12 h at room temperature. The reaction mixture was distilled bulb-to-bulb (Kugelrohr) under reduced pressure (0.08 mm Hg, 40 ^oC) to remove residual epoxide (11 g, 80 mmol) followed by second distillation (0.08 mm Hg, 125 ^oC) to yield (*S*)-non-8-ene-1,2-diol nonane-1,2-diol (9.7 g, 43%, > 99% enantiomeric excess based on Mosher ester analysis) as colorless oil; Similar procedure with the above recovered epoxide (11 g, 79 mmol) and (*S*,*S*)-Jacobson catalyst (*S*,*S*)-**39** (0.43 g, 0.70 mmol) resulted in (*R*)- non-8-ene-1,2-diol (10 g, 44%, > 99% ee by Mosher ester analysis[6]) as colorless oil: $[\alpha]_D^{25}$ for (*R*)-**29**: 0.63 (c 4.30, $CHCl_3$); for (*S*)-**29** −2.1 (c1.42, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ1.29-1.54 (m, 6H), 2.01-2.14 (m, 3H), 2.20-2.22 (m, 1H), 3.44 (ddd, *J* = 10.9, 7.5, 4.9 Hz, 1H), 3.62-3.76 (m, 2H), 4.91-5.05 (m, 2 H), 5.81 (ddt, *J* = 17.1, 10.3, 6.6 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) 25.8, 29.2, 29.5, 33.4, 34.1, 67.2, 72.7, 114.7, 139.3; IR (neat): 3370, 2928, 2853, 1463; EIMS *m/z* 158 (M^+); HRMS for $C_9H_{18}O_2$: calcd 158.1307; found 158.1306.

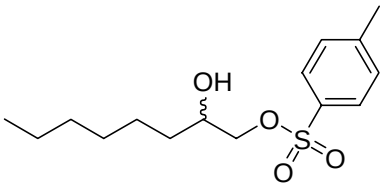
[5] Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobson, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 1307.
[6] Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc*. **1973**, *24*, 512.



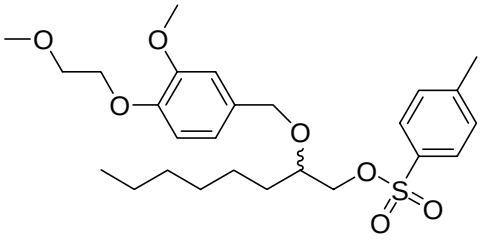
General procedure 4: (*S*)-2-Hydroxynon-8-enyl 4-methylbenzenesulfonate (*S*)-30: To a solution of (*S*)-non-8-ene-1,2-diol (3.3 g, 21 mmol) in CH_2Cl_2 (80 mL) were added Bu_2SnO (1.0 g, 4.1 mmol), *p*-toluenesulfonyl chloride (3.9 g, 21 mmol), and triethyl amine (2.1 g, 21 mmol). The reaction mixture was stirred for 3 h followed by dilution with water (50 mL). Organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (SiO_2, 20% ethyl acetate/hexanes) to yield **(***S***)**-2-hydroxynon-8-enyl 4-methylbenzenesulfonate (4.9 g, 76%) as white waxy solid.



(*R*)-2-Hydroxynon-8-enyl 4-methylbenzenesulfonate (*R*)-30: Performing the general procedure 4 with (*R*)-non-8-ene-1,2-diol (5.0 g, 32 mmol), Bu_2SnO (1.6 g, 6.3 mmol), *p*-toluenesulfonyl chloride (6.0 g, 32 mmol) and triethyl amine (4.3 mL, 32 mmol) gave, after purification by chromatography (SiO_2, 20% ethyl acetate/hexanes), 7.3 g (74%) of (*R*)-2-hydroxynon-8-enyl 4-methylbenzenesulfonate as white waxy solid.

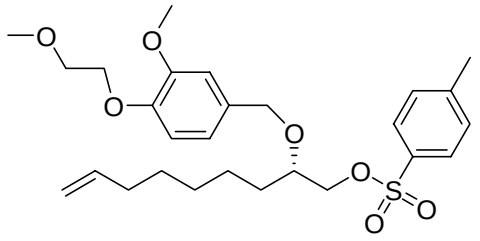


2-Hydroxyoctyl 4-methylbenzenesulfonate 39: Performing the general procedure 4 with octane-1,2-diol (1.0 g, 6.8 mmol), Bu_2SnO (0.34 g, 1.4 mmol), *p*-toluenesulfonyl chloride (1.3 g, 6.8 mmol) and triethyl amine (0.70 g, 6.8 mmol) gave, after purification by chromatography (SiO_2, 20% ethyl acetate/hexanes), 1.6 g (79%) of 2-hydroxyoctyl 4-methylbenzenesulfonate as white waxy solid.^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (t, *J* = 6.7 Hz, 3H), 1.13-1.23 (m, 10H), 2.32 (s, 3H), 2.90 (d, *J* = 4.9 Hz, 1H), 3.67-3.80 (m, 1H), 3.80 (dd, *J* = 9.9, 6.6 Hz, 1H), 3.91 (dd, *J* = 9.9, 3.5 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.69 (d, *J* = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 21.2, 22.0, 24.8, 28.8, 31.3, 32.4, 68.9, 127.6, 129.6, 132.4, 144.7; IR (neat) 3535, 3057, 2926, 1598, 1455.



General procedure 5: **2-(3-Methoxy-4-(2-methoxyethoxy)benzyloxy)octyl-4-methylbenzene sulfonate *rac*-47**: A solution of 2-hydroxyoctyl 4-methylbenzenesulfonate (0.12 g, 0.4 mmol), 2,2,2-trichloroacetimidic acid 3-methoxy-4-(2-methoxyethoxy)benzyl ester (0.20 g, 0.80 mmol) and 10-camphorsulfonic acid (9.0 mg, 0.039 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 24 h, and then diluted with saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated and the crude product was purified by flash chromatography (SiO_2, 25%

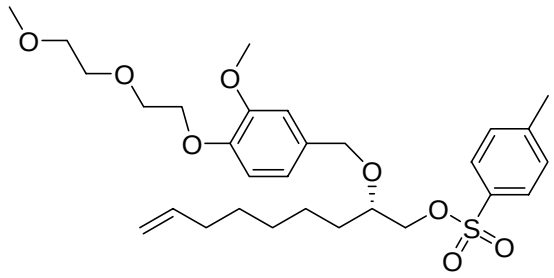
ethyl acetate/hexanes) to yield *rac*-47 (0.14 g, 72%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.65 Hz, 1H), 1.20-1.44 (m, 10H), 2.42 (s, 3H), 3.44 (s, 3H), 3.54-3.60 (m, 1H), 3.77 (t, *J* = 5.0 Hz, 2H), 3.85 (s, 3H), 3.97-4.07 (m, 2H), 4.14 (t, *J* = 5.0 Hz, 2H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 6.76-6.87 (m, 3H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 21.5, 22.4, 25.0, 29.0, 31.2, 31.6, 55.7, 59.0, 68.3, 70.9, 71.6, 71.9, 76.0, 111.6, 113.3, 120.2, 127.8, 129.7, 131.3, 132.8, 144.7, 147.8, 149.5, 163.4; IR (neat) 2929, 2870, 1597, 1515, 1464; EIMS *m/z* 494 (M^+); HRMS for $C_{26}H_{38}O_7S$: calcd 494.2338; found 494.2354.



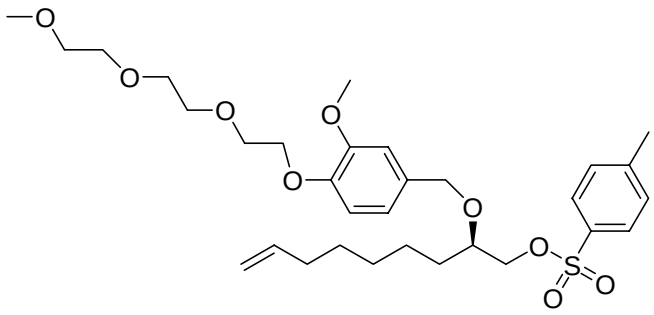
(*S*)-2-(3-Methoxy-4-(2-methoxyethoxy)benzyloxy)non-8-enyl-4-methylbenzenesulfonate

14a: Performing the general procedure 5 with (*S*)-alcohol (1.0 g, 3.2 mmol), imidate **5a** (2.9 g, 8.0 mmol) and camphorsulfonic acid (74 mg, 0.32 mmol) gave, after purification by flash chromatography (SiO_2, 20% ethyl acetate/hexanes), 1.1 g (2.2 mmol, 68%) of (*S*)-2-(3-methoxy-4-(2-methoxyethoxy)benzyloxy)non-8-enyl-4-methylbenzenesulfonate as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22-1.45 (m, 8H), 1.99 (q, *J* = 7.0 2H), 2.42 (s, 3H), 3.43 (s, 3H), 3.54-3.58 (m, 1H), 3.77 (t, *J* = 5.0 Hz, 2H), 3.86 (s, 3H), 3.98-4.04 (m, 2H), 4.15 (t, *J* = 5.0 Hz, 2H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 4.91-4.98 (m, 2H), 5.76 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 6.76-6.90 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 24.9, 28.6, 28.9, 31.2, 33.6, 55.8, 59.1, 68.4, 70.9, 71.6, 72.0, 76.0, 109.5, 111.6,

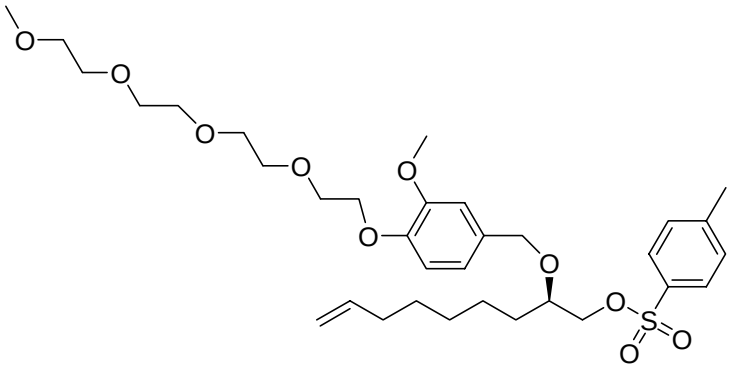
113.5, 114.3, 120.2, 127.9, 129.8, 131.3, 132.9, 138.8, 144.8, 147.9, 149.6; IR (neat) 3066, 2931, 1640, 1596, 1514, 1463; EIMS *m/z* 506 (M^+); HRMS for $C_{27}H_{38}O_7S$: calcd 506.2338; found 506.2354.



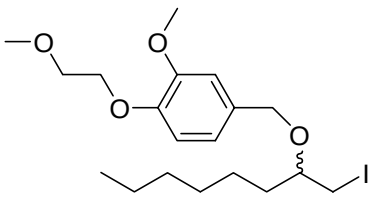
(*S*)-2-(3-Methoxy-4-(2-(2-methoxyethoxy)ethoxy)benzyloxy)non-8-enyl-4-methyl benzenesulfonate 14b: Performing the general procedure 5 with (*S*)-alcohol (1.0 g, 3.2 mmol), imidate **5b** (2.6 g, 6.4 mmol) and camphorsulfonic acid (74 mg, 0.32 mmol) gave, after purification by flash chromatography (SiO_2, 40% ethyl acetate/hexanes), 1.2 g (2.1 mmol, 66%) of(S)-2-(3-methoxy-4-(2-(2-methoxyethoxy)ethoxy)benzyloxy)non-8-enyl-4-methylbenzenesulfonate as an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22-1.53 (m, 8H), 1.97-2.07 (m, 2H), 2.44 (s, 3H), 3.39 (s, 3H), 3.55-3.63 (m, 3H), 3.71-3.75 (m, 2H), 3.85 (s, 3H), 3.89 (t, *J* = 5.1 Hz, 2H), 3.99-4.10 (m, 2H), 4.20 (t, *J* = 5.2 Hz, 2H), 4.43(d, *J* = 11.2 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 5.72-5.86 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 6.77- 6.90(m, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 21.2, 24.5, 28.3, 28.5, 30.9, 33.2, 55.4, 58.6, 68.3, 69.2, 70.3, 71.2, 71.6, 75.6, 111.4, 113.1, 114.0, 119.9, 127.5, 129.5, 131.0, 132.5, 138.4, 144.5, 147.5, 149.3; IR (neat) 3073, 2928, 1645, 1598, 1515; MS *m/z* 378 $(M - C_7H_8O_3S)^+$.



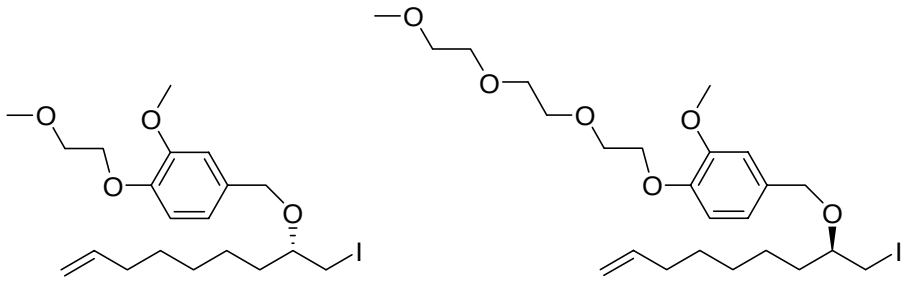
(*R*)-2-(3-Methoxy-4-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzyloxy)non-8-enyl-4-methyl benzenesulfonate 14c: Performing the general procedure 5 with (*R*)-alcohol (1.3 g, 4.2 mmol), imidate **5c** (4.1 g, 9.2 mmol) and camphorsulfonic acid (97 mg, 0.42 mmol) gave, after purification by flash chromatography (SiO_2, 50% ethyl acetate/hexanes), 1.7 g (2.1 mmol, 70%) of (*R*)-2-(3-methoxy-4-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzyloxy)non-8-enyl-4-methyl benzenesulfonate as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12-1.40 (m, 8), 1.92 (q, *J* = 6.9, 2H), 2.35 (s, 3H), 3.29 (s, 3H), 3.47 (t, *J* = 4.6 Hz, 2H), 3.48-3.52 (m, 1H), 3.57-3.61 (m, 4H), 3.66-3.67 (m, 2H), 3.76 (s, 3H), 3.80 (t, *J* = 5.0 Hz, 2H), 3.91-3.99 (m, 2H), 4.10 (t, *J* = 5.0 Hz, 2H), 4.34 (d, *J* = 11.0 Hz, 1H), 4.41 (d, *J* = 11.0 Hz, 1H), 4.84-4.92 (m, 2H), 5.70 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 6.69-6.80 (m, 3H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.3, 24.6, 28.4, 28.6, 30.9, 33.3, 55.5, 58.7, 68.3, 69.3, 70.2, 70.3, 70.5, 71.3, 71.6, 75.6, 111.5, 113.3, 114.1, 120.0, 127.6, 129.6, 131.0, 132.6, 138.5, 144.5, 147.6, 149.3; IR (neat) 3067, 2935, 1639, 1596, 1514, 1456; EIMS *m/z* 594 (M^+); HRMS $C_{31}H_{46}O_9S$: calcd 594.2863; found 594.2886.



(*R*)-2-(3-Methoxy-4-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethoxy)benzyloxy)non-8-enyl -4-methylbenzenesulfonate 14d: Performing the general procedure 5 with (*R*)-alcohol (1.0 g, 3.2 mmol), imidate **5d** (3.6 g, 7.4 mmol) and camphorsulfonic acid (74 mg, 0.32 mmol) gave, after purification by flash chromatography (SiO_2, 60% ethyl acetate/hexanes) 1.3 g (66%) of (R)-2-(3-methoxy-4-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethoxy)benzyloxy)non-8-enyl-4-methylbenzenesulfonate as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18-1.44 (m, 8H), 1.94-2.02 (m, 2H), 2.42 (s, 3H), 3.35 (s, 3H), 3.47-3.57 (m, 3H), 3.60-3.73 (m, 10H), 3.82 (s, 3H), 3.83-3.88 (m, 2H), 3.99-4.01 (m, 2H), 4.15 (t, *J* = 5.2 Hz, 2H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.48-4.50 (d, *J* = 11.5 Hz, 1H), 4.88-4.99 (m, 2H), 5.75 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 6.73-6.77 (m, 1H), 6.83 (m, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 21.6, 24.9, 28.6, 28.9, 31.2, 33.6, 55.8, 58.9, 68.5, 69.5, 70.5, 70.7, 71.6, 71.8, 72.0, 76.0, 111.7, 113.4, 114.3, 120.3, 127.8, 129.8, 131.2, 132.8, 138.8, 144.8, 147.9, 149.6; IR (neat) 3078, 2927, 1644, 1608, 1515, 1454.

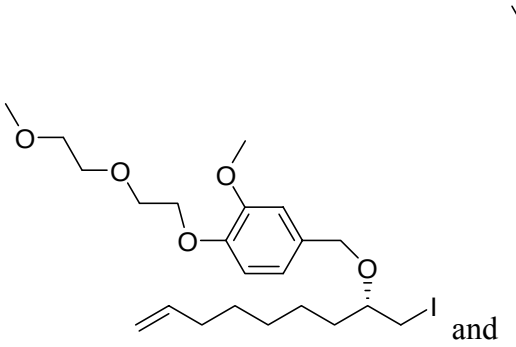


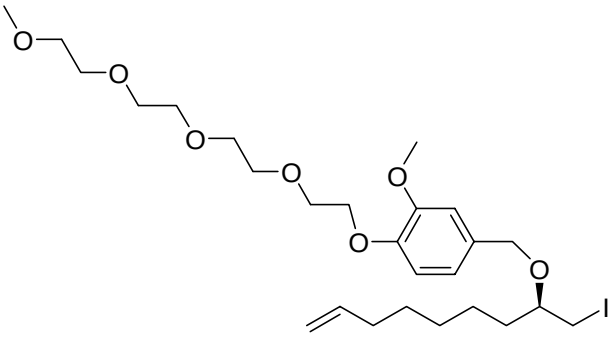
4-((1-Iodooctan-2-yloxy)methyl)-2-methoxy-1-(2-methoxyethoxy)benzene *rac*-51: A solution of *rac*-**47** (0.13 g, 0.26 mmol) and NaI (0.39 g, 2.6 mmol) in acetone was refluxed for 20 h followed by concentration of the reaction mixture. The concentrate was diluted with water (20 mL) and ethyl acetate (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated to yield *rac*-**51** as light brown oil (0.12 g, 98%):^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.9 Hz, 3H), 1.25-1.62 (m, 10H), 3.28-3.28 (m, 2H), 3.44 (s, 3H), 3.79 (t, *J* = 5.0 Hz, 2H), 3.87 (s, 3H), 4.15 (t, *J* = 5.0 Hz, 2H), 4.43 (d, *J* = 11.3 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 6.86 (s, 2H), 6.97 (s, 1H).



General procedure 6: mixture **M56a** of **(*S*)-4-((1-Iodonon-8-en-2-yloxy)methyl)-2-methoxy-1-(2-methoxyethoxy)benzene 56a** and **(*S*)-4-((1-Iodonon-8-en-2-yloxy)methyl)-2-methoxy-1-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzene 56c**: A solution of **14a** (0.99 g, 2.0 mmol), **14c** (0.76 g, 1.3 mmol) and NaI (2.4 g, 16 mmol) in acetone (35 mL) was refluxed for 20 h followed by concentration under reduced pressure. The concentrate was treated with water and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated to yield a mixture of **56a** and **56c** as light brown oil (1.6 g, 99%) which was used in next step with out further purification. However, for characterization purposes, a small sample (90 mg) of the above mixture was separated by flash column chromatography (SiO_2) upon which **56a** (ethyl acetate/hexanes = 1:4) eluted followed by **56c** (ethyl acetate/hexanes = 1:1) as

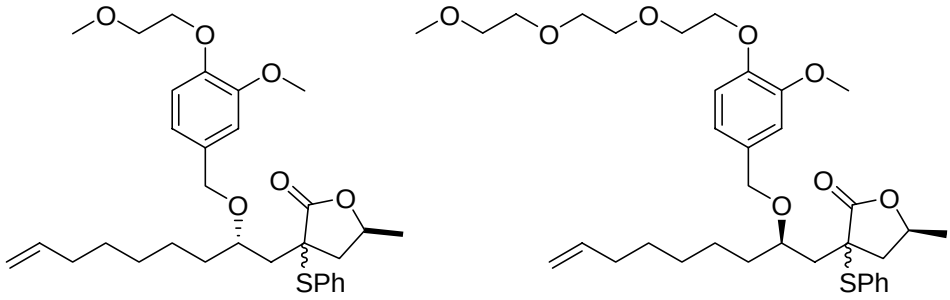
colorless oils. For **56a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27-1.61 (m, 8H), 1.97-2.11 (m, 2H), 3.21-3.35 (m, 3H), 3.43 (s, 3H), 3.76 (t, *J* = 4.9 Hz, 2H), 3.86 (s, 3H), 4.14 (t, *J* = 4.9 Hz, 2H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.89-5.03 (m, 2H), 5.78 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 6.85 (s, 2H), 6.95 (s, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 10.4, 25.0, 28.7, 28.9, 33.6, 34.5, 55.8, 59.1, 68.5, 70.9, 71.2, 77.4, 111.8, 113.5, 114.3, 120.2, 131.4, 138.8, 147.8, 149.6; EIMS *m/z* 462; HRMS $C_{20}H_{31}O_4I$: calcd 462.1267; found 462.1244; for **56c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27-1.57 (m, 8H), 1.98 (q, *J* = 7.0, 2H), 3.20-3.26 (m, 3H), 3.34 (s, 3H), 3.51-3.54 (m, 2 H), 3.62-3.66 (m, 4H), 3.70-3.72 (m, 2H), 3.79-3.90 (m, 5 H), 4.13 (t, *J* = 4.7Hz, 2H), 4.37 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H) 4.85-4.98 (m, 2H), 5.67-5.81 (m, 1H), 6.81 (s, 2H), 6.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.3, 24.7, 28.4, 28.6, 33.4, 34.2, 55.7, 58.9, 68.1, 69.2, 69.9, 70.1, 70.2, 70.9, 71.4, 111.5, 113.1, 114.1, 120.1, 131.1, 138.6, 147.3, 149.1; EIMS *m/z* 550 (M^+); HRMS $C_{24}H_{39}O_6I$: calcd 550.1791; found 550.1793.



and


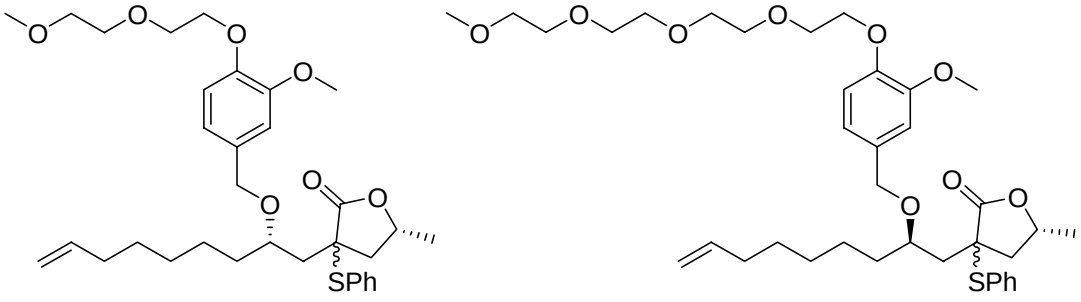
Mixture **M56b** of **(*R*)-4-((1-Iodonon-8-en-2-yloxy)methyl)-2-methoxy-1-(2-(2-methoxy ethoxy)ethoxy) benzene 56b** and **(*R*)-4-((1-Iodonon-8-en-2-yloxy)methyl)-2-methoxy-1-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethoxy)benzene 56d**: Performing the general procedure 6 with **14b** (0.78 g, 1.4 mol), **14d** (1.3 g, 2.0 mmol) and NaI (2.5 g, 17 mmol) gave a mixture of **56b** and **56d** (1.8 g, 99%) as light brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29-1.42 (m, 6H) (a, a'), 1.60-1.68 (m, 2H) (a, a'), 2.04 (q, *J* = 7.2, 7.2 Hz, 2H) (a, a'), 3.26-3.32 (m, 3H) (a, a'),

3.37 (s, 3H) (a'), 3.40 (s, 3H) (a), 3.54-3.56 (m, 2H) (a'), 3.57-3.59 (m, 2H) (a), 3.64-3.75 (m, 12H) (a + a'), 3.86-3.91 (m, 5H) (a, a'), 4.17-4.22 (m, 2H) (a, a'), 4.44 (d, *J* = 11.5 Hz, 1 H) (a, a'), 4.56 (d, *J* = 11.5 Hz, 1H) (a, a'), 4.93-5.02 (m, 2H) (a, a'), 5.76-5.85 (ddt, *J* = 17.0, 10.3, 6.6, 6.4 Hz, 1H) (a, a'), 6.84-6.91 (m, 2H) (a, a'), 6.97 (s, 1H) (a, a').

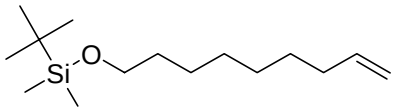


General procedure 7: (3*RS*,*5*S)-3-((*S*)-2-(3-Methoxy-4-(2-methoxyethoxy)benzyloxy)non-8-enyl)-5-methyl-3-(phenylthio)-dihydrofuran-2(3H)-one (*S*,*S*)-15a and **(3*RS*,5*S*)-3-((*R*)-2-(3-Methoxy-4-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzyloxy)non-8-enyl)-5-methyl-3-(phenylthio)-dihydrofuran-2(3H)-one (*R*,*S*)-15c**: NaHMDS (1 M in THF, 3.2 mL, 3.2 mmol) was added to a solution of (*S*)-5-methyl-3-phenylsulfanyldihydrofuran-2-one (*S*)-**49** (0.70 g, 3.2 mmol) in THF (20 mL) at 0 ^{o}C. The mixture was stirred for 30 min at this temperature and then a solution of **M56a** (1.5 g, 3.0 mmol) in HMPA (3.5 mL) was added. The reaction mixture was allowed to warm to room temperature over 2 h followed by refluxing it for 14 h. Then the reaction mixture was cooled to room temperature and quenched with saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2) to give (*S*,*S*)-**15a** (25% ethyl acetate/hexanes, 0.50 g, 76%) followed by (*R*,*S*)-**15c** (50% ethyl acetate/hexanes,

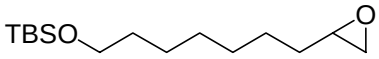
0.79 g, 69%) as oils. For **15a**: ^{1}H NMR (500 MHz, $CDCl_3$, major isomer) δ 1.06 (d, *J* = 6.4 Hz, 3H), 1.22-1.41 (m, 6H), 1.54-1.62 (m, 2H), 1.95 (dd, *J* = 13.5, 7.1 Hz, 2H), 2.00-2.15 (m, 4H), 2.71 (dd, *J* = 13.5, 7.6 Hz, 2H), 3.44 (s, 3H), 3.67-3.72 (m, 1H), 3.77-3.80 (m, 2H), 3.86 (s, 3H), 4.14-4.16 (m, 2H), 4.24 (d, J = 10.5 Hz, 1H), 4.28-4.34 (m, 1H), 4.42 (d, *J* = 10.5 Hz, 1H), 4.94-5.05 (m, 2H), 5.77-5.86 (ddt, *J* = 17.0, 10.1, 6.9 Hz, 1H), 6.80-6.93 (m, 3H), 7.34-7.43 (m, 3H), 7.57 (d, *J* = 6.9 Hz, 2H); ^{13}CNMR (75 MHz, $CDCl_3$, major isomer) δ 21.3, 24.3, 28.9, 29.3, 33.7, 42.1, 42.3, 55.2, 56.0, 59.2, 68.8, 70.9, 71.1, 73.2, 76.4, 112.4, 113.9, 114.4, 120.6, 129.1, 129.9, 130.8, 131.8, 137.1, 139.0, 148.0, 149.8, 176.8. MS *m/z* 542 (M^+). For **15c** ^{1}H NMR (500 MHz, $CDCl_3$, major isomer) δ 1.18 (d, *J* = 6.4 Hz, 3H), 1.23-1.41 (m, 6H), 1.50-1.63 (m, 2H), 1.89 (dd, *J* = 14.2, 6.4 Hz, 1H), 1.95-2.11 (m, 4H), 2.85 (dd, *J* = 14.0, 7.6 Hz, 1H), 3.38 (s, 3H), 3.55-3.56 (m, 2H), 3.64-3.70 (m, 4H), 3.74-3.75 (m, 2H), 3.84-3.89 (m, 5H), 3.93-3.96 (m, 1H), 4.15-4.21 (m, 2H), 4.36-4.44 (m, 2H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.94-5.02 (m, 2H), 5.80 (ddt, *J* = 17.0, 10.3, 6.9 Hz, 1H), 6.80-6.93 (m, 3H), 7.33-7.42 (m, 3H), 7.57 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$, major isomer) δ 21.5, 24.5, 28.9, 29.4, 33.6, 33.7, 39.6, 40.2, 54.9, 56.0, 59.1, 68.7, 69.7, 70.4, 70.6, 70.7, 70.9, 72.0, 73.3, 75.6, 111.8, 113.6, 114.4, 120.0, 129.1, 129.8, 130.5, 131.6, 136.8, 139.0, 147.8, 149.7, 177.5 HRMS for $C_{35}H_{50}O_8SNa$ $(M + Na)^+$: calcd 653.3124; found 653.3109.



(3*RS*,5*R*)-3-((*S*)-2-(3-Methoxy-4-(2-(2-methoxyethoxy)ethoxy)benzyloxy)non-8-enyl)-5-methyl-3-(phenylthio)-dihydrofuran-2(3H)-one (*S*,*R*)-**15b** and **(3*RS*,5*R*)-3-((*R*)-2-(3-Methoxy-4-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethoxy)benzyloxy)non-8-enyl)-5-methyl-3-(phenylthio)-dihydrofuran-2(3H)-one (*S*,*R*)-15d**: Following the general procedure 7 with **M56b** (1.8 g, 3.2 mmol) and (*R*)-**49** (0.71 g, 3.4 mmol) gave, after purification by flash column chromatography, **15b** (40% ethyl acetate/hexanes) (0.57 g, 72%) followed by **15d** (60% ethyl acetate/hexanes) (0.88 g, 70%) as colorless oils. For **15b**: ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 1.18 (d, *J* = 6.6 Hz, 3H), 1.24-1.39 (m, 6H), 1.52-1.64 (m, 2H), 1.66 (s, 1 H), 1.85-1.94 (m, 1H), 1.98-2.13 (m, 4H), 2.85 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.39 (s, 3H), 3.56-3.58 (m, 2H), 3.71-3.74 (m, 2H), 3.84-3.96 (m, 6H), 4.19 (t, *J* = 5.2 Hz, 2H), 4.35-4.44 (m, 2H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.92-5.03 (m, 2H), 5.79 (ddt, *J* = 16.9, 10.0, 6.6 Hz, 1H), 6.81-6.94 (m, 3H), 7.32-7.43 (m, 2H), 7.57 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer) δ 21.3, 24.4, 28.7, 29.2, 33.6, 39.4, 40.1, 54.7, 55.9, 59.0, 68.5, 69.5, 70.2, 70.6, 71.8, 73.1, 75.4, 111.7, 113.4, 114.3, 119.9, 128.9, 129.6, 130.3, 131.4, 136.6, 138.8, 147.6, 149.5, 177.3. :For **15d** ^{1}H NMR (500 MHz, $CDCl_3$, major isomer) δ 1.05 (d, *J* = 6.4 Hz, 3H), 1.28-1.42 (m, 6H), 1.48-1.63 (m, 2H), 1.91-2.11 (m, 5H), 2.71 (dd, *J* = 13.7, 7.3 Hz, 1H), 3.36 (s, 3H), 3.53-3.54 (m, 2H), 3.62-3.68-3.72 (m, 11H), 3.84 (s, 3H), 3.85-3.89 (m, 2H), 4.15 (t, *J* = 5.3 Hz, 2H), 4.22 (d, *J* = 10.5 Hz, 1H), 4.26-4.34 (m, 2H), 4.41 (d, *J* = 10.5 Hz, 2H), 4.94 (d, *J* = 10.1 Hz, 1H), 4.93-5.01 (m, 2H), 5.80 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 6.79-6.90 (m, 3H), 7.32-7.40 (m, 3H), 7.56 (d, *J* = 6.9 Hz, 2H); 13C NMR (126 MHz, $CDCl_3$, major isomer) δ 21.0, 24.1, 28.6, 29.1, 33.3, 33.5, 41.8, 42.1, 54.9, 55.7, 58.8, 68.5, 69.5, 70.3, 70.4, 70.6, 70.7, 71.8, 72.9, 76.0, 112.2, 113.5, 114.2, 120.3, 128.8, 129.6, 130.5, 131.4, 136.6, 136.8, 138.7, 147.7, 149.5, 176.5; IR (neat) cm^{-1} 1763, 1592, 1514, 1455; HRMS for $C_{37}H_{54}O_9SNa$ $(M + Na)^+$: calcd 697.3386; found 697.3403.

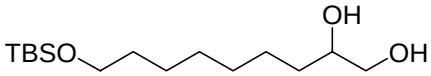


***tert*-Butyldimethyl-non-8-enyloxy-silane**: *tert*-Butyldimethylsilyl chloride (19 g, 0.13 mol) was added to a stirred solution of non-8-en-1-ol (14 g, 0.1mol) and imidazole (9.3 g, 0.14 mol) in dichloromethane at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 20 min, 1 h at room temperature. The reaction mixture was diluted with water, organic layer was separated and the aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated to give *tert*-butyldimethyl-non-8-enyloxy-silane (25 g, 99%) as colorless oil. The crude reaction mixture was taken to the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.91 (s, 9H), 1.32 (s, 8H), 1.40-1.55 (m, 2H), 2.05 (q, *J* = 7.0 Hz, 2H), 3.61 (t, *J* = 6.3 Hz, 2H), 4.92-5.02 (m, 1H), 5.74-5.88 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ-5.2, 18.4, 25.9, 26.1, 29.0, 29.2, 29.4, 33.0, 33.9, 63.3, 114.2, 139.2; IR (neat) cm^{-1} 2933, 2858, 1471; EIMS *m/z* 241 (M − CH_3), 199 (M − C_4H_9); HRMS for (M − CH_3)$^{+}$ $C_{14}H_{29}OSi$: calcd 241.1987; found 241.1984.



(7*R*,7*S*)-*tert*-Butyldimethyl-(7-oxiranylheptyloxy)silane 63: *m*-Chloroperbenzoic acid (25 g, 0.11 mol, 75% w/w in H_2O) was added to a solution of *tert*-butyldimethyl-non-8-enyloxysilane (25 g, 98 mmol) in dichloromethane (325 mL) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 20 min, room temperature for 1 h and treated with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was further extracted with dichloromethane. The combined

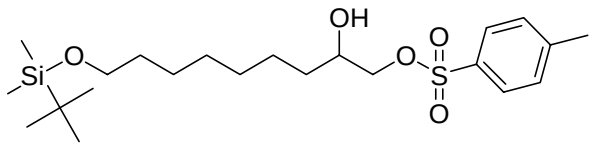
organic layers were dried over $MgSO_4$, concentrated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, 20% Ethyl acetate/hexanes) to give *tert*-butyldimethyl-(7-oxiranylheptyloxy)silane (26 g, 98%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ0.02 (s, 6H), 0.87 (s, 9H), 1.30-1.51 (m, 12H), 2.43 (dd, J = 4.9, 2.7 Hz, 1H), 2.69-2.73 (m, 1H), 2.84-2.90 (m, 1H), 3.57 (t, J = 6.59 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, 18.4, 25.7, 26.0, 29.4, 29.5, 32.5, 32.8, 47.1, 52.3, 63.2; IR (neat) 2933, 2856, 1464; EIMS *m/z* 215 (M $-C_4H_9)^+$; HRMS for (M $-C_4H_9)^+$ $C_{11}H_{23}O_2Si$: calcd 215.1467; found 215.1471.



9-(*tert*-Butyldimethylsilanyloxy)nonane-1,2-diol 65: The (*R,R*)-Jacobson catalyst[7] (0.28 g, 0.46 mmol) was dissolved in *tert*-butyldimethyl-(7-oxiranylheptyloxy)silane (25 g, 92 mmol), AcOH (110 μL, 1.8 mmol) and 0.3 mL THF. The solution was cooled to 0 °C, treated with H_2O (0.74 mL, 41 mmol) and stirred for 12 h at room temperature. The reaction mixture was distilled bulb-to-bulb (Kugelrohr) under reduced pressure (0.08 mm Hg, 120-130 °C) to remove residual epoxide (14 g, 52 mmol) followed by second distillation (0.08 mm Hg, 180-190 °C) to yield (*S*)-9-(*tert*-Butyldimethylsilanyloxy)nonane-1,2-diol (12 g, 43%, > 99% enantiomeric excess based on Mosher ester analysis) as colorless oil; Similar procedure with the above recovered epoxide (14g, 51.3 mmol) and (*S,S*)-Jacobson catalyst (0.28 g, 0.46mmol) resulted in (*R*)-9-(*tert*-butyl-dimethyl silanyloxy) nonane-1,2-diol (12 g, 45%, > 99% ee by Mosher ester analysis)[8] as colorless oil: $[\alpha]_D^{25}$ for (*R*)-diol: −0.24 (c 5.83); for (*S*)-diol: 1.07 (c 1.49); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.87 (s, 9H), 1.28-1.50 (m, 12H), 3.38-3.44 (m, 1H), 3.57 (t, J = 6.6 Hz,

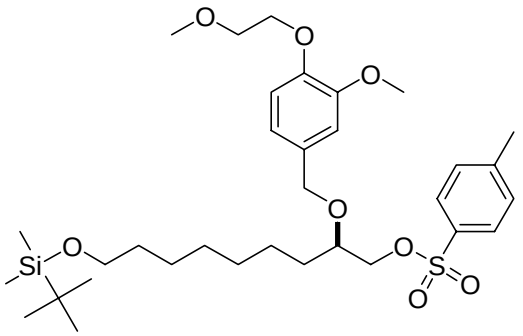
[7] Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobson, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 1307.
[8] Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc*. **1973**, *24*, 512.

2H), 3.65-3.78 (br m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.2, 18.4, 25.6, 25.8, 26.0, 29.4, 29.7, 32.9, 33.1, 63.3, 66.8, 72.4. EIMS *m/z* 259 $(M - CH_3O)^+$; HRMS for $(M - CH_3O)^+$ $C_{14}H_{31}O_2Si$: calcd 259.2093; found 259.2091.

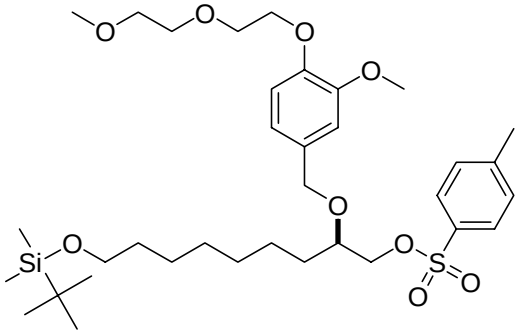


Benzenesulfonic acid 9-(*tert*-butyldimethylsilanyloxy)-2-hydroxynonyl ester 66:

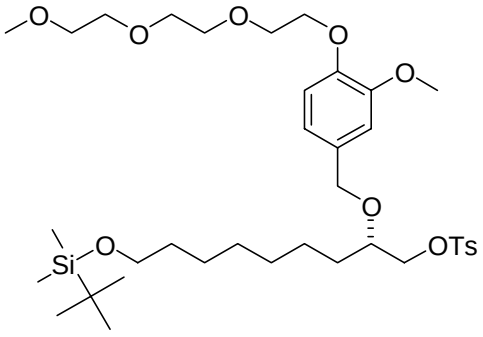
To a solution of (*R*)-9-(*tert*-butyldimethylsilanyloxy)nonane-1,2-diol (12 g, 41 mmol) in CH_2Cl_2 (80 mL) were added Bu_2SnO (2.0 g, 8.1 mmol), *p*-TsCl (7.7 g, 41 mmol), and Et_3N (5.6 mL, 41 mmol). After 3 h, the reaction mixture was concentrated and the crude product was purified by flash chromatography (SiO_2, EtOAc/hexanes = 1:3) to yield toluene-4-sulfonic acid (*R*)-9-(*tert*-butyldimethylsilanyloxy)-2-hydroxynonyl ester (14 g, 76%) as white waxy solid; similar procedure with (*S*)-diol (11 g, 38 mmol) yielded (*S*)-sulfonyl ester (12 g, 72%) as while waxy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.86 (s, 9H), 1.20-1.48 (m, 12H), 2.41 (s, 3H), 2.54 (br s, 1H), 3.56 (t, *J* = 6.4 Hz, 2H), 3.74-3.89 (m, 2H), 3.98 (dd, *J* = 9.9, 3.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3, 18.3, 21.5, 25.1, 25.6, 25.9, 29.2, 29.4, 32.6, 32.7, 63.2, 69.2, 73.9, 127.9, 129.9, 132.7, 144.9; HRMS for $C_{22}H_{40}O_5SSiNa$: calcd 467.2263; found 467.2287.



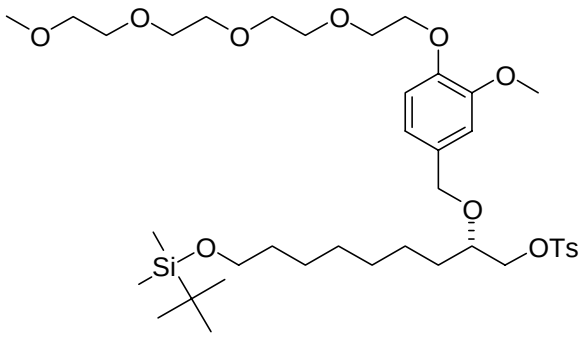
General procedure 8: Toluene-4-sulfonic acid (*R*)-9-(*tert*-butyldimethylsilanyloxy)-2-[3-methoxy-4-(2-methoxyethoxy)benzyloxy]nonyl ester (67a): A solution of (*R*)-9-(*tert*-butyldimethylsilanyloxy)-2-hydroxynonyl ester (2.3 g, 5.2 mmol), 2,2,2-trichloroacetimidic acid 3-methoxy-4-(2-methoxyethoxy)benzyl ester (3.7 g, 10 mmol) and 10-camphorsulfonic acid (0.12 g, 0.52 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 24 h, and then diluted with saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated and the crude product was purified by flash chromatography (SiO_2, EtOAc/hexanes = 3:7) to yield **67a** (2.0 g, 60%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.18-1.46 (m, 12 H), 2.43 (s, 3H), 3.44 (s, 3H), 3.55-3.60 (m, 3H), 3.76-3.79 (m, 2H), 3.86 (s, 3H), 4.00 (t, *J* = 4.39 Hz, 2H), 4.14 (t, *J* = 4.39 Hz, 2H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 6.74-6.86 (m, 3H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, 18.4, 21.6, 25.1, 25.7, 26.0, 29.3, 29.5, 31.3, 32.8, 55.8, 59.1, 63.2, 68.2, 70.9, 71.7, 72.0, 76.1, 111.6, 113.1, 120.3, 127.9, 129.9, 131.3, 132.8, 144.9, 147.8, 149.4; IR (neat) 2927, 2856, 1597, 1514, 1461; HRMS $(M + Na)^+$ for $C_{33}H_{54}O_8SiSNa$: calcd 661.3206; found 661.3209.



Toluene-4-sulfonic acid (*R*)-9-(*tert*-butyldimethylsilanyloxy)-2-{3-methoxy-4-[2-(2-methoxy ethoxy)ethoxy]benzyloxy}nonyl ester (67b): Performing the general procedure 8 with (*R*)-9-(*tert*-butyldimethylsilanyloxy)-2-hydroxynonyl ester (2.3 g, 5.2 mmol), 2,2,2-trichloroacetimidic acid 3-methoxy-4-[2-(2-methoxyethoxy)ethoxy]benzyl ester (4.6 g, 11 mmol) and 10-camphorsulfonic acid (0.12 g, 0.52 mmol) gave, after purification by flash chromatography (SiO_2,ethyl acetate/hexanes = 4:6), **67b** (2.2 g, 62%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.23-1.48 (m, 12H), 2.42 (s, 3H), 3.36 (s, 3H), 3.52-3.62 (m, 5H), 3.68-3.73 (m, 2H), 3.82 (s, 3H), 3.86 (t, *J* = 5.5 Hz, 2H), 3.94-4.06 (m, 2H), 4.17 (t, *J* = 4.9 Hz, 2H), 4.40 (d, *J* = 11.2 Hz, 1H), 4.47 (d, *J* = 11.2 Hz, 1H), 6.74-6.85 (m, 3H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3, 21.5, 25.1, 25.2, 25.7, 25.9, 29.2, 29.5, 31.3, 32.8, 55.9, 58.9, 63.1, 68.7, 69.6, 70.6, 71.6, 71.9, 72.0, 76.2, 112.0, 113.8, 120.3, 127.9, 129.8, 131.5, 133.1, 144.7, 148.0, 149.7; IR (neat) 2928, 2856, 1597, 1514, 1461.

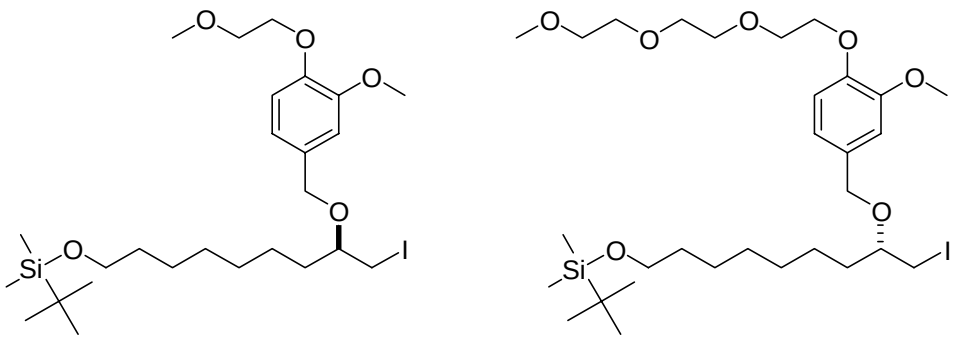


Toluene-4-sulfonic acid (*S*)-9-(*tert*-butyldimethylsilanyloxy)-2-(3-methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}benzyloxy)nonyl ester (67c): Performing the general procedure 8 with (*S*)-9-(*tert*-butyldimethylsilanyloxy)-2-hydroxynonyl ester (2.3 g, 5.2 mmol) 2,2,2-trichloroacetimidic acid 3-methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}benzyl ester (5.1 g, 11 mmol) and 10-camphorsulfonic acid (0.12 g, 0.52 mmol) gave, after purification by flash chromatography (SiO_2, ethyl acetate/hexanes = 1:1), **67c** (2.4 g, 63%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.22-1.48 (m, 12H), 2.43 (s, 3H), 3.36 (s, 3H), 3.53-3.60 (m, 5H), 3.62-3.68 (m, 4H), 3.71-3.74 (m, 2H), 3.83 (s, 3H), 3.87 (t, *J* = 5.3 Hz, 2H), 3.97-4.05 (m, 2H), 4.16 (t, *J* = 5.0 Hz, 2H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 6.73-6.76 (m, 1H), 6.84-6.86 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.2, 18.4, 21.7, 25.2, 25.8, 26.0, 29.4, 29.6, 31.4, 32.9, 55.9, 59.1, 63.3, 68.6, 69.6, 70.6, 70.7, 70.9, 71.7, 72.0, 72.1, 76.2, 111.7, 113.5, 120.3, 128.0, 129.9, 131.3, 132.9, 144.8, 148.0, 149.6; IR (neat) 2927, 2856, 1597, 1514, 1461; HRMS $(M + Na)^+$ for $C_{37}H_{62}O_{10}SiSNa$: calcd 749.3731; found 749.3740.



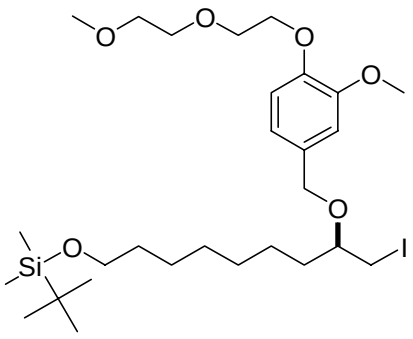
Toluene-4-sulfonic acid (*S*)-9-(*tert*-butyldimethylsilanyloxy)-2-[3-methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)benzyloxy]nonyl ester (67d): Performing the general procedure 8 with (*S*)-9-(*tert*-butyldimethylsilanyloxy)-2-hydroxynonyl ester (2.3 g, 5.2 mmol)

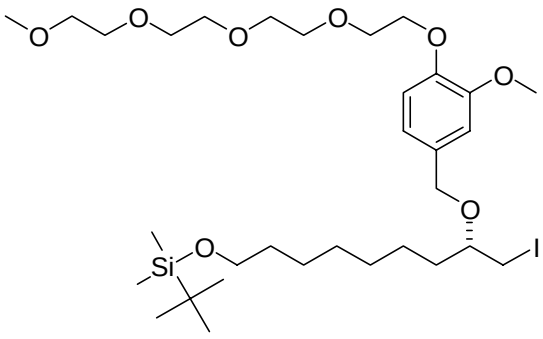
2,2,2-trichloroacetimidic acid 3-methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy) benzyl ester (5.5 g, 11 mmol) and 10-camphorsulfonic acid (0.12 mg, 0.52 mmol) gave, after purification by flash chromatography (SiO_2, ethyl acetate/hexanes = 3:2), **67d** (2.4 g, 63%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.16-1.50 (m, 12H), 2.41 (s, 3H), 3.35 (s, 3H), 3.52 (t, *J* = 4.6 Hz, 2H), 3.57 (t, *J* = 6.6 Hz, 2H), 3.61-3.67 (m, 9H), 3.71 (t, *J* = 4.6 Hz, 2H), 3.82 (s, 3H), 3.84-3.87 (m, 2H), 3.96-4.04 (m, 2H), 4.15 (t, *J* = 5.0 Hz, 2H), 4.40 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 6.75 (m, 1H), 6.81-6.86 (m, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ -5.4, 18.2, 21.5, 24.9, 25.5, 25.8, 29.1, 29.3, 31.1, 32.6, 55.7, 58.8, 63.0, 68.5, 69.4, 70.3, 70.4, 70.6, 71.5, 71.7, 71.8, 75.9, 111.6, 113.3, 120.1, 127.7, 129.7, 131.1, 132.7, 144.6, 147.7, 149.5; IR (neat) 2928, 1514, 1461; HMRS $(M + Na)^+$ for $C_{39}H_{66}O_{11}SiSNa$: calcd 793.3993; found 793.3977.



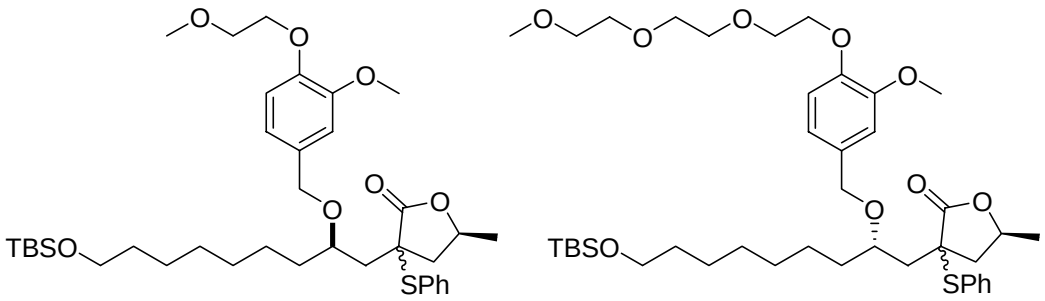
General procedure 9: *tert*-Butyl-{(*R*)-9-iodo-8-[3-methoxy-4-(2-methoxyethoxy) benzyloxy] nonyloxy}dimethylsilane (68a) and ***tert*-Butyl-[(*S*)-9-iodo-8-(3-methoxy-4-{2-[2-(2-methoxy ethoxy)ethoxy]ethoxy}benzyloxy)nonyloxy] dimethylsilane (68c):** A solution of **67a** (1.9 g, 3.0 mmol), **67c** (2.3 g, 3.2 mmol) and NaI (9.2 g, 61 mmol) in acetone (35 mL) was refluxed for 20 h followed by concentration under reduced pressure. The concentrate was treated with water and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and

concentrated to yield a mixture of **68a** and **68c** as light brown oil (3.9 g, 98%) which was used in next step with out further purification. However, characterization purposes a small sample (0.1 g) of the mixture **M68a** was subjected to flash column chromatography (SiO_2) gave **68a** (ethyl acetate/hexanes = 1:4) followed by **68c** (ethyl acetate/hexanes = 1:1) as colorless oils. For **68a**: ^{1}H NMR (500 MHz, $CDCl_3$) ẟ ^{1}H NMR (500 MHz,$CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.30-1.64 (m, 12H), 3.21-3.33 (m, 3H), 3.46 (s, 3H), 3.60 (t, *J* = 6.6 Hz, 2H), 3.76-3.82 (m, 2H), 3.88 (s, 3H), 4.18 (t, *J* = 4.9 Hz, 2H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 6.84-6.89 (m, 2H), 6.98 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ‑5.2, 10.5, 18.5, 25.3, 25.8, 26.1, 29.4, 29.6, 32.9, 34.7, 56.0, 59.4, 63.3, 68.5, 71.0, 71.4, 77.7, 111.9, 113.6, 120.4, 131.7, 147.7, 149.7; IR (neat) 2929, 2857, 1593, 1514, 1463; HRMS (ESI) $(M + Na)^+$ for $C_{26}H_{47}O_5SiINa$: calcd 617.2135; found 617.2152. For **68c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.30-1.62 (m, 12H), 3.26-3.34 (m, 3H), 3.39 (s, 3H), 3.55-3.63 (m, 4H), 3.65-3.72 (m, 4H), 3.75 (dd, *J* = 6.2, 3.4 Hz, 2H), 3.88-3.90 (m, 5H), 4.17-4.22 (m, 2H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 6.87-6.89 (m, 2H), 6.98 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.2, 10.5, 18.4, 25.3, 25.8, 26.1, 29.4, 29.6, 32.9, 34.7, 56.0, 59.1, 63.3, 68.6, 69.6, 70.5, 70.6, 70.7, 71.3, 71.9, 77.6, 111.9, 113.5, 120.4, 131.4, 147.9, 149.6; IR (neat) 2929, 2857, 1593, 1515; HRMS $(M + Na)^+$ for $C_{30}H_{55}O_7SiINa$: calcd 705.2660; found 705.2686.





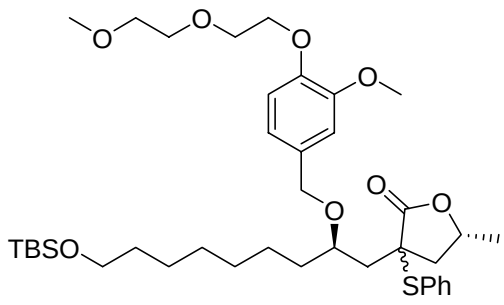
***tert*-Butyl-{(*R*)-9-iodo-8-{3-methoxy-4-[2-(2-methoxyethoxy)ethoxy]benzyloxy} nonyloxy) dimethyl-silane (68b)** and ***tert*-Butyl-{(*S*)-9-iodo-8-[3-methoxy-4-(2-{2-[2-(2-methoxyethoxy) ethoxy]ethoxy}ethoxy)benzyloxy]nonyloxy}dimethylsilane (68d):** Performing the general procedure 9 with **67b** (2.1 g, 3.1 mmol), **67d** (2.4g, 3.1 mmol) and NaI (9.2 g, 61 mmol) gave a mixture **M68b** as light brown oil (4.2 g, 99%) which was used in next step with out further purification. However, subjecting a small sample (0.1 g) of the mixture **M68b** (0.1 g) to flash column chromatography (SiO_2) gave **68b** (ethyl acetate/hexanes 2:3) followed by **68d** (ethyl acetate/hexanes 3:2) as colorless oils. For **68b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.26-1.68 (m, 12H), 3.25-3.33 (m, 3H), 3.41 (s, 3H), 3.58-3.62 (m, 4H), 3.72-3.76 (m, 2H), 3.88 (s, 3H), 3.89-3.91 (m, 2H), 4.20 (t, *J* = 5.3 Hz, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 6.88 (s, 2H), 6.97 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.2, 10.6, 18.5, 25.3, 25.8, 26.1, 29.4, 29.6, 32.9, 34.7, 56.1, 59.2, 63.3, 68.5, 69.5, 70.7, 71.3, 71.9, 77.6, 111.9, 113.4, 120.5, 131.5, 147.7, 149.5; IR (neat) 2929, 2857, 1593, 1515, 1463; HRMS (ESI) $(M + Na)^+$ for $C_{28}H_{51}O_6SiINa$: calcd 661.2397; found 661.2407. For **68d**: 1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.30-1.61 (m, 12H), 3.24-3.33 (m, 3H), 3.37 (s, 3H), 3.52-3.56 (m, 2H), 3.58-3.62 (m, 2H), 3.62-3.69 (m, 8H), 3.71-3.75 (m, 2H), 3.84-3.89 (m, 5H), 4.20 (t, *J* = 5.0 Hz, 2H), 4.43 (d, *J* = 11.0 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 1H), 6.83-6.89 (m, 2H), 6.96 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.4, 10.3, 18.1, 25.0, 25.5, 25.8, 29.1, 29.3, 32.6, 34.4, 55.7, 58.8, 63.0, 68.4, 69.4, 70.3, 70.4, 70.6, 71.0, 71.7, 77.2, 111.6, 113.3, 120.1, 131.1, 147.7, 149.4; IR (neat) IR (neat) 2929, 2857, 1593, 1515, 1463; HRMS (ESI) $(M + Na)^+$ for $C_{32}H_{59}O_8SiINa$: calcd 749.2922; found 749.2944.

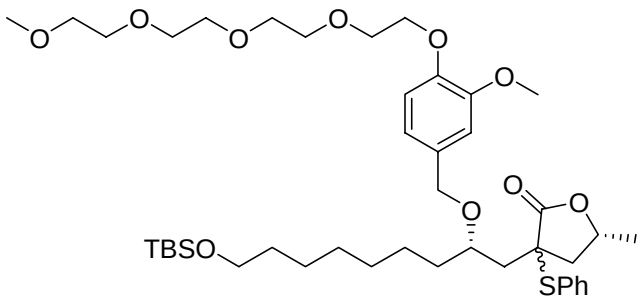


General procedure 10: (3*RS*,5*S*)-3-{(*R*)-9-(*tert*-Butyldimethylsilanyloxy)-2-[3-methoxy-4-(2-methoxyethoxy)benzyloxy]nonyl}-5-methyl-3-phenylsulfanyldihydrofuran-2-one 61a and **(3*RS*,5*S*)-3-[(*S*)-9-(*tert*-Butyldimethylsilanyloxy)-2-(3-methoxy-4-{2-[2-(2-methoxyethoxy) ethoxy]ethoxy}benzyloxy)nonyl]-5-methyl-3-phenylsulfanyldihydrofuran-2-one 61c:**

A solution of NaHMDS (1.0 M in THF, 5.9 mL, 5.9 mmol) was added to a solution of (*S*)-5-Methyl-3-phenylsulfanyldihydrofuran-2-one (*S*)-**49** (1.2 g, 5.9 mmol) in THF (20 mL) at 0 ^{o}C. The mixture was stirred for 30 min at this temperature and then a solution of iodide **M68a** (3.6 g, 5.6 mmol) in HMPA (3.5 mL) was added. The reaction mixture was allowed to warm to room temperature over 2 h followed by refluxing it for 14 h. Then the reaction mixture was cooled to room temperature and quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$ followed by concentration under reduced pressure. The crude product was purified by flash chromatography (SiO_2) to gave **61a** (25% ethyl acetate/hexanes) (1.3 g, 69%) followed by **61c** (50% ethyl acetate/hexanes) (1.5 g, 71%) as an oils. For **61a**: ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.03 (d, *J* = 6.0 Hz, 6H), 1.21-1.37 (m, 10H), 1.48-1.56 (m, 2H), 1.90-2.15 (m, 3H), 2.69 (dd, *J* = 13.7, 7.1 Hz, 1H), 3.41 (s, 3H), 3.60 (t, *J* = 6.6 Hz, 2H), 3.66-3.75 (m, 3H), 3.84 (s, 3H), 4.10-4.14 (m, 2H), 4.22 (d, *J* = 10.4 Hz,

1H), 4.25-4.33 (m, 1H), 4.41 (d, *J* = 10.4 Hz, 1H), 6.78-6.88 (m, 2H), 6.92 (s, 1H), 7.29-7.40 (m, 3H), 7.55 (dd, *J* = 8.0, 1.4 Hz, 2H); IR (neat) 2929, 1763, 1516, 1458. For **61c**: ^{1}H NMR (500 MHz, $CDCl_3$, major isomer) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.21-1.28 (m, 8H), 1.46-1.52 (m, 3H), 1.55-1.62 (m, 1H), 1.86 (dd, *J* = 14.2, 6.0 Hz, 1H), 1.92- 2.09 (m, 2H), 2.81 (dd, *J* = 14.2, 7.8 Hz, 1H), 3.35 (s, 3H), 3.51-3.52 (m, 2H), 3.58 (t, *J* = 6.4 Hz, 2H), 3.62-3.66 (m, 4H), 3.71-3.72 (m, 2H), 3.84- 3.94 (m, 6H), 4.15 (t, *J* = 5.3 Hz, 2H), 4.32-4.40 (m, 2H), 4.53 (d, *J* = 11.0 Hz, 1H), 6.78-6.91 (m, 3H), 7.30-7.38 (m, 3H), 7.54 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.3, 18.3, 21.3, 24.5, 25.7, 25.9, 29.3, 29.7, 32.8, 33.4, 39.4, 40.1, 54.8, 55.9, 58.9, 63.2, 68.6, 69.5, 70.2, 70.4, 70.6, 70.7, 71.8, 73.0, 75.4, 76.8, 77.3, 111.7, 113.5, 119.8, 128.9, 129.6, 130.3, 131.4, 136.6, 147.6, 149.5, 177.3; IR (neat) 2929, 1763, 1515, 1463; MS *m/z* 785 $(M + Na)^+$; HMRM (ESI) for $C_{41}H_{66}O_9SSiNa$: calcd 785.4095; found 785.4124.

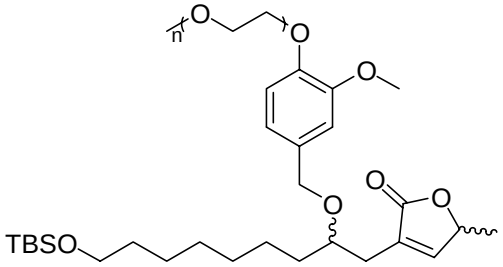




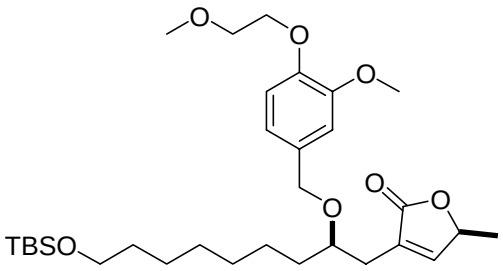
(3*RS*,5*R*)-3-((*R*)-9-(*tert*-Butyldimethylsilanyloxy)-2-{3-methoxy-4-[2-(2-methoxyethoxy)ethoxy]benzyloxy}nonyl)-5-methyl-3-phenylsulfanyldihydrofuran-2-one 61b and **(3*RS*,5*R*)-3-{(*S*)-9-(*tert*-Butyldimethylsilanyloxy)-2-[3-methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)benzyloxy]nonyl}-5-methyl-3-phenylsulfanyldihydrofuran-2-one 61d:**

Performing the general procedure 10 with NaHMDS (1.0 M in THF, 6.0 mL, 6.0 mmol), (*R*)-5-Methyl-3-phenylsulfanyldihydrofuran-2-one (*R*)-**49** (1.3 g, 6.0 mmol) and iodide **M68b** (3.9 g,

5.7 mmol) gave, after purification by flash column chromatography, **61b** (2:3 ethyl acetate/hexanes) (1.5 g, 73%) as pale yellow oil followed by **61d** (7:3 ethyl acetate/hexanes) (1.6 g, 70%) as pale yellow oil: For **61b**: ^{1}H NMR (500 MHz, $CDCl_3$, major isomer) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.24-1.32 (m, 8H), 1.49-1.55 (m, 3H), 1.57-1.63 (m, 1H), 1.88 (dd, *J* = 14.2, 6.0 Hz, 1H), 1.94-1.97 (m, *J* = 2.3 Hz, 1H), 2.03-2.10 (m, 1H), 2.84 (dd, *J* = 14.2, 7.8 Hz, 1H), 3.38 (s, 3H), 3.56-3.57 (m, 2H), 3.60 (t, *J* = 6.6 Hz, 2H), 3.71-3.73 (m, 2H), 3.86-3.89 (m, 5H), 3.90-3.95 (m, 1H), 4.18 (t, *J* = 5.3 Hz, 2H), 4.34-4.43 (m, 2H), 4.55 (d, *J* = 11.0 Hz, 1H), 6.81-6.92 (m, 3H), 7.32 - 7.41 (m, 3H), 7.56 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.2, 18.4, 21.4, 24.7, 25.8, 26.0, 29.4, 29.9, 32.9, 33.6, 39.5, 40.2, 54.9, 56.0, 59.1, 63.3, 68.7, 69.7, 70.3, 70.8, 72.0, 73.2, 75.6, 76.8, 77.4, 111.9, 113.7, 120.0, 129.0, 129.7, 130.5, 131.6, 136.8, 147.8, 149.7, 177.4; IR (neat) 2929, 1763, 1515, 1463; EIMS *m/z* 646.7 (M − C_4H_9); For **61d**: ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.05 (d, *J* = 6.3 Hz, 3H), 1.23-1.36 (m, 8H), 1.51-1.61 (m, 4H), 1.95 (dd, *J* = 13.7 Hz, 7.1 Hz, 1H), 2.03-2.18 (m, 2H), 2.70 (dd, *J* = 13.6, 7.5 Hz, 1H), 3.38 (s, 3H), 3.54- 3.74 (m, 15H), 3.86-3.89 (m, 5H), 4.09-4.25 (m, 3H), 4.27-4.36 (m, 1H), 4.42 (d, *J* = 10.4 Hz, 1H), 6.79-6.92 (m, 3H), 7.34-7.41 (m, 3H), 7.55-7.58 (m, 2H); ^{13}C NMR (76 MHz, $CDCl_3$) δ −5.2, 18.4, 21.2, 24.4, 25.8, 26.0, 29.4, 29.8, 32.9, 33.5, 42.0, 42.3, 55.2, 55.9, 59.1, 63.3, 68.6, 69.6, 70.6, 73.2, 76.3, 112.2, 113.4, 120.5, 129.0, 129.8, 130.6, 131.5, 137.0, 147.8, 149.5, 176.8; IR (neat) 2929, 1763, 1516, 1458; HRMS (ESI) $(M + Na)^+$ for $C_{43}H_{70}O_{10}SSiNa$: calcd 829.4357; found 829.4396.



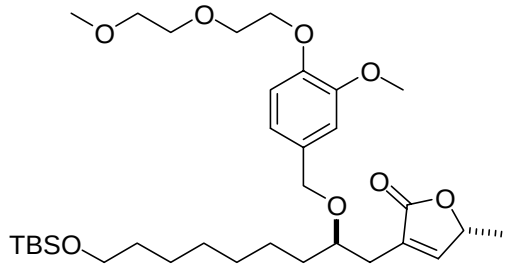
Lactone mixture M61: *m*-chloroperbenzoic acid (0.28 g, 1.6 mmol) was added to a solution of a mixture of **61a** (0.27 g, 0.4 mmol), **61b** (0.29 g, 0.4 mmol), **61c** (0.31 g, 0.4 mmol), **61d** (0.32 g, 0.4 mmol) in CH_2Cl_2 (30 mL) at 0 ^oC. The reaction mixture was stirred for 30 min and then quenched with saturated $NaHCO_3$ solution. Layers were separated and the aqueous layer was further extracted with CH_2Cl_2 followed by drying the combined organic layers with $MgSO_4$ and concentration. The crude product in 3.5 mL of DMF was heated in microwave[9] (personal chemistry microwave, 150W, ramped to 160 ^oC over 2 min and heated for 5 min at that temperature) for 5 min at 160 ^oC. Removal of DMF under reduced pressure followed by purification by flash column chromatography on silica gel under gradient elution gave **69a** (0.20 g, 88%) (25% ethyl acetate/hexanes), **69b** (0.21 g, 85%) (40% ethyl acetate/hexanes), **69c** (0.23 g, 89%) (60% ethyl acetate/hexanes) and **69d** (0.24 g, 85%) (80% ethyl acetate/hexanes) as pale yellow oils.



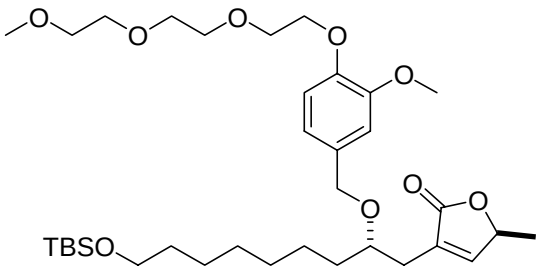
(*S*)-3-{(*R*)-9-(*tert*-Butyldimethylsilanyloxy)-2-[3-methoxy-4-(2-methoxyethoxy)benzyloxy] nonyl}-5-methyl-5H-furan-2-one 69a: ^1H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.86 (s, 9H),

[9] Moghaddam, F. M.; Ghaffarzadeh, M. *Tetrahedron Lett*., **1996**, *37*, 1855.

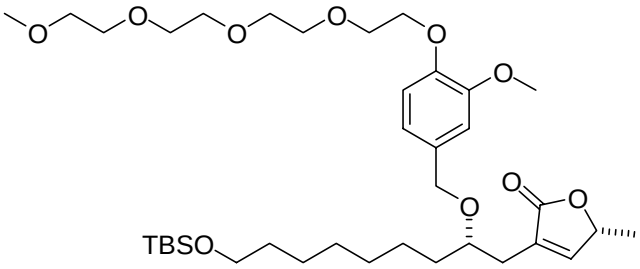
1.23-1.31 (m, 8H), 1.35 (d, J = 6.9 Hz, 3H), 1.42-1.49 (m, 2H), 1.53-1.58 (m, 2H), 2.48 (d, J = 6.0 Hz, 2H), 3.41 (s, 3H), 3.56 (t, J = 6.6 Hz, 2H), 3.62-3.67 (m, 1H), 3.72 (t, J = 4.6 Hz, 2H), 3.82 (s, 3H), 4.11-4.13 (m, 2H), 4.40 (d, J = 11.5 Hz, 1H), 4.44 (d, J = 11.5 Hz, 1H), 4.92 (q, J = 6.6 Hz, 1H), 6.78-6.84 (m, 3H), 7.05 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.3, 18.3, 19.1, 25.2, 25.7, 25.9, 29.3, 29.6, 32.7, 33.9, 55.8, 59.1, 63.2, 68.5, 70.9, 76.5, 77.5, 111.7, 113.6, 120.2, 130.5, 131.7, 147.7, 149.6, 151.4, 173.9; IR (neat) 2930, 2856, 1756, 1515, 1464.



(*R*)-3-((*R*)-9-(*tert*-Butyldimethylsilanyloxy)-2-{3-methoxy-4-[2-(2-methoxyethoxy)ethoxy] benzyloxy}nonyl)-5-methyl-5H-furan-2-one 69b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.29-1.31 (m, 8H), 1.38 (d, J = 6.4 Hz, 3H), 1.40-1.61 (m, 4H), 2.51-2.53 (m, 2H), 3.40 (s, 3H), 3.57-3.61 (m, 4H), 3.66-3.69 (m, 1H), 3.72-3.74 (m, 2H), 3.86 (s, 3H), 3.89 (t, J = 5.0 Hz, 2H), 4.19 (t, J = 5.5 Hz, 2H), 4.43 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 11.5 Hz, 1H), 4.99 (q, J = 6.9 Hz, 1H), 6.81-6.88 (m, 3H), 7.09 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.5, 18.1, 18.9, 25.1, 25.5, 25.8, 29.2, 29.5, 32.6, 33.7, 55.7, 58.8, 63.0, 68.5, 69.4, 70.5, 70.8, 71.7, 76.4, 77.3, 111.7, 113.5, 120.1, 130.3, 131.6, 147.6, 149.4, 151.3, 173.7; IR (neat); 2930, 2856, 1755, 1515, 1464;

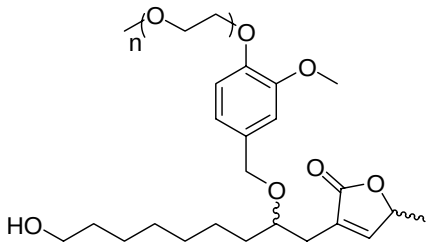


(*S*)-3-[(*S*)-9-(*tert*-Butyldimethylsilanyloxy)-2-(3-methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy] ethoxy}benzyloxy)nonyl]-5-methyl-5H-furan-2-one 69c: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.05 (s, 6H), 0.80 (s, 9H), 1.16-1.20 (m, 8H), 1.26 (d, *J* = 6.9 Hz, 2H), 1.40-1.49 (m, 4H), 2.41 (s, 2H), 3.27 (s, 3H), 3.44-3.45 (m, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 3.54-3.61 (m, 5H), 3.61-3.65 (m, 2H), 3.75 (s, 3H), 3.77 (t, *J* = 5.0 Hz, 2H), 4.07 (t, *J* = 5.0 Hz, 2H), 4.34 (d, *J* = 11.0 Hz, 1H), 4.37 (d, 11.0 Hz, 1H), 4.88 (q, *J* = 6.4 Hz, 1H), 6.72-6.78 (m, 3H), 7.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.5, 18.0, 18.8, 25.0, 25.4, 25.7, 29.1, 29.4, 32.5, 33.6, 55.6, 58.6, 62.9, 68.4, 69.3, 70.2, 70.3, 70.5, 70.7, 71.6, 76.3, 77.2, 111.6, 113.4, 120.0, 130.2, 131.5, 147.6, 149.3, 151.3, 173.6; IR (neat) 2929, 2856, 1755, 1515. HRMS for $C_{35}H_{60}O_9SiNa$: calcd 675.3904, found 675.3875.



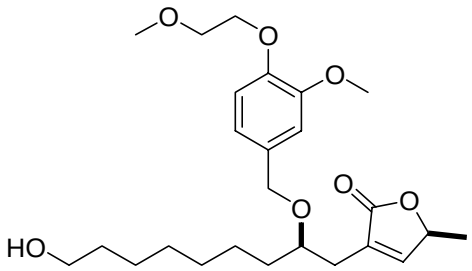
(*R*)-3-{(*S*)-9-(*tert*-Butyldimethylsilanyloxy)-2-[3-methoxy-4-(2-{2-[2-(2-methoxyethoxy) ethoxy]ethoxy}ethoxy)benzyloxy]nonyl}-5-methyl-5H-furan-2-one 69d: ^{1}H NMR (500 MHz,

$CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.28-1.34 (m, 8H), 1.39 (d, *J* = 6.9 Hz, 3H), 1.49-1.60 (m, 4H), 2.51 (d, *J* = 6.4 Hz, 2H), 3.38 (s, 3H), 3.53-3.56 (m, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.65-3.70 (m, 9H), 3.71-3.75 (m, 2H), 3.85 (s, 3H), 3.87 (t, *J* = 5.3 Hz, 2H), 4.17 (t, *J* = 5.3 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.95 (q, *J* = 6.9 Hz, 1H), 6.80-6.88 (m, 3H), 7.07 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.2, 18.4, 19.2, 25.4, 25.8, 26.1, 29.5, 29.7, 29.8, 32.9, 34.0, 56.0, 59.1, 63.3, 68.7, 69.7, 70.6, 70.7, 70.9, 71.1, 72.0, 76.7, 77.6, 111.9, 113.7, 120.4, 130.7, 131.8, 147.9, 149.6, 151.5, 174.0; IR (neat); 2929, 2857, 1754, 1515, 1463; HRMS for $C_{37}H_{64}O_{10}SiNa$: calcd 719.4166, found 719.4186.

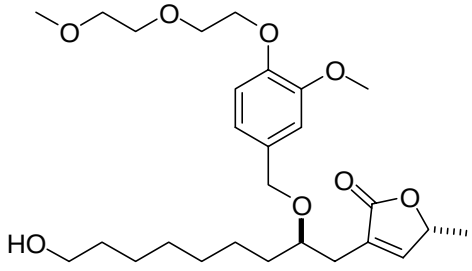


Alcohol mixture M70: Acetyl chloride[10] (11 μL) was added to a 1:1:1:1 mixture of **69a**, **69b**, **69c** and **69d** (0.26 g, 0.39 mmol) in methanol at 0 °C and stirred for 15 min. Then the solution was concentrated to yield the alcohol **M70**. The resulted mixture of alcohol **M70** (0.20 g, 99%) was spectroscopically pure and was used in next step with out further purification. However, spectroscopic data for individual compounds was obtained by repeating the above experimental procedure with individual compounds.

[10] Khan, A. T.; Mondal, E. *Synlett*, **2003**, *5*, 694.

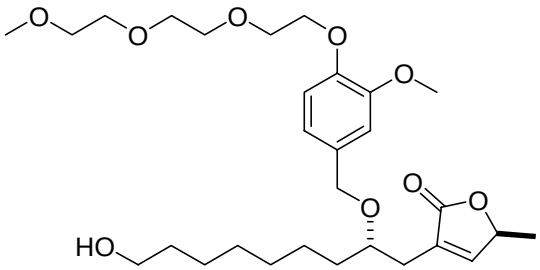


General procedure 11: (*S*)-3-{(*R*)-9-Hydroxy-2-[3-methoxy-4-(2-methoxyethoxy)benzyloxy] nonyl}-5-methyl-5H-furan-2-one 70a: Acetyl chloride (11 μL) was added to a solution of **69a** (30 mg, 0.053 mmol) in methanol and the mixture was stirred for 15 min. Concentration of the reaction mixture gave the alcohol **70a** (23 mg, 99%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.34 (m, 8H), 1.37 (d, *J* = 7.1 Hz, 3H), 1.40-1.56 (m, 4H), 1.85 (br s, 1H), 2.49 (d, *J* = 5.5 Hz, 2H), 3.42 (s, 3H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.63-3.67 (m, 1H), 3.73-3.79 (m, 2H), 3.84 (s, 3H), 4.13 (t, *J* = 4.94 Hz, 2H), 4.43 (s, 2H), 4.94 (q, *J* = 6.59 Hz, 1H), 6.78-6.86 (m, 3H), 7.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 25.2, 25.6, 29.3, 29.5, 29.6, 32.7, 33.9, 55.8, 59.2, 62.8, 68.5, 70.9, 76.4, 111.8, 113.5, 120.4, 130.5, 131.7, 147.8, 149.6, 151.6, 174.0; IR (neat) 3406, 2928, 1751, 1515, 1456; EIMS *m/z* 450 (M^+); HRMS for $C_{25}H_{38}O_7$: calcd 450.2617; found 467.2637.

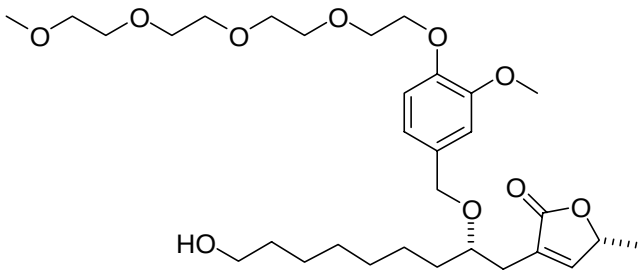


(*R*)-3-((*R*)-9-Hydroxy-2-{3-methoxy-4-[2-(2-methoxyethoxy)ethoxy]benzyloxy}nonyl)-5-methyl-5H-furan-2-one 70b: General procedure 11 was performed with **69b** (20 mg, 0.032

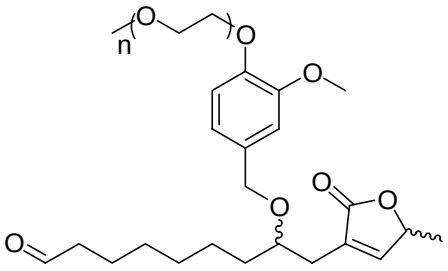
mmol) to give **70b** (16 mg, 99%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26-1.33 (m, 8H),1.37 (d, *J* = 6.9 Hz, 3H), 1.39-1.57 (m, 4H), 1.81 (br s, 1H), 2.50-2.54 (m, 2H), 3.39 (s, 3H), 3.56-3.59 (m, 2H), 3.62 (t, *J* = 6.64, 2H), 3.63-3.69 (m, 1H), 3.71-3.74 (m, 2H), 3.85 (s, 3H), 3.88 (t, *J* = 5.50 Hz, 2H), 4.17 (t, *J* = 5.0 Hz, 2H), 4.44 (s, 2H), 4.97-5.01 (m, 1H), 6.80 - 6.88 (m, 3H), 7.08 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.1, 25.2, 25.7, 29.4, 29.6, 29.7, 32.8, 34.0, 56.0, 59.1, 63.0, 68.6, 69.7, 70.8, 71.1, 72.0, 76.5, 77.6, 112.0, 113.6, 120.5, 130.6, 131.7, 147.9, 149.6, 151.6, 174.1; IR (neat) 3446, 2929, 2857, 1751, 1593, 1515, 1456. EIMS *m/z* 494.



(*S*)-3-[(*S*)-9-Hydroxy-2-(3-methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}benzyloxy) nonyl]-5-methyl-5H-furan-2-one 70c: General procedure 11 with **69c** (35 mg, 0.054 mmol) was performed to give **70c** (29 mg, 99%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23-1.32 (m, 8H), 1.35 (d, *J* = 6.9 Hz, 3H), 1.38-1.57 (m, 4H), 1.92 (br s, 1H), 2.46-2.54 (m, 2H), 3.36 (s, 3H), 3.51-3.54 (m, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.62-3.67 (m, 5H), 3.70-3.73 (m, 2H), 3.83 (s, 3H), 3.85(t, *J* = 5.0 Hz, 2H), 4.15 (t, *J* = 5.5 Hz, 2H), 4.43 (s, 2H), 3.97 (q, *J* = 6.9 Hz, 1H), 6.78-6.86 (m, 3H), 7.08 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.1, 25.2, 25.6, 29.3, 29.5, 29.6, 32.7, 33.9, 55.9, 59.0, 62.8, 68.6, 69.6, 70.5, 70.6, 70.8, 71.0, 71.9, 76.4, 77.5, 111.9, 113.6, 120.4, 130.5, 131.7, 147.8, 149.5, 151.6, 174.0; EIMS *m/z* 583 $(M + H)^+$, 582 (M^+); HRMS for $C_{29}H_{46}O_9$: calcd 538.3142; found 538.3109.

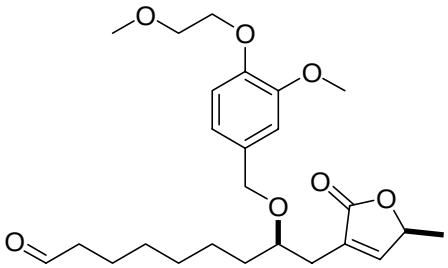


(*R*)-3-{(*S*)-9-Hydroxy-2-[3-methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy} ethoxy)benzyloxy]nonyl}-5-methyl-5H-furan-2-one 70d: General procedure with **69d** (30 mg, 0.043) was performed to give **70d** (25 mg, 99%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20-1.29 (m, 8H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.37-1.54 (m, 4H), 2.27 (br s, 1H), 2.46 (d, *J* = 6.0 Hz, 2H), 3.32 (s, 3H), 3.48-3.52 (m, 2H), 3.55 (t, *J* = 6.6 Hz, 2H), 3.58-3.65 (m, 9H), 3.66-3.69 (m, 2H), 3.80 (s, 3H), 3.82 (t, *J* = 5.5 Hz, 2H), 4.12 (t, *J* = 5.0 Hz, 2H), 4.40 (s, 2H), 4.90-4.94 (m, 1H), 6.75-6.84 (m, 3H), 7.05 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.1, 25.1, 25.6, 29.3, 29.4, 29.5, 32.6, 33.8, 55.8, 58.9, 62.6, 68.6, 69.5, 70.4, 70.5, 70.7, 70.9, 71.8, 76.3, 77.4, 77.5, 111.9, 113.6, 120.3, 130.4, 131.6, 147.8, 149.5, 151.5, 173.9; IR (neat) 3400, 2929, 1752, 1514, 1456; EIMS *m/z* 583 $(M + H)^+$, 582 (M^+); HRMS for $C_{31}H_{50}O_{10}$: calcd 582.3404; found 582.3430.

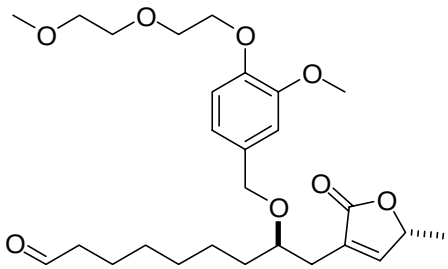


Adldehyde mixture M62: *o*-Iodoxybenzoic acid (IBX) (0.40 g, 1.1 mmol) was added to a mixture of alcohols **M70** (0.18 g, 0.36 mmol) in ethyl acetate (10 mL). The resulting suspension was heated, open to the atmosphere, with an oil bath set to 80 ^{o}C until TLC indicated complete conversion (3 h). Then the reaction mixture was cooled to room temperature, filtered and

concentrated to yield a mixture of aldehyde that on column chromatography on silica gel by gradient elution (25-70% EtOAc/hexanes) gave the four aldehydes **62** (0.16 g, 0.32 mmol, 90%) as separate oils.

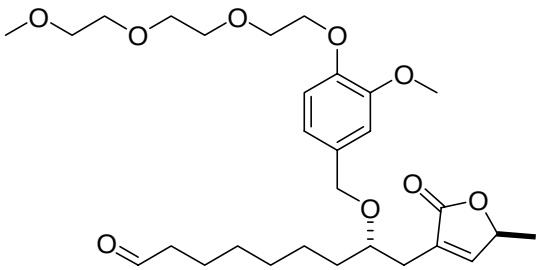


(*R*)-8-[3-Methoxy-4-(2-methoxyethoxy)benzyloxy]-9-((*S*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl)nonanal (62a): ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.25-1.35 (m, 8H), 1.38 (d, *J* = 7.1 Hz, 3H), 1.44-1.63 (m, 2H), 2.41 (td, *J* = 7.1, 1.6 Hz, 2H), 2.50 (d, *J* = 5.5 Hz, 2H), 3.43 (s, 3H), 3.61-3.72 (m, 1H), 3.75-3.78 (m, 2 H), 3.85 (s, 3H), 4.11-4.16 (m, 2H), 4.44 (s, 2H), 4.95 (q, *J* = 6.6 Hz, 1H), 6.78-6.89 (m, 3H), 7.07 (s, 1H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 22.0, 25.1, 29.1, 29.4, 29.6, 33.9, 43.9, 55.9, 59.2, 68.5, 71.1, 76.5,111.8, 113.6, 120.4, 130.5, 131.7, 147.8, 149.6, 151.6, 174.0, 202.8; IR (neat) 2927, 1751, 1720, 1514, 1465; HRMS (ESI) for $(M + Na)^+$ $C_{25}H_{36}O_7Na$: calcd 471.2359; found 471.2380.

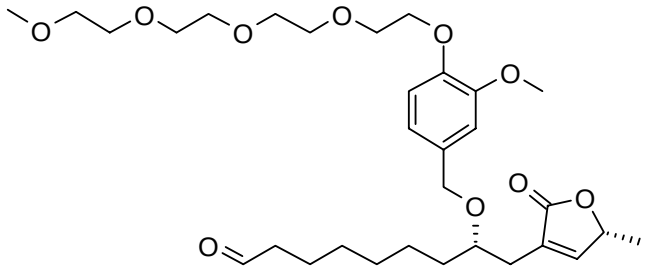


(*R*)-8-{3-Methoxy-4-[2-(2-methoxyethoxy)ethoxy]benzyloxy}-9-((*R*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl)nonanal (62b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27-1.32 (m, 8H), 1.35 (d, *J* = 6.9 Hz, 3H), 1.41-1.59 (m, 2H), 2.39 (t, *J* = 6.6 Hz, 2H), 2.49 (br s, 2H), 3.36 (s, 3H), 3.52-3.57 (m, 2H), 3.62-3.67 (m, 1 H), 3.67-3.72 (m, 2H), 3.82 (s, 3H), 3.85 (t, *J* = 5.3 Hz, 2H), 4.15

(t, *J* = 5.3 Hz, 2H), 4.42 (s, 2H), 4.94-4.98 (m, 1H), 6.79 - 6.85 (m, 3H), 7.09 (s, 1H), 9.73 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.0, 21.9, 25.0, 29.0, 29.3, 29.6, 33.8, 43.8, 55.9, 59.0, 68.6, 69.6, 70.7, 71.0, 71.9, 76.5, 77.5, 111.9, 113.6, 120.3, 130.5, 131.6, 147.8, 149.5, 151.6, 173.9, 202.7; HRMS (ESI) for $(M + Na)^+$ $C_{27}H_{40}O_8Na$: calcd 515.2621; found 515.2625.

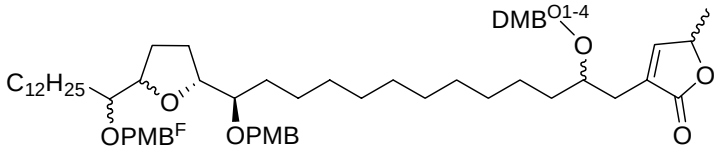


(*S*)-8-(3-Methoxy-4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}benzyloxy)-9-((*S*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl)nonanal 62c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24-1.28 (m, 8H), 1.35 (d, *J* = 6.6 Hz, 2H), 1.41-1.59(m, 2H), 2.40 (t, *J* = 7.4 Hz, 2H), 2.49 (br s, 2H), 3.36 (s, 3H), 3.42-3.54 (m, 2H), 3.60-3.76 (m, 9H), 3.83-3.93 (m, 5H), 4.15 (t, *J* = 5.2 Hz, 2H), 4.33 (s, 2H), 4.97 (q, *J* = 6.2 Hz, 1H), 6.79-6.86 (m, 3H), 7.08 (s, 1H), 9.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 21.9, 25.1, 29.0, 29.3, 29.6, 33.8, 43.8, 55.9, 59.0, 68.6, 69.6, 70.5, 70.7, 71.0, 71.9, 76.5, 76.6, 77.5, 111.9, 113.6, 120.4, 130.5, 131.6, 147.8, 149.5, 151.6, 174.0, 202.8; IR (neat) 2927, 1751, 1515, 1457; EIMS *m/z* 537 $(M + H)^+$, 536 (M^+); HRMS for $C_{29}H_{44}O_9$: calcd 536.2985; found 536.2986.



(*S*)-8-[3-Methoxy-4-(2-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}ethoxy)benzyloxy]-9-((*R*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl)nonanal 62d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.37 (m, 8H), 1.39 (d, *J* = 6.6 Hz, 2H), 1.43-1.65 (m, 2H), 2.42 (td, *J* = 7.1, 1.6 Hz, 2H), 2.51 (d, *J* = 5.5 Hz, 2H), 3.38 (s, 3H), 3.53-3.56 (m, 2H), 3.61-3.76 (m, 13H), 3.82-3.92 (m, 5H), 4.17 (t, *J* = 5.2 Hz, 2H), 4.44 (s, 2H), 4.91-5.03 (m, 1H), 6.84 (m, 3H), 7.08 (s, 1H), 9.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 21.9, 25.1, 29.1, 29.4, 29.7, 33.9, 43.8, 55.9, 59.0, 68.6, 69.6, 70.6, 70.8, 71.0, 71.9, 76.5, 76.7, 77.5, 111.9, 113.6, 120.4, 130.5, 131.6, 147.8, 149.6, 151.6, 174.0, 202.8; IR (neat) 2926, 2855, 1751, 1719, 1515, 1457; HRMS (ESI) $(M + Na)^+$ for $C_{31}H_{48}O_{10}Na$: calcd 603.3145; found 603.3154.

3-[(13*R)*-2-(3-methoxy-4-n-oligoethoxy-benzyloxy)-13-(4-methoxy-benzyloxy)-13-((2*R*)-5-{1-[4-(3-perfluoropropyloxy)benzyloxy]tridecyl}-tetrahydrofuran-2-yl)tridec-9-en-yl]-5-methyl-5*H*-furan-2-one (M79)



A solution of sodium hexamethyldisilazane (NaHMDS) (1.0 M in THF, 0.28 mL, 0.28 mmol) was added under argon to a solution of the sulfone mixture **M13** (0.30 g, 0.26 mmol) in THF at – 78 ºC. The reaction mixture was stirred for 30 min at – 78 ºC followed by the addition of a

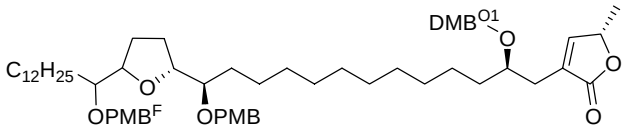
solution of the aldehyde mixture **M62** (0.14 g, 0.28 mmol) in THF. The resulting mixture was then warmed to room temperature overnight and H_2O was added. The layers were separated and the aqueous layer was further extracted with Et_2O (3 x 20mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by gradient flash chromatography (ethyl acetate/hexanes 20%, 40%, 60% and then pure ethyl acetate) on silica gel to yield the mixture **M79** (0.27 g, 0.18 mmol, 71%) as an oil; LCMS (APCI)[11] for **M79**: **M79a** *m/z*: 1159 $(M_1 + 1)^+$, 1176 $(M_1 + H_2O)^+$, 1203 $(M_2 + 1)^+$, 1220 $(M_2 + H_2O)^+$, 1264 $(M_3 + H_2O)^+$, 1308 $(M_4 + H_2O)^+$; **M79b** *m/z*: 1259 $(M_1 + 1)^+$, 1276 $(M_1 + H_2O)^+$, 1303 $(M_2 + 1)^+$, 1320 $(M_2 + H_2O)^+$, 1347 $(M_3 + 1)^+$, 1364 $(M_3 + H_2O)^+$, 1391 $(M_4 + 1)^+$, 1408 $(M_4 + H_2O)^+$, 367 $[C_4F_9(CH_2)_3OC_6H_4CH_2]^+$; **M79c** *m/z*: 1376 $(M_1 + H_2O)^+$, 1403 $(M_2 + 1)^+$, 1420 $(M_2 + H_2O)^+$, 1447 $(M_3 + 1)^+$, 1464 $(M_3 + H_2O)^+$, 1491 $(M_4 + 1)^+$, 1508 $(M_4 + H_2O)^+$, 467 $[C_6F_{13}(CH_2)_3OC_6H_4CH_2]^+$; **M79d** *m/z*: 1459 $(M_1 + 1)^+$, 1476 $(M_1 + H_2O)^+$, 1520 $(M_2 + H_2O)^+$, 1564 $(M_3 + H_2O)^+$, 1608 $(M_4 + H_2O)^+$, 1444 $[M_1 - CH_3O]^+$, 1488 $[M_2 - CH_3O]^+$, 567 $[C_8F_{17}(CH_2)_3OC_6H_4CH_2]^+$.

Hydrogenation of M79: A solution of alkene **M79** (0.27 g, 0.18 mmol), Wilkinson's catalyst (22 mg, 0.024 mmol) in ethanol was stirred under H_2 atmosphere (1.0 atm) for 18 h and then filtered through a pad of celite. The filtrate was concentrated to give **M11** (0.32 g) as dark brown oil. The crude product was subjected to simultaneous purification and demixing as described below.

Demixing of final 16 compounds mixture M11:

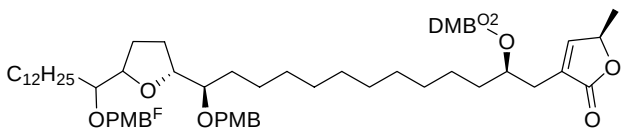
OEG demixing: Purification and OEG demixing of the final mixture M**11** was done simultaneously by a careful flash column chromatography on silica gel. Gradient elution was performed with ethyl acetate/hexanes (20%, 40%, 60%, 80% then pure ethyl acetate). Compounds eluted in the following order: **11-O1** (52 mg), **11-O2** (66 mg), **11-O3** (55 mg), and **11-O4** (50 mg, contaminated by Wilkinson catalyst). LCMS data for the four fractions are given below.

3-{(2*R*,13*R*)-2-[3-Methoxy-4-(2-methoxyethoxy)benzyloxy]-13-(4-methoxybenzyloxy)-13-((2*R*)-5-{1-[4-(3-perfluoropropyloxy)benzyloxy]tridecyl}-tetrahydrofuran-2-yl)tridecyl}-(5*S*)-5-methyl-5*H*-furan-2-one (11-O1).



LCMS (APCI) for **11-O1**: **11-O1-F5** *m/z*: 1178 $(M + H_2O)^+$, 965, 581, 267 $[C_2F_5(CH_2)_3OC_6H_4CH_2]^+$; **11-O1-F9** *m/z*: 1278 $(M + H_2O)^+$, 1139 $(M - PMB)^+$, 581, 367 $[C_4F_9(CH_2)_3OC_6H_4CH_2]^+$; **11-O1-F13** *m/z*: 1378 $(M + H_2O)^+$, 1239 $(M - PMB)^+$, 581, 467 $[C_6F_{13}(CH_2)_3OC_6H_4CH_2]^+$; **11-O1-F17** *m/z*: 1478 $(M + H_2O)^+$, 581, 567, $[C_8F_{17}(CH_2)_3OC_6H_4CH_2]^+$.

3-{(2*R*,13*R*)-2-[3-Methoxy-4-[(2-methoxyethoxy)ethoxy]benzyloxy]-13-(4-methoxybenzyloxy)-13-((2*R*)-5-{1-[4-(3-perfluoropropyloxy)benzyloxy]tridecyl}-tetrahydrofuran-2-yl)tridecyl}-(5*R*)-5-methyl-5*H*-furan-2-one (11-O2):



LCMS (APCI) for **11-O2**: **11-O2-F5** *m/z*: 1222 $(M + H_2O)^+$, 581, 561, 267

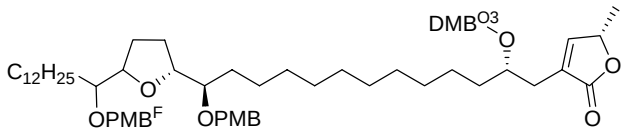
$[C_2F_5(CH_2)_3OC_6H_4CH_2]^+$; **11-O2-F9** *m/z*: 1322 $(M + H_2O)^+$, 581, 561, 367

$[C_4F_9(CH_2)_3OC_6H_4CH_2]^+$; **11-O2-F13** *m/z*: 1422 $(M + H_2O)^+$, 581, 561, 467

$[C_6F_{13}(CH_2)_3OC_6H_4CH_2]^+$; **11-O2-F17** *m/z*: 1522 $(M + H_2O)^+$, 581, 567

$[C_8F_{17}(CH_2)_3OC_6H_4CH_2]^+$.

3-{(2*S*,13*R*)-2-(3-Methoxy-4-{[(2-methoxy-ethoxy)-ethoxy]-ethoxy}-benzyloxy)-13-(4-meth oxy-benzyloxy)-13-((2*R*)-5-{1-[4-(3-perfluoropropyloxy)benzyloxy]tridecyl}-tetrahydro furan-2-yl)tridecyl}-(5*S*)-5-methyl-5*H*-furan-2-one (11-O3).



LCMS (APCI) for **11-O3**: **11-O3-F5** *m/z*: 1266 $(M + H_2O)^+$, 581, 561, 267

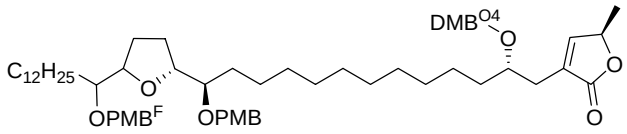
$[C_2F_5(CH_2)_3OC_6H_4CH_2]^+$; **11-O3-F9** *m/z*: 1366 $(M + H_2O)^+$, 581, 561, 403, 367

$[C_4F_9(CH_2)_3OC_6H_4CH_2]^+$; **11-O3-F13** *m/z*: 1466 $(M + H_2O)^+$, 581, 561, 467

$[C_6F_{13}(CH_2)_3OC_6H_4CH_2]^+$; **11-O3-F17** *m/z*: 1566 $(M + H_2O)^+$, 581, 567

$[C_8F_{17}(CH_2)_3OC_6H_4CH_2]^+$.

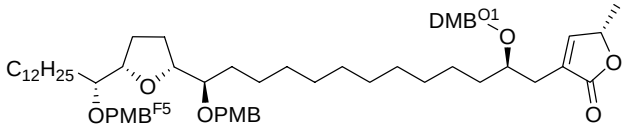
3-{(2*S*,13*R*)-2-[3-Methoxy-4 -({[(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-benzyloxy]-13 -(4-methoxy-benzyloxy)-13-((2*R*)–5-{1-[4-(3-perfluoropropyloxy)-benzyloxy]-tridecyl} tetrahydrofuran -2-yl)tridecyl}-(5*R*) -5-methyl-5*H*-furan-2-one (11-O4).



LCMS (APCI) for **11-O4**: **11-O4-F5** *m/z*: 1310 $(M + H_2O)^+$, 279; **11-O4-F9** *m/z*: 1410 $(M + H_2O)^+$, 279; **11-O4-F13** *m/z*: 1510 $(M + H_2O)^+$, 279; **11-O4-F17** *m/z*: 1610 $(M + H_2O)^+$, 279.

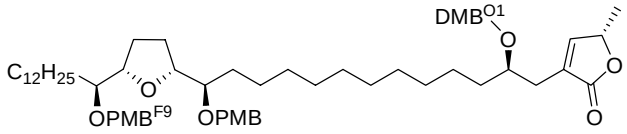
General procedure: Fluorous demixing 11-O1: Semiprep HPLC separation was carried out on Waters HPLC system using FluoroFlash HPLC column (20 x 250 mm). The mixture **11-O1** (52 mg) was dissolved in 1.5 mL of CH_3CN and filtered through a Wattman filter paper (0.45 μm pore size). Two separations using 1.5 mL and another separation using 1 mL were carried out. The column was eluted under a linear gradient plus an isocratic for 35min with a flow rate of 15 mL/min. The gradient started with 85% CH_3CN/15% H_2O and ended with 100% CH_3CN in 25min. The isocratic was performed with 100% CH_3CN for 10min elution. In each injection, the four fractions with retention time of ~10min, ~15min, ~19min and ~23min were collected separately and concentrated to give **11-O1-F5** (2.5 mg, 2.0 μmol), **11-O1-F9** (4.7 mg, 4.0 μmol), **11-O1-F13** (8.8 mg, 6.0 μmol) and **11-O1-F17** (23 mg, 15 μmol) respectively.

(*S*)-3-[(2*R*,13*R*)-13-(4-Methoxy-benzyloxy)-2-[3-methoxy-4-(2-methoxy-ethoxy)- benzyloxy] -13-((2*R*,5*S*)-5-{(*R*)-1-[4-(4,4,5,5,5-pentafluoro-pentyloxy)-benzyloxy]-tridecyl}-tetrahydro-furan-2-yl)-tridecyl]-5-methyl-5*H*-furan-2-one (11-O1-F5)



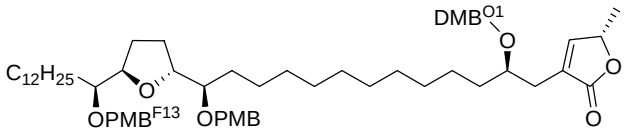
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.6 Hz, 3H), 1.25-1.36 (m, 36H), 1.39 (d, *J* = 6.9 Hz, 3H), 1.42-1.58 (m, 6H), 1.82-1.91 (m, 2H), 2.02-2.11 (m, 3H), 2.21-2.32 (m, 3H), 2.52 (d, *J* = 5.5 Hz, 2H), 3.32-3.37 (m, 1H), 3.45 (s, 3H), 3.51-3.54 (m,1H), 3.65-3.73 (m, 1H), 3.77-3.79 (m, 5H), 3.86 (s, 3H), 3.88- 3.93 (m, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 4.15-4.17 (m, 2H), 4.42-4.50 (m, 2H), 4.53 (t, *J* = 10.3 Hz, 2H), 4.62 (d, *J* = 11.0 Hz, 1 H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.93-4.97 (m, 1H), 6.81-6.97 (m, 1H), 7.07 (s, 1H), 7.23-7.32 (m, 4H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −117.1 (t, *J* = 19.7 Hz, 2F), −84.2 (3F);

(*S*)-3-[(2*R*,13*R*)-13-(4-Methoxy-benzyloxy)-2-[3-methoxy-4-(2-methoxy-ethoxy)-benzyloxy]-13-((2*R*,5*S*)-5-{(*S*)-1-[4-(4,4,5,5,6,6,7,7,7-nonafluoro-heptyloxy)-benzyloxy]-tridecyl}-tetra hydro-furan-2-yl)-tridecyl]-5-methyl-5*H*-furan-2-one (11-O1-F9)



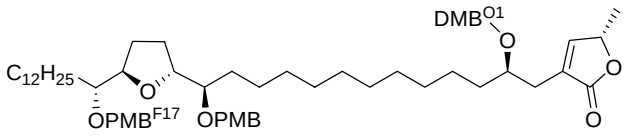
^{1}H NMR (500 MHz,$CDCl_3$) δ 0.89 (t, *J* = 6.6 Hz, 3H), 1.26-1.36 (s, 36H), 1.39 (d, *J* = 6.6 Hz, 3H), 1.43-1.65 (m, 6H), 1.77-1.91 (m, 2H), 2.07-2.14 (m, 3H), 2.22-2.41 (m, 3 H), 2.52 (d, *J* = 6.0 Hz, 2H), 3.31-3.42 (m, 2H), 3.45 (s, 3H), 3.64-3.72 (m, 1 H), 3.76-3.81 (m, 5H), 3.86 (s, 3H), 3.93-3.97 (m, 2H), 4.01 (t, *J* = 5.8 Hz, 2H), 4.16 (t, *J* = 4.9 Hz, 2H), 4.41-4.50 (m, 2H), 4.55 (d, *J* = 11.0 Hz, 2H), 4.65-4.77 (m, 2H), 4.92-4.98 (m, 1H), 6.81-6.89 (m, 7H), 7.07 (s, 1H), 7.26-7.28 (m, 4H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −124.8 (2F), −123.2 (2F), −113.4 (2F), −79.8 (3F);

(*S*)-3-[(2*R*,13*R*)-13-(4-Methoxy-benzyloxy)-2-[3-methoxy-4-(2-methoxy-ethoxy)-benzyloxy]-13-((2*R*,5*R*)-5-{(*S*)-1-[4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-nonyloxy)-benzyloxy]-tridecyl}-tetrahydro-furan-2-yl)-tridecyl]-5-methyl-5*H*-furan-2-one (11-O1-F13)



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.25-1.36 (m, 36H), 1.39 (d, *J* = 6.9 Hz, 3H), 1.42-1.65 (m, 6H),1.92-1.96 (m, 2H), 2.07-2.13 (m, 3H), 2.26-2.36 (m, 3H), 2.52 (d, *J* = 5.5 Hz, 2H), 3.29-3.32 (m, 1H), 3.45 (s, 3H), 3.55-3.59 (m, 1H), 3.67-3.72 (m, 1H), 3.76-3.82 (m, 5H), 3.86 (s, 3H), 3.98-4.07 (m, 4H), 4.16 (t, *J* = 5.04 Hz, 2H), 4.43 (d, *J* = 11.0 Hz, 2H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 2H), 4.62-4.66 (m, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.95 (q, *J* = 6.6 Hz, 1H), 6.81-6.89 (m, 7H), 7.07 (s, 1H), 7.24- 7.30 (m, 4H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −124.9 (2F), −122.2 (2F), −121.7 (2F), −120.7 (2F), −113.2 (2F), −79.6 (3F);

(*S*)-3-{(2*R*,13*R*)-13-((2*R*,5*R*)-5-{(*R*)-1-[4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-hepta decafluoro-undecyloxy)-benzyloxy]-tridecyl}-tetrahydro-furan-2-yl)-13-(4-methoxy-benzyloxy)-2-[3-methoxy-4-(2-methoxy-ethoxy)-benzyloxy]-tridecyl}-5-methyl-5*H*-furan-2-one (11-O1-F17)

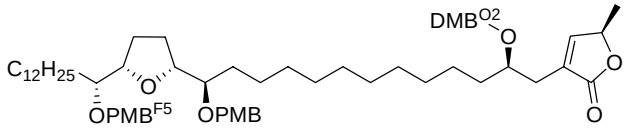


^{1}H NMR (500 MHz,$CDCl_3$) δ 0.81 (t, *J* = 6.9 Hz, 3H), 1.18-1.29 (m, 36H), 1.31 (d, *J* = 6.9 Hz, 3H), 1.34-1.55 (m, 6H), 1.82-1.87 (m, 2H), 1.97-2.04 (m, 3H), 2.18-2.28 (m, 3H), 2.44 (d, *J* = 5.5 Hz, 2H), 3.20-3.28 (m, 2H), 3.37 (s, 3H), 3.69-3.72 (m, 5H), 3.78 (s, 3H), 3.93 (t, *J* = 5.7 Hz,

2H), 3.94-3.99 (m, 2H), 4.08 (t, *J* = 5.0 Hz, 2H), 4.34 - 4.41 (m, 2H), 4.50 (d, *J* = 11.0 Hz, 2H), 4.70 (d, *J* = 11.0 Hz, 2H), 4.85-4.89 (m, 1H), 6.73-6.80 (m, 7H), 6.99 (s, 1H), 7.19-7.22 (m, 4H); ^{13}C NMR (126 MHz,$CDCl_3$) δ 14.2, 19.2, 20.7, 22.8, 25.4, 25.8, 28.0, 28.9, 29.4, 29.7, 31.2, 32.0, 34.1, 55.3, 55.9, 59.2, 66.4, 68.6, 71.0, 72.6, 77.6, 81.4, 111.8, 113.7, 114.2, 120.4, 129.5, 130.7, 131.6, 131.9, 132.0, 147.9, 149.7, 151.5, 158.0, 159.0, 174.0 ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −124.9 (2F), −122.2 (2F), −121.5 (2F), −120.7 (4F), −120.5 (2F), −113.2 (2F), −79.6 (3F).

Demixing of 11-O2: Mixture **11-O2** (66 mg) was demixed by general procedure to give compounds **11-O2-F5** (6.3 mg), **11-O2-F9** (7.4 mg), **11-O2-F13** (9.5 mg) and **11-O2-F17** (33 mg).

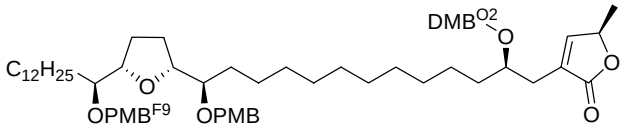
(*R*)-3-[(2*R*,13*R*)-13-(4-Methoxy-benzyloxy)-2-{3-methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-benzyloxy}-13-((2*R*,5*S*)-5-{(*R*)-1-[4-(4,4,5,5,5-pentafluoro-pentyloxy)-ben zyloxy]-tridecyl}-tetrahydro-furan-2-yl)-tridecyl]-5-methyl-5*H*-furan-2-one (11-O2-F5)



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.26-1.35 (m, 36H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.42 - 1.60 (m, 6H), 1.82 - 1.91 (m, 2H), 2.05 - 2.12 (m, 3H), 2.21-2.32 (m, 3H), 2.52 (m, 2H), 3.21-3.28 (m, 1H), 3.32-3.38 (m, 2H), 3.40 (s, 3H), 3.51-3.56 (m, 1H), 3.57-3.59 (m, 1H), 3.65-3.71 (m, 1H), 3.72-3.75 (m, 1H), 3.78 (s, 3H), 3.86 (s, 3H), 3.87-3.91 (m, 4H), 4.19 (t, *J* = 5.3 Hz, 2H), 4.42 - 4.50 (m, 3H), 4.50-4.57 (m, 2H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.76-4.83 (m, 1H), 4.85 (d, *J* = 6.4Hz, 1H), 4.94-5.01 (m, 1H), 6.83-6.88 (m, 7 H), 7.09

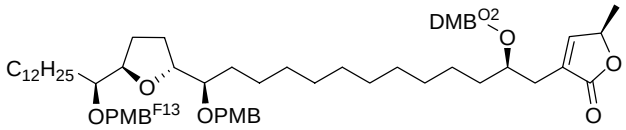
(s, 1H), 7.23-7.31 (m, 4H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −117.1 (t, *J* = 19.7 Hz, 2F), −84.2 (3F).

(*R*)-3-[(2*R*,13*R*)-13-(4-Methoxy-benzyloxy)-2-{3-methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-benzyloxy}-13-((2*R*,5*S*)-5-{(*S*)-1-[4-(4,4,5,5,6,6,7,7,7-nonafluoro-heptyloxy)-benzyloxy]-tridecyl}-tetrahydro-furan-2-yl)-tridecyl]-5-methyl-5H-furan-2-one (11-O2-F9)



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.26-1.32 (m, 36 H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.40-1.61 (m, 6H), 1.83-1.87 (m, 2H), 2.07-2.12 (m, 3H), 2.26-2.36 (m, 3H), 2.52 (br s, 2H), 3.21-3.29 (m, 1H), 3.34-3.39 (m, 2H), 3.40 (s, 3H), 3.55-3.60 (m, 2H), 3.65-3.71 (m, 1H), 3.72-3.75 (m, 2H), 3.79 (s, 3H), 3.86 (s, 3H), 3.87-3.91 (m, 2H), 3.95-3.96 (m, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 4.19 (t, *J* = 5.3 Hz, 2H), 4.42-4.51 (m, 2H), 4.54-4.57 (m, 2H), 4.73 (dd, *J* = 11.2, 3.0 Hz, 2H), 4.76-4.82 (m, 2H), 4.94-5.01 (m, 1H), 6.81-6.90 (m, 7H), 7.08 (s, 1H), 7.25-7.30 (m, 4H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −124.8 (2F), −123.2 (2F), −113.4 (2F), −79.8 (3F).

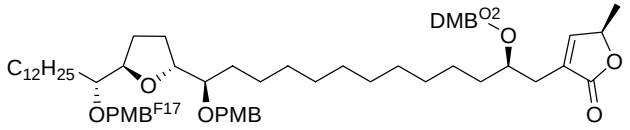
(*R*)-3-[(2*R*,13*R*)-13-(4-Methoxy-benzyloxy)-2-{3-methoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-benzyloxy}-13-((2*R*,5*R*)-5-{(*S*)-1-[4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-nonyloxy)-benzyloxy]-tridecyl}-tetrahydro-furan-2-yl)-tridecyl]-5-methyl-5*H*-furan-2-one(11-O2-F13)



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.25-1.32 (m, 36H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.40 (s, 2 H), 1.40-1.60 (m, 6H), 1.89-1.96 (m, 2H), 2.06-2.15 (m, 3H), 2.50-2.53 (m, 2H),

3.29-3.32 (m, 2H), 3.40 (s, 3H), 3.53-3.60 (m, 2H), 3.66-3.72 (m, 1H), 3.72-3.75 (m, 2H), 3.80 (s, 3H), 3.86 (s, 3H), 3.87-3.91 (m, 2H), 3.98-4.07 (m, 4H), 4.19 (t, *J* = 5.3 Hz, 2H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.53 (d, *J* = 11.0 Hz, 1H), 4.64 (d, *J* = 11.0 Hz, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.96-5.01 (m, 1H), 6.81-6.90 (m, 7H), 7.09 (s, 1H), 7.24-7.33 (m, 4H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −124.9 (2F), −122.2 (2F), −121.7 (2F), −120.7 (2F), −113.2 (2F), −79.6 (3F);

(*R*)-3-((2*R*,13*R*)-13-((2*R*,5*R*)-5-{(*R*)-1-[4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-hepta decafluoro-undecyloxy)-benzyloxy]-tridecyl}-tetrahydro-furan-2-yl)-13-(4-methoxy-benzyloxy)-2-{3-cmethoxy-4-[2-(2-methoxy-ethoxy)-ethoxy]-benzyloxy}-tridecyl)-5-methyl-5*H*-furan-2-one (11-O2-F17)

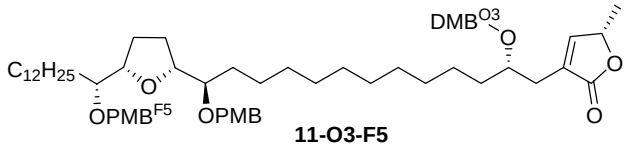


^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.26-1.31 (m, 36H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.41-1.62 (m, 6H), 1.92-1.99 (m, 2H), 2.05-2.14 (m, 3H), 2.27-2.36 (m, 3H), 2.52 (br s, 2H), 3.28-3.35 (m, 1H), 3.39 (s, 3H), 3.57-3.58(m, 2H), 3.65-3.71 (m, 2H), 3.71-3.76 (m, 2H), 3.78 (s, 3H), 3.86 (s, 3H), 3.87-3.92 (m, 3H), 4.03-4.06 (m, 5H), 4.19 (t, *J* = 5.3 Hz, 2H), 4.43 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.96-5.01 (m, 1H), 6.81-6.91 (m, 7H), 7.08 (s, 1H), 7.26-7.32 (m, 4H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 14.1, 19.1, 20.6, 22.7, 25.4, 25.7, 27.7, 28.0, 28.3, 28.9, 29.4, 29.7, 31.2, 32.0, 34.0, 55.3, 55.9, 59.1, 66.4, 68.7, 69.7, 70.8, 71.1, 72.0, 72.7, 77.3, 81.4, 82.4, 111.9, 113.7, 114.3, 120.4, 129.5, 130.7, 131.6, 131.8, 132.0, 147.9, 149.6, 151.6, 158.0, 159.0, 174.1; ^{19}F NMR

(282.4 MHz, $CDCl_3$) δ −124.9 (2F), −122.2 (2F), −121.5 (2F), −120.7 (4F), −120.5 (2F), −113.2 (2F), −79.5 (3F).

Demixing of 11-O3: Mixture **11-O3** (55 mg) was demixed by general procedure to give compounds **11-O3-F5** (3.8 mg), **11-O3-F9** (5.9 mg), **11-O3-F13** (6.6 mg) and **11-O3-F17** (15 mg).

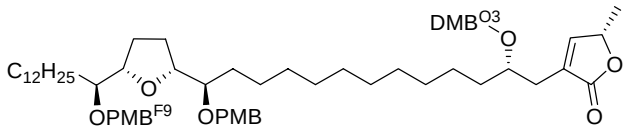
(*S*)-3-[(2*S*,13*R*)-13-(4-Methoxy-benzyloxy)-2-(3-methoxy-4-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-benzyloxy)-13-((2*R*,5*S*)-5-{(*R*)-1-[4-(4,4,5,5,5-pentafluoro-pentyloxy)-benzyloxy]-tridecyl}-tetrahydro-furan-2-yl)-tridecyl]-5-methyl-5*H*-furan-2-one (11-O3-F5)



11-O3-F5

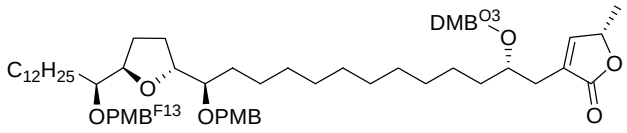
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.1 Hz, 3H), 1.26-1.36 (m, 36H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.40-1.64 (s, 6H), 1.84-1.90 (m, 2H), 2.01-2.11 (m, 3H), 2.21-2.32 (m, 3H), 2.53 (d, *J* = 5.0 Hz, 2H), 3.31-3.36 (m, 1H), 3.38 (s, 3H), 3.50-3.58 (m, 3H), 3.65-3.69 (m, 4H), 3.73-3.75 (m, 2H), 3.78 (s, 3H), 3.85 (s, 3H), 3.87-3.94 (m, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 4.17 (t, *J* = 5.0 Hz, 2H), 4.43 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H) 4.50-4.57 (m, 2H), 4.62 (d, *J* = 11.0 Hz, 1H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.99 (q, *J* = 6.6 Hz, 1H), 6.81 - 6.90 (m, 7H), 7.08 (s, 1H), 7.23-7.32 (m, 4H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −117.1 (t, *J* = 19.7 Hz, 2F), −84.2 (3F).

(*S*)-3-[(2*S*,13*R*)-13-(4-Methoxy-benzyloxy)-2-(3-methoxy-4-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-benzyloxy)-13-((2*R*,5*S*)-5-{(*S*)-1-[4-(4,4,5,5,6,6,7,7,7-nonafluoro-heptyloxy)-benzyloxy]-tridecyl}-tetrahydro-furan (11-O3-F9)



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.26-1.34 (s, 36H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.41-1.64 (m, 6H), 1.81-1.90 (m, 2H), 2.06-2.12 (m, 3H), 2.27-2.36 (m, 3 H), 2.53 (d, *J* = 4.6 Hz, 2H), 3.34-3.41 (m, 5H), 3.54-3.58 (m, 2H), 3.65-3.69 (m, 5H), 3.73- 3.75 (m, 2H), 3.79 (s, 3H), 3.86 (s, 3H), 3.88 (t, *J* = 5.0 Hz, 2H), 3.93-3.96 (m, 2H), 4.01 (t, *J* = 5.7 Hz, 2H), 4.17 (t, *J* = 5.3 Hz, 2H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.55 (dd, *J* = 11.0, 1.8 Hz, 2H), 4.73 (dd, *J* = 11.2, 3.0 Hz, 2H), 4.96-5.01 (m, 1H), 6.82-6.88 (m, 7H), 7.08 (s, 1H), 7.26-7.28 (m, 4H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −124.8 (2F), −123.2 (2F), −113.4 (2F), −79.8 (3F);

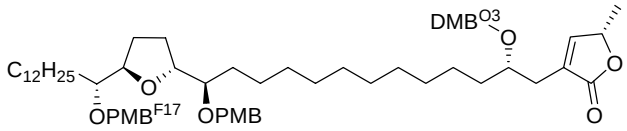
(*S*)-3-[(2*S*,13*R*)-13-(4-Methoxy-benzyloxy)-2-(3-methoxy-4-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-benzyloxy)-13-((2*R*,5*R*)-5-{(*S*)-1-[4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-nonyloxy)-benzyloxy]-tridecyl}-tetrahydro-furan-2-yl)-tridecyl]-5-methyl-*H*-furan-2-one (11-O3-F13)



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.4 Hz, 3H), 1.25-1.36 (m, 36H), 1.37 (d, *J* = 6.4 Hz, 3H), 1.40-1.64 (m, 6H), 1.90-1.96 (m, 2H), 2.07-2.11 (m, 3H), 2.26-2.36 (m, 3H), 2.52 (br s,

2H), 3.28-3.33 (m, 1H), 3.39 (s, 3H), 3.56 (br s, 3H), 3.65-3.74 (m, 8H), 3.79 (s, 3H), 3.86-3.88 (m, 5H), 4.01-4.04 (m, 3H), 4.17 (br s, 2H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 2H), 4.61-4.66 (m, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.96-5.02 (m, 1H), 6.81-6.89 (m, 7H), 7.09 (s, 1H), 7.24-7.31 (m, 4H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −124.9 (2F), −122.2 (2F), −121.7 (2F), −120.7 (2F), −113.2 (2F), −79.6 (3F).

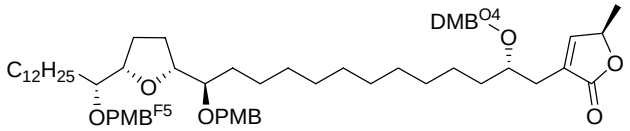
(*S*)-3-{(2*S*,13*R*)-13-((2*R*,5*R*)-5-{(*R*)-1-[4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-hepta decafluoro-undecyloxy)-benzyloxy]-tridecylnonyl}-tetrahydro-furan-2-yl)-13-(4-methoxy-benzyloxy)-2-(3-methoxy-4-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-benzyloxy)-tridecyl}-5-methyl-5*H*-furan-2-one (M11-O3-F17)



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.26-1.33 (m, 36H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.40-1.65 (m, 6H), 1.89-1.96 (m, 2H), 2.07-2.13 (m, 3H), 2.26-2.38 (m, 3H), 2.52 (2, 2H), 3.29-3.33 (m, 1H), 3.38 (s, 3H), 3.55-3.56 (m, 2H), 3.65-3.69 (m, 5H), 3.73-3.76 (m, 2H), 3.78 (s, 3H), 3.86 (s, 3H), 3.88 (t, *J* = 5.0 Hz, 2H), 4.00-4.05 (m, 5H), 4.17 (t, *J* = 5.3 Hz, 2H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 2H), 4.78 (d, *J* = 11.5 Hz, 2H), 4.96-5.01 (m, 1H), 6.82-6.88 (m, 7H), 7.09 (s, 1H), 7.25-7.29 (m, 4H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 2.0, 14.2, 19.2, 20.7, 22.8, 25.4, 25.8, 28.1, 28.9, 29.5, 29.8, 31.3, 32.0, 34.1, 55.3, 56.0, 59.1, 66.4, 68.7, 69.7, 70.6, 70.9, 71.1, 72.0, 72.7, 81.4, 82.4, 112.0, 113.7, 114.3, 120.4, 129.6, 130.8, 131.6, 131.8, 132.1, 148.0, 149.7, 151.6, 158.0, 159.1, 174.1 ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −124.9 (2F), −122.2 (2F), −121.5 (2F), −120.7 (4F), −120.5 (2F), −113.2 (2F), −79.6 (3F).

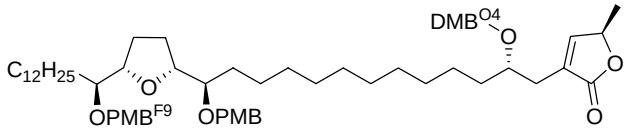
Demixing of 11-O4: Mixture **11-O4** (45 mg) was demixed by general procedure to give compounds **11-O4-F5** (3.8 mg), **11-O4-F9** (6.1 mg), **11-O4-F13** (5.4 mg) and **11-O4-F17** (13 mg).

(*R*)-3-[(2*S*,13*R*)-13-(4-Methoxy-benzyloxy)-2-[3-methoxy-4-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-benzyloxy]-13-((2*R*,5*S*)-5-{(*R*)-1-[4-(4,4,5,5,5-pentafluoro-pentyl oxy)-benzyloxy]-tridecyl}-tetrahydro-furan-2-yl)-tridecyl]-5-methyl-5*H*-furan-2-one (11-O4-F5)



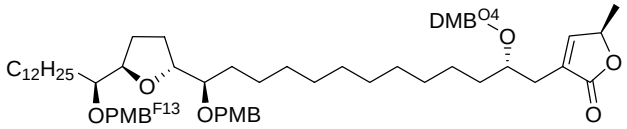
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.25-1.37 (s, 36H),1.39 (d, *J* = 6.9 Hz, 3H), 1.42-1.64 (m, 6H), 1.82-1.91 (m, 2H), 2.06-2.11 (m, 3H), 2.23-2.32 (m, 3H), 2.52 (d, *J* = 4.6 Hz, 2H), 3.31-3.35 (m, 1H), 3.38 (s, 3H), 3.51-3.57 (m, 3H), 3.64-3.71 (m, 9H), 3.72-3.75 (m, 2H), 3.78 (s, 3H), 3.85 (s, 3H), 3.86-3.93 (m, 4H), 4.02 (t, *J* = 5.7 Hz, 2H), 4.17 (t, *J* = 5.0 Hz, 1H), 4.43 (d *J* = 11.5, 1H), 4.47 (d, *J* = 11.5 Hz, 1H) 4.53 (m, 2H), 4.62 (d, *J* = 11.0 Hz, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.93-4.98 (m, 1H), 6.80-6.88 (m, 7H), 7.07 (s, 1H), 7.23-7.31 (m, 4H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −117.1 (t, *J* = 19.7 Hz, 2F), −84.2 (3F).

(*R*)-3-[(2*S*,13*R*)-13-(4-Methoxy-benzyloxy)-2-[3-methoxy-4-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-benzyloxy]-13-((2*R*,5*S*)-5-{(*R*)-1-[4-(4,4,5,5,6,6,7,7,7-nonafluoro-heptyloxy)-benzyloxy]-tridecyl}-tetrahydro-furan-2-yl)-tridecyl]-5-methyl-5*H*-furan-2-one (11-O4-F9)



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.26-1.36 (m, 36H), 1.39 (d, *J* = 6.4 Hz, 3H), 1.42-1.65 (m, 6H), 1.81-1.91 (m, 2H), 2.05-2.12 (m, 3H), 2.21-2.32 (m, 3H), 2.52 (d, *J* = 5.5 Hz, 2H), 3.36-3.42 (m, 5H), 3.53-3.59 (m, 2H), 3.64-3.74 (m, 12H), 3.79 (s, 3H), 3.86 (s, 3H), 3.88 (t, *J* = 5.0 Hz, 2H), 3.94-3.96 (d, *J* = 4.1 Hz, 2H), 4.02 (t, *J* = 6.0 Hz, 2H), 4.17 (t, *J* = 5.0 Hz, 2H), 4.43 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.56 (d, *J* = 11.0 Hz, 1H), 4.73 (dd, *J* = 11.5, 2.7 Hz, 2H), 4.96 (q, *J* = 6.9 Hz, 1H), 6.80-6.89 (m, 7H), 7.07 (s, 1H), 7.26-7.28 (m, 4H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −124.9 (2F), −123.2 (2F), −113.4 (2F), −79.9 (3F).

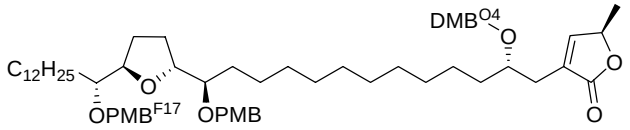
(*R*)-3-[(2*S*,13*R*)-13-(4-Methoxy-benzyloxy)-2-[3-methoxy-4-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-benzyloxy]-13-((2*R*,5*R*)-5-{(*S*)-1-[4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-nonyloxy)-benzyloxy]-tridecyl}-tetrahydro-furan-2-yl)-tridecyl]-5-methyl-5*H*-furan-2-one (11-O4-F13)



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.25-1.36 (m, 36H), 1.39 (d, *J* = 6.9 Hz, 3H), 1.41-1.65 (m, 6H) 1.87-1.95 (m, 2H), 2.06-2.14 (m, 3H), 2.26-2.37 (m, 3H), 2.52 (d, *J* = 5.5 Hz, 2H), 3.28-3.33 (m, 1H), 3.38 (s, 3H), 3.53-3.58 (m, 3H), 3.64-3.69 (m, 11H), 3.72-3.75 (m, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 3.88 (t, *J* = 5.3 Hz, 2H), 3.97-4.07 (m, 4H), 4.17 (t, *J* = 5.3 Hz, 2H), 4.43 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.55 (d, *J* = 9.6 Hz, 2H), 4.62-4.66 (m, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.96 (q, *J* = 6.6 Hz, 1H), 6.80-6.88 (m, 7H), 7.07 (s, 1H), 7.24-

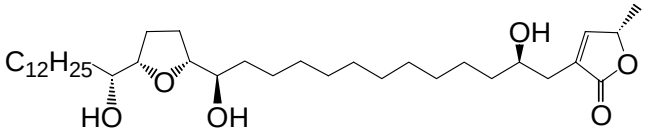
7.31 (M, 4H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −124.9 (2F), −122.2 (2F), −121.7 (2F), −120.7 (2F), −113.2 (2F), −79.6 (3F).

(*R*)-3-{(2*S*,13*R*)-13-((2*R*,5*R*)-5-{(*R*)-1-[4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Hepta decafluoro-undecyloxy)-benzyloxy]-tridecyl}-tetrahydro-furan-2-yl)-13-(4-methoxy-benzyloxy)-2-[3-methoxy-4-(2-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-benzyloxy]-tridecyl}-5-methyl-5*H*-furan-2-one (11-O4-F17)



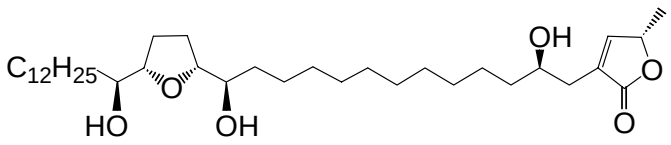
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.26-1.38 (m, 36H), 1.38-1.66 (m, 9H), 1.91-2.00 (m, 2H), 2.05-2.14 (m, 3H), 2.27-2.38 (m, 3H), 2.52 (d, *J* = 5.5 Hz, 2H), 3.28-3.33 (m, 1H), 3.38 (s, 3H), 3.54-3.56 (m, 2H), 3.63-3.71 (m, 11H), 3.73-3.74 (m, 3 H), 3.77-3.83 (m, 3H), 3.86 (s, 3H), 3.87-3.90 (m, 2H), 3.98-4.07 (m, 4H), 4.17 (t, *J* = 5.3 Hz, 2H), 4.43 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.53-4.60 (m, 2H), 4.66 (d, *J* = 2.3 Hz, 1H), 4.69 (d, *J* = 2.8 Hz, 1H) 6.81 - 6.90 (m, 7H), 7.07 (s, 1H), 7.25-7.32 (m, 4H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −124.9 (2F), −122.2 (2F), −121.5 (2F), −120.7 (4F), −120.5 (2F), −113.1 (2F), −79.5 (3F).

General procedure for one-pot global deprotection and detagging of fluorous-oeg double-tagged murisolin isomers (**general procedure 3**) **3-{(2*R*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*S*)-5-((1*R*)-1-hydroxytridecyl)tetrahydrofuran -2-yl]tridecyl}-(5*S*)-5-methyl-5*H*-furan-2-one (10-O1-F5)**



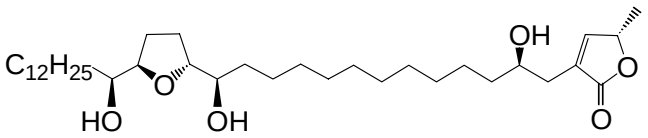
A solution of butenolide **11-O1-F5** (2.7 mg, 2.3 μmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.84 mg, 3.7 μmol) in CH_2Cl_2/H_2O (1.0 mL/0.05 mL) was stirred at room temperature for 1 h followed by dilution with CH_2Cl_2 (5.0 mL) and brine (1.5 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried over $MgSO_4$, and concentrated to give the crude product. The crude product was directly subjected to purification with semi-prep HPLC on a Chiralcel OD column 2 x 20 cm. The column was eluted under a linear gradient plus a isocratic condition for 45 min. The gradient started with hexanes/2-propanol (94/6) and ended with hexanes/2-propanol (90/10) in 30 min followed by isocratic elution with hexanes/2-propanol for (90/10) for 15 min. The flow rates in both are 10 mL/min. The butenolide **10-O1-F5** (0.5 mg, 37%) resulted as white waxy solid. Compounds **10-O2-F13**, **10-O3-F13**, **10-O4-F17** were further purified by semi-prep HPLC using a SymmetryPrep^{TM} C18 7μm 19x300mm column. The column was eluted under a linear gradient plus an isocratic for 45min. The gradient started with 80% CH_3OH/20% H_2O and ended with 100% CH_3OH in 30min. The isocratic was a 100% CH_3OH 15 min elution. The flow rates in both are 12mL/min.

3-{(2*R*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*S*)-5-((1*S*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*S*)-5-methyl-5*H*-furan-2-one (10-O1-F9).



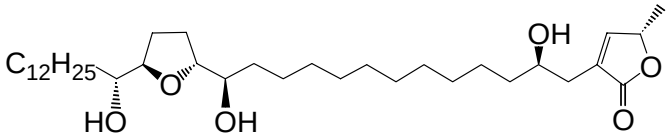
Using general procedure 3, butenolide **11-O1-F9** (4.0 mg, 3.2 μmol) was used to yield **10-O1-F9** (1.1 mg, 59%) as white waxy solid.

3-{(2*R*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*R*)-5-((1*S*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*S*)-5-methyl-5*H*-furan-2-one (10-O1-F13).



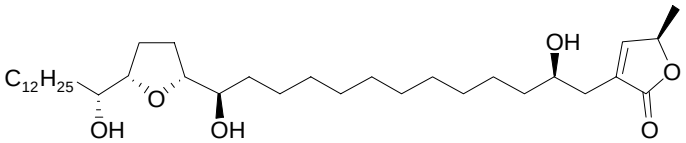
Using general procedure, butenolide **11-O1-F13** (9.0 mg, 6.6 μmol) was used to yield **10-O1-F13** (1.9 mg, 50%) as white waxy solid.

3-{(2*R*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*R*)-5-((1*R*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*S*)-5-methyl-5*H*-furan-2-one (10-O1-F17).



Using general procedure 3, butenolide **11-O1-F17** (21 mg, 14.3 μmol) was used to yield **M10-O1-F17** (2.7 mg, 33%) as white waxy solid.

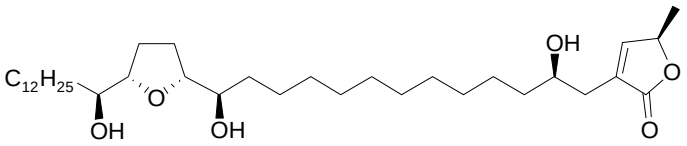
3-{(2*R*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*S*)-5-((1*R*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*R*)-5-methyl-5*H*-furan-2-one (10-O2-F5).



Using general procedure 3, butenolide **11-O2-F5** (11 mg, 9.3 μmol) was used to yield **10-O1-F5** (0.70 mg, 13%) as white waxy solid. ^{1}H NMR (600MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.1 Hz, 3H),

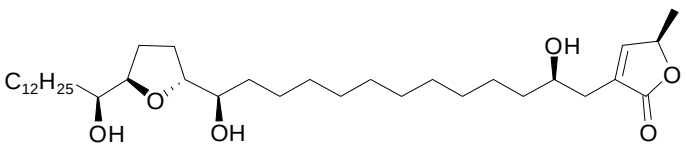
1.27-1.40 (m, 36H), 1.45 (m, 3H), 1.50 (m, 6H), 1.60 (m, 3H), 1.77-1.81 (m, 2H), 1.96 (m, 2H), 2.43 (m, 1H), 2.55 (d, *J* = 14.5 Hz, 1H), 3.47 (m, 1H), 3.87 (m, 3H), 3.92 (m,1H), 5.07 (m, 1H), 7.20 (m, 1H); LC-MS (ESI) *m/z*: 619.5 $(M + K)^+$, 603.5 $(M + Na)^+$, 581.5 $(M + H)^+$, 563.5 $M + H - H_2O)^+$, 545.5 $(M + H - 2H_2O)^+$, 527.5 $(M + H - 3H_2O)^+$;

3-{(2*R*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*S*)-5-((1*S*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*R*)-5-methyl-5*H*-furan-2-one (10-O2-F9).



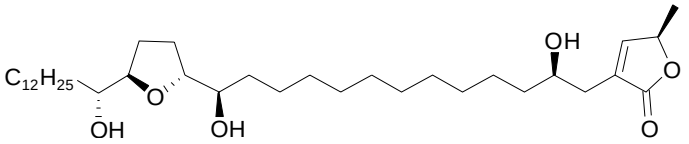
Using general procedure 3, butenolide **11-O2-F9** (14 mg, 10 μmol) was used to yield **10-O2-F9** (1.1 mg, 18%) as white waxy solid. ^{1}H NMR (600MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.27-1.40 (m, 36H), 1.44 (d, *J* = 6.8Hz, 3H), 1.46-1.51 (m, 6H), 1.66 (m, 3H), 1.73-1.76 (m, 2H), 1.93-1.97 (m, 2H), 2.41 (dd, J_1 = 15.1Hz, J_2 = 8.3Hz, 1H), 2.54 (d, *J* = 15.1 Hz, 1H), 3.42-3.45 (m, 2H), 3.82-3.88 (m, 3H), 5.07 (qq, J_1 = 6.8Hz, J_2 = 1.4Hz, 1H), 7.19 (q, *J* = 1.3Hz, 1H); LC-MS (ESI) *m/z*: 619.5 $(M + K)^+$, 603.5 $(M + Na)^+$, 581.5 $(M + H)^+$, 563.5 $(M + H - H_2O)^+$, 545.5 $(M + H - 2H_2O)^+$, 527.5 $(M + H - 3H_2O)^+$;

3-{(2*R*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*R*)-5-((1*S*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*R*)-5-methyl-5*H*-furan-2-one (10-O2-F13).



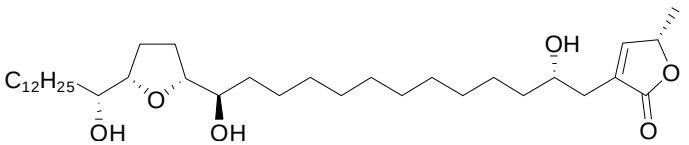
Using general procedure 3, butenolide **11-O2-F13** (12 mg, 8.7 μmol) was used to yield **10-O2-F13** (0.90 mg, 18%) as white waxy solid. ^{1}H NMR (600MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.1Hz, 3H), 1.27-1.39 (m, 43H), 1.44 (d, *J* = 6.7Hz, 3H), 1.56 (m, 3H), 1.86-1.93 (m, 2H), 2.01 (m, 1H), 2.41 (dd, J_1 = 14.5Hz, J_2 = 8.0Hz, 1H), 2.54 (d, *J* = 14.6 Hz, 1H), 3.40 (m, 1H), 3.83-3.84 (m, 4H), 5.07 (q, *J* = 6.0Hz, 1H), 7.19 (m, 1H); LC-MS (ESI) *m/z*: 619.5 $(M + K)^+$, 603.5 $(M + Na)^+$, 581.5 $(M + H)^+$, 563.5 $(M + H - H_2O)^+$, 545.5 $(M + H - 2H_2O)^+$, 527.5 $(M + H - 3H_2O)^+$

3-{(2*R*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*R*)-5-((1*R*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*R*)-5-methyl-5*H*-furan-2-one (10-O2-F17).



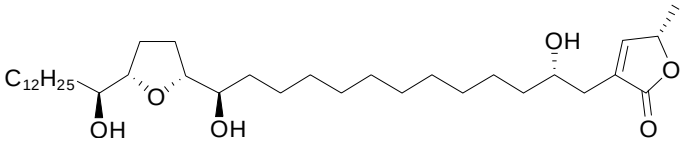
Using general procedure 3, butenolide **11-O2-F17** (28 mg, 19 μmol) was used to yield **10-O2-F17** (1.8 mg, 16%) as white waxy solid. ^{1}H NMR (600MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.1Hz, 3H), 1.27-1.35 (m, 39H), 1.37-1.43 (m, 3H), 1.44 (d, *J* = 6.8Hz, 3H), 1.48-1.51 (m, 3H), 1.70 (m, 2H), 1.98-2.00 (m, 2H), 2.41 (dd, J_1 = 15.1Hz, J_2 = 8.3Hz, 1H), 2.54 (d, *J* = 15.1 Hz, 1H), 3.41 (q, *J* = 6.0Hz, 2H), 3.81 (q, *J* = 6.6Hz, 4H), 3.83-3.86 (m, 1H), 5.07 (q, *J* = 6.9Hz, 1H), 7.19 (m, 1H); LC-MS (ESI) *m/z*: 619.5 $(M + K)^+$, 603.5 $(M + Na)^+$, 581.5 $(M + H)^+$, 563.5 $(M + H - H_2O)^+$, 545.5 $(M + H - 2H_2O)^+$, 527.5 $(M + H - 3H_2O)^+$;

3-{(2*S*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*S*)-5-((1*R*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*S*)-5-methyl-5*H*-furan-2-one (10-O3-F5).



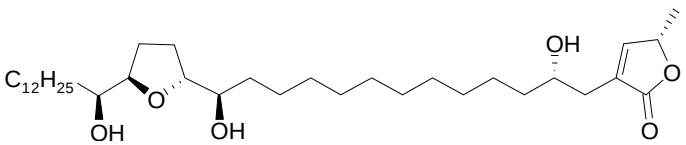
Using general procedure 3, butenolide **11-O3-F5** (3.8 mg, 3.0 μmol) was used to yield **10-O3-F5** (1.0 mg, 57%) as white waxy solid. ^{1}H NMR (600MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.9Hz, 3H), 1.28-1.32 (m, 34H), 1.39-1.41 (m, 2H), 1.46 (d, *J* = 6.8Hz, 3H), 1.50-1.53 (m, 6H), 1.59 (m, 3H), 1.75-1.84 (m, 2H), 1.94-2.01 (m, 2H), 2.43 (dd, J_1 = 15.1Hz, J_2 = 8.2Hz, 1H), 2.56 (d, *J* = 15.6 Hz, 1H), 3.47-3.48 (m, 1H), 3.84-3.86 (m, 3H), 3.93 (m, 1H), 5.08 (q, *J* = 6.5Hz, 1H), 7.19 (m, 1H); LC-MS (ESI) *m/z*: 619.5 $(M + K)^+$, 603.5 $(M + Na)^+$, 581.5 $(M + H)^+$, 563.5 $(M + H - H_2O)^+$, 545.5 $(M + H - 2H_2O)^+$, 527.5 $(M + H - 3H_2O)^+$;

3-{(2*S*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*S*)-5-((1*S*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*S*)-5-methyl-5*H*-furan-2-one (10-O3-F9).



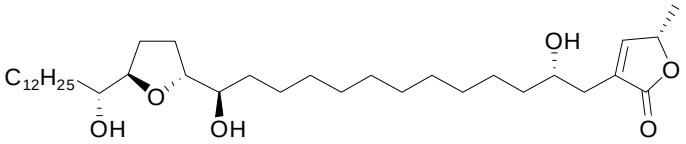
Using general procedure 3, butenolide **11-O3-F9** (6.4 mg, 4.7 μmol) was used to yield **1O-O3-F9** (1.8 mg, 66%) as white waxy solid. ^{1}H NMR (600MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.8Hz, 3H), 1.27-1.41 (m, 36H), 1.44 (d, *J* = 6.5Hz, 3H), 1.48 (m, 6H), 1.64 (m, 3H), 1.77 (m, 2H), 1.95 (m, 2H), 2.41 (dd, J_1 = 15.2Hz, J_2 = 8.3Hz, 1H), 2.54 (d, *J* = 14.4 Hz, 1H), 3.44 (m, 2H), 3.85 (m, 3H), 5.07 (q, *J* = 6.1Hz, 1H), 7.19 (m, 1H); LC-MS (ESI) *m/z*: 619.5 $(M + K)^+$, 603.5 $(M + Na)^+$, 581.5 $(M + 1)^+$, 563.5 $(M + H - H_2O)^+$, 545.5 $(M + H - 2H_2O)^+$, 527.5 $(M + H - 3H_2O)^+$;

3-{(2*S*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*R*)-5-((1*S*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*S*)-5-methyl-5*H*-furan-2-one (10-O3-F13).



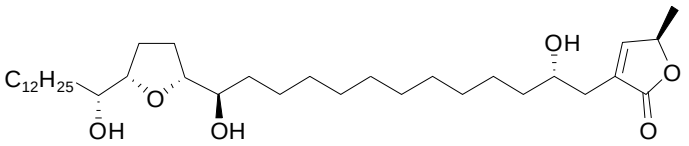
Using general procedure 3, butenolide **11-O3-F13** (7.5 mg, 5.2 μmol) was used to yield **10-O3-F13** (1.4 mg, 46%) as white waxy solid. ^{1}H NMR (600MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.9Hz, 3H), 1.27-1.31 (m, 34H), 1.39 (m, 4H), 1.44 (d, *J* = 6.8Hz, 3H), 1.47-1.51 (m, 4H), 1.58-1.66 (m, 4H), 1.86-1.94 (m, 2H), 1.99-2.03 (m, 1H), 2.41 (dd, J_1 = 15.2Hz, J_2 = 8.3Hz, 1H), 2.54 (d, *J* = 14.9 Hz, 1H), 3.40 (q, *J* = 4.5Hz, 1H), 3.82-3.88 (m, 4H), 5.07 (q, *J* = 6.5Hz, 1H), 7.19 (m, 1H); LC-MS (ESI) *m/z*: 619.5 $(M + K)^+$, 603.5 $(M + Na)^+$, 581.5 $(M + H)^+$, 563.5 $(M + H - H_2O)^+$, 545.5 $(M + H - 2H_2O)^+$, 527.5 $(M + H - 3H_2O)^+$

3-{(2*S*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*R*)-5-((1*R*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*S*)-5-methyl-5*H*-furan-2-one (10-O3-F17).



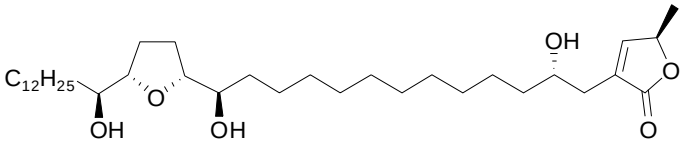
Using general procedure 3, butenolide **11-O3-F17**(17 mg, 11 μmol) was used to yield **10-O3-F17** (1.2 mg, 19%) as white waxy solid. ^{1}H NMR (600MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.0Hz, 3H), 1.27-1.35 (m, 33H), 1.39-1.43 (m, 4H), 1.44 (d, *J* = 6.8Hz, 3H), 1.47-1.51 (m, 3H), 1.56 (m, 3H), 1.69-1.71 (m, 2H), 1.98-2.00 (m, 2H), 2.27 (m, 2H), 2.41 (dd, J_1 = 15.1Hz, J_2 = 8.2Hz, 1H), 2.54 (dt, J_1 = 15.1Hz, J_2 = 1.6Hz, 1H), 3.41 (q, *J* = 6.0Hz, 2H), 3.81 (q, *J* = 6.4Hz, 2H), 3.85-3.86 (m, 1H), 5.07 (q, *J* = 6.3Hz, 1H), 7.19 (m, 1H); LC-MS (ESI) *m/z*: 619.5 $(M + K)^+$, 603.5 $(M + Na)^+$, 581.5 $(M + H)^+$, 563.5 $(M + H - H_2O)^+$, 545.5 $(M + H - 2H_2O)^+$, 527.5 $(M + H - 3H_2O)^+$

3-{(2*S*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*S*)-5-((1*R*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*R*)-5-methyl-5*H*-furan-2-one (10-O4-F5).



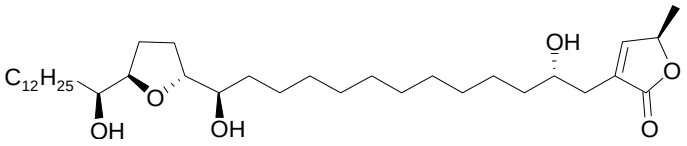
Using general procedure 3, butenolide **11-O4-F5** (3.8 mg, 2.9 μmol) was used to yield **10-O4-F5** (0.5 mg, 30%) as white waxy solid. ^{1}H NMR (600MHz, $CDCl_3$) δ 0.89 (t, J = 6.9Hz, 3H), 1.26-1.34 (m, 34H), 1.37-1.39 (m, 3H), 1.44 (d, J = 6.8Hz, 3H), 1.47-1.51 (m, 5H), 1.61 (m, 3H), 1.73-1.83 (m, 2H), 1.92-1.99 (m, 2H), 2.40 (dd, J_1 = 15.2Hz, J_2 = 8.3Hz, 1H), 2.55 (d, J = 15.2Hz, 1H), 3.44-3.66 (m, 1H), 3.81-3.86 (m, 3H), 3.90-3.92 (m, 1H), 5.06 (qq, J_1 = 6.9Hz, J_2 = 1.4Hz, 1H), 7.19 (q, J = 1.2Hz, 1H); LC-MS (ESI) *m/z*: 619.5 $(M + K)^+$, 603.5 $(M + Na)^+$, 581.5 $(M + H)^+$, 563.5 $(M + H - H_2O)^+$, 545.5 $M + H - 2H_2O)^+$, 527.5 $(M + H - 3H_2O)^+$

3-{(2*S*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*S*)-5-((1*S*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*R*)-5-methyl-5*H*-furan-2-one (10-O4-F9).



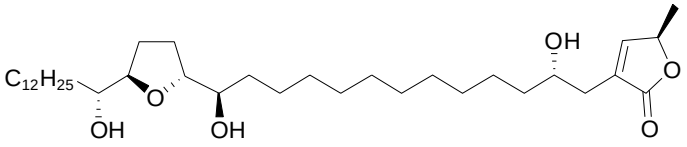
Using general procedure 3, butenolide **11-O4-F9** (6.1 mg, 4.4 μmol) was used to yield **10-O4-F9** (0.8 mg, 31%) as white waxy solid. ^{1}H NMR (600MHz, $CDCl_3$) δ 0.89 (t, J = 6.9Hz, 3H), 1.27-1.41 (m, 36H), 1.44 (d, J = 6.7Hz, 3H), 1.48 (m, 6H), 1.62 (m, 3H), 1.77 (m, 2H), 1.95 (m, 2H), 2.40 (dd, J_1 = 14.5Hz, J_2 = 7.6Hz, 1H), 2.55 (d, J = 14.6Hz, 1H), 3.44 (m, 2H), 3.83 (m, 3H), 5.06 (q, J = 6.5Hz, 1H), 7.19 (m, 1H); LC-MS (ESI) *m/z*: 619.5 $(M + K)^+$, 603.5 $(M + Na)^+$, 581.5 $(M + H)^+$, 563.5 $(M + H - H_2O)^+$, 545.5 $(M + H - 2H_2O)^+$, 527.5 $(M + H - 3H_2O)^+$

3-{(2*S*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*R*)-5-((1*S*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*R*)-5-methyl-5*H*-furan-2-one (10-O4-F13).



Using general procedure 3, butenolide **11-O4-F13** (5.4 mg, 3.6 μmol) was used to yield **10-O4-F13** (0.5 mg, 24%) as white waxy solid. ^{1}H NMR (600MHz, $CDCl_3$) δ 0.89 (t, J = 6.9Hz, 3H), 1.27-1.30 (m, 34H), 1.37-1.41 (m, 4H), 1.44 (d, J = 6.8Hz, 3H), 1.48-1.52 (m, 4H), 1.60-1.66 (m, 3H), 1.84-1.99 (m, 2H), 2.00-2.03 (m, 2H), 2.40 (dd, J_1 = 15.0Hz, J_2 = 8.4Hz, 1H), 2.55 (d, J = 14.9Hz, 1H), 3.40-3.41 (m, 1H), 3.82-3.87 (m, 4H), 5.06 (q, J = 6.8Hz, 1H), 7.19 (m, 1H); LC-MS (ESI) *m/z*: 619.5 $(M + K)^+$, 603.5 $(M + Na)^+$, 581.5 $(M + H)^+$, 563.5 $(M + H - H_2O)^+$, 545.5 $(M + H - 2H_2O)^+$, 527.5 $(M + H - 3H_2O)^+$

3-{(2*S*,13*R*)-2,13-Dihydroxy-13-[(2*R*,5*R*)-5-((1*R*)-1-hydroxytridecyl)tetrahydrofuran-2-yl] tridecyl}-(5*R*)-5-methyl-5*H*-furan-2-one (10-O4-F17).



Using general procedure 3, butenolide **11-O4-F17** (13 mg, 8.2 μmol) was used to yield **10-O4-F17** (0.9 mg, 21%) as white waxy solid. ^{1}H NMR (600MHz, $CDCl_3$) δ 0.89 (t, J = 6.9Hz, 3H), 1.27-1.28 (m, 37H), 1.41 (m, 4H), 1.44 (d, J = 6.8Hz, 3H), 1.48-1.50 (m, 4H), 1.66-1.70 (m, 2H), 2.00 (m, 2H), 2.41 (dd, J_1 = 15.2Hz, J_2 = 8.3Hz, 1H), 2.54 (d, J = 15.7Hz, 1H), 3.42 (m, 2H),

3.82-3.86 (m, 3H), 5.07 (q, J = 6.7Hz, 1H), 7.19 (m, 1H); LC-MS (ESI) m/z: 619.5 $(M + K)^+$, 603.5 $(M + Na)^+$, 581.5 $(M + H)^+$, 563.5 $(M + H - H_2O)^+$, 545.5 $(M + H - 2H_2O)^+$, 527.5 $(M + H - 3H_2O)^+$

2. CHAPTER 2:

Tetrafibricin: Synthesis of C1-C20 and C21-C40 fragments

2.1. INTRODUCTION

In course of a screening program for fibrinogen receptor antagonists, Kamiyama and co-workers isolated tetrafibricin, a non-peptidic antagonist, from the culture broth of *streptomyces neyagawaensis NR0577*.[49] Platelet aggregation is known to have a vital role in normal heamostasis and thrombosis. "Platelets first adhere and spread onto the thrombogenic components of the vascular subendothelium at the sites of vascular lesions. Upon stimulation by an agonist such as ADP, collagen or thrombin, the fibrinogen receptors (GPIIb/IIIa), which exist as Ca^{+2} dependent heterodimer complexes, acquire the ability to bind fibrinogen through conformational changes within the molecules. Fibrinogen binding to the receptors on the surface of platelets is prerequisite for platelet aggregation. Thus, fibrinogen receptor antagonism is a good target for a platelet aggregation inhibitor."[49] Although many types of fibrinogen receptor antagonists have been reported,[50] most of them are peptide mimetics of RGDS (Arg-Gly-Asp-Ser), which is the minimal sequence in fibrinogen that is considered necessary to recognize fibrinogen receptors during aggregation. Tetrafibricin inhibited the binding of fibrinogen to its receptors with an IC_{50} of 46 nM and inhibited aggregation of human platelets induced by ADP, collagen, and thrombin. The ability of tetrafibricin to block fibrinogen from binding to its glycoprotein receptor makes it a viable target for the potential therapeutic intervention of arterial thrombotic deceases such as coronary occlusion and myocardiac infarction.[51]

The Kamiyama group elucidated the structure of tetrafibricin (Figure 2.1) by carrying out various NMR, MS and other experiments.[52] The molecular formula was determined as $C_{41}H_{67}NO_{13}$ from HRFAB-MS (Calcd: 782.4691, Found: *m/z* 782.4676 $(M + H)^+$). Positive color reactions to ninhydrin and 2,4-dinitrophenylhydrazine suggested the presence of primary amino

and carbonyl groups respectively. The IR spectral data of **1** suggested the presence of carboxyl and/or carbonyl (3000-2500, 1710 cm $^{-1}$) along with hydroxyl and/or amino (3400, 1100-1000 cm^{-1}) functionalities. UV data indicated the presence of a conjugated tetraenoic acid chromophore. Due to the instability of **1** in DMSO-*d6*, a D_2O solution of **1** purged with argon was used for the NMR experiments. A combination of the ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, HSQC and HMBC experiments were used to deduce partial structures. Additional NMR experiments on a solution of *N*-acetyldihydrotetrafibricin methyl ester in DMSO-*d6* were carried out to establish the complete connectivity of the partial structures. The structure of tetrafibricin as proposed by the Kamiyama group without addressing the stereochemistry is shown in Figure 2.1.

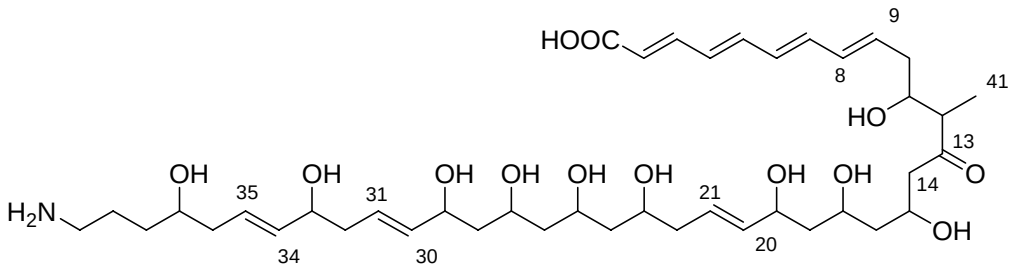


Figure 2.1 Structure of Tetrafibricin **1** as proposed by Kamiyama and co-workers

Kishi and co-workers developed the concept and logic for a universal NMR database approach to assign the relative and absolute configuration of an unknown compound without degradation and/or derivatization.[53] They have demonstrated the feasibility, reliability, and applicability of this approach in the stereochemical assignment of the desertomycin/oasomycin class of natural products,[54] as well as the mycolactones.[55] In 2003, the Kishi group reported the

elucidation of the complete stereochemistry of tetrafibricin by using the NMR databases in achiral and chiral solvents without degradation of the carbon framework (Figure 2.2).[56]

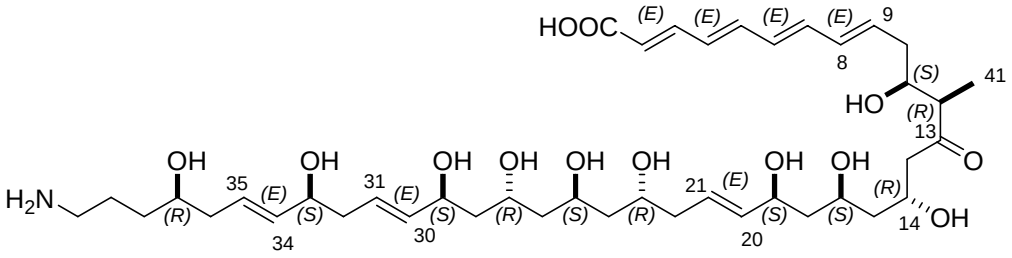


Figure 2.2 Complete stereochemistry of Tetrafibricin **1** as proposed by Kishi and Co-workers

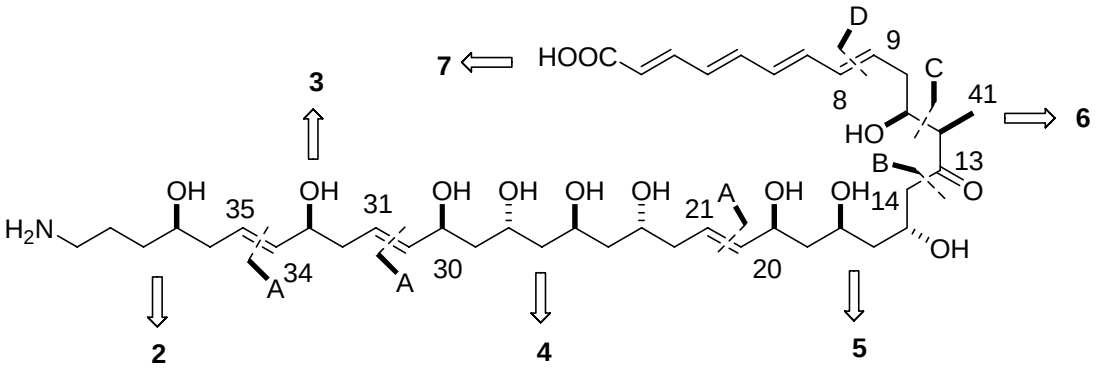
The interesting biological properties and unique structure containing primary amine, conjugated tetraenoic acid, and 1,3- and 1,5-diols render tetrafibricin an excellent target for a synthetic study. The development of an efficient, convergent synthesis of tetrafibricin will allow the synthesis of its multiple stereoisomers and facilitate structure-activity relationship studies designed to probe its biological properties.

To date, only two research groups have communicated their efforts toward the synthesis of tetrafibricin. A sequence of chemoselective cross-metathesis reactions and enantioselective allyltitanations of aldehydes has been used by Cossy and BouzBouz to prepare the C1-C13, C15-C26, and C27-C40 fragments of tetrafibiricn.[57] Roush and Lira accomplished the synthesis of C1-C19 fragment of tetrafibricin[58] via a highly diastereoselective double allylboration developed in their laboratory.[59]

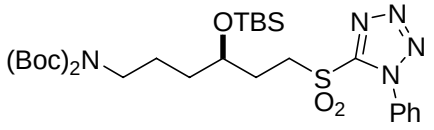
2.2. RESULTS AND DISCUSSION

2.2.1. Synthetic analysis of Tetrafibricin 1

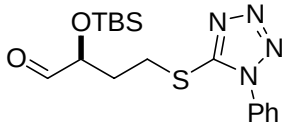
Our retrosynthetic analysis towards the synthesis of tetrafibricin is outlined in Figure 2.3. We envisioned that a series of Kocienski-Julia olefination reactions with appropriate aldehyde and sulfones will allow the formation of C20-C21, C30-C31 and C34-C35 bonds. This suggested us fragments C35-C40 **2**, C31-C34 **3**, and C21-C30 **4** as potential building blocks for the construction of C20-C40 carbon frame work of tetrafibricin **1**. Disconnection at C13-C14 bond provides fragments C14-C20 **5**and C9-C13 **6**, which are expected to be coupled by alkylation of anion of dithiane **6** with iodide **5**. Disconnection at C8-C9 provided fragment C1-C8 **7** as potential partner for Horner-Wadsworth-Emmons (HWE) olefination.



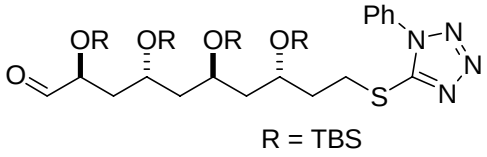
A = Kocienski-Julia olefination; **B** = Dithiane alkylation; **C** = Asymmetric aldol; **D** = HWE olefination



2 (C35-C40 Fragment)

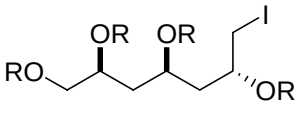


3 (C31-C34 Fragment)

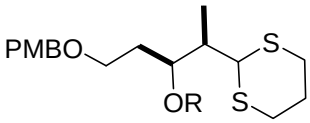


R = TBS

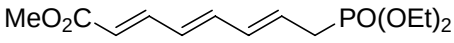
4 (C21-C30 Fragment)



5 (C14-C20 Fragment)



6 (C9-C13 Fragment)



7 (C1-C8 Fragment)

Figure 2.3 Retrosynthesis of Tetrafibricin **1**

2.2.2. Preparation of Sulfone 2: The (C35-C40) Fragment

Our plan for the synthesis of sulfone 2 is shown in figure 2.4. Disconnection at C40-N and C35-S bonds in 2 suggested **19** as potential precursor. Continuing this analysis by a disconnection at

C35-C36 bond led (*R*)-**12**, which can be prepared from the commercially available pent-4-en-1-ol **8** (figure 2.4).

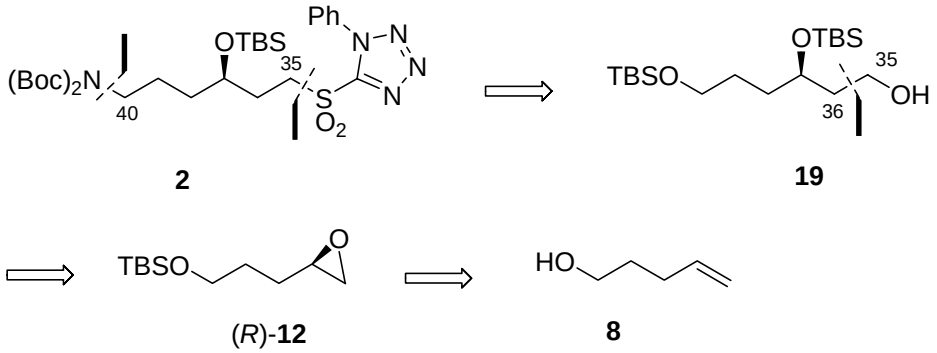
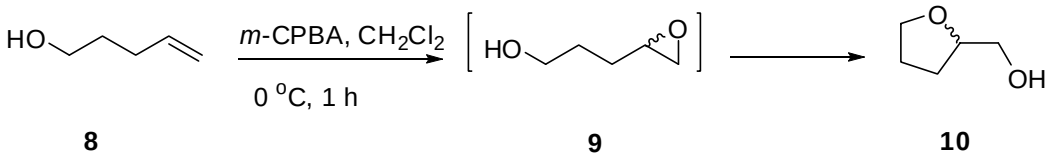


Figure 2.4 Synthetic analysis of sulfone **2**

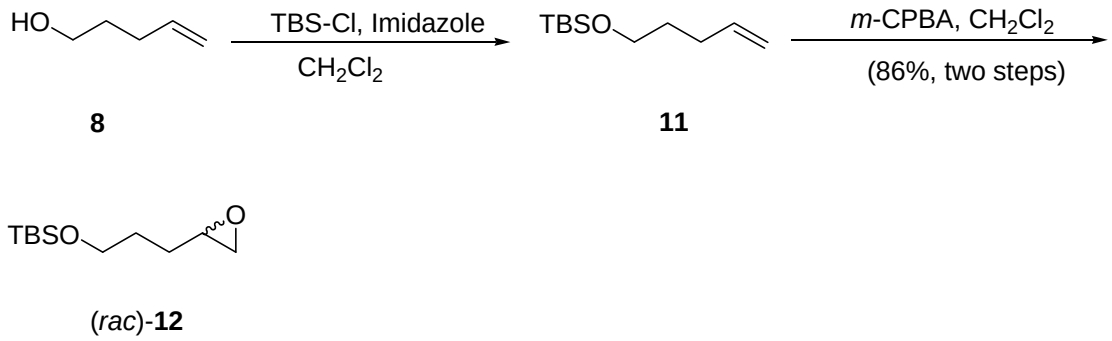
Our efforts toward the synthesis of enantiopure epoxide (*R*)-**12** commenced from the commercially available pent-4-en-1-ol **8** as shown in scheme 2.1. Alkene **8** was reacted with *m*-chloroperbenzoic acid in dichloromethane at 0 ^{o}C for 1 h to generate the corresponding epoxide **9**. However, the resulting epoxide **9** rapidly cyclized to form *rac*-(tetrahydrofuran-2-yl)methanol **10** upon concentration of the crude reaction mixture.



Scheme 2.1 Attempted epoxidation of alcohol **8**

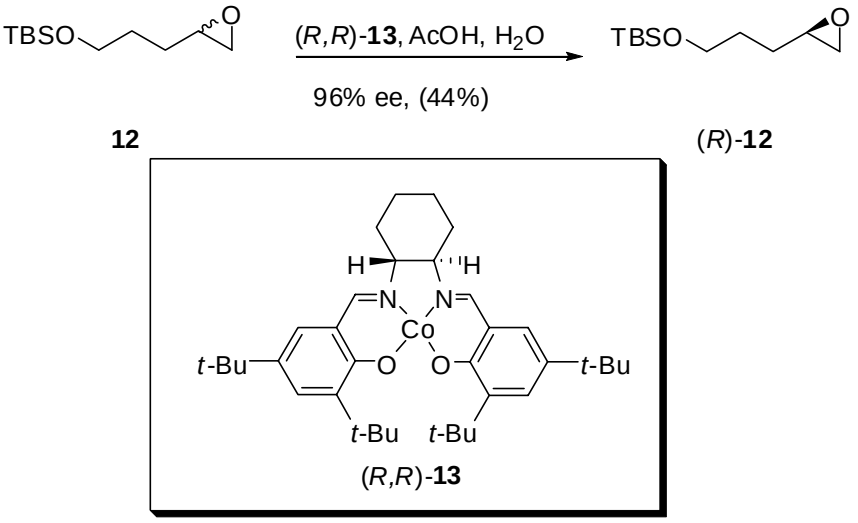
The above result indicated the necessity of initial protection of the primary alcohol **8** before attempting an epoxidation. Hence, pent-4-en-1-ol **8** was reacted with TBS chloride in

presence of imidazole in dichloromethane to afford TBS ether **11** as a crude product (scheme 2.2). The unpurified TBS ether **11** was treated with *m*-chloroperbenzoic acid in dichloromethane to afford racemic epoxide **12** in 86% overall yield for two steps.



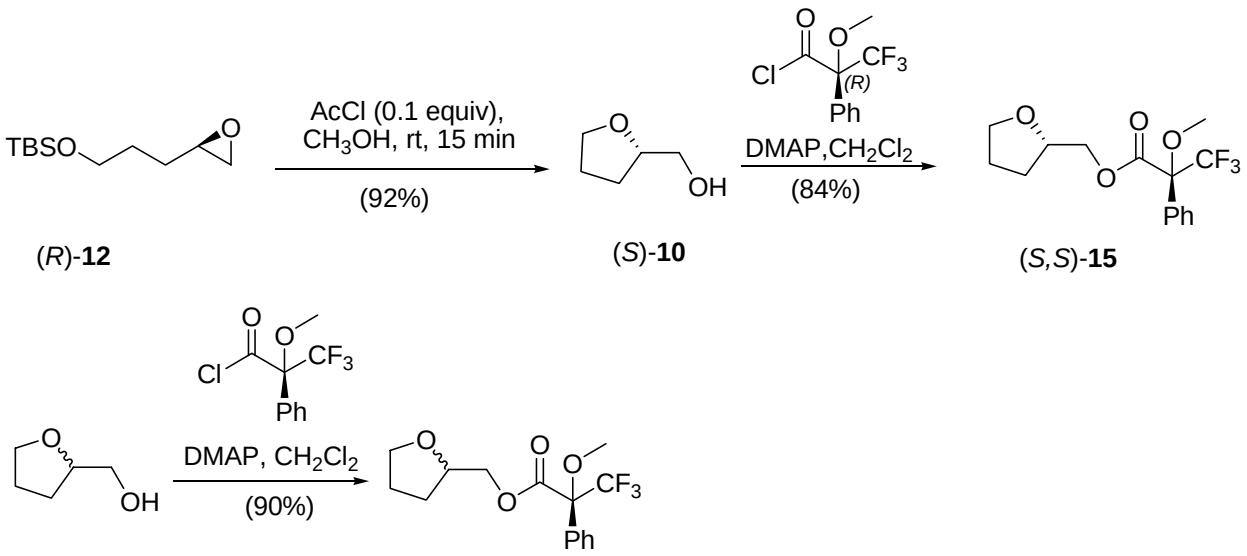
Scheme 2.2 Synthesis of epoxide (*rac*)-**12**

The racemic epoxide **12** was subjected to kinetic resolution with (*R*,*R*)-Jacobsen catalyst (*R*,*R*)-**13**[60] to afford (*R*)-*tert*-butyldimethyl(3-(oxiran-2-yl)propoxy)silane (*R*)-**12** in 44% yield and in greater than 96% enantiomeric excess (ee) purity (scheme 2.3). It is well known in the literature that kinetic resolution of terminal epoxide with (*R, R*)-Jacobsen catalyst (*R*,*R*)-**13** will provide *R*-epoxide.[61] The absolute configuration of epoxide (*R*)-**12** was assigned by this literature precedent.



Scheme 2.3 Hydrolytic kinetic resolution of the racemic epoxide **12**

The enantiomeric purity of epoxide (*R*)-**12** was assayed by ^{1}H NMR spectroscopy and GC analysis of Mosher esters as shown in scheme 2.4. A small portion (100 mg) of (*R*)-**12** was treated with methanolic HCl (made from CH_3COCl and methanol) to effect the removal of TBS protecting group and simultaneous opening of the epoxide to form (*S*)-(tetrahydrofuran-2-yl)methanol (*S*)-10 (92% yield). Then alcohol (*S*)-**10** was acylated with (*R*)-α-methoxy-α-trifluoromethyl phenylacetyl chloride (*R*)-**14** (DMAP, CH_2Cl_2) to give the Mosher ester (*S*,*S*)-**15** (84% yield). Similarly, racemic alcohol **10** was acylated with (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (*R*)-**14** to give ester (*R*/*S*,*S*)-**15** (90% yield).[62]



Scheme 2.4 Synthesis of Mosher ester

The ^{13}C NMR spectrum (125 MHz) of compound (*R*/*S*,*S*)-**15** showed peaks corresponding to two diastereomers at 25.7, 25.8 ppm and 27.9, 28.0 ppm (figure 2.5). However, ^{13}C NMR spectrum of compound (*S*,*S*)-**15** showed peaks for only one diasteromer at 25.7 and 28.0 ppm, reflecting the high enantiomericpurity of epoxide (*R*)-**12**.

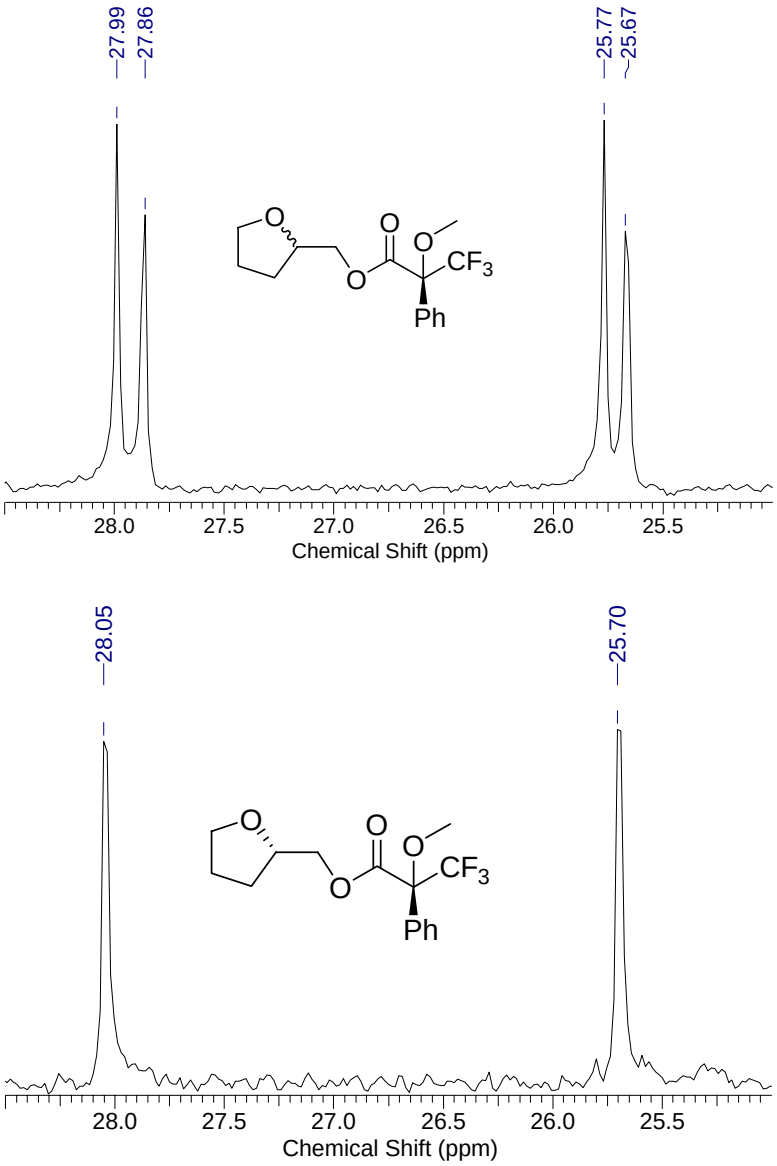
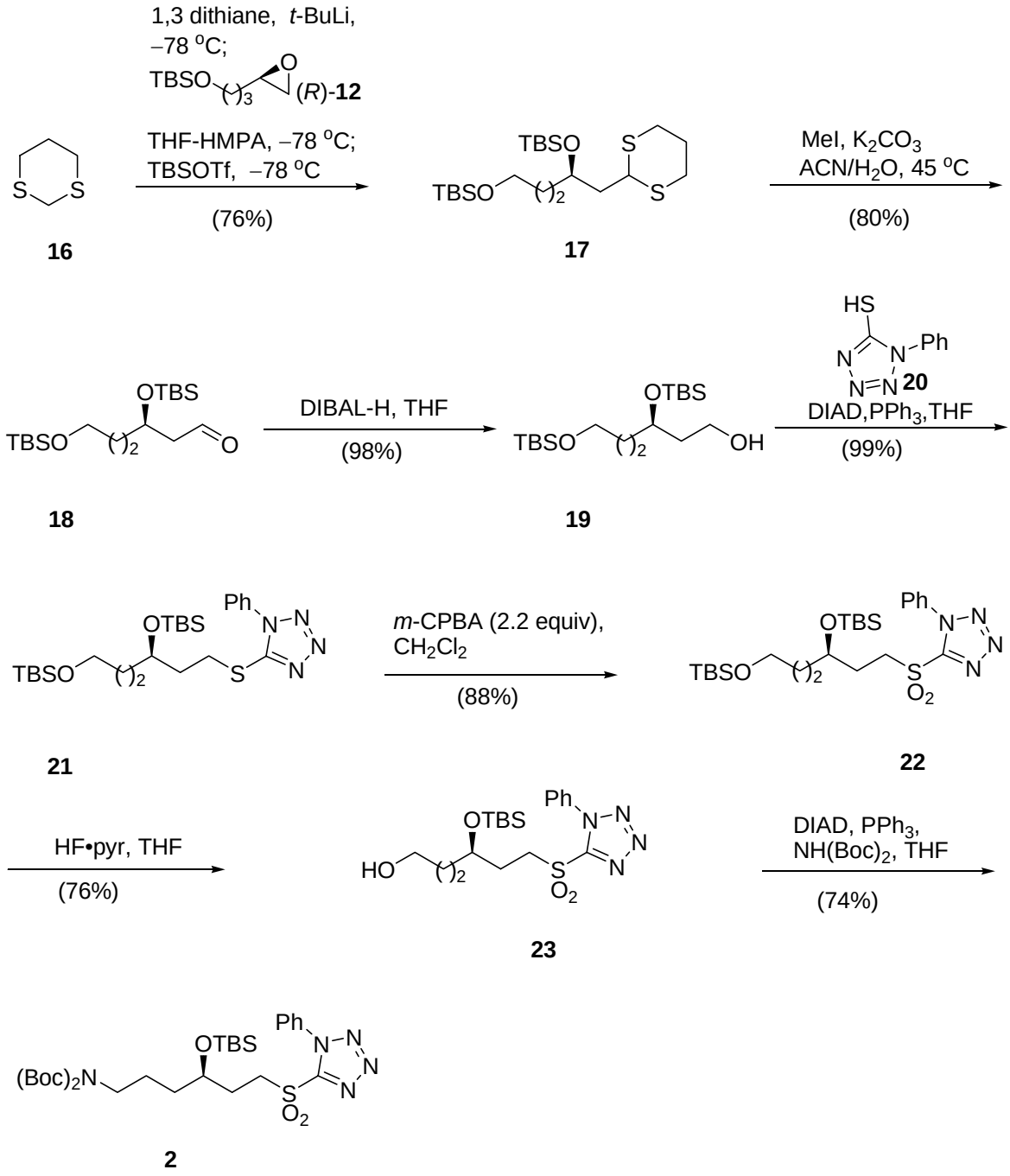


Figure 2.5 Comparison of selected resonances of the ^{13}C NMR spectra of (*R*/*S*,*S*)**-15** (top) with (*S*,*S*)-**15** (bottom)

GC analyses of (*R*/*S*,*S*)-**15** and (*S*,*S*)-**15** were performed to obtain the quantitative data of enantiomeric purity of epoxide (*R*)-**12**. GC analysis of (*R*/*S*,*S*)-**15** showed two peaks with similar intensity at 11.1 and 11.2 min corresponding to two diastereomers. With similar GC analysis of (*S*,*S*)-**15**, the enantiomeric excess (ee) was determined as 96%.

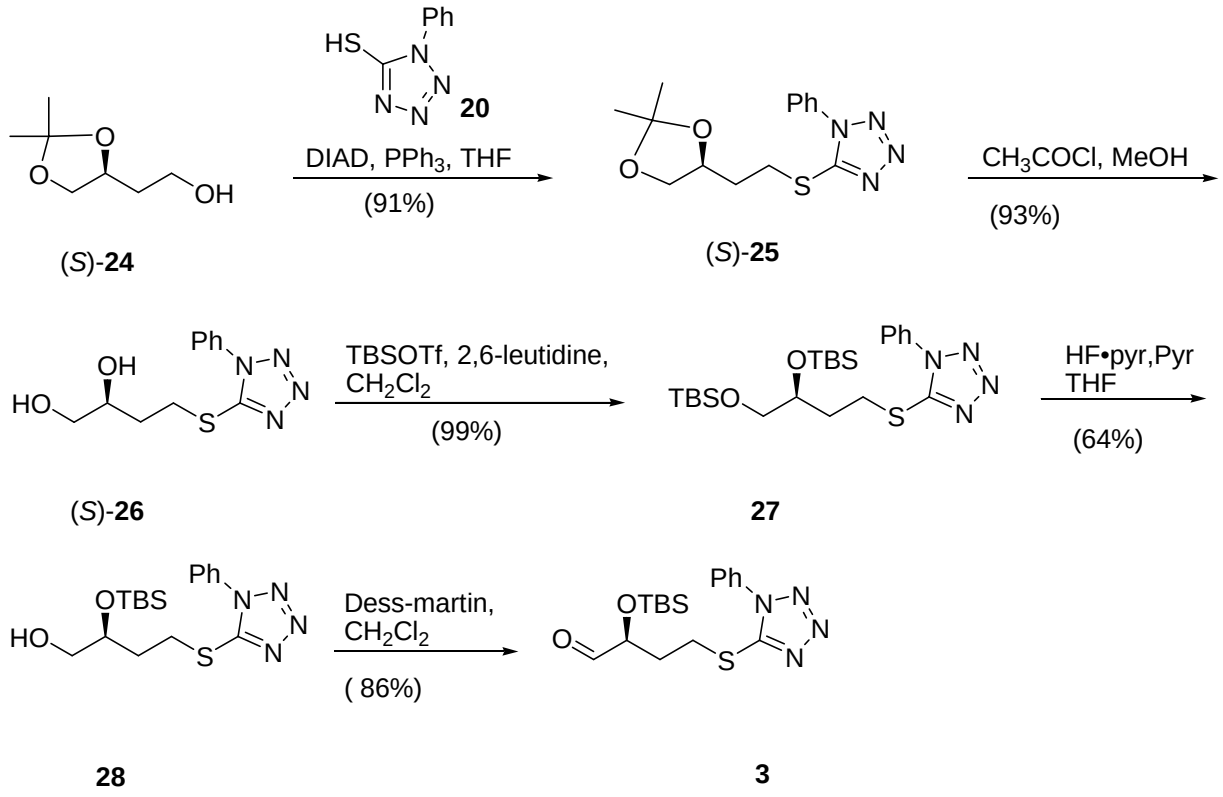
With enantiopure epoxide (*R*)-**12** in hand, we then attempted its alkylation with lithiated dithiane **16**. Epoxide (*R*)-**12** was reacted with lithiated 1,3-dithane **16** followed by trapping the resulting secondary alcoxide (not shown) with TBS-triflate to afford alkyl dithiane **17** in 83% yield (scheme 2.5). Initial attempts to convert the dithiane **17** to aldehyde **18** were unsuccessful under standard literature conditions such as [I_2,$CaCO_3$, ACN-H_2O],[63] [$PhI(CF_3CO_2)_2$, CH_3OH],[64] [$Hg(ClO_4)_3$, $CaCO_3$, THF-H_2O],[65,66] [$Hg(ClO_4)_3$,2,6-lutidine,THF-H_2O].[67] However, reaction of dithiane **17** with CH_3I and K_2CO_3 in ACN-H_2O (6:1) at 45 ^oC for 5 h gave the aldehyde **18** in 80% yield.[68] Reduction of aldehyde **18** with DiBAL-H gave the corresponding alcohol **19** in 98% yield. The alcohol **19** was then converted to alkylthiophenyltetrazole **21** in 99% yield by reacting it with 1-phenyl-1*H*-tetrazole-5-thiol **20** in presence of diisopropylazodicarboxylate (DIAD). Oxidation of sulfide **21** to the corresponding sulfone **22** was carried out with *m*-CPBA (88% yield). The primary TBS group in compound **22** was then selectively removed with HF•pyr in THF to give alcohol **23** in 76% yield. The primary alcohol **23** was reacted with di-*tert*-butyl-iminodicarboxylate in presence of DIAD to provide sulfone **2** in 74% yield.[69]



Scheme 2.5 Synthesis of sulfone **2**

2.2.3. Synthesis of Aldehyde 3: The (C31-C34) Fragment

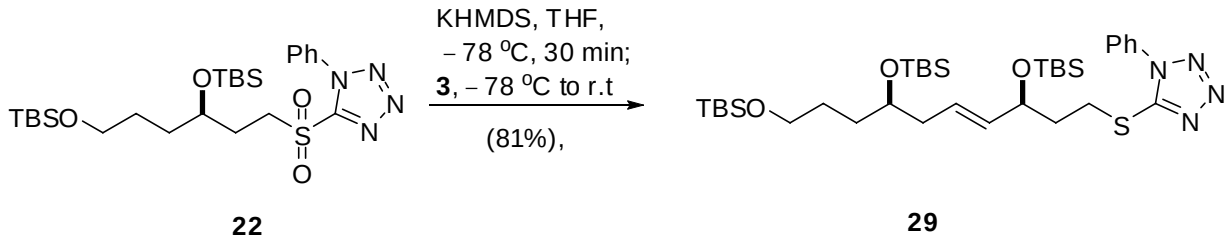
Synthesis of compound **3** commenced with commercially available (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (*S*)-**24** as shown in scheme 2.6. Incorporation of the thiotetrazole via the Mitsunobu protocol,[70] employing commercially available 1-phenyl-1*H*-tetrazole-5-thiol **20**, furnished the corresponding sulfide **25** in 91% yield. Removal of acetonide protecting group using HCl in methanol (0.1 equiv AcCl in MeOH) gave diol **26** in 93% yield. Bis-silylation of diol **26** with TBS-triflate gave sulfide **27** in 99% yield. Selective deprotection of the primary TBS group was accomplished with HF•pyr in 64% yield. Oxidation of alcohol **28** was oxidized with Dess-Martin reagent to furnish **5** in 86% yield.



Scheme 2.6 Synthesis of aldehyde **3**

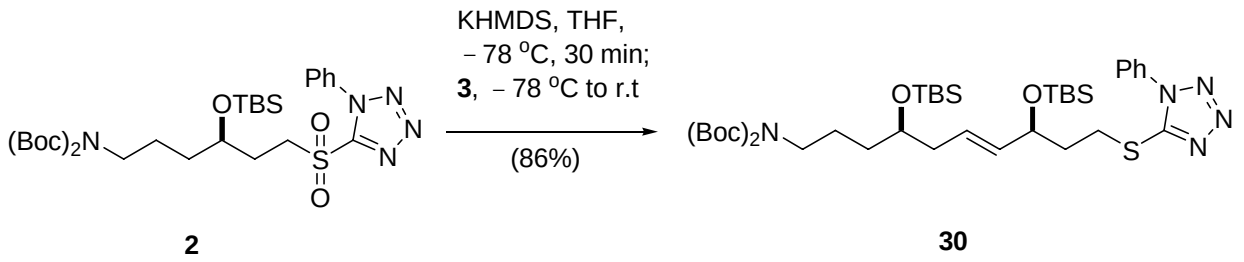
2.2.4. Kocienski-Julia olefination of sulfone 2 with aldehyde 3

With compound **2** and **3** in hand, we attempted the Kocienski-modified[71] Julia olefination[72] of aldehyde **3** with sulfones **2** and **22** to forge the *trans* C(34-35) double bond. Treatment of sulfone **22** with potassium bis(trimethylsilyl)amide (KHMDS) in THF at –78 ^{o}C for 30 min was followed by the addition of aldehyde **3** and warming to ambient temperature. Purification of the crude product provided *trans* C(34,35)-olefinic isomer **29** along with a minor isomer (10/1 ratio, in 89% yield). The minor isomer was not separable from the *E*-isomer **29** by silica chromatography. However, purification by prep HPLC with Whelk-*O* column using 98/2 hexane/isopropanol solvent furnished pure *E*-isomer **29** in 81% yield. The *E* geometry was confirmed by the large NMR coupling constant (J_{H34-35} = 15.6 Hz).



Scheme 2.7 Kocienski-Julia olefination of sulfone **22** with aldehyde **3**

Kocienski-Julia olefination was then attempted with sulfone **2** and aldehyde **3**. Anion of sulfone was initially generated with KHMDS at at –78 ^{o}C followed by the addition of aldehyde **3**. The trans C(34-35) olefin **30** was obtained tagather with a minor isomer after purification of the crude product by silica chromatography (95% yield, 9/1 mixture). Pure (*E*)-isomer **30** was obtained (86%) by preparative chiral HPLC with Whelk-*O* column using 95/5 hexanes/isopropanol as solvent. The identity of (*E*)-isomer **30** was again evident from the large NMR coupling constant ($J_{H34-H35}$ = 15.4 Hz) of the olefinic protons.



2 **30**

Scheme 2.8 Kocienski-Julia olefination of sulfone **2** with aldehyde **30**

2.2.5. Synthesis of Aldehyde 4: The (C21-C30) Fragment

The retrosynthetic analysis of compound **4** is outlined in figure 2.6. Disconnection at the C24-C25 and C25-C26 bonds gave compounds **31**, **16**, and **32** as potential precursors for the synthesis of fragment **4**. We further envisioned the synthesis of compound **31** from *D*-arabitol and compound **32** from the commercially available (*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (*R*)-**24**.

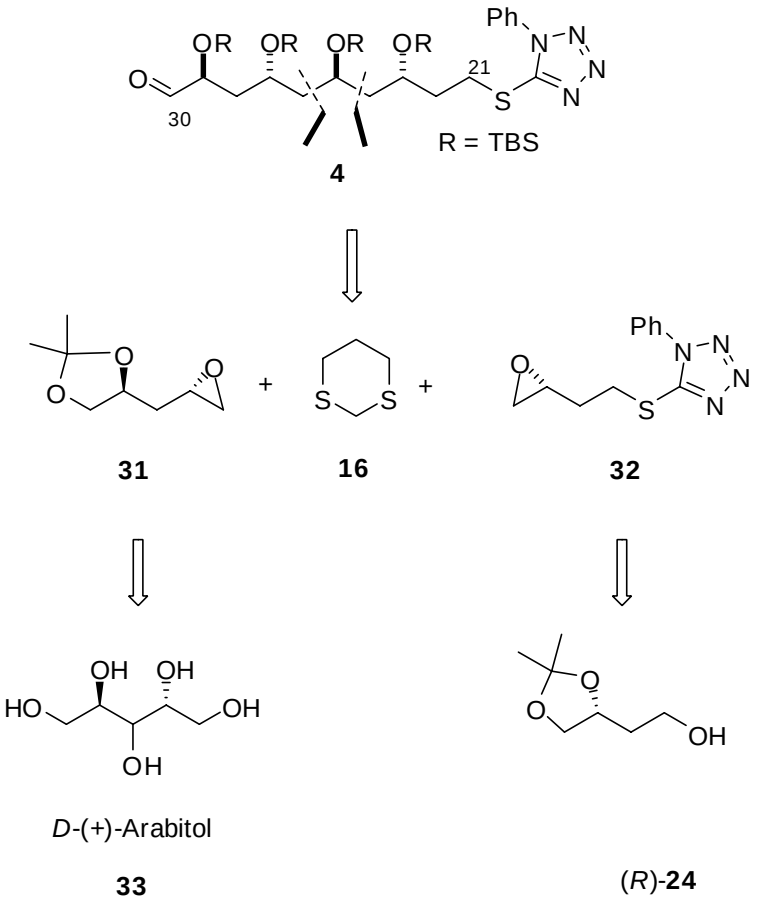
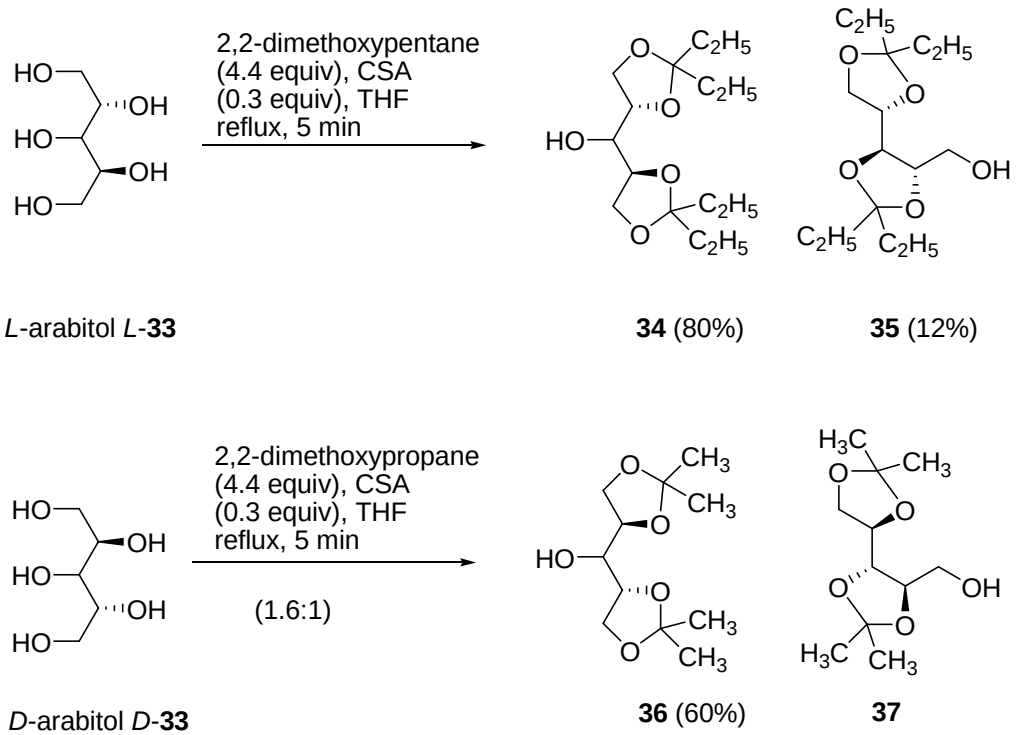


Figure 2.6 Retrosynthesis of aldehyde **4**

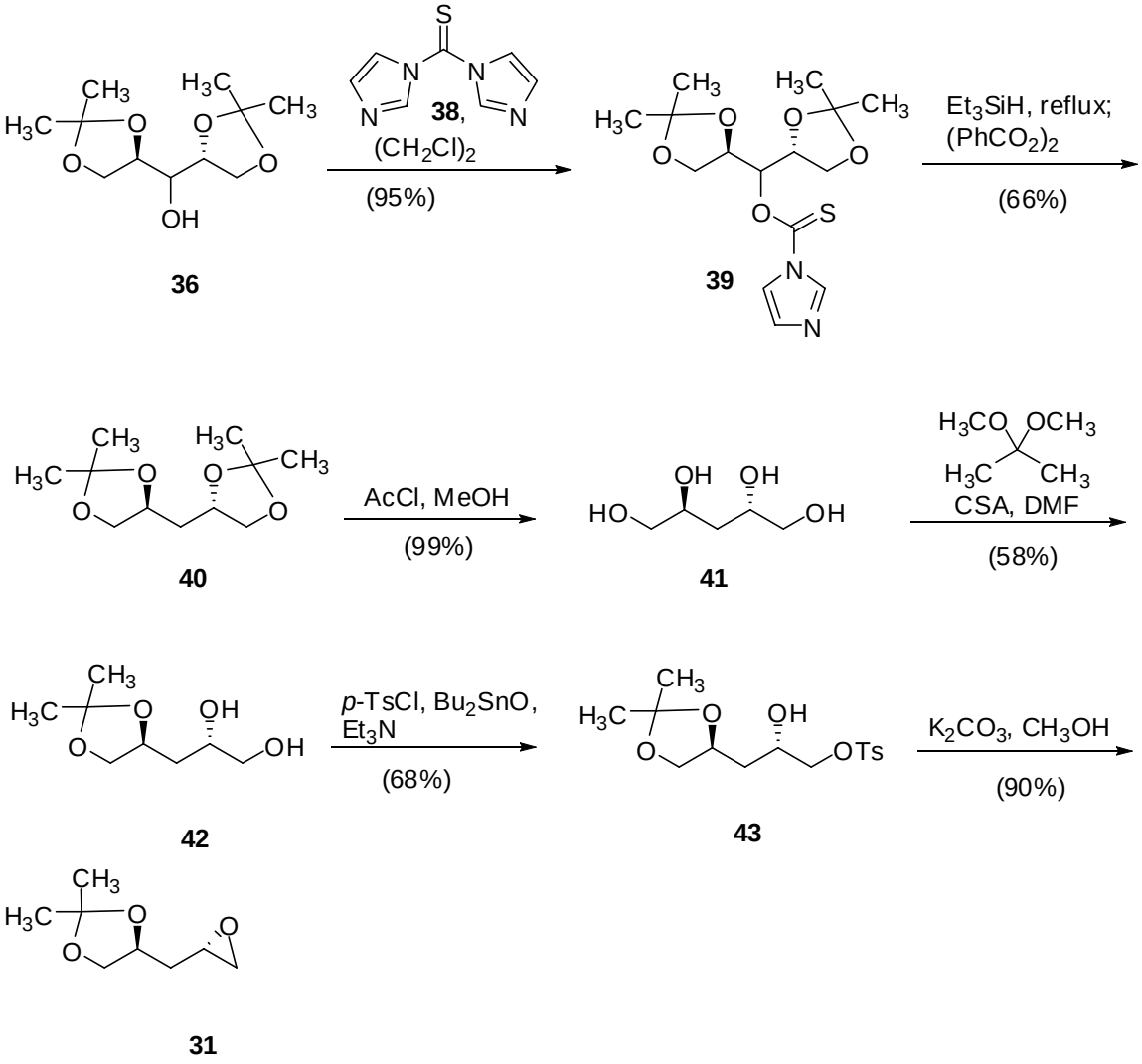
The first step towards the synthesis of compound **31** was the regioselective protection of arabitol **33** as the 1,2:4,5-*bis*-acetal product **36**. Literature reports revealed that the protection of arabitol as its *bis*-acetonide under typical conditions ($CuSO_4$, H_2SO_4, acetone, 18 h, rt) resulted in the formation of the undesired 2,3:4,5-di-*O*-isopropylidene arabitol **37**.[73] Linclau et al. reported that[74] using 3,3-dimethoxy-pentane (4.4 equiv), CSA (0.3 equiv) and short reaction time (5 min) led to the formation of di-*O*-isopentylidene acetal **34** (scheme 2.9) as the major product (80% isolated yield). Gratifyingly, employing the identical reaction conditions with *D*-**33** and 2,2-dimethoxy-propane gave 1,2:4,5-bis-acetal **36** in 60% isolated yield along with **37** (yield not determined).



Scheme 2.9 Regioselective protection of arabitol 33

The synthesis of compound **40** from 1,2:4,5-bis-acetal **36** requires reduction of the secondary hydroxyl group. To this end, the secondary alcohol **36** was reacted with *N*,*N*-thiocarbonyldi-imidazole **38** using 1,2-dichloroethane as solvent under refluxing conditions.[75] Purification of the crude product by silica chromatography furnished carbothioate **39** in 95% yield. Reduction of compound **39** with Et_3SiH/benzoyl peroxide afforded compound **40** in 66% yield. A solution of compound **40** in methanol was treated with acetyl chloride (~ 0.1 equiv) and stirred for 30 min at room temperature. Concentration of the reaction mixture gave tetrol **41** as white solid (99% yield). One of the two 1,2- diols in tetrol **41** was protected with 2,2-dimethoxypropane (DMF, CSA) to furnish diol **42** in 58% yield.[76] The primary hydroxy group of the diol **42** was selectively functionalized as tosylate **43** in 68% yield by reacting it with *p*-toluenesulfonyl chloride in presence of catalytic amount (0.2 equiv) of dibutyltin oxide.[77,78] The

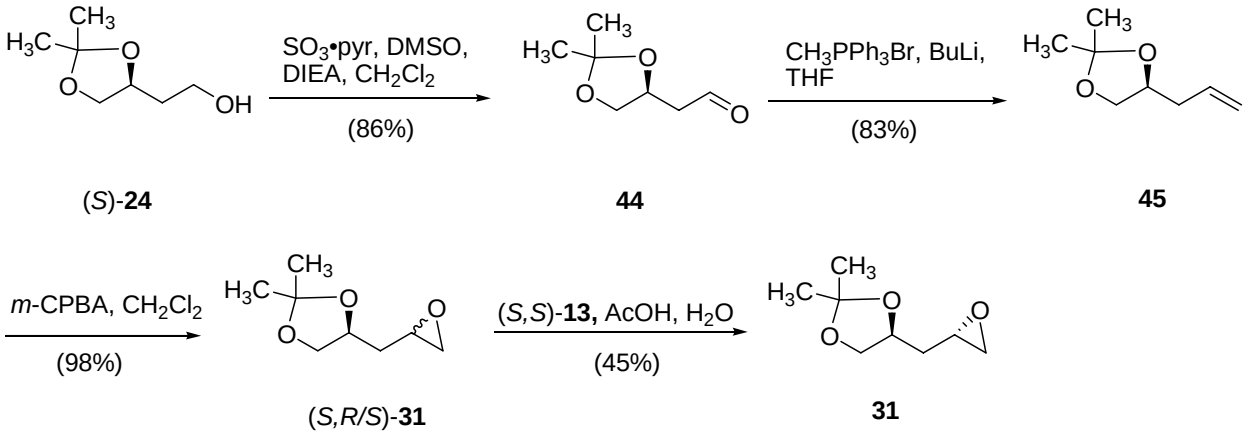
primary tosylate **43** was then converted to epoxide **31** (K_2CO_3, methanol) in 90% yield (scheme 2.10).



Scheme 2.10 Synthesis of epoxide **31**

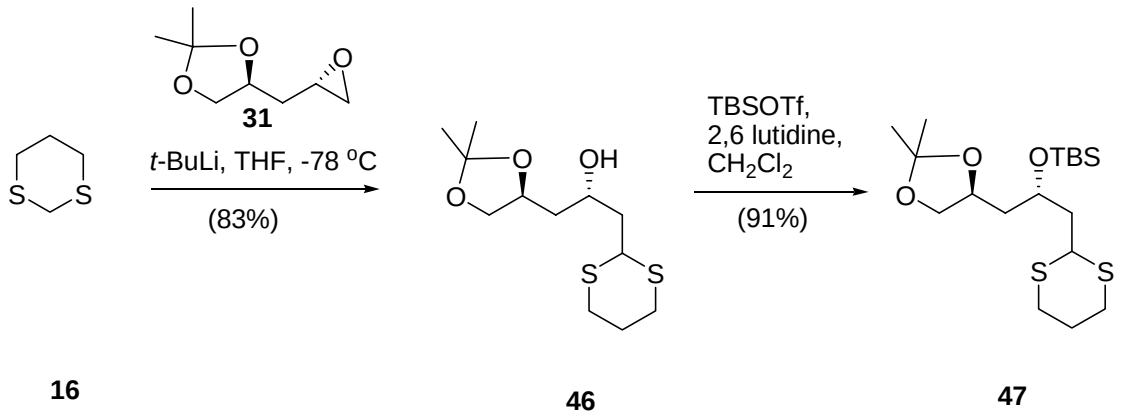
This seven-step synthesis of epoxide **31** was used initially, but we latter accomplished a four-step synthesis as shown in scheme 2.11. Oxidation of the commercially available (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (*S*)-**24** using the Parikh-Doering protocol[79] (SO_3•pyr, DMSO) gave the corresponding aldehyde **44** in 86% yield. Aldehyde **44** was then subjected to

Wittig olefination (CH_3PPh_3Br, BuLi, THF) to give alkene **45** in 83% yield. Alkene **45** was oxidized to the corresponding epoxide (*S,R/S*)-**31** using *m*-CPBA in 98% yield. Epoxide (*S,R/S*)-**31** (1/1 diastereomeric mixture) was subjected to hydrolytic kinetic resolution conditions with (*S,S*)-Jacobsen catalyst (*S,S*)-**13** to afford diastereomerically pure (by 500 MHz ^{1}H NMR) epoxide **31** in 45% yield.



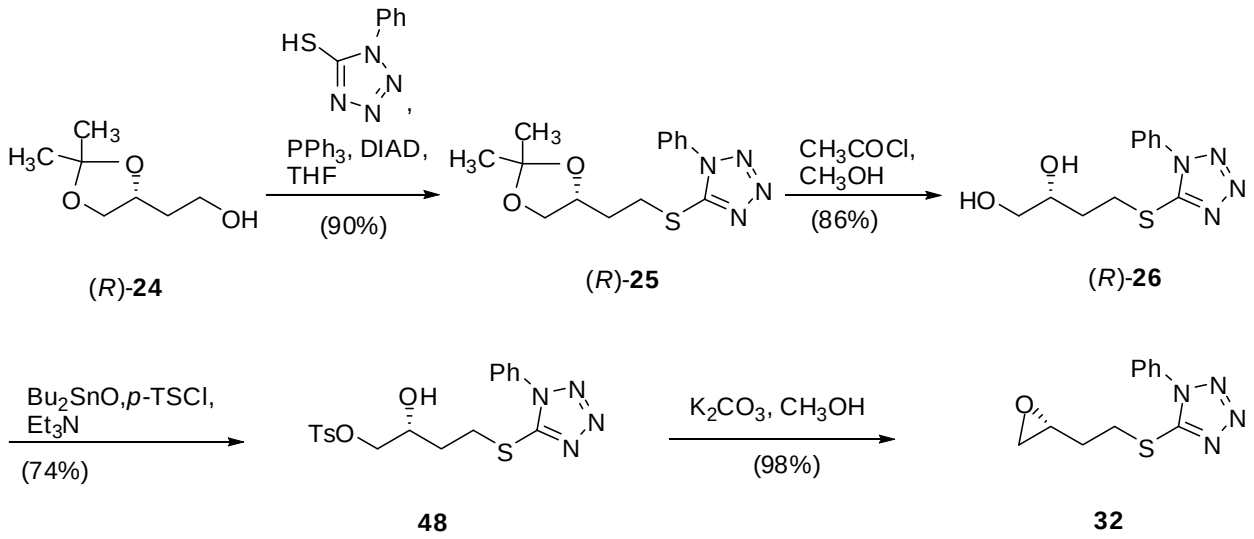
Scheme 2.11 A four-step route for the synthesis of epoxide **31**

The synthesis of compound **47** from **31** is shown in scheme 2.12. 1,3-Dithiane **16** was lithiated with *t*-BuLi at −78 ^{o}C, followed by the addition of a solution of epoxide **31** in THF/HMPA. This led to the alkylation of epoxide **31** to give secondary alcohol **46** in 83% yield. The alcohol **46** was then reacted with TBS-triflate in presence of 2,6-lutidine to give alkyldithiane **47** in 91% yield.



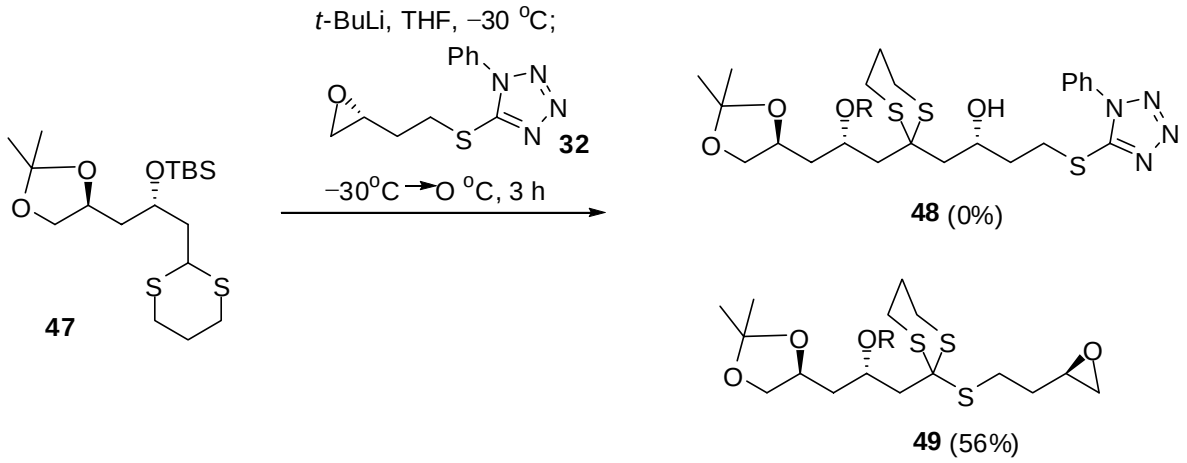
Scheme 2.12 Synthesis of dithiane **47**

Epoxide **32**, the coupling partner for dithiane **47**, was synthesized from the commercially available (*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl) ethanol (*R*)-**24** in four steps as described in scheme 2.13. A mixture of alcohol (*R*)-**24**, 1-phenyl-1*H*-tetrazole-5-thiol **20**, triphenylphosphine and diisopropylazodicarboxylate in THF was stirred at room temperature for 3 h. Standard workup and purification of the crude product by silica chromatography gave compound (*R*)-**25** in 90% yield. Exposure of compound (*R*)-**25** to methanolic HCl (AcCl in methanol) gave diol (R)-**26** in 86% yield. Selective sulfonation (*p*-TsCl, Et_3N) of primary alcohol in presence of dibutyltinoxide gave the tosylate **48** in 74% yield. Treatment of tosylate **48** with potassium carbonate in methanol gave epoxide **32** in 98% yield.



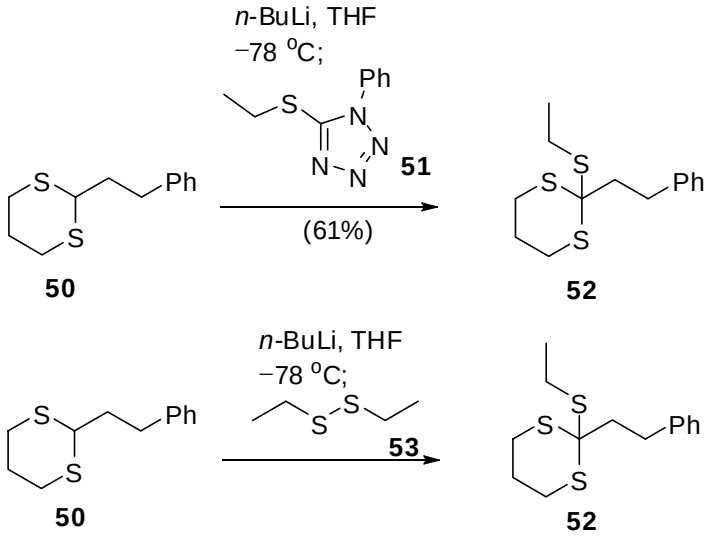
Scheme 2.13

We then attempted the alkylation of dithiane **47** with epoxide **32**, as shown in scheme 2.14. Dithiane **47** was reacted with *n*-BuLi at −30 ^{o}C for 30 min followed by the addition of a solution of epoxide **32** in THF. Standard workup and purification afforded an unexpected product **49** in 56% yield. The structure of compound **49** was consistent with ^{1}H NMR and 2D NMR (HH-COSY, HMQC and HMBC) data. However, molecular weight detected by high resolution mass spectrometry (HRMS, EI) was 479.1780, which corresponds to the fragment ion with molecular formula $C_{21}H_{39}O_4SiS_3$ (M – CH_3).



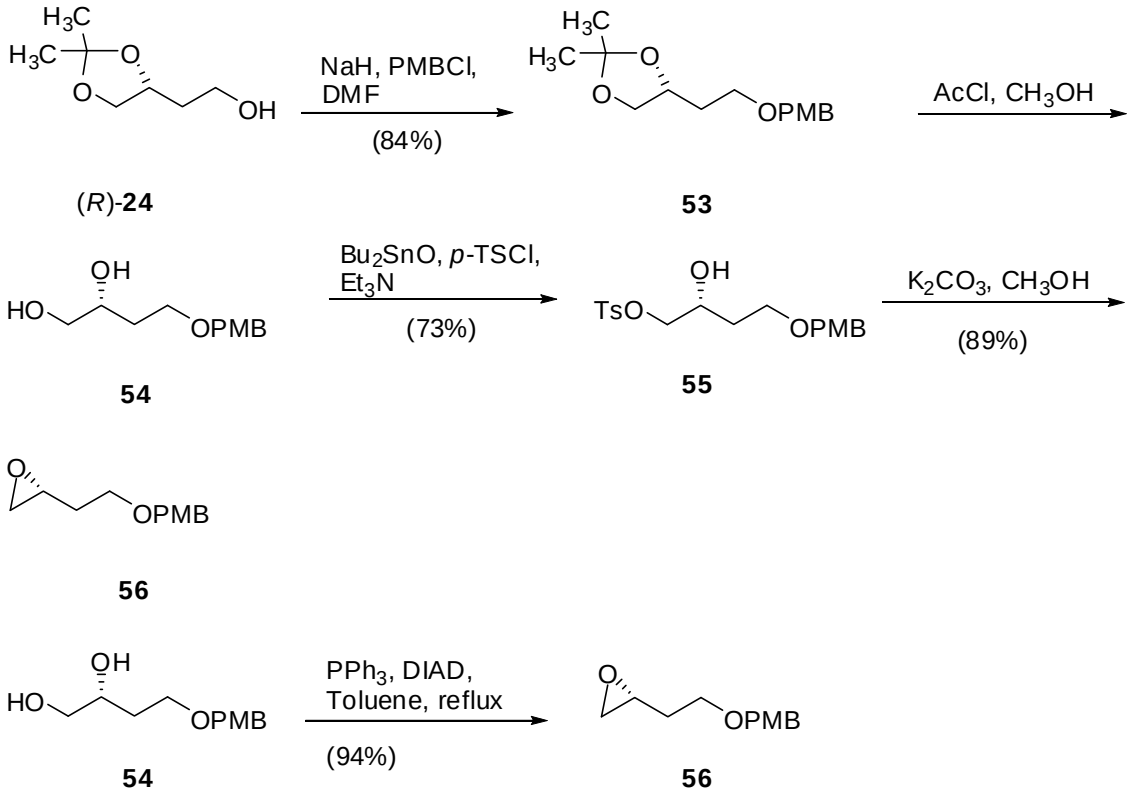
Scheme 2.14 Alkylation of dithiane 47 with epoxide 32

The proposed structure of **49** was supported with a model study conducted by Ms. Reena Bajpai (Scheme 2.15). Dithiane **50** was reacted with *n*-BuLi followed by the addition of tetrazole **51** to form compound **52** in 61% yield. An authentic sample of compound **52** was prepared by reacting anion of dithiane **50** with 1,2-diethyldisulfane. NMR data of the authentic sample was identical to compound **52**.



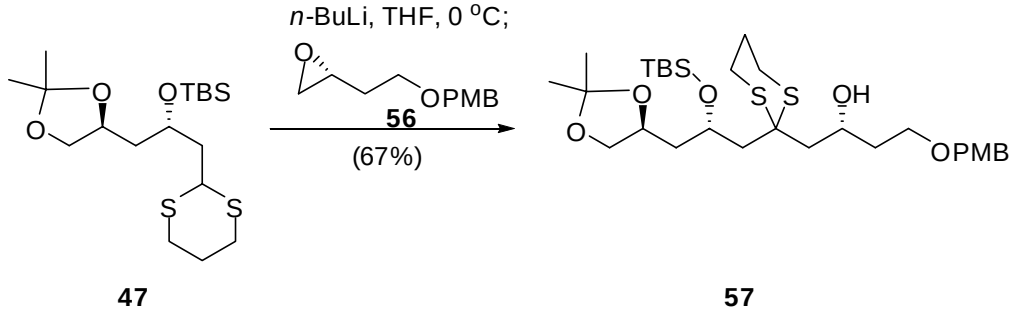
Scheme 2.15 Synthesis of compound 52 by two different methods

By considering the above results, we've decided to alkylate the dithiane **47** with epoxide **56** before the introduction of thiophenyltetrazole functionality. To this end, compound **56** with PMB-ether on the other terminus of the epoxide was envisioned as a suitable coupling partner for the lithiated dithiane **47** (scheme 2.16). A four-step synthesis of epoxide **56** from (*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (*R*)-**24** was pursued as described in scheme 2.16. Deprotonation of alcohol (*R*)-**24** with NaH followed by addition of PMB-Cl gave the PMB-ether **53** in 84% yield. Removal of 1,2-diol protecting group under catalytic acidic conditions (AcCl in methanol) gave the diol **54** in 87% yield. *p*-Toluenesulfonation of the primary alcohol **54** followed by reacting the resulted tosylate **55** with potassium carbonate in methanol gave the desired epoxide **56** in 65% yield (two steps). Alternatively, reaction of 1,2-diol **54**, with DIAD and PPh_3 [80] in toluene at reflux to furnished epoxide **56** in 94% yield.



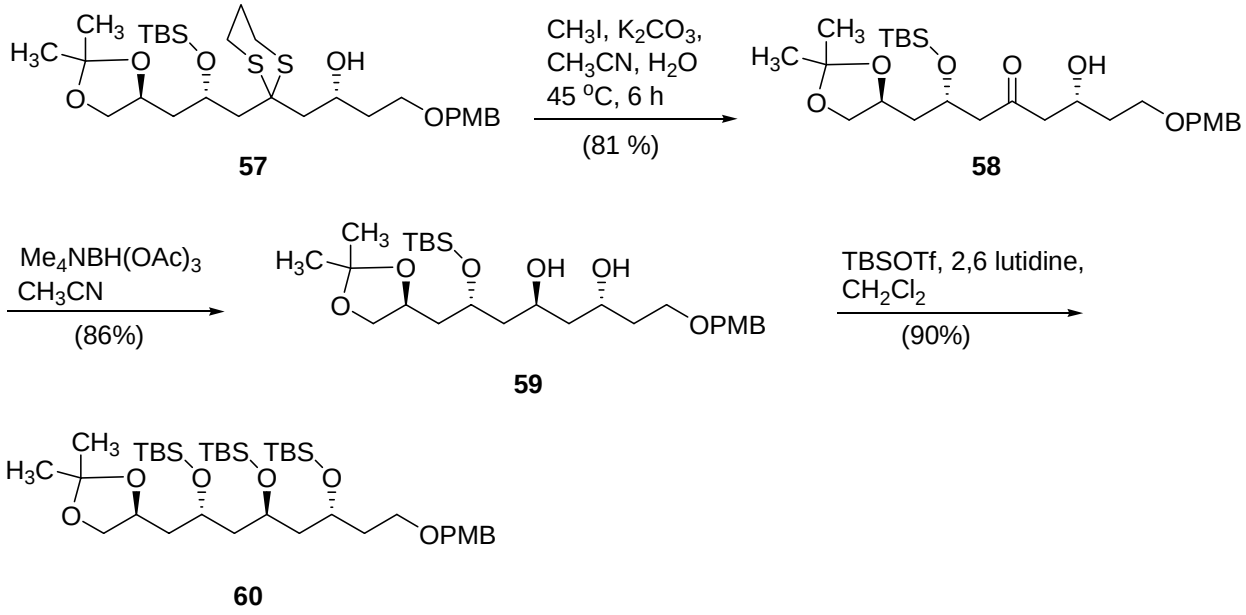
Scheme 2.16 Synthesis of epoxide 56

Dithiane **47** was reacted with *n*-BuLi for 20 min at 0 ^{o}C[81] followed by addition of epoxide **56** to afford compound **57** in 67% yield (scheme 2.17).



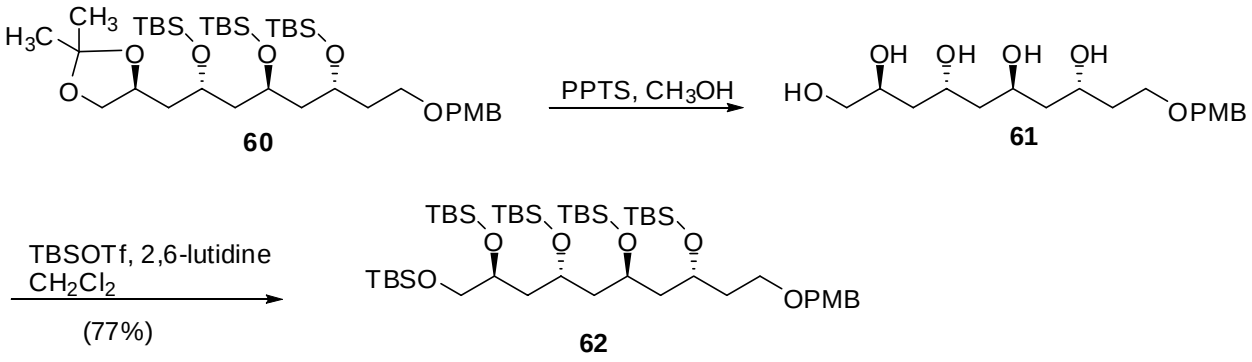
Scheme 2.17 Alkylation of dithiane **47** with epoxide **56**

Dithiane **57** was treated with methyl iodide and potassium carbonate in acetonitrile-water to furnish ketone **58** in 81% yield (scheme 2.18). The subsequent hydroxyl-directed *syn* reduction of the β-hydroxy ketone **58** with tetramethylammoniumtriacetoxy borohydride ($Me_4NHB(OAc)_3$) proceeded smoothly, affording the corresponding 1,3-*anti*-diol **59** in 86% yield as a single observable diastereomer by 500 MHz ^{1}H NMR spectroscopy. Silylation of diol **59** (TBSOTf, 2,6-lutidine) gave the compound **60** in 90% yield.



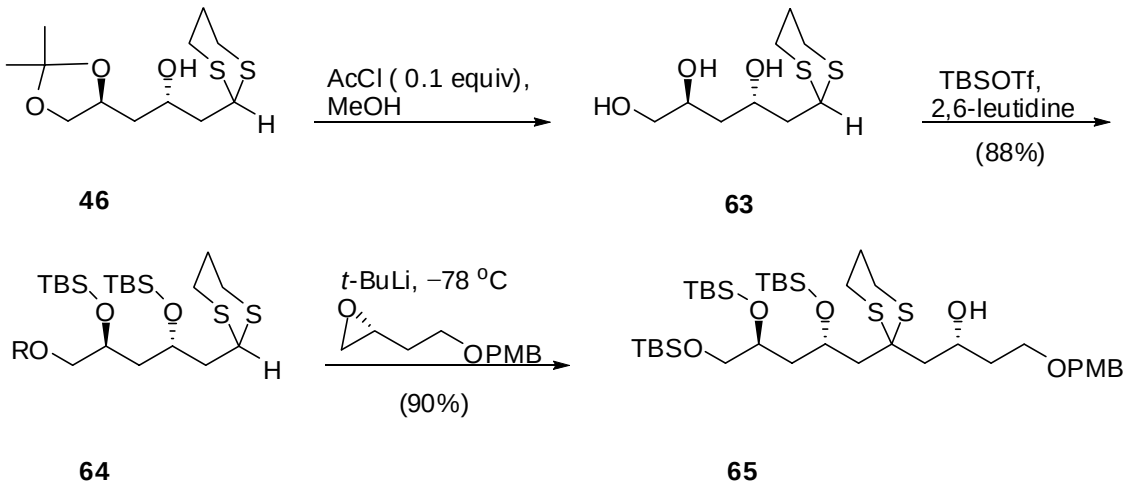
Scheme 2.18 Synthesis of PMB-ether **60**

Selective removal of 1,2-diol protecting group was attempted by treating the compound **60** with pyridinium paratoluenesulfonate (PPTS, 0.1 equiv) in methanol. Unfortunately, this resulted in loss of both acetonide and TBS protecting groups to afford **61**. The crude compound was reacted with excess TBSOTf to yield the compound **62** in 77% yield (scheme 2.19).



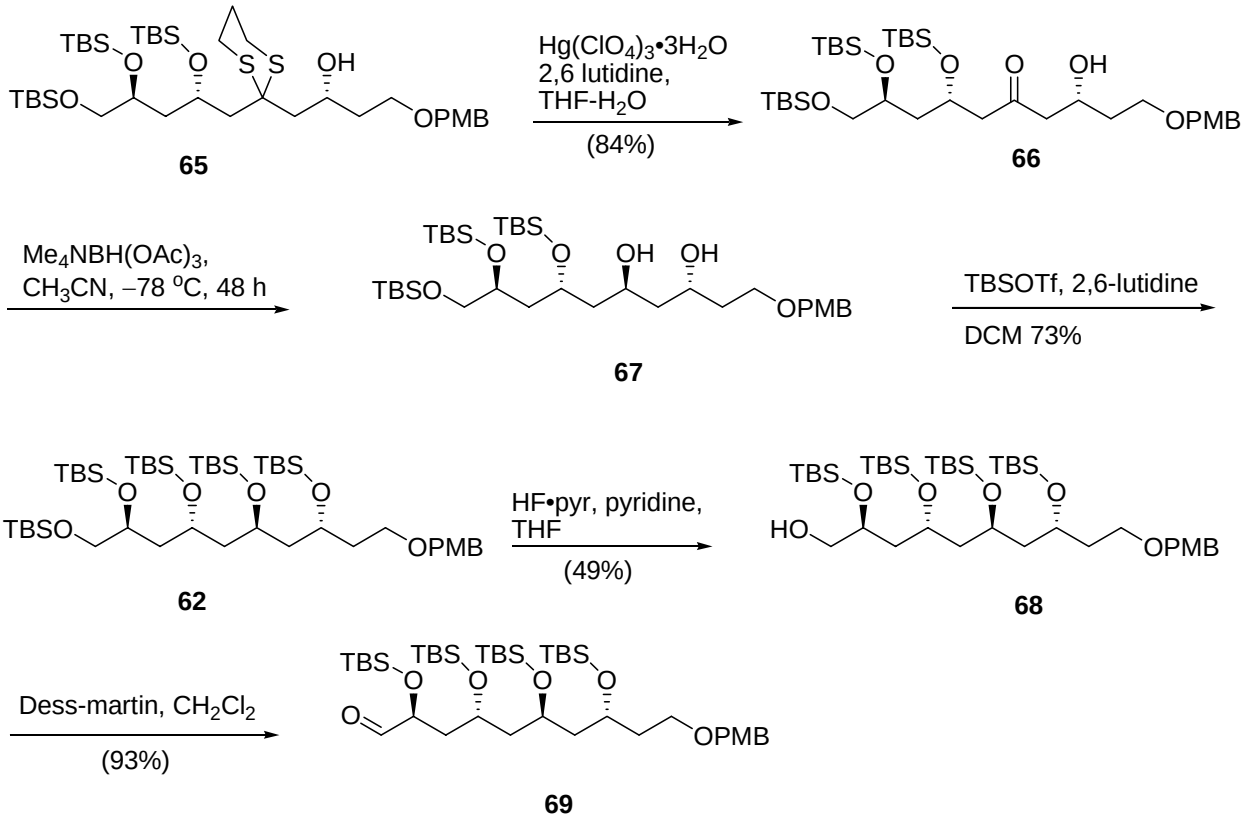
Scheme 2.19 Synthesis of PMB-ether 62

To avoid the selective cleavage of acetonide in presence of silyl ethers, an alternative synthetic path was envisioned wherein the acetonide can be cleaved in the earlier stages of the fragment synthesis (scheme 2.20). Compound **46** was subjected to catalytic acidic conditions (AcCl in methanol) to provide triol **63**, which was then reacted with TBSOTf to form the *tris*-silyl ether **64** in 88% yield. Compound **64** was lithiated with *t*-BuLi followed by addition of epoxide **56** to effect the alkylation to afford the compound **65** in 90% yield.[82]



Scheme 2.20 Synthesis of compound 65

Hydrolysis of the dithiane **65** with mercuric perchlorate in presence of 2,6-lutidine in aqueous THF provided the β-hydroxy ketone **66** in 84% yield. Hydroxy-directed *syn*-reduction with $Me_4NHB(OAc)_3$ gave the 1,3-*anti*-diol **67** which was then silylated to give the compound **62** in 73% yield. Monodesilylation of **62** with HF•pyr gave the primary alcohol **68** in 49% yield (84% based on recovered **62**). Oxidation of alcohol **68** with Dess-Martin reagent furnished aldehyde **69** in 93% yield (scheme 2.21). The above conversion of alcohol **68** to aldehyde **69** was done immediately before using **69** in the next step.



Scheme 2.21 Synthesis of aldehyde **69**

2.2.6. Synthesis of Iodide 5: The (C14-C20) Fragment

The retrosynthetic analysis of iodide **5** is outlined in figure 2.7. Disconnection at the C16-C17 bond provided **71** and **75** as potential precursors. We further envisioned the synthesis of **71** from (*S*)-**24** and **75** from (*S*)-**74**.

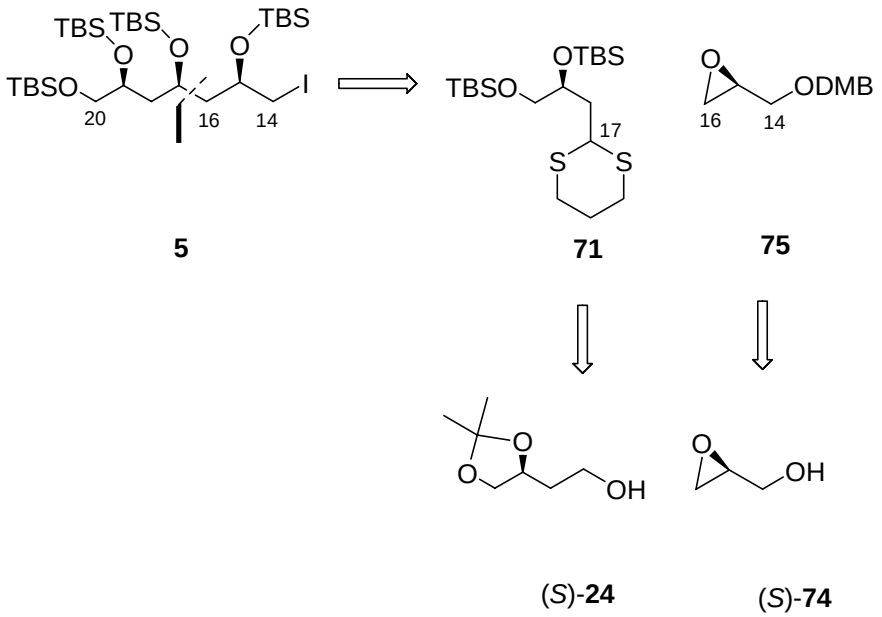
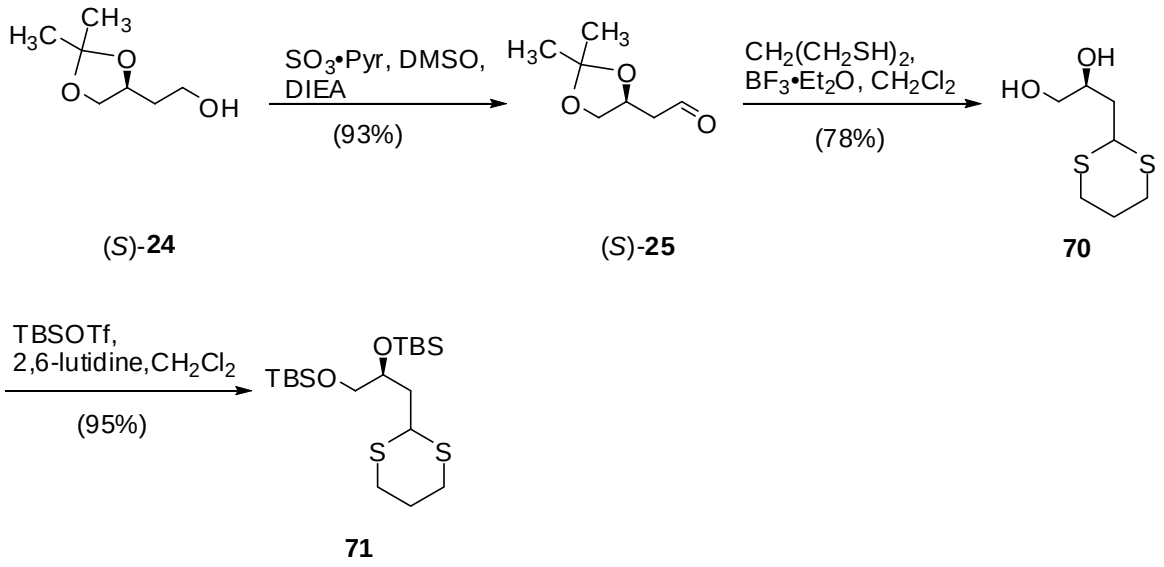


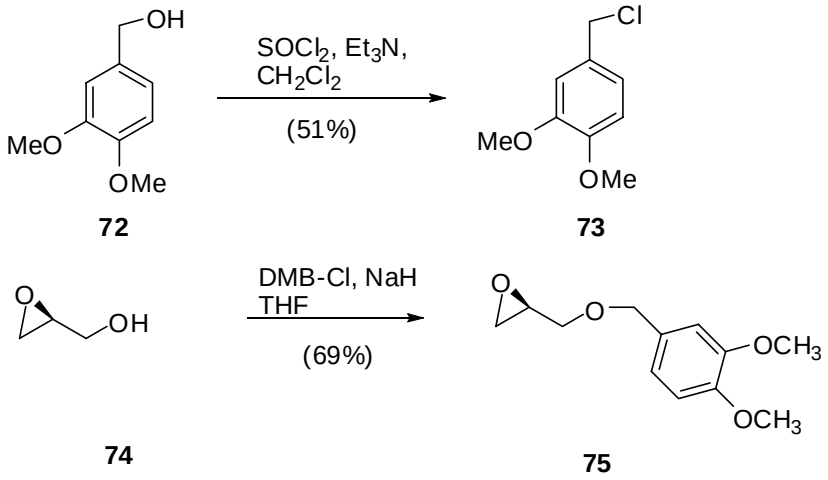
Figure 2.7 Retrosynthetic analysis of iodide **5**

Synthesis of compound **5** commenced from commercially available (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (*S*)-**24**. Oxidation of alcohol (*S*)-**24** to aldehyde (*S*)-**25** was accomplished with SO_3•pyr in 93% yield (scheme 2.22). Reaction of aldehyde (*S*)-**25** with propane-1,3-dithiol and BF_3•OEt_2 resulted[83] in both conversion of aldehyde functionality to a dithiane and cleavage of 1,2-diol protecting group to afford compound **70** in 78% yield. Silylation of the diol **70** (TBSOTf and 2,6-lutidine) proceeded smoothly to give compound **71** in 95% yield.



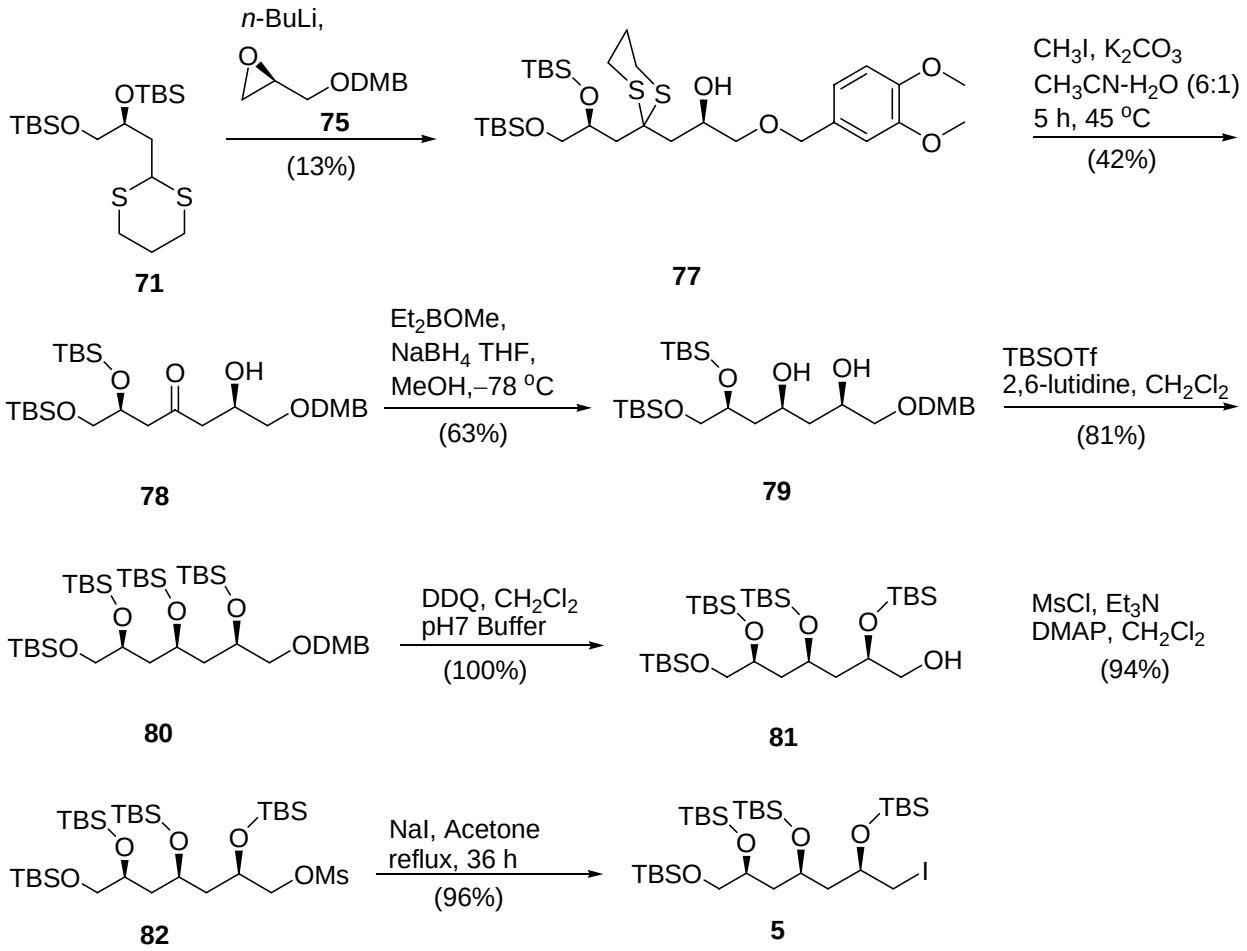
Scheme 2.22 Synthesis of dithiane 71

Epoxide **75** was prepared from commercially available (*S*)-glycidol **74**. 3,4-dimethoxybenzyl alcohol **72** was reacted with $SOCl_2$ and triethylamine in dichloromethane to form 3,4-dimethoxybenzyl chloride (DMBCl) **73** in 51% yield.[84] Deprotonation of (*S*)-glycidol **74** with NaH followed by addition of DMBCl gave the epoxide **75** in 69% yield (scheme 2.23).



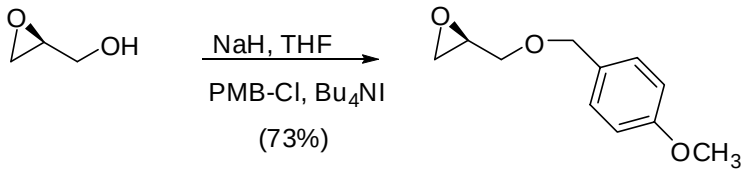
Scheme 2.23 Synthesis of epoxide **75**

Lithiation of dithiane **71** with *n*-BuLi followed by the addition of epoxide **75** resulted the desired product **77** in 13% yield along with 51% of recovered dithiane **71** (scheme 2.24). Dithiane **77** was then reacted with iodomethane and potassium carbonate in aqueous acetonitrile to afford the β-hydroxy ketone **78** in 42% yield. Apparently, the poor yields of the above two reactions were due to labiality of the DMB protecting group to the reaction conditions or to flash column chromatography on SiO_2. The *syn*-diol **79** was prepared via Et_2BOMe-mediated $NaBH_4$ reduction of **79** in 63% yield. The diol **79** was reacted with TBSOTf and 2,6-lutidine to form the compound **80** in 81% yield. The DMB-ether **80** was treated with DDQ to afford the alcohol **81** in quantitative yield. The primary alcohol **81** was then reacted with MsCl and triethyl amine in presence of DMAP to form the mesylate **82** in 94% yield.[85] The mesylate **82** was subjected to Finkelstein reaction conditions (NaI, acetone, reflux) to give the iodide **5** in 96% yield.



Scheme 2.24 Synthesis of iodide **5**

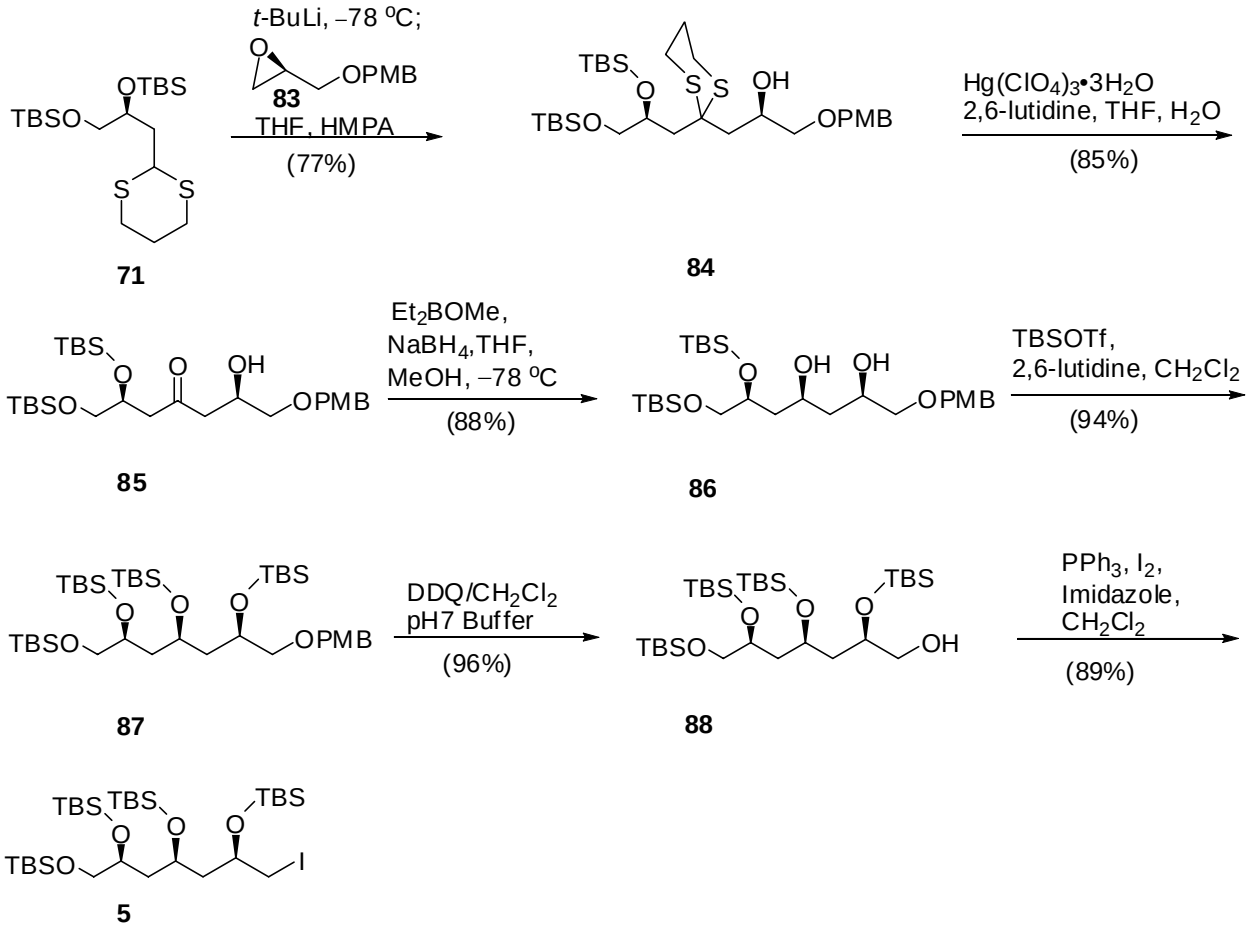
To address the issue of instability of the DMB- group, we replaced it with PMB-protecting group during the scale-up of the iodide **5**. The required PMB-epoxide **83** was prepared by deprotonating the (*S*)-glycidol **74** with NaH followed by the addition of PMB-Cl and tetrabutyl ammonium iodide (Bu_4NI) (scheme 2.25, 73% yield).



74 **83**

Scheme 2.25 Synthesis of epoxide **83**

Dithiane **71** was treated with *t*-BuLi at –78 ^{o}C followed by alkylation with PMB-epoxide **83** to afford compound **84** in 77% yield. Hydrolysis of dithiane **84** to ketone using mercuryperchlorate [$Hg(ClO_4)_3 \bullet 3H_2O$] and 2,6-lutidine in aqueous THF gave the β-hyxroxy ketone **85** in 85% yield. The β-hydroxyketone **85** was subjected to diethymethoxyborane mediated reduction with $NaBH_4$ to afford the *syn*-diol **86** in 88% yield. The secondary hydroxyl groups in diol **86** were protected as TBS ethers by reacting it with TBS-triflate and 2,6-lutidine to form compound **87** in 94% yield. The PMB-ether **87** was reacted with DDQ in CH_2Cl_2/pH 7 buffer (19:1) to afford the alcohol **81** in 96% yield (scheme 2.26). The alcohol **81** was then directly converted to iodide **5** in 89% using iodine, triphenylphosphine and imidazole in dichloromethane solvent.[86]



Scheme 2.26 Synthesis of iodide **5**

2.2.7. Synthesis of Dithiane 6: The (C9-C13) Fragment

Disconnection of C11-C12 bond in **6** provides oxazolidinone **88** and aldehyde **89** as potential starting materials for combination by an Evans asymmetric aldol reaction[36] (figure 2.8).

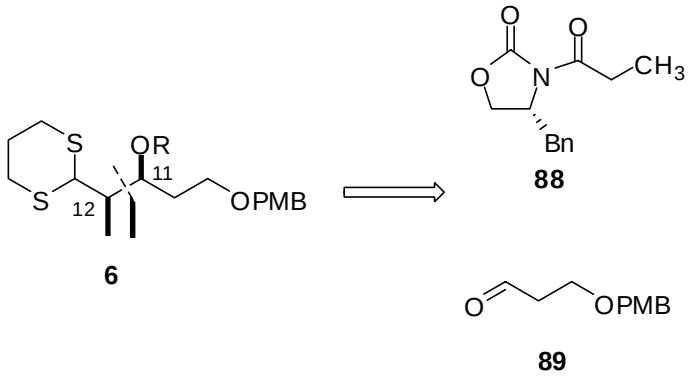
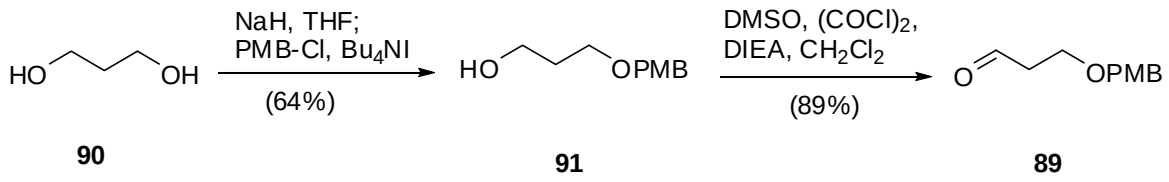


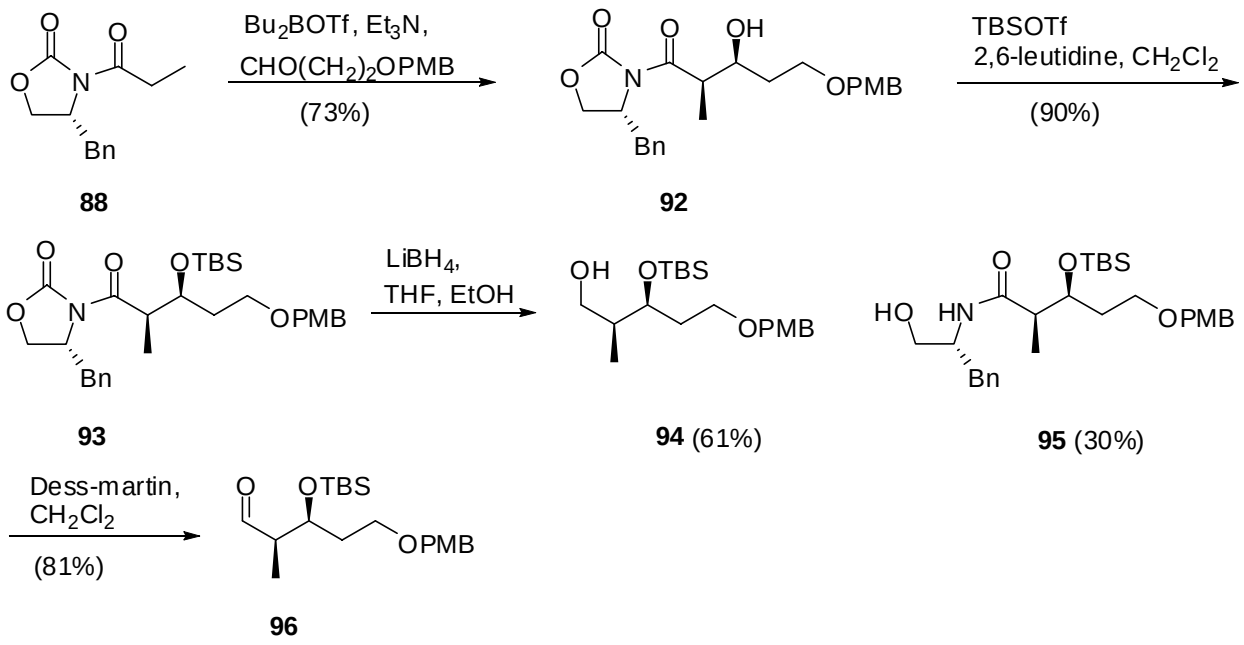
Figure 2.8 Retrosynthesis of dithiane **6**

Aldehyde **89** was prepared from commercially available propane-1,3-diol **90** as shown in scheme 2.27. Diol **90** was treated with NaH followed by addition of PMB-Cl and tetrabutylammonium iodide to form the PMB-ether **91** in 64% yield. Alcohol **91** was subjected to Swern oxidation conditions to afford aldehyde **89** in 89% yield.



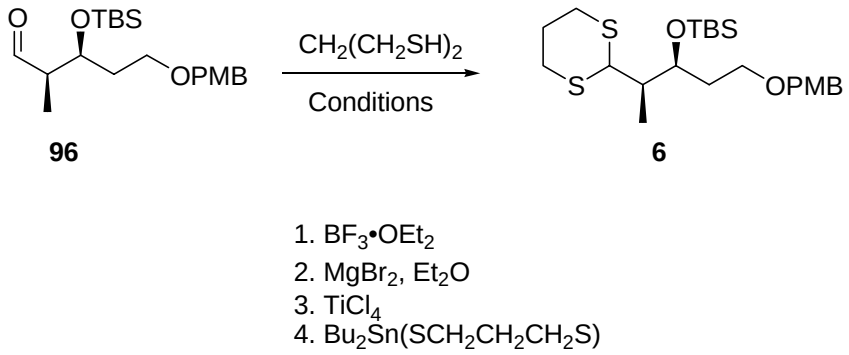
Scheme 2.27 Synthesis of aldehyde **89**

Boron mediated aldol reaction of (*R*)-*N*-propionyl imide **88** with aldehyde **89** gave the adduct **92** as a single isomer in 73% yield.[87] Protection of the secondary alcohol in **92** as TBS-ether (TBSOTf, 2,6-lutidine) gave compound **93** in 90% yield. Reductive removal of the chiral auxillary with $LiBH_4$ resulted in modest selectivity and gave the primary alcohol **94** in 61% yield along with undesired compound **95** in 30% yield (scheme 2.28). The alcohol **94** was oxidized with Dess-Martin reagent to give the aldehyde **96** in 81% yield.



Scheme 2.28 Synthesis of aldehyde **96**

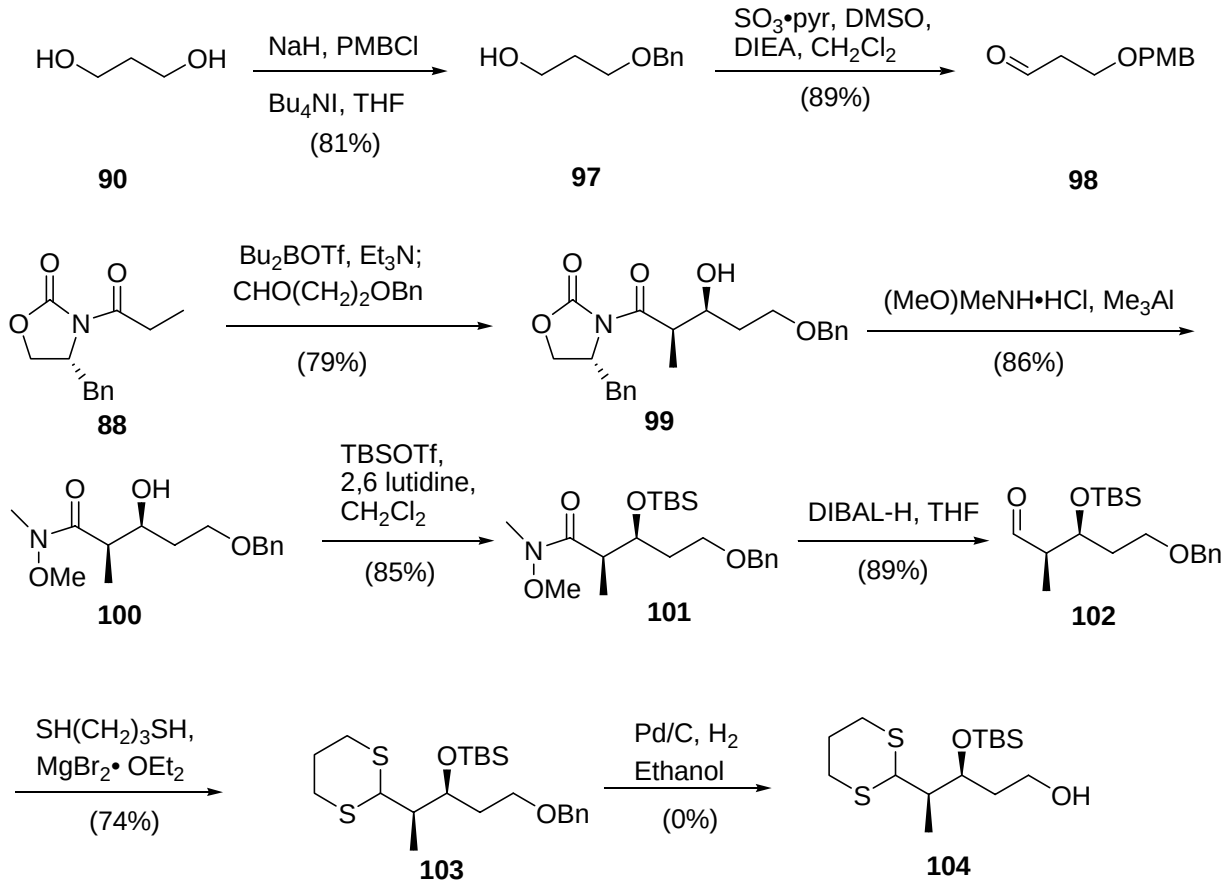
Efforts towards the conversion of aldehyde **96** to dithiane **6** are shown in scheme 2.29. Propane-1,3-diol and BF_3•OEt_2 were added to a solution of aldehyde **96** in CH_2Cl_2 at[88] −78 ^oC. [89]This reaction led to decomposition of aldehyde **96** with no detectable formation of dithiane **6**. We then tested the use of $TiCl_4$[90,] in CH_2Cl_2 at −78 ^oC and found the same result as BF_3•OEt_2. Employment of mild reaction conditions with $MgBr_2$•OEt_2[91] was also not successful and resulted in degradation of aldehyde **96**. We suspected that the problem with these reactions might be the instability of PMB group to Lewis acids. Hence, was envisioned that switching to a more stable benzyl group would be a viable alternative.



Scheme 2.29 Efforts toward the conversion of aldehyde **96** to dithiane **6**

Alcohol **97** was prepared from propane-1,3-diol **90** in 81% yield under standard conditions (NaH, BnCl, Bu_4NI). Alcohol **97** was subjected to Parikh-Doering oxidation conditions (SO_3•pyr, DMSO, DIEA) to produce aldehyde **98** in 89% yield (scheme 2.30). Evans asymmetric aldol reaction of aldehyde **98** with propionyl oxazolidinone **88** gave compound **99** as a single isomer (by ^1H and ^{13}C NMR spectroscopy) in 79% yield.[92] Treatment of oxazolidine **99** with the aluminum amide of the *N,O*-dimethyl hydroxylamine [Me(MeO)NH•HCl], $AlMe_3$, CH_2Cl_2] furnished amide[93,94] **100** in 86% yield. The secondary alcohol in **100** was protected as TBS ether to give compound **101** in 85% yield. Reduction of amide **101** with DiBAL-H gave the corresponding aldehyde **102** in 89% yield. Reaction of aldehyde **102** with propane-1,3-dithiol and $MgBr_2$•OEt_2 gave the corresponding dithiane **103** in 74% yield. With the dithiane **103** in hand, efforts were focused on removal of benzyl protecting group in compound **103**. Initial attempts to remove the benzyl protecting group under Pd-catalyzed hydrogenation conditions were unsuccessful. Addition of excess of Pd/C was also not effective in driving the reaction due to strong poisoning effect of sulfur coordinating to palladium. Since the removal of benzyl protecting group in presence of dithiane functionality was not possible, an alternative strategy

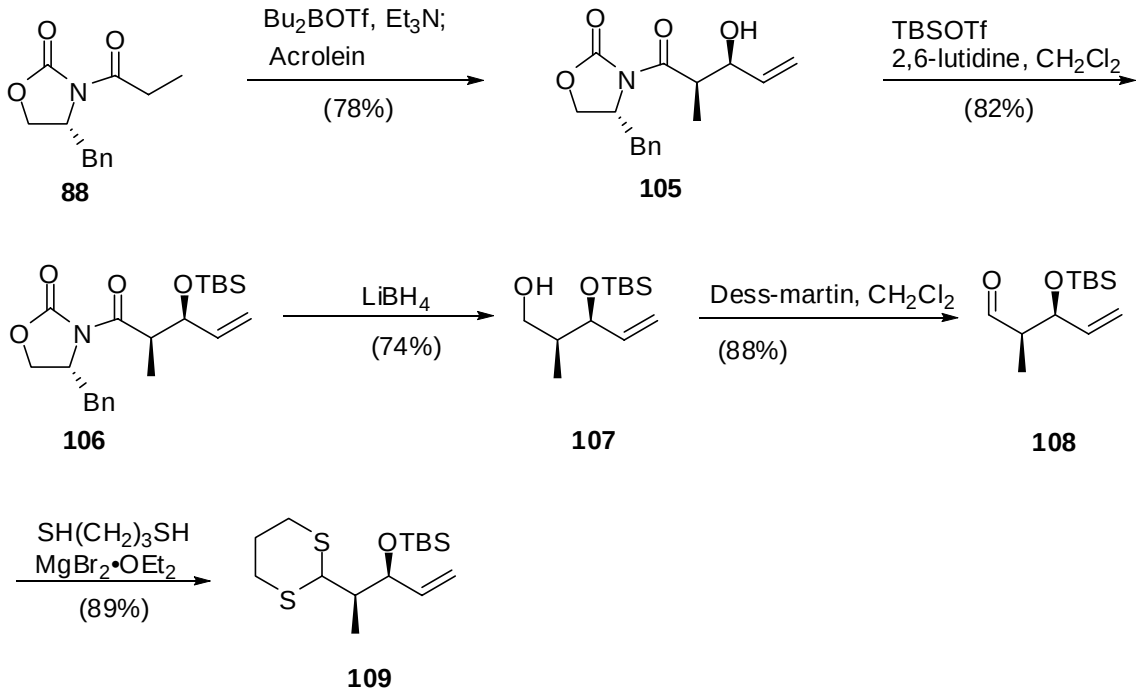
was envisioned wherein alkene was introduced into C9-C13 fragment, which can be converted to alcohol by hydroboration-oxidation sequence.



Scheme 2.30 Synthesis of dithiane 103

Our approach towards the synthesis of dithiane **109** has been illustrated in scheme 2.31. Asymmetric aldol reaction of freshly distilled acrolein with oxazolidinone **88** gave the aldol product **105** in 78% yield as a single isomer by ^{1}H and ^{13}NMR spectroscopy.[95] The secondary alcohol in compound **105** was protected as TBS-ether **106** using TBSOTf and 2,6-lutidine in 82% yield (scheme 2.31). Reduction of compound **106** with $LiBH_4$ gave the corresponding alcohol **107** in 74% yield. The primary alcohol **107** was reacted with Dess-Martin reagent in

dichloromethane to afford aldehyde **108** in 88% yield. Addition of propane-1,3-dithiol and $MgBr_2$•OEt_2 to aldehyde **108** in THF furnished dithiane **109** in 89% yield.



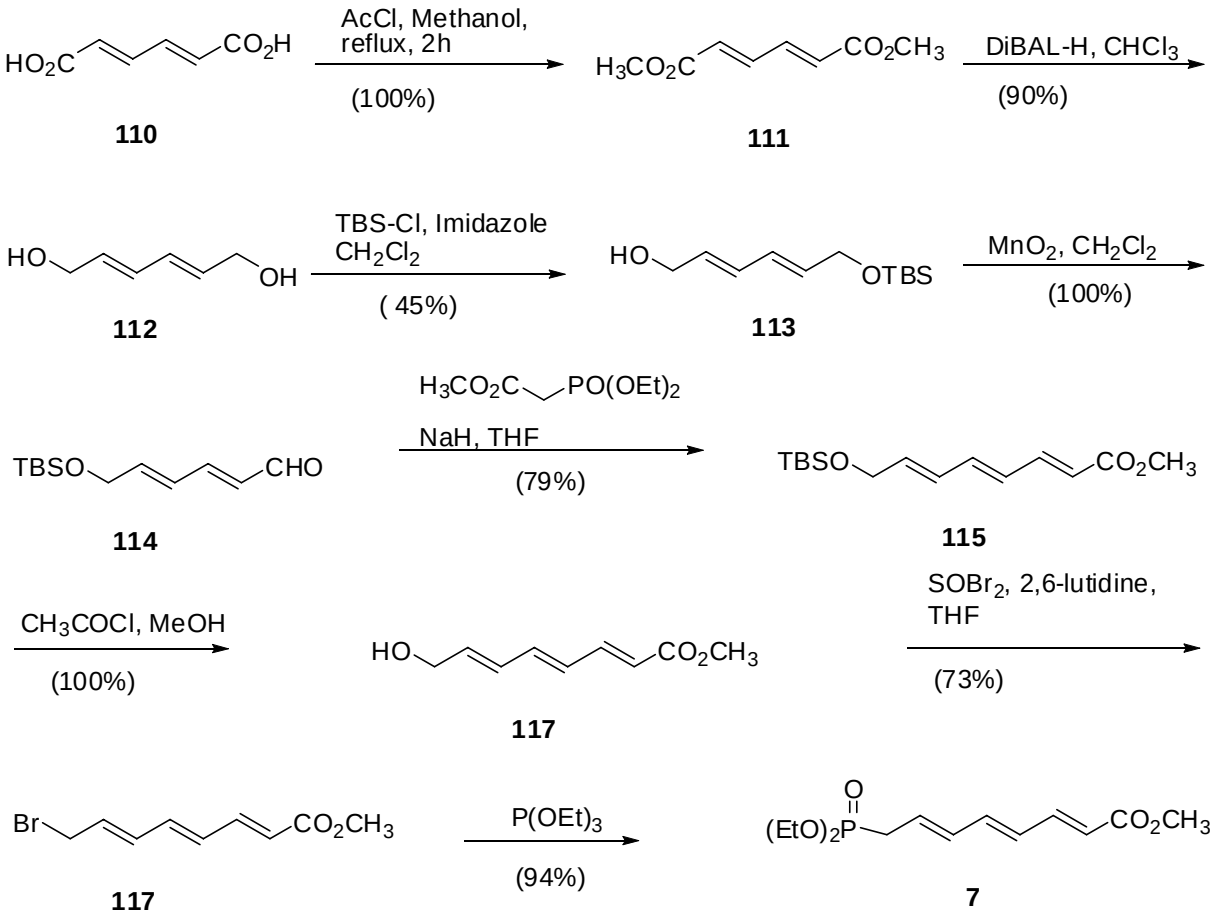
88 **105** **106** **107** **108** **109**

Scheme 2.31 Synthesis of dithiane **109**

2.2.8. Synthesis of Phosphonate 7: The (C1-C8) Fragment

Synthesis of phosphonate **7** commenced from *trans-trans*-muconic acid **110**. Muconic acid was treated with acetyl chloride in methanol and refluxed for 2 h to give (2*E*,4*E*)-dimethyl hexa-2,4-dienedioate **111** in 98% yield (scheme 2.32). The ester **111** was soluble in chloroform but was partially soluble in THF. Hence the ester **111** was dissolved in chloroform and reduced with DiBAL-H to furnish diol **112** in 90% yield. Reaction of diol **112** with TBS-Cl and imidazole in DMF gave the desired mono-TBS ether **113** in 45% isolated yield along with recovered **112** and bis-TBS-ether (not shown). The TBS ether **113** was readily separated from the crude product by flash column chromatography. Addition of MnO_2 to a solution of alcohol **113** in

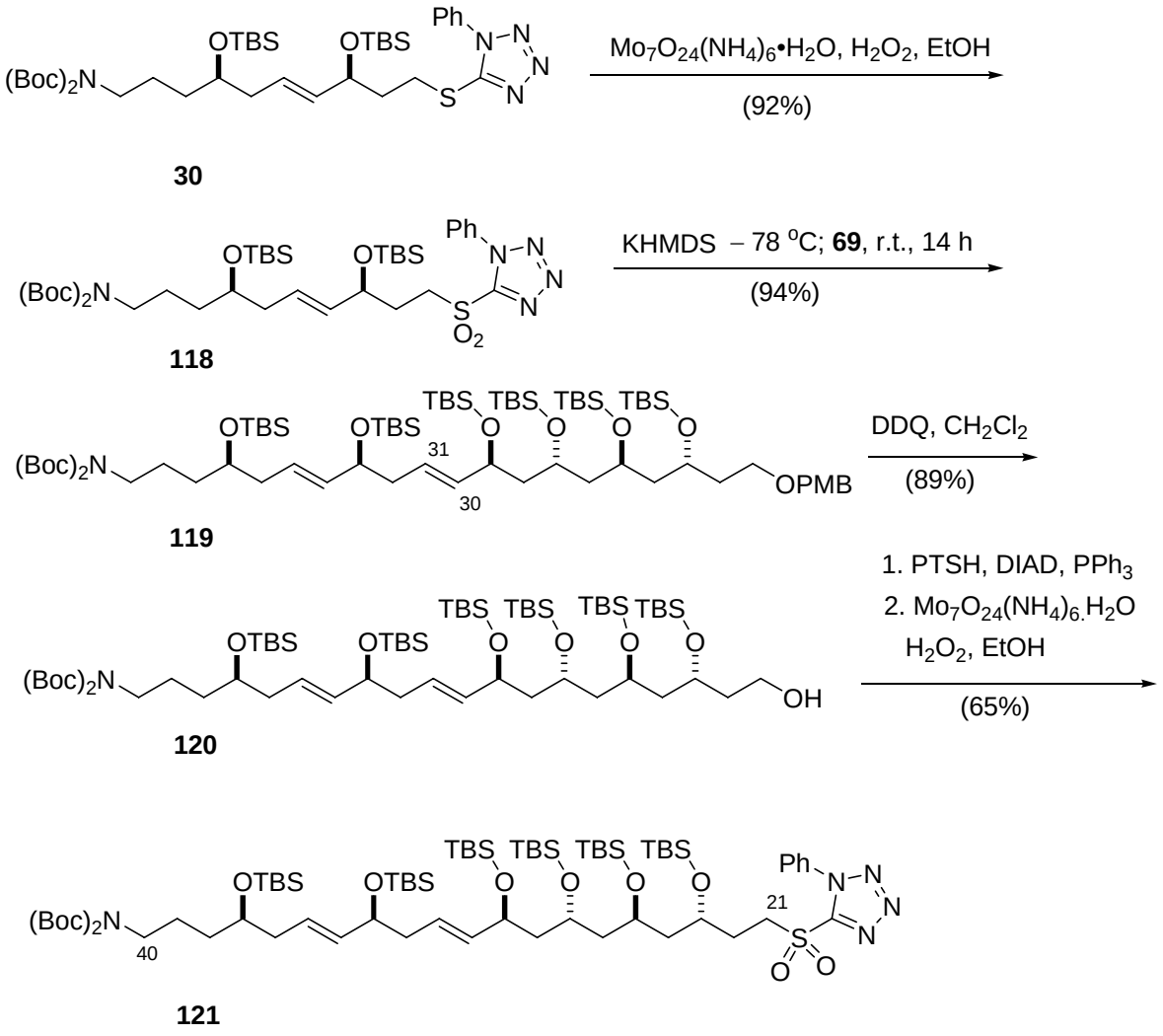
dichloromethane efficiently converted the alcohol to aldehyde **114** in quantitative yield.[96] Aldehyde **114** was treated with sodium salt of triethylphosphonoacetate to deliver the ester **115** in 79% yield. Catalytic acidic conditions (AcCl in methanol) were employed to cleave the TBS ether affording alcohol **116** in quantitative yield as white solid. Alcohol **116** was then treated with $SOBr_2$ in presence of 2,6-lutidine to afford the corresponding bromide **117** as white solid in 73% yield. The bromide **117** was reacted with an excess triethylphosphite[97] in refluxing toluene to give the desired phosphonate **7** as waxy solid in 94% yield.



Scheme 2.32 Synthesis of Phosphonate 7: The (C1-C8) Fragment

2.2.9. Synthesis of Sulfone 121: The (C21-C40) Fragment

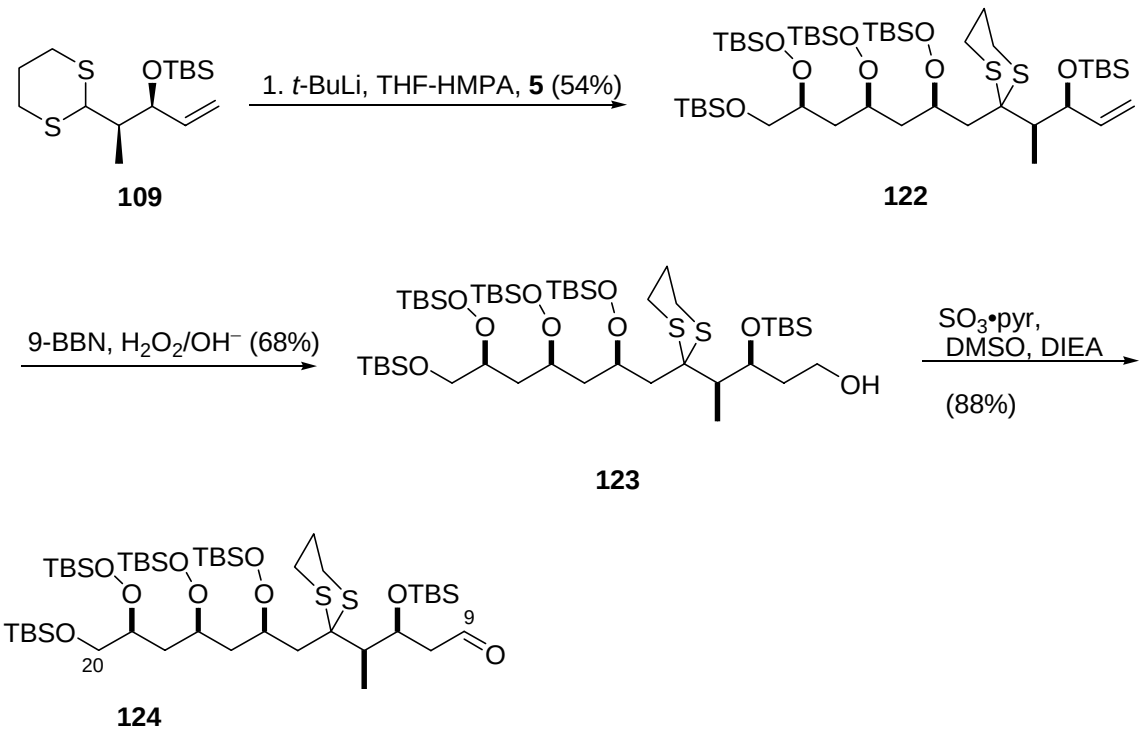
With all six fragments (**2-7**) in hand, we began assembly of the C21-C40 carbon framework of tetrafibricin (scheme 2.33). Efforts toward the oxidation of sulfide **30** to sulfone **118** using *m*-CPBA resulted in a messy reaction product due to competing oxidation of olefin to epoxide. However, Mo-catalyst [$Mo_7O_{24}(NH_4)_6$•H_2O, H_2O_2][98] provided a smooth conversion of sulfide **30** to sulfone **118** in 92% yield. Deprotonation of sulfone **118** with KHMDS at −78 ^oC, followed by addition of aldehyde **69** and warming to ambient temperature overnight provided the PMB-ether **119** as a sole C(30,31) (*E*)-olefinic isomer ($J_{H30,31}$ = 15.4 Hz) in 94% yield. Removal of PMB protecting group (DDQ, pH 7 buffer, CH_2Cl_2)[99] provided the primary alcohol **119** in 88% yield. Incorporation of the thiotetrazole via the Mitsunobu protocol, employing commercially available 1-phenyl-1*H*-tetrazole-5-thiol (PTSH), followed by oxidation ($Mo_7O_{24}(NH_4)_6$•H_2O, H_2O_2) of the derived sulfide (not shown) furnished sulfone **121** (C21-C40 fragment, 65% yield, two steps).



Scheme 2.33 Synthesis of C21-C40 fragment

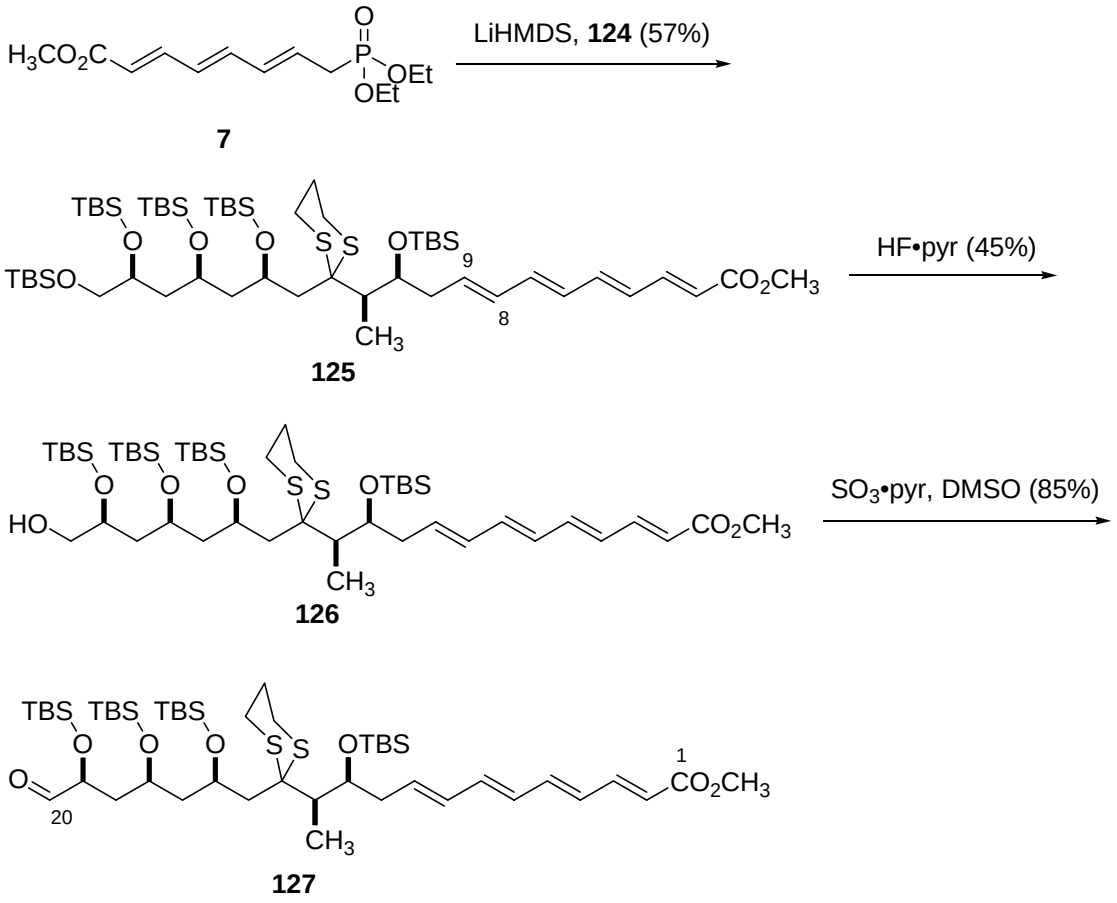
2.2.10. Synthesis of Aldehyde 127: The (C1-C20) Fragment

Efforts toward the synthesis of C1-C20 fragment commenced with alkylation of dithiane **109** with iodide **5**. Deprotonation of dithiane **109** with *t*-BuLi followed by addition of iodide **5** provided alkene **122** in 54% yield (scheme 2.34). Hydroboration/oxidation of alkene **122** provided the primary alcohol **123** in 64% yield. Oxidation of the primary alcohol **123** with SO_3•pyr provided aldehyde **124** in 60% yield.



Scheme 2.34 Synthesis of C9-C20 fragment

The formation of C8-C9 double bond was then carried out by deprotonation of phosphonate **7** with LiHMDS, generating a dark orange colored anion, which was then added to aldehyde **124** furnishing conjugated methyl ester **125** ($J_{H8\text{-}H9}$ = 15.1) in 57% yield (scheme 2.35). The primary TBS-ether **125** was cleaved with HF•pyr to provide the primary alcohol **126** in modest yield (45%). Oxidation of alcohol **126** to aldehyde **127** was then carried out with SO_3•pyr (82% yield).

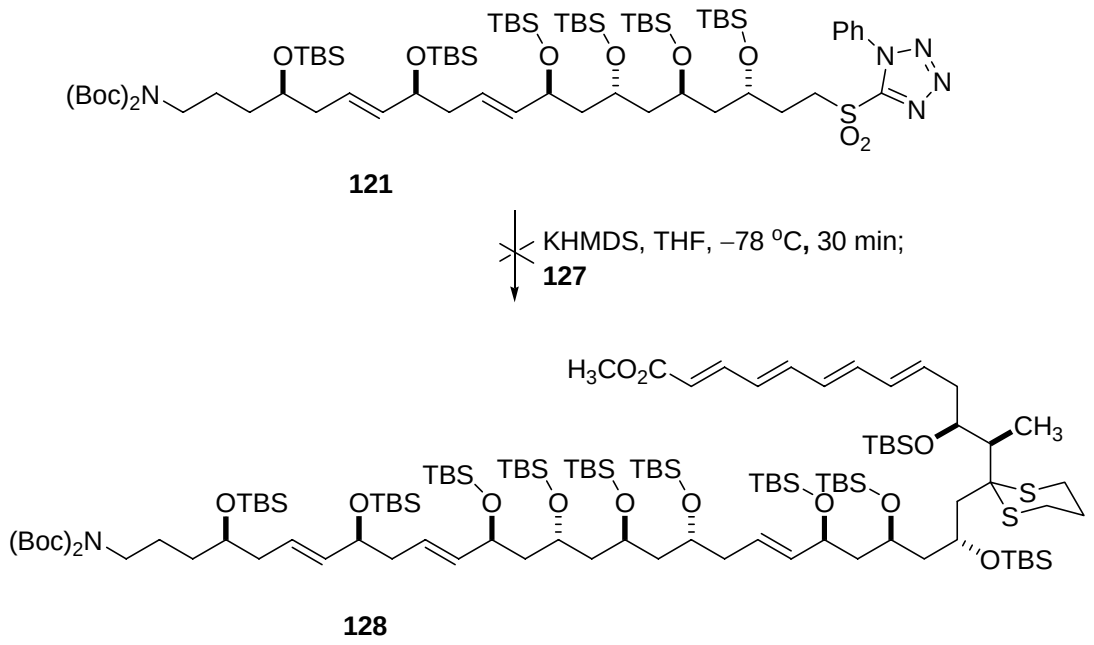


Scheme 2.35 Synthesis of C1-C20 fragment

2.2.11. Effort towards the assembly of C1-20 and C21-C40 fragments:

With two half fragments (C1-20 and C21-C40) of tetrafibricin in hand, Kocienski-Julia olefination of sulfone **121** (15.0 mg, 10.1 μmol) with aldehyde **127** (10.0 mg, 10.3 μmol) was attempted. KHMDS was added to a solution of sulfone **121** in THF at −78 ^{o}C and the mixture was reacted for 30 min to generate the corresponding sulfone anion (scheme 2.36). Then a solution of aldehyde **127** in THF was added and the reaction mixture was stirred overnight. Unfortunately, product **128** was not formed, leading to decomposition of both sulfone and aldehyde (multiple spots on TLC). Presumably aldehyde **127** is not stabe under the reaction

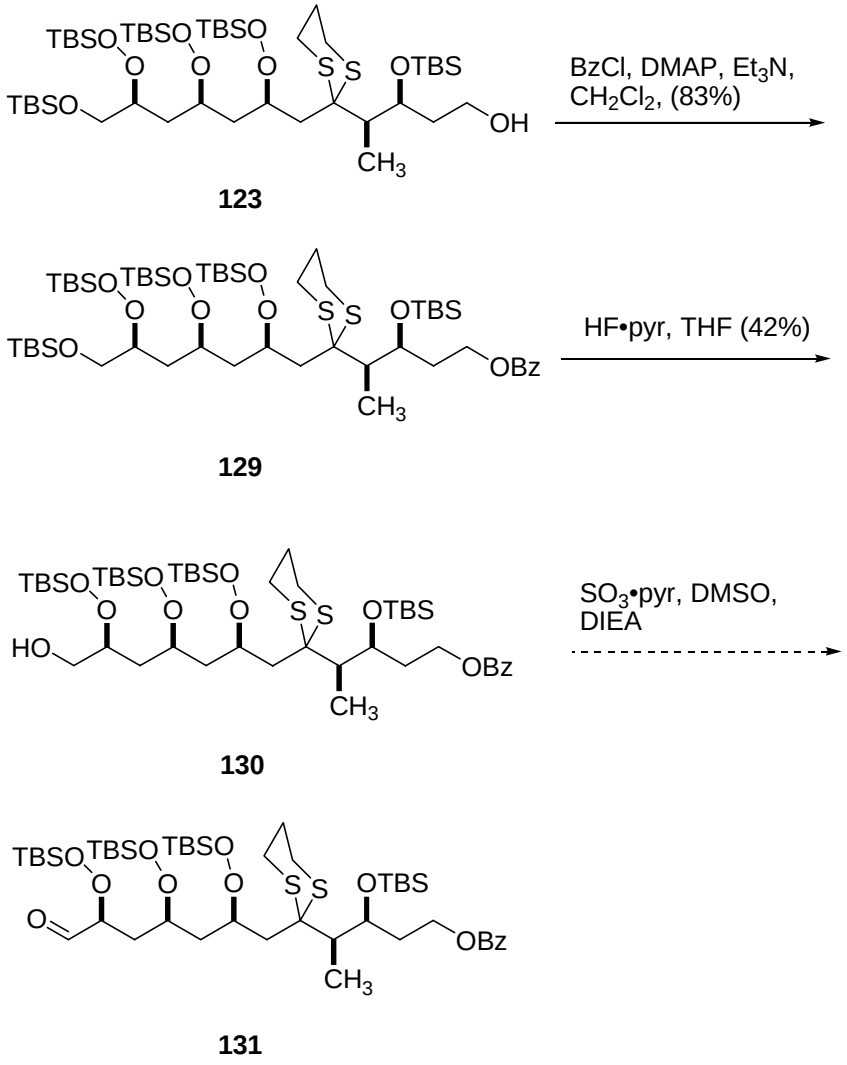
conditions due to C10 acidic protons. We could not re-attempt this reaction due to the lack of aldehyde and its precursors. Further synthetic studies are currently in progress in the Curran group.



Scheme 2.36 Attempted Kocienski-Julia olefination of aldehyde 127 with sulfone 121

We've also considered the following synthetic route for the assembly of tetrafibricin carbon framework. The primary alcohol **123** was protected as benzoate **129** in 83% yield (scheme 2.37). Cleavage of the primiary TBS ether with HF•pyr gave the primary alcohol **130** in modest yield (39%). With the primary alcohol **130** in hand, we attempted its oxidation to aldehyde using Dess-Martin reagent. However, this reaction led to a messy product, presumably due to the sensitivity of dithiane functionality towards Dess-Martin reagent,[100] with no detectable amount of aldehyde. Although we could not proceed further due to the lack of alcohol **126**, we

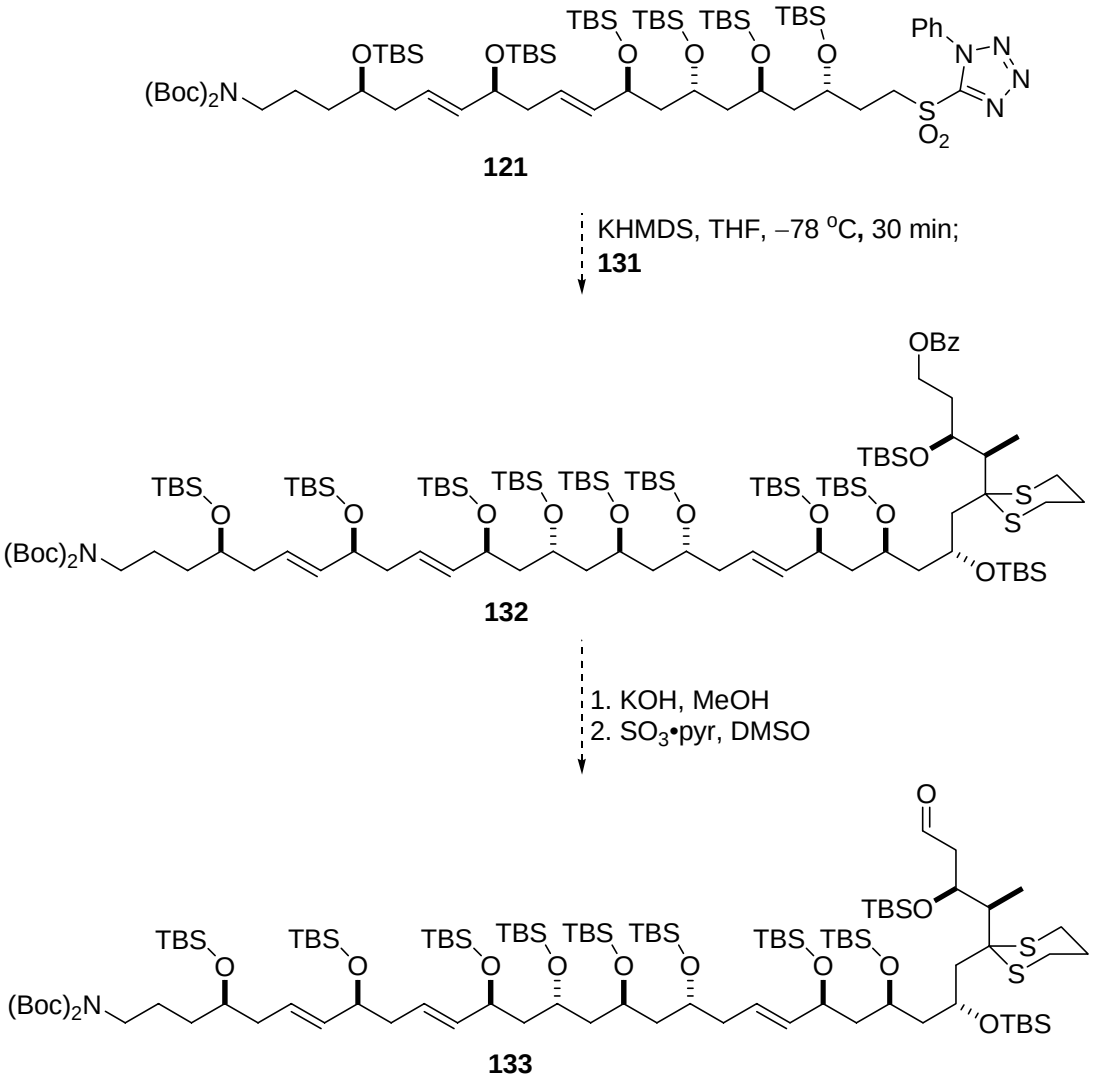
envision that this alcohol can be smoothly oxidized to aldehyde **131** with SO_3•pyr or Swern oxidation reagents.



Scheme 2.37 Synthesis of alcohol 130

We propose that the aldehyde **131** can be carried through the following sequence of steps to complete the synthesis of tetrafibricin. Reaction of aldehyde **131** with sulfone **121** under Kocienski-Julia olefination conditions will provide olefin **132** (scheme 2.38). Removal of

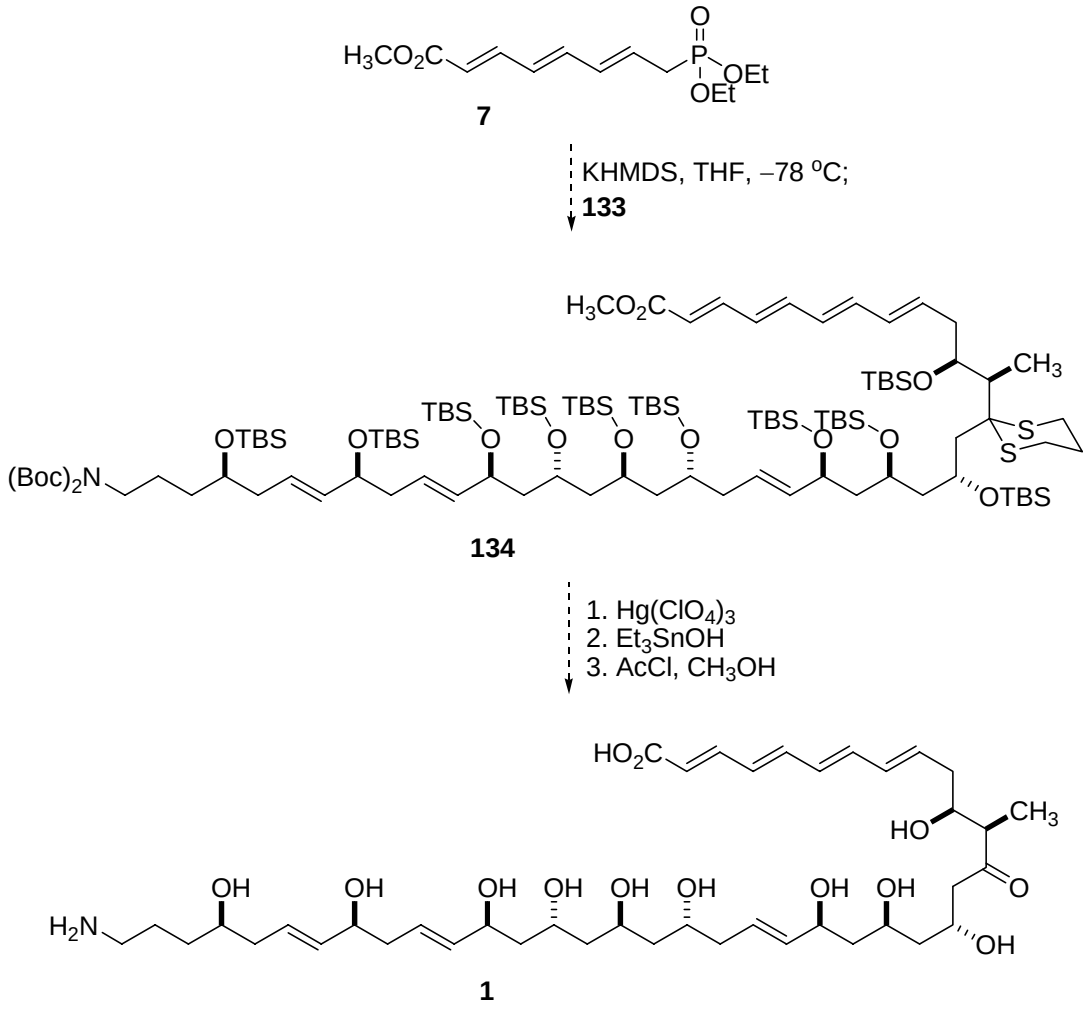
benzoate ester to furnish the corresponding primary alcohol (not shown), followed by the oxidation of alcohol to aldehyde can provide C9-C40 fragment **133**.



Scheme 2.38 Proposed synthesis of aldehyde 133

Horner-Wadsworth-Emmons olefination of aldehyde **133** with lithiated anion of phosphonate **7** will provide tetrafibricin carbon framework **134**. The following three deprotection steps can be pursued to provide the proposed structure of tetrafibricin (scheme 2.39). Hydrolysis

of dithiane, hydrolysis of methyl ester (Et_3SnOH)[101], followed by global deprotection (removal of TBS and Boc protecting groups) with methanolic HCl (AcCl, MeOH) will furnish tetrafibricin **1**.



Scheme 2.39 Proposed synthesis of tetrafibricin

2.3. CONCLUSION

A convergent synthesis of the proposed structure of tetrafibricin **1** has been explored. In this approach, we envisioned a series of Kocienski-Julia olefination reactions with appropriate

aldehydes and sulfones to afford fragments **2** (C35-C40), **3** (C31-C35) and **69** (C21-C30). Synthesis of sulfone **2** (C35-C40) has been achieved in 11 steps starting with the commercially available pent-4-en-1-ol **8** in an overall 25% yield. The secondary alcohol stereocenter (C37) was established via hydrolytic kinetic resolution of racemic epoxide **12** in 96% ee. Synthesis of aldehyde **3** (C31-C34) commenced with the commercially available (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (*S*)-**24** in 5 steps in overall 46% yield. Synthesis of aldehyde **69** (C21-C30) involved the alkylation of 1,3-dithiane **16** with epoxides **31** and **56**. Two synthetic routes have been developed for the synthesis of epoxide **31**. The first one commenced from the commercially available D-arabital in **7** steps in overall 13% yield. We latter established a four step synthesis of epoxide **31** beginning with the commercially available (*S*)-**24** in 31% yield. A total of 16 steps are involved in the synthesis of **69** in 4.5% overall yield. Disconnection at C13-C14 bond of tetrafibricin provided fragments **5** (C14-C20) and **109** (C9-C13). Synthesis of iodide **5** was achieved with the commercially available starting materials, (*S*)-**24** and (*S*)-**74**, in 10 steps in overall 23% yield. Dithiane **109** was synthesized from acrolein in 5 steps in 37% yield. Disconnection at C8-C9 bond in **1** provided phosphonate **7** (C1-C8), that was synthesized from the commercially available *trans*-*trans*-muconic acid **110** in 8 steps in overall 22% yield.

With all six fragments of tetrafibricin **1** in hand, we've attempted their assembly. This began with Kocienski-Julia olefination of sulfone **2** with aldehyde **3** to form *trans*-olefin **30** (C31-C40) in 86% isolated yield. Oxidation of sulfide **30** to sulfone **118** followed by subjecting it to Julia-Kocienski olefination with aldehyde **69** (C21-C30) afforded *E*-olefin **119** (C21-C40) in 94% yield. PMB-ether **119** was advanced to sulfone **121** to attempt another Kocienski-Julia olefination.

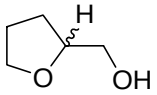
Alkylation of dithiane **109** with iodide **5** provided C9-C20 carbon skeleton **122** which was advanced to aldehyde **124** in two steps. Horner-Wadsworth-Emmons olefination of phosphonate **7** (C1-C8) with aldehyde **124** (C9-C20) provided **125** (C1-C20) which was advanced to aldehyde **127** in two steps. With this we've successfully completed the synthesis of two half fragments, aldehyde **127** (C1-C20) and sulfone **121** (C21-C40), of tetrafibricin. Although the Kocienski-Julia olefination of sulfone **121** with aldehyde **127** was unsuccessful in our hand, we envision that the proposed sequence of steps will complete the synthesis of tetrafibricin.

2.4. EXPERIMENTAL

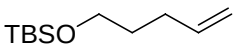
General:

All reactions were run under argon unless otherwise noted. Toluene, THF, and benzene were freshly distilled from sodium/benzophenone. Dichloromethane was distilled from CaH_2. Other reagents were used as they were received from Aldrich. 4Å Molecular sieves were dried at 150 ^oC for at least 24 h before use. New compounds were characterized by ^1H NMR, ^{13}C NMR, IR spectroscopy, optical rotation, and mass spectrometry. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance DPX 300 (300 MHz), Avance DRX 500 (500 MHz) and Avance 600 (600 MHz) spectrometers. Chemical shifts were reported in ppm. $CDCl_3$ was used as the NMR solvent unless otherwise noted. In reporting spectral data, the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, br = broad. Coupling constants were measured in Hertz (Hz). Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film deposition on NaCl plates unless otherwise noted. Peaks are reported in wavenumbers (cm^{-1}). Low resolution mass spectra were obtained on a Fision Autospec in EI mode at 70 eV and reported in *m/z* units. High resolution mass spectra were obtained on a VG Autospec double focusing instrument and are reported in units of *m/z*. Optical rotations are measured on a Perkin-Elmer 241 polarimeter at the Na D-line (λ = 589 nm) using a 1 dm cell at 20 ^oC. HPLC analyses were conducted by using Waters 600 controller and Waters 2487 dual λ absorbance detector or polymer laboratory PL-ELS 1000 detector controlled with the Millennium™ program. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} glass backed plates with a layer thickness of 0.25 mm manufactured by E. Merck. TLC visualization was performed by illumination with a 254 nm UV lamp or by staining with phosphomolybdic acid in ethanol (50 mg/mL) and subsequent heating. Flash column

chromatography was performed on silica gel (230-400 mesh ASTM) purchased from Sorbtech or Bodman.



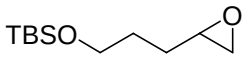
***rac*-(Tetrahydrofuran-2-yl)methanol (10)**:[12] To a solution of *m*-CPBA (77% w/w in H_2O, 4.40 g, 19.4 mmol) in dichloromethane (200 mL) at 0 ^oC was added neat pent-4-en-1-ol **8** (1.52 g, 17.7 mmol). The reaction mixture was stirred at room temperature for 2 h followed by quenching it with saturated aqueous sodiumbicarbonate solution. Organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography gave the title compound **10** (1.5 g, 83%) as waxy solid. ^1H NMR was identical to the commercial sample.[2]



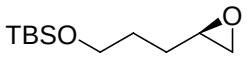
***tert*-Butyldimethyl(pent-4-enyloxy)silane (11):** To a solution of pent-4-en-1-ol **8** (6.00 g, 69.8 mmol) in dichloromethane (400 ml) at 0 ^oC was added *tert*-butyldimethylsilyl chloride (11.6 g, 76.7 mmol) and imidazole (5.70 g, 83.7 mmol). The above reaction mixture was stirred at 0 ^oC for 20 min and room temperature for 1.5 h followed by quenching it with water (200 mL). The organic layer was separated and aqueous layer was extracted with dichloromethane (100 x 2 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to give the title compound **11** (14.0 g) as an oil. The crude compound was taken to the next step without further

[12] CAS # 97-99-4; commercially available from Aldrich.

purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.09 (s, 9H), 1.56-1.68 (m, 2H), 2.07-2.16 (m, 2H), 4.93-5.07 (m, 2H), 5.83 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.2, 18.4, 26.0, 30.1, 32.1, 62.6, 114.6, 138.6.

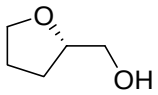


(*rac*)-*tert*-Butyldimethyl(3-(oxiran-2-yl)propoxy)silane (12): *m*-Chloroperbenzoic acid (75% w/w in H_2O, 16.0 g) was added to a solution of *tert*-butyldimethyl(pent-4-enyloxy)silane **11** (14.0 g, 69.8 mmol) in dichloromethane at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 20 min and room temperature for 1 h followed by quenching it with saturated aqueous $NaHCO_3$ solution (200 mL). The layers were separated and aqueous layer was further extracted with dichloromethane (100 x 2 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Bulb-to-bulb (Kugelrohr) distillation of the crude product under reduced pressure (0.1 mbar, 90-105 ^{o}C oven temperature) gave the title compound **12** (13.0 g, 86%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.53-1.76 (m, 4H), 2.49 (dd, *J* = 4.9, 2.7 Hz, 1H), 2.74-2.79 (m, 1H), 2.91-2.99 (m, 1H), 3.59-3.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3, 18.3, 25.9, 29.0, 29.1, 47.0, 52.1, 62.6; IR (neat) cm^{-1} 2954, 2857, 1472, 1256; EIMS (M – *t*Bu)$^+$ 159; HRMS for $C_7H_{15}O_2Si$ (M – *t*Bu)$^+$: Calcd 159.0841; found 159.0828.

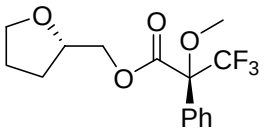


(*R*)-*tert*-Butyldimethyl(3-(oxiran-2-yl)propoxy)silane [(*R*)-12]: The (*R,R*)-Jacobsen catalyst (*R,R*)-**13**[102] (111 mg, 0.184 mmol) was dissolved in *tert*-butyldimethyl(3-(oxiran-2-yl)propoxy)silane **12** (8.00 g, 36.8 mmol), AcOH (44 μL) and THF (0.4 mL). The solution was

cooled to 0 °C, water was added (0.37 mL, 20.3 mmol) and stirred for 16 h at room temperature. Bulb-to-bulb (Kugelrohr) distillation of crude product under reduced pressure (0.08 mm Hg, 90-105 °C) gave (*R*)-*tert*-butyldimethyl(3-(oxiran-2-yl)propoxy)silane (*R*)-**12** (3.50 g, 16.2 mmol, 44%, > 96% ee based on Mosher ester analysis) as colorless oil: $[\alpha]_D$ 3.74 (*c* 4.30 $CHCl_3$). Data was identical to (*rac*)-**12**.



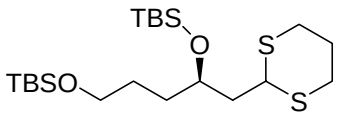
(*S*)-(Tetrahydrofuran-2-yl)methanol [(*S*)-10]:[13] To a solution of (*R*)-*tert*-butyldimethyl(3-(oxiran-2-yl)propoxy)silane (*R*)-**12** (100 mg, 0.460 mmol) in methanol (5 mL) was added a drop of acetyl chloride at room temperature. The reaction mixture was stirred for 20 min at room temperature followed by concentration. Purification of the crude product by flash column chromatography (SiO_2, 50% ethyl acetate in hexanes) gave the title compound **(*S*)-10** (43 mg, 92%) as a waxy solid. ^{1}H NMR was identical to the commercial sample.



(*S*)-((*S*)-Tetrahydrofuran-2-yl)methyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate [(*S,S*)-15]: To a solution of (*S*)-(tetrahydrofuran-2-yl)methanol (*S*)-**10** (20.0 mg, 0.196 mmol) in dichloromethane (2 mL) was added (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (*R*)-**14** (50.0 mg, 0.196 mmol) and DMAP (24.0 mg, 0.196 mmol). The reaction mixture was stirred at room temperature for 2 h followed by concentration. The crude product was purified by

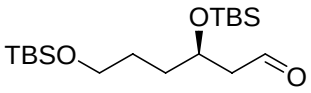
[13] CAS # 57203-01-7

flash column chromatography (SiO_2, 25% ethyl acetate in hexanes) to yield the title compound (52 mg, 84%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61-1.67 (m, 1H), 1.84-1.91 (m, 2H), 1.95-2.04 (m, 1H), 3.59 (s, 3H), 3.74-3.85 (m, 2H), 4.14-4.21 (m, 1H), 4.29-4.37 (m, 2H), 7.39-7.59 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 28.1, 55.6, 67.8, 68.5, 76.0, 84.8 (q, $J_{C\text{-}F}$ = 27.9 Hz, 1C), 123.3 (q, $J_{C\text{-}F}$ = 289.2 Hz, 1C), 127.5, 128.5, 129.6, 132.4, 166.6; HRMS for $C_{15}H_{17}O_4F_3Na$ $(M + Na)^+$: Calcd 341.0977; found 341.0983.

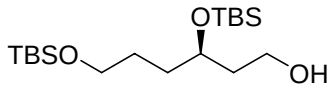


(*R*)-2-(2,5-bis(*tert*-Butyldimethylsilyloxy)pentyl)-1,3-dithiane (17): *t*-BuLi (1.7 M in pentane, 10.0 mL, 17.0 mmol) was added to a solution of 1,3-dithiane **16** (1.80 g, 15.0 mmol) in THF (60 mL) at −78 °C. After 30 min at −78 °C, (*R*)-*tert*-butyldimethyl(3-(oxiran-2-yl)propoxy)silane (*R*)-**12** (3.24 g, 15.0 mmol) in THF (3 mL) was added followed by the addition of dry HMPA (1 mL). After 2 h −10 °C, the reaction mixture was cooled to −78 °C followed by slow addition of TBSOTf (4.36 g, 3.8 mL, 16.5 mmol). After 1 h, the mixture was warmed to room temperature and quenched with water (100 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) to provide the title compound **17** (5.6 g, 83%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.07 (s, 3H), 0.10 (s, 3H), 0.90 (s, 18H), 1.50-1.53 (m, 4H), 1.73-1.92 (m, 3H), 2.05-2.15 (m, 1H), 2.70-2.95 (m, 4H), 3.55-3.60 (m, 2H), 3.92-4.01 (m, 1H), 4.10 (dd, *J* = 8.7, 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −4.5, −4.3, 18.1, 18.4, 26.0, 28.0. 30.2,

30.7, 33.7, 42.5, 44.2, 63.2, 68.4; EIMS $(M - t\text{Bu})^+$ 393; HRMS for $C_{17}H_{37}O_2S_2Si_2$ $(M - t\text{Bu})^+$: Calcd 393.1774; found 393.1780.

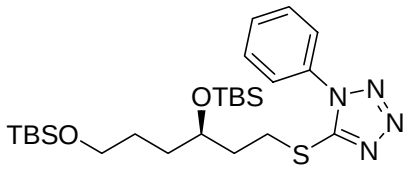


(*R*)-3,6-bis(*tert*-Butyldimethylsilyloxy)hexanal (18): Methyl iodide (0.2 mL) and K_2CO_3 (258 mg, 1.87 mmol) were added to a solution of (*R*)-2-(2,5-bis(*tert*butyldimethyl silyloxy)pentyl)-1,3-dithiane **17** (800 mg, 1.77 mmol) in aqueous acetonitrile ($MeCN/H_2O$, 6:1/2.1 mL). The reaction mixture was stirred for 5 h at 45 ^oC and then diluted with ether and water. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 20% ethyl acetate in hexanes) to give the title compound **18** (514 mg, 80%) as an oil: $[\alpha]_D$ –3.74 (*c* 1.15 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.05 (s, 3H), 0.07 (s, 3H), 0.86 (s, 9H), 0.88 (s, 9H), 1.47-1.65 (m, 4H), 2.49-2.54 (m, 2H), 3.57-3.63 (m, 2H), 4.19-4.26 (m, 1H), 9.79-9.81 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3, –4.7, –4.4, 18.0, 18.3, 25.7, 25.9, 28.4, 34.2, 50.7, 62.9, 68.1, 202.2; IR (neat) cm^{-1} 2954, 2929, 2851, 2721, 1723, 1470, 1249; EIMS $(M - t\text{Bu})^+$ 303; HRMS for $C_{14}H_{31}O_3Si_2$ $(M - t\text{Bu})^+$: Calcd 303.1812; found 303.1805.



(*R*)-3,6-bis(*tert*-Butyldimethylsilyloxy)hexan-1-ol (19): DiBAL-H (1.0 M in hexane, 2.38 mL, 2.38 mmol) was added to a solution of (*R*)-3,6-bis(*tert*-butyldimethyl silyloxy)hexanal **18** (0.66 g, 1.83 mmol) in THF (20 mL) at –78 ^oC and the mixture was stirred for 1 h. The reaction

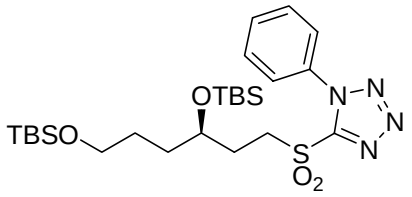
mixture was warmed to 0 ^{o}C, followed by the addition of ethanol (1 mL) and saturated sodium-potassium tartarate solution (15 mL). After stirring for 1 h, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (25% ethyl acetate in hexanes) provided the title compound **19** (650 mg, 98%) as an oil: $[\alpha]_D$ –21.0 (*c* 0.2 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 18H), 1.47-1.53 (m, 2H), 1.54-1.60 (m, 2H), 1.62-1.69 (m, 1H), 1.76-1.83 (m, 1H), 2.60 (br s, 1H), 3.57-3.63 (m, 2H), 3.67-3.72 (m, 1H), 3.78-3.83 (m, 1H), 3.91-3.95 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ –5.2, –4.7, –4.3, 18.0, 18.4, 25.9, 26.0, 28.7, 33.3, 37.9, 60.2, 63.2, 71.7; IR (neat) cm^{-1} 3366, 2953, 2930, 2857, 1471, 1254, 1096, 835, 775.



(*R*)-5-(3,6-bis(*tert*-Butyldimethylsilyloxy)hexylthio)-1-phenyl-1H-tetrazole (21):

Diisopropylazodicarboxylate (589 mg, 2.90 mmol) was added to a solution of (*R*)-3,6-bis(*tert*-butyldimethylsilyloxy)hexan-1-ol **19** (0.65 g, 1.8 mmol), 1-phenyl-1H-tetrazole-5-thiol **20** (486 mg, 2.73 mmol) and triphenylphosphine (621 mg, 2.36 mmol) in THF (20 mL) at 0 ^{o}C. The reaction mixture was stirred at room temperature for 2.5 h and quenched with saturated NaCl (20 mL) solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (10% ethyl acetate in hexanes) provided (*R*)-5-(3,6-bis(*tert*-butyldimethylsilyloxy)hexylthio)-1-phenyl-1H-tetrazole **21** (940 mg, 99%) as an

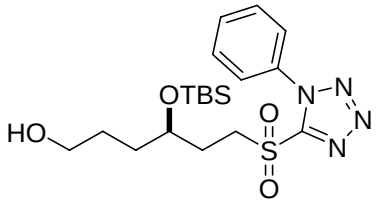
oil: $[\alpha]_D$ –17.8 (*c* 0.28 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.047 (s, 3H), 0.053 (s, 3H), 0.88 (s, 18H), 1.48-1.60 (m, 4H), 1.89-2.05 (m, 2H), 3.36-3.50 (m, 2H), 3.55-3.64 (m, 2H), 3.82-3.88 (m, 1H), 7.51-7.59 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ –5.2, –4.5, –4.3, 18.1, 18.3, 25.9, 26.0, 28.4, 29.6, 33.3, 36.0, 63.1, 74.3, 123.8, 129.8, 130.1, 133.8, 154.4; HRMS for $C_{25}H_{46}N_4O_2SSi_2Na$ $(M + Na)^+$: Calcd 545.2778; found 545.2780.



(*R*)-5-(3,6-bis(*tert*-Butyldimethylsilyloxy)hexylsulfonyl)-1-phenyl-1H-tetrazole (22):

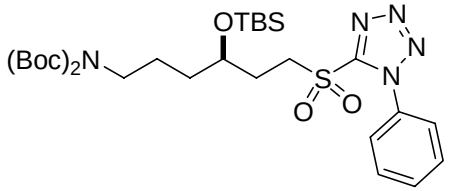
m-Chloroperperbenzoic acid (684 mg, 3.95 mmol) was added to a solution of (*R*)-5-(3,6-bis(*tert*-butyldimethylsilyloxy)hexylthio)-1-phenyl-1H-tetrazole **21** (0.94 g, 1.8 mmol) in dichloromethane (20 mL) at 0 ^oC. The mixture was stirred for 2 h at 0 ^oC followed by overnight stirring at room temperature. The mixture was quenched with saturated $NaHCO_3$ solution (25 mL) followed by separation of the layers. The aqueous layer was extracted with dichloromethane and combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) gave the title compound **22** (863 mg, 88%) as an oil: $[\alpha]_D$ –4.1 (*c* 1.0 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 0.902 (s, 9H), 1.48-1.67 (m, 4H), 2.01-2.10 (m, 1H), 2.11-2.20 (m, 1H), 3.58-3.66 (m, 2H), 3.77 (ddd, *J* = 14.7, 11.0, 4.6 Hz, 1H), 3.85 (ddd, *J* = 14.7, 11.5, 5.5 Hz, 1H), 3.90-3.96 (m, 1H), 7.59-7.63 (m, 3H), 7.69-7.71 (m, 2H); ^{13}C NMR (126 MHz, $CHCl_3$) δ –5.2, –4.6, –4.4, 18.1, 18.3, 25.9, 26.0, 28.4, 28.8, 33.2, 52.6, 62.9, 69.9,

125.1, 129.7, 131.4, 133.1, 153.5; IR (neat) cm^{-1} 2953, 2930, 2857, 1499, 1463, 1343, 1254, 1096, 836, 776; HRMS for $C_{25}H_{46}N_4O_4SSi_2Na$ $(M + Na)^+$: Calcd 577.2676; found 577.2680.

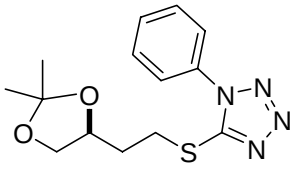


(*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(1-phenyl-1H-tetrazol-5-ylsulfonyl)hexan-1-ol (23):

A solution of HF•pyr (10 mL, prepared by slow addition of 6 mL HF•pyr to a solution 24 mL pyridine in 50 mL THF at 0 ^oC) was added to a solution of (*R*)-5-(3,6-bis(*tert*-butyldimethylsilyloxy) hexylsulfonyl)-1-phenyl-1H-tetrazole **22** (0.10 g, 0.18 mmol) in THF at 0 ^oC. The reaction mixture was stirred for 6 h at room temperature. The reaction was slowly quenched with saturated aqueous $NaHCO_3$ solution, followed by extraction of aqueous layer with ethyl acetate. The combined organic layers were washed with $CuSO_4$ solution, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography to yield the title compound **23** (81 mg, 76%) as an oil: $[\alpha]_D$ –1.1 (*c* 0.72 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (d, 6H), 0.88-0.99 (m, 9H), 1.57-1.65 (m, 6H), 2.06-2.21 (m, 2H), 3.67 (br s, 1H), 3.74-3.87 (m, 2H), 3.95 (m, 2H), 7.26-7.73 (m, 5H); ^{13}C NMR (75 MHz, $CHCl_3$) δ –4.5, –4.4, 18.1, 25.9, 28.4, 28.8, 33.1, 52.3, 62.8, 69.8, 125.2, 129.8, 131.5, 133.2, 153.6; IR (neat) cm^{-1} 3377, 2953, 2930, 2885, 2858, 1596, 1498, 1463, 1343; EIMS $(M + H)^+$ 441; HRMS for $C_{15}H_{23}N_4O_4SiS$ $(M - t\text{Bu})^+$: Calcd 383.1209; found 383.1203.



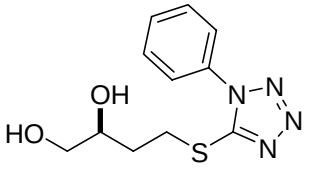
(*R*)-4-(*tert*-butyldimethylsilyloxy)-6-(1-phenyl-1H-tetrazol-5-ylsulfonyl) *N*,*N*-diBoc-hexan-1-amine (2): To a solution of (*R*)-4-(*tert*-butyldimethylsilyloxy)-6-(1-phenyl-1H-tetrazol-5-ylsulfonyl) hexan-1-ol **23** (120 mg, 0.27 mmol) in THF (1 mL)were added triphenylphosphine (107 mg, 0.41 mmol), di-*tert*-butyl-iminodicarboxylate (94 mg, 0.43 mmol) and diisopropylazodicarboxylate (99 mg, 0.49 mmol). After 16 h, the reaction mixture was concentrated and the crude product was purified by flash column chromatography to yield the title compound **2** (128 mg, 74%) as an oil: $[\alpha]_D$ −3,3 (*c* 1.21 $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.075 (s, 3H), 0.084 (s, 3H), 0.90 (s, 9H), 1.41-1.69 (m, 22H), 2.01-2.08 (m, 1H), 2.11-2.18 (m, 1H), 3.57 (t, *J* = 7.0 Hz, 2H), 3.74-3.86 (m, 2H), 3.89-3.93 (m, 1H), 7.60-7.64 (m, 3H), 7.69-7.72 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ –4.5, –4.3, 18.1, 24.9, 25.9, 28.2, 28.9, 34.0, 46.2, 52.6, 69.7, 82.3, 125.1, 129.8, 131.5, 133.1, 152.8, 153.5; IR (neat) cm^{-1} 2955, 2930, 2857, 1734, 1695, 1344; HRMS for $C_{29}H_{49}N_5O_7SiSNa$: Calcd 662.3020; found 662.3020.



(*S*)-5-(2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethylthio)-1-phenyl-1*H*-tetrazole: [(*S*)-25]:

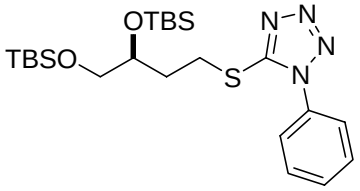
Diisoprop ylazodicarboxylate (2.8 g, 14 mmol) was added to a solution of (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (*S*)-**24** (1.2 g, 8.2 mmol), 1-phenyl-1H-tetrazole-5-thiol **20** (2.60 g, 14.8 mmol) and triphenylphosphine (3.00 g, 11.5 mmol) in THF (20 mL) at 0 ^{o}C. The mixture

was stirred at room temperature for 3 h and then quenched with water (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (25% ethyl acetate in hexanes) to provide the title compound (*S*)-**25** (2.28 g, 7.44 mmol, 91%) as an oil: $[\alpha]_D$ –1.0 (*c* 1.0 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.39 (s, 3H), 1.98-2.18 (m, 2H), 3.36-3.55 (m, 2H), 3.59 (dd, *J* = 8.1, 6.6 Hz, 1H), 4.06 (dd, *J* = 8.1, 6.1 Hz, 1H), 4.18-4.27 (m, 1H), 7.53 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 26.9, 29.6, 33.4, 68.9, 74.2, 109.2, 123.7, 129.8, 130.1, 133.6, 154.1; IR (neat) cm^{-1} 3070, 2985, 2933, 2868, 1570, 1500, 1066; EIMS $(M - CH_3)^+$ 291; HRMS for $C_{13}H_{15}N_4O_2S$ $(M - CH_3)^+$: Calcd 291.0916; found 291.0919.

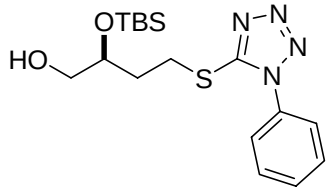


(*S*)-4-(1-Phenyl-1H-tetrazol-5-ylthio)butane-1,2-diol [(*S*)-26]: To a solution of (*S*)-5-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethylthio)-1-phenyl-1H-tetrazole (*S*)-**25** (810 mg, 2.64 mmol) in methanol (10 mL) was added a drop of acetyl chloride (21 mg). After 30 min, the mixture was concentrated and the crude product was purified by flash column chromatography (SiO_2, 80% ethyl acetate in hexanes) to provide the title compound (*S*)-**26** (650 mg, 2.45 mmol, 93%) as viscous oil: $[\alpha]_D$ –7.5 (*c* 1.82 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.90-2.09 (m, 2H), 2.55 (br s, 1H), 3.42-3.55 (m, 1H), 3.56-3.68 (m, 2H), 3.68-3.81 (m, 1H), 3.85-4.13 (m, 2H), 7.58 (br s, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.8, 33.7, 66.4, 69.5, 124.0, 129.9, 130.4, 133.5, 155.1; IR

(neat) cm^{-1} 3384, 2936, 1644, 1596, 1499, 1462, 1388, 1318, 1280; EIMS $(M + H)^+$ 267; HRMS for $C_{10}H_{11}N_4O_1S(M - CH_3O)^+$: Calcd 235.0653; found 235.0658.

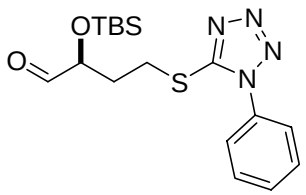


(*S*)-5-(3,4-bis(*tert*-Butyldimethylsilyloxy)butylthio)-1-phenyl-1H-tetrazole (27): To a solution of (*S*)-4-(1-phenyl-1H-tetrazol-5-ylthio)butane-1,2-diol (*S*)-**26** (830 mg, 3.14 mmol) in dichloromethane (30 mL) at −78 ^oC were added 2,6-lutidine (1.98 g, 18.5 mmol) and TBSOTf (1.70 g, 6.45 mmol). The reaction mixture was stirred at −78 ^oC for 1 h followed by warming it to 0 ^oC. The reaction mixture was poured into water followed by separation of the organic layer. The aqueous layer was extracted with dichloromethane and the combined organic extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 5% ethyl acetate in hexanes) to yield the title compound **27** (1.54 g, 3.11 mmol, 99%) as an oil: $[\alpha]_D$ −22.6 (*c* 0.72 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.07 (s, 6H), 0.87 (s, 9H), 0.89 (s, 9H), 1.90-1.98 (m, 1H), 2.09-2.16 (m, 1H), 3.41-3.47 (m, 2H), 3.50-3.60 (m, 2H), 3.80-3.85 (m, 1H), 7.53-7.60 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.3, −4.7, −4.2, 18.1, 18.3, 25.9, 26.0, 29.5, 33.6, 66.9, 71.7, 123.9, 129.8, 130.1, 133.8, 154.5; IR (neat) cm^{-1} 2929, 2857, 1598, 1501, 1472, 1388, 1253, 837; HRMS for $C_{23}H_{42}N_4O_2Si_2S$ $(M + Na)^+$: Calcd 517.2465; found 517.2424.

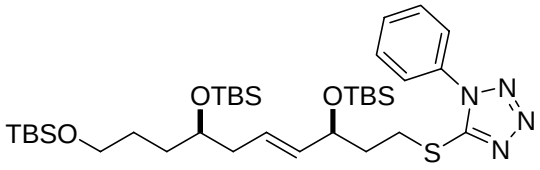


(*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-(1-phenyl-1H-tetrazol-5-ylthio)butan-1-ol (28):

To a solution of (*S*)-5-(3,4-bis(*tert*-Butyldimethylsilyloxy)butylthio)-1-phenyl-1H-tetrazole **27** (810 mg, 1.63 mmol) in THF (10 mL) at 0 ^{o}C was added HF•py (20 mL, prepared by slow addition of 6 mL HF•py to a solution of 24 mL pyridine in 50 mL THF at 0 ^{o}C). The mixture was stirred for 1 h at 0 ^{o}C and 5 h at room temperature. The reaction mixture was treated with saturated aqueous $NaHCO_3$ solution (40 mL) and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sat. aq. $CuSO_4$, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 25% ethyl acetate in hexanes) to yield the title compound **28** (396 mg, 1.04 mmol, 64%) as an oil: $[\alpha]_D$ –6.76 (*c* 4.36 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.89 (s, 9H), 2.06-2.11 (m, 2H), 2.38 (dd, *J* = 6.9, 5.0 Hz, 1H), 3.33-3.41 (m, 1H), 3.44-3.51 (m, 1H), 3.55 (ddd, *J* = 11.5, 7.3, 4.6 Hz, 1H), 3.62 (dt, *J* = 10.1, 5.0 Hz, 1H), 3.92 (dt, *J* = 10.5, 5.0 Hz, 1H), 7.53-7.58 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ –4.6, –4.5, 18.1, 25.8, 29.1, 33.3, 65.8, 71.2, 123.8, 129.8, 130.2, 133.6, 154.3; IR (neat) cm^{-1} 3441, 3064, 2929, 2884, 2857, 1597, 1500, 1388, 1251; HRMS for $C_{13}H_{19}N_4O_2SiS$ (M – *t*Bu)$^+$: Calcd 323.0998; found 323.0995.

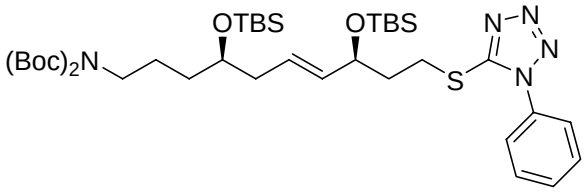


(*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-(1-phenyl-1H-tetrazol-5-ylthio)butanal (3): To a solution of (*S*)-2-(*tert*-butyldimethylsilyloxy)-4-(1-phenyl-1H-tetrazol-5-ylthio)butan-1-ol **28** (0.11 g, 0.28 mmol) in dichloromethane (5 mL) was added sodium bicarbonate (solid, 73 mg) and dess-martin reagent (184 mg, 0.430 mmol). The reaction mixture was stirred for 1.5 h and then quenched with sat. aq. $NaHCO_3$ solution (2 mL). The layers were separated and the aqueous layer was extracted with dichloromethane. Combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 15% ethyl acetate in hexanes) to provide the title compound **3** (91 mg, 0.24 mmol, 86%) as an oil: $[\alpha]_D$ −13.1 (*c* 2.57 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 2.19 (sex, *J* = 6.9 Hz, 1H), 2.24-2.31 (m, 1H), 3.47 (t, *J* = 6.9 Hz, 2H), 4.17 (dd, *J* = 7.3, 4.6 Hz, 1H), 7.52-7.59 (m, 5H), 9.64 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ –4.9, –4.5, 18.2, 25.8, 28.7, 32.0, 76.1, 123.9, 129.9, 130.2, 133.6, 153.8, 202.9; IR (neat) cm^{-1} 3071, 2953, 2855, 2709, 1735, 1593, 1500, 1390; HRMS for $C_{17}H_{27}N_4O_2SSi$ $(M + H)^+$: Calcd 379.1624; found 379.1648.



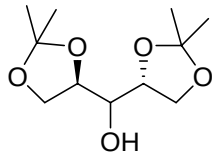
5-((3*S*,7*R*,*E*)-3,7,10-*tris*(*tert*-Butyldimethylsilyloxy)dec-4-enylthio)-1-phenyl-1H-tetrazole (29): KHMDS (0.5 M in toluene, 0.2 mL, 0.1 mmol) was added to a solution of sulfone **22** (47 mg, 86 μmol) in THF (1 mL) at −78 °C. After 30 min, a solution of aldehyde **3** (42.4 mg, 0.112 mmol) in THF (1 mL) wad added. After stirring for 1 h at −78 °C, the mixture was warmed to room temperature and stirred for additional 12 h. Water (1 mL) was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate. The combined organic layers

were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) to give the title compound (54 mg, 89%) as a clear oil. This was further purified by preparative HPLC using Whelk-O column (98/2 hexanes/*i*-propanol) to yield pure *E*-isomer of the title compound **29** (49.2 mg, 81%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 6H), 0.05 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.37-1.63 (m, 4H), 1.97-2.02 (m, 2H), 2.19 (t, *J* = 6.0 Hz, 2H), 3.39-3.47 (m, 2H), 3.58 (t, *J* = 6.0 Hz, 2H), 3.67-3.73 (m, 1H), 4.24 (q, *J* = 6.0 Hz, 1H), 5.44 (dd, *J* = 15.6, 6.9 Hz, 1H), 5.62 (dt, *J* = 15.1, 7.3 Hz, 1H), 7.52-7.61 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ –5.2, –4.7, –4.5, –4.3, –4.0, 18.2, 18.2, 18.4, 26.0, 26.1, 28.9, 29.5, 32.9, 37.5, 40.0, 63.4, 71.9, 72.2, 123.9, 127.7, 129.8, 130.1, 133.8, 134.6, 154.5; IR (neat) cm^{-1} 2954, 2929, 2852, 1597, 1503, 1462, 1389, 1246; HRMS for $C_{35}H_{66}N_4O_3SSi_3$ $(M)^+$: Calcd 729.4061; found729.4048.



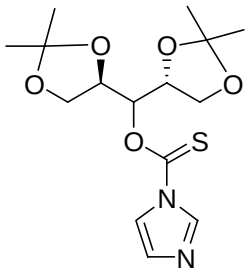
(4*R*,8*S*,*E*)-4,8-*bis*(*tert*-butyldimethylsilyloxy)-10-(1-phenyl-1*H*-tetrazol-5-ylthio)-*N*,*N*-*bis*(Boc) dec-6-en-1-amine (30): KHMDS (0.5 M in toluene, 0.45 ml, 0.225 mmol) was added to a solution of sulfone **2** (130 mg, 0.187 mmol) in THF (5 mL) at –78 ^{o}C. After 30 min, a solution of (*S*)-2-(*tert*-butyldimethylsilyloxy)-4-(1-phenyl-1H-tetrazol-5-ylthio)butanal **3** (92.3 mg, 0.244 mmol) in THF (2 mL) was added. The reaction mixture was stirred at –78 ^{o}C for 1.5 h followed by overnight stirring at room temperature. The reaction mixture was quenched with water and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, concentrated and the crude product was purified by flash column

chromatography to yield an E/Z mixture (9/1) of product (95 mg, 95%) as an oil. Further purification y preparative HPLC with Whelk-O column (95/5 hexane/*i*-propanol) provided pure *E*-isomer **30** (127 mg, 86%): $[\alpha]_D$ +4.3 (*c* 0.21 $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 6H), 0.05 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 1.37-1.44 (m, 2H), 1.50 (s, 18H), 1.62-1.70 (m, 2H), 1.98-2.01 (m, 2H), 2.18 (t, *J* = 6.4 Hz, 2H), 3.39-3.47 (m, 2H), 3.50-3.57 (m, 2H), 3.66-3.70 (m, 1H), 4.23 (q, *J* = 6.0 Hz, 1H), 5.44 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.60 (dt, *J* = 15.4, 7.1 Hz, 1H), 7.54-7.60 (m, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ –4.7, –4.5, –4.3, –4.0, 18.1, 18.2, 25.2, 25.9, 28.2, 29.5, 33.8, 37.5, 40.0, 46.6, 71.8, 72.1, 82.0, 123.9, 127.5, 129.8, 130.1, 133.8, 134.8, 152.7, 154.5; IR (neat) cm^{-1} 2955, 2928, 2856, 1740, 1698, 1501, 1367, 1124; HRMS $(M + Na)^+$ for $C_{39}H_{69}N_5O_6Si_2SNa$: Calcd 814.4405; found 814.4401.

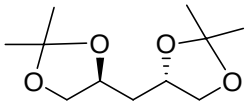


***bis*((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methanol (36):**[14] To a refluxing suspension of D-arabitol *D*-**33** (1.00 g, 6.58 mmol) in 3,3-dimethoxypropane (3.50 mL, 28.9 mmol) and THF (10 mL) was added CSA (0.457 g, 1.97 mmol) and the reaction mixture was stirred at reflux for 5 min. Triethylamine (2 mL) was added to the refluxing reaction mixture, and the mixture was concentrated in vacuo and loaded directly onto a silica gel column (35% ethyl acetate in hexanes) to yield the title compound **36** (917 mg, 60%) as a colorless oil. Data same as reported in the literature.[3]

[14] CAS # 73543-86-9: Francisco, C. G.; Leon, E. I.; Martin, A.; Moreno, P.; Rodriguez, M. S.; Suarez, E. *J. Org. Chem.* **2001**, *61*, 6967.

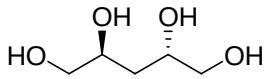


***O-bis*((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methyl 1H-imidazole-1-carbothioate (39):** To a solution of alcohol **36** (1.62 g, 6.95 mmol) in 1,2-dicholoroethane (25 mL) was added *N*,*N*-thiocarbonyldi-imidazole **38** (2.16 g, 12.1 mmol) and the mixture was stirred for 6 h at reflux. The resultant reaction mixture was concentrated and purified by flash column chromatography to give the title compound **39** (2.26 g, 95%) as a yellow oil.[1]H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 12H), 3.81 (m, 1H), 4.02-4.14 (m, 3H), 4.41-4.53 (m, 2H), 5.89-5.92 (m, 1H), 7.03 (s, 1H), 7.65 (s, 1H), 8.36 (s, 1H); [13]C NMR (75 MHz, $CDCl_3$) δ 24.6, 24.7, 25.8, 26.0, 64.9, 65.4, 74.2, 74.6, 80.6, 109.2, 109.3, 117.7, 130.7, 136.7, 184.3.

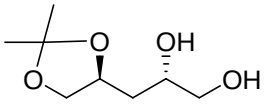


***bis*((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methane (40):** To a solution of compound **39** (1.80 g, 5.28 mmol) was added Et_3SiH (40 mL) and the reaction mixture was brought to reflux. Benzoyl peroxide (0.26 g, 1.1 mmol) was added and the reaction mixture, and was refluxed for 2 h, with similar quantity added after 30, 60, and 90 min. The reaction mixture was concentrated and the crude material was purified by flash column chromatography (gradient, 25 to 50% ethyl acetate in hexanes) to yield the title compound **40** (1.14 g, 66%) as a pale yellow oil. [1]H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 6H), 1.40 (s, 6H), 1.80 (t, J = 6.4 Hz, 2H), 3.55-3.58 (m, 2H), 4.11 (dd, J

= 7.8, 6.0 Hz, 2H), 4.19-4.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8, 27.0, 38.4, 69.9, 73.7, 108.9.



(2*S*,4*S*)-pentane-1,2,4,5-tetraol (41):[15][103] To a solution of compound **40** in methanol (10 mL) was added acetyl chloride (20 μL). The reaction mixture was stirred for 30 min at room temperature followed by concentration to yield the title compound (175 mg, 99%) **41** as a white solid.

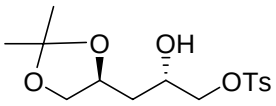


(*S*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)propane-1,2-diol (42)[16]**:** To a solution of compound **41** (56.3 mg, 0.413 mmol) in DMF (10 mL) was added 2,2-dimethoxypropane (47.4 mg, 0.455 mmol) and CSA (9.6 mg, 0.041 mmol). The reaction mixture was stirred for 15 min and then quenched with triethylamine (20 mg). Concentration of the reaction mixture followed by purification of the crude product by flash column chromatography gave the title compound **42** (42.2 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.42 (s, 3H), 1.67 (ddd, *J* = 14.2, 7.8, 3.7 Hz, 1H), 1.74 (ddd, *J* = 18.3, 8.7, 4.1 Hz, 1H), 2.83 (brs 2H), 3.50 (dd, *J* = 11.5, 7.3 Hz,

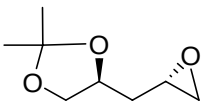
[15] CAS # 92691-36-6 Data was same as reported in the literature: Ley, S. V.; Anthony, N. J.; Armstrong, A.; Brasca, M. G.; Clarke, T.; Culshaw, D.; Greck, C.; Grice, P.; Jones, A. B. *Tetrahedron*. **1989**, *45*, 7161.

[16] CAS # 173395-90-9

1H), 3.58 (t, J = 7.8 Hz, 1H), 3.66 (dd, J = 11.5, 3.7 Hz, 1H), 3.90-3.95 (m, 1H), 4.09 (dd, J = 8.3, 6.0 Hz, 1H), 4.30-4.35 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.7, 27.0, 36.4, 66.9, 69.5, 69.6, 73.4; IR (neat) cm^{-1} 2294, 2988, 1374, 1057; HRMS for $C_7H_{13}O_4$ (M – CH_3): Calcd 161.0815; found 161.0814.



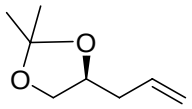
(*S*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-hydroxypropyl 4-methylbenzenesulfonate (43): To a solution of diol **42** (760 mg, 4.31 mmol) in CH_2Cl_2 (35 mL) were added Bu_2SnO (107 mg, 0.430 mmol), *p*-TsCl (863 mg, 4.53 mmol) and Et_3N (480 mg, 4.74 mmol). After 3 h, the reaction mixture was concentrated and the crude product was purified by flash column chromatography (SiO_2, 50% ethyl acetate in hexanes) to yield the title compound **43** (968 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.38 (s, 3H), 1.67-1.72 (m, 2H), 2.46 (s, 3H), 2.67 (d, J = 4.6 Hz, 1H), 3.56 (t, J = 8.3 Hz, 1H), 3.95 (dd, J = 11.5, 8.3 Hz, 1H), 4.05-4.09 (m, 3H), 4.26-4.31 (m, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.7, 25.6, 27.0, 36.0, 67.1, 69.4, 72.9, 73.4, 109.2, 128.1, 130.0, 132.7, 145.2; HRMS for $C_{14}H_{19}O_6S$: Calcd 315.0902; found 315.0894.



(*S*)-2,2-Dimethyl-4-((*S*)-oxiran-2-ylmethyl)-1,3-dioxolane (31):[17] To a solution of alcohol **43** (900 mg, 2.72 mmol) in MeOH/CH_2Cl_2 (5/1, 12 mL) was added K_2CO_3 (565 mg, 4.09 mmol).

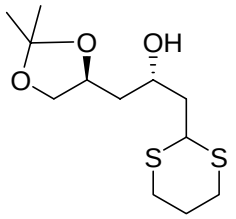
[17] CAS # 101977-98-4

The reaction mixture was stirred for 2 h followed by concentration. Then it was diluted with ethyl acetate (10 mL) and washed with water (5 mL x 2). The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography to yield the title compound **31** (387 mg, 90%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.36 (s, 3H), 1.49 (ddd, *J* = 13.8, 7.3, 5.5 Hz, 1H), 1.91 (ddd, *J* = 14.2, 7.8, 4.1 Hz, 1H), 2.45 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.75 (t, *J* = 4.6 Hz, 1H), 2.97-3.00 (m, 1H), 3.53 (t, *J* = 7.3 Hz, 1H), 4.05 (dd, *J* = 7.8, 5.6 Hz, 1H), 4.22 -4.27 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.6, 26.9, 37.1, 47.1, 49.3, 69.3, 73.6, 108.9; IR (neat) cm^{-1} 2987, 2942, 2872, 1454, 1371, 1060; HRMS for $C_7H_{11}O_3$ $(M - CH_3)^+$: Calcd 143.0708; found 143.0706.

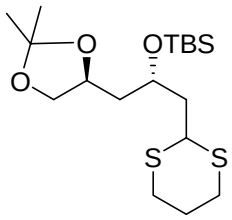


(*S*)-4-Allyl-2,2-dimethyl-1,3-dioxolane (45): To a solution of CH_3PPh_3Br (15.8 g, 44.2 mmol) in THF (500 mL) at 0 ^oC was added *n*-BuLi (1.6 M in hexane, 27.6 mL, 44.2 mmol). The reaction mixture was stirred for 20 min followed by cooling it to –78 ^oC. A solution of aldehyde **44** (4.9 g, 34 mmol) in THF (5 mL) was slowly added to the above reaction mixture. After 30 min, it was allowed to warm to room temperature and stirred overnight. The reaction mixture was poured into saturated aqueous NH_4Cl (300 mL) and the aqueous layer was extracted with Et_2O (2 x 300 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (SiO_2, 20% ethyl acetate in hexanes) afforded the title compound **45** (4.0 g, 83%) a volatile oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.43 (s, 3H), 2.25-2.34 (m, 1H), 2.37-2.48 (m, 1H), 3.59 (dd, *J* = 8.2, 7.1 Hz, 1H),

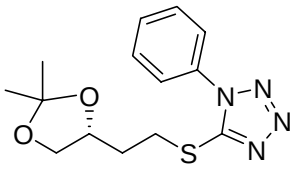
4.03 (dd, J = 8.2, 6.0 Hz, 1H), 4.13-4.21 (m, 1H), 5.07-5.17 (m, 2H), 5.81 (ddt, J = 17.0, 10.4, 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 26.9, 38.1, 69.0, 75.2, 109.0, 117.7, 133.7.



(*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(1,3-dithian-2-yl)propan-2-ol (46): *t*-BuLi (1.7 M in pentane, 5.3 mL, 9.0 mmol) was added to a solution of 1,3-dithiane **16** (1.10 g, 9.04 mmol) in THF/HMPA (5 mL/0.3 mL) at −78 ^{o}C. After 30 min, a solution of (*S*)-2,2-dimethyl-4-((*S*)-oxiran-2-ylmethyl)-1,3-dioxolane **31** (1.3 g, 8.2 mmol) in THF (3mL) and HMPA (1mL) was added to the above reaction mixture. After 1 h at −78 ^{o}C, the reaction mixture was allowed to warm to 0 ^{o}C, followed by quenching it with saturated aqueous NH_4Cl solution. Aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 25% ethyl acetate in hexanes) to yield the title compound **46** (1.9 g, 83%) as an oil: $[\alpha]_D$ +6.75 (*c* 0.80 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.42 (s, 3H), 1.69-1.79 (m, 2 H), 1.84-1.99 (m, 3H), 2.10-2.16 (m, 1H), 2.67 (d, J = 5.0 Hz, 1H), 2.82-2.95 (m, 4H), 3.59 (t, J = 7.8 Hz, 1H), 4.09 (dd, J = 8.2, 6.0 Hz, 1H), 4.14-4.20 (m, 1H), 4.27 (dd, J = 8.9, 5.3 Hz, 1H), 4.31-4.36 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.6, 25.9, 26.9, 30.1, 30.3, 39.8, 42.8, 44.2, 66.1, 69.4, 73.4, 108.9; IR (neat) cm^{-1} 3435, 2983, 2935, 2899, 1456, 1423, 1370; EIMS (M^+) 278; HRMS for $C_{12}H_{22}O_3S_2$ (M^+): Calcd 278.1010; found 278.1006.

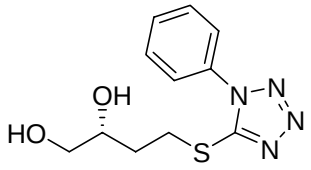


***tert*-butyl((*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(1,3-dithian-2-yl)propan-2-yloxy) dimethylsilane (47):** To a solution of alcohol **46** (320 mg, 1.15 mmol) and 2,6-lutidine in CH_2Cl_2 at −78 ^oC was added and TBSOTf. The reaction mixture was stirred for 1.5 h followed by pouring it into water (25 mL). Organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography to yield the title compound **47** (410 mg, 91%) as an oil: $[\alpha]_D$ −1.65 (*c* 4.79 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 1.30 (s, 3H), 1.36 (s, 3H), 1.59 (ddd, *J* = 13.7, 8.2, 5.0 Hz, 1H), 1.77 (ddd, *J* = 13.7, 7.8, 4.6 Hz, 1H), 1.79-1.88 (m, 3H), 2.05-2.11 (m, 1H), 2.75-2.87 (m, 4H), 3.44 (t, *J* = 7.8 Hz, 1H), 3.99-4.09 (m, 3H), 4.11-4.16 (m, 1H), 4.13 (dtd, *J* = 10.5, 7.8, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.6, −4.4, 25.8, 25.9, 27.1, 30.3, 30.5, 41.4, 43.6, 43.9, 66.6, 69.9, 72.8, 77.3, 108.5.

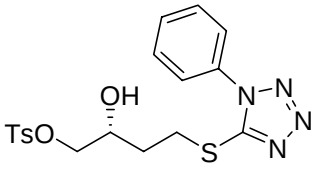


(*R*)-5-(2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethylthio)-1-phenyl-1H-tetrazole (25): $[\alpha]_D$ +12.3 (*c* 1.19 $CHCl_3$): Diisopropylazodicarboxylate (2.80 g, 14.0 mmol) was added to a solution of (*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (1.2 g, 8.2 mmol), 1-phenyl-1H-tetrazole-5-thiol (2.60 g, 14.8 mmol) and triphenylphosphine (3.00 g, 11.5 mmol) in THF (20 mL) at 0 ^oC. The reaction

mixture was stirred at room temperature for 3 h and quenched with water (20 mL). The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (25% ethyl acetate in hexanes) provided (*R*)-5-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethylthio)-1-phenyl-1H-tetrazole **25** (2.23 g, 7.29 mmol, 89%) as an oil.

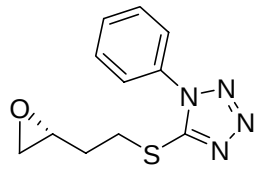


(*R*)-4-(1-Phenyl-1H-tetrazol-5-ylthio)butane-1,2-diol 26: $[\alpha]_D$ +11 (*c* 0.78 $CHCl_3$); To a solution of (*R*)-5-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethylthio)-1-phenyl-1H-tetrazole (600 mg, 1.96 mmol) in methanol (10 mL) was added a drop of acetyl chloride (~ 21 mg). After 30 min, the reaction mixture was concentrated and the crude product was purified by flash column chromatography (80% ethyl acetate in hexanes) to provide (*R*)-4-(1-phenyl-1H-tetrazol-5-ylthio)butane-1,2-diol (510 mg, 86 %) as a viscous oil.



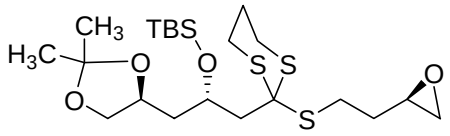
(*R*)-2-Hydroxy-4-(1-phenyl-1H-tetrazol-5-ylthio)butyl 4-methylbenzenesulfonate 48: To a solution of (*R*)-4-(1-phenyl-1H-tetrazol-5-ylthio)butane-1,2-diol (290 mg, 1.28 mmol) in CH_2Cl_2 (10 mL) were added Bu_2SnO (64 mg, 0.26 mmol), *p*-toluenesulfonyl chloride (244 mg, 1.28

mmol), and triethyl amine (130 mg, 1.28 mmol). The reaction mixture was stirred for 3 h followed by dilution with water (10 mL). Organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, ethyl acetate/hexanes = 1:1) to yield the title compound (400 mg, 74%): $[\alpha]_D$ +10.0 (*c* 0.74 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.87-2.03 (m, 2H), 2.39 (s, 3H), 3.43-3.50 (m, 2H), 3.92-4.03 (m, 4H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.53 (s, 5H), 7.75 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4, 29.2, 32.7, 66.9, 73.1, 123.6, 127.7, 129.7, 129.8, 130.1, 132.3, 133.3, 144.9, 154.4; IR (neat) cm^{-1} 3400, 3060, 2946, 1597, 1499, 1387, 1357, 1243; HRMS for $C_{18}H_{20}N_4O_4S_2$: calcd 443.0824; found 443.0804.

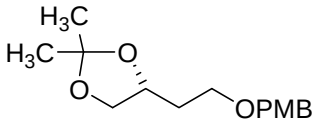


(*R*)-5-(2-(Oxiran-2-yl)ethylthio)-1-phenyl-1H-tetrazole 32: To a solution of (*R*)-2-hydroxy-4-(1-phenyl-1H-tetrazol-5-ylthio)butyl 4-methylbenzenesulfonate (440 mg, 1.05 mmol) in CH_3OH-DCM (9:1 10 mL) was added K_2CO_3 (173 mg, 1.25 mmol). The reaction mixture was stirred at room temperature for 1 h followed by concentration. Then it was diluted with dichloromethane (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and concentrated to provide the title compound (211 mg, 81%) as an oil: $[\alpha]_D$ +15.0 (*c* 1.13 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.92 (td, *J* = 14.2, 6.9 Hz, 1H), 2.21-2.29 (t, *J* = 4.6 Hz, 1H), 2.52 (dd, *J* = 4.6, 2.7 Hz, 1H), 2.74-2.78 (m, 1H), 3.01-3.06 (m, 1H), 3.45-3.54 (m,

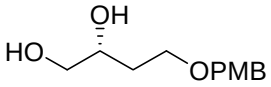
2H), 7.49-7.56 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.8, 32.0, 46.8, 50.6, 123.7, 129.8, 130.1, 133.5, 153.9; IR (neat) cm^{-1} 3056, 2991, 2924, 1596, 1500, 1461; HRMS (EI) for $C_{11}H_{12}N_4O_1S$: Calcd 248.0732; found 248.0721.



***tert*-Butyl((*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(2-(2-((*R*)-oxiran-2-yl)ethyl thio)-1,3-dithian-2-yl)propan-2-yloxy)dimethylsilane (49):** *t*-BuLi (1.7 M in pentane, 0.14 mL, 0.24 mmol) was added to a solution of compound **47** in THF (0.8 mL) at –30 ^{o}C. After 30 min, epoxide **32** (58.9 mg, 0.284 mmol) in THF (0.2 mL) was added to the reaction mixture and stirred for additional 30 min at –30 ^{o}C. Then the mixture was warmed to 0 ^{o}C and for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 25% ethyl acetate in hexanes) to yield the title compound **49** (66 mg, 56%) as colorless oil. $[\alpha]_D$ –21.2 (*c* 1.72 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.16 (s, 3H), 0.89 (s, 9H), 1.33 (s, 3H), 1.41 (s, 3H), 1.61 (ddd, *J* = 13.7, 8.3, 4.6 Hz, 1H), 1.81-1.87 (m, 3H), 2.04-2.09 (m, 1H), 2.23-2.29 (m, 3H), 2.53 (dd, *J* = 5.0, 2.8 Hz, 1H), 2.58-2.71 (m, 4H), 2.78-2.80 (m, 1H), 2.99-3.04 (m, 1H), 3.14-3.35 (m, 2H), 3.51-3.54 (m, 1H), 4.06 (dd, *J* = 7.8, 5.5 Hz, 1H), 4.17-4.23 (m, 1H), 4.26-4.31 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ –4.2, –3.8, 18.1, 24.6, 25.9, 26.1, 27.1, 27.5, 27.8, 29.6, 31.9, 43.3, 47.2, 51.4, 52.0, 60.4, 67.2, 70.1, 73.2, 108.6; IR (neat) cm^{-1} 2983, 2953, 2855, 1472, 1252; HRMS (EI) for $C_{21}H_{39}O_4SiS_3$ $(M - CH_3)^+$: Calcd 479.1779; found 479.1780.

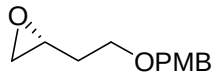


(*R*)-4-(2-(4-Methoxybenzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolane (53):[18]Alcohol (*R*)-**24** (1.30 g, 8.07 mmol) was added slowly over 10 min to a suspension of NaH (271 mg, 11.3 mmol) in DMF (15 mL) at 0 ^{o}C. The mixture was stirred for 30 min followed by the addition of *p*-methoxybenzyl chloride (1.33 g, 8.48 mmol). The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was quenched with methanol (1 mL) and poured into water (100 mL). The aqueous layer was extracted with ether and the combined organic extracts were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (SiO_2, 25% Ethylacete in hexanes) gave the title compound **53** as colorless oil: $[\alpha]_D$ 0.87 (*c* 1.2 $CHCl_3$); ^{1}H NMR (500 MHz, $CHCl_3$) δ 1.36 (s, 3H), 1.41 (s, 3H), 1.79-1.89 (m, 1H), 1.89-1.97 (m,1H), 3.50-3.60 (m, 3H), 3.81 (s, 3H), 4.06 (dd, *J* = 8.2, 6.0 Hz, 1H), 4.17-4.25 (m, 1H), 4.44 (s, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.9, 27.0, 33.9, 55.3, 66.8, 69.7, 72.8, 74.0, 108.6, 113.9, 129.3, 130.5, 159.3; IR (neat) cm^{-1} 2985, 2936, 2865, 1613, 1514, 1248; HRMS (EI) for $C_{12}H_{18}O_4$ $(M)^+$: Calcd 226.1205; found 226.1199.

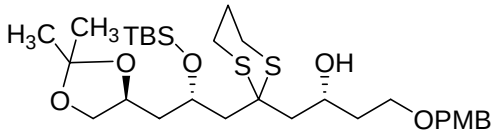


[18] CAS # 213978-60-0

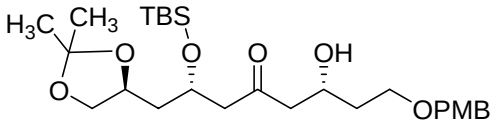
(*R*)-4-(4-Methoxybenzyloxy)butane-1,2-diol (54): To a solution of compound **53** (1.70 g, 6.04 mmol) in methanol (25 mL) was added acetyl chloride (~100 mg). The reaction mixture was stirred at room temperature for 2 h followed by concentration of the reaction mixture. The crude product was purified by flash column chromatography (SiO_2, 80% ethyl acetate in hexanes) to yield the title **54** compound as clear colorless oil: $[\alpha]_D$ –2.6 (*c* 1.4 $CHCl_3$); HRMS (EI) for $C_{15}H_{22}O_4$ $(M)^+$: Calcd 266.1518; found 266.1514.



(*R*)-2-(2-(4-Methoxybenzyloxy)ethyl)oxirane (56): To a solution of diol **54** (800 mg, 3.98 mmol) in toluene (15 mL) were added PPh_3 (1.30 g, 4.97 mmol) and DIAD (1.00 g, 4.97 mmol). The reaction mixture was refluxed overnight followed by concentration of the reaction mixture. The crude reaction product was purified by flash column chromatography (SiO_2, 25% ethyl acetate in hexanes) to yield the title compound **56** (779 mg, 94%) as an oil: $[\alpha]_D$ 12 (*c* 1.0 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72-1.82 (m, 1H), 1.85-1.95 (m, 1H), 2.53 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.79 (t, *J* = 4.6 Hz, 1H), 3.03-3.10 (m, 1H), 3.55-3.64 (m, 2H), 3.81 (s, 3H), 4.47 (s, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.0, 47.2, 50.1, 55.3, 66.8, 72.8, 113.9, 129.3, 130.4, 159.3; IR (neat) cm^{-1} 2997, 2924, 2860, 1613, 1513; HRMS (EI) for $C_{12}H_{16}O_3$ $(M)^+$: Calcd 208.1099; found 208.1094.

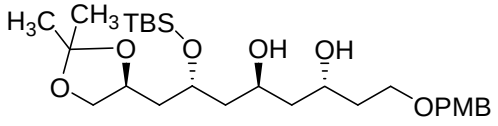


(*R*)-4-(4-Methoxybenzyloxy)-1-(2-((*S*)-2-(*tert*-butyldimethylsilyloxy)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)-1,3-dithian-2-yl)butan-2-ol (57): To a solution of compound **47** (0.33 g, 0.84 mmol) in THF (1.2 mL) at 0 ^{o}C was added *n*-BuLi (1.6 M in hexane, 0.6 mL). The reaction mixture was stirred at 0 ^{o}C for 20 min, followed by cooling to –20 ^{o}C. Then a solution of epoxide **56** (0.18 g, 0.88 mmol) in THF (0.5 mL) was added and stirred at –10 ^{o}C for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 25% ethyl acetate in hexanes) to yield the title compound **57** (340 mg, 67%) as clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 1.34 (s, 3H), 1.41 (s, 3H), 1.52-1.80 (m, 3H), 1.88-2.19 (m, 5H), 2.20-2.39 (m, 2H), 2.75-2.99 (m, 4H), 3.51 (t, *J* = 7.9 Hz, 1H), 3.57-3.63 (m, 3H), 3.80 (s, 3H), 4.06 (dd, *J* = 13.5, 7.7 Hz, 1H), 4.12-4.23 (m, 3H), 4.45 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.2, –3.7, 14.3, 18.0, 24.7, 25.9, 26.0, 26.2, 26.7, 27.1, 37.7, 43.0, 46.7, 48.2, 51.2, 55.3, 60.4, 67.0, 67.5, 68.0, 70.1, 72.9, 73.3, 108.6, 113.8, 129.4, 130.4, 159.2; IR (neat) cm^{-1} 3497, 2974, 2932, 2856, 1613, 1514, 1249, 1093; HRMS (EI) for $C_{30}H_{52}O_6SiS_2$ $(M)^+$: Calcd 600.2975; found 600.2955.



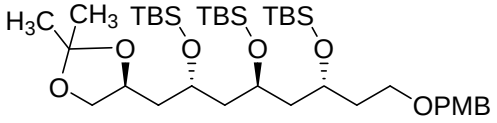
(2*S*,6*R*)-8-(4-Methoxybenzyloxy)-2-(*tert*-butyldimethylsilyloxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-hydroxyoctan-4-one (58): To a solution of compound **57** (135 mg, 0.224 mmol) in acetonitrile and water (6/1, 3 mL) were added MeI (80 mg, 0.56 mmol) and K_2CO_3 (34 mg, 0.35 mmol). The reaction mixture was stirred at 45 ^{o}C for 6 h. The reaction mixture was

diluted with Et_2O (5 mL), dried over $MgSO_4$, concentrated and purified by flash column chromatography (SiO_2, 25% ethyl acetate in hexanes) to yield the title compound **58** (93 mg, 81%) as an oil.^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 1.36 (s, 3H), 1.42 (s, 3H), 1.64 (ddd, *J* = 13.8, 8.3, 6.7 Hz, 1H), 1.71-1.86 (m, 3H), 2.60-2.68 (m, 4H), 3.41 (d, *J* = 3.2 Hz, 1H), 3.49 (t, *J* = 7.8 Hz, 1H), 3.61-3.70 (m, 2H), 3.83 (s, 3H), 4.06 (dd, *J* = 7.8, 6.0 Hz, 1H), 4.13-4.20 (m, 1H), 4.25-4.31 (m, 1H), 4.33-4.38 (m, 1H), 4.47 (s, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –4.7, –4.5, 18.0, 25.9, 27.1, 36.2, 41.6, 50.9, 52.0, 55.3, 66.2, 66.4, 67.6, 69.8, 72.7, 72.9, 108.8, 113.9, 129.3, 130.2, 159.3, 209.5; IR (neat) cm^{-1} 3466, 2952, 2931, 1708, 1514, 1302, 1090, 777; HRMS (ES) for $C_{27}H_{46}O_7SiNa$ $(M + Na)^+$: Calcd 533.2911; found 533.2886.

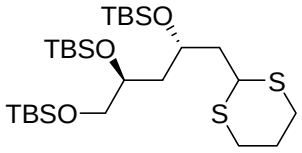


(3*R*,5*S*,7*R*)-1-(4-Methoxybenzyloxy)-7-(*tert*-butyldimethylsilyloxy)-8-((*S*)-2,2-dimeth yl-1,3-dioxolan-4-yl)octane-3,5-diol (59): To a solution of compound **58** (88 mg, 0.17 mmol) in acetonitrile (0.54 mL) at –25 ^{o}C was added a solution of $(CH_3)_4NBH(OAc)_3$ (68 mg, 0.26 mmol) in acetic acid (0.1 mL). The reaction mixture was stirred at that temperature for 48 h, quenched with aqueous sodium potassium tartarate (1.0 M, 0.8 mL), diluted with ethyl acetate and neutralized with sodium bicarbonate. The aqueous layer was extracted with ethyl acetate; the combined organic layers were dried over $MgSO_4$ and concentrated to yield the title compound (76 mg, 86%) as an oil. The crude compound **59** was taken to the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.14 (s, 3H), 0.90 (s, 9H), 1.34 (s, 3H), 1.38 (s, 3H), 1.50-1.62 (m, 3H), 1.66-1.75 (m, 2H), 1.78-1.92 (m, 3H), 3.48 (t, *J* = 8.0 Hz, 1H),

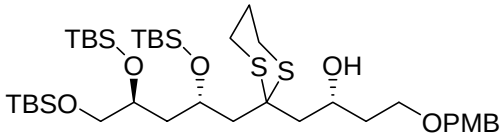
3.57 (brs, 1H), 3.60-3.71 (m, 2H), 3.80 (s, 3H), 3.89 (brs, 1H), 4.05 (dd, *J* = 7.8, 6.0 Hz, 1H), 4.09-4.24 (m, 3H), 4.26-4.34 (m, 1H), 4.45 (s, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (76 MHz, $CDCl_3$) δ –4.8, –4.4, 18.0, 25.9, 27.1, 36.9, 40.4, 43.1, 43.9, 55.3, 66.0, 68.4, 68.8, 69.3, 69.9, 70.1, 72.8, 73.0, 108.9, 113.9, 129.3, 130.3, 159.4; IR (neat) cm^{-1} 3449, 2984, 2934, 2857, 1613, 1514, 1249; HRMS (EI) for $C_{27}H_{48}O_7SiNa$ $(M + Na)^+$: Calcd 535.3067; found 535.3072.



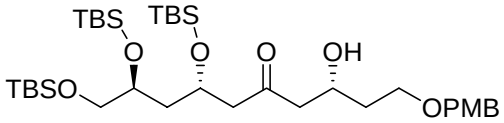
(*S*)-4-((2*S*,4*S*,6*R*)-8-(4-Methoxybenzyloxy)-2,4,6-*tris*(*tert*-butyldimethylsilyloxy)octyl)-2,2-dimethyl-1,3-dioxolane (60): To a solution of compound **59** (44.0 mg, 0.0858 mmol) in dichloromethane (5 mL) at 0 ^oC were added TBSOTf (46.5 mg, 0.176 mmol) and 2,6-lutidine (54.3, 0.506 mmol). The reaction mixture was stirred at that temperature for 1 h followed by quenching it with water. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude reaction mixture by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) gave the title compound **60** (50 mg, 80%) as clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 18H), 0.88 (s, 18H), 0.89 (s, 9H), 1.33 (s, 3H), 1.38 (s, 3H), 1.48-1.87 (m, 8H), 3.42-3.52 (m, 3H), 3.75-3.84 (m, 4H), 3.85-3.94 (m, 2H), 4.00-4.04 (m, 1H), 4.13-4.26 (m, 1H), 4.41 (s, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (76 MHz, $CDCl_3$) δ ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.4, –4.2, –4.1, –3.7, –3.5, 18.1, 26.0, 27.2, 37.9, 41.3, 46.3, 47.3, 55.3, 66.7, 67.4, 67.5, 67.7, 70.0, 72.7, 108.6, 113.8, 129.3, 130.8, 159.1; IR (neat) cm^{-1} 2953, 2857, 1511, 1250; HRMS (EI) for $C_{39}H_{76}O_7Si_3Na$ $(M + Na)^+$: Calcd 129.0552; found129.0550.



2-((2*S*,4*S*)-2,4,5-*tris*(*tert*-butyldimethylsilyloxy)pentyl)-1,3-dithiane (64): To a solution of (*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(1,3-dithian-2-yl)propan-2-ol **46** (1.9 g. 6.8 mmol) in methanol (16 mL) was added acetyl chloride (200 μL). The reaction mixture was stirred for 1 h followed by concentration. To the crude compound (triol, **63**) in dichloromethane (30 mL) were added 2,6-lutidine (2.4 g, 22.4 mmol) and TBSOTf (5.90 g, 22.4 mmol) at 0 ^{o}C. After 1 h, the reaction mixture was poured into water. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) provided the title compound **64** (3.25 g, 88%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.08 (s, 3H), 0.10 (s, 6H), 0.12 (s, 3H), 0.89 (s, 9H), 0.90 (s, 18H), 1.47-1.56 (m, 1H), 1.76-1.96 (m, 4H), 2.06-2.19 (m, 1H), 2.75-2.94 (m, 4H), 3.42 (dd, *J* = 10.2, 5.8 Hz, 1H), 3.54 (dd, *J* = 10.2, 5.2 Hz, 1H), 3.69-3.79 (m, 1H), 4.02-4.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.2, –4.3, –4.1, –3.9, –3.8, 18.2, 18.5, 26.1, 30.4, 30.8, 43.4, 44.0, 44.2, 67.0, 67.8, 71.2; IR (neat) cm^{-1} 2954, 2929, 2897, 2857, 1472, 1463, 1255; HRMS for $C_{23}H_{51}O_3S_2Si_3$ (M – *t*-Bu): Calcd 523.2587; found 523.2607.

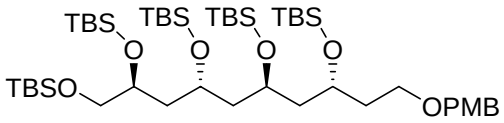


(*R*)-1-(2-((2*S*,4*S*)-2,4,5-*tris*(*tert*-Butyldimethylsilyloxy)pentyl)-1,3-dithian-2-yl)-4-(4-methoxybenzyloxy)butan-2-ol (65): *t*-BuLi (1.7 M in pentane, 1 mL, 1.7 mmol) was added to a solution of 2-((2*S*,4*S*)-2,4,5-*tris*(*tert*-butyldimethylsilyloxy)pentyl)-1,3-dithiane **64** (0.9 g, 1.55 mmol) in THF (2.4 mL)-HMPA (0.6 mL) at –78 ^{o}C. After 10 min, (*R*)-2-(2-(4-methoxybenzyloxy)ethyl)oxirane **56** (0.36 g, 1.7 mmol) in THF (1 mL) was added. The reaction mixture was stirred at –78 ^{o}C for 15 min, then warmed to 0 ^{o}C and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (SiO_2, 20% ethyl acetate in hexanes) provided the title compound **65** (1.1 g, 90%) as an oil: $[\alpha]_D$ –5.0 (*c* 0.9 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09-0.16 (m, 18H), 0.91 (s, 9H), 0.93 (s, 9H), 0.94 (s, 9H), 1.66-2.47 (m, 11H), 2.68-2.83 (m, 2H), 2.84-3.04 (m, 2H), 3.46-3.74 (m, 5H), 3.81 (s, 3H), 4.18-4.33 (m, 2H), 4.47 (s, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (76 MHz, $CDCl_3$) δ –5.3, –4.4, –3.8, –3.6, –3.1, 14.2, 18.0, 18.2, 18.4, 24.6, 26.0, 26.3, 37.6, 45.0, 46.5, 48.3, 51.4, 55.1, 60.3, 66.9, 67.4, 67.5, 67.9, 71.3, 72.7, 113.7, 129.2, 130.4, 159.1; IR (neat) cm^{-1} 2953, 2928, 2855, 1614, 1514, 1463, 1250; HRMS for $C_{39}H_{76}O_6S_2Si_3Na$: Calcd 811.4289; found 811.4284.



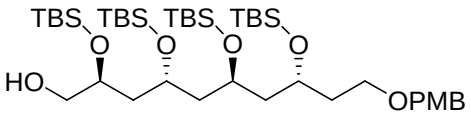
(3*R*,7*S*,9*S*)-1-(4-Methoxybenzyloxy)-7,9,10-*tris*(*tert*-butyldimethylsilyloxy)-3-hydro xydecan-5-one (66): To a solution of (*R*)-1-(2-((2*S*,4*S*)-2,4,5-tris(*tert*-butyldimethylsilyloxy) pentyl)-1,3-dithian-2-yl)-4-(4-methoxybenzyloxy)butan-2-ol **65** (610 mg, 0.77 mmol) in THF/H_2O (4:1, 10 mL) and 2.6-lutidine (662 mg, 6.18 mmol) was added $Hg(ClO_4)_3$•H_2O (1.05

g, 2.32 mmol) in portions at 0 °C. After 45 min, the mixture was filtered through a pad of celite and the filter cake was rinsed with ethyl acetate. The filtrate was diluted with ethyl acetate and saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to yield the title compound **66** (454 mg84%) as an oil: $[\alpha]_D$ –6.53 (*c* 1.73 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 6H), 0.12 (s, 3H), 0.13 (s, 6H), 0.89 (s, 9H), 0.92 (s, 9H), 0.93 (s, 9H), 1.48-1.60 (m, 1H), 1.70-1.83 (m, 3H), 2.54-2.70 (m, 4H), 3.36-3.43 (m, 2H), 3.50-3.63 (m, 3H), 3.64-3.76 (m, 1H), 3.80 (s, 3H), 4.15-4.35 (m, 2H), 4.44 (s, 2H), 8.87 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), ^{13}C NMR (75 MHz, $CHCl_3$) δ –5.3, –4.5, –4.3, –4.2, –3.9, 18.0, 18.2, 18.4, 25.9, 25.99, 26.0, 36.2, 43.4, 50.9, 52.1, 55.3, 66.3, 67.0, 67.6, 67.8, 71.2, 72.9, 113.9, 129.3, 130.4, 159.3, 209.9; IR (neat) cm^{-1} 3509, 2954, 2929, 2857, 1709, 1614, 1514, 1472, 1251; HRMS for $C_{36}H_{70}O_7Si_3Na$ $(M + Na)^+$: Calcd 721.4327; found 721.4329.



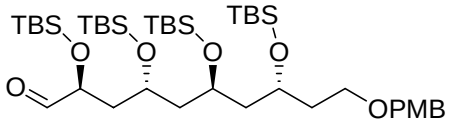
1-(((3*R*,5*S*,7*R*,9*S*)-3,5,7,9,10-*pentakis*(*tert*-Butyldimethylsilyloxy)decyloxy)methyl)-4-methoxybenzene (62): To a solution of (3*R*,7*S*,9*S*)-1-(4-methoxybenzyloxy)-7,9,10-*tris*(*tert*-butyldimethylsilyloxy)-3-hydro xydecan-5-one **66** (445 mg, 0.64 mmol) in acetonitrile (2 mL) at –25 °C was added $(CH_3)_4NBH(OAc)_3$ (253 mg, 0.96 mmol) as a solution in acetic acid (0.4 mL). The reaction mixture was stirred at that temperature for 48 h, quenched with aqueous sodium potassium tartarate solution (1.0 M, 3 mL), diluted with ethyl acetate and neutralized with sodium bicarbonate. The aqueous layer was extracted with ethyl acetate; the combined organic

layers were dried over $MgSO_4$ and concentrated. To the crude compound **67** (412 mg) in dichloromethane at 0 ^oC were added 2,6-lutidine (189 mg, 1.77 mmol) and TBSOTf (327 mg, 1.24 mmol). The reaction mixture was stirred at that temperature for 1 h and quenched with water. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) to yield the title compound **62** (434 mg, 73%) as an oil: ^1H NMR (600 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.055 (s, 3H), 0.06 (s, 3H), 0.063 (s, 3H), 0.07 (s, 3H), 0.076 (s, 6H), 0.08 (s, 3H), 0.082 (s, 3H), 0.084 (s, 3H), 0.877 (s, 9H), 0.88 (s, 9H), 0.883 (s, 9H), 0.888 (s, 9H), 0.90 (s, 9H), 1.45-1.50 (m, 1H), 1.52-1.58 (m, 1H), 1.59-1.67 (m, 3H), 1.67-1.75 (m, 2H), 1.79-1.84 (m, 1H), 3.41 (dd, *J* = 10.2, 5.5 Hz, 1H), 3.49-3.54 (m, 3H), 3.76-3.80 (m, 1H), 3.81 (s, 3H), 3.83-3.87 (m, 1H), 3.87-3.92 (m, 2H), 4.42 (s, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 9.6 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ –5.2, –4.4, –4.2, –3.8, –3.7, –3.5, –3.4, 18.1, 18.2, 18.3, 18.5, 26.1, 26.1, 26.1, 26.1, 37.7, 42.6, 46.0, 46.8, 55.3, 66.8, 67.2, 67.4, 67.5, 67.6, 70.8, 72.6, 113.8, 129.2, 130.9, 159.1; HRMS for $C_{48}H_{100}O_7Si_5Na$ $(M + Na)^+$: Calcd 951.6213; found 951.6311.



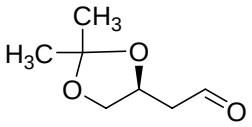
(2*S*,4*R*,6*S*,8*R*)-10-(4-Methoxybenzyloxy)-2,4,6,8-*tetrakis*(*tert*-butyldimethylsilyloxy) decan-1-ol (68): To a solution of 1-(((3*R*,5*S*,7*R*,9*S*)-3,5,7,9,10-*pentakis*(*tert*-butyldimethylsilyloxy) decyloxy)methyl)-4-methoxybenzene **62** (70 mg, 0.075 mmol) in THF (0.5 mL) was added HF•py in pyridine (1 mL). The reaction mixture was stirred at room temperature for 6 h followed by quenching the reaction with saturated aqueous sodium bicarbonate solution (5 mL). Aqueous

layer was extracted with ethyl acetate. The combined organic layers were dried over over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) provided the title compound **68** (30 mg, 49%) (84% based on recovered sm) as colorless oil along with recovered starting material **62** (29 mg, 0.031 mmol): $[\alpha]_D$ +16.5 (*c* 0.2 $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.072 (s, 6H), 0.08 (s, 6H), 0.10 (s, 3H), 0.104 (s, 3H), 0.88 (s, 18H), 0.883 (s, 9H), 0.91 (s, 9H), 1.55-1.73 (m, 7H), 1.80-1.85 (m, 1H), 1.91 (t, *J* = 6.0 Hz, 1H), 3.44 (ddd, *J* = 11.8, 7.1, 5.2 Hz, 1H), 3.50 (t, *J* = 7.1 Hz, 2H), 3.61 (ddd, *J* = 11.0, 5.5, 3.6 Hz, 1H), 3.80-3.85 (m, 6H), 3.85-3.89 (m, 1H), 4.41 (ddd, *J* = 19.8, 11.5, 5.0 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ –4.3, –4.3, –4.2, –3.7, –3.6, –3.59, –3.5, 18.1, 18.2, 26.0, 37.5, 42.4, 46.3, 46.5, 55.3, 66.6, 66.7, 67.1, 67.2, 67.4, 70.4, 72.6, 113.7, 129.2, 130.8, 159.1; IR (neat) cm^{-1} 3420, 2950, 2925, 2929, 2852, 1614, 1511, 1462, 1251, 1102; HRMS for $C_{42}H_{86}O_7Si_4Na$ $(M + Na)^+$: Calcd 837.5348; found 837.5363.



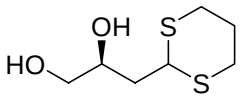
(2*S*,4*R*,6*S*,8*R*)-10-(4-Methoxybenzyloxy)-2,4,6,8-*tetrakis*(*tert*-butyldimethylsilyloxy) decanal (69): To a solution of (2*S*,4*R*,6*S*,8*R*)-10-(4-methoxybenzyloxy)-2,4,6,8-tetrakis(*tert*-butyldimethylsilyloxy) decan-1-ol **68** (28 mg, 0.034 mmol) in DCM (2 mL) were added solid $NaHCO_3$ (15 mg) and dess-martin reagent (17 mg, 0.041 mmol). The reaction mixture was stirred at room temperature for 1 h followed by quenching the reaction with saturated $NaHCO_3$ solution. Organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$, concentrated and the crude product was

purified by flash column chromatography (10% ethyl acetate in hexanes) to yield the title compound **69** (26 mg, 93%) as an oil: ^{1}H NMR (600 MHz, CD_2Cl_2) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.08 (s, 9H), 0.09 (s, 6H), 0.10 (s, 3H), 0.97 (s, 9H), 0.88 (s, 9H), 0.89 (s, 9H), 0.93 (s, 9H), 1.53-1.60 (m, 2H), 1.66-1.81 (m, 6H), 3.47-3.52 (m, 2H), 3.79 (s, 3H), 3.82-3.86 (m, 1H), 3.91-3.95 (m, 1H), 3.95-4.00 (m, 1H), 4.15-4.18 (m, 1H), 4.38 (s, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 9.58 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ –4.3, –3.9, –3.8, –3.5, –3.4, –3.1, –3.0, 18.5, 18.7, 26.3, 26.4, 38.4, 41.2, 46.3, 47.1, 55.8, 67.2, 67.6, 67.6, 68.0, 73.1, 76.1, 114.1, 129.7, 131.6, 159.7, 203.8; IR (neat) cm^{-1}; 2954, 2929, 2894, 2857, 1736, 1653, 1635, 1558, 1251; HRMS for $C_{42}H_{84}O_7Si_4Na$ $(M + Na)^+$: Calcd 835.5192; found 835.5197.

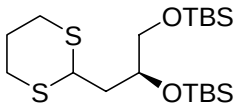


(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)acetaldehyde (*S*)-25: To a solution of (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (*S*)-**24** (5.00 g, 34.1 mmol) in dichloromethane (200 mL) at 0 ^{o}C was added diisopropylethylamine (26.3 mL, 153.9 mmol) and stirred for 5 min. DMSO (24.3 mL, 341 mmol) was added to the above reaction mixture and stirred for another 10 min. At this time, SO_3•pyr (13.6 g, 85.5 mmol) was added and the mixture was stirred for 45 min. saturated aqueous $NaHCO_3$ was added to the reaction mixture and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (35% ethyl acetate in hexanes) to yield the title compound (*S*)-**25** (4.30 g, 29.4 mmol, 86%) as an oil: $[\alpha]_D$ +8.1 (*c* 3.8 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.42 (s, 3H), 2.65 (ddd, *J* = 17.3, 6.0, 1.1 Hz), 2.85 (ddd, *J* =

17.3, 6.6, 1.9 Hz, 1H), 3.60 (dd, *J* = 8.5, 6.9 Hz, 1H), 4.19 (dd, *J* = 8.5, 6.0 Hz, 1H), 4.54 (p, *J* = 6.3 Hz, 1H), 9.8 (t, *J* = 1.4 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 25.5, 26.9, 47.9, 69.2, 70.7, 109.3, 199.9; IR (neat) cm^{-1} 2987, 2936, 2735, 1725, 1372, 1217; HRMS (EI) for $C_6H_9O_3$ $(M - CH_3)^+$: Calcd 129.0552; found129.0550.

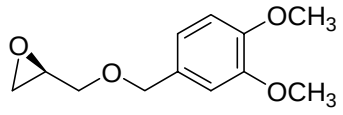


(*S*)-3-(1,3-Dithian-2-yl)propane-1,2-diol (70): To a solution of aldehyde (*S*)-**25** (1.80 g, 12.5 mmol) in CH_2Cl_2 (130 mL) were added 1,3-propanedithiol (2.60 mL, 37.5 mmol, 3 equiv) and BF_3•Et_2O (4.7 mL) at 0 °C for 1 h. The reaction mixture was diluted with ether, washed with 3% aqueous NaOH. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with saturated aqueous NH_4Cl solution, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (100% ethyl acetate) to yield the title compound **70** (1.9 g, 9.8 mmol, 78%): $[\alpha]_D$ –9.5 (*c* 0.4 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79-1.99 (m, 3H), 2.08-2.18 (m, 1H), 2.49 (br s, 1H), 2.81-2.98 (m, 5H), 3.48 (dd, *J* = 11.0, 7.1 Hz, 1H), 3.67 (dd, *J* = 11.0, 2.2 Hz, 1H), 3.99-4.10 (m, 1H), 4.26 (dd, *J* = 8.8, 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 25.8, 30.0, 30.3, 38.5, 43.8, 66.5, 69.1; IR (neat) cm^{-1} 3386, 2931, 2899, 1422, 1276; EIMS (M^+) 194, $(M - H_2O)^+$ 176; HRMS for $C_7H_{14}O_2S_2$: Calcd 194.0435; found 194.0442.



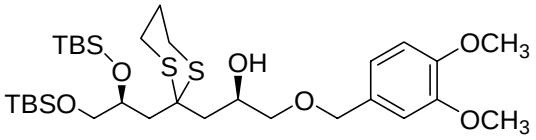
(*S*)-2-(2,3-*bis*(*tert*-Butyldimethylsilyloxy)propyl)-1,3-dithiane (71): To a solution of (*S*)-3-(1,3-dithian-2-yl)propane-1,2-diol **70** (1.4 g, 7.2 mmol) in dichloromethane (30 mL) were added

2,6-lutidine (0.88 mL, 15 mmol) and TBSOTf (1.7 mL, 15 mmol) at –78 ^{o}C. Then the mixture was warmed to 0 ^{o}C and stirred for additional 1 h. It was poured into water (30 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) gave the title compound **71** (2.9 g, 6.9 mmol, 95%): $[\alpha]_D$ –28.3 (*c* 11.9 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.09 (s, 3H), 0.13 (s, 3H), 0.90 (s, 18H), 1.77 (ddd, *J* = 13.7, 8.8, 4.7 Hz, 1H), 1.84-1.97 (m, 1H), 1.99-2.16 (m, 2H), 2.78-2.91 (m, 4H), 3.40 (dd, *J* = 10.1, 6.6 Hz, 1H), 3.58 (dd, *J* = 10.1, 5.0 Hz, 1H), 3.92-4.00 (m, 1H), 4.16 (dd, *J* = 10.1, 4.7 Hz, 1H); ^{13}C NMR (75 MHz, $CHCl_3$) δ –5.3, –4.7, –4.2, 18.1, 18.3, 25.9, 26.0, 26.1, 29.9, 30.5, 40.4, 43.8, 67.5, 69.5; IR (neat) cm^{-1} 2929, 2897, 2857, 1472, 1256; EIMS (M^+) 422, $(M - CH_3)^+$ 407, $(M - t\text{Bu})^+$ 365; HRMS for $C_{19}H_{42}O_2Si_2S_2$: Calcd 422.2165; found 422.2150.



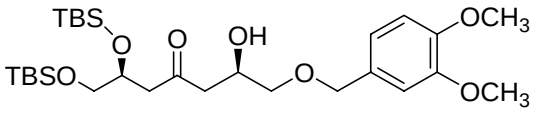
(*R*)-2-((3,4-Dimethoxybenzyloxy)methyl)oxirane (75): To a solution of sodium hydride (2.43 g, 101 mmol) in THF (40 mL) at 0 ^{o}C was added (*S*)-glycidol (5.00 g, 67.6 mmol) in THF (10 mL). After 1h, 3,4-dimethoxybenzyl chloride (18.8 g, 101 mmol) and tetra-*n*-butylammonium iodide (2.50 g, 10.2 mmol) were added. The reaction mixture was allowed to warm to room temperatuare and stirred overnight. Then it was poured into water (100 mL) and the aqueous layer was extracted with Et_2O (4 x 100 mL). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$ and concentrated. Flash column chromatography on silica gel (25% EtOAc in hexanes) gave the title compound **75** (10.5 g, 69%) as a pale yellow oil: ^{1}H NMR

(300 MHz, $CHCl_3$) δ 2.56 (dd, *J* = 4.9, 2.7 Hz, 1H), 2.75 (dd, *J* = 4.9, 4.1 Hz, 1H), 3.13 (ddt, *J* = 5.8, 4.1, 2.7 Hz, 1H), 3.36 (dd, *J* = 11.2, 5.8 Hz, 1H), 3.71 (dd, *J* = 11.5, 3.0 Hz, 1H), 3.82 (s, 3H), 3.84 (s, 3H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 6.76 - 6.89 (m, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 44.1, 50.7, 55.7, 70.5, 73.0, 110.9, 111.1, 120.2, 130.4, 148.6, 149.0; HRMS for $C_{12}H_{12}O_4$: Calcd 224.1049; found 224.0999.

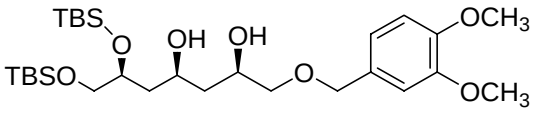


(*R*)-1-(2-((*S*)-2,3-bis(*tert*-Butyldimethylsilyloxy)propyl)-1,3-dithian-2-yl)-3-(3,4-dimethoxybenzyloxy)propan-2-ol (77): To a solution of compound **71** (2.90 g, 6.86 mmol) in THF (60 mL) at 0 ^oC was added *n*-BuLi (1.6 M in hexane, 4.3 mL). The reaction mixture was stirred at room temperature for 15 min followed by re-cooling it to 0 ^oC. A solution of epoxide **76** (1.69 g, 7.54 mmol) in THF (1 mL) was added and allowed to stir at room temperature overnight. The reaction mixture was poured into saturated aqueous NH_4Cl, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (SiO_2, 25% ethyl acetate in hexanes) to provide the title compound **77** (580 mg, 13%) as an oil along with recovered compound **71** (1.47 g, 3.47 mmol). $[\alpha]_D$ −8.58 (*c* 2.47 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.07 (s, 3H), 0.09 (s, 3H), 0.84 (s, 9H), 0.88 (s, 9H), 1.82-2.04 (m, 4H), 2.24 (dd, *J* = 15.4, 8.2 Hz, 1H), 2.59 (dd, *J* = 15.8, 2.7 Hz, 1H), 2.65-2.96 (m, 4H), 3.14 (d, *J* = 2.7 Hz, 1H), 3.32-3.45 (m, 3H), 3.57 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.00-4.10 (m, 1H), 4.22-4.34 (m, 1H), 4.47 (s, 2H), 6.77-6.90 (m, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ

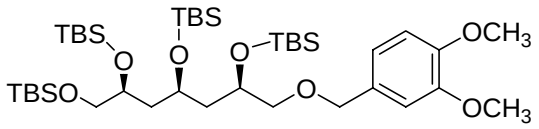
–5.3, –3.9, 18.0, 18.3, 24.7, 26.0, 26.4, 43.6, 51.6, 55.7, 67.3, 67.5, 70.9, 73.0, 74.1, 110.8, 111.0, 120.2, 130.7, 148.4, 148.9; IR (neat) cm^{-1} 3508, 2929, 2856, 1608, 1594, 1516, 1258, 835; HRMS for $C_{31}H_{58}O_6Si_2S_2Na$: Calcd 669.3111; found 669.3151.



(2R,6S)-1-(3,4-Dimethoxybenzyloxy)-6,7-bis(tert-butyldimethylsilyloxy)-2-hydroxy heptan-4-one (78): A mixture of DMB ether **77** (580 mg, 0.896 mmol), methyl iodide (1 mL) and K_2CO_3 (1.15 g) were dissolved in aqueous acetonitrile (MeCN:H_2O, 6:1, 14 mL) and stirred for 5 h at 45 ^oC. The reaction mixture was poured into water (15 mL) and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (SiO_2, 25% ethyl acetate in hexanes) gave the title compound (210 mg, 42%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9H), 0.05 (s, 3H), 0.85 (s, 9H), 0.88 (s, 9H), 2.56 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.64-2.75 (m, 3H), 3.04 (d, *J* = 3.6 Hz, 1H), 3.34-3.50 (m, 3H), 3.57 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 4.11-4.22 (m, 1H), 4.23-4.32 (m, 1H), 4.49 (s, 2H), 6.82-6.89 (m, 3H); ^{13}C NMR (75 MHz, $CHCl_3$) δ –5.5, –5.4, –5.0, –4.6, 14.1, 17.9, 18.2, 20.9, 25.7, 25.8, 47.4, 48.3, 55.7, 55.8, 60.2, 66.6, 66.9, 69.5, 73.0, 73.2, 110.9, 111.1, 120.3, 130.4, 148.6, 149.0, 209.4; IR (neat) cm^{-1} 2954, 2929, 2857, 1712, 1516, 1258.

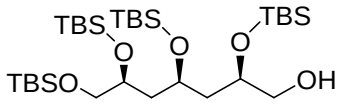


(2*R*,4*S*,6*S*)-1-(3,4-Dimethoxybenzyloxy)-6,7-*bis*(*tert*-butyldimethylsilyloxy)heptane-2,4-diol (79): To a solution of compound **78** (200 mg, 0.359 mmol) in THF (3.2 mL) and methanol (0.8 mL) at –78 ^{o}C was added diethylmethoxyborane (1.0 M in THF, 0.44 mL, 0.44 mmol). After 30 min, sodium borohydride (19 mg, 0.50 mmol) was added in portions and the mixture and was stirred for 3 h at –78 ^{o}C. Water was added (2.5 mL) followed by diluting the mixture with ether (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (25% ethyl acetate in hexanes) to yield the title compound (126 mg, 63%) as a colorless oil: $[\alpha]_D$ −11.1 (*c* 1.67 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.09 (s, 6H), 0.89 (s, 18H), 1.53-1.80 (m, 4H), 3.40-3.50 (m, 3H), 3.56-3.63 (m, 1H), 3.74 (brs, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 3.98 (brs, 1H), 4.02-4.17 (m, 3H), 4.50 (s, 2H), 6.81-6.89 (m, 3H); ^{13}C NMR (126 MHz, $CHCl_3$) δ –5.6, –5.0, –4.4, 17.8, 18.1, 25.7, 25.7, 40.0, 42.3, 55.6, 55.7, 67.4, 69.6, 70.6, 71.9, 73.1, 74.0, 110.7, 111.0, 120.2, 130.6, 148.4, 148.8; IR (neat) cm^{-1} 3472, 2953, 2857, 1564, 1517, 1464, 1257.



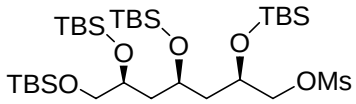
4-(((2*R*,4*S*,6*S*)-2,4,6,7-*tetrakis*(*tert*-Butyldimethylsilyloxy)heptyloxy)methyl)-1,2-dimethoxybenzene (80): To a solution of compound **79** (190 mg, 0.339 mmol) in dichloromethane (3 mL) at 0 ^{o}C were added 2,6-lutidine (79.9 mg, 0.746 mmol) and TBSOTf (185 mg, 0.698 mmol). After 1 h, the mixture was poured into water, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ concentrated. The crude product was purified by flash column chromatography (10% ethyl

acetate in hexanes) to yield the title compound (215 mg, 81%) as an oil: $[\alpha]_D$ –1.54 (*c* 2.60 $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 0.04-0.07 (m, 24H), 0.87-0.89 (m, 36H), 1.56-1.63 (m, 2H), 1.69-1.76 (m, 2H), 3.32 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.42 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.45 (dd, *J* = 9.1, 6.0 Hz, 1H), 3.52 (dd, *J* = 9.3, 4.4 Hz, 1H), 3.78-3.82 (m, 1H), 3.83-3.87 (m, 1H), 3.88 (s, 6H), 3.95-4.01 (m, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.67 (d, *J* = 11.8 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.89 (s, 1H); ^{13}C NMR (75 MHz, $CHCl_3$) δ –5.3, –4.6, –4.3, –4.1, 18.0, 18.2, 18.4, 26.0, 42.6, 42.9, 55.8, 55.9, 66.8, 67.8, 69.2, 70.7, 73.2, 74.8, 110.8, 111.0, 120.1, 131.2, 148.4, 149.0; IR (neat) cm^{-1} 2954, 2929, 2894, 2857, 1517, 1471, 1256, 1104, 835; HRMS for $C_{40}H_{82}O_7Si_4Na$: Calcd 809.5035; found 809.5085.

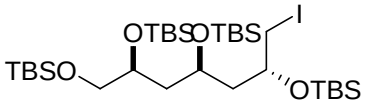


(2*R*,4*S*,6*S*)-2,4,6,7-*tetrakis*(*tert*-Butyldimethylsilyloxy)heptan-1-ol (81): A solution of (((2*R*,4*S*,6*S*)-2,4,6,7-*tetrakis*(*tert*-butyldimethylsilyloxy)heptyloxy)methyl)-4-methoxybenzene **80** (1.10 g, 1.45 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (428 mg, 1.88 mmol) in CH_2Cl_2/pH 7 buffer (19 mL/1 mL) was stirred at room temperature for 1 h followed by dilution with CH_2Cl_2 (20 mL) and saturated sodium bicarbonate solution (30 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography to yield the title compound (890 mg, 96%) as an oil: $[\alpha]_D$ –1.9 (*c* 0.63 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.05-0.10 (m, 24H), 0.89-0.90 (m, 36H), 1.59-1.82 (m, 4H), 2.71 (dd, *J* = 7.8, 5.5 Hz, 1H), 3.38-3.52 (m, 3H), 3.53-3.58 (m, 1H), 3.61-3.78 (m, 1H), 3.90-3.98 (m, 2H); ^{13}C NMR (75 MHz, $CHCl_3$) δ –5.3, –3.27, –2.3, –4.7, –4.6, –4.58, –4.55,

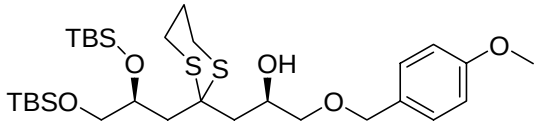
–4.5, –4.4, –4.3, –3.9, 14.2, 18.0, 18.1, 18.12, 18.4, 22.7, 25.9, 26.0, 26.04, 31.7, 41.8, 42.3, 66.5, 67.2, 67.8, 69.9, 70.8; HRMS for $C_{31}H_{72}O_5Si_4Na$: Calcd 659.4355; found 659.4352.



(2*R*,4*R*,6*S*)-2,4,6,7-*tetrakis*(*tert*-Butyldimethylsilyloxy)heptylmethanesulfonate (82): To a solution of alcohol **81** (380 mg, 0.6 mmol), triethylamine (78 mg, 0.80 mmol), and DMAP (20 mg) in dichloromethane (6 mL) at 0 ^oC was added methanesulfonyl chloride (82 mg, 0.70 mmol). The solution was stirred for 45 min and quenched via addition of saturated sodium bicarbonate solution. Organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography to yield the title compound **82** (392 mg, 92%) as an oil: $[\alpha]_D$ –1.93 (*c* 15.5 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.0637 (s, 3H), 0.07 (s, 9H), 0.09 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 0.893 (s, 9H), 0.90 (s, 18H), 1.62-1.82 (m, 4H), 3.00 (s, 3H), 3.45 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.51 (dd, *J* = 9.9, 5.2 Hz, 1H), 3.67-3.79 (m, 1H), 3.87-3.98 (m, 1H), 4.01 (dd, *J* = 10.1, 6.9 Hz, 1H), 4.07 - 4.18 (m, 2H), 4.35 (dd, *J* = 10.2, 2.5 Hz, 1 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ –5.3, –4.6, –4.5, –4.4, –4.2, –4.0, 14.2, 18.0, 18.1, 18.4, 22.7, 25.9, 25.9, 26.0, 31.7, 37.4, 41.5, 42.4, 66.4, 67.6, 67.7, 70.6, 73.3; IR (neat) cm^{-1} 2955, 2930, 2887, 2857, 1472, 1463, 1361, 1256, 1179, 1106; HRMS for $C_{32}H_{74}O_7Si_4SNa$ (M + Na) Calcd 737.4130; found 737.4129.

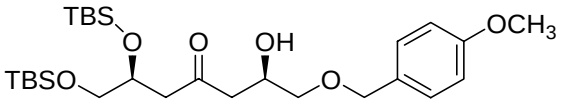


(2*S*,4*R*,6*R*)-1,2,4,6-*tetrakis*(*tert*-Butyldimethylsilyloxy)-7-iodoheptane 5: To a solution of (2*R*,4*R*,6*S*)-2,4,6,7-*tetrakis*(*tert*-butyldimethylsilyloxy)heptyl methanesulfonate **82** (380 mg, 0.53 mmol) in acetone (10 mL) was added Sodium iodide (398 mg, 2.65 mmol). The reaction mixture was refluxed for 36 h and then the acetone was removed under reduced pressure. The resulting solid was suspended in 50% ethyl acetate in hexanes and washed with saturated aqueous sodium bicarbonate, brine and water. Drying the organic layer with $MgSO_4$ and concentration provided the title compound **5** (380 mg, 96%) as an oil: $[\alpha]_D$ –3.2 (*c* 0.53 $CHCl_3$) ^{1}H NMR (500 MHz, $CHCl_3$) δ 0.058 (s, 3H), 0.06 (s, 3H), 0.079 (s, 3H), 0.08 (s, 3H), 0.087 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.13 (s, 3H), 0.899 (s, 9H), 0.90 (s, 9H), 0.91 (s, 9 H), 0.92 (s, 9H), 1.63 (ddd, *J* = 13.9, 7.3, 5.4 Hz, 1H), 1.68 (ddd, *J* = 3.9, 7.3, 5.4 1H), 1.73 (ddd, *J* = 13.9, 7.6, 5.0 Hz, 1H), 1.80 (ddd, *J* = 13.9, 7.3, 5.0 Hz, 1H), 3.21 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.35 (dd, *J* = 10.1, 4.1 Hz, 1H), 3.46-3.52 (m, 2H), 3.67 (tt, *J* = 7.3, 4.7 Hz, 1H), 3.74 - 3.79 (m, 1H), 3.83 (tt, *J* = 7.3, 5.0 Hz, 1H); ^{13}C NMR (126 MHz,$CDCl_3$) δ –5.2, –5.2, –4.4, –4.3, –4.2, –4.1, –3.9, 15.3, 18.1, 18.1, 18.2, 18.5, 26.0, 26.1, 42.8, 45.3, 66.8, 67.6, 68.3, 70.7; IR (neat) cm^{-1} 2929, 2857, 1472, 1408, 1389; HRMS for $C_{27}H_{62}O_4Si_4I$ $(M - tBu)^+$: Calcd 689.2770; found 689.2789.



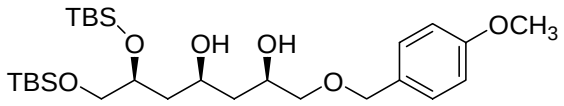
(*R*)-1-(2-((*S*)-2,3-bis(*tert*-Butyldimethylsilyloxy)propyl)-1,3-dithian-2-yl)-3-(4-methoxybenzyloxy)propan-2-ol (84): *t*-BuLi (1.7 M in pentane, 1 mL, 1.7 mmol) was added to a solution of

(*S***)**-2-(2,3-bis(*tert*-butyldimethylsilyloxy)propyl)-1,3-dithiane **71** (682 mg, 1.61 mmol) in THF (2.4 mL) and HMPA (0.7 mL) at –78 ^{o}C. After 10 min, (*R*)-2-((4-methoxybenzyloxy)methyl) oxirane **83** (196 mg, 1.77 mmol) in THF (1 mL) was added. After 15 min, it was warmed to 0 ^{o}C and stirred for 1 h. The reaction mixture was poured into saturated aqueous NH_4Cl solution (20 mL) and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography (SiO_2, 20% ethyl acetate in hexanes) to provide the title compound **84** (765 mg, 77%) as an oil: $[\alpha]_D$ –1.0 (*c* 0.24 $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.08 (doubled, 6H), 0.10 (s, 3H), 0.13 (s, 3H), 0.88 (s, 9H), 0.92 (s, 9H), 1.90-1.99 (m, 3H), 2.03-2.06 (m, 1H), 2.26 (dd, *J* = 15.4, 8.2 Hz, 1H), 2.60 (dd, *J* = 15.4, 3.0 Hz, 1H), 2.73-2.77 (m, 1H), 2.84-2.93 (m, 3H), 3.11 (d, *J* = 3.0 Hz, 1H), 3.39-3.45 (m, 3H), 3.60 (dd, *J* = 9.6, 4.7 Hz, 1H), 3.81 (s, 3H), 4.06-4.10 (m, 1H), 4.27-4.33 (m, 1H), 4.50 (s, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3, –3.9, 18.0, 18.3, 24.8, 26.0 (doubled), 26.5, 43.7, 43.8, 51.7, 55.2, 67.5, 67.6, 71.0, 72.9, 74.2, 113.7, 129.3, 159.2; IR (neat) cm^{-1} 3467, 2953, 2927, 2855, 1613, 1513, 1249, 1100, 835; EIMS (M – *t*Bu)$^+$ 559; HRMS for $C_{26}H_{47}O_5Si_2S_2$ (M – *t*Bu)$^+$: Calcd 559.2404; found 559.2411.



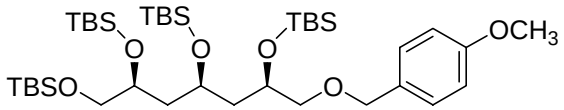
(2*R*,6*S*)-1-(4-Methoxybenzyloxy)-6,7-*bis*(*tert*-butyldimethylsilyloxy)-2-hydroxyheptan-4-one (85): A solution of ((*R*)-1-(2-((*S*)-2,3-*bis*(*tert*-butyldimethylsilyloxy)propyl)-1,3-dithian-2-yl)-3-(4-methoxybenzyloxy)propan-2-ol **84** (2.00 g, 3.24 mmol) in THF/H_2O (4:1, 45 mL) was cooled to 0 ^{o}C followed by addition of 2.6-lutidine (2.9 mL) at once and $Hg(ClO_4)_3$•H_2O (3.5 g) in

portions. The reaction mixture was stirred at 0 °C for 1.5 h then filtered through a pad of celite and followed by a rinse with ethyl acetate. The filtrate was diluted with ethyl acetate and saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography (SiO_2, 25% ethyl acetate in hexanes) to yield the title compound (1.44 g, 85%) as an oil: $[\alpha]_D$ −7.36 (*c* 0.53 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.05 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 0.88 (s, 9H), 2.55 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.65-2.74 (m, 3H), 3.02 (d, 1H), 3.36-3.48 (m, 3H), 3.57 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.81 (s, 3H), 4.14-4.20 (s, 1H), 4.22-4.29 (s, 1H), 4.49 (s, 2H), 6.89 (d, *J* = 8.5, 2H), 7.26 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ –5.3, –5.3, –4.8, –4.4, 18.1, 18.4, 25.9, 26.0, 47.5, 48.5, 55.4, 66.8, 67.0, 69.7, 73.0, 73.1, 113.9, 129.5, 130.1, 159.4, 209.8; IR (neat) cm^{-1} 3456, 2954, 2929, 2856, 1720, 1609, 1507, 1462, 1246, 1099, 837; HRMS for $C_{27}H_{50}O_6NaSi_2$ $(M + Na)^+$: Calcd 549.3044; found 549.3051.



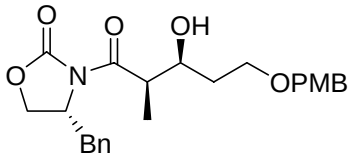
(2*R*,4*S*,6*S*)-1-(4-Methoxybenzyloxy)-6,7-*bis*(*tert*-butyldimethylsilyloxy)heptane-2,4-diol (86): To a solution of (2*R*,6*S*)-1-(4-methoxybenzyloxy)-6,7-*bis*(*tert*-butyldimethylsilyloxy)-2-hydroxyhe ptan-4-one (2.1 g, 4.0 mmol) in THF (32 mL) and methanol (8 mL) at –78 °C was added diethylmethoxyborane (1.0 M in THF, 4.4 mL, 4.4 mmol) and the reaction mixture was stirred at that temperature for 30 min. Sodium borohydride (181 mg, 4.8 mmol) was added in portions to the above reaction mixture and was stirred for 3 h at –78 °C. The reaction mixture was quenched with H_2O (25 mL) and diluted with Et_2O (100 mL). The layers were separated and

the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated and purified by flash column chromatography (25% ethyl acetate in hexanes) to yield the title compound (1.85 g, 88%) as a colorless oil: $[\alpha]_D$ −8.29 (*c* 1.52 $CHCl_3$); ^1H NMR (600 MHz, $CHCl_3$) δ 0.07 (s, 3H), 0.07 (s, 3H), 0.10 (s, 6H), 0.89 (s, 9H), 0.90 (s, 9H), 1.56-1.17 (m, 4H), 3.39-3.45 (m, 2H), 3.48 (dd, *J* = 10.2, 6.6 Hz, 1H), 3.6 (dd, *J* = 10.2, 4.4 Hz, 1H), 3.65 (br s, 1H), 3.81 (s, 3H), 3.87-3.93 (m, 1H), 3.94 (br s, 1H), 4.02-4.12 (m, 2H), 4.50 (s, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ −5.3, −4.7, −4.1, 18.1, 18.4, 25.9, 26.0, 26.1, 40.3, 42.5, 55.3, 67.7, 69.9, 70.9, 72.3, 73.1, 74.2, 113.9, 129.4, 130.4, 159.3; IR (neat) cm^{-1} 3436, 2953, 2929, 2857, 1613, 1514, 1250, 1094; 835; 777; HRMS for $C_{27}H_{52}O_6NaSi_2(M + Na)^+$: Calcd 551.3200; found 551.3206.



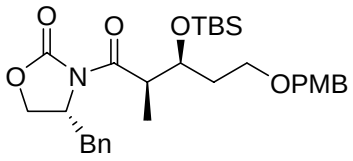
1-(((2R,4S,6S)-2,4,6,7-*tetrakis*(*tert*-Butyldimethylsilyloxy)heptyloxy)methyl)-4-methoxybenzene (87): To a solution of (2*R*,4*S*,6*S*)-1-(4-methoxybenzyloxy)-6,7-*bis*(*tert*-butyldimethyl silyloxy)heptane-2,4-diol **86** (1.8 g, 3.4 mmol) in dichloromethane (30 mL) at 0 ^oC were added 2,6-lutidine (1.13 g, 10.5 mmol) and TBSOTf (2.00 g, 7.83 mmol). The reaction mixture was stirred at that temperature for 1 h. Then the mixture was poured into water (30 mL) and layers were separated. The aqueous layer was extracted with dichloromethane, the combined organic extracts were dried over $MgSO_4$, and concentrated. Purification of the crude product by flash column chromatography (10% ethyl acetate in hexanes) gave the title compound (2.4 g, 94%) as an oil: $[\alpha]_D$ 0.41 (*c* 0.72 $CHCl_3$); ^1H NMR (601 MHz, $CHCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 0.90 (s, 27 H), 1.55-1.62 (m, 2H), 1.67-1.75 (m, 2H), 3.30

(dd, *J* = 9.9, 6.3 Hz, 1H), 3.40 (dd, *J* = 9.9, 3.6 Hz, 1H), 3.45 (dd, *J* = 10.2, 6.3 Hz, 1H), 3.51 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.78-3.85 (m, 5H), 3.93-3.99 (m, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (151 MHz, $CHCl_3$) δ –5.3, –5.2, –4.6, –4.6, –4.4, –4.3, –4.1, –4.0, 18.0, 18.2, 18.2, 18.5, 26.0, 26.0, 26.1, 42.7, 42.9, 55.3, 66.8, 67.8, 69.2, 70.7, 72.9, 74.6, 113.7, 129.2, 130.8, 159.1; IR (neat) cm^{-1} 2955, 2929, 2895, 2857, 1614, 1514, 1472, 1251; HRMS for $C_{39}H_{80}O_6NaSi_4(M + Na)^+$: Calcd 779.4930; found 551.4893.



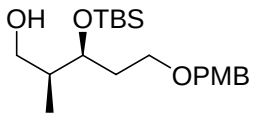
(*R*)-3-((2*R*,3*S*)-5-(4-Methoxybenzyloxy)-3-hydroxy-2-methylpentanoyl)-4-benzyloxa zolidin-2-one (92): Di-*n*-butylboryl trifluoromethanesulfonate (1.0 M solution in DCM, 2.3 mL, 2.3 mmol) was added slowly to a solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one (450 mg,1.93 mmol) in dichloromethane (5 mL) at 0 ^{o}C and stirred for 5 min followed by drop wise addition of triethylamine (255 mg, 2.51 mmol). The above reaction mixture was stirred for 10 min and then cooled to −78 ^{o}C. Freshly prepared aldehyde **89** (413 mg, 2.13 mmol, 1.1 equiv) was added slowly to the above reaction mixture. After 1 h, the solution was warmed to 0 ^{o}C and stirred at that temperature for 1 h. The reaction mixture was slowly quenched by addition of 3 mL of 3:1 pH 7 aqueous buffer: methanol at 0 ^{o}C followed by the addition of 2.5 mL of 2:1 methanol: 30% aqueous H_2O_2 and stirring for an additional 1 h. The volatiles were removed (rotovap) and the residue was extracted with ether (3 x 5 mL). The combined organic extracts were washed with sat.aq. $NaHCO_3$ solution, sat. aq. NaCl solution, dried over $MgSO_4$ and

concentrated. The crude product was purified by flash column chromatography (SiO_2, 50% ethyl acetate in hexanes) to provide the title compound (750 mg, 90%). $[\alpha]_D$ −68.1 (*c* 1.2 $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 1.29 (d, *J* = 7.1 Hz, 3H), 1.70-1.77 (m, 1H), 1.83-1.91 (m, 1H), 2.79 (dd, *J* = 13.5, 9.6 Hz, 1H), 3.27 (dd, *J* = 13.5, 3.3 Hz, 1H), 3.32 (d, *J* = 2.5 Hz, 1H), 3.61-3.66 (m, 1H), 3.67-3.70 (m, 1H), 3.79-3.84 (m, 4H), 4.14-4.23 (m, 3H), 4.45 (s, 2H), 4.67-4.71 (m, 1H), 6.88 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 7.4 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 7.1 Hz, 1H), 7.35 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 11.1, 33.7, 37.7, 42.5, 55.18, 55.21, 66.0, 68.0, 70.4, 72.8, 113.8, 127.3, 128.9, 129.3, 129.4, 130.1, 135.1, 153.0, 159.2, 176.6; IR (neat) cm^{-1} 3448, 2935, 2864, 1779, 1695, 1513, 1247; EIMS *m/z* (M^+) 427; HRMS (EI) for $C_{24}H_{29}O_7NO_6$: Calcd 427.1995; found 427.1961.



(*R*)-3-((2*R*,3*S*)-5-(4-Methoxybenzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-methylpen tanoyl)-4-benzyloxazolidin-2-one (93): To a solution of compound **92** (720 mg, 1.68 mmol) in dichloromethane (20 mL) were added 2,6-lutidine (217 mg, 2.02 mmol) and TBSOTf (490 mg, 1.85 mmol) at −78 °C. After 15 min, the reaction mixture was warmed to 0 °C stirring for 2 h. The reaction mixture was poured into water and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography to provide the title compound (848 mg, 93%) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.92 (s, 9H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.84-2.02 (m, 2H), 2.77 (d, *J* = 13.2, 9.3 Hz, 1H), 3.26 (dd, *J* = 13.2, 2.7 Hz, 1H), 2.48-3.55

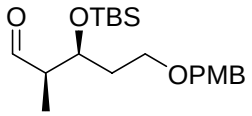
(m, 1H), 3.59-3.66 (m, 1H), 3.81 (s, 3H), 3.83-3.96 (m, 2H), 4.08 (dd, *J* = 8.8, 1.7 Hz, 1H), 4.11-4.19 (m, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.50-4.60 (m, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 7.20-7.38 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.7, –4.4, 13.7, 14.2, 18.0, 21.1, 25.8, 35.1, 37.7, 43.1, 55.3, 55.5, 60.4, 65.9, 66.0, 71.1, 72.6, 113.7, 127.3, 128.9, 129.3, 129.5, 130.7, 135.4, 152.9, 159.1, 175.5; IR (neat) cm^{-1} 2955, 2931, 2856, 1781, 1695, 1514, 1384, 1248; HRMS for $C_{30}H_{43}NO_6Si$: Calcd 541.2860; found 541.2881.



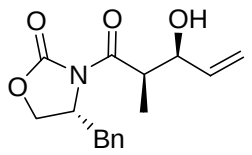
(2*S*,3*S*)-5-(4-Methoxybenzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-methylpentan-1-ol (94):

To a solution of compound **93** (840 mg, 1.55 mmol) in THF (3 mL) at 0 ^{o}C was added ethanol (0.45 mL, 7.8 mmol) and $LiBH_4$ (2.0 M in THF, 3.88 mL). The reaction mixture was stirred for 1 h at 0 ^{o}C followed by an additional 1 h at room temperature. Then it was cooled to 0 ^{o}C, quenched with sat. aq. sodium-potassium tartarate solution (5 mL), diluted with ethyl acetate (15 mL) and sat. aq. sodium-potassium tartarate solution (10 mL). The reaction mixture was stirred for 30 min at room temperature followed by separation of layers. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (25% ethyl acetate in hexanes) to provide the title compound (348 mg, 61%) as an oil**:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.10 (s, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 1.71-1.81 (m, 2H), 1.90-2.00 (m, 1H), 2.89 (br s, 1H), 3.46-3.54 (m, 3H), 3.61-3.67 (m, 1H), 3.79 (s, 3H), 3.90-3.95 (m, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.3 (d, *J* = 11.4 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* =

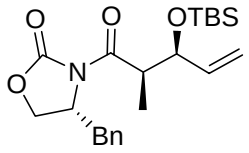
8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.8, –4.5, 12.3, 14.2, 17.9, 25.8, 32.8, 40.0, 55.2, 65.8, 66.8, 72.5, 72.6, 113.7, 129.3, 130.4, 159.1; IR (neat) cm^{-1} 3414, 2955, 2929, 1607, 1250.



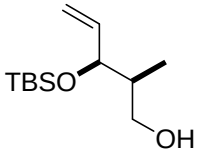
(2*R*,3*S*)-5-(4-Methoxybenzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-methylpentanal (96): To a solution of alcohol **94** (350 mg, 0.896 mmol) in DCM (5 mL) was added sodium bicarbonate (98.9 mg, 1.17 mmol) and dess-martin reagent (456 mg, 1.08 mmol) at room temperature. The reaction mixture was stirred for 45 min followed by pouring it into saturated aqueous sodiumbicarbonate solution. The aqueous layer was extracted with DCM, the combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (SiO_2, 15% ethyl acetate in hexanes) afforded the title compound (266 mg, 81%) as an oil: $[\alpha]_D$ –47.2 (*c* 1.12 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.70-1.89 (m, 2H), 2.44-2.52 (m, 1H), 3.49 (t, *J* = 6.0 Hz, 2H), 3.82 (s, 3H), 4.29-4.34 (m, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 9.78 (d, *J* = 1.1 Hz, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ –4.4, –4.3, 8.0, 18.3, 26.0, 35.0, 52.0, 55.5, 66.7, 69.7, 73.0, 114.0, 129.6, 131.0, 159.7, 205.0; IR (neat) cm^{-1} 2954, 2930, 2857, 2709, 1726, 1613, 1514, 1250; HRMS for $C_{20}H_{34}O_4SiNa$: Calcd 389.2124; found 389.2092.



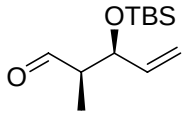
(*R*)-4-Benzyl-3-((2*R*,3*S*)-3-hydroxy-2-methylpent-4-enoyl)oxazolidin-2-one (105): Di-*n*-butyl boryltrifluoromethanesulfonate (1.0 M in CH_2Cl_2, 29.8 mL, 29.8 mmol) was added slowly to a solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one (5.8 g, 24.9 mmol) in dichloromethane (50 mL) at 0 ^oC and stirred for 5 min followed by drop wise addition of triethylamine (4.5 mL, 32.3 mmol). After 10 min, the mixture cooled to –78 ^oC and freshly distilled acrolein (1.5 g, 27.4 mmol) was added. After 1 h, the solution was warmed to 0 ^oC and stirred at that temperature for 1 h. The reaction was slowly quenched by addition of 100 mL of 3:1 pH 7 aqueous buffer: methanol at 0 ^oC followed by the addition of 80 mL of 2:1 methanol: 30% aqueous H_2O_2 and stirring for an additional 1 h. The volatiles were removed (rotovap) and the residue was extracted with ether (3 x 100 mL). The combined organic extracts were washed with sat.aq. $NaHCO_3$ solution, sat. aq. NaCl solution, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 30% ethyl acetate in hexanes) to provide the title compound (5.6 g, 78%) as white solid. $[\alpha]_D$ –51 (*c* 0.94 $CHCl_3$); ^1H NMR (601 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.9 Hz, 3H), 2.82 (dd, *J* = 13.4, 9.6 Hz, 1H), 3.17 (br s, 1H), 3.25 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.90 (qd, *J* = 7.1, 3.8 Hz, 1H), 4.19 (dd, *J* = 9.1, 2.7 Hz, 1H), 4.21-4.25 (m, 1H), 4.49-4.52 (m, 1H), 4.72 (ddt, *J* = 12.4, 7.7, 3.0 Hz, 1H), 5.23 (dt, *J* = 10.7, 1.7 Hz, 1H), 5.36 (dt, *J* = 17.3, 1.7 Hz, 1H), 5.88 (ddd, *J* = 17.3, 10.7, 5.5 Hz, 1H), 7.22 (d, *J* = 6.9 Hz, 2H), 7.27-7.31 (m, 1H), 7.32-7.36 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 11.1, 37.7, 42.5, 55.1, 66.2, 72.7, 116.2, 127.3, 128.9, 129.4, 135.0, 137.3, 153.2, 176.4; IR (neat) cm^{-1}; 3496, 2981, 1779, 1697, 1388; HRMS for $C_{12}H_{22}O_2Si$ $(M + Na)^+$: Calcd 312.1212; found 312.1217.



(*R*)-4-Benzyl-3-((2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-methylpent-4-enoyl)oxazolidin-2-one (106): To a solution of (*R*)-4-benzyl-3-((2*R*,3*S*)-3-hydroxy-2-methylpent-4-enoyl) oxazolidin-2-one **105** (4.2 g, 14.5 mmol) in dichloromethane (150 mL) were added 2,6-lutidine (1.90 g, 17.4 mmol) and TBSOTf (4.2 g, 16 mmol) at −78 ^{o}C. After 15 min, it was warmed to 0 ^{o}C and allowed to stir for 2 h. The reaction was quenched with water, organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography (15% ethyl acetate in hexanes) to provide the title compound (4.8 g, 82%) as an oil: $[\alpha]_D$ −50.8 (*c* 0.94 $CHCl_3$); ^{1}H NMR (601 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.89 (s, 9H), 1.22 (d, *J* = 6.9 Hz, 3H), 2.78 (dd, *J* = 13.5, 9.9 Hz, 1H), 3.29 (dd, *J* = 13.1, 3.0 Hz, 1H), 3.99 (dq, *J* = 6.9, 6.9 Hz, 1H), 4.12-4.18 (m, 2H), 4.32-4.36 (m, 1H), 4.59-4.63 (m, 1H), 5.09-5.13 (m, 1H), 5.18-5.23 (m, 1H), 5.86 (ddd, *J* = 17.0, 10.4, 6.6 Hz, 1H), 7.22-7.23 (m, 2H), 7.28-7.30 (m, 1H), 7.32-7.36 (m, 2H); ^{13}C NMR (76 MHz, $CDCl_3$) δ −5.0, −4.3, 12.5, 18.2, 25.9, 37.9, 44.1, 55.7, 66.0, 75.3, 115.8, 127.4, 129.0, 129.6, 135.5, 139.3, 153.3, 174.6; IR (neat) cm^{-1} 2956, 2929, 2857, 1782, 1701, 1381; EIMS $(M - CH_3)^+$ 388, $(M - t\text{Bu})^+$ 346; HRMS for $C_{18}H_{24}NO_4Si$: Calcd 346.1475; found 346.1473.

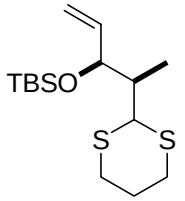


(2*S*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpent-4-en-1-ol (107): To a solution of (*R*)-4-benzyl-3-((2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-methylpent-4-enoyl)oxazolidin-2-one **106** (3.12 g, 7.73 mmol) in THF (40 mL) and ethanol (2.3 mL, 39 mmol) at 0 ^{o}C was added $LiBH_4$ (2.0 M in THF, 19.3 mL). After 1 h, it was warmed to room temperature and stirred for an additional 1 h. Then it was cooled to 0 ^{o}C, quenched with sat. aq. sodium-potassium tartarate solution (10 mL) followed by dilution with ethyl acetate (50 mL), sat. aq. sodium-potassium tartarate solution (50 mL). The reaction mixture was stirred for 30 min at room temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography (SiO_2, 15% ethyl acetate in hexanes) to provide the title compound (1.31 g, 74%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.81 (d, J = 7.1 Hz, 3H), 0.92 (s, 9H), 1.84-2.05 (m, 1H), 2.82 (br s, 1H), 3.49-3.52 (m, 1H), 3.63-3.70 (m, 1H), 4.23-4.26 (m, 1H), 5.17-5.27 (m, 2H), 5.89 (ddd, J = 17.0, 10.5, 6.2 Hz, 1H).



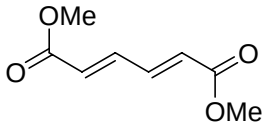
(2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpent-4-enal (108): To a solution of (2*S*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-methylpent-4-en-1-ol (1.20 g, 5.25 mmol) in dichloromethane (20 mL) were added $NaHCO_3$ (solid, 0.60 g, 6.8 mmol) and dess-martin reagent (2.90 g, 6.83 mmol). The reaction mixture was stirred for 1.5 h at room temperature followed by pouring it into sat. aq. $NaHCO_3$ solution (20 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, concentrated and purified by flash column chromatography (SiO_2, 15% ethyl acetate in hexanes)

to yield the title compound (1.04 g, 88%) as an oil: $[\alpha]_D$ −51.6 (*c* 0.5 $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.07 (d, *J* = 6.9 Hz, 3H), 2.39-2.53 (m, 1H), 4.50-4.57 (m, 1H), 5.14 - 5.20 (m, 1H), 5.22-5.30 (m, 1H), 5.74-5.89 (m, 1H), 9.77 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0, −4.2, 8.4, 25.8, 52.8, 52.6, 73.6, 116.1, 138.5, 204.6; IR (neat) cm^{-1} 2957, 2928, 2856, 1726, 1257; EIMS $(M - CH_3)^+$ 213; HRMS for $C_8H_{15}O_2Si$ $(M - CH_3)^+$: Calcd 171.0841; found 171.0842.

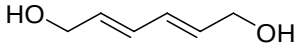


((3*S*,4*R*)-4-(1,3-Dithian-2-yl)pent-1-en-3-yloxy)(*tert*-butyl)dimethylsilane (109): To a solution of (2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-methylpent-4-enal (1.0 g, 4.4 mmol) in ether (15 mL) at 0 ^oC were added $MgBr_2$•OEt_2 (2.3 g, 8.8 mmol) and propane-1,3-dithiol (0.72 g, 6.6 mmol). The reaction mixture was stirred at 0 ^oC for 30 min, room temperature for 30 min followed by quenching the reaction with 1 N NaOH solution (5 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic extracts were washed with 1 N NaOH (5 mL), sat. aq. NaCl, water, dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) to yield the title compound (1.25 g, 89%) as an oil: $[\alpha]_D$ −10 (*c* 0.29 $CHCl_3$); ^{1}H NMR (300 MHz,$CDCl_3$) δ 0.02 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.77-1.92 (m, 2H), 2.01-2.15 (m, 1H), 2.78-2.92 (m, 4H), 4.08 (d, *J* = 6.6 Hz, 1H), 4.32-4.45 (m, 1H), 5.13 (d, *J* = 10.4 Hz, 1H), 5.22 (d, *J* = 17.0 Hz, 1H), 5.80 (ddd, *J* = 17.3, 10.4, 6.6 Hz, 1H);

^{13}C NMR (76 MHz, $CDCl_3$) δ –4.7, –4.0, 11.8, 18.3, 26.0, 26.3, 30.4, 30.9, 44.5, 51.6, 74.5, 115.7, 140.5; IR (neat) cm^{-1} 2928, 2896, 2856, 1472, 1252, 1078, 836, 776; EIMS 318, (M – *t*Bu)$^+$ 261; HRMS for $C_{15}H_{30}OSiS_2$: Calcd 318.1507; found 318.1497.

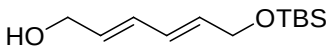


(2*E*,4*E*)-Dimethyl hexa-2,4-dienedioate (111): Acetyl chloride (23 mL) was added slowly to a solution of *trans*,*trans*-muconic acid **110** (8.1 g, 57 mmol) in methanol (150 mL) at 0 ^oC and stirred at that temperature for 5 min followed by refluxing the reaction mixture for 2 h. Then the reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure to give the title compound (9.5 g, 98%) as while solid which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 6H), 6.14-6.26 (m, 2H), 7.26-7.38 (m, 2H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 52.0, 128.1, 141.0, 166.4; HRMS for $C_8H_{10}O_4$: Calcd 170.0579; found 170.0580.

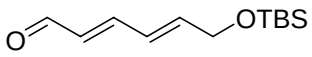


(2*E*,4*E*)-Hexa-2,4-diene-1,6-diol (112): To a solution of (2*E*,4*E*)-dimethyl hexa-2,4-dienedioate **111** (3.23 g, 19.0 mmol) in chloroform (190 mL) at 0 ^oC was added DiBAL-H (1.0 M in hexane, 95 mL) and the reaction mixture was stirred at that temperature for 1 h. Then the reaction mixture was slowly treated with methanol (19 mL) and stirred for additional 15 min at 0 ^oC. Sat. aq. sodium-potassium tartarate (150 mL) was added to the reaction mixture and stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with

ethyl acetate (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to yield the title compound (2.05 g, 18.0 mmol, 95%) as white waxy solid: ^{1}H NMR (300 MHz, CD_3OD) δ 4.20 (d, J = 5.2 Hz, 4H), 5.00 (br s, 2H), 5.84-6.00 (m, 2H), 6.32-6.45 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 63.2, 131.4, 133.5; EIMS $(M)^+$ 114, $(M - H_2O)^+$ 96; HRMS for $C_6H_{10}O_2$: Calcd 114.0681; found 114.0678.

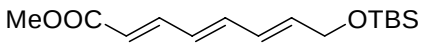


(2*E*,4*E*)-6-(*tert*-Butyldimethylsilyloxy)hexa-2,4-dien-1-ol (113): To a solution of (2*E*,4*E*)-hexa-2,4-diene-1,6-diol (2.00 g, 17.5 mmol) in DMF (150 mL) at room temperature were added imidazole (1.25 g, 18.4 mmol) and *tert*-butyldimethylsilyl chloride (2.77 g, 18.4 mmol, 1.05 equiv). The reaction mixture was stirred for 12 h followed by quenching it with water (150 mL) and dilution with ethyl acetate (150 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography (25% ethyl acetate in hexanes) to yield the title compound (1.8 g, 45%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.92 (s, 9H), 4.16-4.26 (m, 4H), 5.73-5.88 (m, 2H), 6.20-6.32 (m, 2H); ^{13}C NMR (76 MHz, $CDCl_3$) δ −5.2, 18.4, 25.9, 63.0, 63.4, 129.1, 130.6, 131.7, 132.8; IR (neat) cm^{-1} 3357, 2929, 2955, 2885, 2857, 1684, 1472, 1463, 1377.



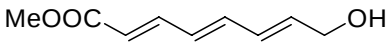
(2*E*,4*E*)-6-(*tert*-Butyldimethylsilyloxy)hexa-2,4-dienal (114): To a solution of (2*E*,4*E*)-6-(*tert*-butyldimethylsilyloxy)hexa-2,4-dien-1-ol (848 mg, 3.71 mmol) in dichloromethane (50 mL) at room temperature was added MnO_2 (3.2 g, 37.1 mmol, activated, obtained from Fulka). The

reaction mixture was stirred at room temperature for 45 min, filtered and the filtrate was concentrated to yield the title compound (839 mg,100%) as an oil: 1H NMR (300 MHz, CD_2Cl_2) δ 0.09 (s, 6H), 0.93 (s,9H), 4.33 (dd, *J* = 3.8, 1.9 Hz, 2H), 6.11 (dd, *J* = 15.4, 8.0 Hz, 1H), 6.34 (dt, *J* = 15.1, 4.1 Hz, 1H), 6.50-6.64 (m, 1H), 7.15 (dd, *J* = 15.1, 11.0 Hz, 1H), 9.54 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ –5.0, 18.8, 26.3, 63.4, 127.2, 131.7, 145.0, 152.1, 194.0; IR (neat) cm^{-1} 2955, 2930, 2857, 2729, 1684, 1646, 1254; HRMS for $C_{16}H_{19}NO_4Na$: Calcd 226.1389; found 226.1384.

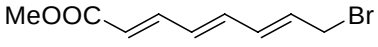


(2*E*,4*E*,6*E*)-Methyl 8-(*tert*-butyldimethylsilyloxy)octa-2,4,6-trienoate (115): To a suspension of NaH (98 mg, 4.1 mmol) in THF (15 mL) at 0 °C was added methyldiethylphosphonoacetate (857 mg, 4.10 mmol). The reaction mixture was stirred at room temperature for 20 min followed by cooling to −78 °C. The above reaction mixture was added via cannula to a solution of (2*E*,4*E*)-6-(*tert*-butyldimet hylsilyloxy)hexa-2,4-dienal (839 mg, 3.71 mmol) in THF (15 mL) at −78 °C. The above reaction mixture was stirred at room temperature for 2 h followed by quenching the reaction with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 5% ethyl acetate in hexanes) to yield the title compound (828 mg, 2.93 mmol, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.92 (s, 9H), 3.75 (s, 3H), 4.28 (d, *J* = 4.7 Hz, 2H), 5.88 (d, *J* = 15.1 Hz, 1H), 5.99 (dt, *J* = 15.1, 4.7 Hz, 1H), 6.28-6.41 (m, 2H), 6.58 (dd, *J* = 14.8, 10.7, 1H), 7.32 (dd, *J* = 15.6, 11.5 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ –5.3, 18.4, 25.9, 51.4, 63.1, 120.2, 128.5, 129.2, 137.8, 140.3, 144.7, 167.4; IR (neat)

cm^{-1} 2947, 2929, 2886, 2857, 1715, 1621; EIMS (M^+) 282, (M – *t*Bu)$^+$ 225; HRMS for $C_{15}H_{26}O_3Si_1$: Calcd 282.1651; found 282.1641.

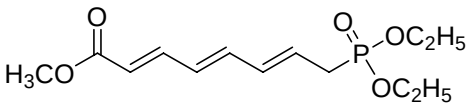


(2*E*,4*E*,6*E*)-Methyl 8-hydroxyocta-2,4,6-trienoate (116): To a solution of (2*E*,4*E*,6*E*)-methyl 8-(*tert*-butyldimethylsilyloxy)octa-2,4,6-trienoate (0.82 g, 2.9 mmol) in 2: 1 mixture of dichloro methane: methanol (40 mL) was added acetyl chloride (~25 mg) at room temperature. After 30 min, the mixture was concentrated to yield the title compound (488 mg, 2.90 mmol, 100%) as pale yellow solid: ^{1}H NMR (601 MHz, $CDCl_3$) δ 1.51 (br s, 1H), 3.76 (s, 3H), 4.27 (d, *J* = 5.2 Hz, 1H), 5.90 (d, *J* = 15.1 Hz, 1H), 6.05 (dt, *J* = 15.1, 5.5 Hz, 1H), 6.30-6.40 (m, 2H), 6.58 (dd, *J* = 14.8, 11.0 Hz, 1H), 7.32 (dd, *J* = 15.4, 11.3 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 51.6, 62.7, 120.5, 129.6, 129.7, 137.3, 140.1, 144.6, 167.6.

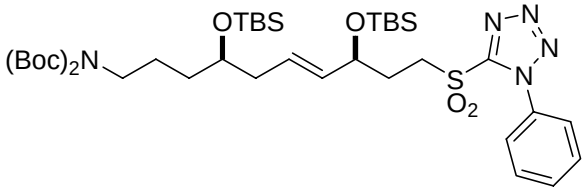


(2*E*,4*E*,6*E*)-Methyl 8-bromoocta-2,4,6-trienoate (117): To a solution of (2*E*,4*E*,6*E*)-methyl 8-hydroxyocta-2,4,6-trienoate (470 mg, 2.79 mml) in THF (10 mL) at –20 ^{o}C were added 2,6-lutidine (658 mg, 6.15 mmol) and thionyl bromide (0.4 ml, 5.0 mmol). The reaction mixture was stirred at –20 ^{o}C for 40 min followed by 2 h at room temperature. Then the mixture was poured into saturated aqueous $NaHCO_3$ solution (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (10% ethyl acetate in hexanes) gave the title compound (473 mg, 73%) as white solid: ^{1}H NMR (500 MHz, $CHCl_3$) δ 3.75 (s, 3H), 4.05 (d, *J* = 7.8 Hz, 2H), 5.92 (d, *J* = 15.1 Hz, 1H), 6.03-6.12 (m, 1H),

6.32-6.41 (m, 2H), 6.53 (dd, J = 15.1, 11.0 Hz, 1H), 7.30 (dd, J = 15.6, 11.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.3, 51.7, 121.9, 131.7, 132.9, 133.8, 138.7, 143.9, 167.3; IR (neat) cm^{-1} 3027, 2989, 2946, 1619, 1430, 1353, 1234, 1195; HRMS for $C_9H_{11}O_2Br$: Calcd 229.9942; found 229.9935.

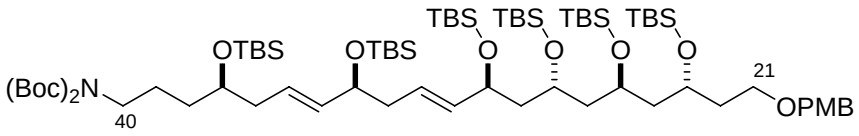


(2*E*,4*E*,6*E*)-Methyl 8-(diethoxyphosphoryl)octa-2,4,6-trienoate (7): To a solution of (2*E*,4*E*,6*E*)-methyl 8-bromoocta-2,4,6-trienoate (469 mg, 2.03 mmol) in 10 mL toluene was added triethylphosphite. The reaction mixture was refluxed over night followed by concentration. Purification of the crude product by flash column chromatography (25 to 100% ethyl acetate in hexanes, gradient flash column) gave the title compound (550 mg, 94%) as waxy solid: ^{1}H NMR (600 MHz, $CHCl_3$) δ 1.32 (t, J = 7.1 Hz, 6H), 2.70 (d, J = 23.0, 7.1 Hz, 2H), 3.75 (s, 3H), 4.08-4.14 (m, 4H), 5.83-5.90 (m, 2H), 6.24-6.30 (m, 2H), 6.54 (dd, J = 15.1, 10.7 Hz, 1H), 7.29 (dd, J = 15.4, 11.3 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 16.1 ($J_{C\text{-}P}$ = 6 Hz), 30.2 ($J_{C\text{-}P}$ = 139 Hz), 51.6, 62.2 ($J_{C\text{-}P}$ = 7 Hz), 120.9, 127.4 ($J_{C\text{-}P}$ = 13 Hz), 129.6 ($J_{C\text{-}P}$ = 5 Hz), 134.2 ($J_{C\text{-}P}$ = 16 Hz), 139.8 ($J_{C\text{-}P}$ = 6 Hz), 144.4, 167.5; EIMS (M^+) 288; HRMS for $C_{13}H_{21}O_5P$: Calcd 288.1127; found 288.1133.



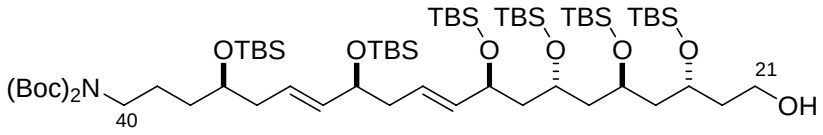
(4*R*,8*S*,*E*)-4,8-*bis*(*tert*-butyldimethylsilyloxy)-10-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)-*N*,*N*-*bis*(Boc)-dec-6-en-1-amine (**118**)**:** To a solution of sulfide **30** (62 mg, 0.078 mmol) in ethanol

(1.5 mL) was added oxidant (0.3 mL, prepared from 0.6 g of $Mo_7O_{24}(NH_4)_6 \cdot 4H_2O$ in 2.5 mL of 30% w/v aq H_2O_2).[104] After 18 h, it was quenched with water (5 mL), and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) to yield the title compound (60 mg, 92%) as an oil: $[\alpha]_D$ +4.47 (*c* 0.67 $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 0.04 (s, 9H), 0.07 (s, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 1.24-1.26 (m, 2H), 1.37-1.41 (m, 2H), 1.49 (s, 18H), 1.60-1.17 (m, 1H), 2.06-3.73 (m, 1H), 3.78 (t, *J* = 8.0 Hz, 2H), 4.33 (q, *J* = 14.8, 7.1 Hz, 1H), 7.57-7.63 (m, 3H), 7.68 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (151 MHz,$CDCl_3$) δ –4.8, –4.5, –4.4, –4.2, 18.1, 18.2, 25.2, 25.9, 25.9, 28.1, 30.3, 33.8, 39.9, 46.5, 52.4, 70.8, 71.6, 82.0, 125.1, 128.4, 129.7, 131.4, 133.1, 133.6, 152.6, 153.5; IR (neat) cm^{-1} 2954, 2930, 2857, 1743, 1696, 1367, 1343, 1124; HRMS $(M + Na)^+$ for $C_{39}H_{69}N_5O_8Si_2SNa$: Calcd 846.4303; found 846.4291.



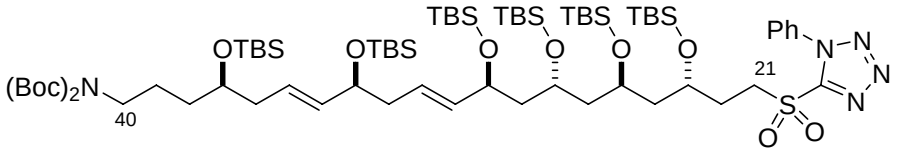
(4*R*,6*E*,8*S*,10*E*,12*S*,14*R*,16*S*,18*R*)-20-(4-methoxybenzyloxy)-4,8,12,14,16,18-hexakis(*tert*-butyldimethylsilyloxy)-*N*,*N*-*bis*(Boc)-icosa-6,10-dien-1-amine (119): KHMDS (0.5 M in toluene, 55 μL, 0.225 mmol`) was added to a solution of sulfone **118** (20 mg, 0.023 mmol, 1 equiv) in THF (1 mL) at −78 °C. After 30 min, a solution of (2*S*,4*R*,6*S*,8*R*)-10-(4-methoxybenzyloxy)-2,4,6,8-tetrakis(*tert*-butyldimethylsilyloxy) decanal **69** (24 mg, 0.029 mmol) in THF (1 mL) was added. The reaction mixture was stirred at −78 °C for 1.5 h followed by overnight stirring at room temperature. The reaction mixture was quenched with water and the

aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography (10% ethyl acetate in hexanes) to yield the title compound **119** (26 mg, 80%) as a colorless oil: $[\alpha]_D$ –1.5 (*c* 0.6 $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 0.00-0.12 (m, 35H), 0.876 (s, 9H), 0.879 (s, 9H), 0.885 (s, 18H), 0.89 (s, 9H), 0.896 (s, 9H), 1.36-1.45 (m, 3H), 1.59-1.84 (m, 9H), 2.15-2.24 (m, 4H), 3.48-3.59 (m, 4H), 3.66-3.70 (m, 1H), 3.81 (s, 3H), 3.83-3.86 (m, 1H), 3.87-3.94 (m, 2H), 4.07 (q, *J* = 6.0 Hz, 1H), 4.18 (td, *J* = 7.7, 3.8 Hz, 1H), 4.42 (s, 2H), 5.41 (dd, *J* = 15.4, 7.7 Hz, 1H), 5.46 (dd, *J* = 15.4, 6.3 Hz, 1H), 5.52-5.58 (m, 2H), 5.87 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ –4.6, –4.5, –4.3, –4.2, –4.1, –3.8, –3.76, –3.5, –3.4, –3.38, –3.3, 18.2, 18.25, 18.3, 25.3, 25.99, 26.0, 26.2, 28.2, 29.8, 33.8, 37.9, 40.2, 41.6, 45.7, 46.68, 46.7, 46.8, 55.3, 66.8, 67.1, 67.2, 67.5, 71.1, 72.0, 72.6, 73.5, 82.0, 114.0, 129.0, 131.0, 152.7, 159.1; IR (neat) cm^{-1} 2955, 2929, 2857, 1748, 1698, 1614, 1514, 1472, 1463, 1252; HRMS $(M + Na)^+$ for $C_{74}H_{148}NO_{12}Si_6Na$: Calcd 1433.9515, found 1433.9498.



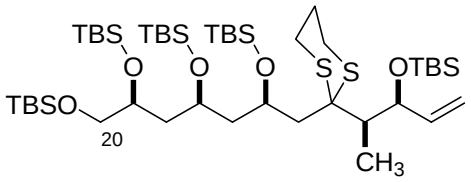
(3*R*,5*S*,7*R*,9*S*,10*E*,13*S*,14*E*,17*R*)-20-amino-3,5,7,9,13,17-hexakis(*tert*-butyldimethylsilyloxy)-*N*,*N*-*bis*(Boc)-icosa-10,14-dien-1-ol (120): DDQ (12 mg, 0.052 mmol) was added to a solution of the PMB-ether **119** (52 mg, 0.037 mmol) in DCM (1 mL) and pH 7 buffer (0.1 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h followed by diluting it with DCM (5 mL) and saturated aqueous $NaHCO_3$ (3 mL). Organic layer was separated and aqueous layer was extracted with DCM (3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography to

yield the title compound (42 mg, 88%) as an oil. ^{1}H NMR (600 MHz, $CHCl_3$) δ :0.01-0.10 (m, 36H), 0.88-0.90 (m, 54H), 1.23-1.47 (m, 6H), 1.51 (s, 18H), 1.55-1.91 (m, 6H), 2.16-2.25 (m, 4H), 2.33 (t, *J* = 5.2 Hz, 1H), 3.50-3.59 (m, 2H), 3.65-3.74 (m, 2H), 3.77-3.91 (m, 3H), 3.95-4.01 (m, 1H), 4.07 (dd, *J* = 11.8, 8.5 Hz, 1H), 4.14 (dd, *J* = 12.6, 6.9 Hz, 1H), 5.39-5.48 (m, 2H), 5.51-5.58 (m, 2H); 13C NMR (151 MHz, $CHCl_3$) δ –4.6, –4.5, –4.4, –4.3, –4.2, –3.6, –3.4, 14.2, 18.1, 18.1, 18.3, 18.3, 22.7, 25.3, 25.4, 26.0, 26.1, 28.2, 31.7, 33.8, 38.5, 40.2, 41.6, 45.3, 46.4, 46.7, 47.2, 60.3, 67.1, 67.4, 69.5, 71.1, 72.0, 73.5, 82.0, 126.5, 126.8, 135.5, 136.0, 152.7.



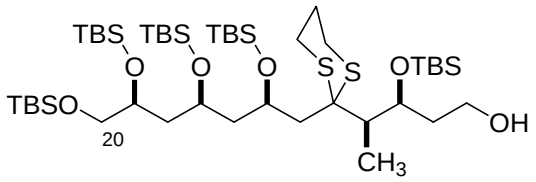
(4*R*,6*E*,8*S*,10*E*,12*S*,14*R*,16*R*,18*S*)-4,8,12,14,16,18-*hexakis*(*tert*-butyldimethylsilyloxy)-20-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)-N,N-*bis*(Boc)-icosa-6,10-dien-1-amine (121): To a solution of alcohol **120** (40 mg, 0.031 mmol) in THF (1 mL) were added thiophenyltetrazole (7.2 mg, 0.040 mmol), triphenylphosphine (12 mg, 0.46 mmol) and DIAD (9.4 mg, .046 mmol) at room temperature. After 16 h, it was diluted with ethyl acetate (5 mL) and water (3 mL). Organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated to yield the crude product (49 mg). To the crude compound in EtOH (1.5 mL) was added a solution of the oxidant (made from 0.6 g of $Mo_7O_{24}(NH_4)_6$•$4H_2O$ in 2.5 mL of 30% w/v aqueous H_2O_2). The reaction mixture was stirred at room temperature for 18 h, quenched with water (4 mL) and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) to yield the title

compound **121** (30 mg, 65%) as an oil. $[\alpha]_D$ –24.1 (*c* 0.12 $CHCl_3$);.^{1}H NMR (600 MHz, $CHCl_3$) δ 0.00-0.11 (m, 36H), 0.88-0.91 (m, 54H), 1.36-1.47 (m ,6H), 1.51 (s, 18H), 1.61-1.76 (m, 6H), 2.02-2.09 (m, 1H), 2.14-2.25 (m, 3H), 3.50-3.59 (m, 2H), 3.66-3.70 (m, 1H), 3.74-2.85 (m, 3H), 3.86-3.91 (m, 1H), 4.05-4.10 (m, 2H), 4.21 (td, *J* = 8.2, 3.4 Hz, 1H), 5.39 (dd, *J* = 15.4, 7.7 Hz, 1H), 5.46 (dd, *J* = 15.4, 6.3 Hz, 1H), 5.53-5.58 (m, 2H), 7.59-7.65 (m, 3H), 7.70-7.72 (m, 2H); ^{13}C NMR (151 MHz, $CHCl_3$) δ –4.6, –4.5, –4.5, –4.3, –4.2, –3.8, –3.8, –3.3, –3.2, 14.2, 18.1, 18.1, 18.3, 18.3, 22.7, 25.3, 26.0, 26.0, 26.1, 28.2, 30.0, 31.7, 33.8, 40.2, 41.6, 44.7, 46.5, 46.7, 46.9, 52.2, 66.8, 67.2, 67.5, 71.0, 72.0, 73.5, 82.0, 125.1, 126.4, 126.9, 129.8, 131.5, 133.2, 135.6, 136.2, 152.7, 153.5; IR (neat) cm^{-1} 2928, 2856, 1501, 1472, 1361, 1251, 1122.



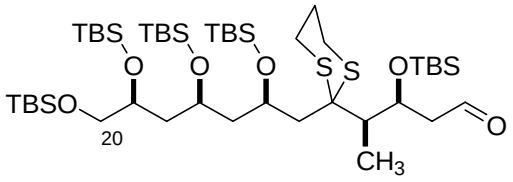
2-((2*R*,4*S*,6*S*)-2,4,6,7-*tetrakis*(*tert*-Butyldimethylsilyloxy)heptyl)-2-((2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)pent-4-en-2-yl)-1,3-dithiane (122): To a solution of compound **109** (122 mg, 0.383 mmol) in THF (0.5mL) and HMPA (0.05 mL) at –78 ^oC was added *t*-BuLi (1.7 M in pentane, 0.25 mL, 0.42 mmol). After 30 min, a solution of iodide **5** (286 mg, 0.383 mmol) in THF (0.1 mL) was added. The reaction mixture was stirred at –78 ^oC for 2 h. The reaction mixture was warmed to 0 ^oC and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate followed by drying of the combined organic extracts over $MgSO_4$. Concentration and purification of the crude compound by flash column chromatography (SiO_2, 5% ethyl acetate in hexanes) provided the title compound (194 mg, 54%) as an oil.^{1}H NMR (600 MHz, $CHCl_3$) δ 0.02 (s, 3H), 0.05 (s, 6H), 0.07 (s, 3H), 0.08 (s, 3H), 0.10 (s, 6H), 0.12 (s, 3H),

0.15 (s, 3H), 0.22 (s, 3H), 0.90 (s, 27H), 0.91 (s, 18H), 1.10 (d, *J* = 6.9Hz, 1H), 1.65 (ddd, *J* = 13.4, 7.4, 5.2 Hz, 1H), 1.69-1.84 (m, 4H), 1.90-1.97 (m, 3H), 2.28 (q, *J* = 6.9 Hz, 1H), 2.51-2.59 (m, 2H), 2.80-2.88 (m, 2H), 3.44 (dd, *J* = 10.2, 7.1 Hz, 1H), 3.62 (dd, *J* = 9.9, 3.5 Hz, 1H) 3.76-3.80 (m, 1H), 4.22 (qn, *J* = 5.2 Hz, 1H), 4.95 (d, J = 7.7 Hz, 1H), 5.02 (d, *J* = 10.7 Hz, 1H), 5.13 (d, *J* = 17.0 Hz, 1H), 5.95 (ddd, *J* = 17.6, 10.2, 7.7 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ –5.3, –5.2, –4.4, –4.2, –4.1, –4.0, –3.8, –3.0, –2.9, 8.9, 14.2, 18.1, 18.3, 18.3, 18.5, 22.7, 24.5, 25.9, 26.1, 26.1, 26.3, 26.3, 31.7, 42.8, 44.0, 44.3, 49.4, 58.2, 67.0, 67.5, 67.8, 71.2, 73.5, 113.6, 143.4.



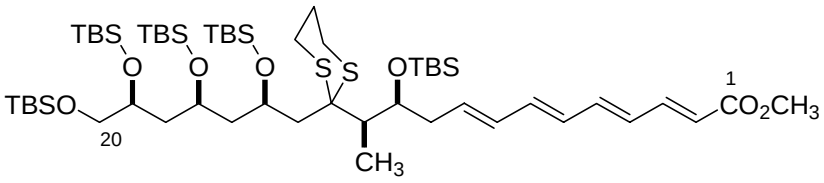
(3*S*,4*R*)-4-(2-((2*R*,4*S*,6*S*)-2,4,6,7-*tetrakis*(*tert*-Butyldimethylsilyloxy)heptyl)-1,3-dithian-2-yl)-3-(*tert*-butyldimethylsilyloxy)pentan-1-ol (123): To a solution of alkene **122** in THF (2 mL) was added 9-BBN (0.5 M in THF, 1.32 mL, 0.66 mmol). The reaction mixture was stirred at room temperature for 10 h. Then the reaction mixture was cooled to 0 ^{o}C, followed by the addition of H_2O_2 and aqueous 3 N NaOH (1.3 mL). The reaction mixture was stirred at room temperature for 6 h. Then the mixture was diluted with ethyl acetate (10 mL) and water (5 mL). Organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined oraganic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) to yield the title compound (128 mg, 64%) as an oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.06 (s, 3H), 0.08 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.12 (s, 3H), 0.14 (s, 6H), 0.19 (s, 3H), 0.89 (s, 9H), 0.894 (s, 18H), 0.90 (s, 9H), 0.904 (s, 9H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.39-2.03 (m, 11H), 2.42 (q,

J = 7.0 Hz, 1H), 2.56-2.66 (m, 2H), 2.79 (ddd, *J* = 13.7, 11.3, 2.5 Hz, 1H), 2.89 (ddd, *J* = 14.3, 11.8, 2.8 Hz, 1H), 3.43 (dd, *J* = 10.2, 7.1 Hz, 1H), 3.62 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.69-3.82 (m, 3H), 3.86-3.91 (m, 1H), 4.18-4.21 (m, 1H), 4.48 (dd, *J* = 9.3, 3.3 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ –5.3, –5.2, –4.4, –4.2, –4.0, –3.9, –3.0, –2.9, 10.1, 14.2, 18.1, 18.3, 18.3, 18.5, 22.7, 24.5, 25.3, 25.4, 26.0, 26.1, 26.2, 27.5, 31.7, 33.4, 34.8, 34.8, 40.7, 41.5, 42.0, 42.6, 44.5, 49.4, 58.1, 60.0, 67.1, 67.4, 67.8, 69.2, 71.2, 72.3; HRMS for $C_{46}H_{102}O_6S_2Si_5Na$ (M + Na): Calcd 977.5862; found 977.5826.



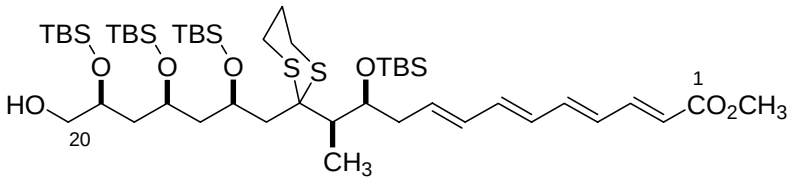
(3*S*,4*R*)-4-(2-((2*R*,4*S*,6*S*)-2,4,6,7-*tetrakis*(*tert*-Butyldimethylsilyloxy)heptyl)-1,3-dithian-2-yl)-3-(*tert*-butyldimethylsilyloxy)pentanal (124): To a solution of alcohol **123** (126 mg, 0.132 mmol) in dichloromethane (5 mL) at 0 ^{o}C was added diisopropylethylamine (77 mg, 0.59 mmol) and the resulting mixture was stirred for 5 min. DMSO (17 mg, 0.21 mmol) was added to the above reaction mixture and stirred for another 10 min. At this time, SO_3•pyr (27 mg, 0.17 mmol) was added and the resulting mixture was stirred for 2 h. saturated aqueous $NaHCO_3$ was added to the above reaction mixture and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 15% ethyl acetate in hexanes) to yield the title compound (76 mg, 60%) as an oil: ^{1}H NMR (600 MHz, CD_2Cl_2) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.07 (s, 6H), 0.09 (s, 3H), 0.117 (s, 3H), 0.12 (s, 3H), 0.18 (s, 3H), 0.22 (s, 3H), 0.89 (s, 3H), 0.89 (s, 9H), 0.895 (s,

9H), 0.898 (s, 9H), 0.90 (s, 9H), 0.905 (s, 9H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.63-1.68 (m, 2H), 1.70-1.82 (m, 3H), 1.86-2.00 (m, 3H), 2.31 (q, *J* = 7.0 Hz, 1H), 2.50-2.60 (m, 2H), 2.62-2.76 (m, 2H), 2.76-2.89 (m, 2H), 3.44 (dd, *J* = 10.2, 6.9 Hz, 1H), 3.61 (dd, *J* = 10.2, 3.8 Hz, 1H), 3.78-3.82 (m, 1H), 3.83-3.88 (m, 1H), 4.22-4.26 (m, 1H), 5.00 (dd, *J* = 8.5, 3.8 Hz, 1H), 9.80 (s, 1H); HRMS for $C_{46}H_{100}O_6S_2Si_5Na$ $(M + Na)^+$: Calcd 975.5705; found 975.5742.



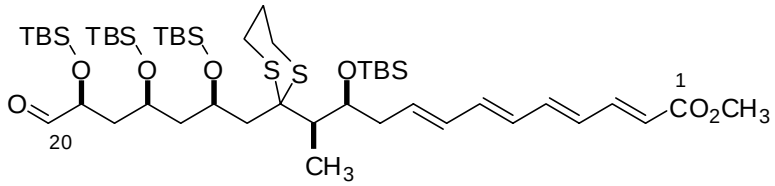
(2*E*,4*E*,6*E*,8*E*,11*S*,12*R*)-Methyl 12-(2-((2*R*,4*S*,6*S*)-2,4,6,7-*tetrakis*(*tert*-butyldimethylsilyloxy) heptyl)-1,3-dithian-2-yl)-11-(*tert*-butyldimethylsilyloxy)trideca-2,4,6,8-tetraenoate (125): To a solution of compound **7** (13 mg, 0.046 mmol) in THF (2 mL) at −78 ^oC was added a solution of LiHMDS in THF (1.0 M in THF, 0.043 mL, 0.043 mmol) and stirred at that temperature for 15 min. A solution of aldehyde **124** (28 mg, 0.029 mmol) in THF (2 mL) was added to the above reaction mixture and stirred for 30 min at −78 ^oC and 0 ^oC for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (5% ethyl acetate in hexanes) to yield the title compound **125** (18 mg, 57%) as an oil. $[\alpha]_D$ 20.6 (*c* 0.67 $CHCl_3$); ^1H NMR (600 MHz, $CHCl_3$) δ 0.05 (m, 30H), 0.89-0.90 (m, 45H), 1.03 (d, *J* = 6.9 Hz, 3H), 1.64-1.86 (m, 7H), 1.87-1.95 (m, 2H), 2.29-2.36 (m, 2H), 2.39-2.52 (m, 2H), 2.70-2.79 (m, 2H), 3.43 (dd, *J* = 9.9, 7.1 Hz, 1H), 3.63 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.72-3.78 (m, 4H), 3.87-3.92 (m, 1H), 4.15-4.21 (m, 1H), 4.51 (dd, *J* = 9.9, 3.8 Hz, 1H), 5.82 (ddd, *J* = 15.1, 9.1, 6.0 Hz, 1H), 5.88 (d, *J* = 15.4 Hz, 1H), 6.08-6.27 (m, 2H), 6.30-

6.40 (m, 2H), 6.57 (dd, *J* = 14.8, 11.0Hz, 1H), 7.33 (dd, *J* = 15.1, 11.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ –5.3, –5.2, –4.4, –4.2, –4.0, –3.9, –3.8, –3.0, –3.0, 9.4, 14.2, 14.3, 18.1, 18.3, 18.5, 22.8, 22.8, 25.9, 26.0, 26.1, 26.2, 26.3, 29.8, 31.7, 32.0, 40.5, 42.2, 42.6, 44.6, 49.7, 51.6, 57.9, 67.0, 67.5, 67.8, 70.9, 71.2, 120.1, 129.7, 130.6, 132.8, 134.3, 137.0, 140.9, 144.7, 167.6; IR (neat) cm^{-1} 2954, 2928, 2856, 1720, 1620, 1598, 1255; MS (API-ES) *m/z* 1109.4 $(M + Na)^+$.

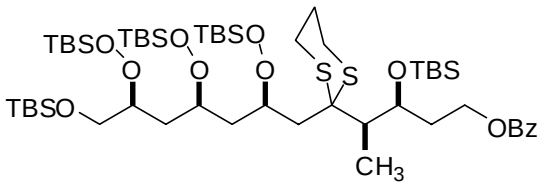


(2*E*,4*E*,6*E*,8*E*,11*S*,12*R*)-Methyl 12-(2-((2*R*,4*S*,6*S*)-2,4,6-*tris*(*tert*-butyldimethyl silyl oxy)-7-hydroxyheptyl)-1,3-dithian-2-yl)-11-(*tert*-butyldimethylsilyloxy)trideca-2,4,6,8-tetraenoate (126): To a solution of compound **125** (33 mg, 0.030 mmol) in THF (2 mL) was added HF•py in pyridine in THF (1.5 mL). The reaction mixture was stirred at room temperature for 6 h and poured into saturated aqueous $NaHCO_3$ solution. Organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) to yield the title compound **126** (11.2 mg, 45%) as an oil. ^{1}H NMR (600 MHz, $CHCl_3$) δ 0.06 (s, 3H), 0.098 (s, 3H), 0.104 (s, 6H), 0.12 (s, 3H), 0.14 (s, 3H), 0.17 (s, 3H), 0.22 (s, 3H), 0.892 (s, 9H), 0.893 (s, 9H), 0.898 (s, 9H), 0.905 (s, 9H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.71-2.04 (m, 7H), 2.28-2.37 (m, 2H), 2.42-2.56 (m, 3H), 2.70-2.77 (m, 1H), 2.78-2.86 (m, 2H), 3.47 (ddd, *J* = 11.5, 7.1, 5.5 Hz, 1H), 3.59 (ddd, *J* = 11.0, 6.0, 4.9 Hz, 1H), 3.76 (s, 3H), 3.90-3.96 (m, 1H), 4.08-4.17 (m, 2H), 4.44 (dd, *J* = 9.9, 3.8 Hz, 1H), 5.81 (ddd, *J* = 15.1, 9.3, 5.8 Hz, 1H), 5.88 (d, *J* = 15.1, 1H), 6.18-6.28 (m, 2H), 6.30-6.40 (m, 2H), 6.57 (dd, *J* = 14.8, 11.2 Hz,

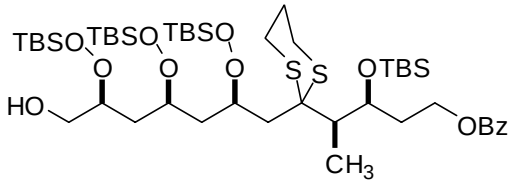
2H), 7.32 (dd, *J* = 15.4, 11.8 Hz, 1H); ^{13}C NMR (151 MHz,$CDCl_3$) δ –4.6, –4.5, –4.3, –4.1, –4.0, –4.0, –2.9, –2.8, 9.5, 18.1, 18.1, 18.2, 18.3, 24.3, 25.7, 26.0, 26.1, 26.2, 29.8, 40.3, 41.4, 42.2, 45.1, 49.2, 51.6, 57.7, 66.5, 66.9, 67.6, 70.3, 70.8, 120.2, 129.8, 130.7, 132.9, 134.2, 136.9, 140.8, 144.7, 167.6.



(2*E*,4*E*,6*E*,8*E*,11*S*,12*R*)-Methyl12-(2-((2*R*,4*S*,6*S*)-2,4,6-*tris*(*tert*-butyldimethylsilyloxy)-7-oxoheptyl)-1,3-dithian-2-yl)-11-(*tert*-butyldimethylsilyloxy)trideca-2,4,6,8-tetraenoate (127): To a solution of alcohol **126** (12.3 mg, 0.0126 mmol) in DCM (2 mL) were added DIEA (37 mg, 0.28 mmol), DMSO (49 mg, 0.63 mmol) and SO_3•pyr (25 mg, 0.16 mmol). The reaction mixture was stirred at 0 ^{o}C for 30 min followed by pouring the reaction mixture into saturated sodium bicarbonate solution. Organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (SiO_2, 10% ethyl acetate in hexanes) to yield the title compound **127** (10 mg, 82%) as an oil: ^{1}H NMR (600 MHz, $CHCl_3$) δ 0.06-0.21 (m, 24H), 0.88-0.93 (m, 36H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.71-2.08 (m, 6H), 2.10-2.16 (m, 1H), 2.29-2.41 (m, 3H), 2.42-2.58 (m, 3H), 2.70-2.81 (m, 2H), 3.76 (s, 3H), 4.00-4.07 (m, 1H), 4.10-4.17 (m, 1H), 4.20-4.26 (m, 1H), 4.43-4.48 (m, 1H), 5.78-5.84 (m, 1H), 5.88 (d, *J* = 15.4 Hz, 1H), 6.17-6.29 (m, 2H), 6.30-6.41 (m, 2H), 6.57 (dd, *J* = 14.6, 11.0 Hz, 1H), 7.30-7.35 (m, 1H), 9.61 (d, *J* = 1.7 Hz, 1H).



(3*S*,4*R*)-4-(2-((2*R*,4*S*,6*S*)-2,4,6,7-*tetrakis*(*tert*-Butyldimethylsilyloxy)heptyl)-1,3-dithian-2-yl)-3-(*tert*-butyldimethylsilyloxy)pentyl benzoate (129): To a solution of alcohol **123** (50 mg, 0.052 mmol) in dichloromethane (5 mL) were added triethyl amine (0.1 mL), DMAP (20 mg) and benzyl chloride (200 mg). The reaction mixture was stirred at room temperature for 2 h and quenched with saturated aqueous sodium bicarbonate solution (5 mL). Organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (SiO_2, 15% ethyl acetate in hexanes) gave the title compound (46 mg, 83%) as an oil: $[\alpha]_D$ 16.3 (*c* 0.7 $CHCl_3$);^{1}H NMR (600 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.07 (s, 3H), 0.08 9s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.13 (s, 3H), 0.14 (s, 3H), 0.16 (S, 3H), 0.19 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 0.905 (s, 9H), 0.909 (s, 9H), 0.915 (s, 9H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.24-1.35 (m, 2H), 1.60-2.13 (m, 8H), 2.42-2.55 (m, 3H), 2.72-2.87 (m, 2H), 3.44 (dd, *J* = 10.2, 7.1 Hz, 1H), 3.63 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.76-3.84 (m, 1H), 3.87-3.94 (m, 1H), 4.18-4.25 (m, 1H), 4.31-4.38 (m, 1H), 4.38-4.46 (m, 1H), 4.66 (d, *J* = 9.1, 3.3 Hz, 1H), 7.42-7.48 (m, 2H), 7.55-7.60 (m, 1H), 8.04-8.09 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ –5.3, –5.2, –4.4, –4.2, –4.0, –3.9, –3.9, –3.8, –3.1, –3.0, 9.8, 14.2, 18.1, 18.1, 18.3, 18.4, 18.5, 22.7, 24.4, 25.9, 26.1, 26.3, 31.7, 37.2, 41.2, 42.6, 44.6, 49.6, 57.8, 62.1, 67.0, 67.5, 67.8, 68.9, 71.2, 128.4, 129.6, 130.3, 133.0, 166.7; IR (neat) cm^{-1} 2950, 2929, 2850, 1723, 1472, 1275, 1252, 1109, 835.



(3*S*,4*R*)-4-(2-((2*R*,4*S*,6*S*)-2,4,6-*tris*(*tert*-Butyldimethylsilyloxy)-7-hydroxyheptyl)-1,3-dithian-2-yl)-3-(*tert*-butyldimethylsilyloxy)pentyl benzoate (130): To a solution of compound **129** (45 mg, 0.042 mmol) in THF (0.5 mL) was added HF•pyr (1 mL) and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with THF (5 mL) and quenched with saturated aqueous sodium bicarbonate (15 mL). Organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (SiO_2, 15% ethyl acetate in hexanes) gave the title compound (16 mg, 39%) as an oil along with recovered compound **130** (20 mg): $[\alpha]_D$ 14.3 (*c* 0.3 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.06-0.20 (m, 24H), 0.88-0.91 (m, 36H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.66-2.20 (m, 11H), 2.44-2.53 (m, 2H), 2.60-2.90 (m, 3H), 3.35-3.51 (m, 1H), 3.55-3.66 (m, 1H), 3.80-3.99 (m, 1H), 4.05-4.18 (m, 2H), 4.29-4.44 (m, 2H), 4.56-4.61 (m, 1H), 7.42-7.47 (m, 2H), 7.54-7.60 (m, 1H), 8.04-8.07 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ –4.6, –4.5, –4.3, –4.1, –3.9, –3.0, –2.9, 10.0, 18.1, 18.1, 18.2, 18.4, 26.0, 26.1, 26.2, 26.4, 37.1, 41.1, 41.4, 45.2, 49.2, 57.6, 62.0, 66.6, 67.0, 67.6, 68.8, 70.3, 128.4, 129.6, 130.3, 133.1, 166.7; IR (neat) cm^{-1} 2954, 2929, 2852, 1724, 1475, 1270, 1249, 1107, 833, 768, 702, 662; HRMS for $C_{47}H_{92}O_7NaSi_4S_2(M + Na)^+$: Calcd 967.5259; found 967.5

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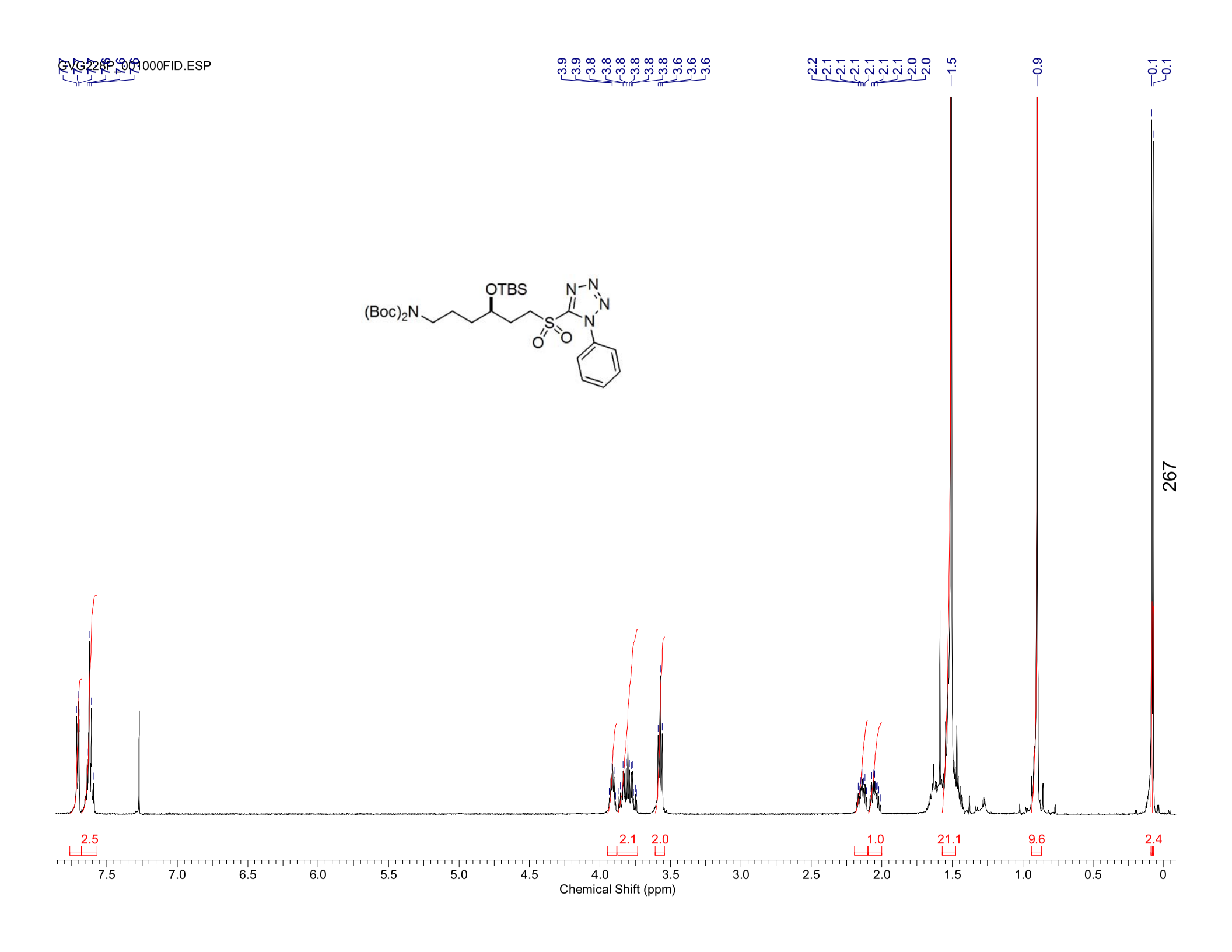
APPENDIX

NMR spectra of selected compounds (chapter 2)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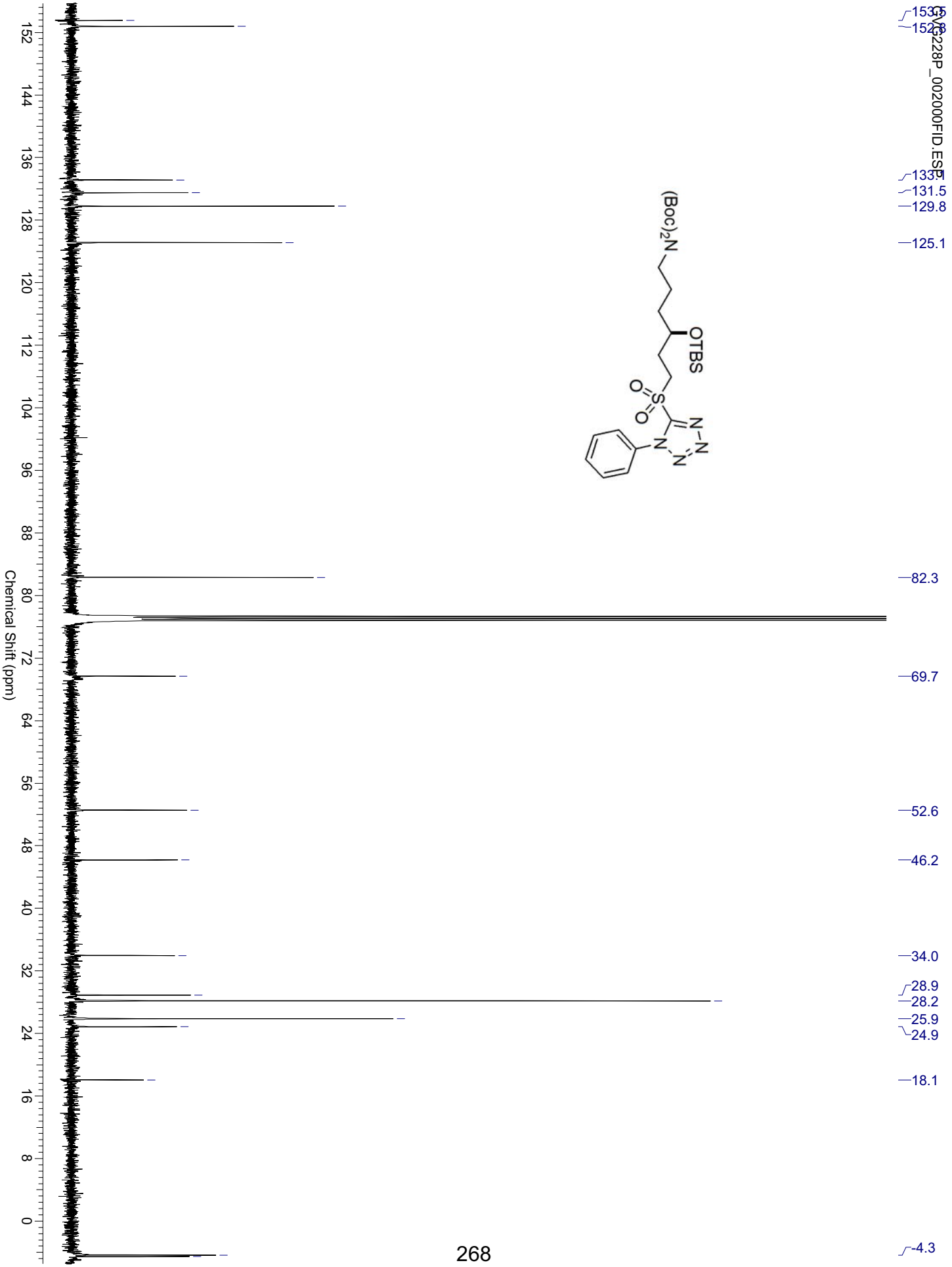
N
N
S
O
O
Chemical Shift (ppm)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152.8
133.1
131.5
129.8
125.1
82.3
69.7
52.6
46.2
34.0
28.9
28.2
25.9
24.9
18.1
-4.3
Chemical Shift (ppm)
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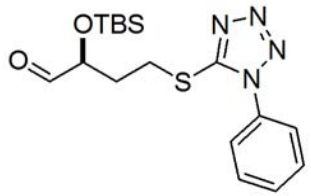
(Boc)2N
OTBS
O
S
O
N
N
N
N

GVG-74-P_001000FID.ESP



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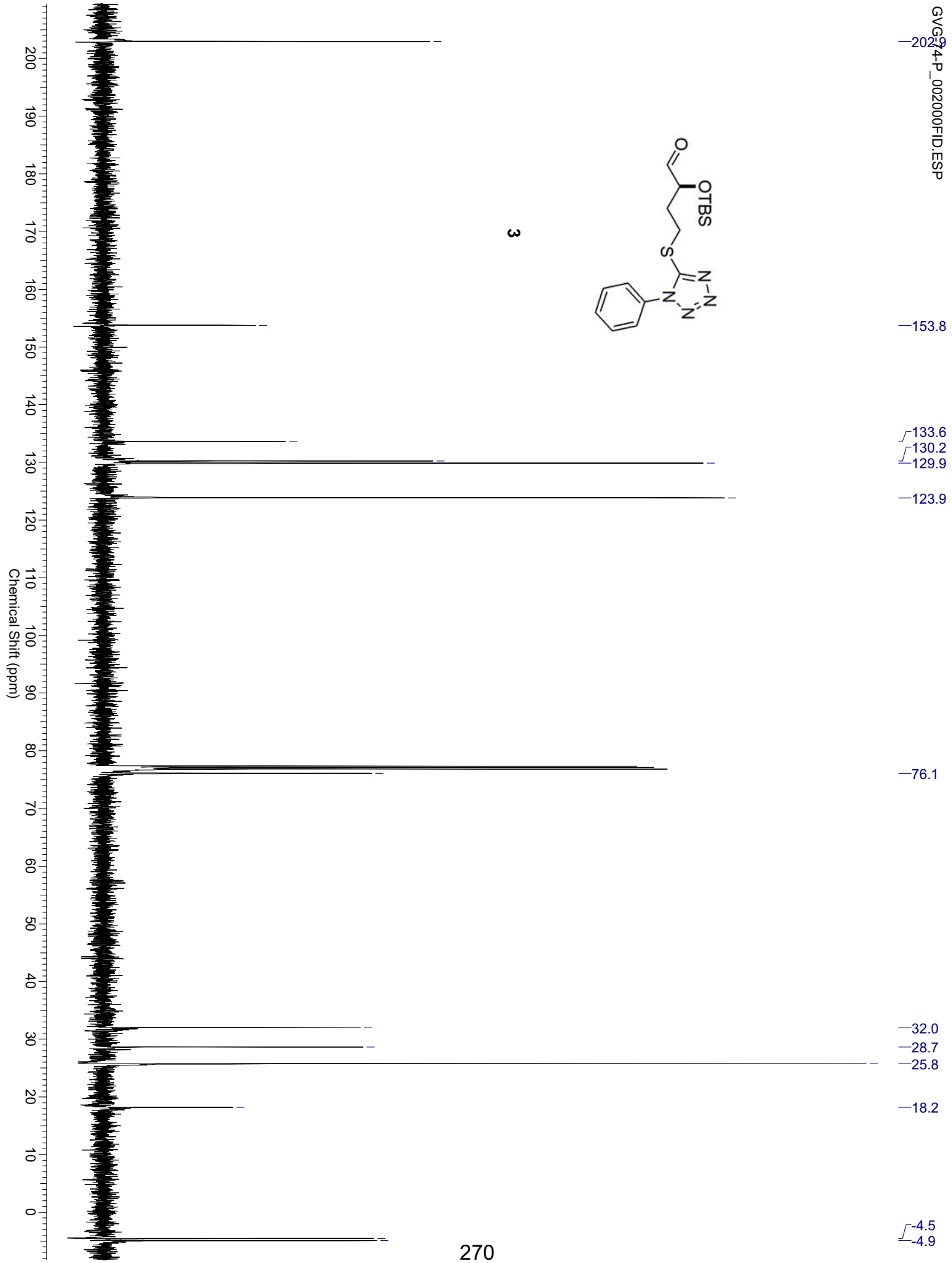
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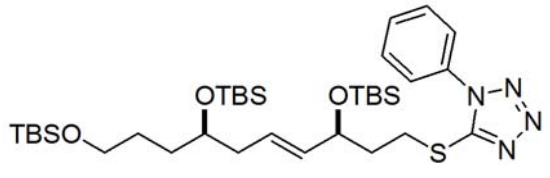
3
OTBS
O
S
N
N
N
N
Chemical Shift (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
202.9
153.8
133.6
130.2
129.9
123.9
76.1
32.0
28.7
25.8
18.2
-4.5
-4.9

GVG-75-PN_001000FID.ESP



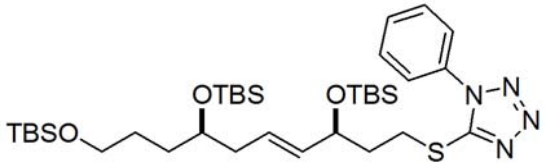
9

271

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

Chemical Shift (ppm)

GVG-75-PN_002000FID.ESP



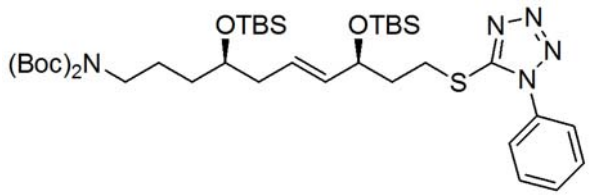
9

272

152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0

Chemical Shift (ppm)

GVG230P_003000FID.ESP



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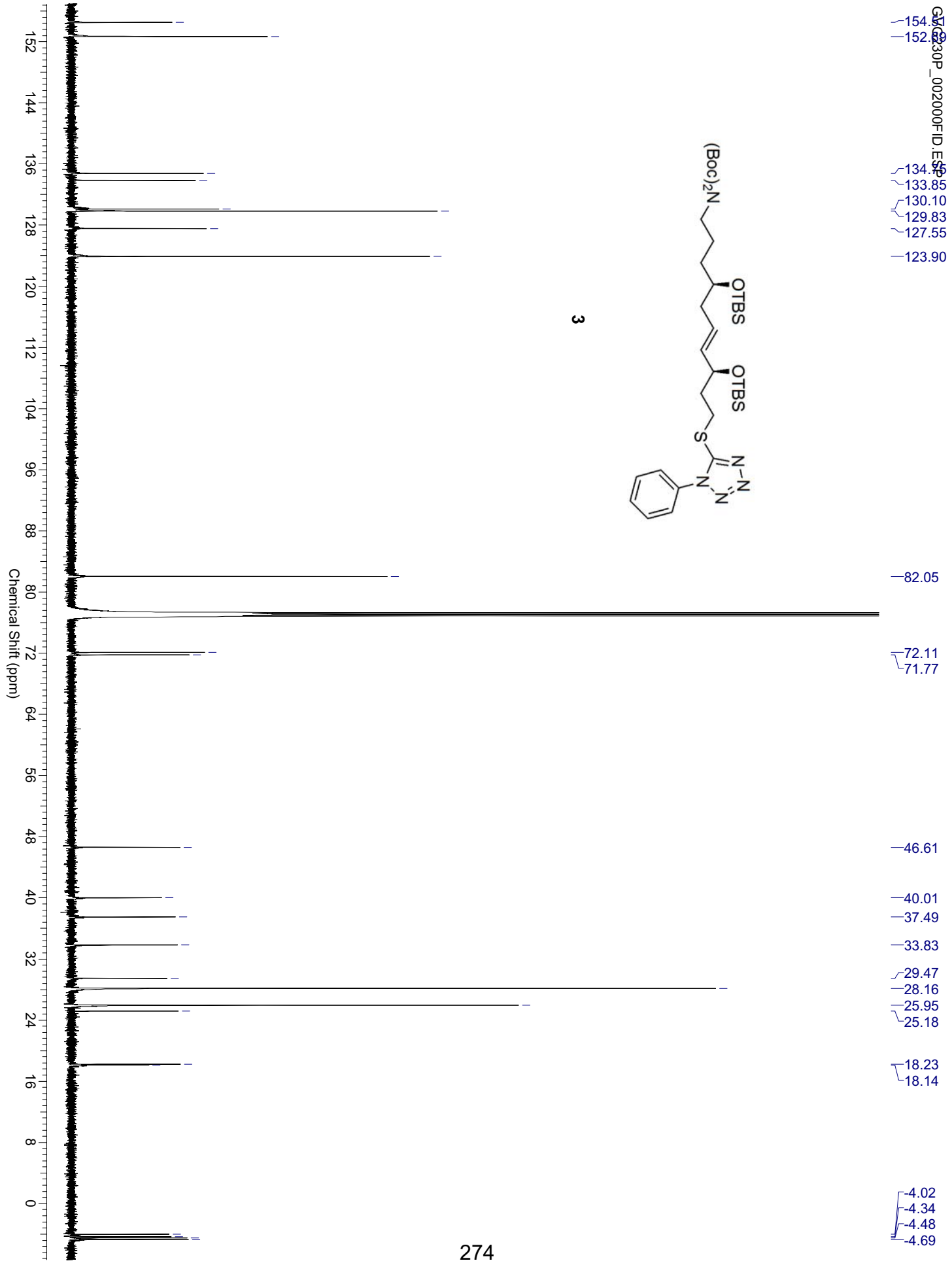
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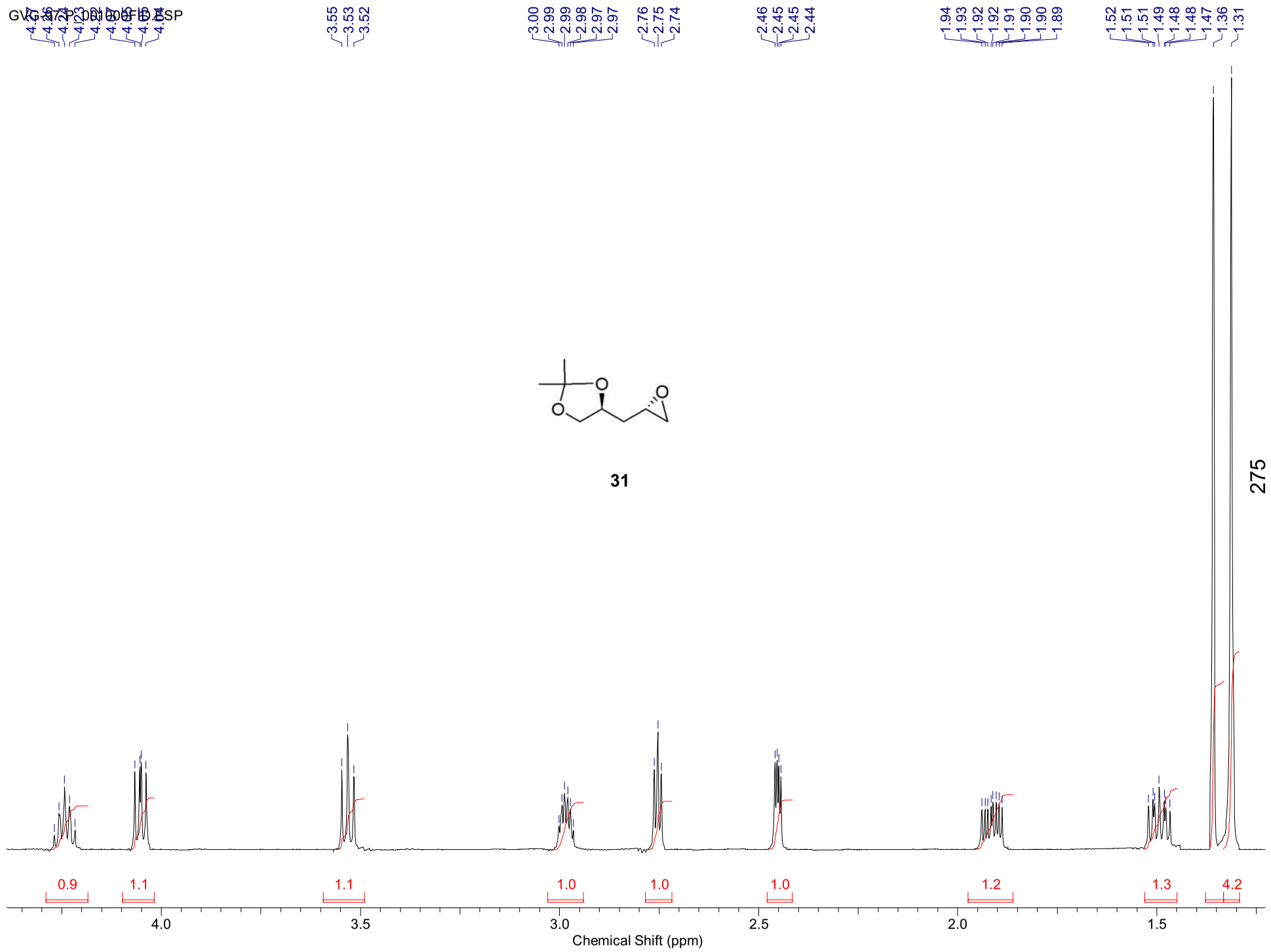
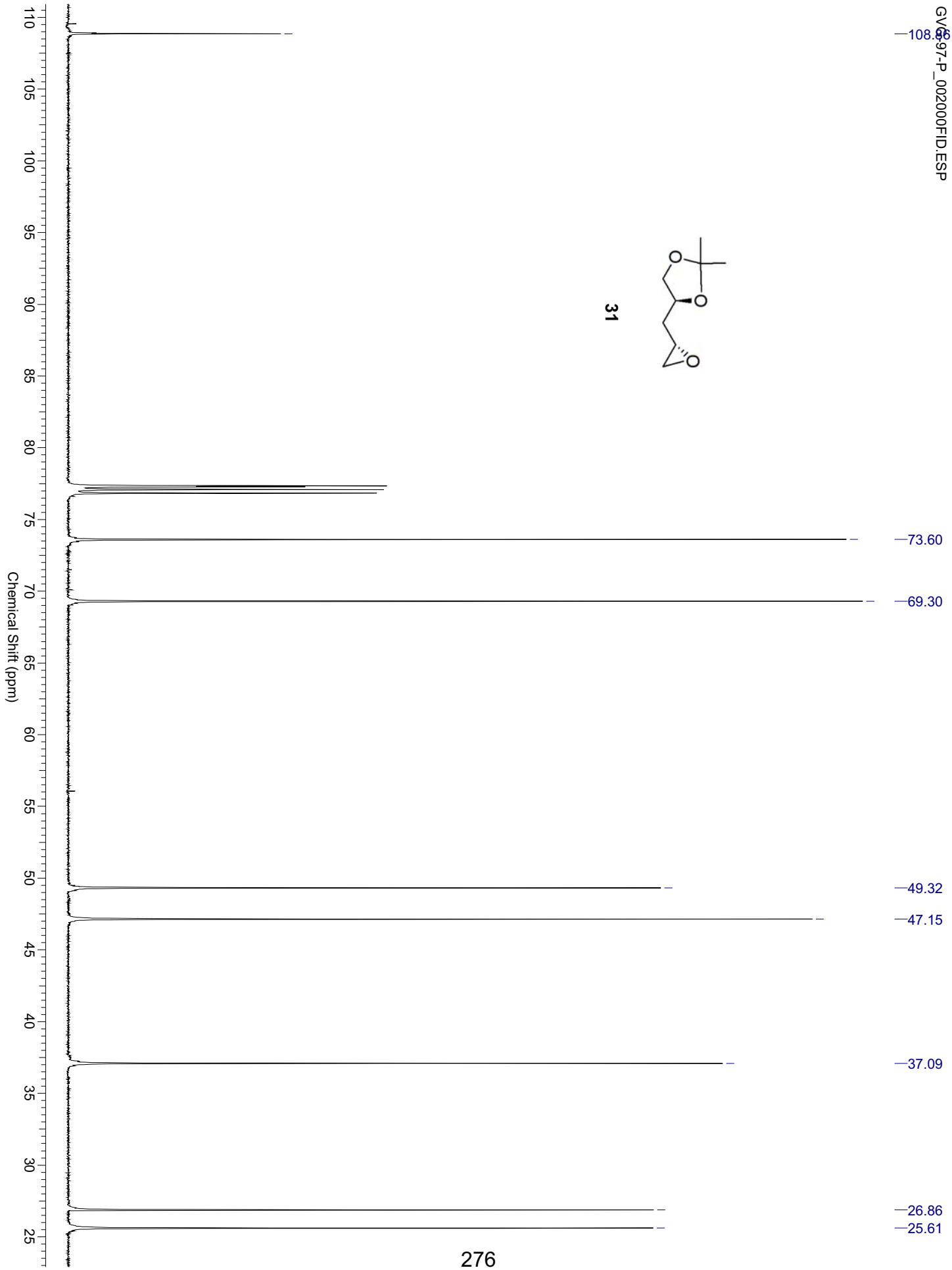
152.89
134.49
133.85
130.10
129.83
127.55
123.90
82.05
72.11
71.77
46.61
40.01
37.49
33.83
29.47
28.16
25.95
25.18
18.23
18.14
-4.02
-4.34
-4.48
-4.69
Chemical Shift (ppm)
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
(Boc)2N
OTBS
OTBS
S
N
N
N
N

3


3.55
3.53
3.52
3.00
2.99
2.99
2.98
2.97
2.97
2.76
2.75
2.74
2.46
2.45
2.45
2.44
1.94
1.93
1.92
1.92
1.91
1.90
1.90
1.89
1.52
1.51
1.51
1.49
1.48
1.48
1.47
1.36
1.31
275
0.9
1.1
1.1
1.0
1.0
1.0
1.2
1.3
4.2
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

31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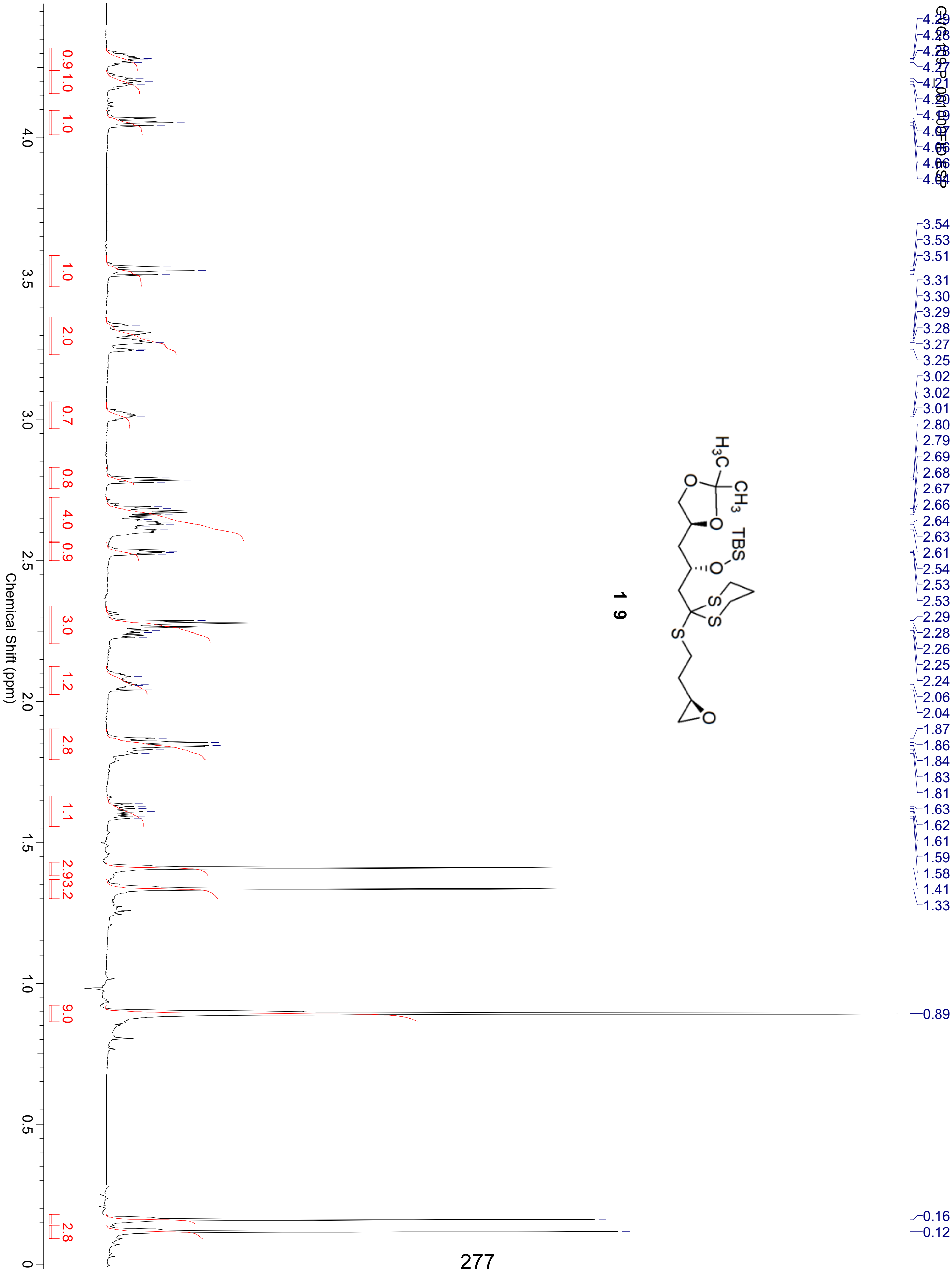
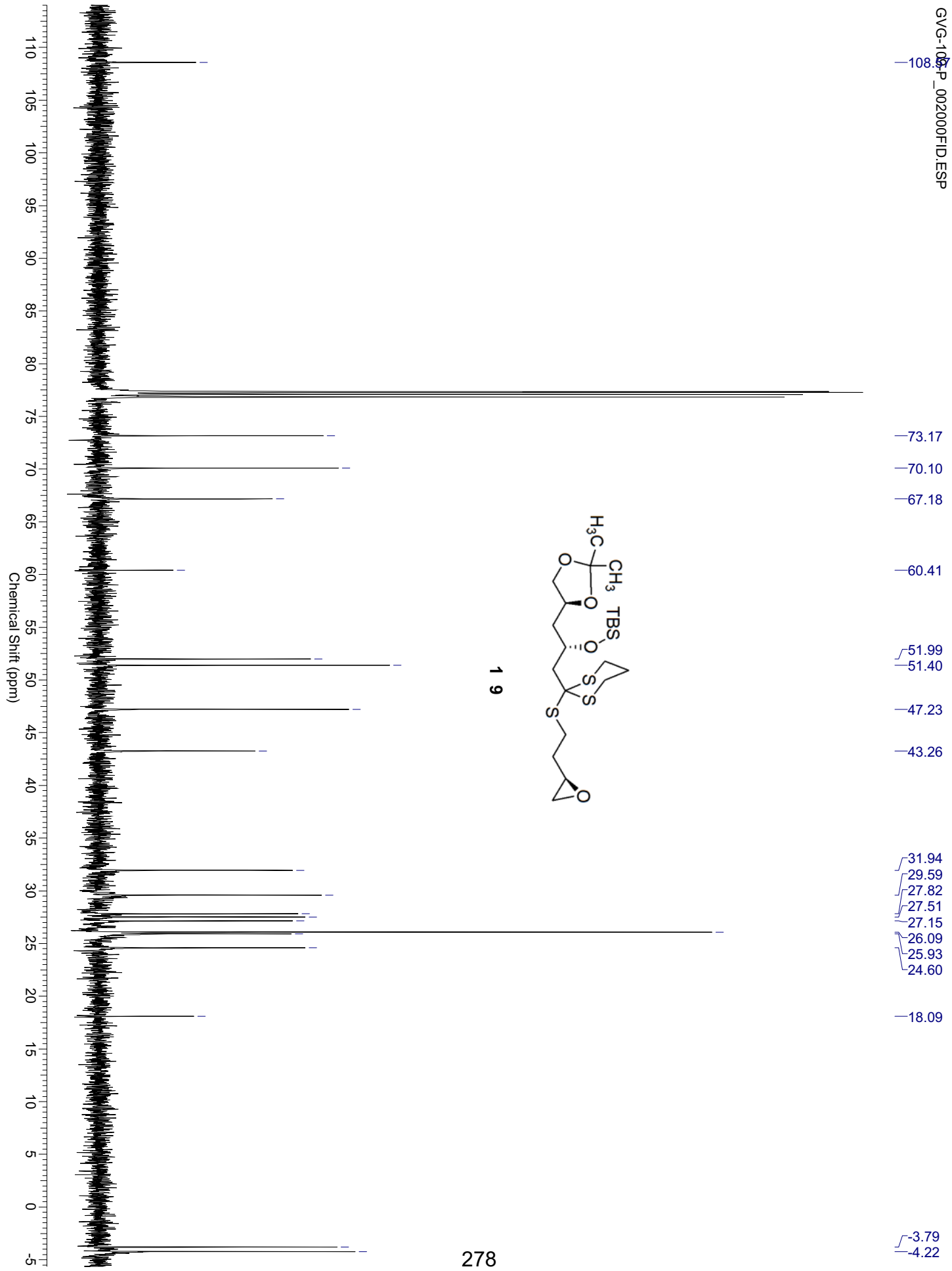
69.30
49.32
47.15
37.09
26.86
25.61
Chemical Shift (ppm)
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25

31



Chemical Shift (ppm)
TBS
19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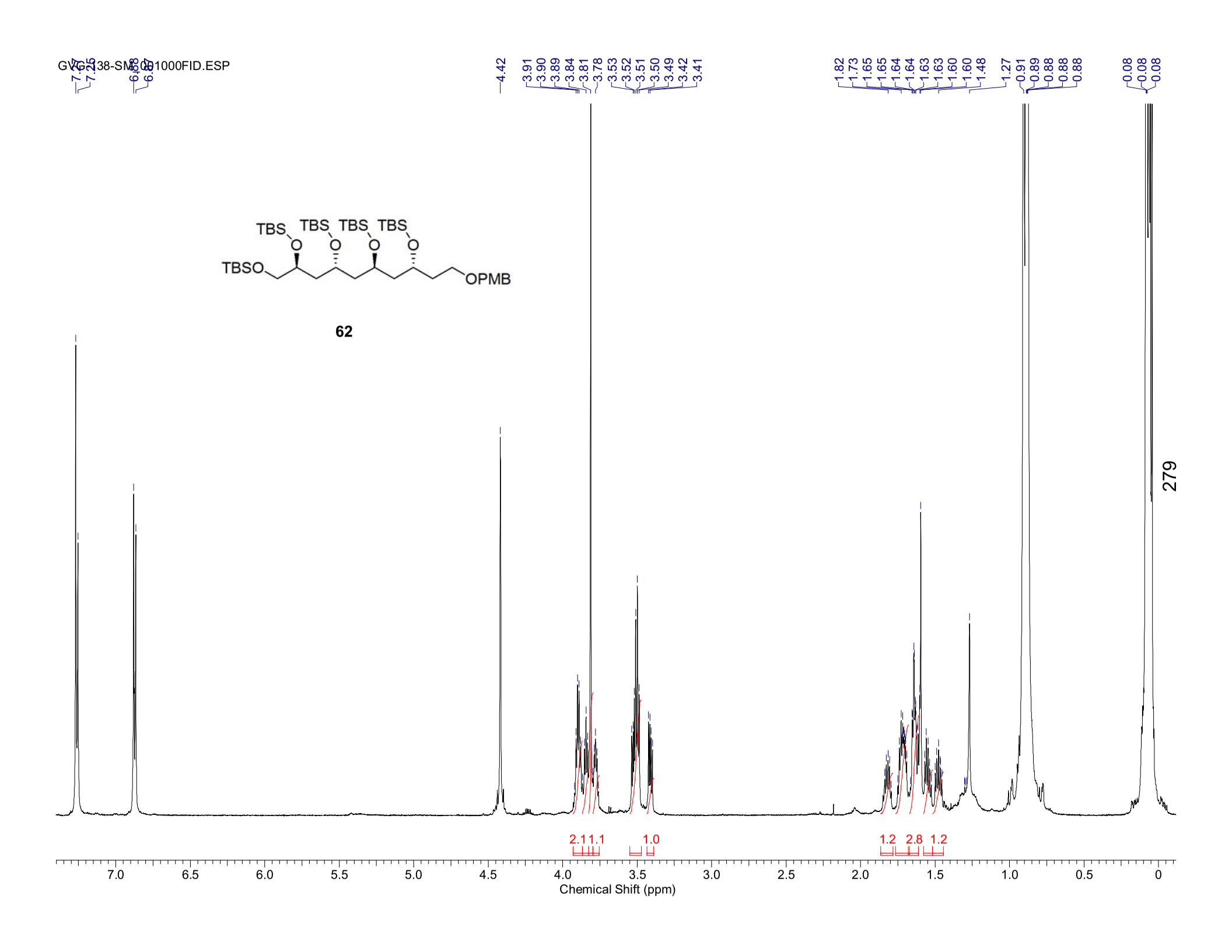
73.17
70.10
67.18
60.41
51.99
51.40
47.23
43.26
31.94
29.59
27.82
27.51
27.15
26.09
25.93
24.60
18.09
-3.79
-4.22
Chemical Shift (ppm)
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
H3C
CH3
TBS
O
S
S
S
O
O
O
1 9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7.27
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6.88
6.87
4.42
3.91
3.90
3.89
3.84
3.81
3.78
3.53
3.52
3.51
3.50
3.49
3.42
3.41
1.82
1.73
1.65
1.65
1.64
1.64
1.63
1.63
1.60
1.60
1.48
1.27
0.91
0.89
0.88
0.88
0.88
0.08
0.08
0.08
TBS
TBS
TBS
TBS
TBSO
OPMB
62
279
2.1
1.1
1.0
1.2
2.8
1.2
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

GVG-138-SM_002000FID.ESP

159.80
130.90
129.22
113.77
72.64
70.78
67.64
67.47
67.40
67.17
66.79
55.34
46.85
45.98
42.56
37.67
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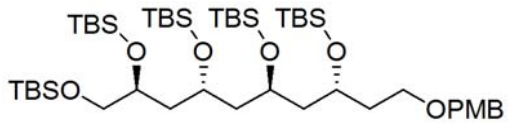
26.07
18.52
18.26
18.17
-3.42
-3.49
-3.67
-4.17
-5.20



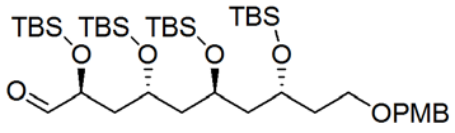
62

280

160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 -8

Chemical Shift (ppm)

GV6513P_001000FID.ESP



69

Chemical Shift (ppm)

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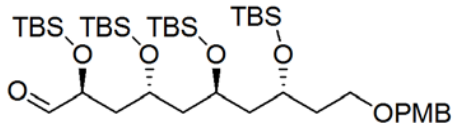
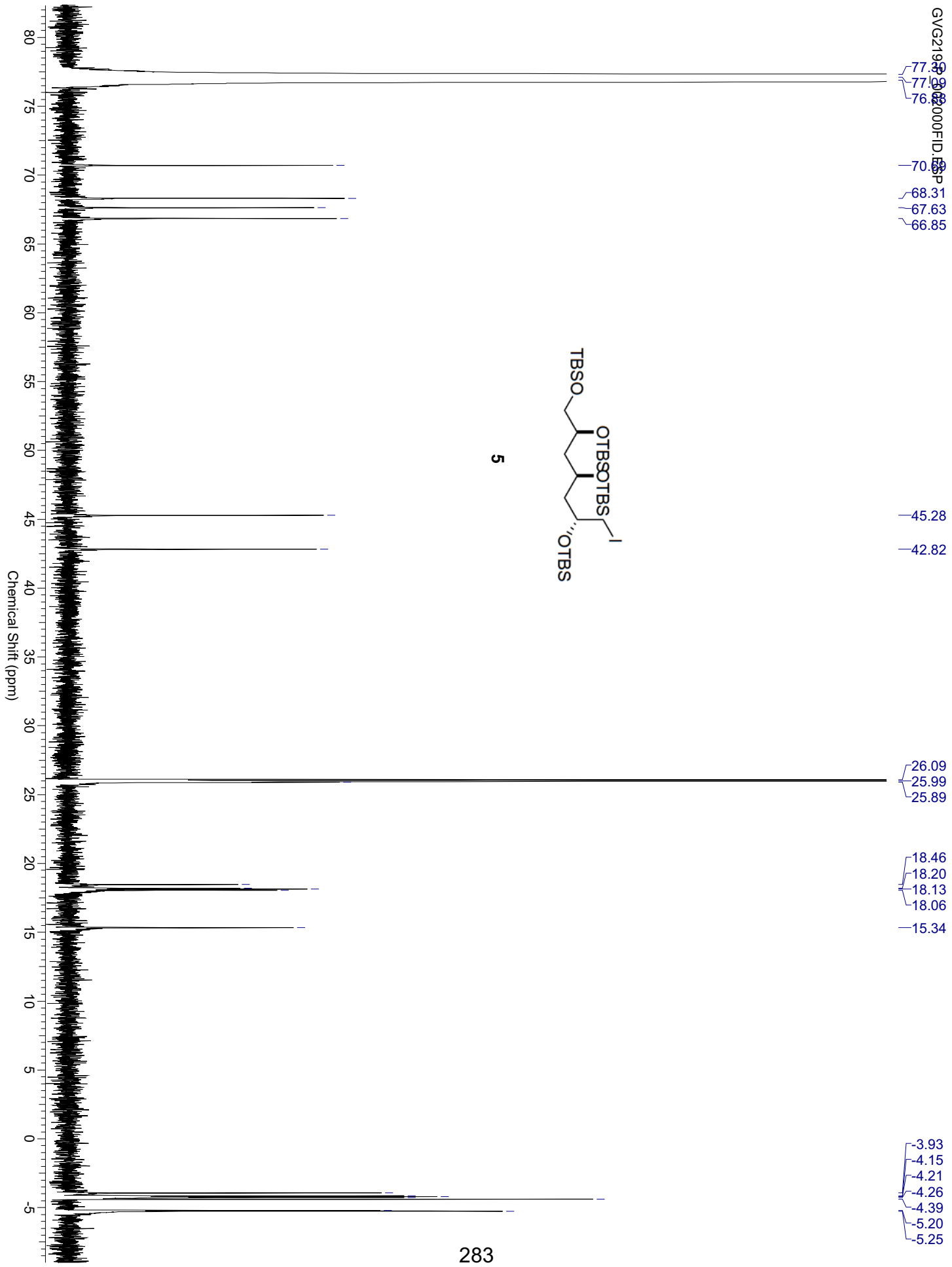


69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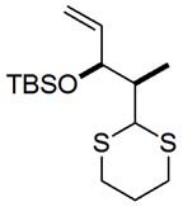
77.30
77.09
76.88
70.69
68.31
67.63
66.85
45.28
42.82
26.09
25.99
25.89
18.46
18.20
18.13
18.06
15.34
-3.93
-4.15
-4.21
-4.26
-4.39
-5.20
-5.25
Chemical Shift (ppm)
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
TBSO
OTBS
OTBS
OTBS
5

GVG347HP_001000FID.ESP



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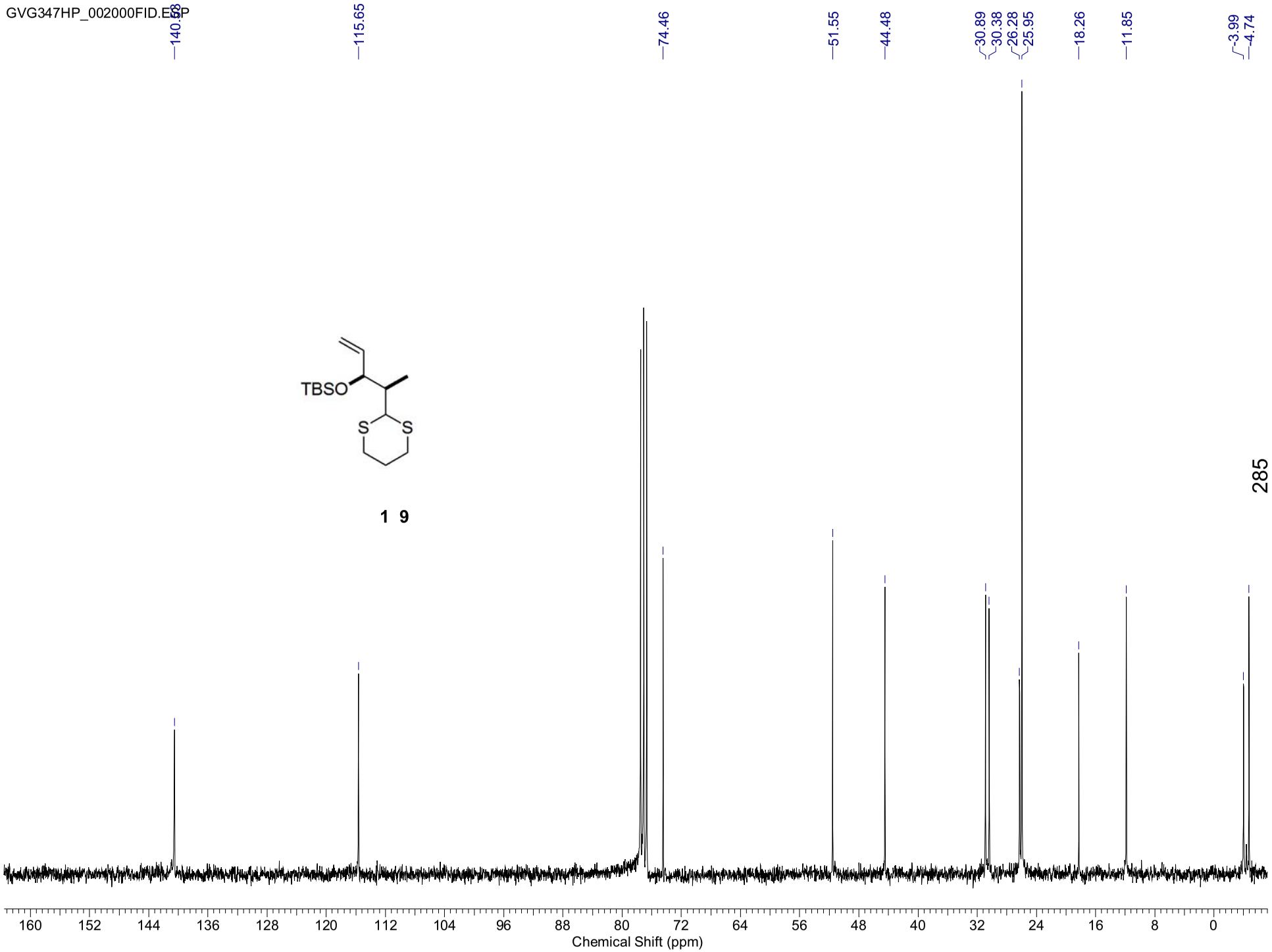

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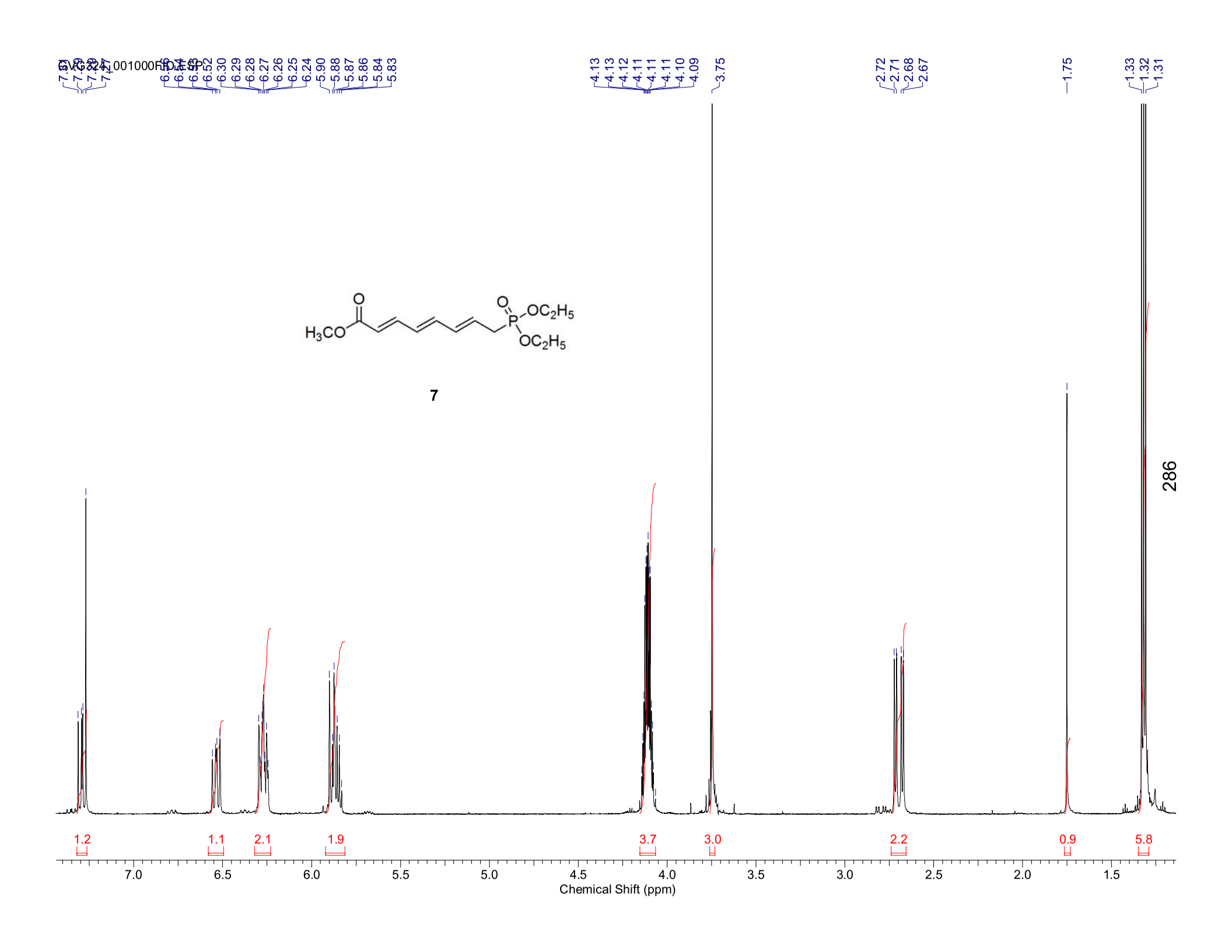
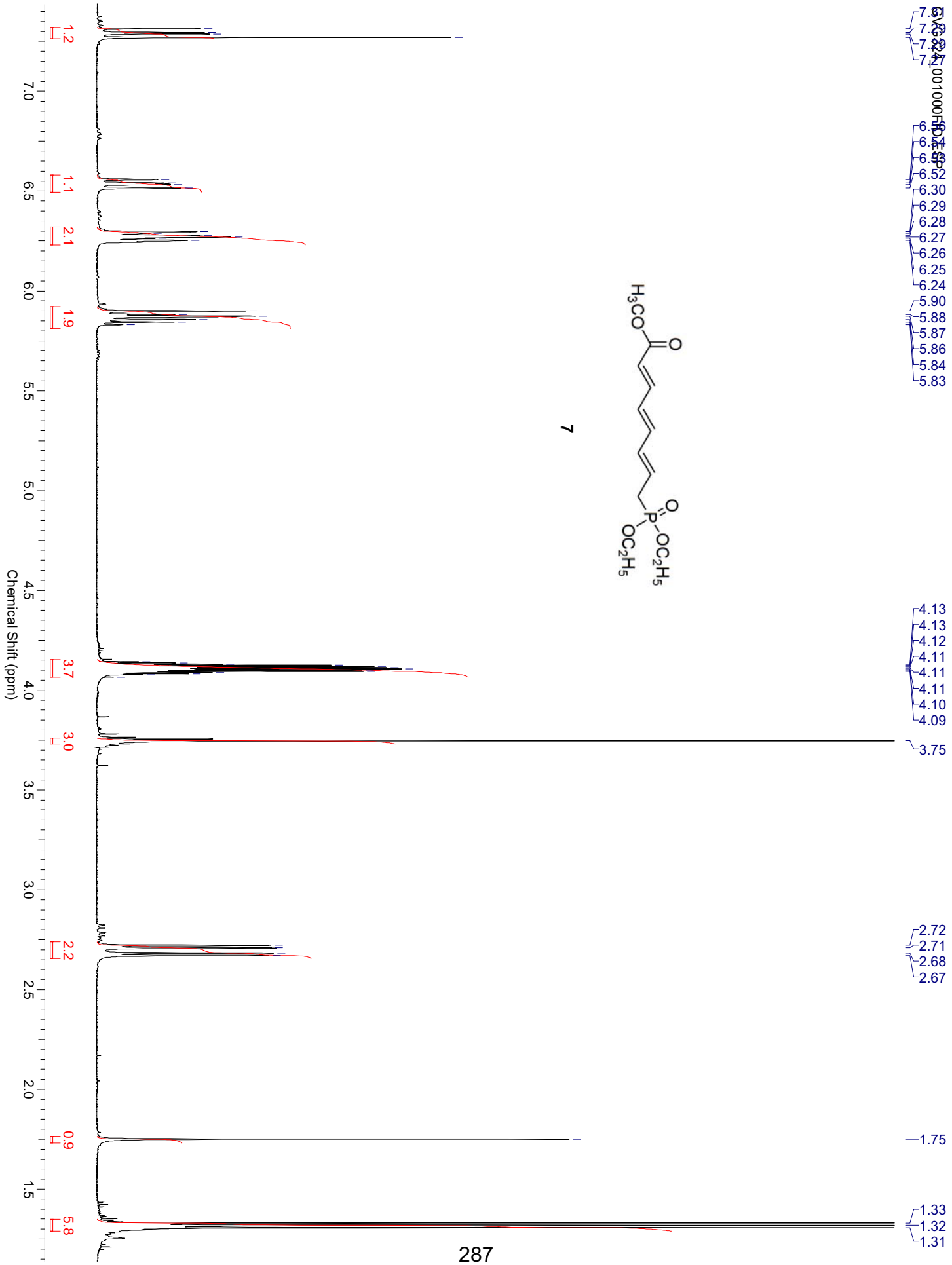
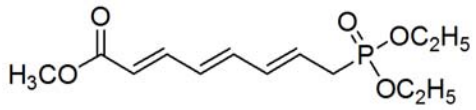

7.31
7.30
7.29
7.27
6.54
6.53
6.52
6.30
6.29
6.28
6.27
6.26
6.25
6.24
5.90
5.88
5.87
5.86
5.84
5.83
4.13
4.13
4.12
4.11
4.11
4.11
4.10
4.09
3.75
2.72
2.71
2.68
2.67
1.75
1.33
1.32
1.31
286
1.2
1.1
2.1
1.9
3.7
3.0
2.2
0.9
5.8
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

7


7.51
7.49
7.39
7.17
6.64
6.52
6.30
6.29
6.28
6.27
6.26
6.25
6.24
5.90
5.88
5.87
5.86
5.84
5.83
4.13
4.13
4.12
4.11
4.11
4.11
4.10
4.09
3.75
2.72
2.71
2.68
2.67
1.75
1.33
1.32
1.31
1.2
1.1
2.1
1.9
3.7
3.0
2.2
0.9
5.8
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)
H3CO
O
OC2H5
P
OC2H5
7

GVG324_002000FID.ESP

167.46
144.44
139.79
139.76
134.34
134.23
129.63
127.41
127.32
120.87
62.16
51.60
31.71
30.79
16.54

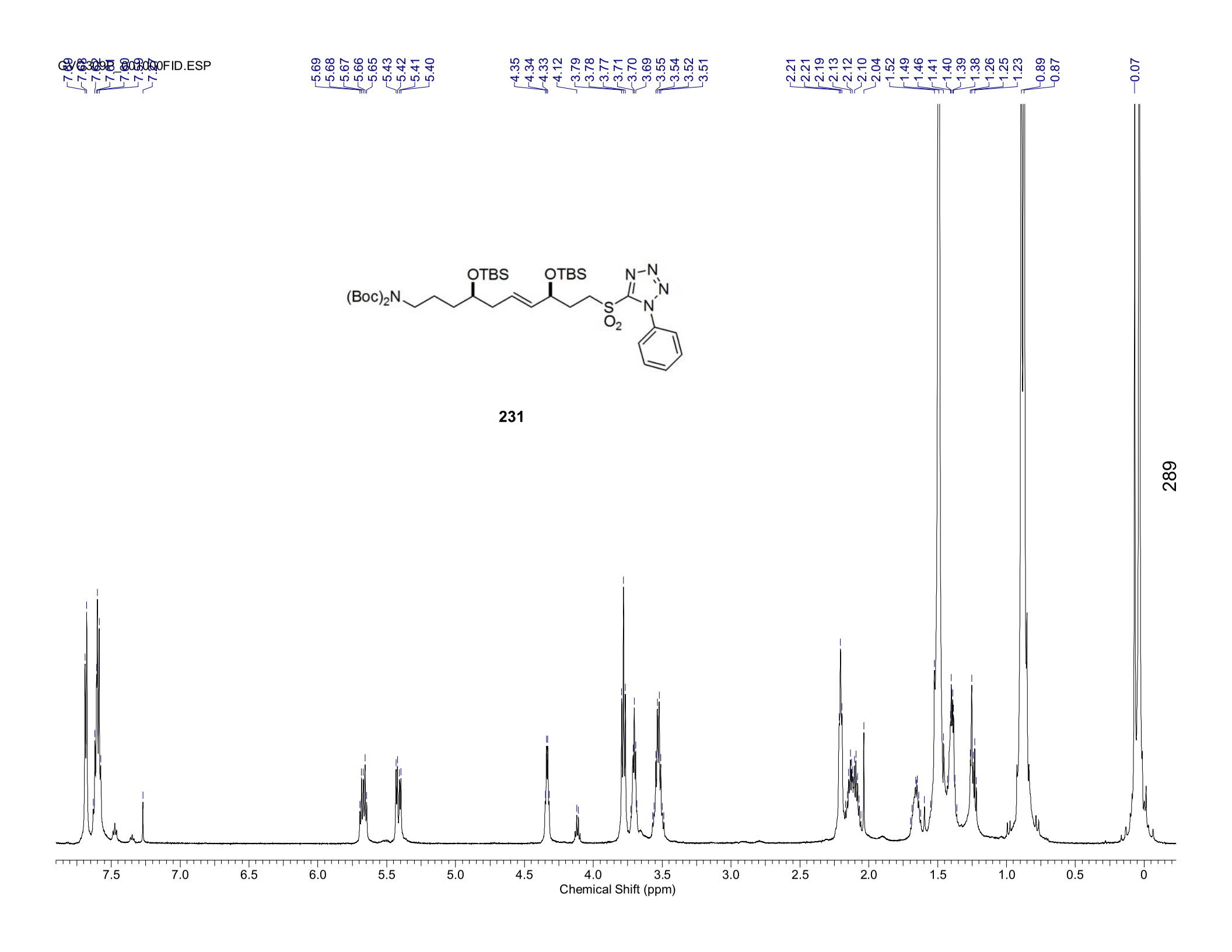


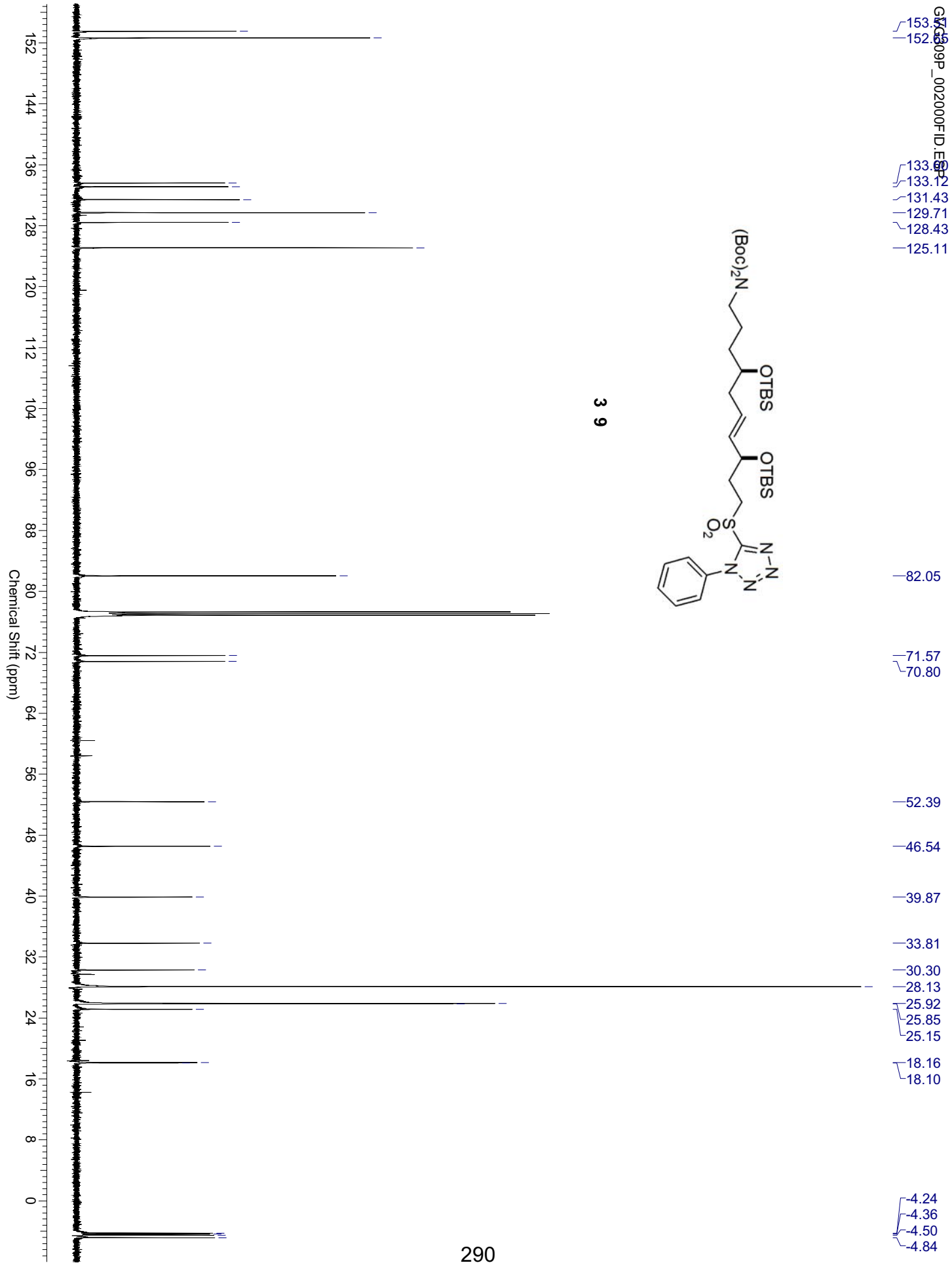
324

288

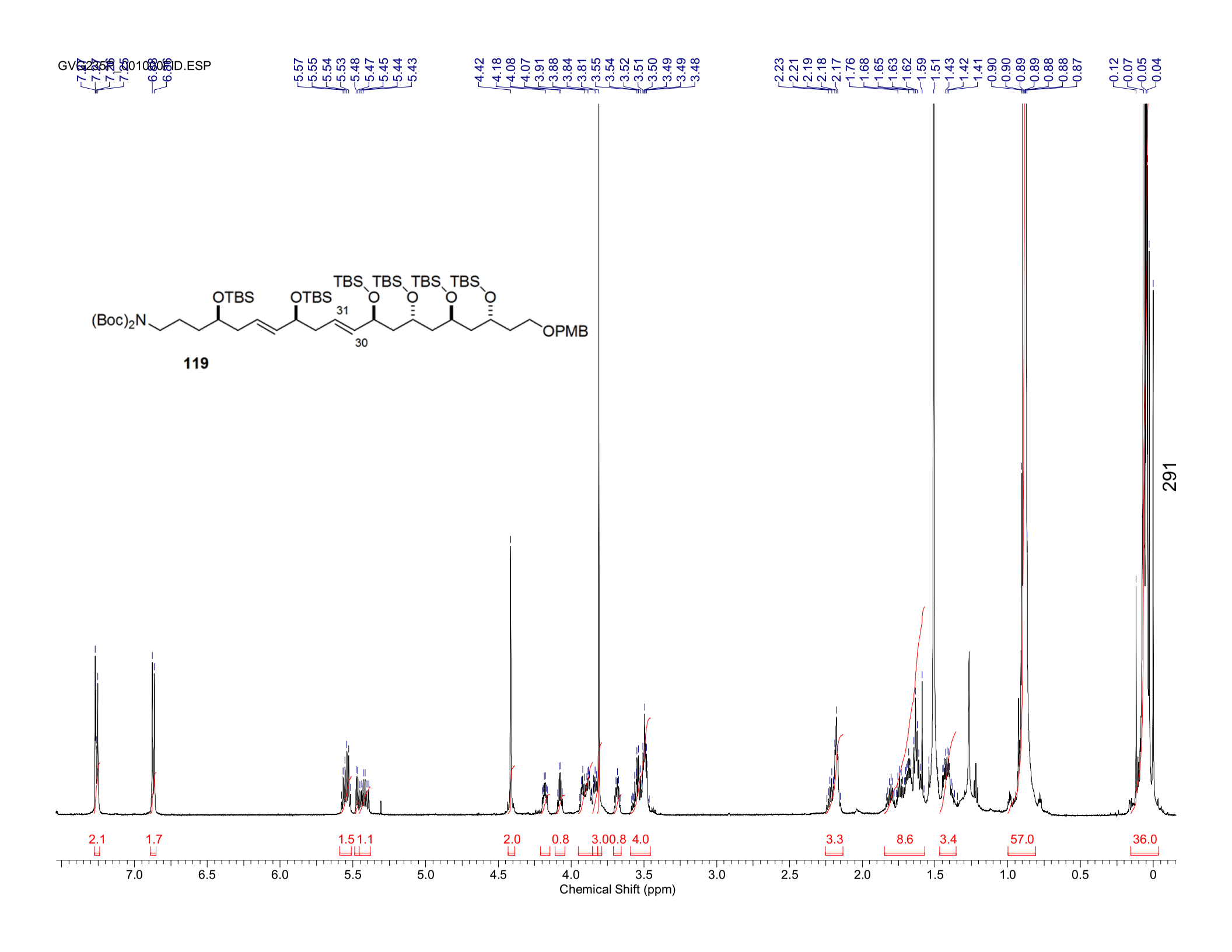
168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16

Chemical Shift (ppm)


OTBS
OTBS
(Boc)2N
N
N
N
S
O2
231
289
Chemical Shift (ppm)

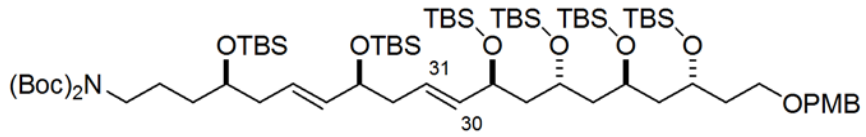

GM-Q309P_002000FID.ESP
153.57
152.85
133.68
133.12
131.43
129.71
128.43
125.11
82.05
71.57
70.80
52.39
46.54
39.87
33.81
30.30
28.13
25.92
25.85
25.15
18.16
18.10
-4.24
-4.36
-4.50
-4.84
Chemical Shift (ppm)
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
(Boc)2N
OTBS
OTBS
S
O2
N
N
N

3 9


OTBS
OTBS
TBS
TBS
TBS
TBS
(Boc)2N
OPMB
31
30
119
Chemical Shift (ppm)
291

gvg314cr_002000fid.esp

159.1
152.7
136.3
135.6
130.9
129.2
126.7
126.4
113.8
82.1
73.5
72.6
72.0
71.1
67.5
67.2
67.1
66.8
55.3
46.7
41.6
40.2
37.9
33.8
28.2
26.2
26.0
18.3
18.3
18.2
-3.3
-3.4
-3.7
-4.1
-4.2
-4.5



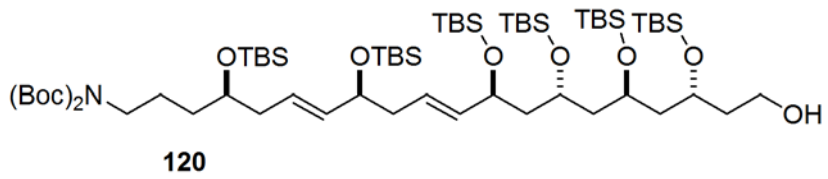
119

292

192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 -8

Chemical Shift (ppm)

GVG317P_001009FID.ESP1.ESP



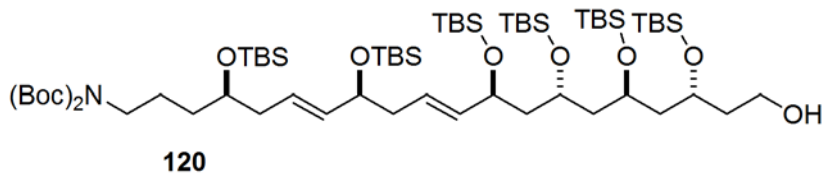
120

293

Chemical Shift (ppm)

GVG317P_002000FID.ESP

152.7
136.0
135.5
126.8
126.5
82.0
73.5
72.0
71.1
69.5
67.4
67.1
60.3
47.2
46.7
46.4
45.3
41.6
40.2
38.5
33.8
31.7
28.2
26.1
26.0
25.3
22.7
18.3
18.1
18.1
14.2
-3.4
-3.6
-4.2
-4.3
-4.5
-4.6



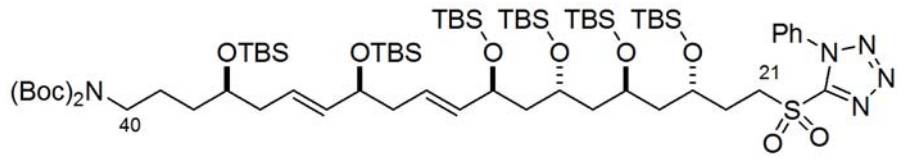
120

294

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

Chemical Shift (ppm)

GVG318P_201000H1ESP



121

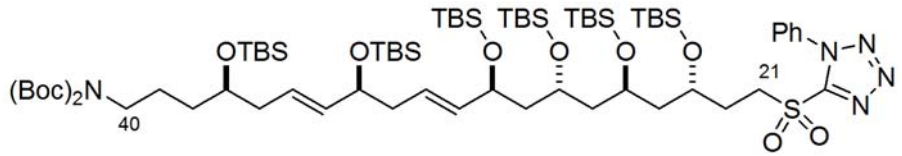
295

2.8 2.0 1.0 2.1 1.1 1.1 2.1 5.5 1.2 8.6 5.5 65.6 41.5

Chemical Shift (ppm)

GVG318P_002000FID.ESP

153.5
152.7
136.2
135.6
133.2
131.5
129.8
126.9
126.4
125.1
82.0
73.5
72.0
71.0
67.5
67.2
66.8
52.2
46.9
46.7
46.5
44.7
41.6
40.2
33.8
30.0
28.2
26.1
26.0
26.0
25.3
18.3
18.3
18.1
18.1
14.2
-3.2
-3.3
-4.2
-4.3



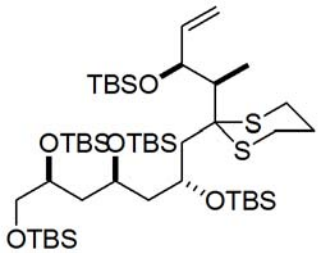
121

296

192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0

Chemical Shift (ppm)

GVG301P_001000FID.ESP



122

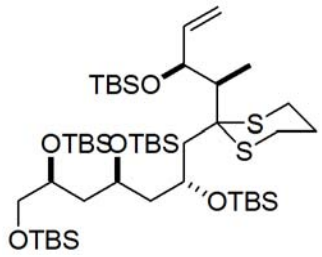
297

1.0 1.2 1.1 1.1 1.2 1.1 1.2 2.3 2.3 1.1 3.7 6.7 3.6 59.9 3.3 3.6

7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

Chemical Shift (ppm)

GVG301P1.002000FID.ESP

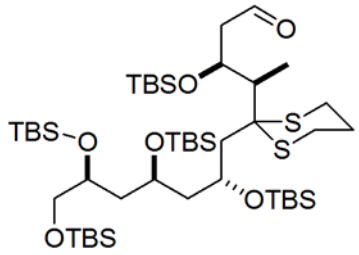


122

298

Chemical Shift (ppm)

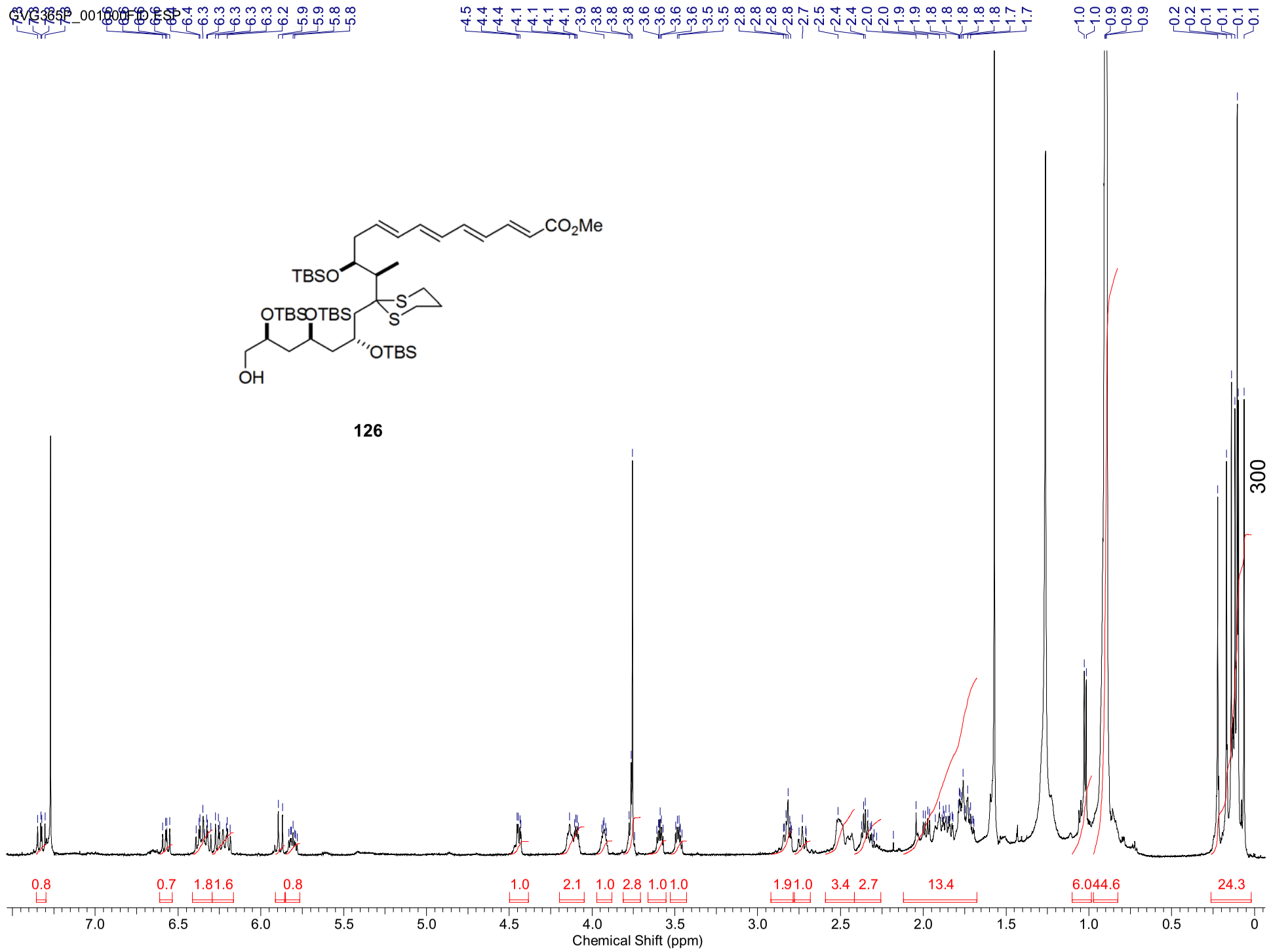
GYG326P_001000FID.ESP

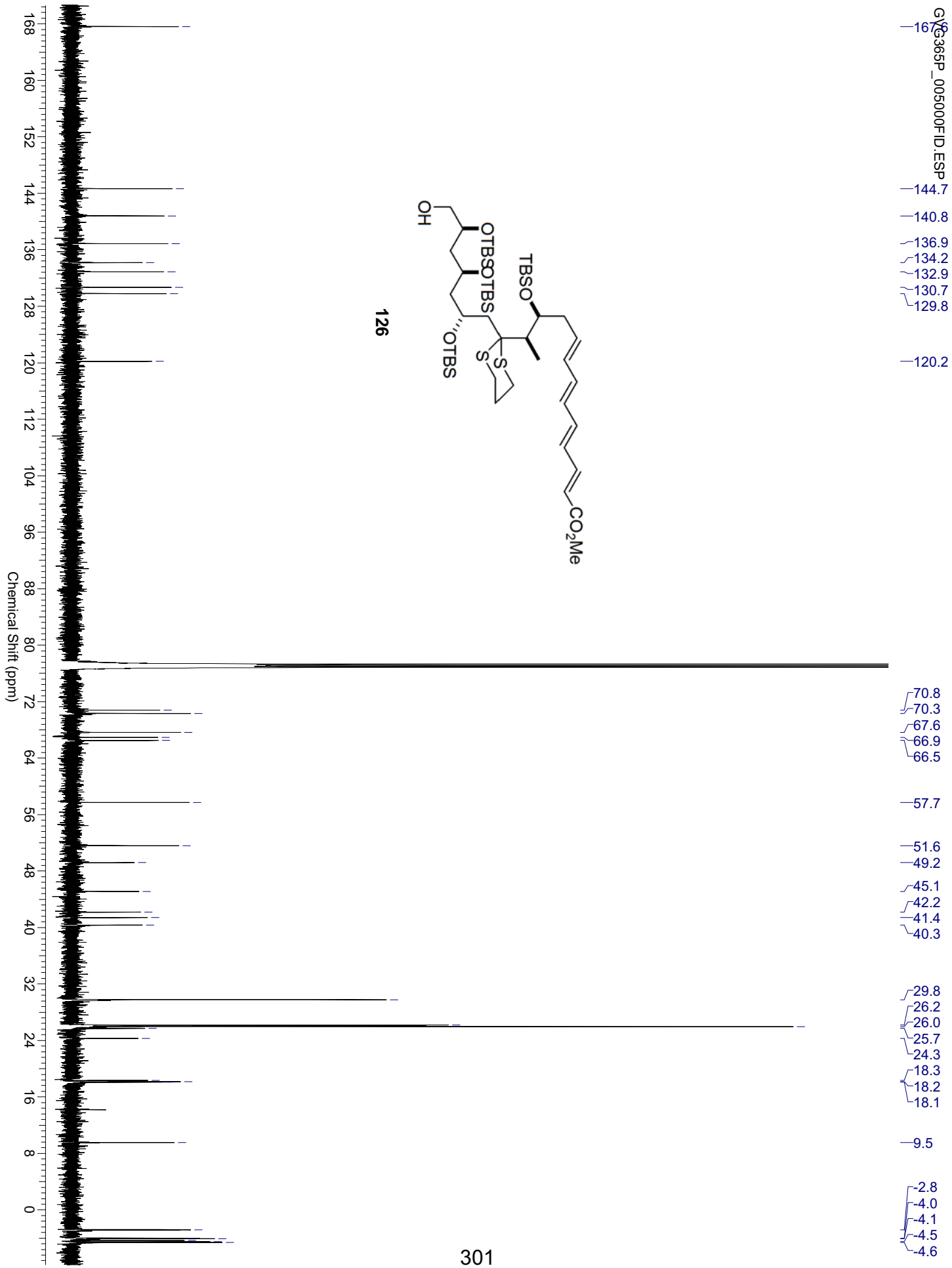


124

299

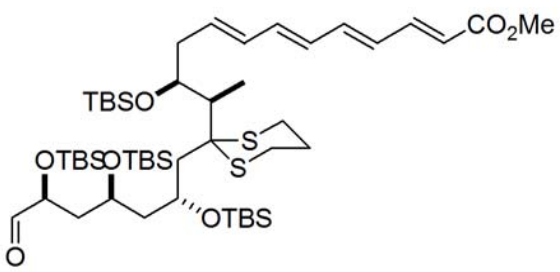
Chemical Shift (ppm)


CVG365F_001D01F1D1ESP
CO2Me
TBSO
OTBS
OTBS
S
S
OTBS
OH
126
300
0.8
0.7
1.8
1.6
0.8
1.0
2.1
1.0
2.8
1.0
1.0
1.9
1.0
3.4
2.7
13.4
6.0
4.6
24.3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


GYG365P_005000FID.ESP
Chemical Shift (ppm)
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
167.6
144.7
140.8
136.9
134.2
132.9
130.7
129.8
120.2
70.8
70.3
67.6
66.9
66.5
57.7
51.6
49.2
45.1
42.2
41.4
40.3
29.8
26.2
26.0
25.7
24.3
18.3
18.2
18.1
9.5
-2.8
-4.0
-4.1
-4.5
-4.6
OH
OTBS
OTBS
OTBS
TBSO
S
S
CO2Me

126

GVG366P_001000FID.ESP



127