# Fluorous mixture synthesis of four stereoisomers of the C21-C40 fragment of tetrafibricin and efforts towards total synthesis of tetrafibricin

by

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Efforts towards the synthesis of natural product tetrafibricin and its stereoisomers are described. Retrosynthesis of the framework of tetrafibricin gives 6 fragments, C1-C8, C9-C13, C14-C20, C21-C30, C31-C34 and C35-C40. Chapter 2 describes the fluorous mixture synthesis of four stereoisomers of the C21–C40 fragment with the aid of fluorous tagging to encode configurations at C37 and C33. After demixing and detagging, the isomers were found to have substantially identical $^{1}H$ NMR spectra. However, there were some small but reliable differences in their $^{13}C$ NMR spectra.

Chapter 3 describes efforts towards total synthesis of tetrafibricin. After making the 6 fragments, different sequences of fragment coupling by a series of Julia-Kocienski reactions were attempted. First the alkylation of dithiane C9-C13 with iodide C14-C20 provided C9-C20 carbon skeleton. Then the first Julia-Kocienski olefination with sulfone C21-C30 and aldehyde C9-C20 gave olefin C9-C30, which was then advanced to aldehyde to attempt another Julia-Kocienski olefination. Fragment C31-C40 was also achieved by Julia-Kocienski olefination of sulfone C35-C40 with aldehyde C31-C34. Then the two big parts, aldehyde C9-C30 and sulfone C31-C40, were coupled together to afford fragment C9-C40 by Julia-Kocienski olefination. Finally, Horner-Wadsworth-Emmons olefination of phosphonate C1-C8 with aldehyde C9-C40 provided C1-C40 to achieve the whole carbon framework 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 |
| **DCM** | Dichloromethane |
| **DDQ** | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |
| **DIAD** | Diisopropylazodicarboxylate |
| **DIBAL-H** | Diisobutylaluminum hydride |
| **DMAP** | Dimethylaminopyridine |
| **DMF** | Dimethylformamide |
| **DMSO** | Dimethyl sulfoxide |
| ***ee*** | Enantiomeric excess |
| **Et** | Ethyl |
| **EtOAc** | Ethyl acetate |
| **FMS** | Fluorous mixture synthesis |
| **HKR** | Hydrolytic kinetic resolution |
| **HMPA** | Hexamethylphosphoramide |

| | |
|---|---|
| **HPLC** | High performance liquid chromatography |
| **HRMS** | High resolution mass spectrometry |
| **IR** | Infrared spectrometry |
| **$IC_{50}$** | Inhibitor concentration necessary to produce 50% inhibition |
| **KHMDS** | Potassium bis(trimethylsilyl)amide |
| **LiHMDS** | Lithium bis(trimethylsilyl)amide |
| **MS** | Low resolution mass spectrometry |
| ***m*-CPBA** | *m*-chloroperbenzoic acid |
| **Me** | Methyl |
| **NMR** | Nuclear magnetic resonance |
| **Ph** | Phenyl |
| **PMB** | *p*-Methoxybenzyl |
| **Pr** | Propyl |
| **PTSH** | 1-Phenyl-1*H*-tetrazole-5-thiol |
| **Pyr** | Pyridine |
| **$R_f$** | Perfluoroalkyl |
| **TBAF** | Tetrabutylammonium fluoride |
| **TBAI** | Tetrabutylammonium iodide |
| **TBS** | *t*-Butyldimethylsilyl |
| **THF** | Tetrahydrofuran |
| **TLC** | Thin layer chromatography |

## PREFACE

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# Chapter 1. Introduction to tetrafibricin and fluorous mixture synthesis

## 1.1 Tetrafibricin

Platelet aggregation plays a key role during normal haemostasis and thrombosis.[1] When stimulated by an agonist such as ADP, collagen or thrombin, the fibrinogen receptors (GPIIb/IIIa) on the platelet surface acquire the high–affinity fibrinogen binding function. Platelets then adhere to the disrupted subenddothethial surface at the sites of vascular lesion. The adherent platelets subsequently release biologically active constituents and aggregate. Interaction of fibrinogen with the GPIIb/IIIa receptor site is essential for normal platelet function. Thus, fibrinogen receptor antagonism is a good mechanism for a platelet aggregation inhibitor.

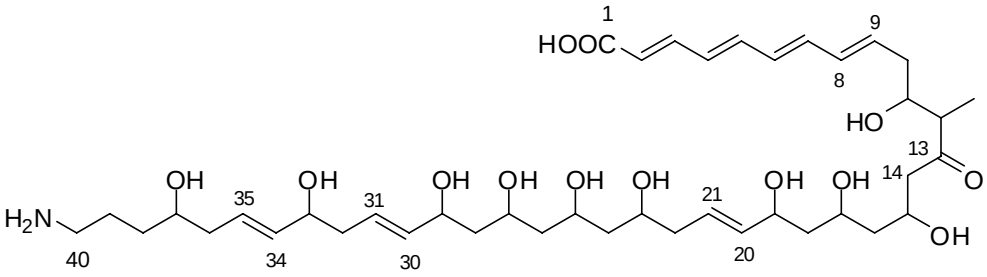
In recent years, many types of fibrinogen receptor antagonists have been reported.[2] Most are peptide mimetics of RGDS (Arg-Gly-Asp-Ser), which is the minimal sequence in fibrinogen that is considered necessary to recognize fibrinogen receptors during aggregation. The disadvantages of the peptide mimetic are the reduced affinity to the receptor and much shorter half-life in vivo. Therefore, the search for non-peptide platelet aggregation inhibitors of microbial origin is important.

Tetrafibricin is a novel nonpeptidic fibrinogen receptor inhibitor isolated from the culture broth of *Streptomyces neyagawaensis* NR0577.[3] Tetrafibricin competitively inhibited (Ki = 9.9 nM) the binding of biotinylated fibrinogen to purified active glycoprotein GPIIb/IIIa immobilized on plastic plates. Tetrafibricin strongly inhibited the binding of fibrinogen to its receptors with an $IC_{50}$ of 46 nM. It also inhibited ADP-, collagen-, and thrombin-induced

aggregation of human platelets with $IC_{50}$'s of 5.6, 11.0 and 7.6 μM, respectively. The ability of tetrafibricin to block fibrinogen from binding to its glycoprotein receptor makes it a candidate for the potential therapeutic intervention of arterial thrombotic diseases such as coronary occlusion.[4]

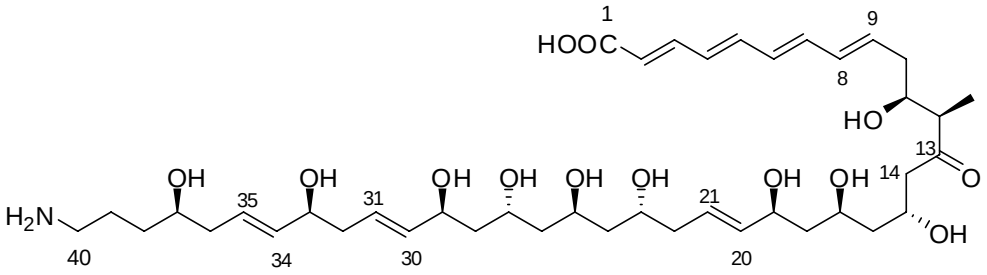
The Kamiyama group elucidated the structure of tetrafibricin by carrying out various NMR, MS and other experiments.[5] The molecular formula was determined as $C_{41}H_{67}NO_{13}$ from HRFAB-MS (Calcd: 782.4691, Found: *m/z* 782.4676 $(M + H)^+$). Positive color reactions to ninhydrin and 2,4-dinitrophenylhydrazine suggested the presence of primary amino and carbonyl groups, respectively. The IR spectrum of tetrafibricin suggested the presence of carboxyl and/or carbonyl groups (3000-2500, 1710 $cm^{-1}$) along with hydroxyl and/or amino groups (3400, 1100-1000 $cm^{-1}$). UV data indicated the presence of a conjugated tetraenoic acid chromophore. Due to the instability of tetrafibricin in DMSO-$d_6$, a $D_2O$ solution of tetrafibricin purged with argon was used for the NMR experiments. A combination of the $^1H$ NMR, $^{13}C$ NMR, $^1H$-$^1H$ COSY, HSQC and HMBC experiments were used to deduce partial structures. Additional NMR experiments on a solution of *N*-acetyldihydrotetrafibricin methyl ester in DMSO-$d_6$ were carried out to establish the complete connectivity of the partial structures. The 2D-dimension structure of tetrafibricin as proposed by the Kamiyama group is shown in Figure 1.1.

**Figure 1.1 Kamiyama's 2D Structure of tetrafibricin**




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 or derivatization.[6] They have demonstrated the feasibility, reliability, and applicability of this approach in the stereochemical assignment of the desertomycin/oasomycin class of natural products, as well as the mycolactones.[7] 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 1.2).[8]

**Figure 1.2 Kishi's 3D structure of tetrafibricin**



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.

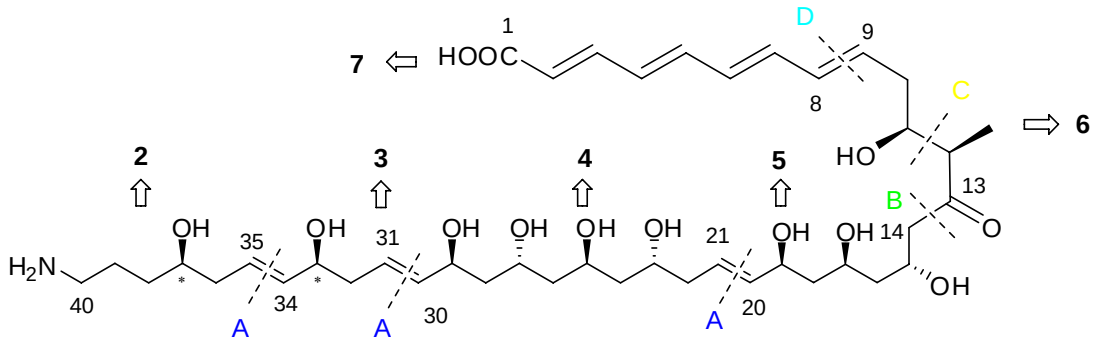
To our knowledge, there is no total synthesis of tetrafibricin. Only three papers have been published towards the total synthesis of tetrafibricin. Cossy's group synthesized the C1-C13, C15-C25, C27-C40 fragments of tetrafibricin by a sequence of chemoselective cross-metathesis reactions and enantioselective allyltitanations of aldehydes.[9] Roush's group reported the synthesis of the C1-C19 fragment of tetrafibricin via a highly diastereoselective double allylboration developed in their laboratory.[10] Very recently, Friestad's group synthesized the C27-C40 fragment of tetrafibricin by asymmetric catalysis to install the oxygen-bearing stereogenic centers to afford 1,5-polyols.[11]

### 1.2 Previous work on tetrafibricin in Curran group

The former Curran group member Dr. Venugopal Gudipati made significant progress towards traditional synthesis of tetrafibricin.[12] The retrosynthetic analysis of tetrafibricin is outlined in Scheme 1.1. It was envisioned that a series of Julia-Kocienski olefination reactions would couple fragments **2**, **3**, **4**, **5** together to form bonds C20-C21, C30-31 and C34-C35. Bond C13-C14 can be formed by alkylation of anion of dithiane with iodide between fragments C14-C20 and C9-

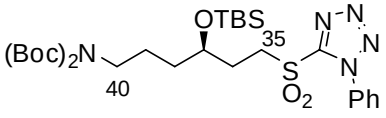
C13. The C8-C9 bond can be connected through Horner-Wadsworth-Emmons (HWE) olefination between fragments **6** and **7.**

**Scheme 1.1 Retrosynthesis of tetrafibricin**

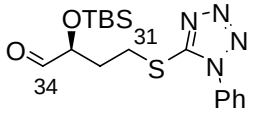



**1**, Tetrafibricin

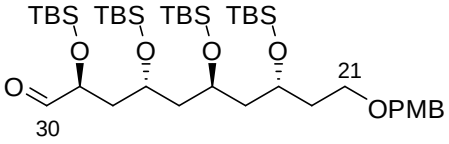
A = Kocienski-Julia olefination; B = Dithiane alkylation; C = Asymmetric aldol; D = HWE olefination



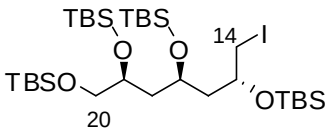

**2**



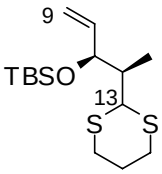

**3**



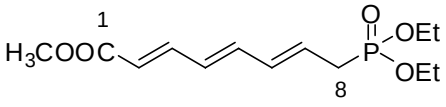

**4**




**5**




**6**

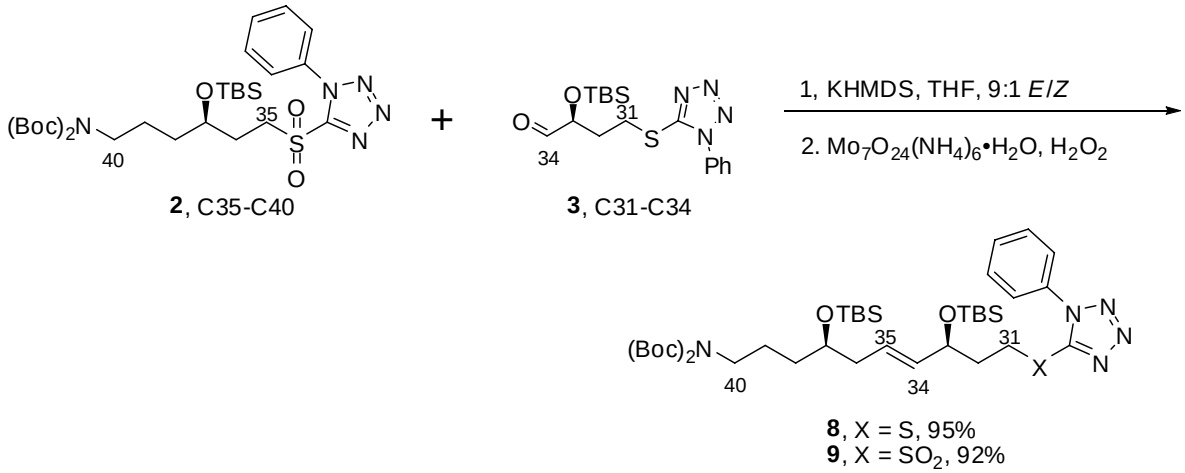



**7**

Dr. Gudipati successfully synthesized all six fragments **2-7**. The synthesis of the bottom fragment C21-C40 **13** of tetrafibricin from **2**, **3** and **4** is shown in Scheme 1.2. With fragments **2** and **3** in hand, Julia-Kocienski olefination was accomplished to give alkene **8** in a 9:1 *E*/*Z* isomeric mixture in 95% yield.[13] Pure (*E*)-isomer was obtained by preparative chiral HPLC. The

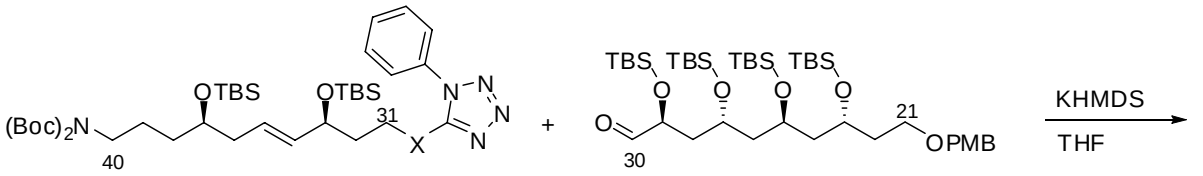
smooth conversion of sulfide to sulfone **9** was accomplished with Mo-catalyst ($Mo_7O_{24}(NH_4)_6$•$H_2O$, $H_2O_2$) in 92% yield.[14] Another Julia-Kocienski olefination reaction between the sulfone **9** and aldehyde **4** provided the PMB-ether as a sole C(30,31) (*E*)-olefinic isomer **10** in 94% yield. Removal of PMB protecting group (DDQ, pH 7 buffer, $CH_2Cl_2$) gave the primary alcohol **11** in 88% yield.[15] Incorporation of the thiotetrazole via the Mitsunobu reaction,[16] employing commercially available 1-phenyl-1*H*-tetrazole-5-thiol, followed by oxidation ($Mo_7O_{24}(NH_4)_6$•$H_2O$, $H_2O_2$) of the derived sulfide furnished sulfone **13** (C21-C40) with 65% yield in two steps.

**Scheme 1.2 Synthesis of the C21-C40 fragment**

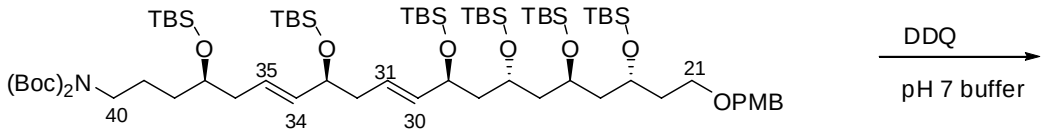



**2**, C35-C40 **3**, C31-C34

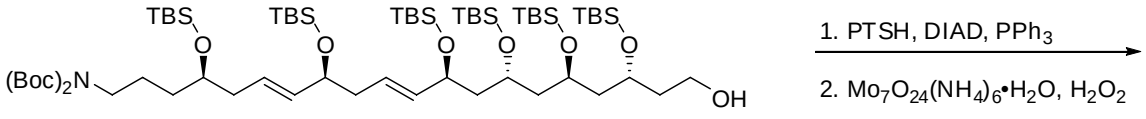
**8**, X = S, 95%
**9**, X = $SO_2$, 92%



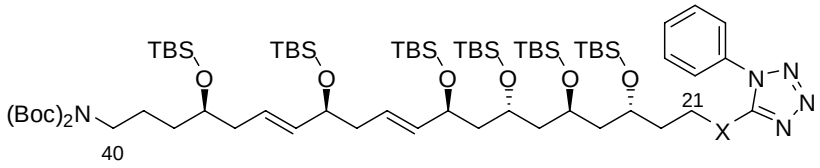

**9**, C31-C40 **4**, C21-C30




**10**, C21-C40, 94%



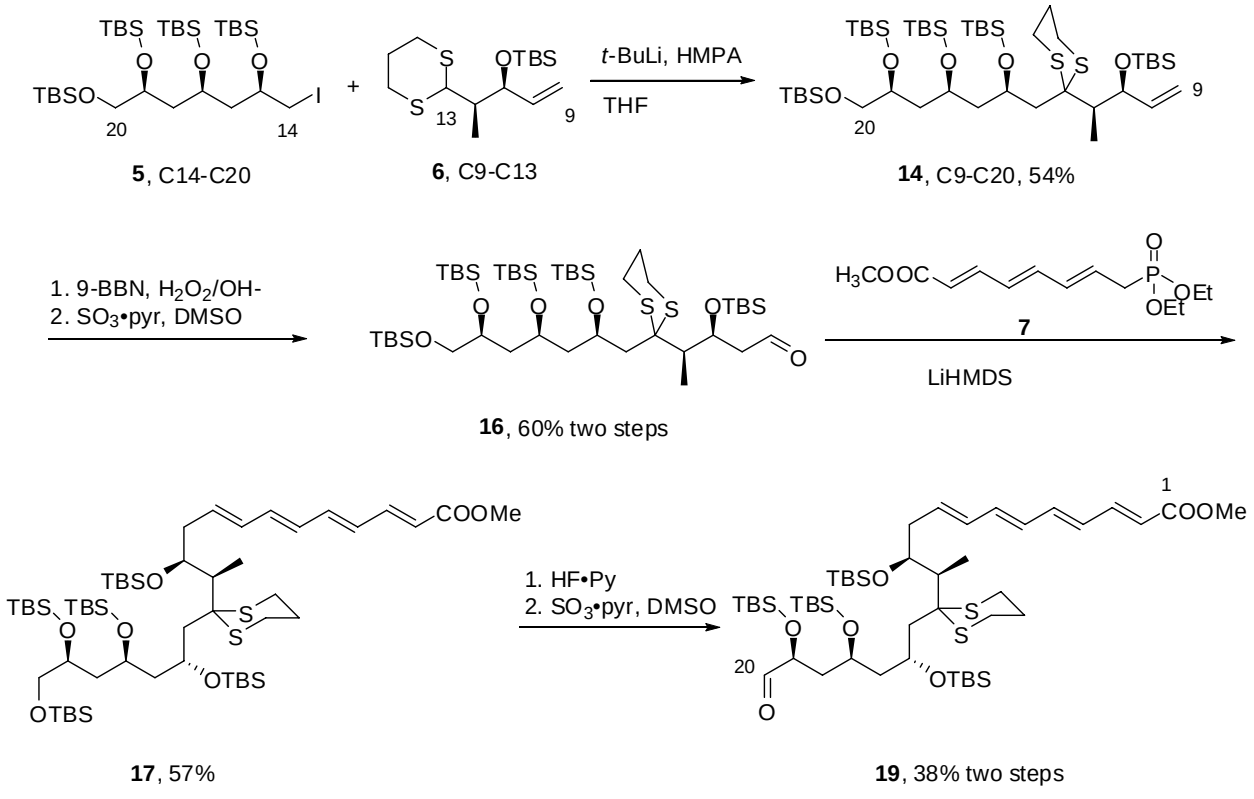

**11**, 89%




**12**, X = S
**13**, X = $SO_2$, C21-C40, 65% two steps

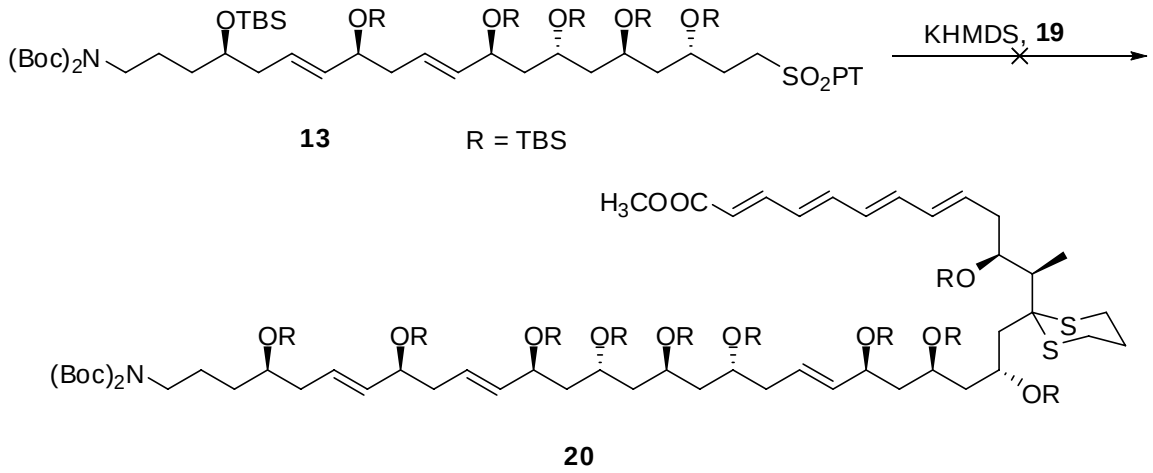
The synthesis of the top fragment C1-C20 **19** from **5**, **6** and **7** is shown in Scheme 1.3. Deprotonation of dithiane **6** with *t*-BuLi followed by addition of iodide **5** to the reaction mixture provided the target alkene **14** in 54% yield. Hydroboration/oxidation of alkene provided the primary alcohol **15** in 68% yield. Oxidation of the primary alcohol with $SO_3$•pyr provided aldehyde **16** in 88% yield. The olefination step was then carried out by deprotonation of phosphonate **7** with LiHMDS followed by adding aldehyde **16** to afford the conjugated methyl ester **17** in 57% yield. The primary TBS-ether was cleaved with HF•pyr to provide the primary alcohol **18** in modest yield (45%). Oxidation of alcohol to aldehyde **19** (C1-C20) was then carried out with $SO_3$•pyr (85% yield).

**Scheme 1.3 Synthesis of the C1-C20 fragment**



The final coupling between **13** (C1-C20) and **19** (C21-C40) was attempted by deprotonating the sulfone with KHMDS at −78 $^{o}$C, followed by addition of aldehyde. Unfortunately, coupled product **20** was not observed (Scheme 1.4).

**Scheme 1.4 Final coupling of fragments C1-C20 and C21-C40**

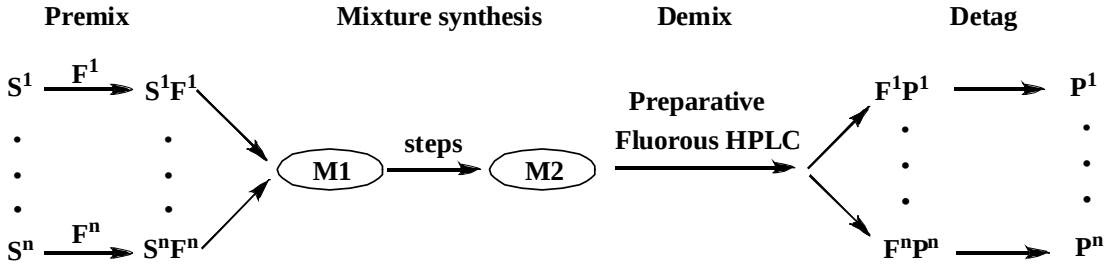



## 1.3 Fluorous mixture synthesis (FMS)

Fluorous mixture synthesis (FMS), reported by the Curran group in 2001, was the first example of solution-phase mixture synthesis with separation tags.[17] In FMS, a series of organic substrates is tagged with a series of fluorous tags of increasing fluorine content. Fluorous tags are usually perfluoroalkyl modified versions of traditional protecting groups. A typical FMS consists of the following steps (Scheme 1.5): 1) Premix: a set of substrates individually are attached to a corresponding set of homologous fluorous tags with increasing fluorine content; 2) Mixture

synthesis: the fluorous-tagged substrates are mixed in one pot and the mixture is conducted through a multi-step synthesis in one-pot or in split-parallel fashion; 3) Demix: the mixture of fluorous tagged products are demixed based on the fluorine content by preparative fluorous HPLC; 4) Detag: the fluorous groups are removed to form the final products.

**Scheme 1.5 Schematic diagram of FMS**




**S = substrate, F = fluorous tag, M = mixture, P = product**

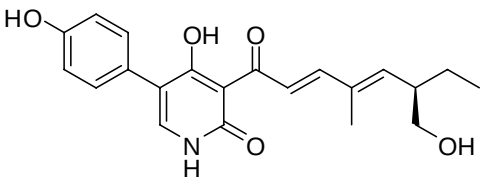
During the past few years, many natural products and their analogs have been made by FMS (Scheme 1.6). If there is only one stereocenter in the target molecule, then the two enantiomeric precursors are tagged with two fluorous different tags to make the quasienantiomers. Then the quasienantiomers are mixed to make a quasiracemate that is conducted through the synthesis. After the steps of demixing and detagging, the two target enantiomers are obtained as pure compounds. The syntheses of mappicine and pyridovericin highlight this application.[18]

When there is more than one stereocenter in the molecule, different tagging strategies are used for FMS. Initially, one tag was used for each isomer. For example, four different fluorous tags were used in the FMS of four isomers of (–)-dictyostatin.[19] However, more stereoisomers can be synthesized through FMS by designing a strategy of tagging and mixing. Later on, multiple tags

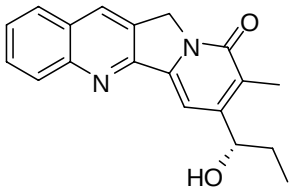
were applied for each isomer. For instance, double tags were used for each isomer in the FMS of lagunapyrone B.[20] Only three different fluorous tags were used in the synthesis of four isomers.

From FMS studies, we can learn how similar or different the stereoisomers are by comparing the various physical and spectral data. This evidence can help assign the structures of those natural products and find out the best bioactivities among them.

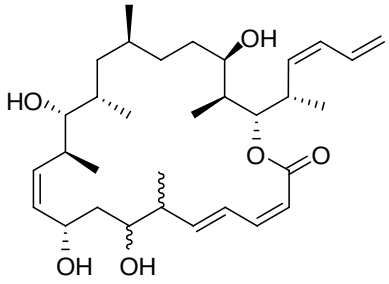
**Scheme 1.6 Representative natural products and their stereoisomers synthesized by FMS**



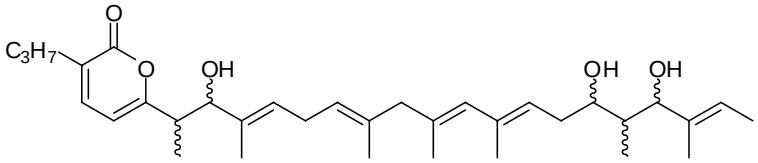

pyridovericin
2 enantiomers




mappicine
2 enantiomers




(−)-dictyostatin
4 diastereomers




lagunapyrone B
4 diastereomers

## Chapter 2. Fluorous mixture synthesis of four stereoisomers of the C21-C40 fragment of tetrafibricin

We were interested in making stereoisomers of tetrafibricin to learn whether the diastereomers had identical spectra or not. Towards the end, we first plan to synthesize four stereoisomers of a large bottom fragment C21-C40 of tetrafibricin by using the technique of fluorous mixture synthesis.

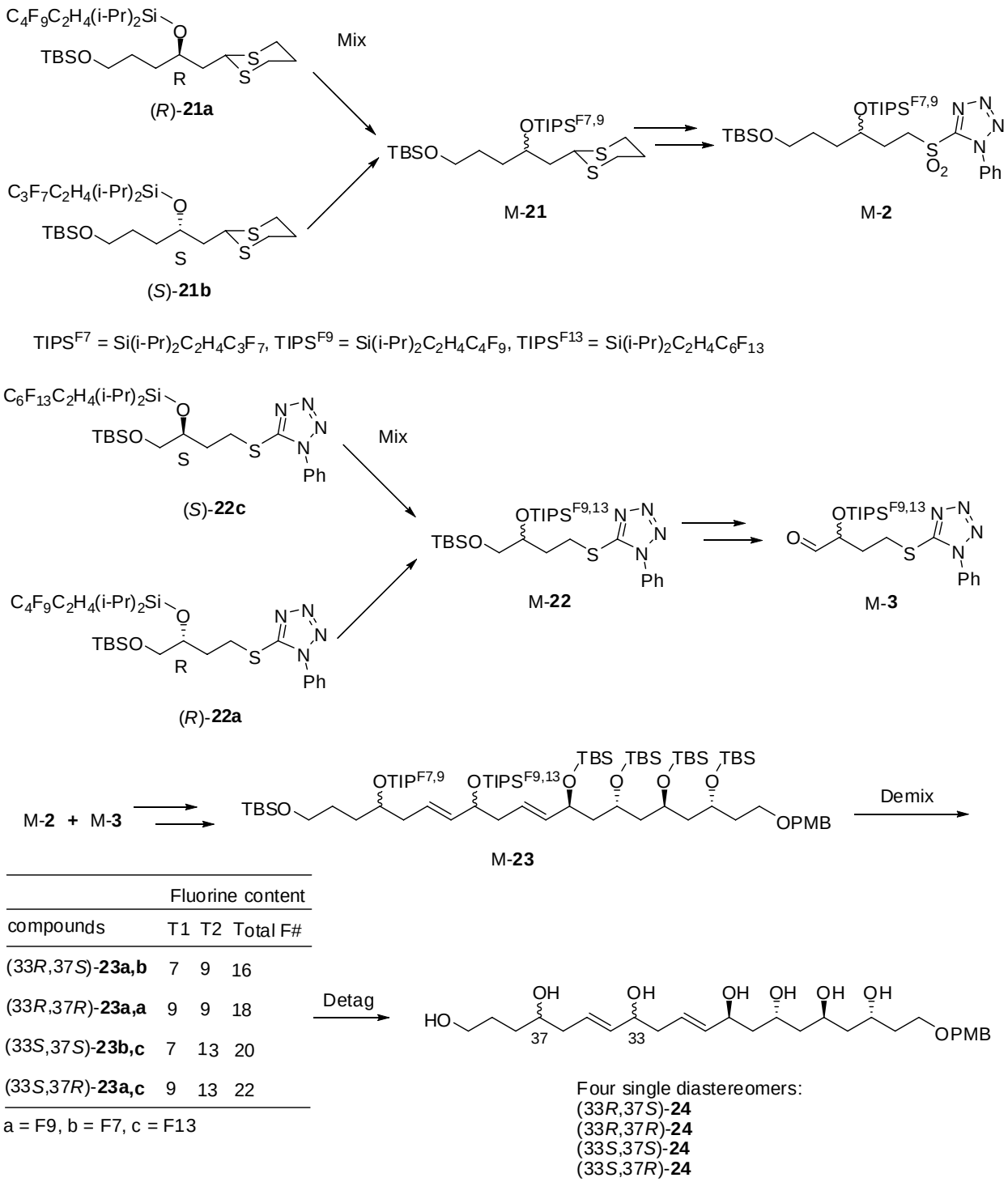
### 2.1 Plan of FMS of four stereoisomers of the C21-C40 fragment of tetrafibricin

In order to synthesize four isomers of the bottom fragment C21-C40 of tetrafibricin, we plan to make the quasiracemic mixtures fragments M-**2** and M-**3** with configurations encoded by fluorous tags in the protecting groups (PG) and keep fragment **4** as the single stereoisomer. We choose the stereocenters in fragments M-**2** and M-**3** because stereocenters are not close to other stereocenters and the reaction selectivity is easy to control. Scheme 2.1 shows our FMS plan.

First, we plan to make (*R*)-**21a** by attaching a fluorous tag containing 9 fluorines ($TIPS^{F9}$ = $Si(i\text{-}Pr)_2C_2H_4C_4F_9$) to the (*R*)-alcohol and make (*S*)-**21b** by attaching a fluorous tag containing 7 fluorines ($TIPS^{F7}$ = $Si(i\text{-}Pr)_2C_2H_4C_3F_7$) to the (*S*)-alcohol. After mixing and several steps of mixture synthesis, we can obtain fragment M-**2** as a quasienantiomer mixture ("quasi" means the compounds have different fluorous tags and are not true isomers). By using the same method, we can achieve fragment M-**3** as another quasienantiomer mixture. Then coupling fragments M-**2** and M-**3** together will provide us a combination of four quasiisomers with different fluorine

numbers. After steps of mixture synthesis and demixing, we can obtain four single quasiisomers **23**. Finally, after detagging, four single diastereomers of the C21-C40 fragment of tetrafibricin will be achieved in the end.

**Scheme 2.1 Plan of FMS of four stereoisomers of the C21-C40 fragment of tetrafibricin**




| | Fluorine content | | |
|---|---|---|---|
| compounds | T1 | T2 | Total F# |
| (33*R*,37*S*)-**23a,b** | 7 | 9 | 16 |
| (33*R*,37*R*)-**23a,a** | 9 | 9 | 18 |
| (33*S*,37*S*)-**23b,c** | 7 | 13 | 20 |
| (33*S*,37*R*)-**23a,c** | 9 | 13 | 22 |

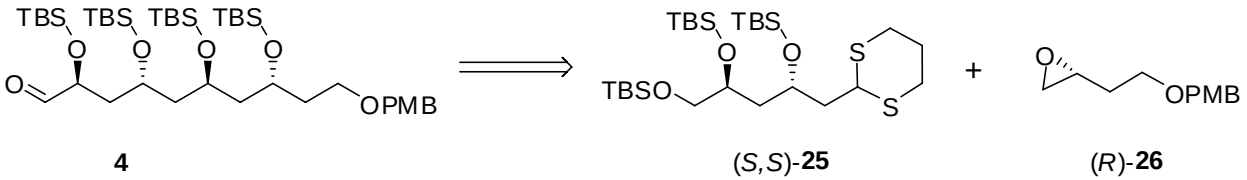
a = F9, b = F7, c = F13

## 2.2 Fragment syntheses

### 2.2.1 Synthesis of the C21-C30 fragment 4

The synthesis of C21-C30 fragment **4** was accomplished by following the procedures from Dr. Gudipati's thesis.[12] The key step of retrosynthesis of fragment **4** is the coupling reaction between dithiane (*S*,*S*)-**25** and epoxide (*R*)-**26** (Scheme 2.2).

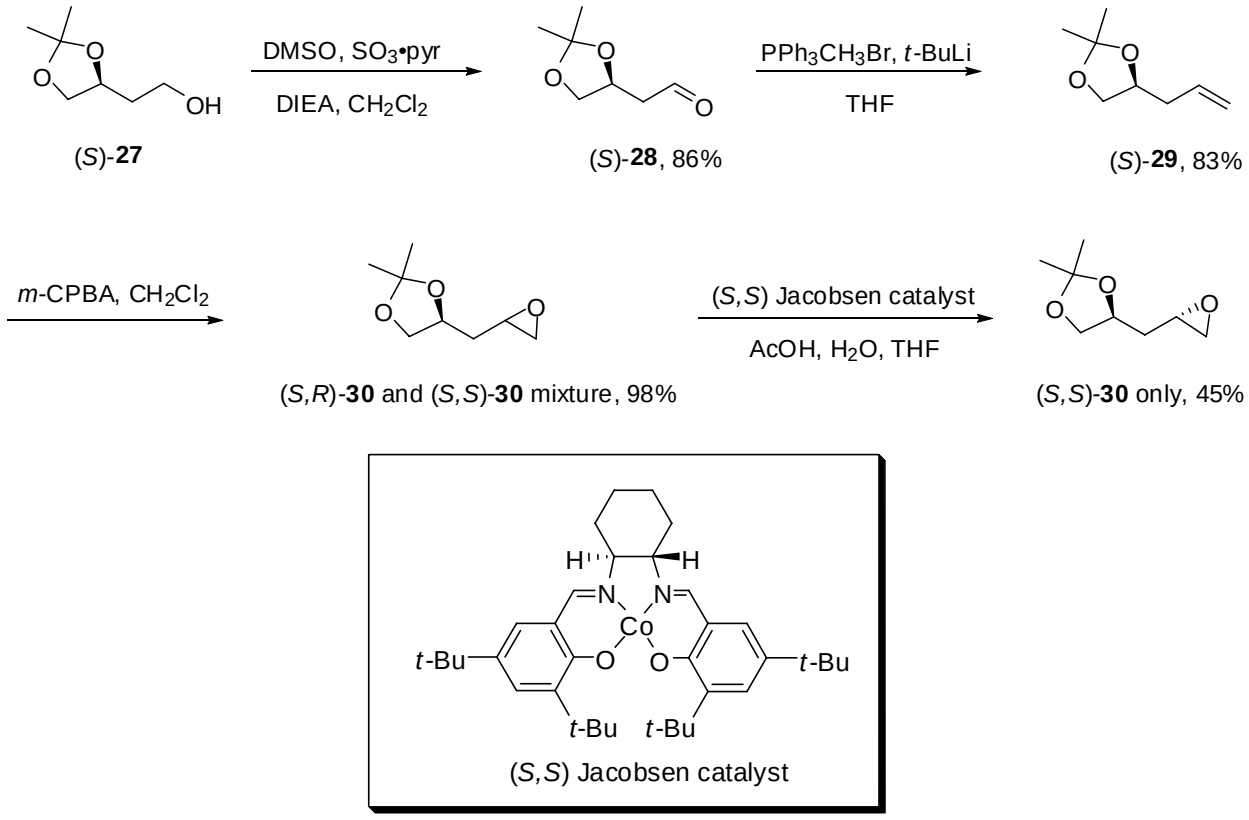
**Scheme 2.2 Retrosynthesis of fragment 4**




**4** (*S*,*S*)-**25** (*R*)-**26**

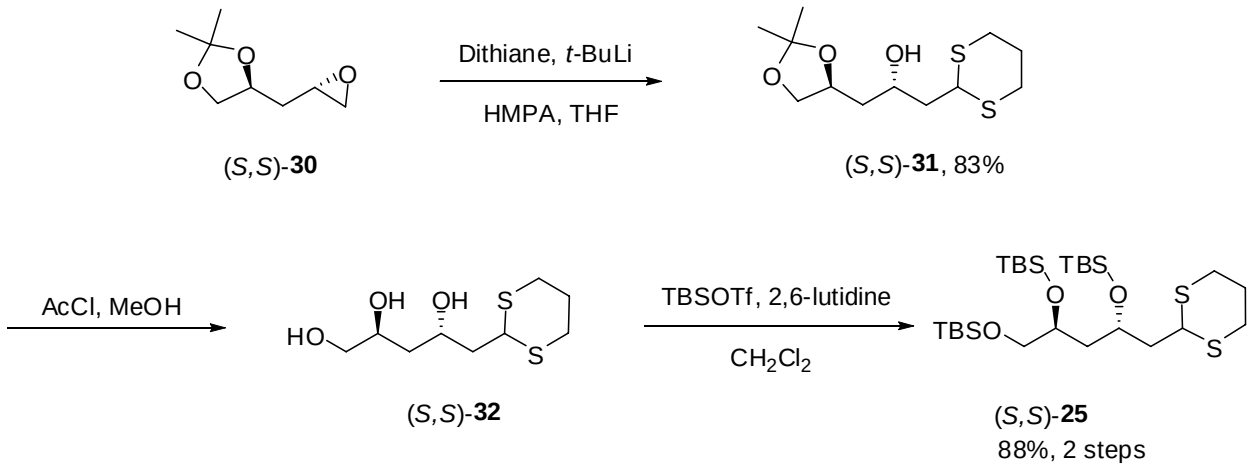
The synthesis of dithiane (*S*,*S*)-**25** started with commercially available alcohol (*S*)-**27** (Scheme 2.3). Oxidation by using the Parikh-Doering protocol gave the corresponding aldehyde (*S*)-**28** in 86% yield.[21] Wittig olefination with $CH_3PPh_3Br$ and *t*-BuLi in THF gave alkene (*S*)-**29** in 83% yield.[22] Alkene (*S*)-**29** was oxidized to a 1:1 mixture of epoxide (*S*,*S*)-**30** and (*S*,*R*)-**30** by using *m*-CPBA in 98% yield. Then the epoxide mixture was subjected to kinetic resolution conditions with (*S*,*S*)-Jacobsen catalyst to afford diastereomerically pure epoxide (*S*,*S*)-**30** in 45% yield.[23]

**Scheme 2.3 Synthesis of epoxide (*S*,*S*)-30**



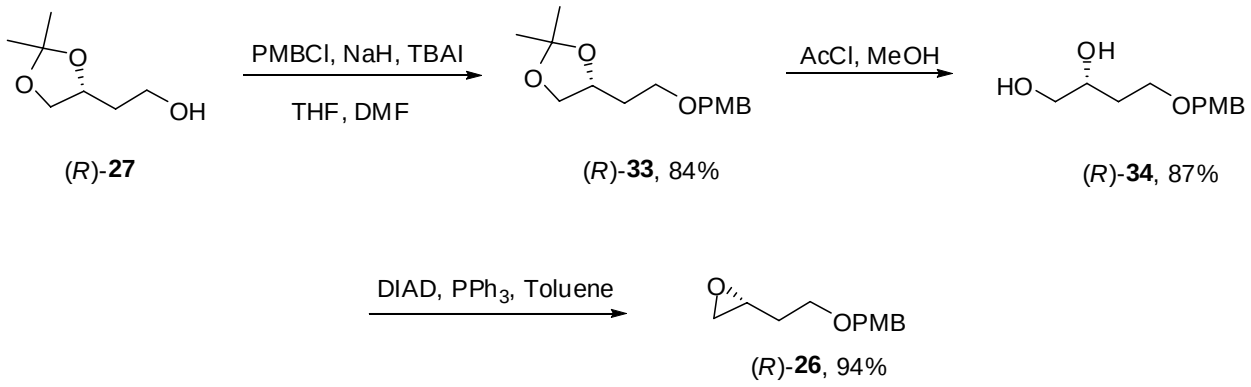

The three-step conversion of epoxide (*S*,*S*)-**30** to tris-silyl ether (*S*,*S*)-**25** is shown in Scheme 2.4. Lithiation of 1,3-dithiane with *t*-BuLi followed by addition of epoxide (*S*,*S*)-**30** gave alcohol (*S*,*S*)-**31** in 83% yield. The alcohol (*S*,*S*)-**31** was subjected to catalytic HCl conditions (generated from AcCl in methanol) to provide triol (*S*,*S*)-**32**, which was then reacted with TBSOTf and 2,6-lutidine to form (*S*,*S*)-**25** in 88% yield.

**Scheme 2.4 Synthesis of dithiane (*S*,*S*)-25**



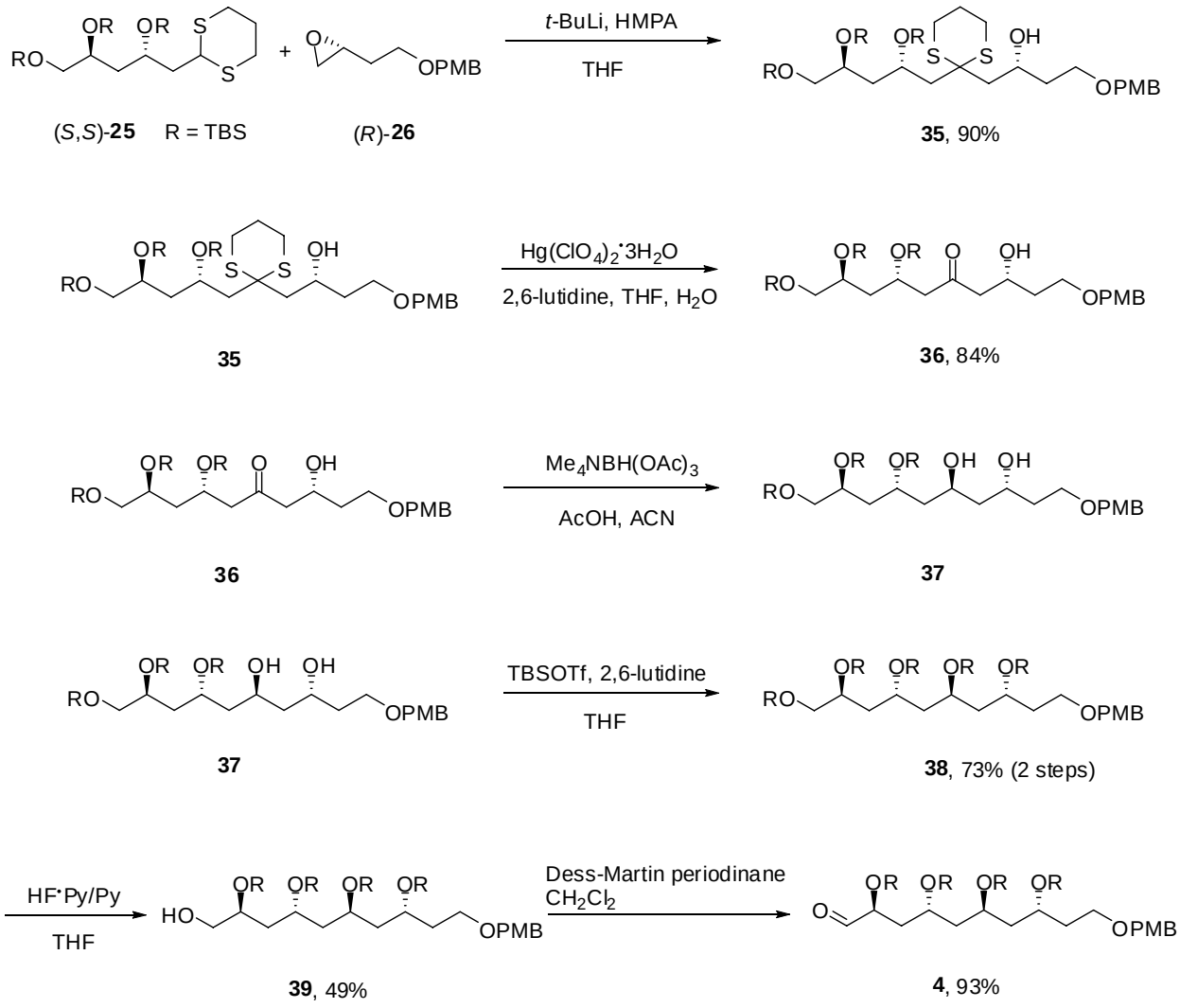

Epoxide (*R*)-**26** was synthesized in three steps (Scheme 2.5). Deprotonation of commercially available alcohol (*R*)-**27** with NaH followed by addition of PMBCl gave the PMB-ether (*R*)-**33** in 84% yield.[24] Removal of 1,2-diol protecting group under catalytic HCl conditions (generated from AcCl in methanol) gave the diol (*R*)-**34** in 87% yield. The 1,2-diol (*R*)-**34** was converted to epoxide (*R*)-**26** in 94% yield by subjecting it to Mitsunobu reaction conditions with DIAD and $PPh_3$ in refluxing toluene.[16]

**Scheme 2.5 Synthesis of epoxide (*R*)-26**




The coupling of dithiane (*S*,*S*)-**25** and epoxide (*R*)-**26** and onward reactions to give fragment **4** are shown in Scheme 2.6. Dithiane (*S*,*S*)-**25** was lithiated with *t*-BuLi followed by addition of epoxide (*R*)-**26** to effect the alkylation to afford the compound **35** in 90% yield.[25] Hydrolysis of the dithiane **35** with mercuric perchlorate in presence of 2,6-lutidine in aqueous THF provided the desired β-hydroxyl ketone **36** in 84% yield.[26] Hydroxyl-directed reduction with $Me_4NHB(OAc)_3$ gave the 1,3-anti diol **37**, which was then silylated with TBSOTf to give the compound **38** in 73% yield.[27] Monodesilylation with HF•pyr in pyridine gave the primary alcohol **39** in 49% yield. Oxidation of alcohol **39** with Dess-Martin reagent furnished aldehyde **4** in 93% yield.[28] The above conversion of alcohol to aldehyde was done immediately before the next step. Finally, fragment **4** (180 mg) was synthesized in 16 steps with an overall yield of 5.8%.

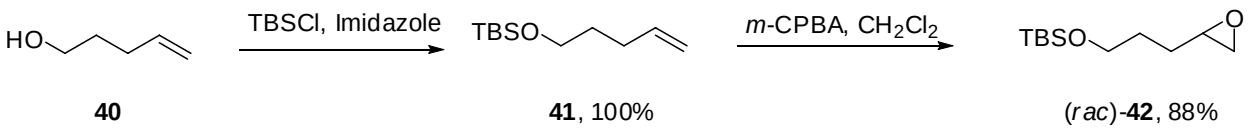
**Scheme 2.6 Synthesis of the C21-C30 fragment 4**




## 2.2.2 Synthesis of the C35-C40 fragment M-2

The synthesis of fragment M-**2** commenced from commercially available pent-4-en-1-ol **40** as shown in Scheme 2.7. Alcohol **40** was protected by reacting it with TBSCl and imidazole in dichloromethane to afford TBS ether **41.** Epoxidation of the alkene **41** with *m*-CPBA in dichloromethane at 0 $^{o}$C for 1 h gave the epoxide (*rac*)-**42**.

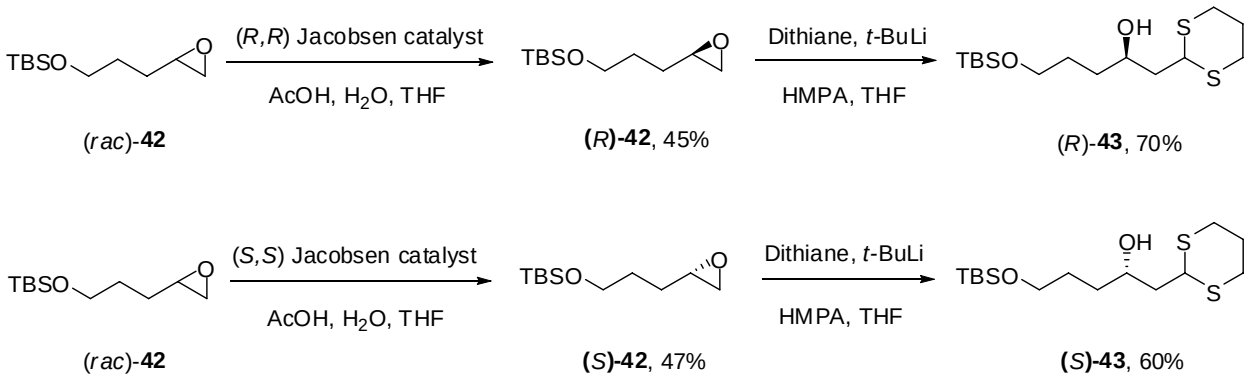
**Scheme 2.7 Synthesis of epoxide (*rac*)-42**




**40** **41**, 100% (*rac*)-**42**, 88%

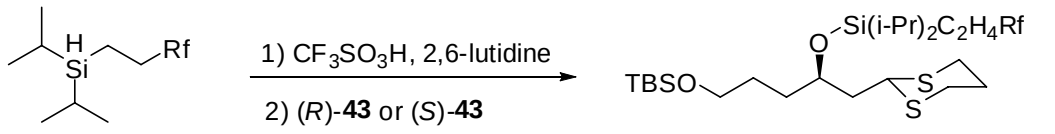
In order to make the quasiracemic fragment M-**2**, we divided the (*rac*)-**42** into two portions (Scheme 2.8). The first portion was subjected to kinetic resolution with (*R*,*R*)-Jacobsen catalyst to afford epoxide (*R*)-**42** in 45% yield.[23] Then the epoxide (*R*)-**42** was treated with lithio-1,3-dithane to give the secondary alcohol (*R*)-**43** in 70% yield. The second portion of (*rac*)-**42** was subjected to kinetic resolution with (*S*,*S*)-Jacobsen catalyst to afford (*S*)-**42** in 47% yield followed by the reaction with lithio-1,3-dithane to give the alcohol (*S*)-**43** in 60% yield.[23]

**Scheme 2.8 Synthesis of alcohols (*R*)-43 and (*S*)-43**




The two enantiomeric alcohols (*R*)-**43** and (*S*)-**43** were tagged with different commercially available fluorous tags **44a** and **44b** (Scheme 2.9). Fluorous silane **44a** was treated with trifluoromethansulfonic acid at 0 °C to generate $^{F9}$TIPSOTf ($^{F}$TIPS = Si(*i*-Pr)$_2$(CH$_2$)$_2$Rf, where Rf is perfluoroalkyl) in situ.[29] This was then reacted with alcohol (*R*)-**43** to afford $^{F9}$TIPS ether (*R*)-**21a** in 88% yield. Similarly, alcohol (*S*)-**43** was protected with $^{F7}$TIPSOTf derived from fluorous silane **44b** to afford (*S*)-**21b** in 90% yield.

**Scheme 2.9 Synthesis of ethers (*R*)-21a and (*S*)-21b**



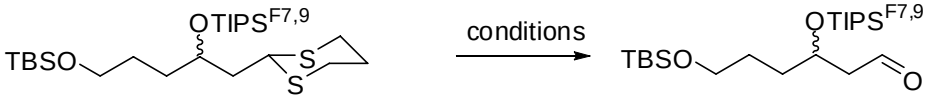

**44a**, Rf = $C_4F_9$
**44b**, Rf = $C_3F_7$

(*R*)-**21a**, Rf = $C_4F_9$, 88%
(*S*)-**21b**, Rf = $C_3F_7$, 90% (not shown)

The two fluorous-tagged quasienantiomers (*R*)-**21a** and (*S*)-**21b** were mixed with 1:1 molar ratio to generate the fluorous mixture M-**21**. Then the efforts were focused on hydrolysis of the dithiane to an aldehyde. The reaction failed by using $CH_3I$, $K_2CO_3$ in ACN-$H_2O$ (6:1) at 45 $^oC$, which only gave the recovered starting material after 5 h.[30] When the reaction mixture was heated up to 65 $^oC$ for 6 h, we obtained a complex TLC and no desired product was observed by mass spectra analysis.

Then we carried out this reaction by using $Hg(ClO_4)_2$, 2,6-lutidine in THF-$H_2O$ under several different conditions (Table 2.1). A first reaction at 0 $^oC$ for 1 h gave only starting material (Entry 1). A similar reaction conducted at room temperature for 36 h gave 14% product and 70% recovered starting material (Entry 2). By further increasing the reaction temperature to 45 $^oC$, finally we obtained the desired aldehyde M-**45** in 90% yield (Entry 3)**.**

**Table 2.1 Synthesis of aldehyde M-45**




M-**21** M-**45**

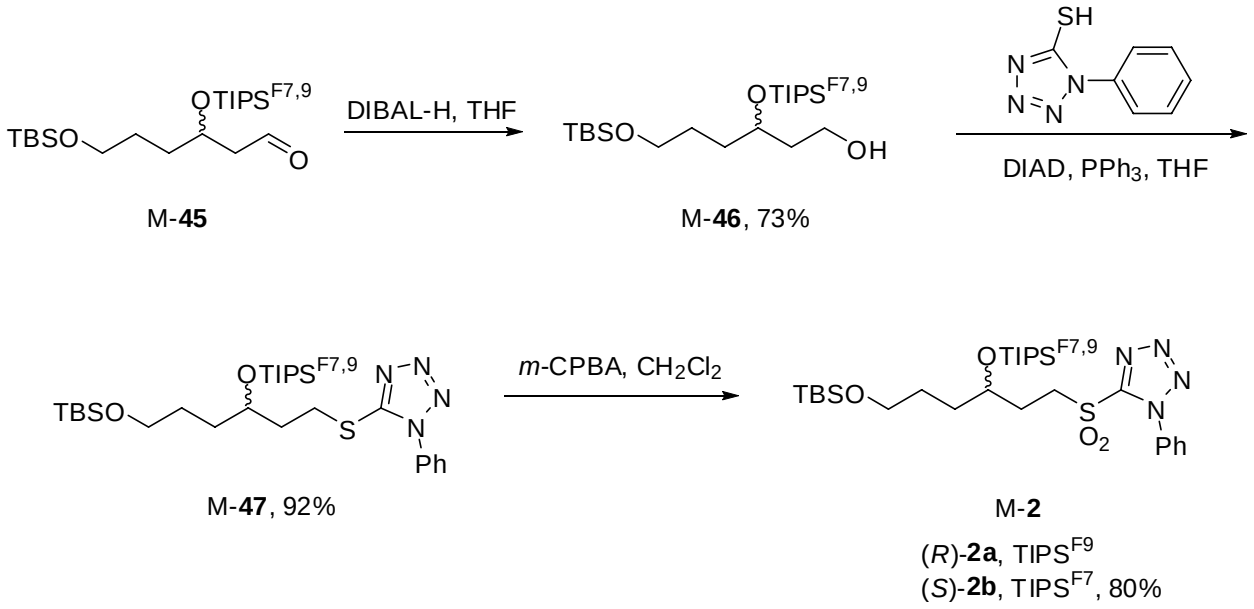
| Entry | Conditions | | | Results |
|---|---|---|---|---|
| 1 | $Hg(ClO_4)_2 \cdot 3H_2O$, 2,6-lutidine, $THF/H_2O$ | 1 h | 0 °C | s.m. |
| 2 | $Hg(ClO_4)_2 \cdot 3H_2O$, 2,6-lutidine, $THF/H_2O$ | 36 h | r.t. | 14% product + 70% s.m. |
| 3 | $Hg(ClO_4)_2 \cdot 3H_2O$, 2,6-lutidine, $THF/H_2O$ | 3 h | 45 °C | 90% |

M-**45** is the first quasiracemate product, so this is an appropriate point to briefly summarize the analysis of quasienantiomers mixture by TLC, $^1$H-NMR, $^{13}$C-NMR and $^{19}$F-NMR. The above quasienantiomers have the same $R_f$ value on TLC plate and can be purified by column chromatography without separation. In $^1$H-NMR spectra, the proton resonances from the quasienantiomers have the identical chemical shifts. For $^{13}$C-NMR spectra, all the carbon peaks have the same chemical shifts except those on the perfluoroalkyl chains, which are split by fluorines and very small in the standard spectra. For $^{19}$F-NMR spectra, by comparison of spectra between the quasienantiomers mixture and the single enantiomers, we can find all the peaks of both quasienantiomers in the spectra of the mixture.

The conversion from the aldehyde M-**45** to the sulfone M-**2** was achieved in 3 steps (Scheme 2.10). Reduction of aldehyde M-**45** with DIBAL-H gave the corresponding alcohol M-**46** in 73%

yield. This was then converted to alkylthiophenyltetrazole M-**47** in 92% yield by a Mitsunobu reaction.[16] Oxidation of sulfide M-**47** to the corresponding sulfone M-**2** was effected with *m*-CPBA (2.2 equiv, 80% yield). Overall, fragment M-**2** (750 mg) was synthesized in 9 steps with overall yield 12.6%.

**Scheme 2.10 Synthesis of the C35-C40 fragment M-2**




M-**45**

M-**46**, 73%

M-**47**, 92%

M-**2**

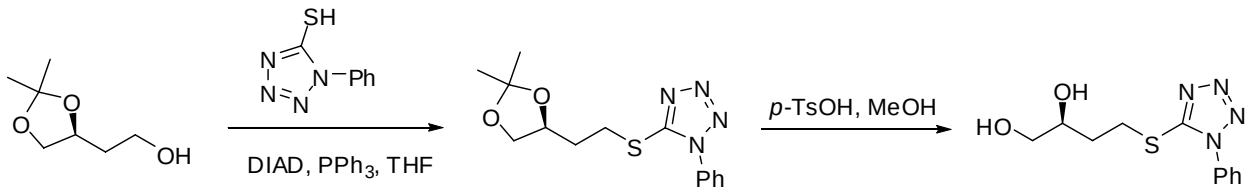
(*R*)-**2a**, TIPS$^{F9}$

(*S*)-**2b**, TIPS$^{F7}$, 80%

### 2.2.3 Synthesis of the C31-C34 fragment M-3

The synthesis of quasiracemic fragment M-**3** began with two commercially available enantiomeric alcohols (*S*)-**27** and (*R*)-**27** (Scheme 2.11). Mitsunobu reactions as above converted the alcohols to the corresponding sulfides (*S*)-**48** and (*R*)-**48** in 79% and 86% yields.[16] Removal of acetonide protecting group under catalytic acidic conditions gave the two enantiomeric diols (*S*)-**49** and (*R*)-**49** each in 93% yield.

**Scheme 2.11 Synthesis of diols (*S*)-49 and (*R*)-49**




(*S*)-**27**
(*R*)-**27** (not shown)

(*S*)-**48**, 79%
(*R*)-**48**, 86%

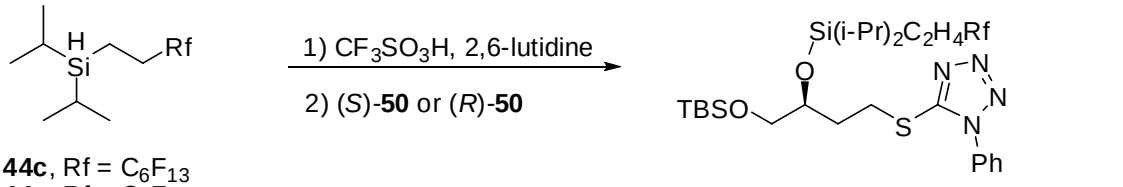
(*S*)-**49**, 93%
(*R*)-**49**, 93% (not shown)

The primary alcohols of **49** were reacted with TBSCl to give ethers (*S*)-**50** and (*R*)-**50** in 83% and 81% over 2 steps, respectively (Scheme 2.12). The two enantiomeric alcohols (*S*)-**50** and (*R*)-**50** were tagged with different fluorous tagging reagents **44c** and **44a**. The perfluorocarbon units in the two fluorous tags are $C_6F_{13}$ for (*S*)-**50** and $C_4F_9$ for (*R*)-**50**.

**Scheme 2.12 Synthesis of ethers (*S*)-22c and (*R*)-22b**


(*S*)-**49**
(*R*)-**49** (not shown)

(*S*)-**50**, 91%
(*R*)-**50**, 90%

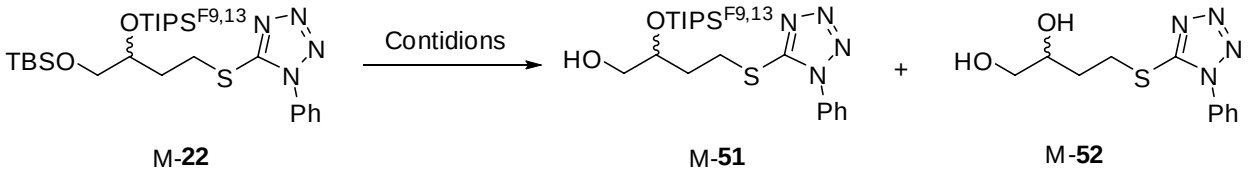



**44c**, Rf = $C_6F_{13}$
**44a**, Rf = $C_4F_9$

(*S*)-**22c**, Rf = $C_6F_{13}$, 90%
(*R*)-**22a**, Rf = $C_4F_9$, 90% (not shown)

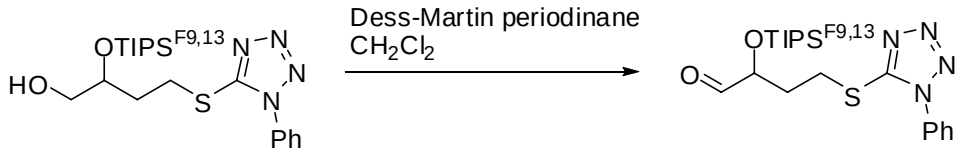
The two fluorous-tagged quasienantiomers (*S*)-**22c** and (*R*)-**22a** were mixed in a 1:1 molar ratio to generate the fluorous mixture M-**22**. The various conditions that were tried for the selective deprotection of primary TBS protecting group are summarized in Table 2.2. Using HF•pyr in pyridine removed both the TBS group and TIPS fluorous group to give the corresponding diol M-**52** (Entry 1 and 2). The target transformation was achieved by using 0.1 equiv of acetyl chloride in methanol at –20 $^{o}$C in 3 h to give the primary alcohol M-**51** in 60% yield (Entry 4). Oxidation of alcohol M-**51** to aldehyde M-**3** with Dess-Martin reagent gave fragment M-**3** in 81% yield. Overall, fragment M-**3** (420 mg) was synthesized in 6 steps with overall yield 34.7%.

**Table 2.2 Synthesis of the C31-C34 fragment M-3**




M-**22** M-**51** M-**52**

| Entry | Reagents | Conditions | Results |
|---|---|---|---|
| 1 | HF•pyr | 0 $^{o}$C 1 h and then r.t. 5 h | M-**52** only |
| 2 | HF•pyr | –20 $^{o}$C 2 h and then r.t. 4 h | M-**52** only |
| 3 | $CH_3COCl$ | –10 $^{o}$C, 2 h | M-**52** only |
| 4 | $CH_3COCl$ | –20 $^{o}$C, 3 h | 60% M-**36** and 25% M-**52** |




M-**51** M-**3**

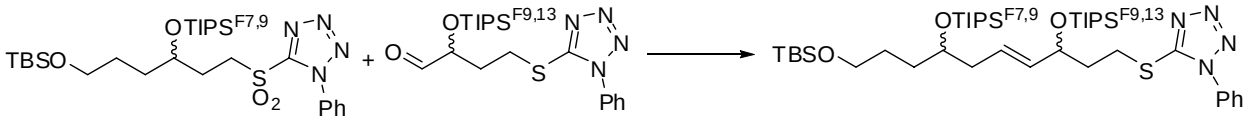
(*R*)-**3a**, TIPS$^{F9}$
(*S*)-**3c**, TIPS$^{F13}$
81%

## 2.3 Coupling of fragments M-2 and M-3 by Julia-Kocienski reaction

Different conditions were explored to accomplish the Julia-Kocienski reaction between fragment M-**2** and M-**3** (Table 2.3).[13] First, the sulfone M-**2** was reacted with KHMDS solution in toluene as the base in THF at –78 $^{o}$C for 30 min followed by the addition of aldehyde M-**3**.

This reaction gave the olefin M-**53** as a mixture of (*E*)- and (*Z*)-isomers with 7:3 ratio in 85% combined yield (Entry 1). The *E/Z* ratio was determined by analytical chiral HPLC analysis with (*S*,*S*) Whelk-O column using 95:5 hexanes/isopropanol. The *E*/*Z* isomers are not separable on regular flash chromatography but can be separated by preparative HPLC on (*S*,*S*) Whelk-O column without demixing any of the quasiisomers. The identity of (*E*)-isomer was evident from 15.0 Hz coupling constant ($J_{H\text{-}H}$) of alkene protons. Then, by using DME as the reaction solvent we obtained the alkene M-**53** with *E/Z* ratio over 9:1 in 80% combined yield (Entry 2).[31]

**Table 2.3 Coupling of fragments M-2 and M-3**




M-**2**
(*R*)-**2a**, TIPS$^{F9}$
(*S*)-**2b**, TIPS$^{F7}$

M-**3**
(*R*)-**3a**, TIPS$^{F9}$
(*S*)-**3c**, TIPS$^{F13}$

M-**53**

| | Fluorine content T1 | T2 | Total F# |
|---|---|---|---|
| (33*R*,37*S*)-**53a,b**, | 9 | 7 | 16 |
| (33*R*,37*R*)-**53a,a**, | 9 | 9 | 18 |
| (33*S*,37*S*)-**53b,c**, | 7 | 13 | 20 |
| (33*S*,37*R*)-**53a,c**, | 9 | 13 | 22 |

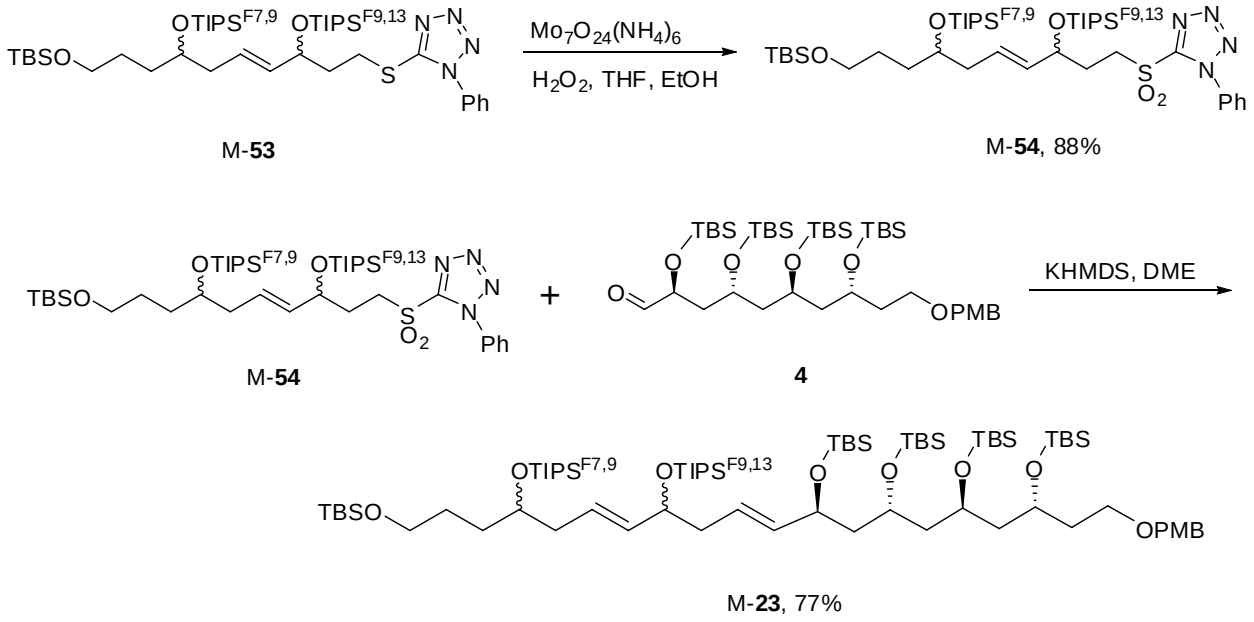
| Entry | Base | Solvent | Combined yield | M-**53** *E/Z* ratio |
|---|---|---|---|---|
| 1 | KHMDS in toluene | THF | 85% | 7:3 |
| 2 | KHMDS in DME | DME | 80% | > 9:1 |

## 2.4 Synthesis of the C21-C40 fragment

The synthesis of the bottom fragment M-**23** C21-C40 is shown in Scheme 2.13. Oxidation of sulfide M-**53** to sulfone M-**54** with Mo-catalyst ($Mo_7O_{24}(NH_4)_6$•$H_2O$, $H_2O_2$) occurred in 88%

yield.[14] Another Julia-Kocienski olefination reaction between sulfone M-**54** and aldehyde **4** again using KHMDS in DME provided M-**23** with *E/Z* ratio over 9:1 in 77% combined yield. As before, the (*E*,*E*) stereoisomer M-**23** was separated by preparative chiral HPLC ((*S*,*S*) Whelk-O column.

**Scheme 2.13 Synthesis of the C21-C40 fragment**

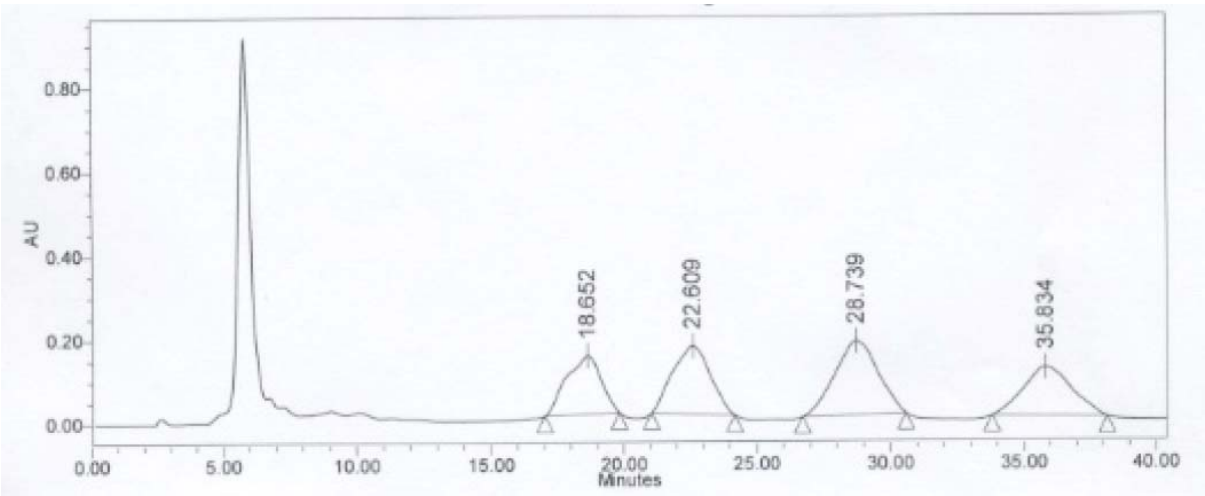



## 2.5 Demixing and detagging of fluorous mixture M-23

We were interested to learn whether we can separate the fluorous mixture to obtain the four individual pure compounds and how similar or different the stereoisomers are. So we decided to demix the fluorous mixture M-**23** at this stage and subsequently to remove the protection groups in order to compare the spectra of the stereoisomers.

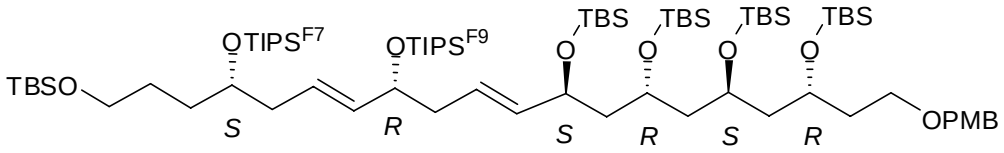
Demixing of M-**23** by preparative fluorous HPLC occurred smoothly to provide quasidiastereomers (33*R*,37*S*)-**23a,b**, (33*R*,37*R*)-**23a,a**, (33*S*,37*S*)-**23b,c**, (33*S*,37*R*)-**23a,c**. A typical chromatography of a preparative injection (20 mg) is shown in Figure 2.1. Even though they differ by only two fluorines, the quasiisomers exhibited good separation and were present in roughly equal amounts.

**Figure 2.1 Preparative HPLC trace of quasidiastereomers 23[(a)]**

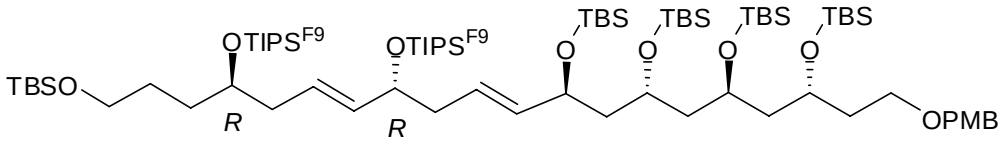



(a) FluoroFlash Column, 100% MeOH, 10 mL/min, 20 mg M-**23** in 1 mL MeOH/injection

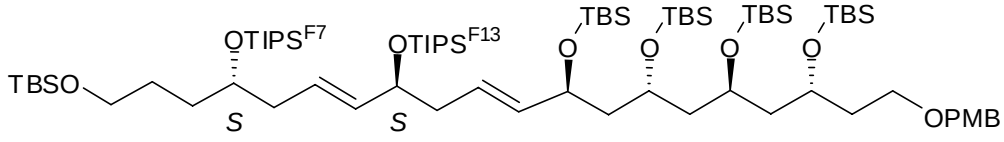
1st peak, 18.65 min, 16F, (33*R*,37*S*)-**23a,b**



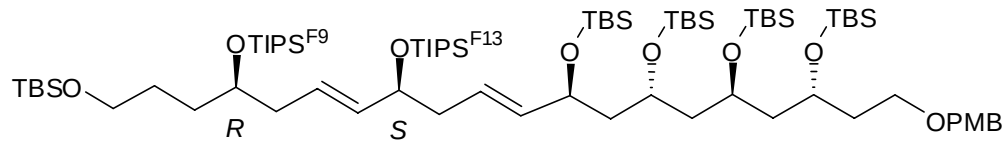

2nd peak, 22.61 min, 18F, (33*R*,37*R*)-**23a,a**




3rd peak, 28.74 min, 20F, (33*S*,37*S*)-**23b,c**



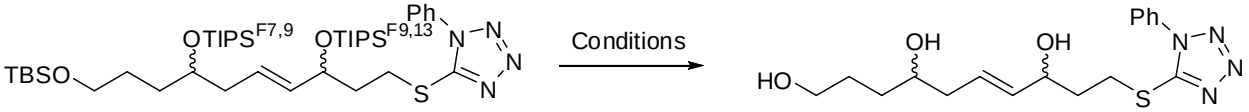

4th peak, 35.83 min, 22F, (33*S*,37*R*)-**23a,c**



With the four quasidiastereomers in hand, efforts were focused on the global deprotection. First, we tried the most common conditions to remove the silyl groups M-**23** by using TBAF. However, we observed a multi-spot TLC and no desired product was detected by mass spectral analysis.

Because the samples of M-**23** are very valuable, we decided to try model reactions to find the best deprotection conditions. Left fragment M-**53** was deprotected under the conditions shown in Table 2.4. First, we tried the acidic conditions by using HCl in MeOH and obtained 70% yield desired product triol M-**55**. The conversion was also achieved by using TMSCl in MeOH in 78% yield and TASF in DMF in 75%.[20] However, when M-**53** was treated with HF•pyr, the product exhibited a complex TLC and no desired product was detected by mass spectral analysis.

**Table 2.4 Model deprotection reactions of M-53**

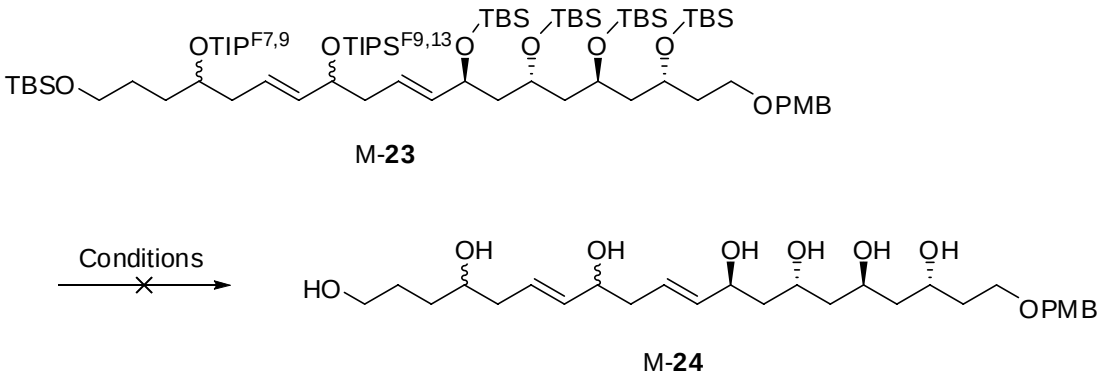



M-**53** M-**55**

| Entry | Conditions | Isolated yield of M-**55** |
|---|---|---|
| 1 | HCl | 70% |
| 2 | TMSCl | 78% |
| 3 | HF•pyr | Complex TLC |
| 4 | TASF | 75% |

With these results in hand, we applied the successful model conditions to M-**23** (Scheme 2.14). However, using HCl in MeOH resulted in a complex TLC. When M-**23** was treated with TMSCl in MeOH, no desired product was detected by mass spectral analysis. Then we carried out the reaction with TASF in DMF. Unfortunately, there was no desired product by $^{1}$H-NMR analysis either.

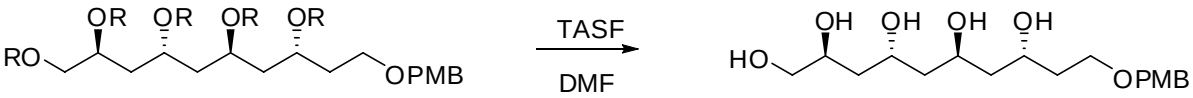
**Scheme 2.14 Deprotection of compound M-23**




Since several conditions worked on M-**53** but not M-**23**, this suggests that the right part of compound M-**23** is a problem. So we next tried the deprotection of the right part of M-**23** as a complementary model reaction (Scheme 2.15). Together, the two models should predict the behavior of M-**23**. Compound **38** was treated with TASF in DMF overnight. Before quenching the reaction by adding water, we observed a new spot which overlapped with TASF on TLC. However, after concentrating the organic extracts, the new spot was gone from the TLC analysis and no desired product was detected by mass spectra and $^{1}$H-NMR spectroscopy. Perhaps we had obtained the penta-ol **56**, but because of the high polarity of **56** it extracted to the water? To test this idea, we repeated the reaction, but instead of adding water, we removed DMF by using

speed-vacuum overnight. After purification of the concentrate by flash column chromatography, we obtained penta-ol **56** in 80% yield.

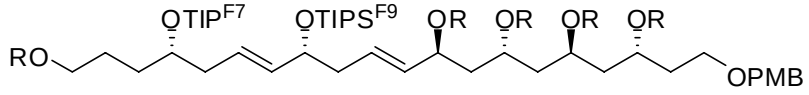
**Scheme 2.15 Model deprotection reaction of 38**




**38** R = TBS **56**, 80%

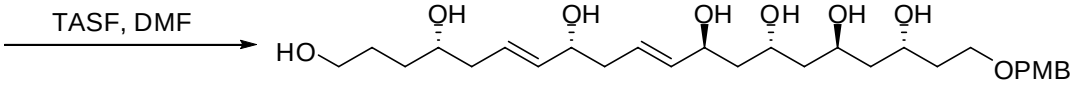
Finally, we applied the successful model conditions with non-aqueous workup to compounds **23** (Scheme 2.16) and obtained the four diastereomers **24** in about 75% yield, respectively.[20]

**Scheme 2.16 Deprotection of compound 23**

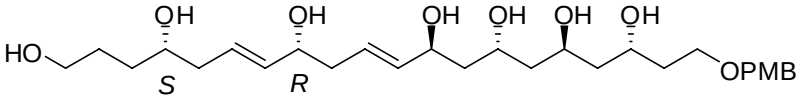



R = TBS

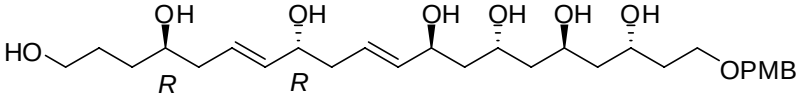
(33*R*,37*S*)-**23a,b**
the other three isomers are not shown



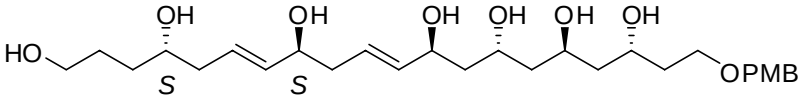

(33*R*,37*S*)-**24**, 75%
the other three isomers are shown below



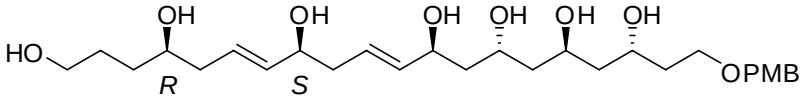

(33*R*,37*S*)-**24**




(33*R*,37*R*)-**24**




(33*S*,37*S*)-**24**




(33*S*,37*R*)-**24**

The 700 MHz $^{1}$H NMR spectra of the four stereoisomers of **24** were substantially identical (See experimental information).[32] However, the 175 MHz $^{13}$C-NMR spectra are very similar but not identical. The $^{13}$C-NMR data of the four stereoisomers are summarized in Table 2.5. By comparison of the chemical shift of alkene carbon 35, we can tell the 33,37-*anti* isomers (*R*,*R* and *S*,*S*) from the *syn* isomers (*R*,*S* and *S*,*R*). The chemical shift was below 128.90 ppm for the *anti* isomers and above 128.90 ppm for the *syn* isomers. Chemical shift differences for C35 of the *syn*/*anti* isomers range from 0.12–0.23 ppm. Furthermore, by comparing the chemical shifts of C35 (again) and C31, we can differentiate the pairs of C33/C37 *syn* and *anti* isomers from each other (*R*,*R* from *S*,*S* and *R*,*S* from *S*,*R*). The chemical shift differences are less, 0.04–0.07 ppm, but the confidence level is increased since there are two values to compare.

**Table 2.5 $^{13}$C-NMR data of four stereoisomers 24**

| | (33*R*,37*S*)-**24** | (33*R*,37*R*)-**24** | (33*S*,37*S*)-**24** | (33*S*,37*R*)-**24** | δ (RR – RS) | δ (SS – RS) | δ (SR – RS) | δ (SS – RR) | δ (SR – RR) | δ (SR – SS) |
|---|---|---|---|---|---|---|---|---|---|---|
| | 160.82 | 160.81 | 160.82 | 160.81 | -0.01 | 0 | -0.01 | 0.01 | 0 | -0.01 |
| C30 | 137.25 | 137.23 | 137.20 | 137.22 | -0.02 | -0.05 | -0.03 | -0.03 | -0.01 | 0.02 |
| C34 | 136.18 | 136.19 | 136.19 | 136.16 | 0.01 | 0.01 | -0.02 | 0 | -0.03 | -0.03 |
| | 131.70 | 131.69 | 131.70 | 131.69 | -0.01 | 0 | -0.01 | 0.01 | 0 | -0.01 |
| | 130.54 | 130.54 | 130.54 | 130.54 | 0 | 0 | 0 | 0 | 0 | 0 |
| C35 | 128.96 | 128.80 | 128.84 | 129.03 | -0.16 | -0.12 | 0.07 | 0.04 | 0.23 | 0.19 |
| C31 | 127.61 | 127.64 | 127.69 | 127.66 | 0.03 | 0.08 | 0.05 | 0.05 | 0.02 | -0.03 |
| | 114.72 | 114.71 | 114.73 | 114.72 | -0.01 | 0.01 | 0 | 0.02 | 0.01 | -0.01 |
| | 73.73 | 73.73 | 73.73 | 73.73 | 0 | 0 | 0 | 0 | 0 | 0 |
| C33 | 73.34 | 73.32 | 73.36 | 73.37 | -0.02 | 0.02 | 0.03 | 0.04 | 0.05 | 0.01 |
| C37 | 72.16 | 72.10 | 72.12 | 72.15 | -0.06 | -0.04 | -0.01 | 0.02 | 0.05 | 0.03 |
| C29 | 70.32 | 70.33 | 70.34 | 70.33 | 0.01 | 0.02 | 0.01 | 0.01 | 0 | -0.01 |
| C21 | 68.27 | 68.27 | 68.28 | 68.27 | 0 | 0.01 | 0 | 0.01 | 0 | -0.01 |
| C23 | 66.90 | 66.89 | 66.93 | 66.90 | -0.01 | 0.03 | 0 | 0.04 | 0.01 | -0.03 |
| C27 | 66.25 | 66.24 | 66.26 | 66.24 | -0.01 | 0.01 | -0.01 | 0.02 | 0 | -0.02 |
| C25 | 66.20 | 66.20 | 66.22 | 66.19 | 0 | 0.02 | -0.01 | 0.02 | -0.01 | -0.03 |
| C40 | 63.03 | 63.03 | 63.03 | 63.03 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 55.66 | 55.65 | 55.67 | 55.66 | -0.01 | 0.01 | 0 | 0.02 | 0.01 | -0.01 |
| C26 | 46.64 | 46.64 | 46.62 | 46.64 | 0 | -0.02 | 0 | -0.02 | 0 | 0.02 |
| C24 | 46.35 | 46.35 | 46.35 | 46.36 | 0 | 0 | 0.01 | 0 | 0.01 | 0.01 |
| C28 | 46.22 | 46.21 | 46.16 | 46.18 | -0.01 | -0.06 | -0.04 | -0.05 | -0.03 | 0.02 |
| C32 | 41.44 | 41.43 | 41.45 | 41.44 | -0.01 | 0.01 | 0 | 0.02 | 0.01 | -0.01 |
| C36 | 41.41 | 41.36 | 41.36 | 41.41 | -0.05 | -0.05 | 0 | 0 | 0.05 | 0.05 |
| C22 | 38.86 | 38.86 | 38.86 | 38.86 | 0 | 0 | 0 | 0 | 0 | 0 |
| C38 | 34.17 | 34.13 | 34.12 | 34.18 | -0.04 | -0.05 | 0.01 | -0.01 | 0.05 | 0.06 |
| C39 | 29.86 | 29.89 | 29.90 | 29.86 | 0.03 | 0.04 | 0 | 0.01 | -0.03 | -0.04 |

## 2.6 Conclusions

We successfully synthesized four stereoisomers of bottom fragment C21-C40 of tetrafibricin through FMS and demixed them by fluorous HPLC and analyzed each isomer by $^{1}$H-NMR and $^{13}$C-NMR. Although the stereoclusters are separated from each other by only three carbon atoms, the $^{1}$H NMR spectra of the isomers are substantially identical. The $^{13}$C NMR spectra are very similar, but not completely identical. We have learned from comparison of the spectra which resonances are diagnostic for differentiating the isomers.

## Chapter 3. Efforts towards total synthesis of tetrafibricin

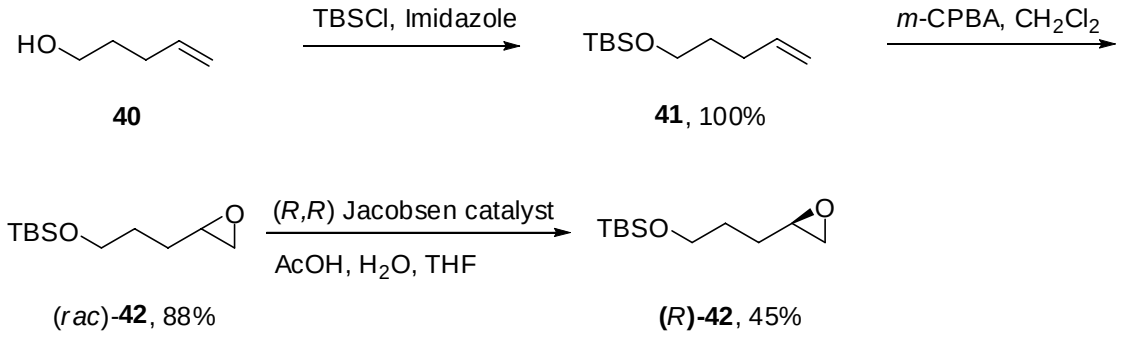
### 3.1 Fragment syntheses of tetrafibricin

To continue our efforts towards total synthesis of tetrafibricin, large amounts of fragments of tetrafibricin were synthesized following the procedure in Dr. Gudipati's thesis.[12]

#### 3.1.1 Synthesis of the C35-C40 fragment 2

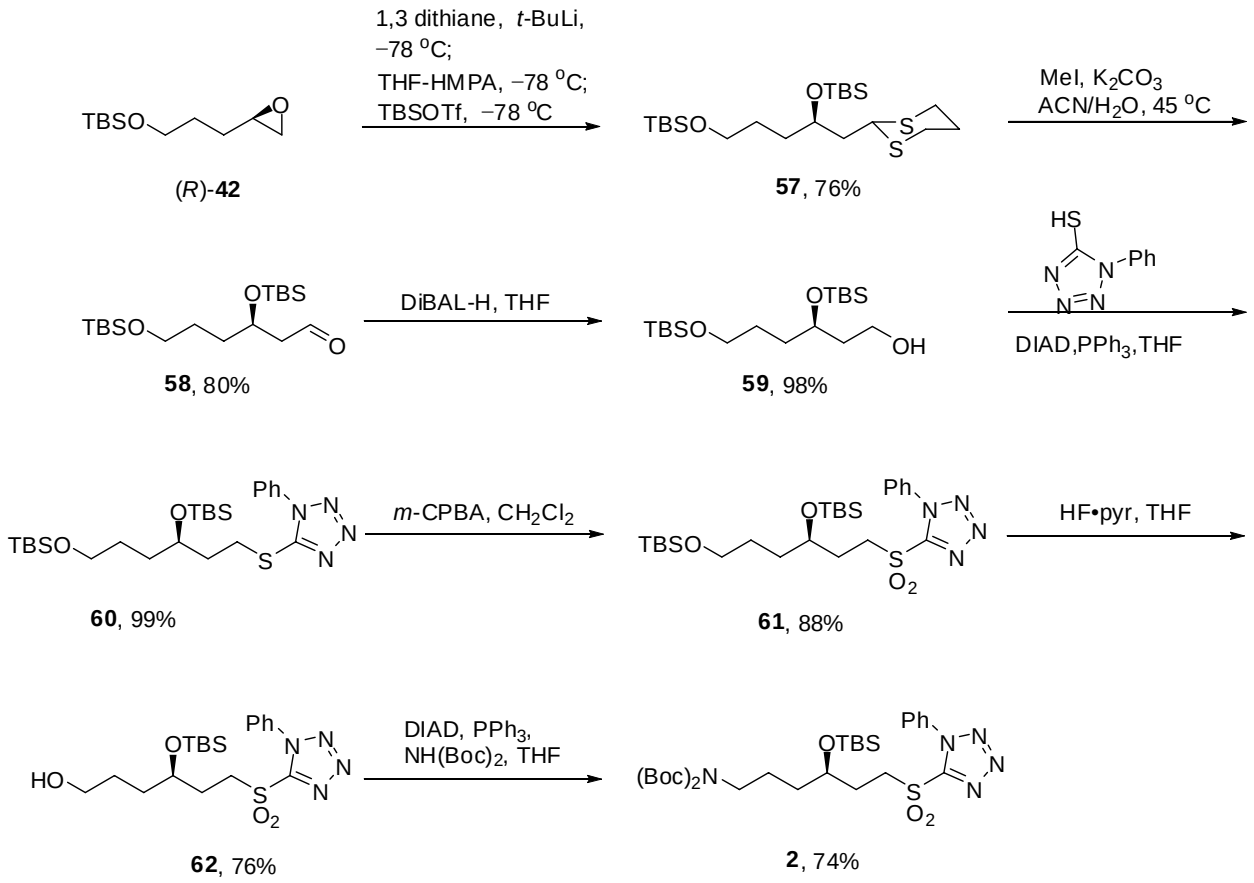
Alcohol **40** was protected by reacting it with TBSCl in presence of imidazole in dichloromethane to afford TBS ether **41** in quantitative yield (Scheme 3.1). Epoxidation of the alkene **41** with *m*-CPBA in dichloromethane at 0 $^{o}$C for 1 h gave the epoxide (*rac*)-**42** in 88% yield. The racemic epoxide **42** was subjected to kinetic resolution with (*R*,*R*)-Jacobsen catalyst to afford the single isomer epoxide (*R*)-**42** in 45% yield.[23]

**Scheme 3.1 Synthesis of epoxide (*R*)-42**



The conversion of (*R*)-**25** to the C35-C40 fragment **2** is shown in Scheme 3.2. Epoxide (*R*)-**42** was reacted with lithiated 1,3-dithiane followed by trapping the resulting secondary alkoxide with TBS-triflate to afford alkyl dithiane **57** in 76% yield. Reaction of dithiane **57** with $CH_3I$ and $K_2CO_3$ in ACN-$H_2O$ (6:1) at 45 $^oC$ for 5 h provided the aldehyde **58** in 80% yield.[33] Reduction of aldehyde **58** with DIBAL-H gave the corresponding alcohol **59** in 98% yield. The alcohol **59** was then converted to alkylthiophenyltetrazole in 99% yield by reacting it with 1-phenyl-1*H*-tetrazole-5-thiol in presence of DIAD. Oxidation of sulfide **60** to the corresponding sulfone **61** was carried out with *m*-CPBA in 88% yield. The primary TBS group in compound **61** was then selectively removed with HF•pyr in THF to give alcohol **62** in 76% yield. The primary alcohol **106** was reacted with di-*tert*-butyl-iminodicarboxylate in presence of DIAD to provide sulfone **2** in 74% yield.[34] Fragment **2** was synthesized from **40** in 10 steps with an overall yield 11.6%.

**Scheme 3.2 Synthesis of the C35-C40 fragment 2**

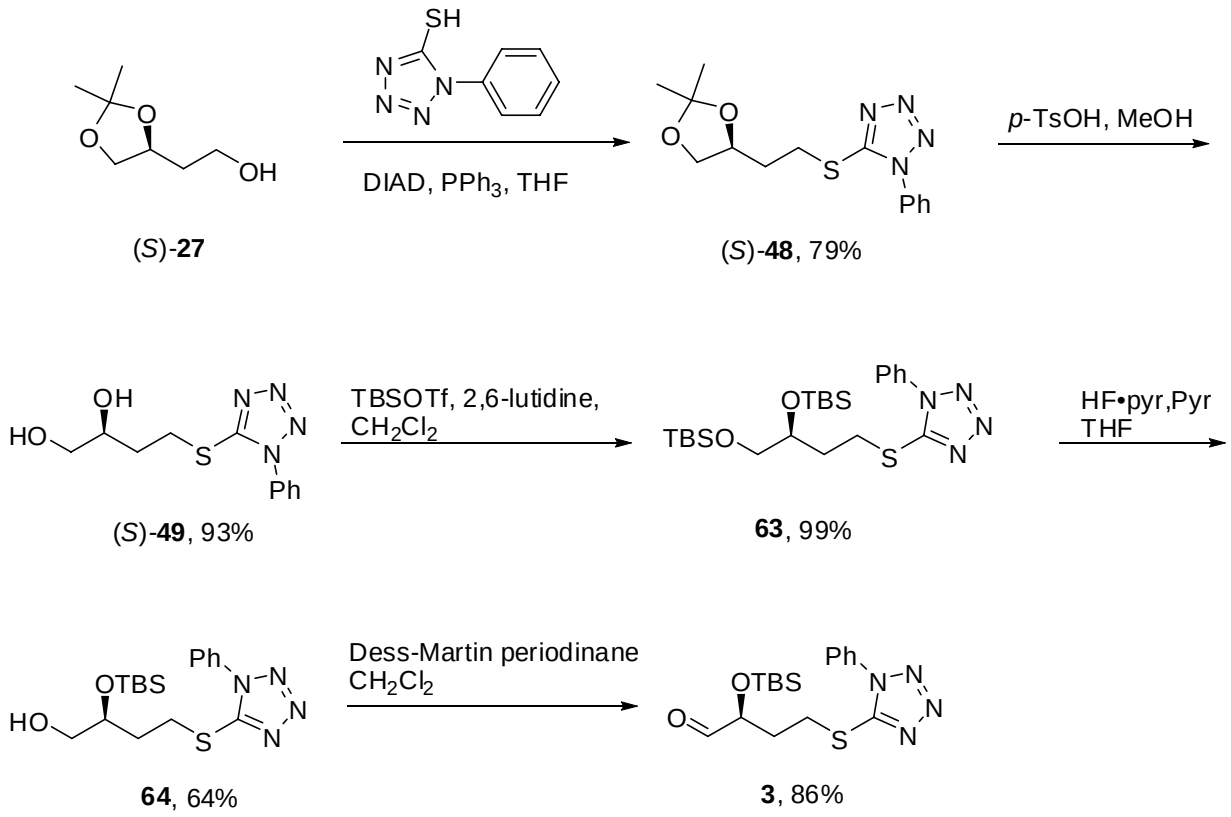



### 3.1.2 Synthesis of the C31-C34 fragment 3

Synthesis of the C31-C34 fragment **3** commenced with commercially available alcohol (*S*)-**27** as shown in Scheme 3.3. Incorporation of the thiotetrazole via the Mitsunobu protocol,[16] employing commercially available 1-phenyl-1*H*-tetrazole-5-thiol, furnished the corresponding sulfide (*S*)-**48** in 79% yield. Removal of acetonide protecting group by using HCl in methanol (0.1 equiv AcCl in MeOH) gave diol (*S*)-**49** in 93% yield. Bis-silylation of diol with TBS-triflate

gave sulfide **63** in 99% yield. Selective deprotection of the primary TBS group was accomplished with HF•pyr in 64% yield. Alcohol **64** was oxidized with Dess-Martin reagent to furnish aldehyde **3** in 86% yield.[28] In summary, fragment **3** was synthesized in 5 steps with overall 34.0% yield.

**Scheme 3.3 Synthesis of the C31-C34 fragment 3**



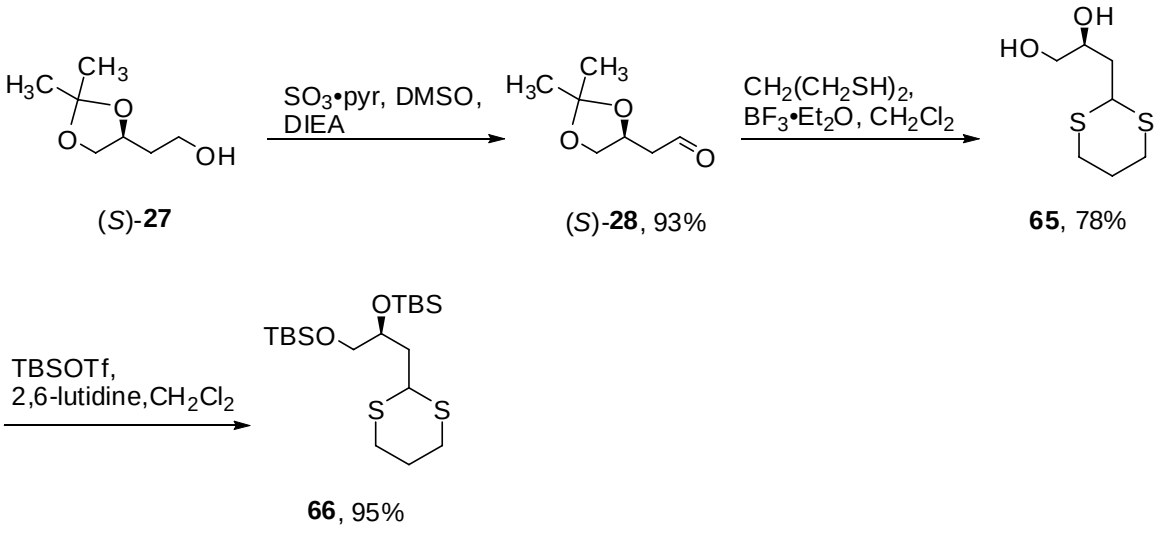

### 3.1.3 Synthesis of the C21-C30 fragment 4

The synthesis of aldehyde **4** is described in Chapter 2.

### 3.1.4 Synthesis of the C14-C20 fragment 5

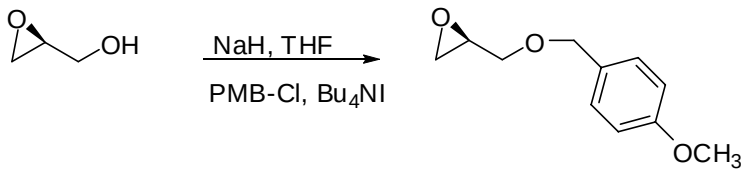
Synthesis of the C14-C20 fragment **5** from commercially available alcohol (*S*)-**27** is summarized in Schemes 3.5 to 3.7. Oxidation of alcohol (*S*)-**27** to aldehyde (*S*)-**28** was accomplished with $SO_3$•pyr in 93% yield (Scheme 3.4). Reaction of aldehyde (*S*)-**28** with propane-1,3-dithiol and $BF_3$•$OEt_2$ resulted in both conversion of aldehyde to a dithiane and cleavage of 1,2-diol protecting group to afford dithiane diol **65** in 78% yield.[35] Silylation of the diol **65** (TBSOTf and 2,6-lutidine) proceeded smoothly to give bis-silyl ether **66** in 95% yield.

**Scheme 3.4 Synthesis of dithiane 66**



The right part of fragment **5**, PMB-epoxide (*R*)-**68**, was prepared by deprotonating the (*S*)-glycidol **67** with NaH followed by the addition of PMBCl and $Bu_4NI$ (Scheme 3.5).[24]

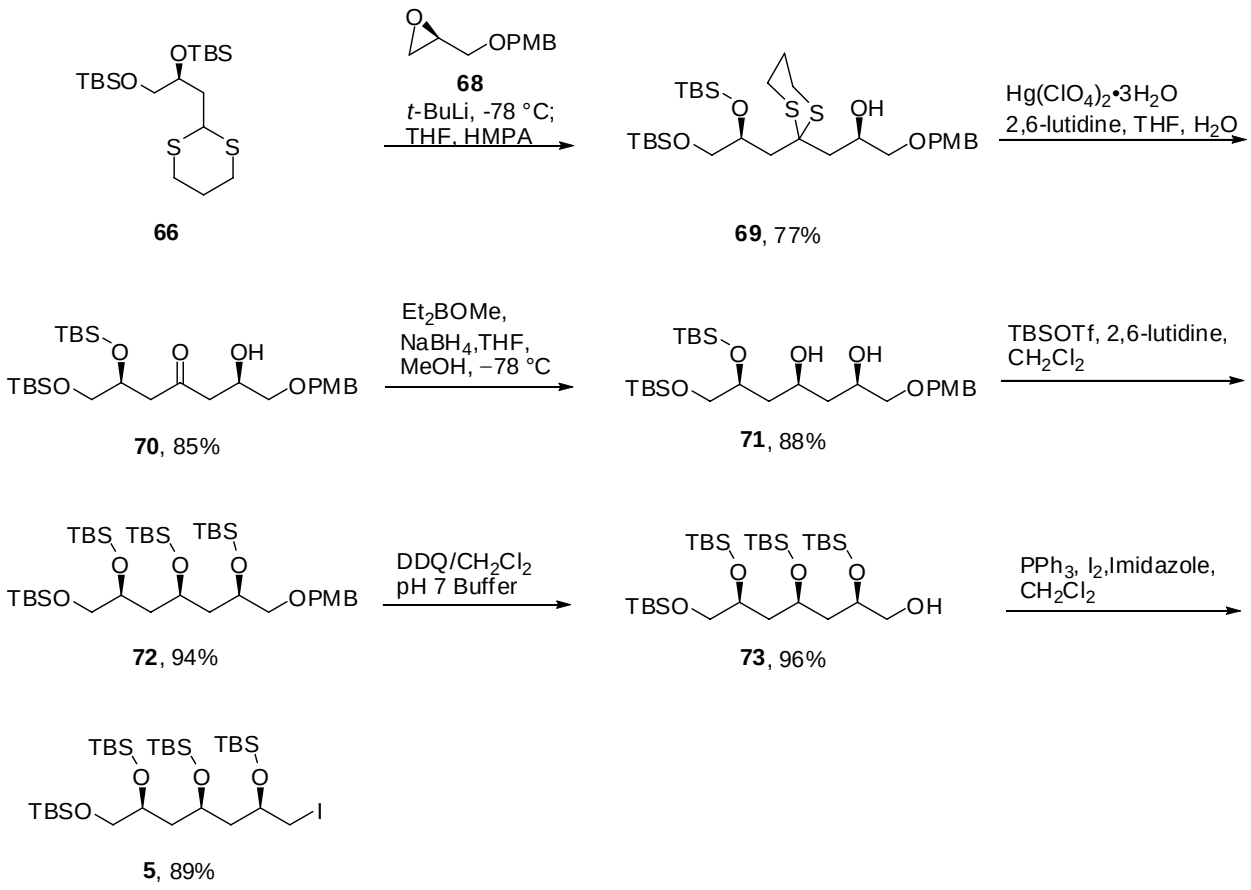
**Scheme 3.5 Synthesis of (*R*)-68**




**67** **68**, 73%

The coupling of **66** and (*R*)-**68** and subsequent steps to make **5** are shown in Scheme 3.6. Dithiane **66** was treated with *t*-BuLi at –78 $^oC$ followed by addition of PMB-epoxide **68** and workup to afford compound **69** in 77% yield (Scheme 3.7). Hydrolysis of dithiane **69** with mercury perchlorate [$Hg(ClO_4)_2 \bullet 3H_2O$] and 2,6-lutidine in aqueous THF gave the β-hydroxy ketone **70** in 85% yield.[26] The β-hydroxy ketone **70** was subjected to diethylmethoxyborane mediated reduction with $NaBH_4$ to afford the *syn*-diol **71** in 88% yield. The secondary hydroxyl groups in diol **71** were protected as TBS ethers by reaction with TBS-triflate and 2,6-lutidine to form compound **72** in 94% yield. The PMB-ether **72** was reacted with DDQ in $CH_2Cl_2$/pH 7 buffer (19:1) to afford the alcohol **73** in 96% yield (Scheme 3.7).[15] The alcohol **73** was then directly converted to iodide **5** in 89% yield by using iodine, triphenylphosphine and imidazole in dichloromethane.[36] Overall, fragment **5** was synthesized in 9 steps with an overall yield 31.9%.

**Scheme 3.6 Synthesis of the C14-C20 fragment 5**

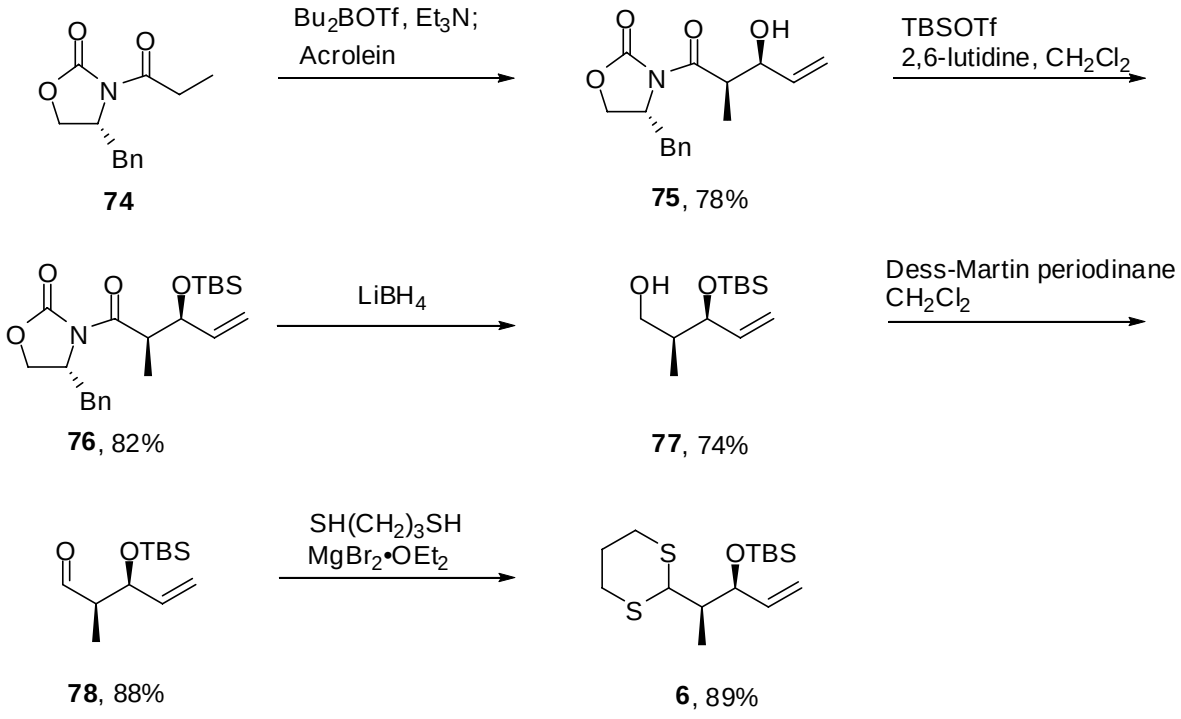



### 3.1.5 Synthesis of the C9-C13 fragment 6

Synthesis of the C9-C13 fragment **6** is illustrated in Scheme 3.7. Asymmetric aldol reaction of freshly distilled acrolein with oxazolidinone **74** gave the aldol product **75** in 78% yield as a single isomer.[37] The secondary alcohol of **75** was protected as TBS-ether **76** with TBSOTf and 2,6-lutidine in 82% yield. Reduction of compound **76** with $LiBH_4$ gave the corresponding alcohol **77** in 74% yield. The primary alcohol **77** was reacted with Dess-Martin reagent in dichloromethane to afford aldehyde **78** in 88% yield.[28] Addition of propane-1,3-dithiol and

$MgBr_2$•$OEt_2$ to aldehyde **78** in THF furnished dithiane **6** in 89% yield.[38] Fragment **6** was synthesized in 5 steps with overall yield 37.1%.

**Scheme 3.7 Synthesis of the C9-C13 fragment 6**

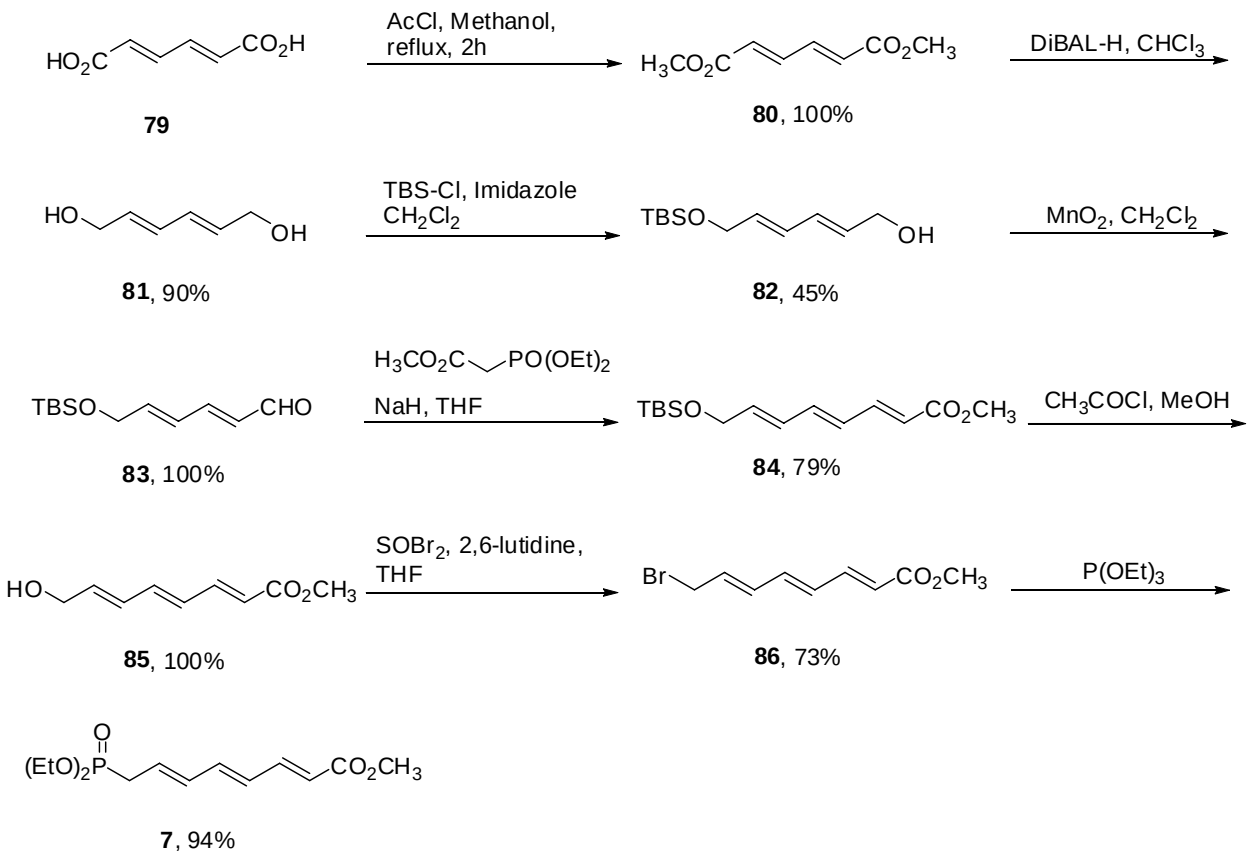



### 3.1.6 Synthesis of the C1-C8 fragment 7

Synthesis of the C1-C8 fragment **7** commenced from *trans-trans*-muconic acid **79** and is summarized in Scheme 3.8. The muconic acid was treated with acetyl chloride in methanol of reflux for 2 h to give (2*E*,4*E*)-dimethylhexa-2,4-dienedioate **80** in quantitative yield. The ester **80** was dissolved in chloroform and reduced with DIBAL-H to furnish diol **81** in 90% yield. Reaction of diol **81** with TBSCl and imidazole in DMF gave the desired mono-TBS ether **82** in

45% isolated yield. Addition of $MnO_2$ to a solution of alcohol **82** in dichloromethane converted the alcohol to aldehyde **83** in quantitative yield.[39] Aldehyde **83** was treated with sodium salt of triethylphosphonoacetate to deliver the ester **84** in 79% yield. Catalytic acidic conditions (AcCl in methanol) were employed to cleave the TBS ether, affording alcohol **85** in quantitative yield as white solid. This was then treated with $SOBr_2$ in presence of 2,6-lutidine to afford the corresponding bromide **86** as white solid in 73% yield. The bromide **86** was reacted with an excess triethylphosphite in refluxing toluene to give the target phosphonate **7** as waxy solid in 94% yield.[40] In summary, fragment **7** was synthesized in 8 steps with overall 22.0% yield.

**Scheme 3.8 Synthesis of the C1-C8 fragment 7**

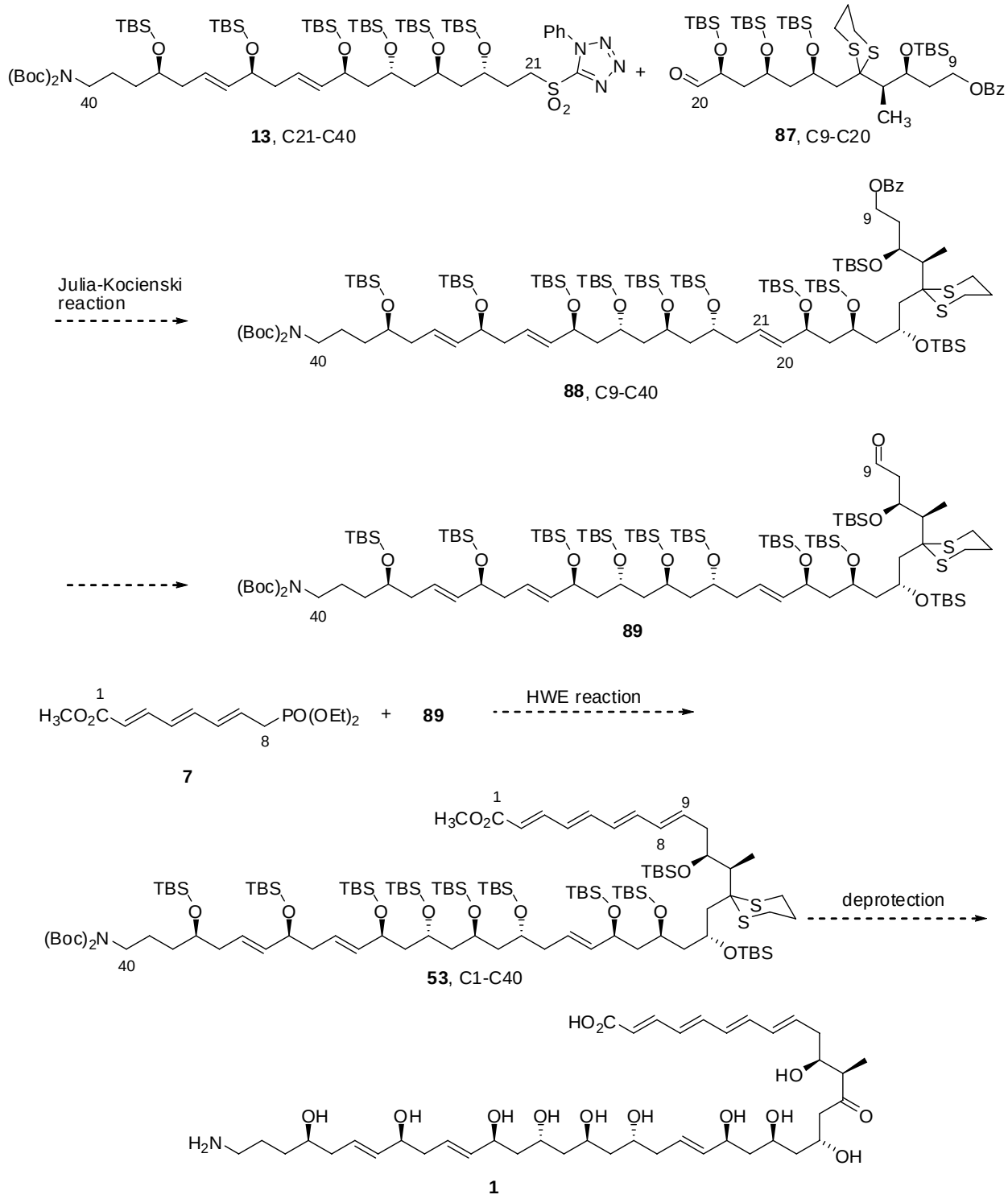


### 3.2 New coupling route: fragment C1-C8 + C9-C20 + C21-C40

#### 3.2.1 Retrosynthesis of tetrafibricin

Dr. Gudipati learned that it was difficult to form the C20-C21 bond by the Julia-Kocienski coupling between fragments C1-C20 and C21-C40. Accordingly, we adopted a new coupling plan shown in Scheme 3.9. Aldehyde **87** (C9-C20) will first be coupled with sulfone **13** (C21-C40) together by Julia-Kocienski reaction to make C20-C21 bond.[13] Then fragment **89** (C9-C40) and fragment **7** (C1-C8) will be coupled by Horner-Wadsworth-Emmons (HWE) reaction to obtain the whole tetrafibricin framework.[41]

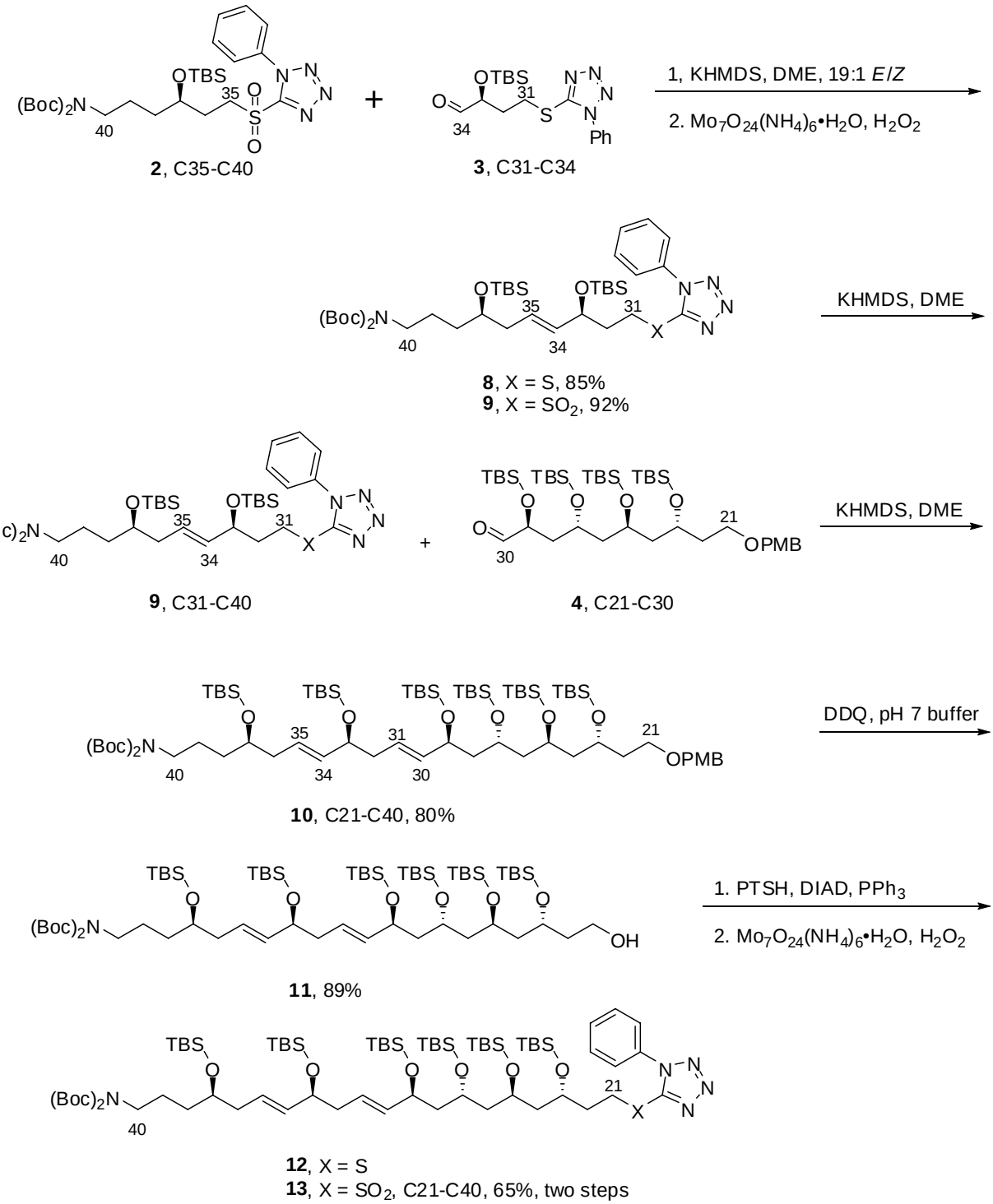
**Scheme 3.9 New coupling route: fragments C1-C8 + C9-C20 + C21-C40**



### 3.2.2 Synthesis of the C21-C40 fragment

To begin the assembly of the fragments, Julia-Kocienski olefination was conducted with sulfone **2** and aldehyde **3** (Scheme 3.10). The anion of the sulfone was generated with KHMDS at –60 $^{o}$C in distilled DME, followed by the addition of aldehyde **3**.[13] The *E* C(34-35) alkene **8** was obtained together with a minor *Z* isomer (85% yield, over 19/1 *E*/*Z* mixture). The Mo-catalyst [$Mo_7O_{24}(NH_4)_6$•$H_2O$, $H_2O_2$] provided a smooth conversion of sulfide **8** to sulfone **9** in 92% yield.[14] Deprotonation of sulfone **9** with KHMDS at –60 $^{o}$C in DME, followed by addition of aldehyde **4** and warming to ambient temperature overnight provided the PMB-ether **10** as a sole C(30-31) (*E*)-isomer in 80% yield. Removal of the PMB protecting group (DDQ, pH 7 buffer, $CH_2Cl_2$) from **10** provided the primary alcohol **11** in 89% yield.[15] Incorporation of the thiotetrazole via the Mitsunobu protocol,[16] 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, furnished sulfone **13** (C21-C40 fragment, 65% yield, two steps).

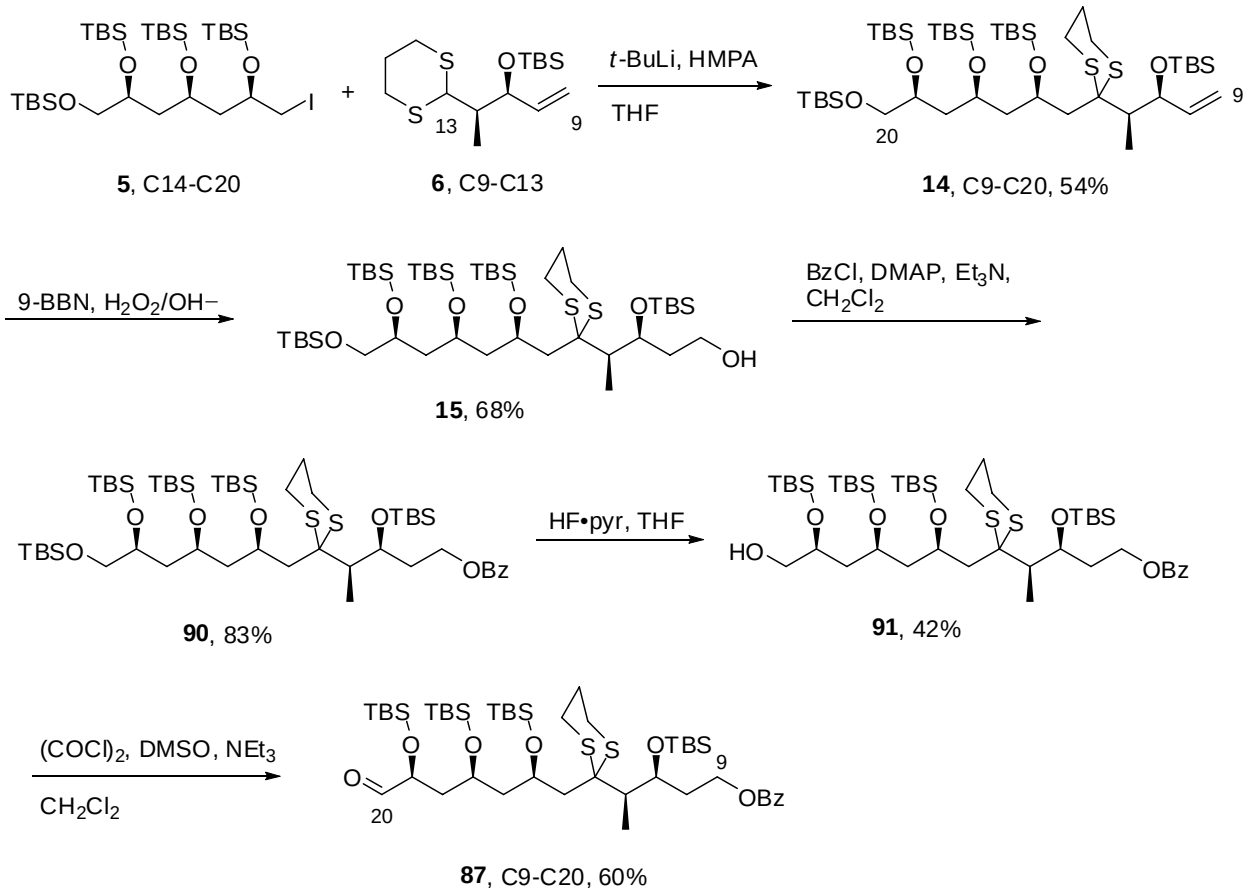
**Scheme 3.10 Synthesis of the C21-C40 fragment**



### 3.2.3 Synthesis of the C9-C20 fragment 87

The assembly of C9-C20 carbon framework of tetrafibricin is shown in Scheme 3.11, and starts with alkylation of dithiane **6** with iodide **5** to make the C13-C14 bond. Deprotonation of dithiane **6** with *t*-BuLi followed by addition of iodide **5** provided alkene **14** in 54% yield. Hydroboration/oxidation of alkene **14** by using 9-BBN and $H_2O_2$ provided the primary alcohol **15** in 68% yield.[42] Benzoylation of alcohol **15** with BzCl, DMAP and $NEt_3$ in dichloromethane provided benzoate **90** in 83% yield. The primary TBS group was then selectively removed by using HF•pyr reagents to afford the alcohol **91** followed by the Swern oxidation to give aldehyde **87** in 60% yield.

**Scheme 3.11 Synthesis of the C9-C20 fragment**

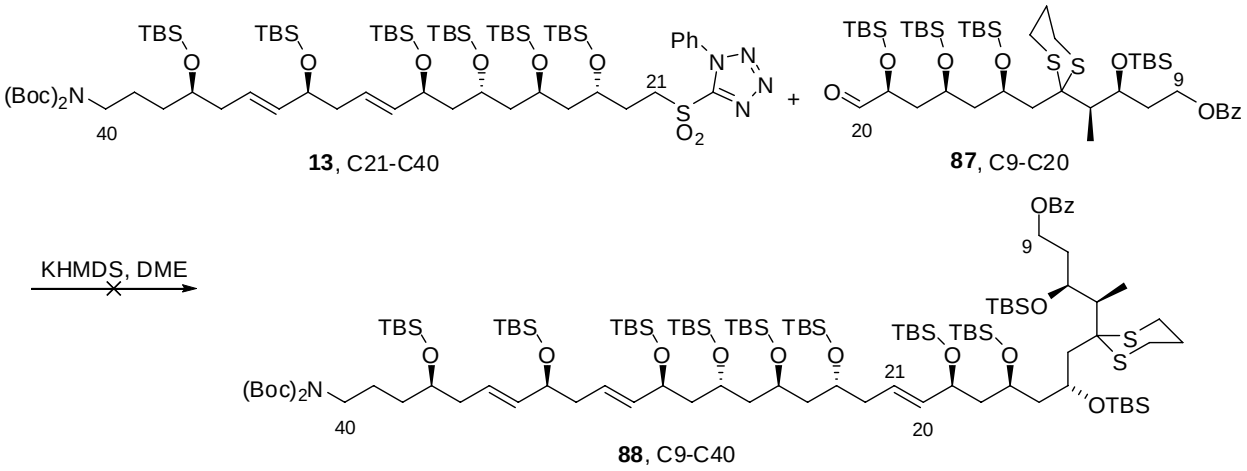



### 3.2.4 Attempts to couple fragments C9-C20 and C21-C40

With two major fragments (C9-C20 and C21-C40) of tetrafibricin in hand, Julia-Kocienski olefination of sulfone **13** with aldehyde **87** was attempted (Scheme 3.12).[13] KHMDS was added to a solution of sulfone **13** in freshly distilled DME at −60 $^{o}$C and the mixture was stirred for 30 min to generate the corresponding sulfone anion. Then a solution of aldehyde **87** in DME was added and the reaction mixture was stirred overnight. Unfortunately, product **88** was not formed,

and neither the sulfone nor the aldehyde was recovered. Several reactions were attempted on scales from 10 mg to 30 mg with similar results. Once again, forming the C20-C21 bond proved to be a roadblock.

**Scheme 3.12 Coupling of fragments C9-C20 and C21-C40**

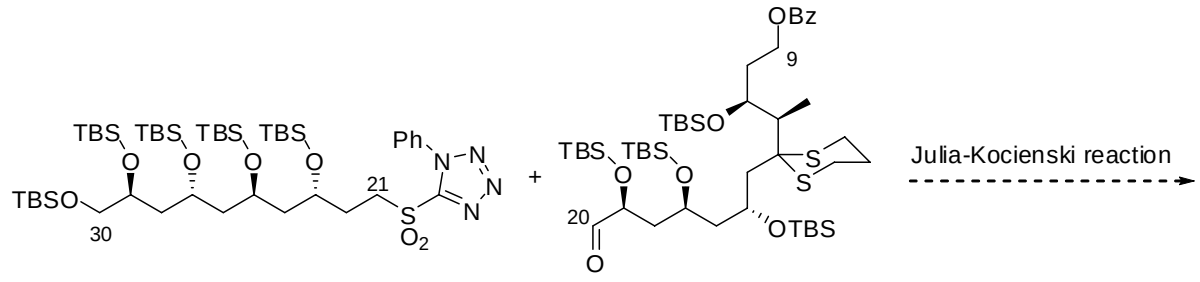



## 3.3 Final coupling route: fragments C1-C8 + C9-C30 + C31-C40

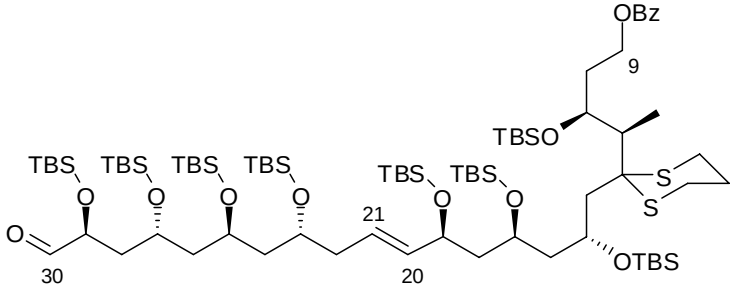
### 3.3.1 Retrosynthesis of tetrafibricin

Since the previous two approaches to fragment coupling both failed on the connection between C20 and C21, we proposed that fragment **87** (C9-C20) would be coupled with fragment **92** (C21-C30) first by Julia-Kocienski reaction to obtain the connection at C20-C21 (Scheme 3.13). Then the fragment **93** (C9-C30) and fragment **9** (C31-C40) will be coupled together to obtain fragment **88** (C9-C40) by another Julia-Kocienski olefination.

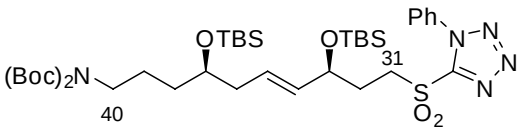
**Scheme 3.13 Coupling of fragments C9-C20 and C21-C30 and C31-C40**



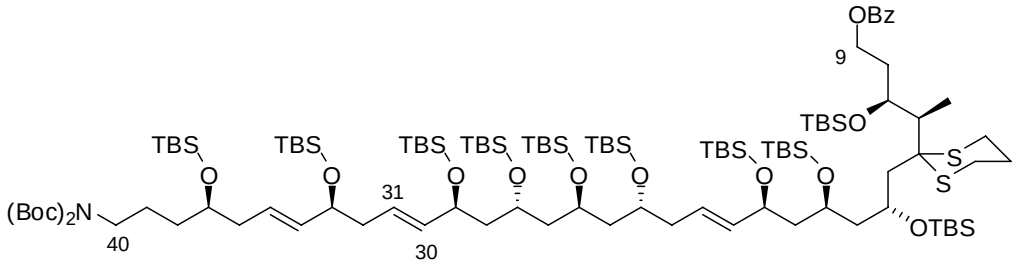

**92**, C21-C30 **87**, C9-C20




**93**, C9-C30




**9**, C31-C40 + **93** HWE reaction

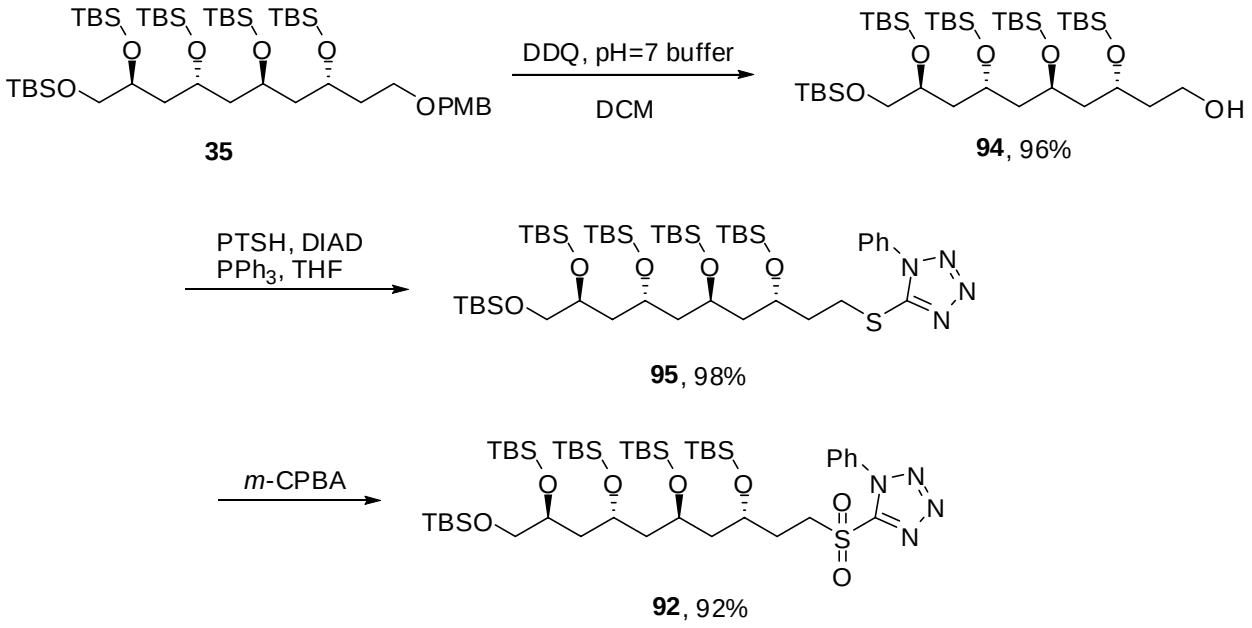



**88**, C9-C40

### 3.3.2 Synthesis of the C21-C30 fragment 92

The synthesis of sulfone **92** (C21-C30) is shown in Scheme 3.14. The PMB protecting group of **35** was first removed by using DDQ with pH 7 buffer in 96% yield,[15] then the alcohol **94** was converted to alkylthiophenyltetrazole **95** in 98% yield by a Mitsunobu reaction.[16] Oxidation of sulfide **95** to the corresponding sulfone **92** was achieved with *m*-CPBA in 92% yield.

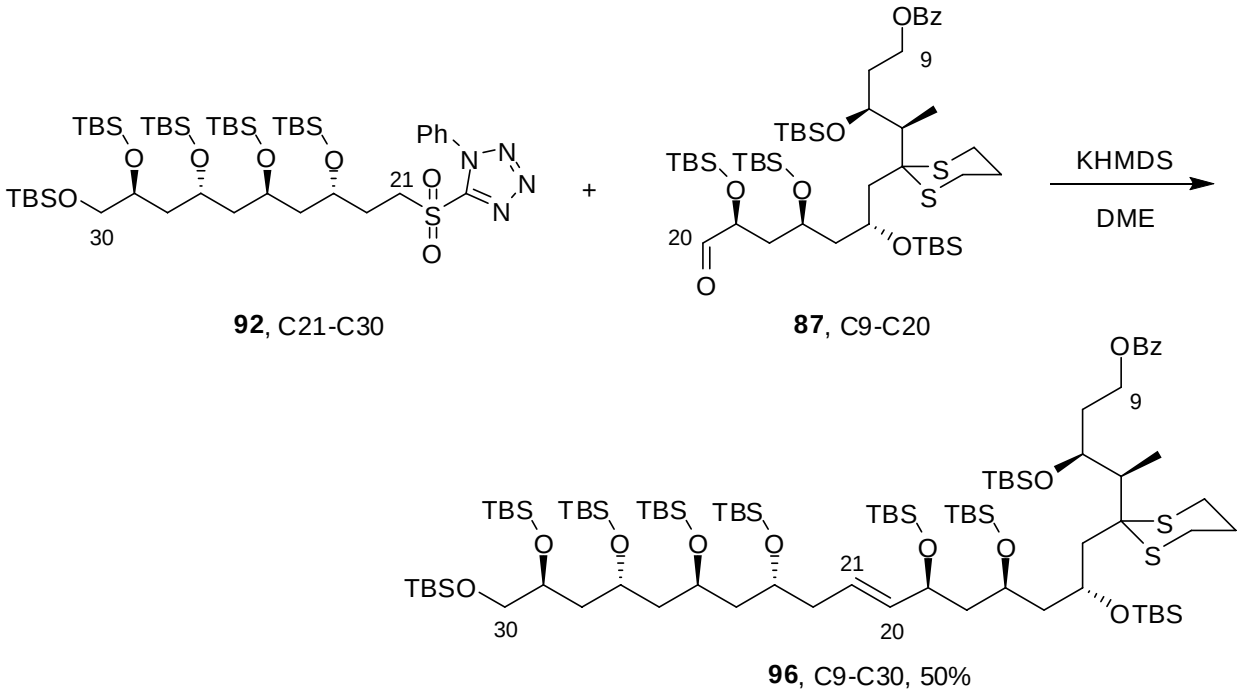
**Scheme 3.14 Synthesis of the C21-C30 fragment**



### 3.3.3 Coupling of fragments C9-20 and C21-C30

To effect the Julia-Kocienski olefination to make the C20-C21 bond, KHMDS was added to a solution of sulfone **92** in DME at −60 °C and the mixture was stirred for 30 min to generate the corresponding sulfone anion (Scheme 3.15). Then a solution of aldehyde **87** in DME was added and the reaction mixture was stirred overnight. The single *E* isomer of olefin **96** was isolated in 50% yield. This is the first successful fragment coupling to make the C20-C21 bond.

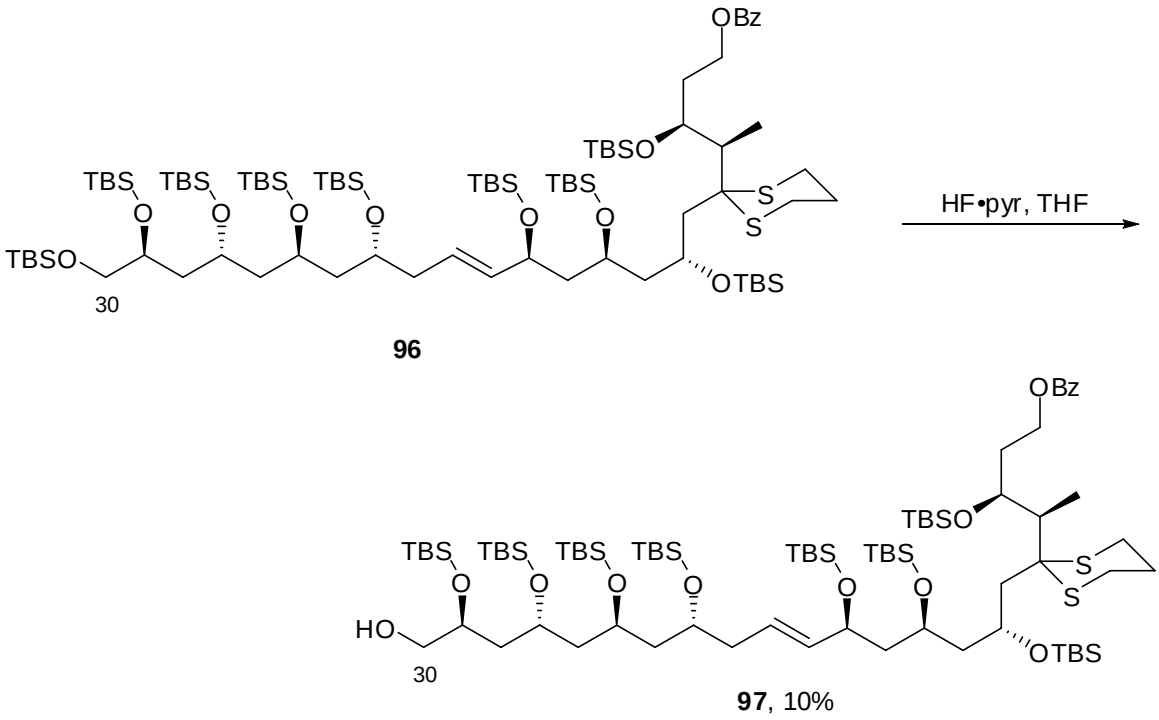
**Scheme 3.15 Coupling of fragments C9-C20 and C21-C30**




Then the primary TBS group of compound **96** was carefully removed by using HF•pyr in THF to obtain alcohol **97** (Scheme 3.16). However, the yield of the selective deprotection was only 10%, presumably because there are 8 other secondary TBS groups. To avoid this big loss of

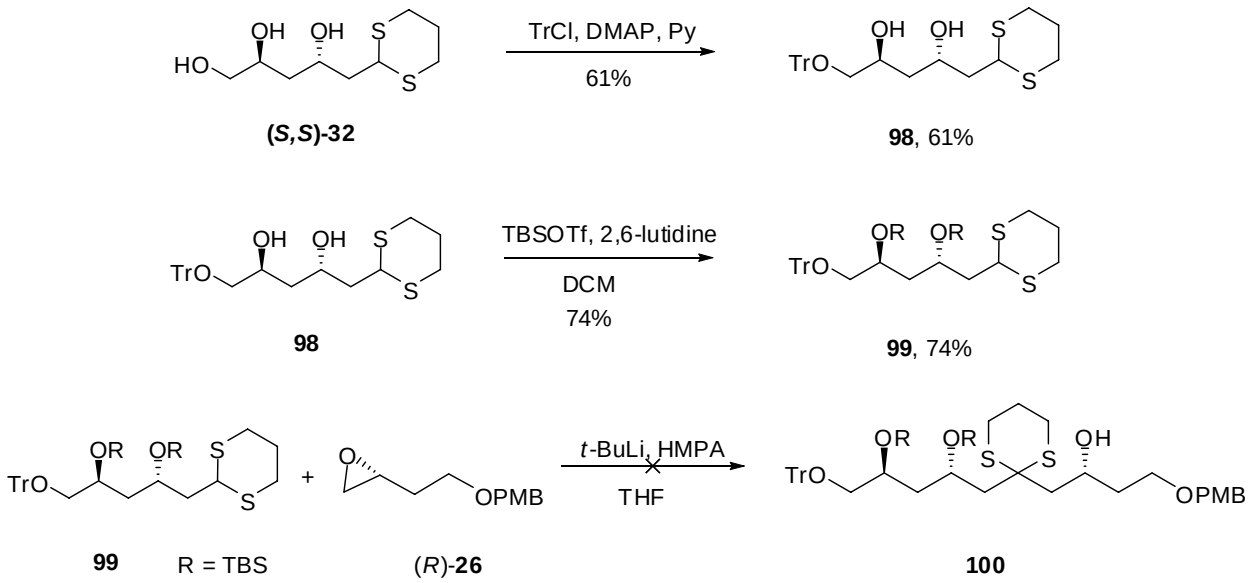
material, we decided to replace the primary TBS group on C30 with a group that was easier remove.

**Scheme 3.16 Deprotection of primary TBS group on C30**



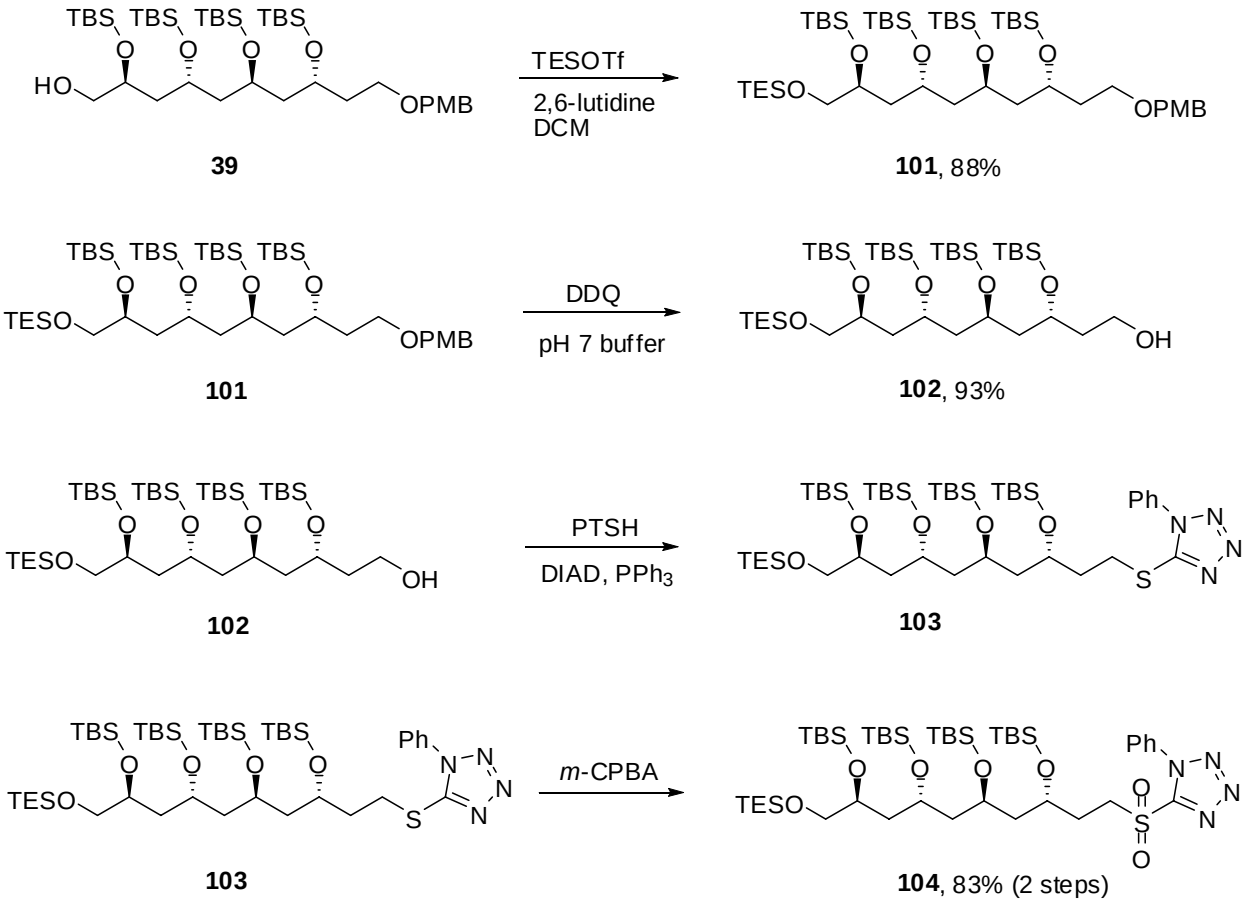

The first target was dithiane **99**, an analog of **25**, in which the primary TBS group is replaced by trityl (triphenylmethane) group (Scheme 3.17). The triol **32** was treated with TrCl and DMAP in pyridine to afford **98** in 61% yield. Then the two secondary alcohols of **98** were protected by TBSOTf with 2,6-lutidine in dichloromethane in 74% yield. However, the coupling reaction between dithiane **99** and epoxide **26** failed to give product **100**.

**Scheme 3.17 Synthesis of the C21-C30 fragment with trityl group**



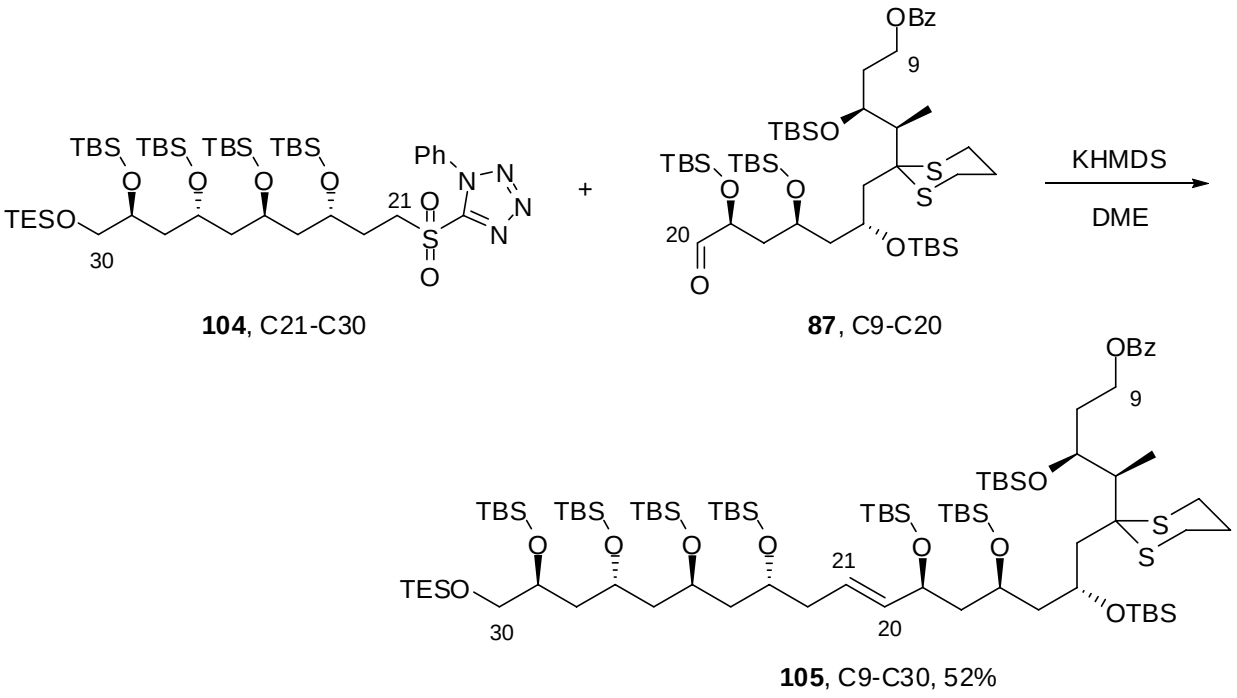

The TES (triethylsilyl) protecting group was selected next because it is similar to the TBS group but is more easily removed (Scheme 3.18). TES protection of the primary alcohol **39** gave the ether **101** in 88% yield. Then deprotection of the PMB group from **101** with DDQ in pH 7 buffer afforded the primary alcohol **102** in 93% yield.[15] Incorporation of the thiotetrazole via the Mitsunobu reaction,[16] employing commercially available 1-phenyl-1*H*-tetrazole-5-thiol, followed by oxidation of the derived sulfide furnished sulfone **104** in 83% yield for two steps.

**Scheme 3.18 Synthesis of the C21-C30 fragment with TES group**




The coupling of sulfone **104** (C21-C30) and aldehyde **87** (C9-C20) is shown in Scheme 3.19. As usual, the sulfone **104** was deprotonated by KHMDS followed by the addition of aldehyde **87** in DME. Once again, the C20-C21 bond formation succeeded. We obtained the single *E* isomer of **105** in 52% yield. The coupling product was characterized by $^{1}$H-NMR and $^{13}$C-NMR spectroscopy. However, we could not obtain its mass spectrum by either ESI (Electrospray ionization) or MALDI (Matrix-assisted laser desorption/ionization) in our department and department of pharmaceutical sciences.

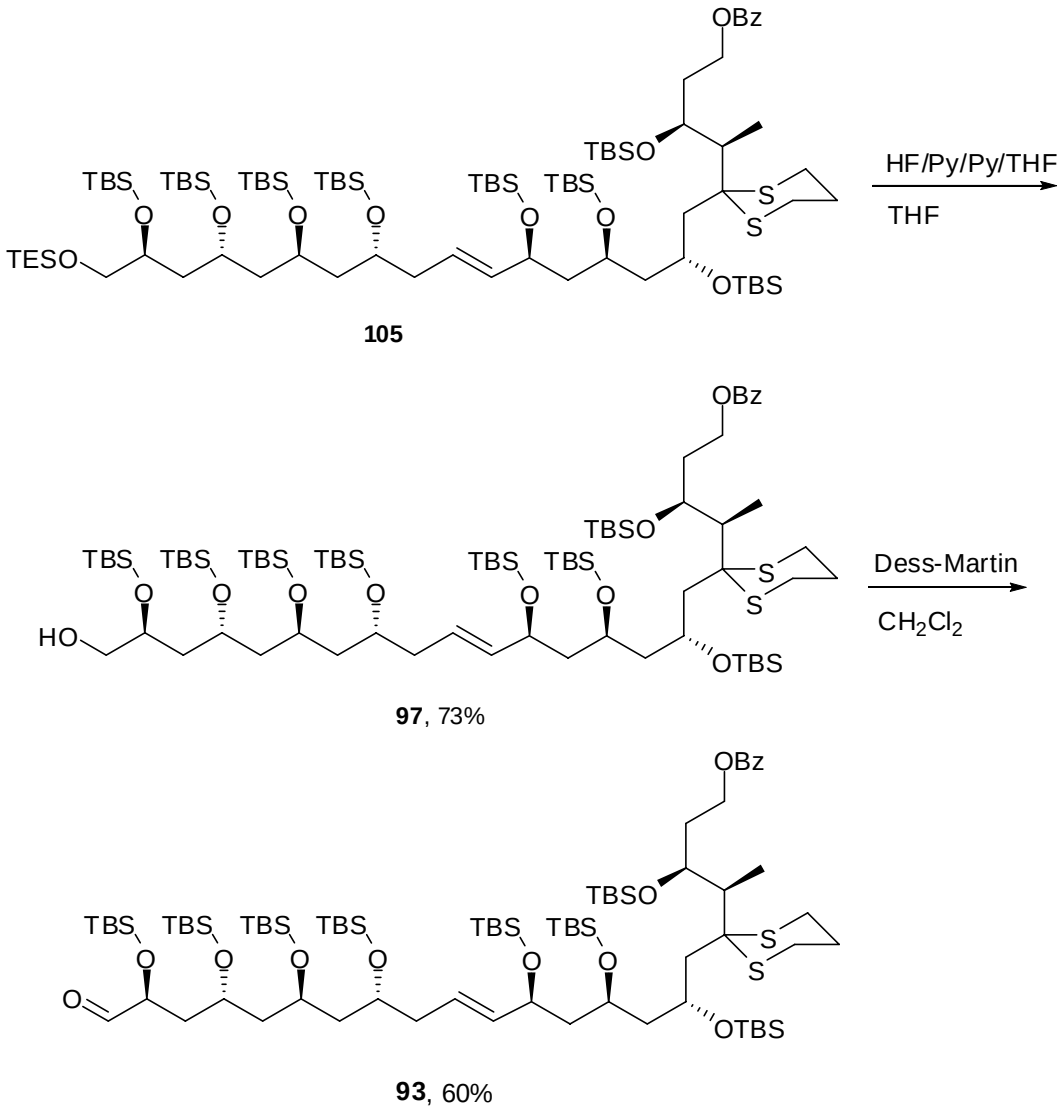
**Scheme 3.19 Coupling of fragments C9-C20 and C21-C30**




### 3.3.4 Synthesis of the C9-C30 fragment

The primary TES protecting group of compound **105** was removed with HF•pyr to provide alcohol **97** in 73% yield (Scheme 3.20). Thus, it indeed proved possible to remove the TES group in good yield in the presence of eight TBS groups. Dess-Martin oxidation of alcohol **97** provided the aldehyde **93** in 60% yield, ready for the further coupling reaction.[28]

**Scheme 3.20 Synthesis of the C9-C30 fragment**

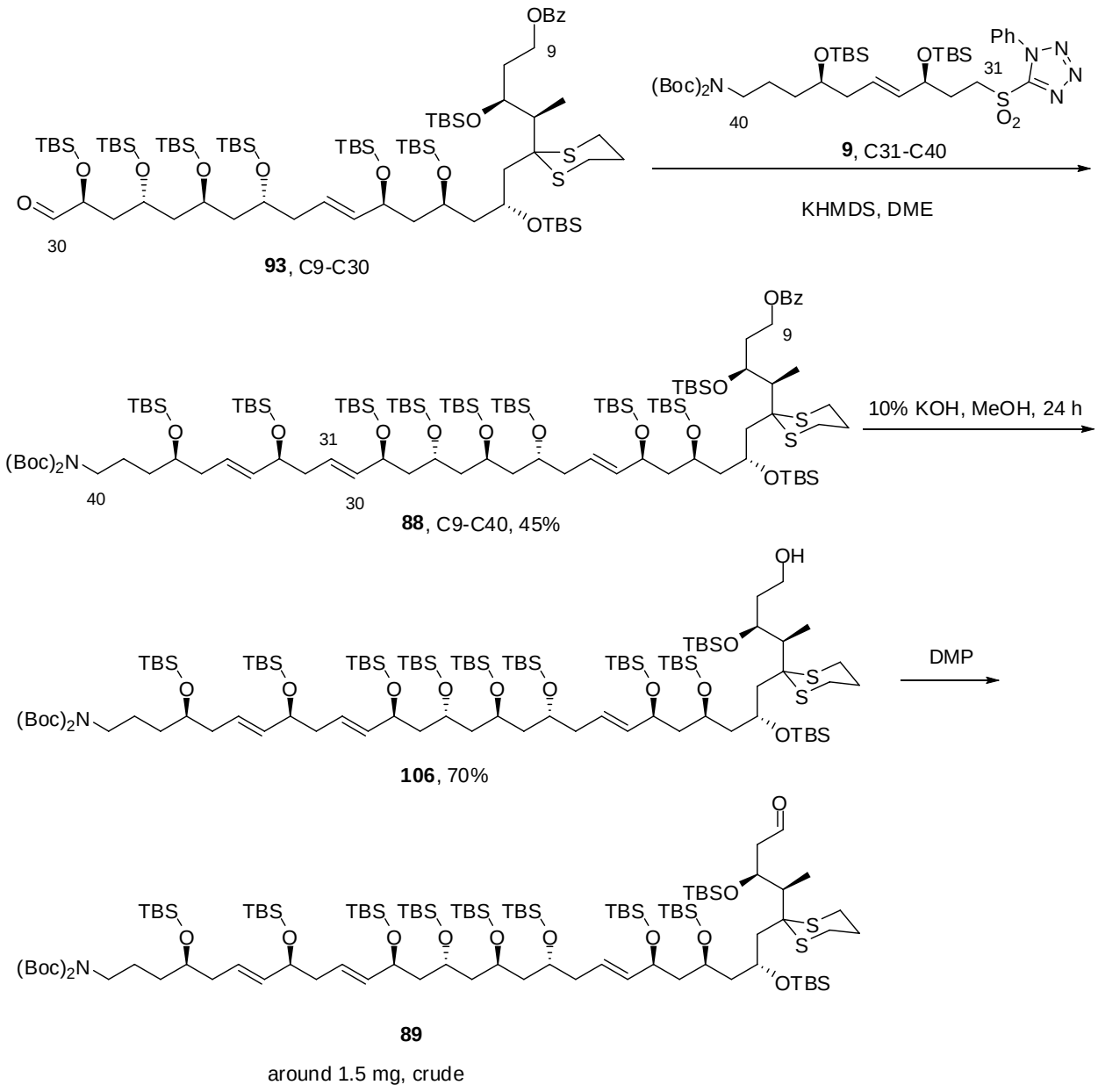



### 3.3.5 Coupling of fragments C9-C30 and C31-C40

With the two major fragments aldehyde **93** (C9-C30) and sulfone **9** (C31-C40) of tetrafibricin in hand, Julia-Kocienski olefination reaction was attempted (Scheme 3.21).[13] KHMDS was added to a solution of sulfone **9** in distilled DME at −60 $^{o}$C and the mixture was stirred for 30

min to generate the corresponding sulfone anion. Then a solution of aldehyde **93** in DME was added and the reaction mixture was stirred overnight. The target coupling product **88** (C9-C40) was isolated in 45% yield. Compound **88** has the complete carbon skeleton and correct oxidation state of tetrafibricin fragment C9-C40. Next the benzoyl group of compound **88** was deprotected by hydrolysis with KOH in methanol followed by the oxidation to afford the aldehyde **89**.

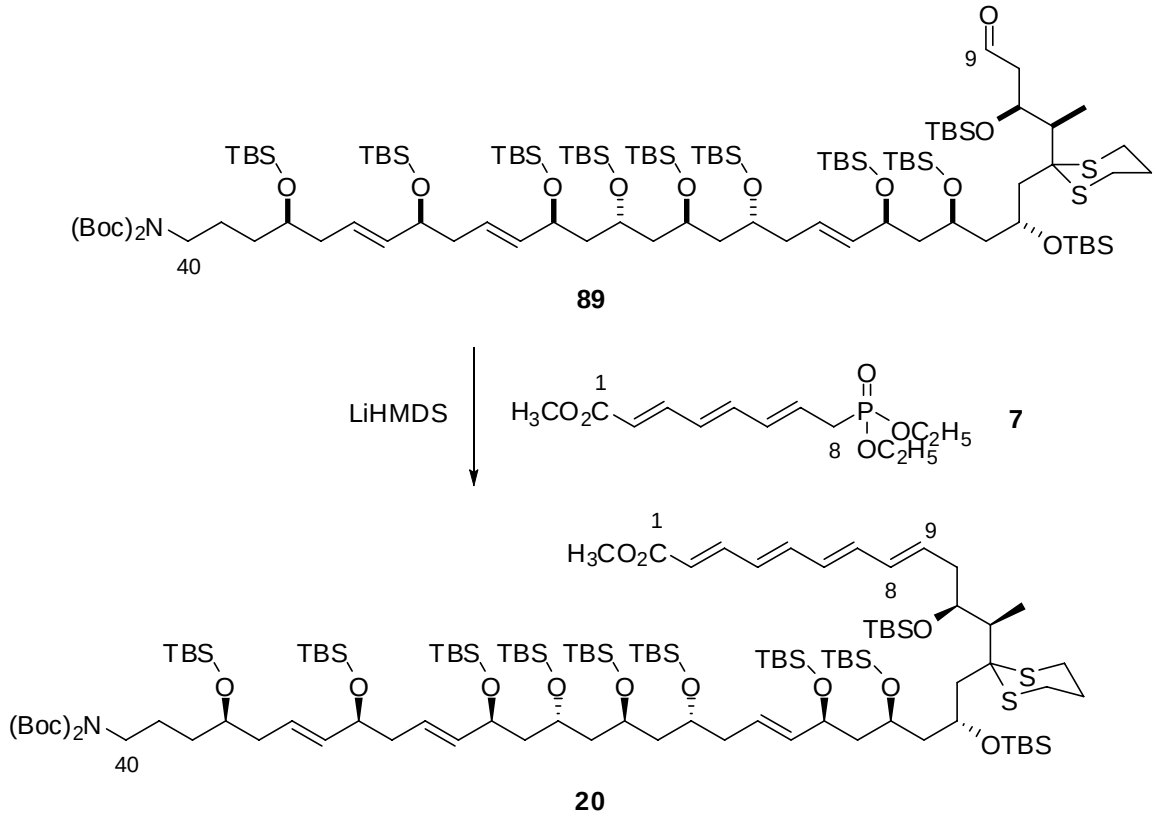
**Scheme 3.21 Coupling of fragments C9-C30 and C31-C40**



### 3.3.6 Coupling of fragments C1-C8 and C9-C40

The final Horner-Wadsworth-Emmons coupling, between the large fragment aldehyde **59** (C9-C40) and phosphonate fragment **7** (C1-C8) is shown in Scheme 3.22.[41] LiHMDS was added to a solution of fragment **7** in THF at −78 $^{o}$C and the mixture was stirred for 30 min to generate the corresponding anion, followed by the addition of aldehyde **59**. The reaction mixture was stirred for 30 min at −78 $^{o}$C and 0 $^{o}$C for 30 min. After workup and purification by HPLC, we obtained the coupling product **20** in 62% yield. This is the first synthesis of a fully protected tetrafibricin. The coupling product was purified by HPLC and characterized by $^{1}$H-NMR spectroscopy only due to the small amount we obtained. And because of the limited amount and high molecular weight of the compound, we could not go further to finish the global deprotection.

**Scheme 3.22 Final coupling of fragments C1-C8 and C9-C40**




## 3.4 Conclusions

A convergent synthesis of the proposed structure of tetrafibricin **1** has been explored. After making six fragments of tetrafibricin **1**, we succeeded their assembly with a series of Julia-Kocienski olefination reactions. This began with alkylation of dithiane **6** with iodide **5** provided C9-C20 carbon skeleton **90** which was then advanced to aldehyde **87**. The first Julia-Kocienski olefination with sulfone **104** (C21-C30) and aldehyde **87** (C9-C20) gave olefin **105** (C9-C30),

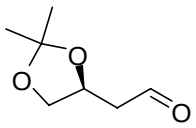
which was then advanced to aldehyde **93** to attempt another Julia-Kocienski olefination. Fragment **9** (C31-C40) was also achieved by Julia-Kocienski olefination of sulfone **2** with aldehyde **3**. Then two big parts aldehyde **93** (C9-C30) and sulfone **9** (C31-C40) were coupled together to afford fragment **88** (C9-C40) by Julia-Kocienski olefination. Finally Horner-Wadsworth-Emmons olefination of phosphonate **7** (C1-C8) with aldehyde **89** (C9-C40) provided **20** (C1-C40) to achieve the whole carbon framework of tetrafibricin. The order of the fragment coupling is crucial in the synthesis of tetrafibricin in order to build the certain bonds. And also other protecting groups for the alcohols on tetrafibricin may be considered in the future synthesis to facilitate the reactions and better characterize the compounds.

## Experimental Procedures and Compound Characterization

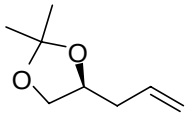
**General:** All reactions were performed under an atmosphere of argon unless otherwise noted. Reaction solvents were freshly dried either by distillation or by passing through an activated alumina column. THF and toluene were freshly distilled from Na/benzophenone. Methylene chloride and $Et_2O$ were dried by activated alumina. All other reagents were purchased commercially and used without further purification unless stated otherwise. Mixtures were magnetically stirred and progress was monitored by TLC with 0.25 mm E. Merck precoated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040-0.063 mm) supplied by Sorbent Technologies.

Products were analyzed by $^{1}H$ NMR, $^{13}C$ NMR, COSY, $^{19}F$ NMR, FT-IR spectroscopy, high and low resolution mass spectrometry, and HPLC. NMR spectra were taken on a Bruker Avance™ 300 or a Bruker Avance™ 500 or a Bruker Avance™ 600 NMR or a Bruker Avance™ 700 spectrometer. Spectra were recorded at room temperature in the indicated deuteriated solvents and chemical shifts are reported in parts per million (ppm) downfield relative to TMS using the residual solvent proton resonance of $CDCl_3$ (7.26 ppm), MeOD (4.87 ppm) or central $CDCl_3$ carbon peak (77.0 ppm), central carbon peak MeOD (47.0 ppm) as the internal standard. In reporting spectral data, the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet doublet, dt = doublet triplet, td = triplet double, ddt = doublet double triplet, dtd = doublet triplet doublet. Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film on NaCl plate. Peaks are reported in wavenumbers ($cm^{-1}$). High resolution mass spectra were obtained on a V/G 70/70 double

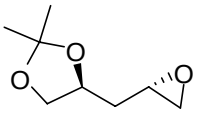
focusing machine and are reported in units of *m*/*z*. HPLC analysis was performed on a Waters 600 E system with a UV detector.



**(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)acetaldehyde ((*S*)-28):** To a solution of alcohol (*S*)-**27** (5.00 g, 34.1 mmol) in dichloromethane (200 mL) at 0 $^{o}$C was added diisopropylethylamine (26.3 mL, 153.9 mmol). After 5 min, DMSO (24.3 mL, 341 mmol) was added and the mixture was stirred for another 10 min. Then $SO_3$•pyr (13.6 g, 85.5 mmol) was added and the resulting mixture was stirred for 45 min. Saturated aqueous $NaHCO_3$ was added and the mixture was 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 residue was purified by flash column chromatography (35% ethyl acetate in hexanes) to yield the aldehyde (*S*)-**28** (4.30 g, 29.4 mmol, 86%) as oil: $[\alpha]_D$ +8.1 (*c* 3.8 $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 9.8 (t, *J* = 1.4 Hz, 1 H), 4.54 (p, *J* = 6.3 Hz, 1 H), 4.19 (dd, *J* = 8.5, 6.0 Hz, 1 H), 3.60 (dd, *J* = 8.5, 6.9 Hz, 1 H), 2.85 (ddd, *J* = 17.3, 6.6, 1.9 Hz, 1 H), 2.65 (ddd, *J* = 17.3, 6.0, 1.1 Hz, 1 H), 1.42 (s, 3 H), 1.37 (s, 3 H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 199.9, 109.3, 70.7, 69.2, 47.9, 26.9, 25.5; IR (neat) cm$^{-1}$ 2987, 2936, 2735, 1725, 1372, 1217; HRMS for $C_6H_9O_3$ $(M - CH_3)^+$: Calcd 129.0552; found129.0550.

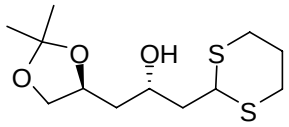


**(*S*)-4-Allyl-2,2-dimethyl-1,3-dioxolane ((*S*)-29) :** To a solution of $CH_3PPh_3Br$ (15.8 g, 44.2 mmol) in THF (500 mL) at 0 $^oC$ was added *n*-BuLi (1.6 M in hexane, 27.6 mL, 44.2 mmol). The reaction mixture was stirred at that temperature for 20 min and then cooled to –78 $^oC$. A solution of the above aldehyde (4.9 g, 34 mmol) in THF (5 mL) was added slowly to the reaction mixture. The mixture was stirred for 30 min at –78 $^oC$ and then warmed to room temperature and stirred overnight. The reaction mixture was poured into saturated aqueous $NH_4Cl$. The layers were separated and the aqueous layer was extracted with $Et_2O$. 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 alkene **(*S*)-29** (4.0 g, 83%) as a volatile oil: $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.4, 7.1 Hz, 1 H), 4.13-4.21 (m, 1 H), 5.07-5.17 (m, 2 H), 4.03 (dd, *J* = 8.2, 6.0 Hz, 1 H), 3.59 (dd, *J* = 8.2, 7.1 Hz, 1 H), 2.37-2.48 (m, 1 H), 2.25-2.34 (m, 1 H), 1.43 (s, 3 H),1.37 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 133.7, 117.7, 109.0, 75.2, 69.0, 38.1, 26.9, 25.7.



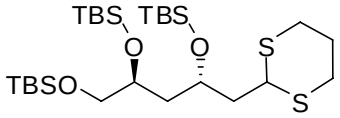
**(*S*)-2,2-dimethyl-4-((*S*)-oxiran-2-ylmethyl)-1,3-dioxolane ((*S,S*)-30):** The above alkene was dissolved in dichloromethane and *m*-CPBA was added at room temperature. The mixture was stirred for overnight. Then the reaction was quenched by adding saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with dichloromethane and the

combined organic extracts were dried over $MgSO_4$ and concentrated. Purification by flash column chromatography ($SiO_2$, 25% ethyl acetate in hexanes) gave the epoxide as a mixture of two diastereomers. The (*S*,*S*)-Jacobsen catalyst (165 mg, 0.27 mmol) was dissolved in the above epoxide (4.2 g, 26.5 mmol), AcOH (65 mg) and THF (0.26 mL). The solution was cooled to 0 $^oC$, treated with water (0.27 mL, 15.0 mmol), and stirred for 16 h at room temperature followed by concentration. Bulb-to-bulb (kugelrohr) distillation of crude product under reduced pressure (0.08 mm Hg, 90-105 $^oC$) gave diastereomerically pure epoxide (*S*,*S*)-**30** (1.89 g, 11.9 mmol, 45%) as colorless oil $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.22 -4.27 (m, 1 H), 4.05 (dd, *J* = 7.8, 5.6 Hz, 1 H), 3.53 (t, *J* = 7.3 Hz, 1 H), 2.97-3.00 (m, 1 H), 2.75 (t, *J* = 4.6 Hz, 1 H), 2.45 (dd, *J* = 4.6, 2.3 Hz, 1 H), 1.91 (ddd, *J* = 14.2, 7.8, 4.1 Hz, 1 H), 1.49 (ddd, *J* = 13.8, 7.3, 5.5 Hz, 1 H), 1.36 (s, 3 H), 1.31 (s, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 108.9, 73.6, 69.3, 49.3, 47.1, 37.1, 26.9, 25.6; 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.

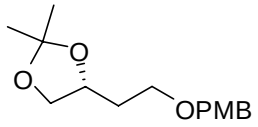



**(*S*)-1-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(1,3-dithian-2-yl)propan-2-ol (31) :** *t*-BuLi (1.7 M in pentane, 5.3 mL, 9.0 mmol) was added to a solution of 1,3-dithiane (1.10 g, 9.04 mmol) in THF/HMPA (5 mL/0.3 mL) at −78 $^oC$. After 30 min, epoxide (*S*,*S*)-**30** (1.3 g, 8.2 mmol) in THF (3 mL) and HMPA (1 mL) was added to the above reaction mixture. After 1 h, the reaction mixture was allowed to warm to 0 $^oC$, treated with saturated aqueous $NH_4Cl$ solution. The layers were 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

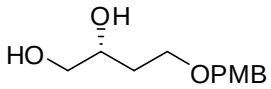
chromatography ($SiO_2$, 25% ethyl acetate in hexanes) to yield the product **31** (1.9 g, 83%) as an oil: $[\alpha]_D$ +6.75 (*c* 0.80 $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 4.31-4.36 (m, 1 H), 4.27 (dd, *J* = 8.9, 5.3 Hz, 1 H), 4.14-4.20 (m, 1 H), 4.09 (dd, *J* = 8.2, 6.0 Hz, 1 H), 3.59 (t, *J* = 7.8 Hz, 1 H), 2.82-2.95 (m, 4 H), 2.67 (d, *J* = 5.0 Hz, 1 H), 2.10-2.16 (m, 1 H), 1.84-1.99 (m, 3 H), 1.69-1.79 (m, 2 H), 1.42 (s, 3 H), 1.36 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 108.9, 73.4, 69.4, 66.1, 44.2, 42.8, 39.8, 30.3, 30.1, 26.9, 25.9, 25.6; 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.




**2-((2*S*,4*S*)-2,4,5-*tris*(*tert*-butyldimethylsilyloxy)pentyl)-1,3-dithiane ((*S*,*S*)-25):** To a solution of the above compound (1.9 g. 6.8 mmol) in methanol (16 mL) was added acetyl chloride (200 μL). After 1 h, the mixture was concentrated to dryness. Then the residue (triol) 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 $^oC$. After 1 h, the reaction was quenched with water. The layers were separated and the aqueous layer was extracted with dichloromethane. 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 provide compound **25** (3.25 g, 88%) as an oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 4.02-4.14 (m, 2 H), 3.69-3.79 (m, 1 H), 3.54 (dd, *J* = 10.2, 5.2 Hz, 1 H), 3.42 (dd, *J* = 10.2, 5.8 Hz, 1 H), 2.75-2.94 (m, 4 H), 2.06-2.19 (m, 1 H), 1.76-1.96 (m, 4 H), 1.47-1.56 (m, 1 H), 0.90 (s, 18 H), 0.89 (s, 9 H), 0.12 (s, 3 H),0.10 (s, 6 H), 0.08 (s, 3 H), 0.06 (s, 6 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 71.2, 67.8, 67.0, 44.2, 44.0, 43.4, 30.8, 30.4, 26.1, 18.5, 18.2, –3.8, –3.9, –4.1, –4.3, –5.2; IR (neat) $cm^{-1}$ 2954, 2929, 2897, 2857, 1472, 1463, 1255.

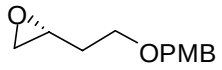



**(*R*)-4-(2-(4-Methoxybenzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolane ((*R*)-33) :** (*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (1.30 g, 8.07 mmol) was added slowly over 10 min to a suspension of NaH (60%, 271 mg, 11.3 mmol) in DMF (15 mL) at 0 $^{o}$C. The mixture was stirred for 30 min followed by the addition of *p*-methoxybenzylchloride (1.33 g, 8.48 mmol). The above reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by adding methanol (1 mL) and then the mixture was poured into water (100 mL). The layers were separated and the aqueous layer was extracted with ether and the combined organic extracts were dried over $MgSO_4$ and concentrated. Purification by flash column chromatography ($SiO_2$, 25% ethyl acetate in hexanes) gave the product (*R*)-**33** (1.53 g, 84%)as colorless oil: $[\alpha]_D$ +0.87 (*c* 1.2 $CHCl_3$); $^1$H NMR (500 MHz, $CHCl_3$) δ 7.25 (d, *J* = 8.2 Hz, 2 H), 6.88 (d, *J* = 8.2 Hz, 2 H), 4.44 (s, 2 H), 4.17-4.25 (m, 1 H), 4.06 (dd, *J* = 8.2, 6.0 Hz, 1 H), 3.81 (s, 3 H), 3.50-3.60 (m, 3 H), 1.89-1.97 (m,1 H), 1.79-1.89 (m, 1 H), 1.41 (s, 3 H), 1.36 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.3, 130.5, 129.3, 113.9, 108.6, 74.0, 72.8, 69.7, 66.8, 55.3, 33.9, 27.0, 25.9; IR (neat) cm$^{-1}$ 2985, 2936, 2865, 1613, 1514, 1248; HRMS for $C_{15}H_{22}O_4$ ($M^+$): Calcd 266.1518; found 266.1514.

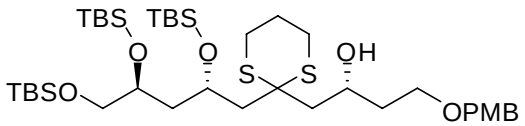



**(*R*)-4-(4-Methoxybenzyloxy)butane-1,2-diol ((*R*)-34):** To a solution of the above compound (1.70 g, 6.04 mmol) in methanol (25 mL) was added acetyl chloride (~100 mg). The reaction mixture was stirred at room temperature for 2 h, followed by concentration of the reaction

mixture. The crude product was purified by flash column chromatography ($SiO_2$, 80% ethyl acetate in hexanes) to yield the diol (*R*)-**34** (1.40 g, 87%)as clear colorless oil: $[\alpha]_D$ –2.6 (*c* 1.4 $CHCl_3$); $^1$H NMR (300 MHz, $CHCl_3$) δ 7.24 (d, *J* = 8.2 Hz, 2 H), 6.88 (d, *J* = 8.2 Hz, 2 H), 4.46 (s, 2 H), 3.81 (s, 3 H), 3.86-3.94 (m, 1 H), 3.58-3.70 (m, 3 H), 3.45-3.54 (m, 1 H), 1.60-1.90 (m, 2 H);$^{13}$C NMR (126 MHz, $CDCl_3$) δ 158.9, 129.6, 129.0, 113.5, 72.5, 67.1, 54.9, 32.8; IR (neat) cm$^{-1}$ 3384, 2934, 1613, 1514, 1249; HRMS for $C_{12}H_{18}O_4$ ($M^+$): Calcd 226.1205; found 226.1199.

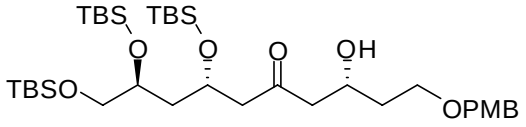



**(*R*)-2-(2-(4-Methoxybenzyloxy)ethyl)oxirane ((*R*)-26):** To a solution of the above diol (800 mg, 3.98 mmol) in toluene (15 mL) were added $PPh_3$ (1.30 g, 4.97 mmol) and DIAD (1.00 g, 4.97 mmol). The mixture was refluxed overnight and concentrated. The crude product was purified by flash column chromatography ($SiO_2$, 25% ethyl acetate in hexanes) to yield epoxide (*R*)-**26** (779 mg, 94%) as oil: $[\alpha]_D$ +12.0 (*c* 1.0 $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 4.47 (s, 2 H), 3.81 (s, 3 H), 3.55-3.64 (m, 2 H), 3.03-3.10 (m, 1 H), 2.79 (t, *J* = 4.6 Hz, 1 H), 2.53 (dd, *J* = 5.0, 2.7 Hz, 1 H), 1.85-1.95 (m, 1 H),,1.72-1.82 (m, 1 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 159.3, 130.4, 129.3, 113.9, 72.8, 66.8, 55.3, 50.1, 47.2, 33.0; IR (neat) cm$^{-1}$ 2997, 2924, 2860, 1613, 1513; HRMS for $C_{12}H_{16}O_3$ ($M^+$): Calcd 208.1099; found 208.1094.



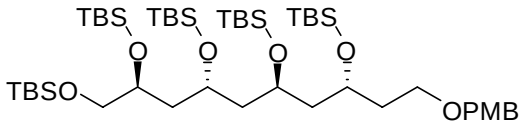

**(*R*)-1-(2-((2*S*,4*S*)-2,4,5-*tris*(*tert*-Butyldimethylsilyloxy)pentyl)-1,3-dithian-2-yl)-4-(4-methoxybenzyloxy)butan-2-ol (35):** *t*-BuLi (1.7 M in pentane, 1 mL, 1.7 mmol) was added to a solution of dithiane (*S*,*S*)-**25** (0.9 g, 1.55 mmol) in THF (2.4 mL)-HMPA (0.6 mL) at –78 $^o$C.

After stirring at –78 °C for 10 min, epoxide (*R*)-**26** (0.36 g, 1.7 mmol) in THF (1 mL) was added. The reaction mixture was stirred at –78 °C for 15 min, then warmed to 0 °C and stirred for 1 h. The reaction was quenched with saturated aqueous $NH_4Cl$ solution. The layers were 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 ($SiO_2$, 20% ethyl acetate in hexanes) to provide compound **35** (1.1 g, 90%) as an oil: $[\alpha]_D$ –5.0 (*c* 0.9 $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 4.47 (s, 2 H), 4.18-4.33 (m, 2 H), 3.81 (s, 3 H), 3.46-3.74 (m, 5 H), 2.84-3.04 (m, 2 H), 2.68-2.83 (m, 2 H), 1.66-2.47 (m, 11 H), 0.94 (s, 9 H), 0.93 (s, 9 H), 0.91 (s, 9 H), 0.09-0.16 (m, 18 H); $^{13}C$ NMR (76 MHz, $CDCl_3$) δ 159.1, 130.4, 129.2, 113.7, 72.7, 71.3, 67.9, 67.5, 67.4, 66.9, 60.3, 55.1, 51.4, 48.3, 46.5, 45.0, 37.6, 26.3, 26.0, 24.6, 18.4, 18.2, 18.0, 14.2, –3.1, –3.6, –3.8, –4.4, –5.3; 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.



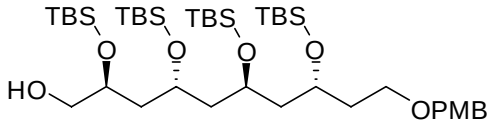

**(3*R*,7*S*,9*S*)-1-(4-Methoxybenzyloxy)-7,9,10-*tris*(*tert*-butyldimethylsilyloxy)-3-hydroxy-decan-5-one (36):** A solution of **35** (610 mg, 0.77 mmol) in THF/$H_2O$ (4:1, 10 mL) was cooled to 0 °C, followed by addition of 2,6-lutidine (662 mg, 6.18 mmol) and $Hg(ClO_4)_2 \bullet H_2O$ (1.05 g, 2.32 mmol) in portions. The reaction mixture was stirred at 0 °C for 45 min and 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 $MgSO_4$ and

concentrated. Purification by flash column chromatography (20% ethyl acetate in hexanes) provided the ketone **36** (454 mg, 84%) as oil: $[\alpha]_D$ –6.53 (*c* 1.73 $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.44 (s, 2 H), 4.15-4.35 (m, 2 H), 3.80 (s, 3 H), 3.64-3.76 (m, 1 H), 3.50-3.63 (m, 3 H), 3.36-3.43 (m, 2 H), 2.54-2.70 (m, 4 H), 1.70-1.83 (m, 3 H), 1.48-1.60 (m, 1 H), 0.93 (s, 9 H), 0.92 (s, 9 H), 0.89 (s, 9 H), 0.13 (s, 6 H), 0.12 (s, 3 H), 0.09 (s, 6 H), 0.08 (s, 3 H); $^{13}C$ NMR (75 MHz, $CHCl_3$) δ 209.9, 159.3, 130.4, 129.3, 113.9, 72.9, 71.2, 67.8, 67.6, 67.0, 66.3, 55.3, 52.1, 50.9, 43.4, 36.2, 26.0, 26.0, 25.9, 18.4, 18.2, 18.0, –3.9, –4.2, –4.3, –4.5, –5.3; 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.



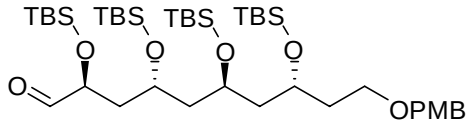

**1-(((3*R*,5*S*,7*R*,9*S*)-3,5,7,9,10-*pentakis*(*tert*-Butyldimethylsilyloxy)decyloxy)methyl)-4-methoxybenzene (38):** To a solution of the above ketone (445 mg, 0.64 mmol) in acetonitrile (2 mL) at –25 °C was added $(CH_3)_4NBH(OAc)_3$ (253 mg, 0.96 mmol) as a solution in acetic acid (0.4 mL). The reaction mixture was stirred at that temperature for 48 h, quenched with 3 mL aqueous 1.0 M sodium potassium tartrate, diluted with ethyl acetate and neutralized with sodium bicarbonate. 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 the crude compound (412 mg) in dichloromethane at 0 °C were added 2,6-lutidine (189 mg, 1.77 mmol) and TBSOTf (327 mg, 1.24 mmol). The resulting mixture was stirred at that temperature for 1 h and then quenched with water. The layers were separated and the aqueous layer was extracted with dichloromethane. 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 compound **38** (434 mg, 73%) as oil: $^1$H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.6 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 4.42 (s, 2 H), 3.87-3.92 (m, 2 H), 3.83-3.87 (m, 1 H), 3.81 (s, 3 H), 3.76-3.80 (m, 1 H), 3.49-3.54 (m, 3 H), 3.41 (dd, *J* = 10.2, 5.5 Hz, 1 H), 1.79-1.84 (m, 1 H), 1.67-1.75 (m, 2 H), 1.59-1.67 (m, 3 H), 1.52-1.58 (m, 1 H), 1.45-1.50 (m, 1 H), 0.90 (s, 9 H), 0.888 (s, 9 H), 0.883 (s, 9 H), 0.88 (s, 9 H), 0.877 (s, 9 H), 0.084 (s, 3 H), 0.082 (s, 3 H), 0.08 (s, 3 H), 0.076 (s, 6 H), 0.07 (s, 3 H), 0.063 (s, 3 H), 0.06 (s, 3 H), 0.055 (s, 3 H), 0.04 (s, 3 H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 159.1, 130.9, 129.2, 113.8, 72.6, 70.8, 67.6, 67.5, 67.4, 67.2, 66.8, 55.3, 46.8, 46.0, 42.6, 37.7, 26.1, 26.1, 26.1, 26.1, 18.5, 18.3, 18.2, 18.1, –3.4, –3.5, –3.7, –3.8, –4.2, –4.4, –5.2; HRMS for $C_{48}H_{100}O_7Si_5Na$ $(M + Na)^+$: Calcd 951.6213; found 951.6311.



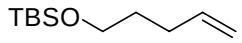

**(2*S*,4*R*,6*S*,8*R*)-10-(4-Methoxybenzyloxy)-2,4,6,8-*tetrakis*(*tert*-butyldimethylsilyloxy) decan-1-ol (39):** To a solution of **38** (70 mg, 0.075 mmol) in THF (0.5 mL) was added HF•pyr in pyridine (1 mL). The reaction mixture was stirred at room temperature for 6 h followed by quenching the reaction with saturated aqueous sodium bicarbonate solution (5 mL). 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 by flash column chromatography ($SiO_2$, 10% ethyl acetate in hexanes) provided the primary alcohol **39** (30 mg, 49%) as colorless oil along with recovered starting material (29 mg, 0.031 mmol): $[\alpha]_D$ +16.5 (*c* 0.2 $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 4.41 (ddd, *J* = 19.8, 11.5, 5.0 Hz, 1 H) 3.85-3.89 (m, 1 H), 3.80-3.85 (m, 6 H), 3.61 (ddd, *J* = 11.0, 5.5, 3.6 Hz,

1 H), 3.50 (t, *J* = 7.1 Hz, 2 H), 3.44 (ddd, *J* = 11.8, 7.1, 5.2 Hz, 1 H), 1.91 (t, *J* = 6.0 Hz, 1 H), 1.80-1.85 (m, 1 H), 1.55-1.73 (m, 7 H), 0.91 (s, 9 H), 0.883 (s, 9 H), 0.88 (s, 18 H), 0.104 (s, 3 H), 0.10 (s, 3 H), 0.08 (s, 6 H), 0.072 (s, 6 H), 0.07 (s, 3 H), 0.05 (s, 3 H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 159.1, 130.8, 129.2, 113.7, 72.6, 70.4, 67.4, 67.2, 67.1, 66.7, 66.6, 55.3, 46.5, 46.3, 42.4, 37.5, 26.0, 18.2, 18.1, –3.5, –3.6, –3.6, –3.7, –4.2, –4.3, –4.3; 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.

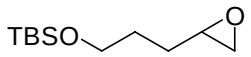



**(2*S*,4*R*,6*S*,8*R*)-10-(4-Methoxybenzyloxy)-2,4,6,8-*tetrakis*(*tert*-butyldimethylsilyloxy) decanal (4):** To a solution of the above primary alcohol (28 mg, 0.034 mmol) in DCM (2 mL) were added solid $NaHCO_3$ (15 mg) and Dess-Martin reagent (17 mg, 0.041 mmol). The reaction mixture was stirred at room temperature for 1 h. Then the reaction was quenched with saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (10% ethyl acetate in hexanes) to yield aldehyde **4** (26 mg, 93%) as an oil used immediately for the next reaction: $^1$H NMR (600 MHz, $CD_2Cl_2$) δ 8.58 (d, *J* = 1.7 Hz, 1 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 4.38 (s, 2 H), 4.15-4.18 (m, 1 H), 3.95-4.00 (m, 1 H), 3.91-3.95 (m, 1 H), 3.82-3.86 (m, 1 H), 3.79 (s, 3 H), 3.47-3.52 (m, 2 H), 1.66-1.81 (m, 6 H), 1.53-1.60 (m, 2 H), 0.97 (s, 9 H), 0.93 (s, 9 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 6 H), 0.08 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); $^{13}$C NMR (151 MHz, $CD_2Cl_2$) δ 203.8, 159.7, 131.6, 129.7, 114.1, 76.1, 73.1, 68.0, 67.6,

67.6, 67.2, 55.8, 47.1, 46.3, 41.2, 38.4, 26.4, 26.3, 18.7, 18.5, –3.0, –3.1, –3.4, –3.5, –3.8, –3.9, –4.3; 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.

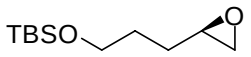



***tert*-Butyldimethyl(pent-4-enyloxy)silane (41):** To a solution of pent-4-en-1-ol (6.00 g, 69.8 mmol) in dichloromethane (400 ml) at 0 $^oC$ were added *tert*-butyldimethylsilyl chloride (11.6 g, 76.7 mmol) and imidazole (5.70 g, 83.7 mmol). The reaction mixture was stirred at 0 $^oC$ for 20 min, then warmed to room temperature and stirred for 1.5 h. Then the reaction was quenched with water. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and concentrated to give the alkene **41** (14.0 g) as an oil. The crude product was taken to the next step without further purification: $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.83 (ddt, $J$ = 17.0, 10.4, 6.6 Hz, 1 H), 4.93-5.07 (m, 2 H), 2.07-2.16 (m, 2 H), 1.56-1.68 (m, 2 H), 0.09 (s, 9 H), 0.06 (s, 6 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 138.6, 114.6, 62.6, 32.1, 30.1, 26.0, 18.4, –5.2.

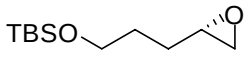



**(*rac*)-*tert*-Butyldimethyl(3-(oxiran-2-yl)propoxy)silane (42):** *m*-Chloroperbenzoic acid (75% w/w in $H_2O$, 16.0 g) was added to a solution of the above alkene (14.0 g, 69.8 mmol) in dichloromethane at 0 $^oC$. The reaction mixture was stirred at 0 $^oC$ for 20 min, then warmed to room temperature and stirred for 1 h followed by adding saturated aqueous $NaHCO_3$ solution. The layers were separated and aqueous layer was further extracted with dichloromethane. 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) gave the epoxide **42** (13.0 g, 88%) as an oil: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 3.59-3.72 (m, 2 H), 2.91-2.99 (m, 1 H), 2.74-2.79 (m, 1 H), 2.49 (dd, *J* = 4.9, 2.7 Hz, 1 H), 1.53-1.76 (m, 4 H), 0.90 (s, 9 H), 0.06 (s, 6 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 62.6, 52.1, 47.0, 29.1, 29.0, 25.9, 18.3, –5.3; IR (neat) cm$^{-1}$ 2954, 2857, 1472, 1256; EIMS $(M - t\text{Bu})^{+}$ :159; HRMS for $C_7H_{15}O_2Si$ $(M - t\text{Bu})^{+}$ : Calcd 159.0841; found 159.0828.

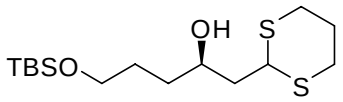



**(*R*)-*tert*-Butyldimethyl(3-(oxiran-2-yl)propoxy)silane ((*R*)-42):** The (*R*,*R*)-Jacobsen catalyst (92 mg, 0.15 mmol) was dissolved in the above epoxide (3.22 g, 14.9 mmol), AcOH (35 μL) and THF (0.17 mL). The solution was cooled to 0 $^{o}$C, treated with water (0.15 mL, 8.2 mmol), and stirred for 16 h at room temperature followed by concentration. Bulb-to-bulb (kugelrohr) distillation of crude product under reduced pressure (0.08 mm Hg, 90-105 $^{o}$C) gave diastereomerically pure epoxide (*R*)-**42** (1.42 g, 6.8 mmol, 45%) as colorless oil: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 3.62-3.69 (m, 2 H), 2.92-2.98 (m, 1 H), 2.75 (t, *J* = 4.5 Hz, 1 H), 2.47 (dd, *J* = 4.8, 2.7 Hz, 1 H), 1.57-1.69 (m, 4 H), 0.90 (s, 9 H), 0.06 (s, 6 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 62.6, 52.2, 47.1, 29.1, 29.0, 25.9, 18.3, –5.3; IR (neat) cm$^{-1}$ 2954, 2857, 1472, 1256.

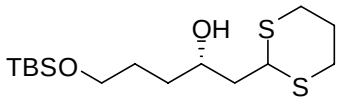



**(*S*)-*tert*-Butyldimethyl(3-(oxiran-2-yl)propoxy)silane ((*S*)-42):** Following the same procedure as above, epoxide (*S*)-**42** (1.75 g, 8.1 mmol, 47%) was obtained as colorless oil: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 3.62-3.69 (m, 2 H), 2.92-2.98 (m, 1 H), 2.75 (t, *J* = 4.5 Hz, 1 H), 2.47 (dd, *J* =

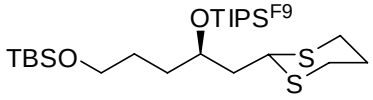
4.8, 2.7 Hz, 1 H), 1.57-1.70 (m, 4 H), 0.90 (s, 9 H), 0.06 (s, 6 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 62.6, 52.2, 47.1, 29.1, 29.0, 25.9, 18.3, –5.3; IR (neat) $cm^{-1}$ 2954, 2857, 1472, 1256.




**(*R*)-5-(*tert*-Butyldimethylsilyloxy)-1-(1,3-dithian-2-yl)pentan-2-ol ((*R*)-43):** *t*-BuLi (1.7 M in pentane, 5.8 mL, 9.9 mmol) was added to a solution of 1,3-dithiane (1.19 g, 9.9 mmol) in THF/HMPA (6.8 mL/3.4 mL) at –78 °C and the mixture was stirred for 30 min. Epoxide (*R*)-**42** (1.44 g, 6.7 mmol) in THF (3.4 mL) and HMPA (1.7 mL) was added to the reaction mixture. The mixture was stirred for 1 h at –78 °C and then allowed to warm to 0 °C and stirred for 2 h. The reaction was quenched by adding saturated aqueous $NH_4Cl$ solution. The layers were 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 ($SiO_2$, 25% ethyl acetate in hexanes) to yield (*R*)-**43** (1.59 g, 70%) as an oil: $[\alpha]_D$ –6.7 (*c* 1.1 $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 4.28 (dd, *J* = 9, 5.4 Hz, 1 H), 3.88-3.98 (m, 1 H), 3.66 (t, *J* = 5.4 Hz, 2 H), 2.78-2.98 (m, 4 H), 2.07-2.18 (m, 1 H), 1.76-1.96 (m, 3 H), 1.42-1.71 (m, 4 H), 0.90 (s, 9 H), 0.07 (s, 6 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 67.9, 63.2, 44.1, 42.8, 34.6, 30.2, 30.0, 28.8, 25.9, 25.8, 18.2, –5.5; HRMS for $C_{15}H_{32}O_2S_2Si$ ($M^+$): Calcd 336.161303; found 336.162389.



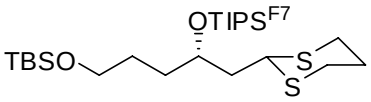

**(*S*)-5-(*tert*-Butyldimethylsilyloxy)-1-(1,3-dithian-2-yl)pentan-2-ol ((*S*)-43):** Following the same procedure as above, (*S*)-**43** (1.54 g, 60%) was obtained as an oil: $[\alpha]_D$ +7.4 (*c* 1.1 $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.25 (dd, *J* = 9, 5.4 Hz, 1 H), 3.87-3.96 (m, 1 H), 3.64 (t, *J* = 5.4 Hz, 2 H), 2.77-2.99 (m, 4 H), 2.03-2.15 (m, 1 H), 1.74-1.93 (m, 3 H), 1.40-1.70 (m, 4 H), 0.90 (s, 9 H), 0.07 (s, 6 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 68.0, 63.3, 44.3, 42.8, 34.7, 30.2, 30.0, 28.9, 26.0, 25.9, 18.3, –5.4; HRMS for $C_{15}H_{32}O_2S_2Si$ ($M^+$): Calcd 336.161303; found 336.162292.




$TIPS^{F9}$ = $Si(i\text{-}Pr)_2C_2H_4C_4F_9$

**(*R*)-8-((1,3-dithian-2-yl)methyl)-13,13,14,14,15,15,16,16,16-nonafluoro-10,10-diisopropyl-2,2,3,3-tetramethyl-4,9-dioxa-3,10-disilahexadecane ((*R*)-21a):** Diisopropyl(3,3,4,4,5,5, 6,6,6-nonafluorohexyl)silane **44a** (1.83 g, 3.9 mmol) was added to a 10 mL flask followed by adding $CF_3SO_3H$ (0.351 mL, 3.9 mmol) dropwise under Ar at 0 $^oC$. The reaction mixture was stirred for 15 min at 0 $^oC$, then warmed to room temperature and stirred for 15 h. Then the homogeneous solution was cooled to 0 $^oC$. A solution of 2,6-lutidine (0.61 mL), alcohol (*R*)-**43** (437 mg, 1.3 mmol) in $CH_2Cl_2$ (5 mL) was added slowly and the reaction mixture was stirred for 4 h. The reaction was quenched by adding saturated $NH_4Cl$ (10 mL) solution at 0 $^oC$. The layers were separated and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) provided (*R*)-**21a** (748 mg, 88%) as oil: $[\alpha]_D$

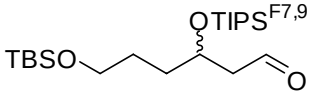
−12.0 (*c* 1.0 $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 4.10 (t, *J* = 7.2 Hz, 2 H), 3.53-3.66 (m, 2 H), 2.74-2.93 (m, 4 H), 2.04-2.24 (m, 3 H), 1.80-1.94 (m, 3 H), 1.47-1.65 (m, 4 H), 1.06 (m, 14 H), 0.88 (s, 11 H), 0.04 (s, 6 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 69.3, 63.0, 44.0, 42.3, 33.7, 30.6, 30.2, 28.0, 26.0, 25.9, 18.3, 17.7, 17.7, 17.7, 17.6, 13.0, 0.8, −5.4; $^{19}$F NMR ($CDCl_3$) −126.0 (2 F), −124.2 (2 F), −116.6 (2 F), −81.0 (3 F); HRMS for $C_{27}H_{49}F_9O_2Si_2S_2K$ $(M + K)^+$: Calcd 735.2206; found 735.2278.




$TIPS^{F7} = Si(i\text{-}Pr)_2C_2H_4C_3F_7$

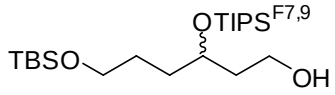
**(*S*)-8-((1,3-dithian-2-yl)methyl)-13,13,14,14,15,15,15-heptafluoro-10,10-diisopropyl-2,2,3,3-tetramethyl-4,9-dioxa-3,10-disilapentadecane ((*S*)-21b):** Diisopropyl(3,3,4,4,5,5,5-heptafluoro pentyl)silane **44b** (1.71 g, 5.5 mmol) was added to a 10 mL flask followed by adding $CF_3SO_3H$ (0.379 mL, 4.2 mmol) dropwise under Ar at 0 $^oC$. The reaction mixture was stirred for 15 min at 0 $^oC$, then warmed to room temperature and stirred for 15 h. Then the homogeneous solution was cooled to 0 $^oC$. A solution of 2,6-lutidine (0.66 mL), alcohol (*S*)-**43** (470 mg, 1.4 mmol) in $CH_2Cl_2$ (5 mL) was added slowly and the reaction mixture was stirred for 4 h. The reaction was quenched by adding saturated $NH_4Cl$ (10 mL) solution at 0 $^oC$. The layers were separated and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) provided (*S*)-**21b** (878 mg, 90%) as oil: $[\alpha]_D$ +11.3 (*c* 1.0 $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 4.10 (t, *J* = 7.2 Hz, 2 H) ), 3.52-3.66 (m, 2 H), 2.73-2.93 (m, 4 H ), 2.05-2.24 (m, 3 H), 1.78-1.94 (m, 3 H), 1.47-1.66 (m, 4 H), 1.05 (m, 14 H), 0.88 (s, 11 H), 0.04

(s, 6 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 69.2, 62.9, 44.0, 42.3, 33.6, 30.6, 30.2, 27.9, 26.0, 25.9, 18.3, 17.8, 17.7, 17.7, 17.6, 12.9, 0.7, –5.4; $^{19}$F NMR ($CDCl_3$) –126.0 (2 F), –124.2 (2 F), –116.6 (2 F), –81.0 (3 F); HRMS for $C_{26}H_{49}F_7O_2Si_2S_2K$ $(M + K)^+$: Calcd 685.2238; found 685.2222.



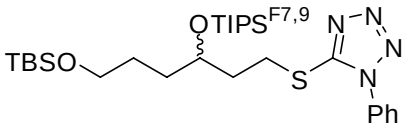

$TIPS^{F7}$ = $Si(i\text{-}Pr)_2C_2H_4C_3F_7$, $TIPS^{F9}$ = $Si(i\text{-}Pr)_2C_2H_4C_4F_9$

**(*Qrac*)-6-(*tert*-Butyldimethylsilyloxy)-3-(perfluoroalkyldiisopropylsilyloxy)hexanal (M-45a,b):** A solution of alcohol M-**21a,b** (1.34 g, 2.0 mmol) in THF/$H_2O$ (4:1, 28 mL) was cooled to 0 $^oC$ followed by addition of 2,6-lutidine (1.9 mL, 16 mmol) at once and $Hg(ClO_4)_2$•$H_2O$ (2.86 g) in portions. The reaction mixture was stirred at 0 $^oC$ for 3 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 $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography ($SiO_2$, 5% ethyl acetate in hexanes) to yield aldehyde M-**45a,b** (831 mg, 72%) as light yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1 H), 4.33-4.37 (m, 1 H), 4.33-4.37 (m, 1 H), 2.57 (m, 2 H), 2.01-2.17 (m, 2 H), 1.47-1.72 (m, 4 H), 1.04 (s, 14 H), 0.88 (s, 11 H), 0.04 (s, 6 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 201.4, 68.5, 62.8, 50.5, 34.3, 28.3, 25.9, 25.3, 18.3, 17.6, 17.6, 17.5, 12.8, 12.7, 0.6, –5.4; $^{19}$F NMR ($CDCl_3$) –127.6 (2 F), –126.0 (2 F), –124.3 (2 F), –117.4 (2 F), –116.7 (2 F), –81.0 (3 F), –80.6 (3 F).



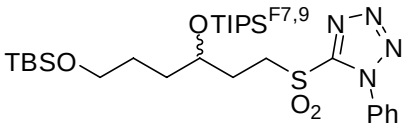

$TIPS^{F7} = Si(i\text{-}Pr)_2C_2H_4C_3F_7$, $TIPS^{F9} = Si(i\text{-}Pr)_2C_2H_4C_4F_9$

**(*Qrac*)-6-(*tert*-Butyldimethylsilyloxy)-3-(diisopropylperfluoroalkylsilyloxy)hexan-1-ol (M-46a,b):** DIBAL-H (1.0 M in hexane, 2.2 mL, 2.2 mmol) was added to a solution of aldehyde M-**45a,b** (811 mg, 1.39 mmol) in THF (20 mL) at −78 °C and the mixture was stirred for 1 h. The reaction mixture was warmed to 0 °C. Then the reaction was quenched with ethanol (1 mL) and saturated sodium-potassium tartrate solution (15 mL) followed by stirring it for 1 h. 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 (25% ethyl acetate in hexanes) provided the alcohol M-**46a,b** (594 mg, 73%) as a clear oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 4.00-4.07 (m, 1 H), 3.78-3.85 (m, 1 H), 3.69-3.76 (m, 1 H), 3.55-3.65 (m, 2 H), 2.01-2.19 (m, 3 H), 1.79-1.88 (m, 1 H), 1.66-1.74 (m, 1 H), 1.57-1.65 (m, 2 H), 1.46-1.55 (m, 2 H), 1.05 (s, 14 H), 0.88 (s, 11 H), 0.04 (s, 6 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 71.8, 63.0, 59.8, 37.8, 33.0, 28.5, 25.9, 25.2, 18.3, 17.6, 17.6, 17.6, 12.8, 0.6, −5.4; $^{19}$F NMR ($CDCl_3$) −127.6 (2 F), −126.0 (2 F), −124.2 (2 F), −117.4 (2 F), −116.7 (2 F), −81.0 (3 F), −80.6 (3 F).



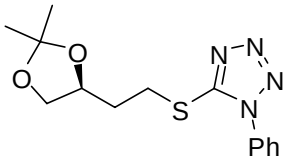

$TIPS^{F7} = Si(i\text{-}Pr)_2C_2H_4C_3F_7$, $TIPS^{F9} = Si(i\text{-}Pr)_2C_2H_4C_4F_9$

**(*Qrac*)-5-(6-(*tert*-Butyldimethylsilyloxy)-3-(perfluoroalkyldiisopropylsilyloxy)hexylthio)-1-phenyl-1*H*-tetrazole (M-47a,b):** Diisopropylazodicarboxylate (0.35 mL) was added to a solution of the above alcohol (574 mg, 0.98 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (486 mg, 1.73 mmol) and triphenylphosphine (460 mg, 1.74 mmol) in THF (15 mL) at 0 $^{o}$C. The reaction mixture was stirred at room temperature for 2.5 h. Then the reaction was quenched by adding 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 (5% ethyl acetate in hexanes) provided the sulfide M-**47a,b** (670 mg, 92%) as oil: $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.52-7.57 (m, 5 H), 3.97 (tt, J = 6, 5 Hz, 1 H), 3.56-3.64 (m, 2 H), 3.38-3.50 (m, 2 H), 1.96-2.16 (m, 4 H), 1.45-1.67 (m, 4 H), 1.03 (s, 14 H), 0.088 (s, 11 H), 0.031 (s, 6 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 154.2, 133.7, 130.0, 129.8, 123.8, 71.4, 62.9, 35.6, 33.3, 29.1, 28.2, 25.9, 25.3, 18.3, 17.7, 17.7, 17.7, 12.6, 0.6, –5.3; $^{19}$F NMR ($CDCl_3$) –127.5 (2 F), –126.0 (2 F), –124.2 (2 F), –117.3 (2 F), –116.7 (2 F), –81.0 (3 F), –80.7 (3 F); HRMS for $C_{30}H_{50}N_4O_2F_7SSi_2$ ($M^+$): Calcd 719.3081; found 719.3055; HRMS for $C_{31}H_{50}N_4O_2F_9SSi_2$ ($M^+$): Calcd 769.3096; found 769.3049.



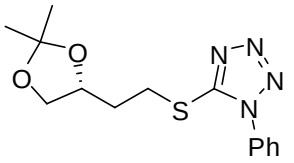

$TIPS^{F7} = Si(i\text{-}Pr)_2C_2H_4C_3F_7$, $TIPS^{F9} = Si(i\text{-}Pr)_2C_2H_4C_4F_9$

**(*Qrac*)-5-(6-(*tert*-Butyldimethylsilyloxy)-3-(perfluoroalkyldiisopropylsilyloxy)hexylsulfonyl)-1-phenyl-1*H*-tetrazole (M-2a,b):** *m*-Chloroperbenzoic acid (590 mg, 3.41 mmol) was added to a solution of the above sulfide (636 mg, 0.85 mmol) in dichloromethane (10 mL) at 0 $^{o}$C. The mixture was stirred for 2 h followed by warming to room temperature and stirring overnight. The reaction was quenched by adding saturated $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane and concentrated. Purification of the crude product by flash column chromatography ($SiO_2$, 10% ethyl acetate in hexanes) to provide sulfone M-**2a,b** (562 mg, 85%) as oil: $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.57-7.70 (m, 5 H), 4.03-4.09 (m, 1 H), 3.75-3.89 (m, 2 H), 3.56-3.67 (m, 2 H), 2.03-2.24 (m, 4 H), 1.47-1.70 (m, 4 H), 1.05 (s, 14 H), 0.88 (s, 11 H), 0.039 (s, 6 H); $^{13}$C NMR (126 MHz, $CHCl_3$) δ 153.4, 133.0, 131.4, 129.7, 125.0, 70.4, 62.6, 52.0, 33.0, 28.3, 25.8, 25.3, 18.2, 17.6, 17.5, 17.5, 12.7, 0.6, −5.5; $^{19}$F NMR ($CDCl_3$) −127.5 (2 F), −126.0 (2 F), −124.2 (2 F), −117.3 (2 F), −116.7 (2 F), −81.0(3 F), −80.7 (3 F); IR (neat) $cm^{-1}$ 2953, 2867, 1499, 1472, 1463, 1347, 1231, 1098, 838, 776; HRMS for $C_{30}H_{50}N_4O_4F_7SSi_2$ $(M + H)^+$: Calcd 751.2980; found 751.3050; HRMS for $C_{31}H_{50}N_4O_4F_9SSi_2$ $(M + H)^+$: Calcd 801.2948; found 801.3012.



**(*S*)-5-(2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethylthio)-1-phenyl-1*H*-tetrazole ((*S*)-48):**

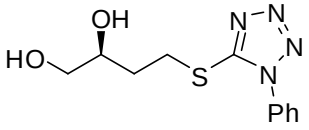
Diisopropylazodicarboxylate (2.8 g, 14 mmol) was added to a solution of alcohol (*S*)-**27** (1.2 g, 8.2 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (2.60 g, 14.8 mmol) and triphenylphosphine (3.00 g, 11.5 mmol) in THF (20 mL) at 0 $^{o}$C. The reaction mixture was stirred at room temperature for 3 h. Then the reaction was quenched with water. The layers were 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 (*S*)-sulfide (*S*)-**48** (1.97 g, 6.45 mmol, 79%) as colorless crystal: $[\alpha]_D$ −1.0 (*c* 1.0 $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.53 (br s, 6 H), 4.18-4.27 (m, 1 H), 4.06 (dd, *J* = 8.1, 6.1 Hz, 1 H), 3.59 (dd, *J* = 8.1, 6.6 Hz, 1 H), 3.36-3.55 (m, 2 H), 1.99-2.20 (m, 2 H), 1.39 (s, 3 H), 1.31 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 154.1, 133.6, 130.1, 129.8, 123.7, 109.2, 74.2, 68.9, 33.4, 29.6, 26.9, 25.5; 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.



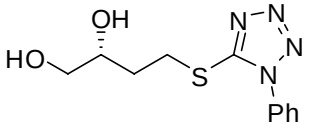
**(*R*)-5-(2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethylthio)-1-phenyl-1*H*-tetrazole ((*R*)-48):**

Following the same procedure as above, the (*R*)-sulfide (*R*)-**48** (2.15 g, 7.03 mmol, 86%) was obtained as colorless crystal: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.53 (br s, 6 H), 4.18-4.27 (m, 1 H),

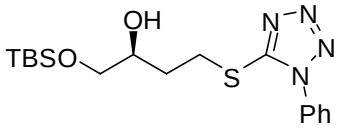
4.06 (dd, *J* = 8.1, 6.1 Hz, 1 H), 3.59 (dd, *J* = 8.1, 6.6 Hz, 1 H), 3.36-3.55 (m, 2 H), 1.99-2.20 (m, 2 H), 1.39 (s, 3 H), 1.31 (s, 3 H).



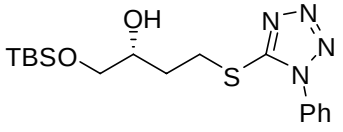

**(*S*)-4-(1-Phenyl-1*H*-tetrazol-5-ylthio)butane-1,2-diol ((*S*)-49):** To a solution of the above (*S*)-sulfide (810 mg, 2.64 mmol) in methanol (10 mL) was treated with a drop of acetyl chloride (21 mg). Then the reaction mixture was stirred for 30 min. Concentration of the reaction mixture followed by purification of the crude product with flash column chromatography ($SiO_2$, 80% ethyl acetate in hexanes) provided the (*S*)-diol (*S*)-**49** (650 mg, 2.45 mmol, 93%) as viscous oil: $[\alpha]_D$ −7.5 (*c* 1.82 $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.58 (br s, 5 H), 3.85-4.13 (m, 2 H), 3.68-3.81 (m, 1 H), 3.56-3.68 (m, 2 H), 3.42-3.55 (m, 1 H), 2.55 (br s, 1 H), 1.90-2.09 (m, 2 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 155.1, 133.5, 130.4, 129.9, 124.0, 69.5, 66.4, 29.8; 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 235.065358; found 235.065690.




**(*R*)-4-(1-Phenyl-1*H*-tetrazol-5-ylthio)butane-1,2-diol ((*R*)-49):** Following the same procedure as above, the (*R*)-diol (*R*)-**49** (650 mg, 2.45 mmol, 93%) was obtained as viscous oil: $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.58 (br s, 5 H), 3.85-4.13 (m, 2 H), 3.68-3.81 (m, 1 H), 3.56-3.68 (m, 2 H), 3.42-3.55 (m, 1 H), 2.55 (br s, 1 H), 1.90-2.09 (m, 2 H).

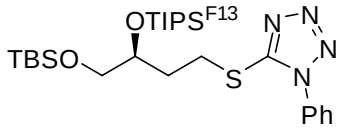



**(*S*)-1-(tert-butyldimethylsilyloxy)-4-(1-phenyl-1*H*-tetrazol-5-ylthio)butan-2-ol ((*S*)-50):** To a solution of the above (*S*)-diol (5.40 g, 20.3 mmol) in dichloromethane (200 ml) at 0 $^{o}$C was added imidazole (1.52 g, 22.3 mmol). *Tert*-butyldimethylsilyl chloride (3.67 g, 24.4 mmol) was added in one portion. The resulting suspension was stirred at room temperature for 14 h. The reaction was quenched with water. The layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to provide compound (*S*)-**50** (6.96 g, 91%) as a colorless oil: $[\alpha]_D$ –3.0 (*c* 1.0 $CHCl_3$) $^1$H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 2 H), 3.77-3.87 (m, 1 H), 3.63-3.67 (dd, *J* = 10.2, 6.3 Hz, 1 H), 3.46-3.58 (m, 3 H), 2.81-2.82 (d, *J* = 4.5 Hz, 1 H), 1.83-2.12 (m, 2 H), 0.90 (s, 9 H), 0.07 (s, 6 H); $^{13}$C NMR (126 MHz, $CHCl_3$) δ 154.5, 133.7, 130.1, 129.8, 123.8, 70.0, 66.8, 32.7, 31.0, 29.8, 25.9, 18.3, –5.4; HRMS for $C_{13}H_{19}N_4O_2SSi$ $(M - C_4H_9)^+$ : Calcd 323.099801; found 323.098886.



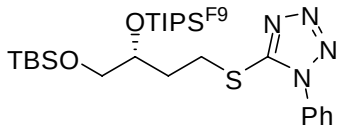

**(*R*)-1-(tert-butyldimethylsilyloxy)-4-(1-phenyl-1*H*-tetrazol-5-ylthio)butan-2-ol ((*R*)-50):** Following the same procedure as above, compound (*R*)-**50** (5.98 g, 90%) was obtained as a colorless oil: $[\alpha]_D$ +3.1 (*c* 1.0 $CHCl_3$) $^1$H NMR (300 MHz, $CDCl_3$) δ 7.53 (s, 2 H), 3.73-3.83 (m, 1 H), 3.59-3.64 (dd, *J* = 9.9, 6.0 Hz, 1 H), 3.43-3.55 (m, 3 H), 2.80-2.81 (d, *J* = 4.2 Hz, 1 H),

1.78-2.08 (m, 2 H), 0.87 (s, 9 H), 0.05 (s, 6 H); HRMS for $C_{13}H_{19}N_4O_2SSi$ $(M - C_4H_9)^+$: Calcd 323.099801; found 323.099465.



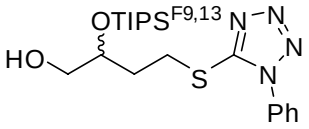

$TIPS^{F13} = Si(i\text{-}Pr)_2C_2H_4C_6F_{13}$

**(*S*)-5-(4-(*tert*-Butyldimethylsilyloxy)-3-(diisopropyl(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-octyl)silyloxy)butylthio)-1-phenyl-1*H*-tetrazole ((*S*)-22c):** Diisopropyl(3,3,4,4,5,5,6,6,7,7,8,8-tridecafluoro-octyl)silane **44c** (540 mg, 1.17 mmol) was added to a 5 mL flask followed by adding $CF_3SO_3H$ (0.081 mL, 0.90 mmol) dropwise under Ar at 0 $^oC$. The reaction mixture was stirred for 15 min at 0 $^oC$, then warmed to room temperature and stirred for 15 h. Then the homogeneous solution was cooled to 0 $^oC$. A solution of 2,6-lutidine (0.144 mL), compound (*S*)-**50** (114 mg, 0.30mmol) in $CH_2Cl_2$ (5 mL) was added slowly and the reaction mixture was stirred for 4 h. The reaction was quenched by adding saturated $NH_4Cl$ (10 mL) solution at 0 $^oC$. The organic layer was separated and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) provided (*S*)-**22c** (230 mg, 90%) as oil: $[\alpha]_D$ −8.7 (*c* 1.1 $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.042 (s, 6 H), 0.84 (s, 9 H), 1.04 (s, 16 H) 1.96-2.18 (m, 4 H), 3.41-3.72 (m, 4 H), 3.94-3.98 (m, 1 H), 7.56 (s, 5 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 154.2, 133.8, 130.0, 129.7, 123.8, 72.3, 66.7, 33.7, 29.0, 25.5, 18.3, 17.6, 17.6, 17.2, 12.8, 12.2, 0.7, –5.3; $^{19}F$ NMR ($CDCl_3$) −126.2 (2 F), −123.3 (2 F), −122.9 (2 F), −122.0 (2 F), −116.6 (2 F), −80.9 (3 F); HRMS for $C_{31}H_{46}F_{13}N_4O_2Si_2S$ $(M + H)^+$: Calcd 841.2672; found 841.2695.



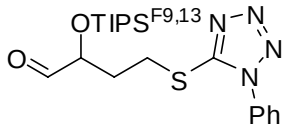

$TIPS^{F9} = Si(i\text{-}Pr)_2C_2H_4C_4F_9$

**(*R*)-5-(4-(*tert*-Butyldimethylsilyloxy)-3-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluoro-hexyl)silyloxy)butylthio)-1-phenyl-1*H*-tetrazole ((*R*)-22a):** Diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silane **44a** (416 mg, 0.90 mmol) was added to a 5 mL flask followed by adding $CF_3SO_3H$ (0.062 mL, 0.69 mmol) dropwise under Ar at 0 $^oC$. The reaction mixture was stirred for 15 min at 0 $^oC$, then warmed to room temperature and stirred for 15 h. Then the homogeneous solution was cooled to 0 $^oC$. A solution of 2,6-lutidine (0.108 mL), compound (*R*)-**50** (86 mg, 0.23mmol) in $CH_2Cl_2$ (5 mL) was added slowly and the reaction mixture was stirred for 4 h. The reaction was quenched by adding saturated $NH_4Cl$ (10 mL) solution at 0 $^oC$. The organic layer was separated and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) provided (*R*)-**22a** (153 mg, 90%) as oil: $[\alpha]_D$ +6.6 (*c* 1.1 $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.042 (s, 6 H), 0.84 (s, 9 H), 1.03 (s, 16 H) 2.03-2.17 (m, 4 H), 3.41-3.73 (m, 4 H), 3.90-3.98 (m, 1 H), 7.53-7.60 (s, 5 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 154.2, 133.7, 130.0, 129.7, 123.7, 72.2, 66.7, 33.7, 29.0, 25.8, 18.3, 17.6, 17.6, 17.5, 12.8, 12.2, 0.7, –5.3; $^{19}F$ NMR ($CDCl_3$) –126.6 (2 F), –124.8 (2 F), –117.2 (2 F), –81.6 (3 F); HRMS for $C_{29}H_{46}F_9N_4O_2Si_2S$ $(M + H)^+$: Calcd 741.2736; found 741.2677.



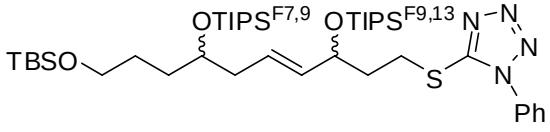

$TIPS^{F9} = Si(i\text{-}Pr)_2C_2H_4C_4F_9$, $TIPS^{F13} = Si(i\text{-}Pr)_2C_2H_4C_6F_{13}$

**(*Qrac*)-2-(diisopropylperfluoroalkylsilyloxy)-4-(1-phenyl-1*H*-tetrazol-5-ylthio)butan-1-ol (M-51):** A solution of sulfide M-**22a,c** (948 mg, 1.2 mmol) in methanol (28 mL) was treated with acetyl chloride (0.28 mL) at – 20 °C. The reaction mixture was stirred at – 20 °C for 3 h. Then the reaction was quenched by adding saturated $NaHCO_3$ (20 mL) solution. 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 (50% ethyl acetate in hexanes) provided the primary alcohol M-**51** (488 mg, 60%) as oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.53-7.57 (m, 5 H), 4.03 (q, *J* = 5.0 Hz, 1 H), 3.44-3.70 (m, 3 H), 3.34-3.38 (m, 1 H), 2.63 (br, 1H), 2.04-2.16 (m, 4 H), 1.037 (s, 14 H), 0.849-0.894 (m, 2 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 154.2, 133.5, 130.1, 129.8, 123.7, 71.7, 65.3, 33.4, 28.4, 17.5, 17.5, 17.5, 12.6, 12.2, 0.5; $^{19}$F NMR ($CDCl_3$) −126.6 (4 F), −124.8 (2 F), −123.8 (2 F), −123.4 (2 F), −122.5 (2 F), −117.2 (2 F), −117.0 (2 F), −81.6 (3 F), −81.3 (3 F); IR (neat) cm$^{-1}$ 3427, 2943, 2868, 2361, 2342, 1598, 1501, 1388, 1239; HRMS for $C_{23}H_{32}N_4O_2F_9SSi$ $(M + H)^+$: Calcd 627.1872; found 627.1858; HRMS for $C_{25}H_{32}N_4O_2F_{13}SSi$ $(M + H)^+$: Calcd 727.1808; found 727.1820.




$TIPS^{F9} = Si(i\text{-}Pr)_2C_2H_4C_4F_9$, $TIPS^{F13} = Si(i\text{-}Pr)_2C_2H_4C_6F_{13}$

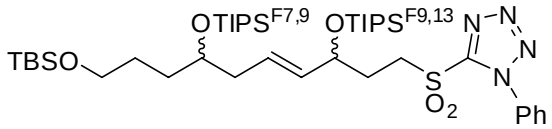
**(*Qrac*)-2-(diisopropylperfluoroalkylsilyloxy)-4-(1-phenyl-1*H*-tetrazol-5-ylthio)butanal (M-3a,c)**: To a solution of the above alcohol (20 mg, 0.026 mmol) in dichloromethane (0.5 mL) was added sodium bicarbonate (solid, 13 mg) followed by Dess-Martin reagent (13 mg, 0.03 mmol). The reaction mixture was stirred for 1.5 h. Then the reaction was quenched by adding saturated aqueous $NaHCO_3$ solution (2 mL), extracted with dichloromethane, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography ($SiO_2$, 15% ethyl acetate in hexanes) to provide aldehyde M-**3a,c** (16 mg, 0.021 mmol, 81%) as oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1 H), 7.53-7.59 (m, 5 H), 4.32 (dd, *J* = 6.0, 5.7 Hz, 1 H), 3.61 (t, *J* = 6.5 Hz, 1 H), 3.20 (t, *J* = 6.5 Hz, 1 H), 2.30-2.37 (m, 2 H), 2.06-2.23 (m, 2 H), 1.00-1.02 (m, 14 H), 0.85-0.94 (m, 2 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 0.6, 1.0, 12.6, 12.6, 17.4, 17.5, 28.2, 32.2, 77.2, 123.8, 129.8, 130.2, 133.6, 153.5, 201.6; $^{19}$F NMR ($CDCl_3$) −126.6 (4 F), −124.8 (2 F), −123.8 (2 F), −123.4 (2 F), −122.5 (2 F), −117.3 (2 F), −117.0 (2 F), −81.6 (3 F), −81.3 (3 F).




$TIPS^{F7} = Si(i\text{-}Pr)_2C_2H_4C_3F_7$, $TIPS^{F9} = Si(i\text{-}Pr)_2C_2H_4C_4F_9$, $TIPS^{F13} = Si(i\text{-}Pr)_2C_2H_4C_6F_{13}$

**(*Qrac*)-5-((*E*)-10-(*tert*-butyldimethylsilyloxy)-3-(perfluoroalkyldiisopropylsilyloxy)-7-(perfluoroalkyldiisopropylsilyloxy)dec-4-enylthio)-1-phenyl-1*H*-tetrazole (M-53a,b/a,c):** KHMDS (0.5 M in DME, 0.45 ml, 0.225 mmol) was added to a solution of sulfone M-**2a,b** (0.13 g, 0.19 mmol) in DME (5 mL) at −78 °C. After 30 min, aldehyde M-**3a,c** (92.3 mg, 0.244 mmol)

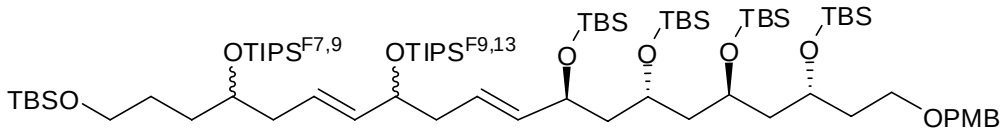
in DME (2 mL) was added. The mixture was stirred at −78 $^{o}$C for 1.5 h, then overnight stirring at room temperature. The reaction was quenched with water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography provided *E/Z* mixture alkene M-**53a,b/a,c** (*E/Z* > 9:1) of product (95 mg, 80%) as oil. The (*E*)-isomer was then separated by preparative chiral HPLC ((*S*,*S*) Whelk-O column, 25 cm × 2.1 mm, hexanes: isopropanol = 95:5) to give the pure compound M-**53a,b/a,c** as colorless oil: $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 5 H), 5.63 (dt, *J* = 16.0, 8.5 Hz, 1 H), 5.44 (dd, *J* = 15.5, 7.0 Hz, 1 H), 4.32 (q, *J* = 6.0 Hz, 1 H), 3.81-3.83 (m, 1 H), 3.52-3.62 (m, 2 H), 3.34-3.47 (m, 2 H), 2.17-2.29 (m, 2 H), 1.98-2.16 (m, 6 H), 1.45-1.55 (m, 4 H), 1.02 (s, 28 H), 0.87 (s, 13 H), 0.02 (s, 6 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 154.5, 134.5, 134.4, 133.7, 130.1, 129.8, 128.0, 123.8, 86.0, 72.8, 72.7, 72.1, 63.1, 39.4, 37.5, 34.7, 34.4, 32.8, 32.7, 31.6, 29.1, 29.0, 28.3, 28.2, 25.9, 25.3, 22.7, 20.7, 18.3, 17.5, 17.5, 14.1, 12.8, 12.7, 12.7; $^{19}$F NMR ($CDCl_3$) −128.2 (2 F), −126.6 (6 F), −124.8 (4 F), −123.8 (2 F), −123.4 (2 F), −122.5 (2 F), −118.0 (2 F), −117.2 (6 F), −81.6(3 F), −81.4 (3 F), −81.2 (3 F);IR (neat) cm$^{-1}$ 2955, 2928, 2856, 1740, 1698, 1501, 1367, 1124; HRMS $(M + Na)^+$ for $C_{46}H_{72}N_4O_3F_{16}Si_3SNa$: Calcd 1171.4275; found 1171.4237. HRMS $(M + Na)^+$ for $C_{47}H_{72}N_4O_3F_{18}Si_3SNa$: Calcd 1221.4243; found 1221.4243. HRMS $(M + Na)^+$ for $C_{48}H_{72}N_4O_3F_{20}Si_3SNa$: Calcd 1271.4211; found 1271.4146. HRMS $(M + Na)^+$ for $C_{49}H_{73}N_4O_3F_{22}Si_3SNa$: Calcd 1321.4179; found 1321.4214.




$TIPS^{F7} = Si(i\text{-}Pr)_2C_2H_4C_3F_7$, $TIPS^{F9} = Si(i\text{-}Pr)_2C_2H_4C_4F_9$, $TIPS^{F13} = Si(i\text{-}Pr)_2C_2H_4C_6F_{13}$

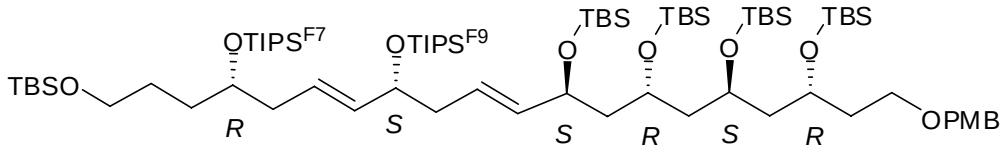
**(*Qrac*)-5-((E)-10-(*tert*-butyldimethylsilyloxy)-3-(perfluoroalkyldiisopropylsilyloxy)-7-(perfluoroalkyldiisopropylsilyloxy)dec-4-enylsulfonyl)-1-phenyl-1*H*-tetrazole (M-54a,b/a,c):** To a solution of sulfide M-**53a,b/a,c** (62 mg, 0.078 mmol) in ethanol (1.5 mL) was added oxidant (0.3 mL, prepared from 0.6 g of $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ in 2.5 mL of 30% w/v aq $H_2O_2$). The reaction mixture was stirred at room temperature for 18 h. Then the reaction was quenched with water. 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 provided ($SiO_2$, 10% ethyl acetate in hexanes) to yield sulfone M-**54a,b/a,c** (60 mg, 88%) as an oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.59-7.70 (m, 5 H), 5.66-5.77 (m, 1 H), 5.46 (dd, *J* = 15.5, 6.6 Hz, 1 H), 4.43 (m, 1 H), 3.75-3.92 (m, 3 H), 3.50-3.65 (s, 2 H), 1.98-2.30 (m, 8 H), 1.45-1.55 (m, 4 H), 1.02 (s, 28 H), 0.87 (s, 13 H), 0.02 (s, 6 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 153.4, 133.4, 133.3, 133.0, 131.4, 129.7, 125.0, 72.0, 71.9, 71.8, 71.5, 71.4, 71.3, 63.0, 52.0, 39.3, 32.8, 32.7, 30.7, 30.5, 30.3, 29.7, 28.3, 26.1, 25.9, 25.8, 25.6, 18.3, 17.6, 17.4, 12.7, 0.5, −5.2; $^{19}$F NMR ($CDCl_3$) −128.1 (2 F), −126.6 (6 F), −124.8 (4 F), −123.8 (2 F), −123.4 (2 F), −122.5 (2 F), −118.0 (2 F), −117.2 (6 F), −81.6(3 F), −81.4 (3 F), −81.2 (3 F); IR (neat) cm$^{-1}$ 2954, 2930, 2857, 1743, 1696, 1367, 1343, 1124; HRMS (M + Na)$^+$ for $C_{46}H_{72}N_4O_5F_{16}Si_3SNa$: Calcd 1203.4147; found 1203.4174. HRMS (M + Na)$^+$ for $C_{47}H_{72}N_4O_5F_{18}Si_3SNa$: Calcd 1253.4103; found 1253.4142. HRMS (M + Na)$^+$ for $C_{48}H_{72}N_4O_5F_{20}Si_3SNa$: Calcd 1303.4099; found 1303.4110. HRMS (M + Na)$^+$ for $C_{49}H_{73}N_4O_5F_{22}Si_3SNa$: Calcd 1353.4044; found 1353.4078.

M-**23a,b/a,c:**



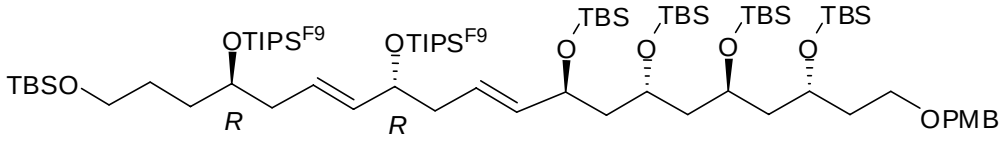

$TIPS^{F7} = Si(i\text{-}Pr)_2C_2H_4C_3F_7$, $TIPS^{F9} = Si(i\text{-}Pr)_2C_2H_4C_4F_9$, $TIPS^{F13} = Si(i\text{-}Pr)_2C_2H_4C_6F_{13}$

KHMDS (0.5 M in DME, 55 μL, 0.225 mmol) was added to a solution of sulfone M-**54a,b/a,c** (20 mg, 0.023 mmol) in 1 mL DME at −78 °C. The reaction mixture was stirred for 30 min followed by addition of aldehyde **4** (24 mg, 0.029 mmol) in DME (1 mL). 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. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to yield compound M-**23a,b/a,c** (25 mg, 77%) as a colorless oil. The (*E*, *E*)-isomer was then separated by preparative chiral HPLC ((*S*,*S*) Whelk-O column, 25 cm × 2.1 mm, hexanes: isopropanol = 95:5). Compound M-**23a,b/a,c** was then demixed by preparative fluorous HPLC (FluoroFlash HPLC Column, 250 mm × 20 ㎜, 100% MeOH) to afford four single quasidiastereomers (33*R*, 37*S*)-**23a,b**, (33*R*, 37*R*)-**23a,a**, (33*S*, 37*S*)-**23b,c**, (33*S*, 37*R*)-**23a,c.**

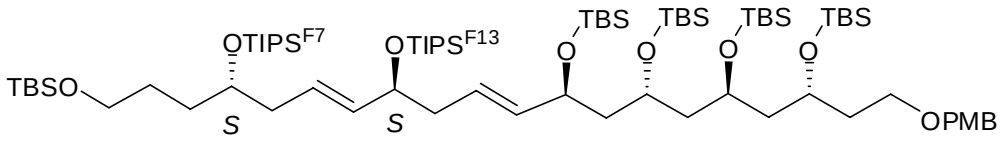



(33*R*, 37*S*)-**23a,b:** $[\alpha]_D$ −1.8 (*c* 0.5 $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.8 Hz, 2 H), 6.86 (d, *J* = 7.8 Hz, 2 H), 5.39-5.60 (m, 4 H), 4.41 (s, 2 H), 4.13-4.23 (m, 2 H), 3.78-3.92 (m,

7 H), 3.54-3.59 (m, 2 H), 3.45-3.51 (m, 2 H), 2.16-2.27 (m, 4 H), 2.03-2.15 (m, 4 H), 1.37-1.82 (m, 12 H), 1.00-1.06 (m, 28 H), 0.85-0.89 (s, 45 H), –0.02-0.01 (m, 30 H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 159.0, 136.8, 135.2, 130.8, 129.1, 126.6, 125.8, 113.7, 73.9, 72.6, 72.2, 70.9, 67.4, 67.0, 66.9, 66.7, 63.1, 46.7, 46.5, 45.6, 41.7, 39.6, 37.8, 26.0, 26.0, 25.9, 25.9, 18.2, 18.1, 18.0, 17.6, 17.6, 17.5, 12.8, 12.8, 12.7, 12.7, –3.5, –3.5, –3.6, –3.9, –4.2, –4.3, –4.7, –5.4; $^{19}$F NMR ($CDCl_3$) –128.2 (2 F), –126.7 (2 F), –124.8 (2 F), –118.0 (2 F), –117.3 (2 F), –81.6 (3 F), –81.2 (3 F).

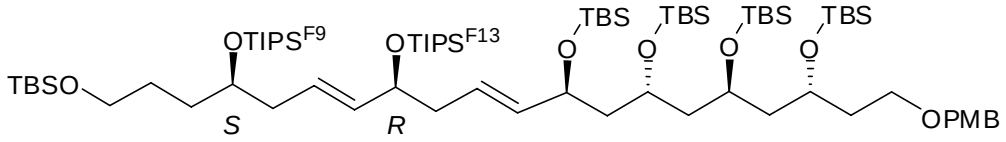



(33*R*, 37*R*)-**23a,a:** $[\alpha]_D$ –4.4 (*c* 1.1 $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.8 Hz, 2 H), 6.86 (d, *J* = 7.8 Hz, 2 H), 5.39-5.60 (m, 4 H), 4.41 (s, 2 H), 4.13-4.23 (m, 2 H), 3.78-3.92 (m, 7 H), 3.54-3.59 (m, 2 H), 3.45-3.51 (m, 2 H), 2.16-2.27 (m, 4 H), 2.03-2.15 (m, 4 H), 1.37-1.82 (m, 12 H), 1.00-1.06 (m, 28 H), 0.85-0.89 (s, 45 H), –0.02-0.01 (m, 30 H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 159.0, 136.6, 135.4, 130.9, 129.1, 126.5, 125.7, 113.7, 73.7, 72.6, 72.3, 70.8, 67.3, 67.0, 67.0, 66.7, 63.2, 46.7, 46.6, 45.7, 42.0, 39.6, 37.8, 26.0, 26.0, 25.9, 25.6, 18.3, 18.1, 18.0, 17.6, 17.6, 17.5, 13.0, 12.8, 12.7, –3.5, –3.9, –4.2, –4.3, –4.7, –5.4; $^{19}$F NMR ($CDCl_3$) –126.7 (4 F), –124.8 (4 F), –117.3 (4 F), –81.6 (6 F).

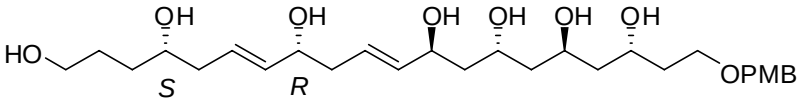



(33*S*, 37*S*)-**23b,c:** $[\alpha]_D$ –7.7 (*c* 0.7 $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.8 Hz, 2 H), 6.86 (d, *J* = 7.8 Hz, 2 H), 5.39-5.60 (m, 4 H), 4.41 (s, 2 H), 4.13-4.23 (m, 2 H), 3.78-3.92 (m, 7 H), 3.54-3.59 (m, 2 H), 3.45-3.51 (m, 2 H), 2.16-2.27 (m, 4 H), 2.03-2.15 (m, 4 H), 1.37-1.82 (m, 12 H), 1.00-1.06 (m, 28 H), 0.85-0.89 (s, 45 H), –0.02-0.01 (m, 30 H); $^{13}$C NMR (150 MHz,

$CDCl_3$) δ 159.0, 136.8, 135.2, 130.8, 129.1, 126.6, 125.8, 113.7, 73.9, 72.6, 72.2, 70.9, 67.4, 67.0, 66.9, 66.7, 63.1, 46.7, 46.5, 45.6, 41.7, 39.6, 37.8, 26.0, 26.0, 25.9, 25.9, 18.2, 18.1, 18.0, 17.6, 17.6, 17.5, 12.8, 12.8, 12.7, 12.7, –3.5, –3.5, –3.6, –3.9, –4.2, –4.3, –4.7, –5.4; $^{19}$F NMR ($CDCl_3$) –128.1 (2 F), –126.7 (2 F), –123.8 (2 F), –123.4 (2 F), –122.5 (2 F), –117.9 (2 F), –117.1 (2 F), –81.3 (3 F), –81.2 (3 F).



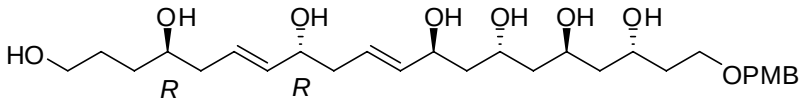

(33*S*, 37*R*)-**23a,c:** $[\alpha]_D$ –1.6 (*c* 0.8 $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.8 Hz, 2 H), 6.86 (d, *J* = 7.8 Hz, 2 H), 5.39-5.60 (m, 4 H), 4.41 (s, 2 H), 4.13-4.23 (m, 2 H), 3.78-3.92 (m, 7 H), 3.54-3.59 (m, 2 H), 3.45-3.51 (m, 2 H), 2.16-2.27 (m, 4 H), 2.03-2.15 (m, 4 H), 1.37-1.82 (m, 12 H), 1.00-1.06 (m, 28 H), 0.85-0.89 (s, 45 H), –0.02-0.01 (m, 30 H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 159.0, 136.8, 135.4, 130.8, 129.1, 126.6, 125.7, 113.7, 74.0, 72.6, 72.3, 70.9, 67.3, 67.0, 66.9, 66.7, 63.2, 46.7, 46.6, 45.6, 41.6, 39.5, 37.8, 26.0, 26.0, 25.9, 25.9, 18.2, 18.1, 18.0, 17.6, 17.6, 17.5, 12.8, 12.8, 12.7, 12.7, –3.5, –3.5, –3.6, –3.9, –4.2, –4.3, –4.7, –5.4; $^{19}$F NMR ($CDCl_3$) –126.6 (4 F), –124.8 (2 F), –123.8 (2 F), –123.4 (2 F), –122.5 (2 F), –117.3 (2 F), –117.0 (2 F), –81.6 (3 F), –81.3 (3 F).




**(4*S*,6*E*,8*R*,10*E*,12*S*,14*R*,16*S*,18*R*)-20-(4-methoxybenzyloxy)icosa-6,10-diene-1,4,8,12,14,16,18-heptaol ((33*R*, 37*S*)-24) :**

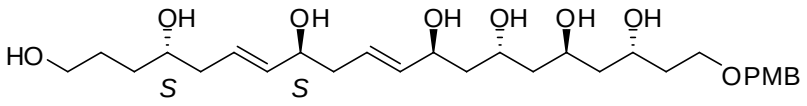
TASF (15 mg) in DMF (0.2 mL) was added to a solution of (33*R*, 37*S*)-**23a,b** (5.0 mg) in DMF (1 mL) at 0 °C. The solution was stirred for overnight after warming to room temperature. DMF

was removed by speed-vacuum. The crude product was purified by flash column chromatography (20% MeOH in $CH_2Cl_2$) to afford compound (33*R*, 37*S*)-**24** (1.1 mg, 75%) as oil: $[\alpha]_D$ +1.0 (*c* 1.1 $CHCl_3$); $^1$H NMR (700 MHz, MeOD) δ 7.26 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 5.63-5.71 (m, 2 H), 5.51-5.59 (m, 2 H), 4.43 (s, 2 H), 4.33 ( m, 1 H), 4.01-4.11 (m, 3 H), 3.96-4.01 (m, 1 H), 3.78 (s, 3 H), 3.53-3.66 (m, 5 H), 2.15-2.31 (m, 4 H), 1.64-1.79 (m, 4 H), 1.47-1.63 (m, 6 H), 1.38-1.45 (m, 2 H); $^{13}$C NMR (175 MHz, MeOD) δ 160.82, 137.25, 136.18, 131.70, 130.54, 128.96, 127.61, 114.72, 73.73, 73.34, 72.16, 70.32, 68.27, 66.90, 66.25, 66,20, 63.03, 55.66, 46.64, 46.35, 46.22, 41.44, 41.41, 38.86, 34.17, 29.86; EIMS $(M + Na)^+$ 549.



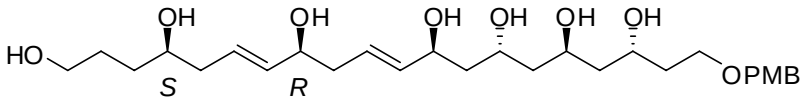

**(4*R*,6*E*,8*R*,10*E*,12*S*,14*R*,16*S*,18*R*)-20-(4-methoxybenzyloxy)icosa-6,10-diene-1,4,8,12,14,16,18-heptaol ((33*R*, 37*R*)-24):**

Following the same procedure as above, compound (33*R*, 37*R*)-**24** was obtained as oil: $[\alpha]_D$ +3.2 (*c* 1.0 $CHCl_3$); $^1$H NMR (700 MHz, MeOD) δ 7.26 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 5.63-5.71 (m, 2 H), 5.51-5.59 (m, 2 H), 4.43 (s, 2 H), 4.33 ( m, 1 H), 4.01-4.11 (m, 3 H), 3.96-4.01 (m, 1 H), 3.78 (s, 3 H), 3.53-3.66 (m, 5 H), 2.15-2.31 (m, 4 H), 1.64-1.79 (m, 4 H), 1.47-1.63 (m, 6 H), 1.38-1.45 (m, 2 H); $^{13}$C NMR (175 MHz, MeOD) δ 160.81, 137.23, 136.19, 131.69, 130.54, 128.80, 127.64, 114.71, 73.73, 73.32, 72.10, 70.33, 68.27, 66.89, 66.24, 66,20, 63.03, 55.65, 46.64, 46.35, 46.21, 41.43, 41.36, 38.86, 34.13, 29.89; EIMS $(M + Na)^+$ 549.



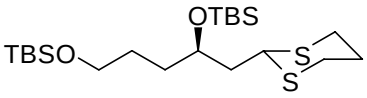

**(4*S*,6*E*,8*S*,10*E*,12*S*,14*R*,16*S*,18*R*)-20-(4-methoxybenzyloxy)icosa-6,10-diene-1,4,8,12,14,16,18-heptaol ((33*S*, 37*S*)-24):**

Following the same procedure as above, compound (33*S*, 37*S*)-**24** was obtained as oil: $[\alpha]_D$ +4.4 (*c* 1.0 $CHCl_3$); $^1$H NMR (700 MHz, MeOD) δ 7.26 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 5.63-5.71 (m, 2 H), 5.51-5.59 (m, 2 H), 4.43 (s, 2 H), 4.33 ( m, 1 H), 4.01-4.11 (m, 3 H), 3.96-4.01 (m, 1 H), 3.78 (s, 3 H), 3.53-3.66 (m, 5 H), 2.15-2.31 (m, 4 H), 1.64-1.79 (m, 4 H), 1.47-1.63 (m, 6 H), 1.38-1.45 (m, 2 H); $^{13}$C NMR (175 MHz, MeOD) δ 160.82, 137.20, 136.19, 131.70, 130.54, 128.84, 127.69, 114.73, 73.73, 73.36, 72.12, 70.34, 68.28, 66.93, 66.26, 66,22, 63.03, 55.67, 46.62, 46.35, 46.16, 41.45, 41.36, 38.86, 34.12, 29.90; EIMS $(M + Na)^+$ 549.

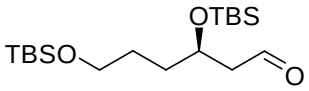



**(4*R*,6*E*,8*S*,10*E*,12*S*,14*R*,16*S*,18*R*)-20-(4-methoxybenzyloxy)icosa-6,10-diene-1,4,8,12,14,16,18-heptaol ((33*S*, 37*R*)-24):**

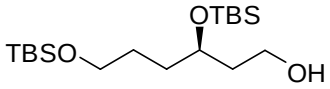
Following the same procedure as above, compound (33*S*, 37*R*)-**24** was obtained as oil: $[\alpha]_D$ +0.8 (*c* 0.8 $CHCl_3$); $^1$H NMR (700 MHz, MeOD) δ 7.26 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 5.63-5.71 (m, 2 H), 5.51-5.59 (m, 2 H), 4.43 (s, 2 H), 4.33 ( m, 1 H), 4.01-4.11 (m, 3 H), 3.96-4.01 (m, 1 H), 3.78 (s, 3 H), 3.53-3.66 (m, 5 H), 2.15-2.31 (m, 4 H), 1.64-1.79 (m, 4 H), 1.47-1.63 (m, 6 H), 1.38-1.45 (m, 2 H); $^{13}$C NMR (175 MHz, MeOD) δ 160.81, 137.22, 136.16, 131.69, 130.54, 129.03, 127.66, 114.72, 73.73, 73.37, 72.15, 70.33, 68.27, 66.90, 66.24, 66,19, 63.03, 55.66, 46.64, 46.36, 46.18, 41.44, 41.41, 38.86, 34.18, 29.86; EIMS $(M + Na)^+$ 549.




**(*R*)-2-(2,5-bis(*tert*-Butyldimethylsilyloxy)pentyl)-1,3-dithiane (57):** *t*-BuLi (1.7 M in pentane, 10.0 mL, 17.0 mmol) was added to a solution of 1,3-dithiane (1.80 g, 15.0 mmol) in THF (60 mL) at −78 $^{o}$C. After 30 min at −78 $^{o}$C, epoxide (*R*)-**42** (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 $^{o}$C, the reaction mixture was cooled to −78 $^{o}$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 dithiane **57** (5.6 g, 83%) as an oil: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 4.10 (dd, *J* = 8.7, 5.8 Hz, 1 H), 3.92-4.01 (m, 1 H), 3.55-3.60 (m, 2 H), 2.70-2.95 (m, 4 H), 2.05-2.15 (m, 1 H), 1.73-1.92 (m, 3 H), 1.50-1.53 (m, 4 H), 0.90 (s, 18 H), 0.10 (s, 3 H), 0.07 (s, 3 H), 0.04 (s, 6 H),; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 68.4, 63.2, 44.2, 42.5, 33.7, 30.7, 30.2, 28.0, 26.0, 18.4, 18.1, –4.3, –4.5, –5.2; 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.

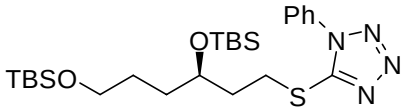



**(*R*)-3,6-bis(*tert*-Butyldimethylsilyloxy)hexanal (58):** Methyl iodide (0.2 mL) and $K_2CO_3$ (258 mg, 1.87 mmol) were added to a solution of dithiane **57** (800 mg, 1.77 mmol) in aqueous acetonitrile (MeCN/$H_2O$, 6:1/2.1 mL). The reaction mixture was stirred for 5 h at 45 $^oC$ and then diluted 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 aldehyde **58** (514 mg, 80%) as an oil: $[\alpha]_D$ –3.74 (*c* 1.15 $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.79-9.81 (m, 1 H), 4.19-4.26 (m, 1 H), 3.57-3.63 (m, 2 H), 2.49-2.54 (m, 2 H), 1.47-1.65 (m, 4 H), 0.88 (s, 9 H), 0.86 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 6 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 202.2, 68.1, 62.9, 50.7, 34.2, 28.4, 25.9, 25.7, 18.3, 18.0, –4.4, –4.7, –5.3; IR (neat) $cm^{-1}$ 2954, 2929, 2851, 2721, 1723, 1470, 1249; EIMS $(M - tBu)^+$ 303; HRMS for $C_{14}H_{31}O_3Si_2$ $(M - tBu)^+$: Calcd 303.1812; found 303.1805.



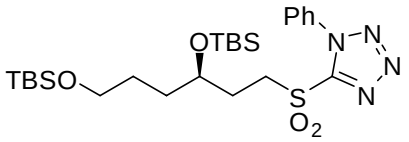

**(*R*)-3,6-bis(*tert*-Butyldimethylsilyloxy)hexan-1-ol (59):** DIBAL-H (1.0 M in hexane, 2.38 mL, 2.38 mmol) was added to a solution of aldehyde **58** (0.66 g, 1.83 mmol) in THF (20 mL) at –78 $^oC$ and the mixture was stirred for 1 h. The reaction mixture was warmed to 0 $^oC$, followed by the addition of ethanol (1 mL) and saturated sodium-potassium tartrate 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

alcohol **59** (650 mg, 98%) as an oil: $[\alpha]_D$ –21.0 (*c* 0.2 $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 3.91-3.95 (m, 1 H), 3.78-3.83 (m, 1 H), 3.67-3.72 (m, 1 H), 3.57-3.63 (m, 2 H), 2.60 (br s, 1 H), 1.76-1.83 (m, 1 H), 1.62-1.69 (m, 1 H), 1.54-1.60 (m, 2 H), 1.47-1.53 (m, 2 H), 0.88 (s, 18 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.03 (s, 6 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 71.7, 63.2, 60.2, 37.9, 33.3, 28.7, 26.0, 25.9, 18.4, 18.0, –4.3, –4.7, –5.2; IR (neat) $cm^{-1}$ 3366, 2953, 2930, 2857, 1471, 1254, 1096, 835, 775.



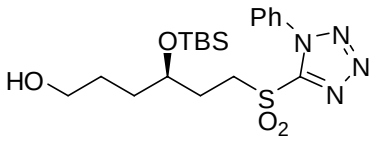

**(*R*)-5-(3,6-bis(*tert*-Butyldimethylsilyloxy)hexylthio)-1-phenyl-1*H*-tetrazole (60):**

Diisopropylazodicarboxylate (589 mg, 2.90 mmol) was added to a solution of alcohol **59** (0.65 g, 1.8 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (486 mg, 2.73 mmol) and triphenylphosphine (621 mg, 2.36 mmol) in THF (20 mL) at 0 °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 sulfide **60** (940 mg, 99%) as an oil: $[\alpha]_D$ –17.8 (*c* 0.28 $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.51-7.59 (m, 5 H), 3.82-3.88 (m, 1 H), 3.55-3.64 (m, 2 H), 3.36-3.50 (m, 2 H), 1.89-2.05 (m, 2 H), 1.48-1.60 (m, 4 H), 0.88 (s, 18 H), 0.053 (s, 3 H), 0.047 (s, 3 H), 0.03 (s, 6 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 154.4, 133.8, 130.1, 129.8, 123.8, 74.3, 63.1, 36.0, 33.3, 29.6, 28.4, 26.0, 25.9, 18.3, 18.1, –4.3, –4.5, –5.2; HRMS for $C_{25}H_{46}N_4O_2SSi_2Na$ $(M + Na)^+$: Calcd 545.2778; found 545.2780.



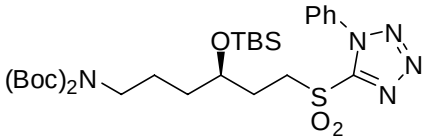

**(*R*)-5-(3,6-bis(*tert*-Butyldimethylsilyloxy)hexylsulfonyl)-1-phenyl-1*H*-tetrazole (61):**

*m*-Chloroperperbenzoic acid (684 mg, 3.95 mmol) was added to a solution of sulfide **60** (0.94 g, 1.8 mmol) in dichloromethane (20 mL) at 0 $^{o}$C. The mixture was stirred for 2 h at 0 $^{o}$C 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 sulfone **61** (863 mg, 88%) as an oil: $[\alpha]_D$ –4.1 (*c* 1.0 $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.69-7.71 (m, 2 H), 7.59-7.63 (m, 3 H), 3.90-3.96 (m, 1 H), 3.85 (ddd, *J* = 14.7, 11.5, 5.5 Hz, 1 H), 3.77 (ddd, *J* = 14.7, 11.0, 4.6 Hz, 1 H), 3.58-3.66 (m, 2 H), 2.11-2.20 (m, 1 H), 2.01-2.10 (m, 1 H), 1.48-1.67 (m, 4 H), 0.902 (s, 9 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.05 (s, 6 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 153.5, 133.1, 131.4, 129.7, 125.1, 69.9, 62.9, 52.6, 33.2, 28.8, 28.4, 26.0, 25.9, 18.3, 18.1, –4.4, –4.6, –5.2; 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.



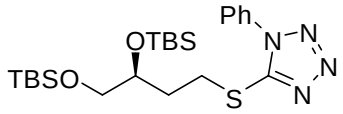

**(*R*)-4-(*tert*-Butyldimethylsilyloxy)-6-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)hexan-1-ol (62):**

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 $^{o}$C) was added to a solution of sulfone **61** (0.10 g, 0.18 mmol) in THF at 0 $^{o}$C. 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 alcohol **62** (81 mg, 76%) as an oil: $[\alpha]_D$ −1.1 (*c* 0.72 $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.26-7.73 (m, 5 H), 3.95 (m, 2 H), 3.74-3.87 (m, 2 H), 3.67 (br s, 1 H), 2.06-2.21 (m, 2 H), 1.57-1.65 (m, 6 H), 0.88-0.99 (m, 9 H),0.09 (d, 6 H); $^{13}$C NMR (75 MHz, $CHCl_3$) δ 153.6, 133.2, 131.5, 129.8, 125.2, 69.8, 62.8, 52.3, 33.1, 28.8, 28.4, 25.9, 18.1, –4.4, –4.5; 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.

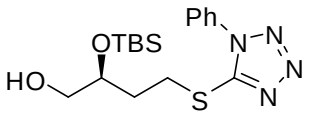



**(*R*)-4-(*tert*-butyldimethylsilyloxy)-6-(1-phenyl-1H-tetrazol-5-ylsulfonyl) *N,N*-diBoc-hexan-1-amine (2)**: To a solution of alcohol **62** (120 mg, 0.27 mmol) in THF (1 mL) were added triphenylphosphine (107 mg, 0.41 mmol), di-*tert*-butyl-iminodicarboxylate (94 mg, 0.43 mmol) and diisopropylazodicarboxylate (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 fragment **2** (128 mg, 74%) as an oil: $[\alpha]_D$ −3,3 (*c* 1.21 $CHCl_3$) $^1$H NMR (500 MHz, $CDCl_3$) δ 7.69-7.72 (m, 2 H), 7.60-7.64 (m, 3 H), 3.74-3.86 (m, 2 H), 3.89-3.93 (m, 1 H), 3.57 (t, *J* = 7.0 Hz, 2 H), 2.11-2.18 (m, 1 H), 2.01-2.08 (m, 1 H), 1.41-1.69 (m, 22 H), 0.90 (s, 9 H), 0.084 (s, 3

H), 0.075 (s, 3 H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 153.5, 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, –4.5; 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.

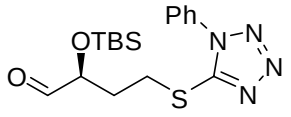



**(*S*)-5-(3,4-bis(*tert*-Butyldimethylsilyloxy)butylthio)-1-phenyl-1*H*-tetrazole (63):** To a solution of diol (*S*)-**49** (830 mg, 3.14 mmol) in dichloromethane (30 mL) at –78 $^{o}$C were added 2,6-lutidine (1.98 g, 18.5 mmol) and TBSOTf (1.70 g, 6.45 mmol). The reaction mixture was stirred at –78 $^{o}$C for 1 h followed by warming it to 0 $^{o}$C. 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 TBS ether **63** (1.54 g, 3.11 mmol, 99%) as an oil: $[\alpha]_D$ –22.6 (*c* 0.72 $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.53-7.60 (m, 6 H), 3.80-3.85 (m, 1 H), 3.50-3.60 (m, 2 H), 3.41-3.47 (m, 2 H), 2.09-2.16 (m, 1 H), 1.90-1.98 (m, 1 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.07 (s, 6 H), 0.05 (s, 3 H), 0.04 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 154.5, 133.8, 130.1, 129.8, 123.9, 71.7, 66.9, 33.6, 29.5, 26.0, 25.9, 18.3, 18.1, –4.2, –4.7, –5.3; 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.



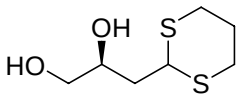

**(*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-(1-phenyl-1H-tetrazol-5-ylthio)butan-1-ol (64):**

To a solution of TBS ether **63** (810 mg, 1.63 mmol) in THF (10 mL) at 0 $^{o}$C was added HF•pyr (20 mL, prepared by slow addition of 6 mL HF•pyr 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 alcohol **64** (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 7.53-7.58 (m, 5 H), 3.92 (dt, *J* = 10.5, 5.0 Hz, 1 H), 3.62 (dt, *J* = 10.1, 5.0 Hz, 1 H), 3.55 (ddd, *J* = 11.5, 7.3, 4.6 Hz, 1 H), 3.44-3.51 (m, 1 H), 3.33-3.41 (m, 1 H), 2.38 (dd, *J* = 6.9, 5.0 Hz, 1 H), 2.06-2.11 (m, 2 H), 0.89 (s, 9 H), 0.08 (s, 6 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 154.3, 133.6, 130.2, 129.8, 123.8, 71.2, 65.8, 33.3, 29.1, 25.8, 18.1, –4.5, –4.6; 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.



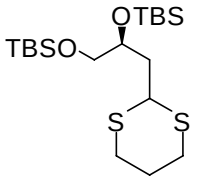

**(*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-(1-phenyl-1*H*-tetrazol-5-ylthio)butanal (3)**: To a solution of alcohol **64** (0.11 g, 0.28 mmol) in dichloromethane (5 mL) was added sodium bicarbonate (solid, 73 mg) and Dess-martin reagent (184 mg, 0.430 mmol). The reaction mixture was stirred

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 aldehyde **3** (91 mg, 0.24 mmol, 86%) as an oil: $[\alpha]_D$ –13.1 (*c* 2.57 $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1 H), 7.52-7.59 (m, 5 H), 4.17 (dd, *J* = 7.3, 4.6 Hz, 1 H), 3.47 (t, *J* = 6.9 Hz, 2 H), 2.24-2.31 (m, 1 H), 2.19 (sex, *J* = 6.9 Hz, 1 H), 0.92 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 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; 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.

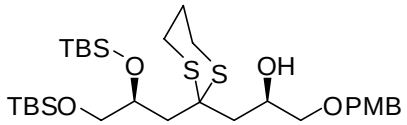



**(*S*)-3-(1,3-Dithian-2-yl)propane-1,2-diol (65):** To a solution of aldehyde (*S*)-**28** (1.80 g, 12.5 mmol) in $CH_2Cl_2$ (130 mL) were added 1,3-propanedithiol (2.60 mL, 37.5 mmol, 3 equiv) and $BF_3$•$Et_2O$ (4.7 mL) at 0 °C for 1 h. The reaction mixture was diluted with ether, washed with 3% aqueous 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 diol **65** (1.9 g, 9.8 mmol, 78%): $[\alpha]_D$ –9.5 (*c* 0.4 $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.26 (dd, *J* = 8.8, 5.5 Hz, 1 H), 3.99-4.10 (m, 1 H), 3.67 (dd, *J* = 11.0, 2.2 Hz, 1 H), 3.48 (dd, *J* = 11.0, 7.1 Hz, 1 H), 2.81-2.98 (m, 5 H), 2.49 (br s, 1 H), 2.08-2.18 (m, 1 H), 1.79-1.99 (m, 3 H); $^{13}C$ NMR (75 MHz, $CHCl_3$) δ 69.1, 66.5, 43.8, 38.5, 30.3, 30.0, 25.8; IR (neat) $cm^{-1}$ 3386, 2931,

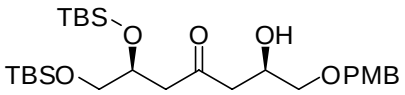
2899, 1422, 1276; EIMS ($M^+$) 194, $(M - H_2O)^+$ 176; HRMS for $C_7H_{14}O_2S_2$: Calcd 194.0435; found 194.0442.



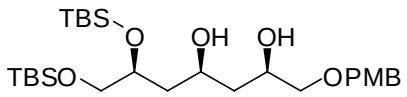

**(*S*)-2-(2,3-*bis*(*tert*-Butyldimethylsilyloxy)propyl)-1,3-dithiane (66):** To a solution of diol **65** (1.4 g, 7.2 mmol) in dichloromethane (30 mL) were added 2,6-lutidine (0.88 mL, 15 mmol) and TBSOTf (1.7 mL, 15 mmol) at –78 °C. Then the mixture was warmed to 0 °C and stirred for additional 1 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 TBS ether **66** (2.9 g, 6.9 mmol, 95%): $[\alpha]_D$ –28.3 (*c* 11.9 $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 4.16 (dd, *J* = 10.1, 4.7 Hz, 1 H), 3.92-4.00 (m, 1 H), 3.58 (dd, *J* = 10.1, 5.0 Hz, 1 H), 3.40 (dd, *J* = 10.1, 6.6 Hz, 1 H), 2.78-2.91 (m, 4 H), 1.99-2.16 (m, 2 H), 1.84-1.97 (m, 1 H), 1.77 (ddd, *J* = 13.7, 8.8, 4.7 Hz, 1 H), 0.90 (s, 18 H), 0.13 (s, 3 H), 0.09 (s, 3 H), 0.06 (s, 6 H); $^{13}$C NMR (75 MHz, $CHCl_3$) δ 69.5, 67.5, 43.8, 40.4, 30.5, 29.9, 26.1, 26.0, 25.9, 18.3, 18.1, –4.2, –4.7, –5.3; 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.



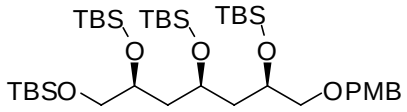

**(*R*)-1-(2-((*S*)-2,3-bis(*tert*-Butyldimethylsilyloxy)propyl)-1,3-dithian-2-yl)-3-(4-methoxybenzyloxy)propan-2-ol (69):** *t*-BuLi (1.7 M in pentane, 1 mL, 1.7 mmol) was added to a solution of dithiane **66** (682 mg, 1.61 mmol) in THF (2.4 mL) and HMPA (0.7 mL) at –78 $^{o}$C. After 10 min, epoxide **68** (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 product **69** (765 mg, 77%) as an oil: $[\alpha]_D$ –1.0 (*c* 0.24 $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 4.50 (s, 2 H), 4.27-4.33 (m, 1 H), 4.06-4.10 (m, 1 H), 3.81 (s, 3 H), 3.60 (dd, *J* = 9.6, 4.7 Hz, 1 H), 3.39-3.45 (m, 3 H), 3.11 (d, *J* = 3.0 Hz, 1 H), 2.84-2.93 (m, 3 H), 2.73-2.77 (m, 1 H), 2.60 (dd, *J* = 15.4, 3.0 Hz, 1 H), 2.26 (dd, *J* = 15.4, 8.2 Hz, 1 H), 2.03-2.06 (m, 1 H), 1.90-1.99 (m, 3 H), 0.92 (s, 9 H), 0.88 (s, 9 H), 0.13 (s, 3 H), 0.10 (s, 3 H), 0.08 (doubled, 6 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 159.2, 129.3, 113.7, 74.2, 72.9, 71.0, 67.6, 67.5, 55.2, 51.7, 43.8, 43.7, 26.5, 26.0, 26.0, 24.8, 18.3, 18.0, –3.9, –5.3; 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.



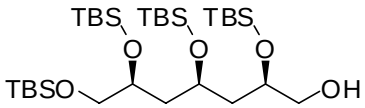

**(2*R*,6*S*)-1-(4-Methoxybenzyloxy)-6,7-*bis*(*tert*-butyldimethylsilyloxy)-2-hydroxyheptan-4-one (70):** A solution of compound **69** (2.00 g, 3.24 mmol) in THF/$H_2O$ (4:1, 45 mL) was cooled to 0 $^oC$ followed by addition of 2.6-lutidine (2.9 mL) at once and $Hg(ClO_4)_2 \bullet 3H_2O$ (3.5 g) in portions. The reaction mixture was stirred at 0 $^oC$ 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 ketone **70** (1.44 g, 85%) as an oil: $[\alpha]_D$ −7.36 (*c* 0.53 $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2 H), 6.89 (d, *J* = 8.5, 2 H), 4.49 (s, 2 H), 4.22-4.29 (s, 1 H), 4.14-4.20 (s, 1 H), 3.81 (s, 3 H), 3.57 (dd, *J* = 9.9, 4.9 Hz, 1 H), 3.36-3.48 (m, 3 H), 3.02 (d, 1 H), 2.65-2.74 (m, 3 H), 2.55 (dd, *J* = 15.6, 7.4 Hz, 1 H), 0.88 (s, 9 H), 0.85 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 6 H); $^{13}C$ NMR (151 MHz, $CDCl_3$) δ 209.8, 159.4, 130.1, 129.5, 113.9. 73.1, 73.0, 69.7, 67.0, 66.8, 55.4, 48.5, 47.5, 26.0, 25.9, 18.4, 18.1, –4.4, –4.8, –5.3, –5.3; 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.



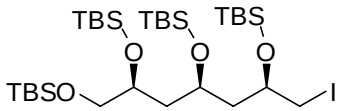

**(2*R*,4*S*,6*S*)-1-(4-Methoxybenzyloxy)-6,7-*bis*(*tert*-butyldimethylsilyloxy)heptane-2,4-diol (71):** To a solution of ketone **70** (2.1 g, 4.0 mmol) in THF (32 mL) and methanol (8 mL) at –78 $^{o}$C was added diethylmethoxyborane (1.0 M in THF, 4.4 mL, 4.4 mmol) and the reaction mixture was stirred 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 $^{o}$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 syn diol **71** (1.85 g, 88%) as a colorless oil: $[\alpha]_D$ –8.29 (*c* 1.52 $CHCl_3$); $^1$H NMR (600 MHz, $CHCl_3$) δ 7.27 (d, *J* = 8.2 Hz, 2 H), 6.89 (d, *J* = 8.5 Hz, 2 H), 4.50 (s, 2 H), 4.02-4.12 (m, 2 H), 3.94 (br s, 1 H), 3.87-3.93 (m, 1 H), 3.81 (s, 3 H), 3.65 (br s, 1 H), 3.6 (dd, *J* = 10.2, 4.4 Hz, 1 H), 3.48 (dd, *J* = 10.2, 6.6 Hz, 1 H), 3.39-3.45 (m, 2 H), 1.56-1.17 (m, 4 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.10 (s, 6 H), 0.07 (s, 3 H), 0.07 (s, 3 H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 159.3, 130.4, 129.4, 113.9, 74.2, 73.1, 72.3, 70.9, 69.9, 67.7, 55.3, 42.5, 40.3, 26.1, 26.0, 25.9, 18.4, 18.1, –4.1, –4.7, –5.3; 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 (72):** To a solution of diol **71** (1.8 g, 3.4 mmol) in dichloromethane (30 mL) at 0 $^{o}$C 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 and 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 TBS ether **72** (2.4 g, 94%) as an oil: $[\alpha]_D$ 0.41 (*c* 0.72 $CHCl_3$); $^1$H NMR (601 MHz, $CHCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.2 Hz, 2 H), 4.47 (d, *J* = 11.8 Hz, 1 H), 4.42 (d, *J* = 11.5 Hz, 1 H), 3.93-3.99 (m, 1 H), 3.78-3.85 (m, 5 H), 3.51 (dd, *J* = 10.2, 4.7 Hz, 1 H), 3.45 (dd, *J* = 10.2, 6.3 Hz, 1 H), 3.40 (dd, *J* = 9.9, 3.6 Hz, 1 H), 3.30 (dd, *J* = 9.9, 6.3 Hz, 1 H), 1.67-1.75 (m, 2 H), 1.55-1.62 (m, 2 H), 0.90 (s, 27 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H); $^{13}$C NMR (151 MHz, $CHCl_3$) δ 159.1, 130.8, 129.2, 113.7, 74.6, 72.9, 70.7, 69.2, 67.8, 66.8, 55.3, 42.9, 42.7, 26.1, 26.0, 26.0, 18.5, 18.2, 18.2, 18.0, –4.0, –4.1, –4.3, –4.4, –4.6, –4.6, –5.2, –5.3; 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.

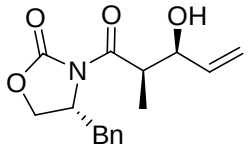



**(2*R*,4*S*,6*S*)-2,4,6,7-*tetrakis*(*tert*-Butyldimethylsilyloxy)heptan-1-ol (73):** A solution of PMB ether **72** (1.10 g, 1.45 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (428 mg, 1.88 mmol) in $CH_2Cl_2$/pH 7 buffer (19 mL/1 mL) was stirred at room temperature for 1 h followed by dilution 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 alcohol **73** (890 mg, 96%) as an oil: $[\alpha]_D$ –1.9 (*c* 0.63 $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 3.90-3.98 (m, 2 H), 3.61-3.78 (m, 1 H), 3.53-3.58 (m, 1 H), 3.38-3.52 (m, 3 H), 2.71 (dd, *J* = 7.8, 5.5 Hz, 1 H), 1.59-1.82 (m, 4 H), 0.89-0.90 (m, 36 H), 0.05-0.10 (m, 24 H); $^{13}$C NMR (75 MHz, $CHCl_3$) δ 70.8, 69.9, 67.8, 67.2, 66.5, 42.3, 41.8, 31.7, 26.0, 26.0, 25.9, 22.7, 18.4, 18.1, 18.1, 18.0, 14.2, –3.9, –4.3, –4.4, –4.5, –4.6, –4.6, –4.6, –4.7, –5.3; HRMS for $C_{31}H_{72}O_5Si_4Na$: Calcd 659.4355; found 659.4352.



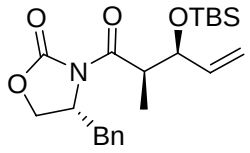

**(2*S*,4*R*,6*R*)-1,2,4,6-*tetrakis*(*tert*-Butyldimethylsilyloxy)-7-iodoheptane (5):** To a solution of alcohol **72** (380 mg, 0.53 mmol) in acetone (10 mL) was added sodium iodide (398 mg, 2.65 mmol). The reaction mixture was refluxed for 36 h and then the acetone was removed under reduced pressure. 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 iodide **5** (380 mg, 96%) as an oil: $[\alpha]_D$ –3.2 (*c* 0.53 $CHCl_3$) $^1$H NMR (500 MHz, $CHCl_3$) δ 3.83 (tt, *J* = 7.3, 5.0 Hz, 1 H), 3.74 - 3.79 (m, 1 H), 3.67 (tt, *J* = 7.3, 4.7 Hz, 1 H), 3.46-3.52 (m, 2 H), 3.35 (dd, *J* = 10.1, 4.1 Hz, 1 H), 3.21 (dd, *J* = 10.0, 5.0 Hz, 1 H), 1.80 (ddd, *J* = 13.9, 7.3, 5.0 Hz, 1 H), 1.73 (ddd, *J* = 13.9, 7.6, 5.0 Hz, 1 H), 1.68 (ddd, *J* = 3.9, 7.3, 5.4, 1 H), 1.63 (ddd, *J* = 13.9, 7.3, 5.4 Hz, 1 H), 0.92 (s, 9 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.899 (s, 9 H), 0.13 (s, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.087 (s, 3 H), 0.08 (s, 3 H), 0.079 (s, 3 H), 0.06 (s, 3 H), 0.058 (s, 3 H); $^{13}$C NMR (126 MHz,$CDCl_3$) δ 70.7, 68.3, 67.6, 66.8, 45.3, 42.8, 26.1, 26.0, 18.5, 18.2, 18.1, 18.1, 15.3, –3.9, –4.1, –4.2, –4.3, –4.4, –5.2, –5.2; IR (neat) cm$^{-1}$ 2929, 2857, 1472, 1408, 1389; HRMS for $C_{27}H_{62}O_4Si_4I$ (M – *t*Bu)$^+$ : Calcd 689.2770; found 689.2789.



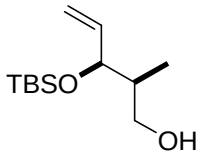

**(*R*)-4-Benzyl-3-((2*R*,3*S*)-3-hydroxy-2-methylpent-4-enoyl)oxazolidin-2-one (75):** Di-*n*-butyl boryltrifluoromethanesulfonate (1.0 M in $CH_2Cl_2$, 29.8 mL, 29.8 mmol) was added slowly to a solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one **74** (5.8 g, 24.9 mmol) in dichloromethane (50 mL) at 0 $^o$C 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 $^o$C and freshly distilled acrolein (1.5 g, 27.4 mmol) was added. After 1 h, the solution was warmed to 0 $^o$C 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 $^o$C 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 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 product **75** (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.

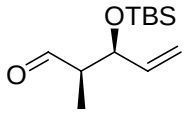



**(*R*)-4-Benzyl-3-((2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-methylpent-4-enoyl)oxazolidin-2-one (76):** To a solution of alcohol **75** (4.2 g, 14.5 mmol) in dichloromethane (150 mL) were added 2,6-lutidine (1.90 g, 17.4 mmol) and TBSOTf (4.2 g, 16 mmol) at –78 $^oC$. After 15 min, it was warmed to 0 $^oC$ 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 TBS ether **76** (4.8 g, 82%) as an oil: $[\alpha]_D$ –50.8 (*c* 0.94 $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.32-7.36 (m, 2 H), 7.28-7.30 (m, 1 H), 7.22-7.23 (m, 2 H), 5.86 (ddd, *J* = 17.0, 10.4, 6.6 Hz, 1 H), 5.18-5.23 (m, 1 H), 5.09-5.13 (m, 1 H), 4.59-4.63 (m, 1 H), 4.32-4.36 (m, 1 H), 4.12-4.18 (m, 2 H), 3.99 (dq, *J* =

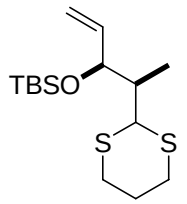
6.9, 6.9 Hz, 1 H), 3.29 (dd, *J* = 13.1, 3.0 Hz, 1 H), 2.78 (dd, *J* = 13.5, 9.9 Hz, 1 H), 1.22 (d, *J* = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 174.6, 153.3, 139.3, 135.5, 129.6, 129.0, 127.4, 115.8, 75.3, 66.0, 55.7, 44.1, 37.9, 25.9, 18.2, 12.5, –4.3, –5.0; 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 (77):** To a solution of **76** (3.12 g, 7.73 mmol) in THF (40 mL) and ethanol (2.3 mL, 39 mmol) at 0 °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 °C, quenched with sat. aq. sodium-potassium tartrate solution (10 mL) followed by dilution with ethyl acetate (50 mL), sat. aq. sodium-potassium tartrate 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 alcohol **77** (1.31 g, 74%) as an oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 17.0, 10.5, 6.2 Hz, 1 H), 5.17-5.27 (m, 2 H), 4.23-4.26 (m, 1 H), 3.63-3.70 (m, 1 H), 3.49-3.52 (m, 1 H), 2.82 (br s, 1 H), 1.84-2.05 (m, 1 H), 0.92 (s, 9 H), 0.81 (d, *J* = 7.1 Hz, 3 H), 0.09 (s, 3 H), 0.06 (s, 3 H).

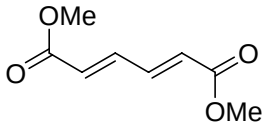



**(2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpent-4-enal (78):** To a solution of alcohol **77** (1.20 g, 5.25 mmol) in dichloromethane (20 mL) were added $NaHCO_3$ (solid, 0.60 g, 6.8 mmol) and Dess-martin reagent (2.90 g, 6.83 mmol). The reaction mixture was stirred for 1.5 h at room temperature 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 aldehyde **78** (1.04 g, 88%) as an oil: $[\alpha]_D$ −51.6 (*c* 0.5 $CHCl_3$);$^1$H NMR (300 MHz, $CDCl_3$) δ 9.77 (d, *J* = 1.4 Hz, 1 H), 5.74-5.89 (m, 1 H), 5.22-5.30 (m, 1 H), 5.14 - 5.20 (m, 1 H), 4.50-4.57 (m, 1 H), 2.39-2.53 (m, 1 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 204.6, 138.5, 116.1, 73.6, 52.8, 52.6, 25.8, 8.4, –4.2, –5.0; 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.

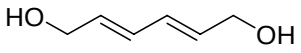



**((3*S*,4*R*)-4-(1,3-Dithian-2-yl)pent-1-en-3-yloxy)(*tert*-butyl)dimethylsilane (6):** To a solution of aldehyde **78** (1.0 g, 4.4 mmol) in ether (15 mL) at 0 $^o$C were added $MgBr_2$•$OEt_2$ (2.3 g, 8.8 mmol) and propane-1,3-dithiol (0.72 g, 6.6 mmol). The reaction mixture was stirred at 0 $^o$C 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

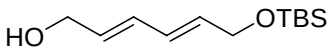
(3 x 10 mL). The combined organic extracts were washed with 1 N NaOH (5 mL), sat. aq. NaCl, water, dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography ($SiO_2$, 10% ethyl acetate in hexanes) to yield the dithiane **6** (1.25 g, 89%) as an oil: $[\alpha]_D$ –10 (*c* 0.29 $CHCl_3$); $^1$H NMR (300 MHz,$CDCl_3$) δ 5.80 (ddd, *J* = 17.3, 10.4, 6.6 Hz, 1 H), 5.22 (d, *J* = 17.0 Hz, 1 H), 5.13 (d, *J* = 10.4 Hz, 1 H), 4.32-4.45 (m, 1 H), 4.08 (d, *J* = 6.6 Hz, 1 H), 2.78-2.92 (m, 4 H), 2.01-2.15 (m, 1 H), 1.77-1.92 (m, 2 H), 1.09 (d, *J* = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.02 (s, 3 H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 140.5, 115.7, 74.5, 51.6, 44.5, 30.9, 30.4, 26.3, 26.0, 18.3, 11.8, –4.0, –4.7; IR (neat) $cm^{-1}$ 2928, 2896, 2856, 1472, 1252, 1078, 836, 776; EIMS 318, $(M - t\text{Bu})^+$ 261; HRMS for $C_{15}H_{30}OSiS_2$ : Calcd 318.1507; found 318.1497.




**(2*E*,4*E*)-Dimethyl hexa-2,4-dienedioate (80):** Acetyl chloride (23 mL) was added slowly to a solution of *trans*,*trans*-muconic acid **79** (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 ester **80** (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 7.26-7.38 (m, 2 H), 6.14-6.26 (m, 2 H), 3.78 (s, 6 H); $^{13}$C NMR (75 MHz, $CHCl_3$) δ 166.4, 141.0, 128.1, 52.0; HRMS for $C_8H_{10}O_4$: Calcd 170.0579; found 170.0580.

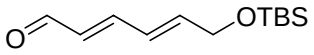



**(2*E*,4*E*)-Hexa-2,4-diene-1,6-diol (81):** To a solution of ester **80** (3.23 g, 19.0 mmol) in chloroform (190 mL) at 0 $^{o}$C was added DIBAL-H (1.0 M in hexane, 95 mL) and the reaction mixture was stirred at that temperature for 1 h. Then the reaction mixture was slowly treated with methanol (19 mL) and stirred for additional 15 min at 0 $^{o}$C. Sat. aq. sodium-potassium tartrate (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 diol **81** (2.05 g, 18.0 mmol, 95%) as white waxy solid: $^{1}$H NMR (300 MHz, $CD_3OD$) δ 6.32-6.45 (m, 2 H), 5.84-6.00 (m, 2 H), 5.00 (br s, 2 H), 4.20 (d, $J$ = 5.2 Hz, 4 H); $^{13}$C NMR (75 MHz, $CD_3OD$) δ 133.5, 131.4, 63.2; EIMS $(M)^+$ 114, $(M - H_2O)^+$ 96; HRMS for $C_6H_{10}O_2$: Calcd 114.0681; found 114.0678.

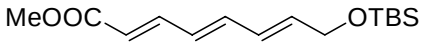



**(2*E*,4*E*)-6-(*tert*-Butyldimethylsilyloxy)hexa-2,4-dien-1-ol (82)**: To a solution of diol **81** (2.00 g, 17.5 mmol) in DMF (150 mL) at room temperature were added imidazole (1.25 g, 18.4 mmol) and *tert*-butyldimethylsilyl chloride (2.77 g, 18.4 mmol, 1.05 equiv). The reaction mixture was stirred 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 product **82** (1.8 g, 45%) as an oil: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 6.20-6.32 (m, 2 H), 5.73-5.88 (m, 2 H), 4.16-4.26 (m, 4 H), 0.92 (s, 9 H), 0.08 (s, 6 H); $^{13}$C NMR (76 MHz, $CDCl_3$)

δ 132.8, 131.7, 130.6, 129.1, 63.4, 63.0, 25.9, 18.4, −5.2; IR (neat) $cm^{-1}$ 3357, 2929, 2955, 2885, 2857, 1684, 1472, 1463, 1377.

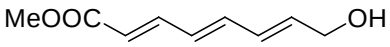



**(2*E*,4*E*)-6-(*tert*-Butyldimethylsilyloxy)hexa-2,4-dienal (83):** To a solution of alcohol **82** (848 mg, 3.71 mmol) in dichloromethane (50 mL) at room temperature was added $MnO_2$ (3.2 g, 37.1 mmol, activated, obtained from Fulka). The reaction mixture was stirred at room temperature for 45 min, filtered and the filtrate was concentrated to yield the aldehyde **83** (839 mg,100%) as an oil: 1H NMR (300 MHz, $CD_2Cl_2$) δ 9.54 (d, *J* = 8.0 Hz, 1 H), 7.15 (dd, *J* = 15.1, 11.0 Hz, 1 H), 6.50-6.64 (m, 1 H), 6.34 (dt, *J* = 15.1, 4.1 Hz, 1 H), 6.11 (dd, *J* = 15.4, 8.0 Hz, 1 H), 4.33 (dd, *J* = 3.8, 1.9 Hz, 2 H), 0.93 (s, 9 H), 0.09 (s, 6 H); $^{13}C$ NMR (75 MHz, $CD_2Cl_2$) δ 194.0, 152.1, 145.0, 131.7, 127.2, 63.4, 26.3, 18.8, –5.0; 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.

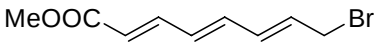



**(2*E*,4*E*,6*E*)-Methyl 8-(*tert*-butyldimethylsilyloxy)octa-2,4,6-trienoate (84):** To a suspension of NaH (98 mg, 4.1 mmol) in THF (15 mL) at 0 $^oC$ was added methyldiethylphosphonoacetate (857 mg, 4.10 mmol). The reaction mixture was stirred at room temperature for 20 min followed by cooling to −78 $^oC$. The above reaction mixture was added via cannula to a solution of aldehyde **83** (839 mg, 3.71 mmol) in THF (15 mL) at −78 $^oC$. 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 ester **84** (828 mg, 2.93 mmol, 79%): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 15.6, 11.5 Hz, 1 H), 6.58 (dd, *J* = 14.8, 10.7, 1 H), 6.28-6.41 (m, 2 H), 5.99 (dt, *J* = 15.1, 4.7 Hz, 1 H), 5.88 (d, *J* = 15.1 Hz, 1 H), 4.28 (d, *J* = 4.7 Hz, 2 H), 3.75 (s, 3 H), 0.92 (s, 9 H), 0.08 (s, 6 H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 167.4, 144.7, 140.3, 137.8, 129.2, 128.5, 120.2, 63.1, 51.4, 25.9, 18.4, –5.3; IR (neat) $cm^{-1}$ 2947, 2929, 2886, 2857, 1715, 1621; EIMS ($M^+$) 282, $(M - tBu)^+$ 225; HRMS for $C_{15}H_{26}O_3Si_1$: Calcd 282.1651; found 282.1641.

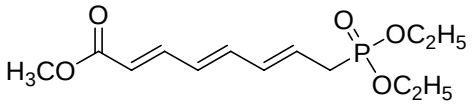



**(2*E*,4*E*,6*E*)-Methyl 8-hydroxyocta-2,4,6-trienoate (85):** To a solution of ester **84** (0.82 g, 2.9 mmol) in 2: 1 mixture of dichloromethane: methanol (40 mL) was added acetyl chloride (25 mg) at room temperature. After 30 min, the mixture was concentrated to yield the alcohol **85** (488 mg, 2.90 mmol, 100%) as pale yellow solid: $^1$H NMR (601 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 15.4, 11.3 Hz, 1 H), 6.58 (dd, *J* = 14.8, 11.0 Hz, 1 H), 6.30-6.40 (m, 2 H), 6.05 (dt, *J* = 15.1, 5.5 Hz, 1 H), 5.90 (d, *J* = 15.1 Hz, 1 H), 4.27 (d, *J* = 5.2 Hz, 1 H), 3.76 (s, 3 H), 1.51 (br s, 1 H); $^{13}$C NMR (76 MHz, $CDCl_3$) δ 167.6, 144.6, 140.1, 137.3, 129.7, 129.6, 120.5, 62.7, 51.6.

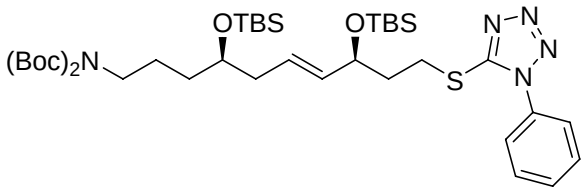



**(2*E*,4*E*,6*E*)-Methyl 8-bromoocta-2,4,6-trienoate (86):** To a solution of alcohol **85** (470 mg, 2.79 ml) in THF (10 mL) at –20 $^o$C were added 2,6-lutidine (658 mg, 6.15 mmol) and thionyl bromide (0.4 ml, 5.0 mmol). The reaction mixture was stirred at –20 $^o$C for 40 min followed by 2 h at room 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

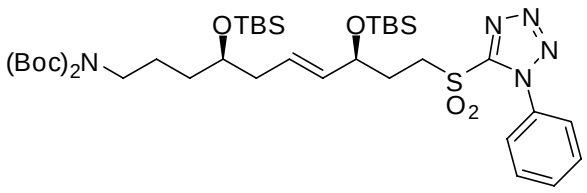
combined organic extracts were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash column chromatography (10% ethyl acetate in hexanes) gave the bromide **86** (473 mg, 73%) as white solid: $^1$H NMR (500 MHz, $CHCl_3$) δ 7.30 (dd, *J* = 15.6, 11.4 Hz, 1 H), 6.53 (dd, *J* = 15.1, 11.0 Hz, 1 H), 6.32-6.41 (m, 2 H), 6.03-6.12 (m, 1 H), 5.92 (d, *J* = 15.1 Hz, 1 H), 4.05 (d, *J* = 7.8 Hz, 2 H), 3.75 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.3, 143.9, 138.7, 133.8, 132.9, 131.7, 121.9, 51.7, 32.3; 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.



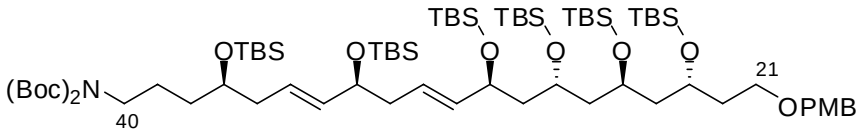

**(2*E*,4*E*,6*E*)-Methyl 8-(diethoxyphosphoryl)octa-2,4,6-trienoate (7):** To a solution of bromide **87** (469 mg, 2.03 mmol) in 10 mL toluene was added triethylphosphite. The reaction mixture was refluxed over night followed by concentration. Purification of the crude product by flash column chromatography (25 to 100% ethyl acetate in hexanes, gradient flash column) gave the fragment **7** (550 mg, 94%) as waxy solid: $^1$H NMR (600 MHz, $CHCl_3$) δ 7.29 (dd, *J* = 15.4, 11.3 Hz, 1 H), 6.54 (dd, *J* = 15.1, 10.7 Hz, 1 H), 6.24-6.30 (m, 2 H), 5.83-5.90 (m, 2 H), 4.08-4.14 (m, 4 H), 3.75 (s, 3 H), 2.70 (d, *J* = 23.0, 7.1 Hz, 2 H), 1.32 (t, *J* = 7.1 Hz, 6 H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 167.5, 144.4, 139.8 ($J_{C\text{-}P}$ = 6 Hz), 134.2 ($J_{C\text{-}P}$ = 16 Hz), 129.6 ($J_{C\text{-}P}$ = 5 Hz), 127.4 ($J_{C\text{-}P}$ = 13 Hz), 120.9, 62.2 ($J_{C\text{-}P}$ = 7 Hz), 51.6, 30.2 ($J_{C\text{-}P}$ = 139 Hz), 16.1 ($J_{C\text{-}P}$ = 6 Hz); 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-ylthio)-*N*,*N*-*bis*(Boc) dec-6-en-1-amine (8)**: KHMDS (0.5 M, 0.45 ml, 0.225 mmol) was added to a solution of sulfone **2** (130 mg, 0.187 mmol) in DME (5 mL) at –60 $^{o}$C. After 30 min, a solution of aldehyde **3** (92.3 mg, 0.244 mmol) in DME (2 mL) was added. The reaction mixture was stirred at –60 $^{o}$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 (over 19/1) of product (85 mg, 85%) as an oil. Further purification by preparative HPLC with Whelk-O column (95/5 hexane/*i*-propanol) provided pure *E*-isomer **8**: $[\alpha]_D$ +4.3 (*c* 0.21 $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.54-7.60 (m, 5 H), 5.60 (dt, *J* = 15.4, 7.1 Hz, 1 H), 5.44 (dd, *J* = 15.4, 6.6 Hz, 1 H), 4.23 (q, *J* = 6.0 Hz, 1 H), 3.66-3.70 (m, 1 H), 3.50-3.57 (m, 2 H), 3.39-3.47 (m, 2 H), 2.18 (t, *J* = 6.4 Hz, 2 H), 1.98-2.01 (m, 2 H), 1.62-1.70 (m, 2 H), 1.50 (s, 18 H), 1.37-1.44 (m, 2 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 6 H), 0.02 (s, 3 H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 154.5, 152.7, 134.8, 133.8, 130.1, 129.8, 127.5, 123.9, 82.0, 72.1, 71.8, 46.6, 40.0, 37.5, 33.8, 29.5, 28.2, 25.9, 25.2, 18.2, 18.1, –4.0, –4.3, –4.5, –4.7; 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.

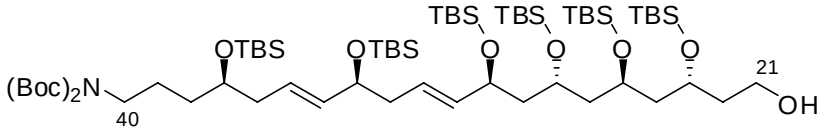



**(4*R*,8*S*,*E*)-4,8-*bis*(*tert*-butyldimethylsilyloxy)-10-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)-*N*,*N*-*bis*(Boc)-dec-6-en-1-amine** (**9**)**:** To a solution of sulfide **8** (62 mg, 0.078 mmol) in ethanol (1.5 mL) was added oxidant (0.3 mL, prepared from 0.6 g of $Mo_7O_{24}(NH_4)_6$•$4H_2O$ in 2.5 mL of 30% w/v aq $H_2O_2$). 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 sulfone **9** (60 mg, 92%) as an oil: $[\alpha]_D$ +4.47 (*c* 0.67 $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.4 Hz, 2 H), 7.57-7.63 (m, 3 H), 4.33 (q, *J* = 14.8, 7.1 Hz, 1 H), 3.78 (t, *J* = 8.0 Hz, 2 H), 2.06-3.73 (m, 1 H), 1.60-1.17 (m, 1 H), 1.49 (s, 18 H), 1.37-1.41 (m, 2 H), 1.24-1.26 (m, 2 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 9 H); $^{13}$C NMR (151 MHz,$CDCl_3$) δ 153.5, 152.6, 133.6, 133.1, 131.4, 129.7, 128.4, 125.1, 82.0, 71.6, 70.8, 52.4, 46.5, 39.9, 33.8, 30.3, 28.1, 25.9, 25.9, 25.2, 18.2, 18.1, –4.2, –4.4, –4.5, –4.8; 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.



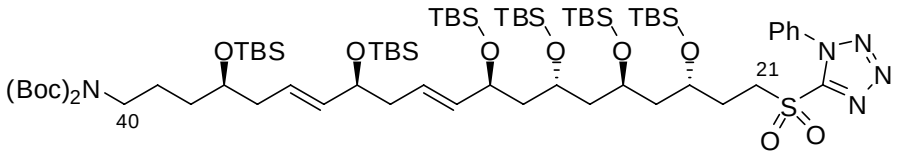

**(4*R*,6*E*,8*S*,10*E*,12*S*,14*R*,16*S*,18*R*)-20-(4-methoxybenzyloxy)-4,8,12,14,16,18-hexakis(*tert*-butyldimethylsilyloxy)-*N*,*N*-*bis*(Boc)-icosa-6,10-dien-1-amine (10):** KHMDS (0.5 M in toluene, 55 μL, 0.225 mmol) was added to a solution of sulfone **9** (20 mg, 0.023 mmol, 1 equiv)

in DME (1 mL) at −60 °C. After 30 min, a solution of aldehyde **4** (24 mg, 0.029 mmol) in DME (1 mL) was added. The reaction mixture was stirred at −60 °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 product **10** (26 mg, 80%) as a colorless oil: $[\alpha]_D$ −1.5 (*c* 0.6 $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2 H), 5.87 (d, *J* = 8.5 Hz, 2 H), 5.52-5.58 (m, 2 H), 5.46 (dd, *J* = 15.4, 6.3 Hz, 1 H), 5.41 (dd, *J* = 15.4, 7.7 Hz, 1 H), 4.42 (s, 2 H), 4.18 (td, *J* = 7.7, 3.8 Hz, 1 H), 4.07 (q, *J* = 6.0 Hz, 1 H), 3.87-3.94 (m, 2 H), 3.83-3.86 (m, 1 H), 3.81 (s, 3 H), 3.66-3.70 (m, 1 H), 3.48-3.59 (m, 4 H), 2.15-2.24 (m, 4 H), 1.59-1.84 (m, 9 H), 1.36-1.45 (m, 3 H), 0.896 (s, 9 H), 0.89 (s, 9 H), 0.885 (s, 18 H), 0.879 (s, 9 H), 0.876 (s, 9 H), 0.00-0.12 (m, 35 H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 159.1, 152.7, 131.0, 129.0, 114.0, 82.0, 73.5, 72.6, 72.0, 71.1,67.5, 67.2, 67.1, 66.8, 55.3, 46.8, 46.7, 46.7, 45.7, 41.6, 40.2, 37.9, 33.8, 29.8, 28.2, 26.2, 26.0, 26.0, 25.3, 18.3, 18.3, 18.2, −3.3, −3.4, −3.4, −3.5, −3.8, −3.8, −4.1, −4.2, −4.3, −4.5, −4.6; 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.



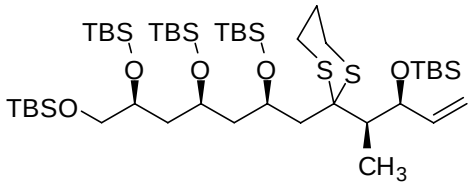

**(3*R*,5*S*,7*R*,9*S*,10*E*,13*S*,14*E*,17*R*)-20-amino-3,5,7,9,13,17-hexakis(*tert*-butyldimethylsilyloxy)-*N*,*N*-*bis*(Boc)-icosa-10,14-dien-1-ol (11)**: DDQ (12 mg, 0.052 mmol) was added to a solution of the PMB-ether **10** (52 mg, 0.037 mmol) in DCM (1 mL) and pH 7 buffer (0.1 mL) at room temperature. 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 alcohol **11** (42 mg, 89%) as an oil. $^1$H NMR (600 MHz, $CHCl_3$) δ 5.51-5.58 (m, 2 H), 5.39-5.48 (m, 2 H), 4.14 (dd, *J* = 12.6, 6.9 Hz, 1 H), 4.07 (dd, *J* = 11.8, 8.5 Hz, 1 H), 3.95-4.01 (m, 1 H), 3.77-3.91 (m, 3 H), 3.65-3.74 (m, 2 H), 3.50-3.59 (m, 2 H), 2.33 (t, *J* = 5.2 Hz, 1 H), 2.16-2.25 (m, 4 H), 1.55-1.91 (m, 6 H), 1.51 (s, 18 H), 1.23-1.47 (m, 6 H), 0.88-0.90 (m, 54 H), 0.01-0.10 (m, 36 H); $^{13}$C NMR (151 MHz, $CHCl_3$) δ 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, 25.4, 25.3, 22.7, 18.3, 18.3, 18.1, 18.1, 14.2, –3.4, –3.6, –4.2, –4.3, –4.4, –4.5, –4.6.



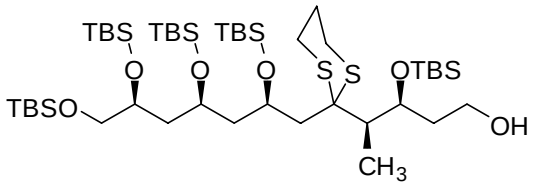

**(4*R*,6*E*,8*S*,10*E*,12*S*,14*R*,16*R*,18*S*)-4,8,12,14,16,18-*hexakis*(*tert*-butyldimethylsilyloxy)-20-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)-N,N-*bis*(Boc)-icosa-6,10-dien-1-amine (13)**: To a solution of alcohol **11** (40 mg, 0.031 mmol) in THF (1 mL) were added thiophenyltetrazole (7.2 mg, 0.040 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 sulfone **13** (30 mg, 65%) as an oil. $[\alpha]_D$ –24.1 (*c* 0.12 $CHCl_3$);.$^1$H NMR (600 MHz, $CHCl_3$) δ 7.70-7.72 (m, 2 H), 7.59-7.65 (m, 3 H), 5.53-5.58 (m, 2 H), 5.46 (dd, *J* = 15.4, 6.3 Hz, 1 H), 5.39 (dd, *J* = 15.4, 7.7 Hz, 1 H), 4.21 (td, *J* = 8.2, 3.4 Hz, 1 H), 4.05-4.10 (m, 2 H), 3.86-3.91 (m, 1 H), 3.74-2.85 (m, 3 H), 3.66-3.70 (m, 1 H), 3.50-3.59 (m, 2 H), 2.14-2.25 (m, 3 H), 2.02-2.09 (m, 1 H), 1.61-1.76 (m, 6 H), 1.51 (s, 18 H), 1.36-1.47 (m ,6 H), 0.88-0.91 (m, 54 H), 0.00-0.11 (m, 36 H); $^{13}$C NMR (151 MHz, $CHCl_3$) δ 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, 31.7, 30.0, 28.2, 26.1, 26.0, 26.0, 25.3, 22.7, 18.3, 18.3, 18.1, 18.1, 14.2, –3.2, –3.3, –3.8, –3.8, –4.2, –4.3, –4.5, –4.5, –4.6; IR (neat) cm$^{-1}$ 2928, 2856, 1501, 1472, 1361, 1251, 1122.



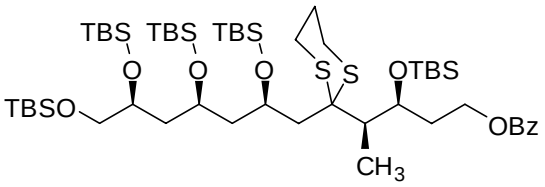

**2-((2*R*,4*S*,6*S*)-2,4,6,7-*tetrakis*(*tert*-Butyldimethylsilyloxy)heptyl)-2-((2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)pent-4-en-2-yl)-1,3-dithiane (14):** To a solution of dithiane **6** (122 mg, 0.383 mmol) in THF (0.5mL) and HMPA (0.05 mL) at –78 $^o$C was added *t*-BuLi (1.7 M in pentane, 0.25 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 $^o$C for 2 h. The reaction mixture was warmed to 0 $^o$C 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 product **14** (194 mg, 54%) as an oil: $^{1}$H NMR (600 MHz, $CHCl_3$) δ 5.95 (ddd, *J* = 17.6, 10.2, 7.7 Hz, 1 H), 5.13 (d, *J* = 17.0 Hz, 1 H), 5.02 (d, *J* = 10.7 Hz, 1 H), 4.95 (d, J = 7.7 Hz, 1 H), 4.22 (qn, *J* = 5.2 Hz, 1 H), 3.76-3.80 (m, 1 H), 3.62 (dd, *J* = 9.9, 3.5 Hz, 1 H), 3.44 (dd, *J* = 10.2, 7.1 Hz, 1 H), 2.80-2.88 (m, 2 H), 2.51-2.59 (m, 2 H), 2.28 (q, *J* = 6.9 Hz, 1 H), 1.90-1.97 (m, 3 H), 1.69-1.84 (m, 4 H), 1.65 (ddd, *J* = 13.4, 7.4, 5.2 Hz, 1 H), 1.10 (d, *J* = 6.9Hz, 1 H), 0.91 (s, 18 H), 0.90 (s, 27 H), 0.22 (s, 3 H), 0.15 (s, 3 H), 0.12 (s, 3 H), 0.10 (s, 6 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.05 (s, 6 H), 0.02 (s, 3 H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 143.4, 113.6, 73.5, 71.2, 67.8, 67.5, 67.0, 58.2, 49.4, 44.3, 44.0, 42.8, 31.7, 26.3, 26.3, 26.1, 26.1, 25.9, 24.5, 22.7, 18.5, 18.3, 18.3, 18.1, 14.2, 8.9, –2.9, –3.0, –3.8, –4.0, –4.1, –4.2, –4.4, –5.2, –5.3.



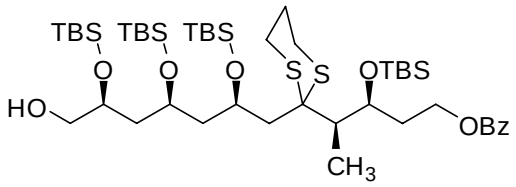

**(3*S*,4*R*)-4-(2-((2*R*,4*S*,6*S*)-2,4,6,7-*tetrakis*(*tert*-Butyldimethylsilyloxy)heptyl)-1,3-dithian-2-yl)-3-(*tert*-butyldimethylsilyloxy)pentan-1-ol (15):** To a solution of alkene **14** in THF (2 mL) was added 9-BBN (0.5 M in THF, 1.32 mL, 0.66 mmol). The reaction mixture was stirred at room 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 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

alcohol **15** (128 mg, 64%) as an oil: $^1$H NMR (600 MHz, $CDCl_3$) δ 4.48 (dd, *J* = 9.3, 3.3 Hz, 1 H), 4.18-4.21 (m, 1 H), 3.86-3.91 (m, 1 H), 3.69-3.82 (m, 3 H), 3.62 (dd, *J* = 10.0, 3.5 Hz, 1 H), 3.43 (dd, *J* = 10.2, 7.1 Hz, 1 H), 2.89 (ddd, *J* = 14.3, 11.8, 2.8 Hz, 1 H), 2.79 (ddd, *J* = 13.7, 11.3, 2.5 Hz, 1 H), 2.56-2.66 (m, 2 H), 2.42 (q, *J* = 7.0 Hz, 1 H), 1.39-2.03 (m, 11 H), 1.06 (d, *J* = 6.9 Hz, 3 H), 0.904 (s, 9 H), 0.90 (s, 9 H), 0.894 (s, 18 H), 0.89 (s, 9 H), 0.19 (s, 3 H), 0.14 (s, 6 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 6 H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 72.3, 71.2, 69.2, 67.8, 67.4, 67.1, 60.0, 58.1, 49.4, 44.5, 42.6, 42.0, 41.5, 40.7, 34.8, 34.8, 33.4, 31.7, 27.5, 26.2, 26.1, 26.0, 25.4, 25.3, 24.5, 22.7, 18.5, 18.3, 18.3, 18.1, 14.2, 10.1, –2.9, –3.0, –3.9, –4.0, –4.2, –4.4, –5.2, –5.3; HRMS for $C_{46}H_{102}O_6S_2Si_5Na$ (M + Na): Calcd 977.5862; found 977.5826.



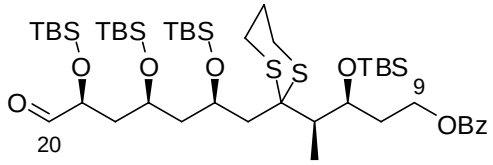

**(3*S*,4*R*)-4-(2-((2*R*,4*S*,6*S*)-2,4,6,7-*tetrakis*(*tert*-Butyldimethylsilyloxy)heptyl)-1,3-dithian-2-yl)-3-(*tert*-butyldimethylsilyloxy)pentyl benzoate (90):** To a solution of alcohol **15** (50 mg, 0.052 mmol) in dichloromethane (5 mL) were added triethyl amine (0.1 mL), DMAP (20 mg) and benzyl 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 benzoate **90** (46 mg, 83%) as an oil: $[\alpha]_D$ 16.3 (*c* 0.7 $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 8.04-8.09 (m, 2 H), 7.55-

7.60 (m, 1 H), 7.42-7.48 (m, 2 H), 4.66 (d, *J* = 9.1, 3.3 Hz, 1 H), 4.38-4.46 (m, 1 H), 4.31-4.38 (m, 1 H), 4.18-4.25 (m, 1 H), 3.87-3.94 (m, 1 H), 3.76-3.84 (m, 1 H), 3.63 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.44 (dd, *J* = 10.2, 7.1 Hz, 1 H), 2.72-2.87 (m, 2 H), 2.42-2.55 (m, 3 H), 1.60-2.13 (m, 8 H), 1.24-1.35 (m, 2 H), 1.10 (d, *J* = 6.9 Hz, 3 H), 0.915 (s, 9 H), 0.909 (s, 9 H), 0.905 (s, 9 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.19 (s, 3 H), 0.16 (S, 3 H), 0.14 (s, 3 H), 0.13 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.08 9s, 3 H), 0.07 (s, 3 H), 0.05 (s, 6 H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 166.7, 133.0, 130.3, 129.6, 128.4, 71.2, 68.9, 67.8, 67.5, 67.0, 62.1, 57.8, 49.6, 44.6, 42.6, 41.2, 37.2, 31.7, 26.3, 26.1, 25.9, 24.4, 22.7, 18.5, 18.4, 18.3, 18.1, 18.1, 14.2, 9.8, –3.0, –3.1, –3.8, –3.9, –3.9, –4.0, –4.2, –4.4, –5.2, –5.3; IR (neat) $cm^{-1}$ 2950, 2929, 2850, 1723, 1472, 1275, 1252, 1109, 835.



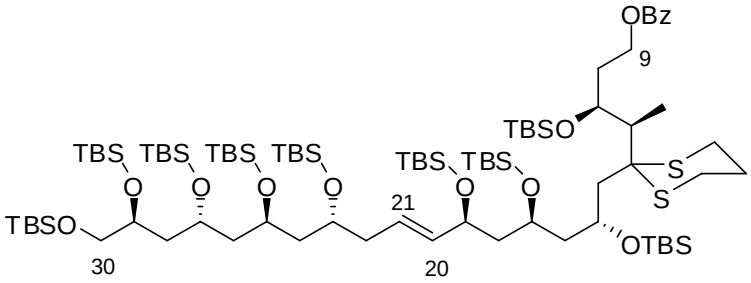

**(3*S*,4*R*)-4-(2-((2*R*,4*S*,6*S*)-2,4,6-*tris*(*tert*-Butyldimethylsilyloxy)-7-hydroxyheptyl)-1,3-dithian-2-yl)-3-(*tert*-butyldimethylsilyloxy)pentyl benzoate (91):** To a solution of benzoate **90** (45 mg, 0.042 mmol) in THF (0.5 mL) was added HF•pyr (1 mL) and the reaction mixture was stirred 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 alcohol **91** (16 mg, 39%) as an oil: $[\alpha]_D$ 14.3 (*c* 0.3 $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.04-8.07 (m, 2 H), 7.54-7.60 (m, 1 H), 7.42-7.47 (m, 2 H), 4.56-4.61

(m, 1 H), 4.29-4.44 (m, 2 H), 4.05-4.18 (m, 2 H), 3.80-3.99 (m, 1 H), 3.55-3.66 (m, 1 H), 3.35-3.51 (m, 1 H), 2.60-2.90 (m, 3 H), 2.44-2.53 (m, 2 H), 1.66-2.20 (m, 11 H), 1.09 (d, $J$ = 6.9 Hz, 3 H), 0.88-0.91 (m, 36 H), 0.06-0.20 (m, 24 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.7, 133.1, 130.3, 129.6, 128.4, 70.3, 68.8, 67.6, 67.0, 66.6, 62.0, 57.6, 49.2, 45.2, 41.4, 41.1, 37.1, 26.4, 26.2, 26.1, 26.0, 18.4, 18.2, 18.1, 18.1, 10.0, –2.9, –3.0, –3.9, –4.1, –4.3, –4.5, –4.6; 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 967.5232.



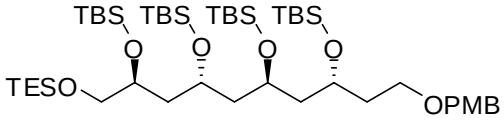

**(3*S*,4*R*)-3-(*tert*-butyldimethylsilyloxy)-4-(2-((2*R*,4*S*,6*S*)-2,4,6-tris(*tert*-butyldimethylsilyloxy)-7-oxoheptyl)-1,3-dithian-2-yl)pentyl benzoate (87):** To a solution of $(COCl)_2$ (17 μL, 0.20 mmol) in $CH_2Cl_2$ was added slowly a solution of DMSO (21 μL, 0.30 mmol) in $CH_2Cl_2$ at –78 $^oC$. Then the reaction mixture was stirred under –78 $^oC$ for 20 min followed by slow addition of alcohol **91** (95mg, 0.10 mmol) in $CH_2Cl_2$. The reaction mixture was stirred for another 30 min. $NEt_3$ (70 μL, 0.50 mmol) was added and the mixture was stirred for 15 min and warmed to 0 $^oC$ and stirred for another 20 min. Saturated aqueous $NaHCO_3$ was added and the mixture was 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 residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to yield the aldehyde **87** (74 mg, 0.078 mmol, 78%) as oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 9.60 (d, $J$ = 1.8 Hz, 1 H), 8.04-8.06 (m, 2 H),

7.54-7.56 (m, 1 H), 7.41-7.46 (m, 2 H), 4.57-4.59 (m, 1 H), 4.35-4.40 (m, 2 H), 4.18-4.25 (m, 1 H), 4.10-4.17 (m, 1 H), 3.97-4.07 (m, 1 H), 2.68-2.92 (m, 2 H), 2.39-2.56 (m, 3 H), 1.69-2.20 (m, 10 H), 1.09 (d, $J$ = 6.9 Hz, 3 H), 0.85-0.93 (m, 36 H), 0.04-0.19 (m, 24 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 203.2, 166.6, 133.0, 130.1, 129.5, 128.4, 74.9, 68.6, 66.9, 65.8, 61.9, 57.6, 49.5, 44.9, 41.1, 41.0, 37.0, 26.2, 26.1, 26.1, 25.9, 25.9, 25.5, 24.3, 18.4, 18.3, 18.0, 18.0, 9.6, –3.1, –4.0, –4.1, –4.2, –4.3, –4.6, –4.7; IR (neat) cm$^{-1}$ 2954, 2930, 2895, 2857, 1723, 1470, 1273, 1255, 1110, 1047, 1005, 836, 808, 775, 711; HRMS for $C_{47}H_{90}O_7NaSi_4S_2(M + Na)^+$: Calcd 965.5103; found 965.5110.



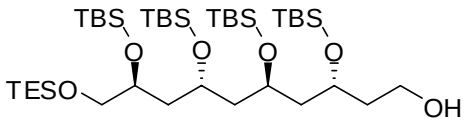

**(3*S*,4*R*)-3-(*tert*-butyldimethylsilyloxy)-4-(2-((2*R*,4*S*,6*S*,10*R*,12*S*,14*R*,16*S*,*E*)-2,4,6,10,12,14,16,17-octakis(*tert*-butyldimethylsilyloxy)heptadec-7-enyl)-1,3-dithian-2-yl)pentyl benzoate (96):** KHMDS (0.5 M in DME, 70 μL, 0.035 mmol) was added to a solution of sulfone **92** (32 mg, 0.032 mmol) in DME at –60 °C. After 30 min, a solution of aldehyde **87** (36 mg, 0.038 mmol) in DME was added. The reaction mixture was stirred at –60 °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 (5% ethyl acetate in hexanes) to yield the alkene **95** (28 mg, 50%) as a colorless oil: $^1$H NMR (700 MHz, $CDCl_3$) δ 8.04-8.06 (m, 2 H), 7.54-7.56 (m, 1 H), 7.41-7.46 (m, 2 H),

5.40-5.50 (m, 2 H), 4.61-4.63 (m, 1 H), 4.39-4.42 (m, 1 H), 4.32-4.34 (m, 1 H), 4.24-4.26 (m, 1 H), 4.14-4.15 (m, 1 H), 3.74-3.89 (m, 5 H), 3.48-3.50 (m, 1 H), 3.34-3.36 (m, 1 H), 2.71-2.85 (m, 2 H), 2.40-2.55 (m, 3 H), 2.24-2.29 (m, 1 H), 2.04-2.11 (m, 2 H), 1.92-2.02 (m, 2 H), 1.42-1.92 (m, 13 H), 1.09 (d, $J$ = 7.0 Hz, 3 H), 0.83-0.97 (m, 81 H), 0.05-0.09 (m, 54 H); $^{13}$C NMR (175 MHz, $CDCl_3$) δ 166.6, 135.7, 133.0, 130.2, 129.6, 128.4, 126.7, 71.2, 71.0, 70.6, 69.2, 68.7, 67.8, 67.4, 67.1, 66.8, 62.0, 57.6, 49.9, 46.9, 46.4, 44.8, 44.4, 42.0, 41.4, 41.1, 37.0, 26.2, 26.1, 26.0, 26.0, 26.0, 18.4, 18.3, 18.2, 18.1, 18.0, 9.8, –3.1, –3.1, –3.4, –3.5, –3.7, –3.8, –3.9, –3.9, –4.0, –4.1, –4.2, –4.4, –4.5, –4.6, –5.3, –5.3.

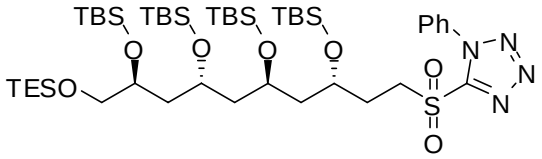



**(5*R*,7*S*,9*R*,11*S*)-7,9,11-tris(*tert*-butyldimethylsilyloxy)-14,14-diethyl-5-(2-(4-methoxybenzyloxy)ethyl)-2,2,3,3-tetramethyl-4,13-dioxa-3,14-disilahexadecane (101):** To a solution of **39** (160 mg, 0.196 mmol) in dichloromethane at –78 $^{o}$C were added 2,6-lutidine (25 mg, 0.235 mmol) and TESOTf (62 mg, 0.235 mmol). The reaction mixture was stirred at –78 $^{o}$C for 3 h followed by warming it to 0 $^{o}$C. 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 ether **39** (160 g, 88%) as an oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.24-7.27 (m, 2 H), 6.85-6.88 (m, 2 H), 4.41 (s, 2 H), 3.75-3.93 (m, 7 H), 3.45-3.52 (m, 3 H), 3.35-3.41 (m, 1 H), 1.40-1.85 (m, 8 H), 0.87-0.98 (m, 45 H), 0.55-0.63 (m, 6 H), 0.02-0.07 (m, 24 H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ

159.0, 130.8, 129.1, 113.7, 72.5, 70.7, 67.3, 67.3, 67.2, 67.0, 66.7, 55.2, 46.8, 45.8, 42.4, 37.6, 26.1, 26.0, 18.4, 18.2, 18.1, 18.0, 7.1, 6.8, 5.7, 4.4, –3.5, –3.6, –3.7, –3.8, –3.9.

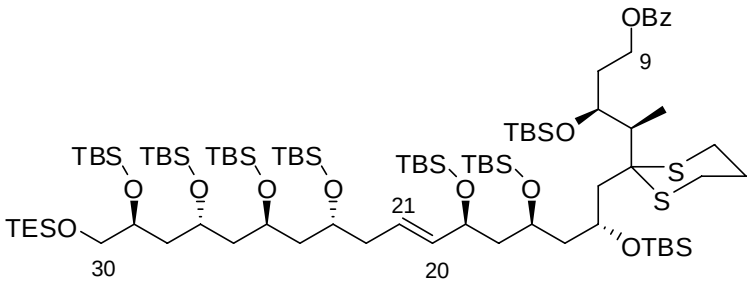



**(3*R*,5*S*,7*R*,9*S*)-3,5,7,9-tetrakis(*tert*-butyldimethylsilyloxy)-10-(triethylsilyloxy)decan-1-ol (102):** DDQ (50 mg, 0.223 mmol) was added to a solution of the PMB-ether **101** (160 mg, 0.172 mmol) in DCM and pH 7 buffer (10:1) at room temperature. The reaction mixture was stirred at room temperature for 2 h followed by diluting it with DCM and saturated aqueous $NaHCO_3$. Organic layer was separated and 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 to yield the alcohol **102** (130 mg, 93%) as an oil: 3.92-4.41 (m, 1 H), 3.67-3.91 (m, 5 H), 3.47-3.52 (m, 1 H), 3.40-3.46 (m, 1 H), 1.40-1.92 (m, 8 H), 0.87-0.98 (m, 45 H), 0.55-0.63 (m, 6 H), 0.02-0.07 (m, 24 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 70.9, 69.6, 67.4, 67.2, 66.9, 60.2, 46.3, 45.3, 42.7, 38.1, 26.0, 26.0, 25.9, 25.9, 18.2, 18.0, 17.9, 7.1, 6.8, 5.6, 4.4, –3.5, –3.7, –3.8, –4.0, –4.3, –4.6, –5.3.



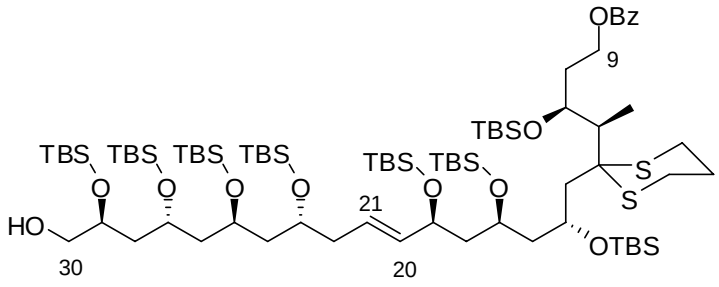

**1-phenyl-5-((3*S*,5*R*,7*R*,9*S*)-3,5,7,9-tetrakis(*tert*-butyldimethylsilyloxy)-10-(triethylsilyloxy)decylsulfonyl)-1*H*-tetrazole (104):** To a solution of alcohol **102** (130 mg, 0.160 mmol) in THF were added thiophenyltetrazole (34 mg, 0.209 mmol), triphenylphosphine

(55 mg, 0.209 mmol) and DIAD (42 mg, .209 mmol) at room temperature. After 16 h, it was diluted with ethyl acetate and water. 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. To the crude compound in dichloromethane was added *m*-CPBA (106 mg, 0.430 mmol) and $NaHCO_3$. The reaction mixture was stirred at room temperature for overnight, quenched with saturated $NaHCO_3$ and extracted with dichloromethane. 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 sulfone **104** (131 mg, 83%) as an oil: $^1$H NMR (700 MHz, $CDCl_3$) δ 7.70-7.71 (m, 2 H), 7.59-7.62 (m, 3 H), 4.04-4.08 (m, 1 H), 3.74-3.92 (m, 5 H), 3.49-3.52 (m, 1 H), 3.34-3.37 (m, 1 H), 2.16-2.23 (m, 1 H), 2.01-2.08 (m, 1 H), 1.63-1.74 (m, 4 H), 1.40-1.51 (m, 2 H), 0.58-0.62 (m, 6 H), 0.83-0.97 (m, 45 H), 0.05-0.09 (m, 24 H); $^{13}$C NMR (175 MHz, $CDCl_3$) δ 153.4, 133.1, 131.4, 129.7, 125.0, 70.5, 67.3, 67.2, 67.1, 67.0, 52.1, 46.9, 44.7, 42.3, 30.0, 26.0, 26.0, 25.9, 25.9, 25.9, 18.2, 18.0, 18.0, 7.1, 6.8, 4.3, –3.4, –3.4, –3.7, –3.8, –3.9, –4.3, –4.4, –4.6.



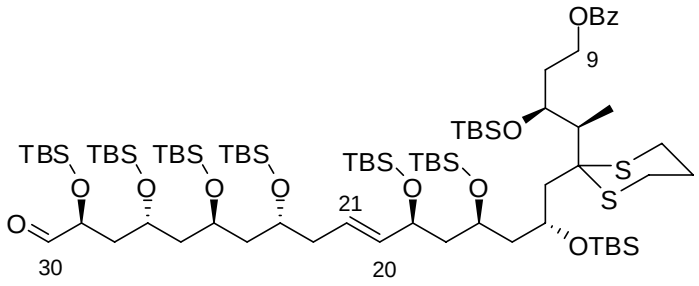

**(3*S*,4*R*)-3-(*tert*-butyldimethylsilyloxy)-4-(2-((2*R*,4*S*,6*S*,10*R*,12*S*,14*R*,16*S*,*E*)-2,4,6,10,12,14,16-heptakis(*tert*-butyldimethylsilyloxy)-17-(triethylsilyloxy)heptadec-7-enyl)-1,3-dithian-2-yl)pentyl benzoate (105):** KHMDS (0.5 M in DME, 140 μL, 0.070 mmol) was added to a solution of sulfone **104** (63 mg, 0.063 mmol) in DME at –60 $^o$C. After 30 min, a

solution of aldehyde **87** (73 mg, 0.077 mmol) in DME was added. The reaction mixture was stirred at –60 $^{o}$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 layers were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography (5% ethyl acetate in hexanes) to yield the alkene **105** (56 mg, 52%) as a colorless oil: $^{1}$H NMR (700 MHz, $CDCl_3$) δ 8.04-8.06 (m, 2 H), 7.54-7.56 (m, 1 H), 7.41-7.46 (m, 2 H), 5.40-5.50 (m, 2 H), 4.61-4.63 (m, 1 H), 4.39-4.42 (m, 1 H), 4.32-4.34 (m, 1 H), 4.24-4.26 (m, 1 H), 4.14-4.15 (m, 1 H), 3.74-3.89 (m, 5 H), 3.48-3.50 (m, 1 H), 3.34-3.36 (m, 1 H), 2.71-2.85 (m, 2 H), 2.40-2.55 (m, 3 H), 2.24-2.29 (m, 1 H), 2.04-2.11 (m, 2 H), 1.92-2.02 (m, 2 H), 1.42-1.92 (m, 13 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 0.83-0.97 (m, 81 H), 0.58-0.62 (m, 6 H), 0.05-0.09 (m, 48 H); $^{13}$C NMR (175 MHz, $CDCl_3$) δ 166.6, 135.7, 133.0, 130.2, 129.6, 128.4, 126.7, 71.2, 70.6, 69.2, 68.7, 67.4, 67.2, 67.1, 67.1, 66.8, 62.0, 57.6, 49.9, 46.9, 46.4, 44.8, 44.3, 42.0, 41.4, 41.1, 37.0, 26.3, 26.2, 26.2, 26.0, 26.0, 26.0, 25.7, 24.6, 24.3, 18.3, 18.2, 18.0, 18.0, 9.8, 7.1, 6.8, 4.4, –3.1, –3.1, –3.2, –3.4, –3.5, –3.7, –3.8, –3.8, –3.9, –4.1, –4.2, –4.4, –4.5, –4.6, –4.7, –5.3.



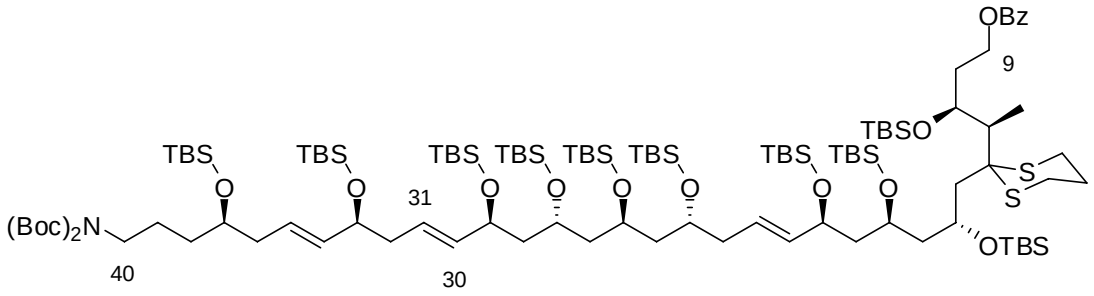

**(3*S*,4*R*)-3-(*tert*-butyldimethylsilyloxy)-4-(2-((2*R*,4*S*,6*S*,10*R*,12*S*,14*R*,16*S*,*E*)-2,4,6,10,12,14,16-heptakis(*tert*-butyldimethylsilyloxy)-17-hydroxyheptadec-7-enyl)-1,3-dithian-2-yl)pentyl benzoate (97):** To a solution of compound **96** (17 mg, 0.010 mmol) in THF

(0.5 mL) was added HF•pyr (1 mL) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with THF and quenched with saturated aqueous sodium bicarbonate. 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 alcohol (1.6 mg, 10%) as an oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 8.04-8.06 (m, 2 H), 7.54-7.56 (m, 1 H), 7.42-7.45 (m, 2 H), 5.40-5.50 (m, 2 H), 4.61-4.64 (m, 1 H), 4.39-4.42 (m, 1 H), 4.32-4.34 (m, 1 H), 4.24-4.26 (m, 1 H), 4.12-4.18 (m, 1 H), 3.73-3.89 (m, 5 H), 3.57-3.63 (m, 1 H), 3.42-3.47 (m, 1 H), 2.71-2.85 (m, 2 H), 2.40-2.55 (m, 3 H), 2.21-2.27 (m, 1 H), 2.04-2.15 (m, 2 H), 1.92-2.02 (m, 2 H), 1.42-1.92 (m, 14 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 0.83-0.97 (m, 72 H), 0.05-0.09 (m, 48 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.6, 135.8, 133.0, 130.2, 129.6, 128.4, 126.4, 71.1, 70.3, 69.2, 68.7, 67.2, 67.1, 66.8, 62.0, 57.7, 49.9, 46.7, 46.4, 44.8, 44.8, 42.0, 41.3, 41.0, 37.0, 26.2, 26.0, 26.0, 25.9, 25.7,24.3, 18.3, 18.1, 18.0, 9.8, –3.1, –3.1, –3.5, –3.5, –3.8, –3.8, –3.9, –4.0, –4.1, –4.1, –4.3, –4.4, –4.5.



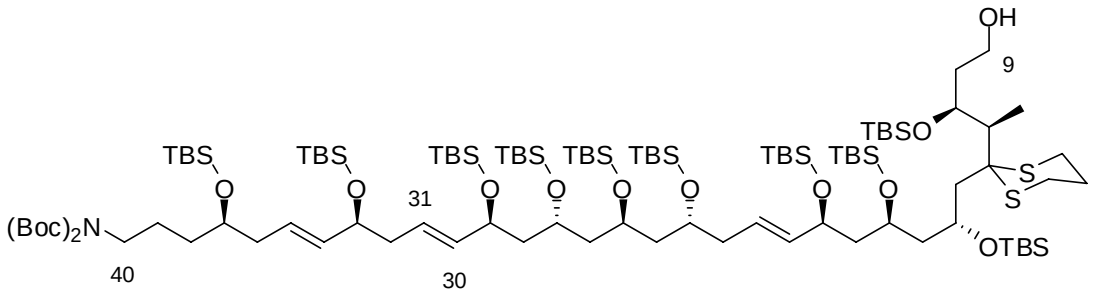

**(3*S*,4*R*)-3-(*tert*-butyldimethylsilyloxy)-4-(2-((2*R*,4*S*,6*S*,10*R*,12*S*,14*R*,16*S*,*E*)-2,4,6,10,12,14,16-heptakis(*tert*-butyldimethylsilyloxy)-17-oxoheptadec-7-enyl)-1,3-dithian-2-yl)pentyl benzoate (93):** To a solution of alcohol **97** (5 mg, 0.003 mmol) in DCM were added solid $NaHCO_3$ (1 mg) and Dess-Martin reagent (3 mg, 0.006 mmol). The reaction mixture was

stirred at room temperature for 3 h. Then the reaction was quenched with saturated $NaHCO_3$ solution. 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 residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to yield the aldehyde **93** (3 mg, 0.0018 mmol, 60%) as oil: $^1$H NMR (600 MHz, $CDCl_3$) δ 9.57 (d, *J* = 1.2 Hz, 1 H), 8.04-8.06 (m, 2 H), 7.54-7.56 (m, 1 H), 7.42-7.45 (m, 2 H), 5.45-5.47 (m, 2 H), 4.59-4.63 (m, 1 H), 4.37-4.42 (m, 1 H), 4.29-4.35 (m, 1 H), 4.24-4.28 (m, 1 H), 4.12-4.18 (m, 2 H), 3.90-3.96 (m, 1 H), 3.80-3.87 (m, 2 H), 3.71-3.77 (m, 1 H), 2.71-2.85 (m, 2 H), 2.40-2.55 (m, 3 H), 2.24-2.29 (m, 1 H), 2.03-2.10 (m, 2 H), 1.92-2.02 (m, 2 H), 1.42-1.92 (m, 13 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 0.83-0.97 (m, 72 H), 0.05-0.09 (m, 48 H).




**(3*S*,4*R*)-4-(2-((2*R*,4*S*,6*S*,7*E*,10*R*,12*S*,14*R*,16*S*,17*E*,20*S*,21*E*,24*R*)-27-(bis(*tert*-butoxycarbonyl)amino)-2,4,6,10,12,14,16,20,24-nonakis(*tert*-butyldimethylsilyloxy)heptacosa-7,17,21-trienyl)-1,3-dithian-2-yl)-3-(*tert*-butyldimethylsilyloxy)pentyl benzoate (88):** KHMDS (0.5 M in DME, 14 μL, 0.007 mmol) was added to a solution of sulfone **93** (8 mg, 0.005 mmol) in DME at –60 $^o$C. After 30 min, a solution of aldehyde **9** (6 mg, 0.007 mmol) in DME was added. The reaction mixture was stirred at –60 $^o$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

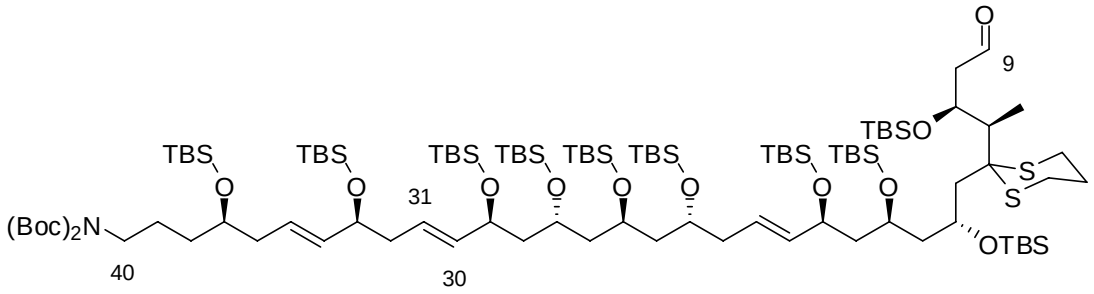
organic layers were dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography (5% ethyl acetate in hexanes) to yield the product **88** (5 mg, 45%) as a colorless oil: $^1$H NMR (600 MHz, $CDCl_3$) δ 8.04-8.06 (m, 2 H), 7.54-7.56 (m, 1 H), 7.41-7.46 (m, 2 H), 5.50-5.58 (m, 2 H), 5.38-5.48 (m, 4 H), 4.59-4.63 (m, 1 H), 4.39-4.42 (m, 1 H), 4.30-4.36 (m, 1 H), 4.24-4.26 (m, 1 H), 4.17-4.21 (m, 1 H), 4.12-4.17 (m, 1 H), 4.05-4.09 (m, 1 H), 3.80-3.90 (m, 3 H), 3.71-3.77 (m, 1 H), 3.65-3.70 (m, 1 H), 3.48-3.58 (m, 2 H), 2.71-2.85 (m, 2 H), 2.40-2.55 (m, 2 H), 2.24-2.29 (m, 1 H), 2.12-2.23 (m, 5 H), 1.92-2.02 (m, 6 H), 1.60-1.80 (m, 11 H), 1.50 (s, 18 H),1.35-1.45 (m, 4 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 0.83-0.97 (m, 90 H), 0.05-0.09 (m, 60 H).




**di-tert-butyl (4*R*,6*E*,8*S*,10*E*,12*S*,14*R*,16*S*,18*R*,20*E*,22*S*,24*S*,26*R*)-4,8,12,14,16,18,22,24,26-nonakis(*tert*-butyldimethylsilyloxy)-27-(2-((2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-5-hydroxypentan-2-yl)-1,3-dithian-2-yl)heptacosa-6,10,20-trienyliminodicarbonate (106):**

KOH(aq) was added to a solution of benzoate **88** (1.5 mg, 0.00068 mmol) in MeOH at room temperature. The reaction mixture was heated to 50 $^o$C and stirred for 24h. 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 (5% ethyl acetate in hexanes) to yield the product **88** (1 mg, 0.00048 mmol, 70%) as a colorless oil: $^1$H NMR (600 MHz, $CDCl_3$) δ 5.50-5.58 (m, 2 H), 5.38-5.48 (m, 4

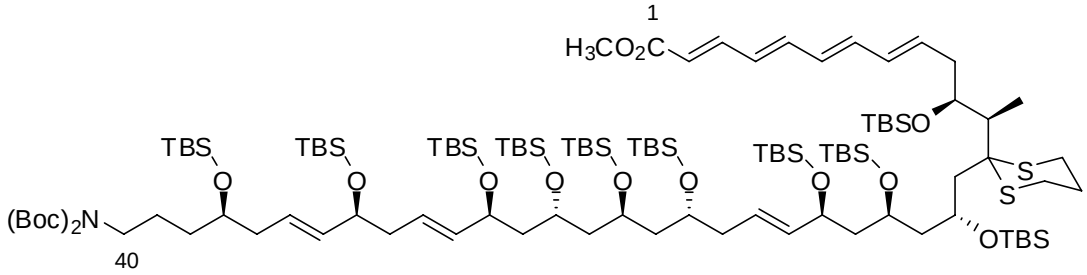
H), 4.42-4.47 (m, 1 H), 4.22-4.27 (m, 1 H), 4.16-4.22 (m, 1 H), 4.11-4.16 (m, 1 H), 4.04-4.10 (m, 1 H), 3.80-3.92 (m, 3 H), 3.62-3.79 (m, 4 H), 3.48-3.58 (m, 1 H), 3.07-3.13 (m, 1 H), 2.86-2.94 (m, 1 H), 2.73-2.81 (m, 1 H), 2.55-2.69 (m, 2 H), 2.37-2.44 (m, 1 H), 1.92-2.32 (m, 10 H), 1.60-1.92 (m, 13 H), 1.50 (s, 14 H), 1.43-1.45 (m, 8 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 0.86-0.93 (m, 90 H), 0.02-0.18 (m, 60 H).




**di-tert-butyl (4*R*,6*E*,8*S*,10*E*,12*S*,14*R*,16*S*,18*R*,20*E*,22*S*,24*S*,26*R*)-4,8,12,14,16,18,22,24,26-nonakis(*tert*-butyldimethylsilyloxy)-27-(2-((2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-5-oxopentan-2-yl)-1,3-dithian-2-yl)heptacosa-6,10,20-trienyliminodicarbonate (89):**

To a solution of alcohol **88** (2.5 mg, 0.0012 mmol) in DCM were added solid $NaHCO_3$ and Dess-Martin reagent (1 mg, 0.0023 mmol). The reaction mixture was stirred at room temperature for 2 h. Then the reaction was quenched with saturated $NaHCO_3$ solution. 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 residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to yield the aldehyde **89** (0.0015 mg, 60%) as oil $^1$H NMR (600 MHz, $CDCl_3$) δ 9.80-9.82 (1 H), 5.50-5.58 (m, 2 H), 5.35-5.48 (m, 4 H), 4.93-4.98 (m, 1 H), 4.12-4.25 (m, 3 H), 4.05-4.10 (m, 1 H), 3.80-3.90 (m, 3 H), 3.71-3.77 (m, 1 H), 3.63-3.70 (m, 1 H), 3.48-3.58 (m, 2 H), 2.50-2.88 (m, 4 H), 2.37-2.43 (m, 1 H), 2.22-2.32

(m, 3 H), 1.90-2.12 (m, 10 H), 1.60-1.90 (m, 13 H), 1.50 (s, 18 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 0.82-0.92 (m, 90 H), 0.00-0.20 (m, 60 H).




**(2*E*,4*E*,6*E*,8*E*,11*S*,12*R*)-methyl 12-(2-((2*R*,4*S*,6*S*,7*E*,10*R*,12*S*,14*R*,16*S*,17*E*,20*S*,21*E*,24*R*)-27-(bis(*tert*-butoxycarbonyl)amino)-2,4,6,10,12,14,16,20,24-nonakis(*tert*-butyldimethylsilyloxy)heptacosa-7,17,21-trienyl)-1,3-dithian-2-yl)-11-(*tert*-butyldimethylsilyloxy)trideca-2,4,6,8-tetraenoate (20):** To a solution of fragment **7** (1 mg, 0.003 mmol) in THF at -78 $^{o}$C was added a solution of LiHMDS (0.003 mmol) in THF and stirred for 15 min. A solution of aldehyde **89** (1.5 mg, 0.0007 mmol) in THF was added to the above reaction mixture and stirred for 30 min at -78 $^{o}$C for 30 min and 0 $^{o}$C 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 residue was purified by flash column chromatography to yield the product **20** (1.0 mg, 0.00045 mmol, 62%): $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30-7.35 (m, 1 H), 6.54-6.63 (m, 1 H), 6.30-6.40 (m, 1 H), 6.15-6.30 (m, 2 H), 5.79-5.81 (m, 2 H), 5.50-5.58 (m, 2 H), 5.38-5.48 (m, 5 H), 4.55-4.60 (m, 1 H), 4.20-4.30 (m, 3 H), 4.10-4.15 (m, 1 H), 3.80-3.90 (m, 3 H), 3.75 (s, 3 H), 3.71-3.75 (m, 1 H), 3.65-3.70 (m, 1 H), 3.48-3.58 (m, 2 H), 2.71-2.85 (m, 2 H), 2.40-2.55 (m, 2 H), 2.24-2.29 (m, 1 H), 2.12-2.23 (m, 5 H), 1.92-2.02 (m, 6 H), 1.60-1.80 (m, 11 H), 1.50 (s, 18 H),1.35-1.45 (m, 4 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 0.83-0.97 (m, 90 H), 0.05-0.09 (m, 60 H).

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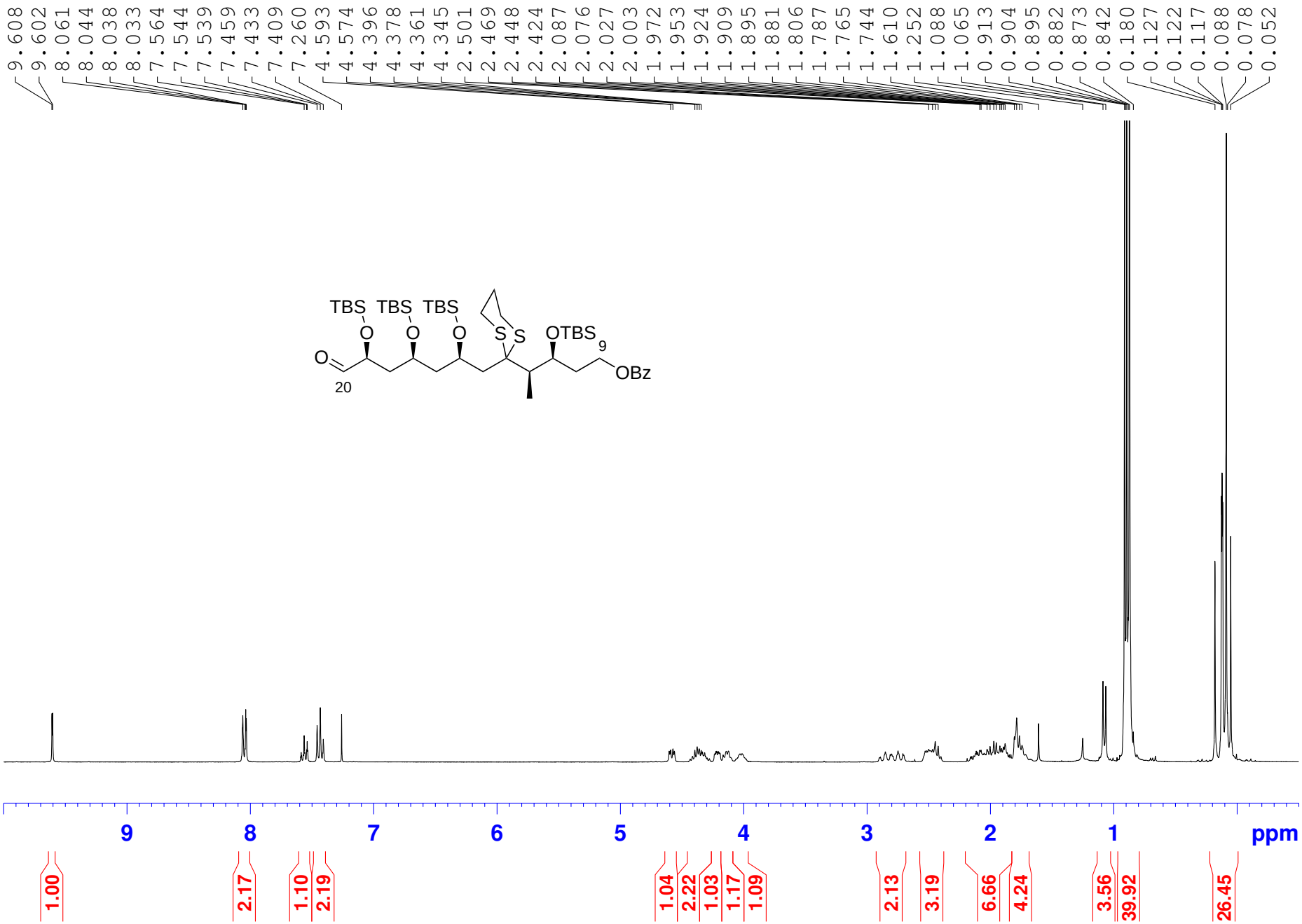
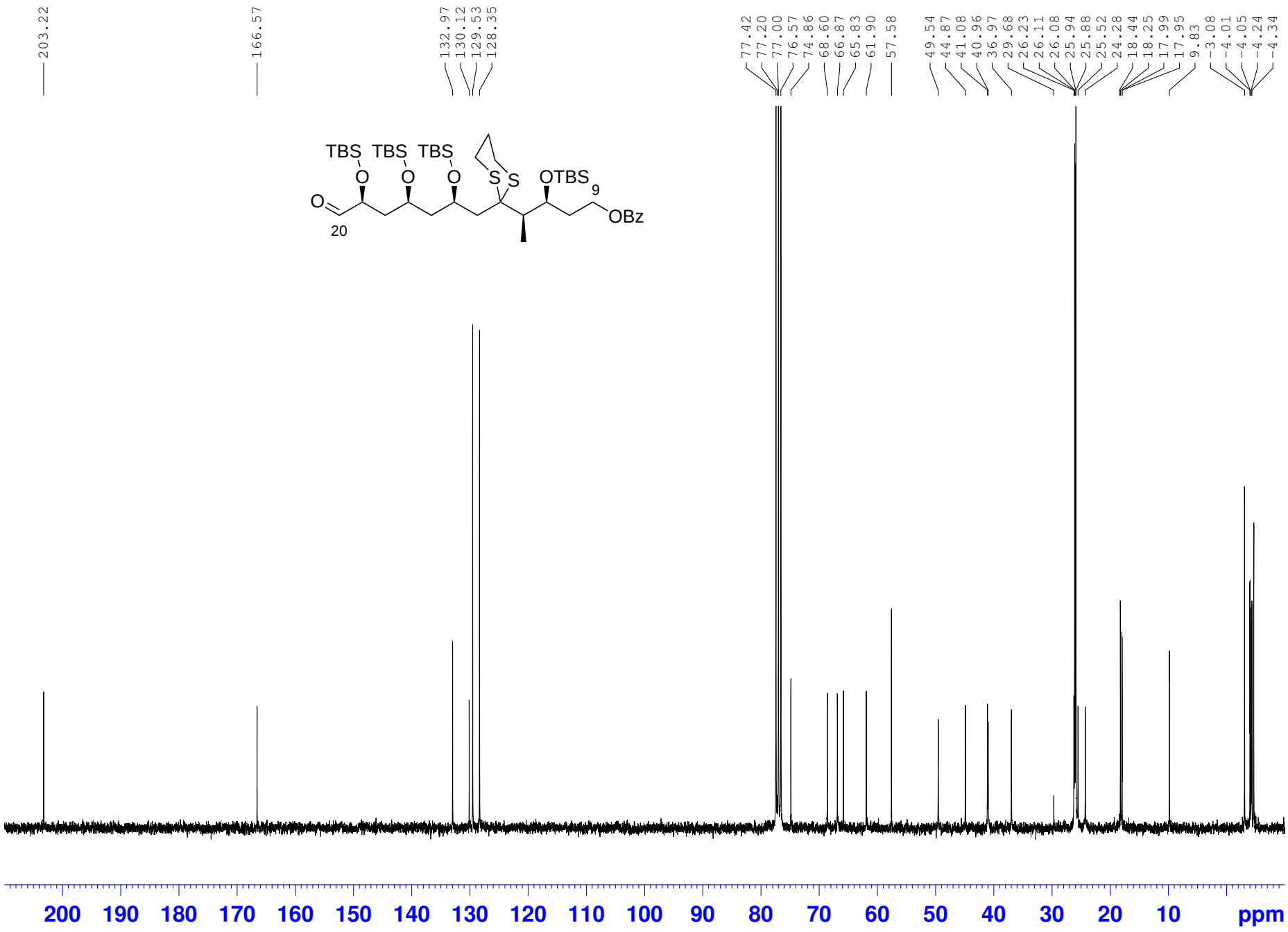
# APPENDIX

NMR spectra of compounds **87**, **104**, **105**, **97**, **93**, **88**, **106** and **20** are listed below.

87, 300MHz, CDCl3



87, 75MHz, CDCl3



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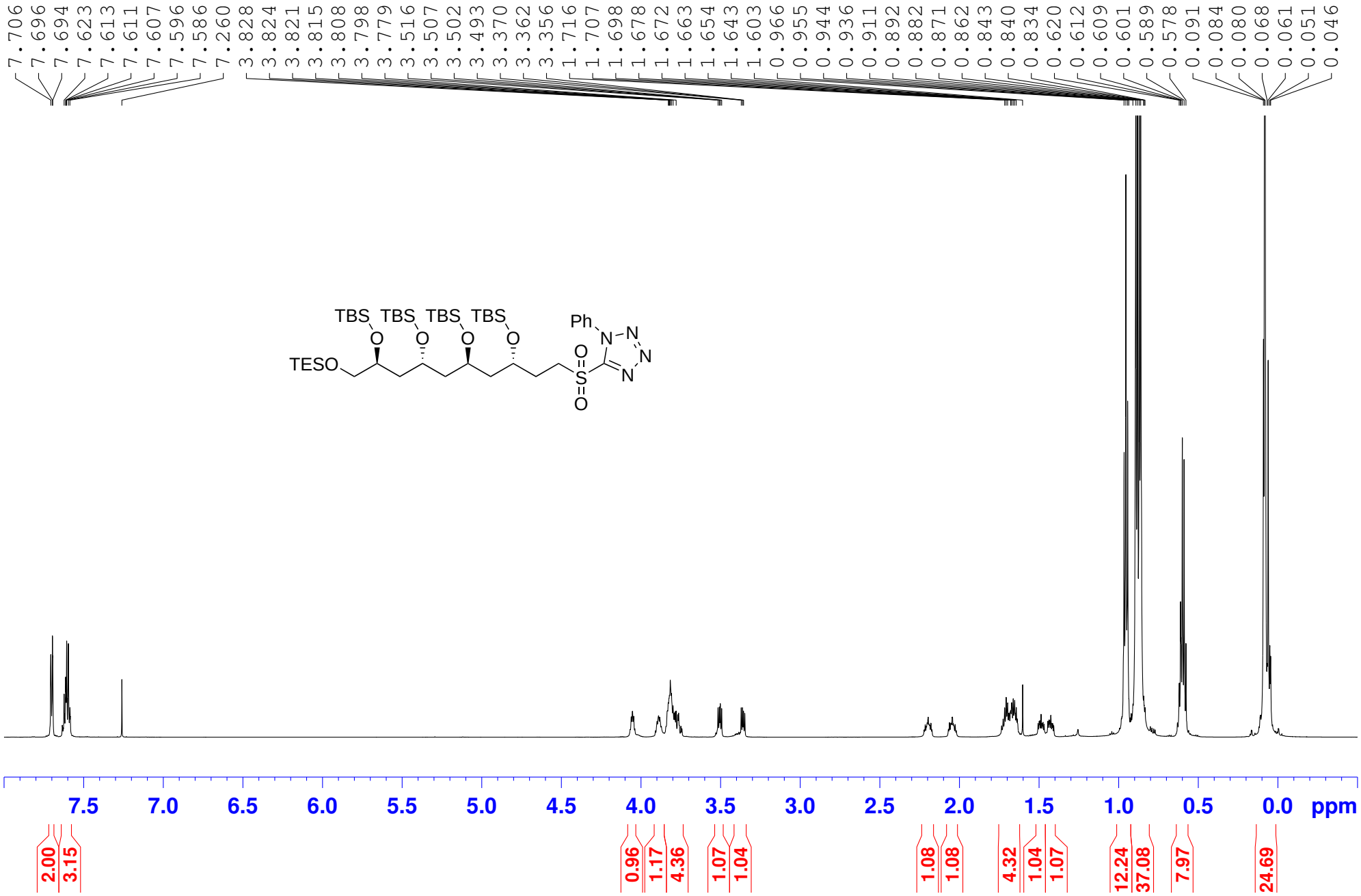

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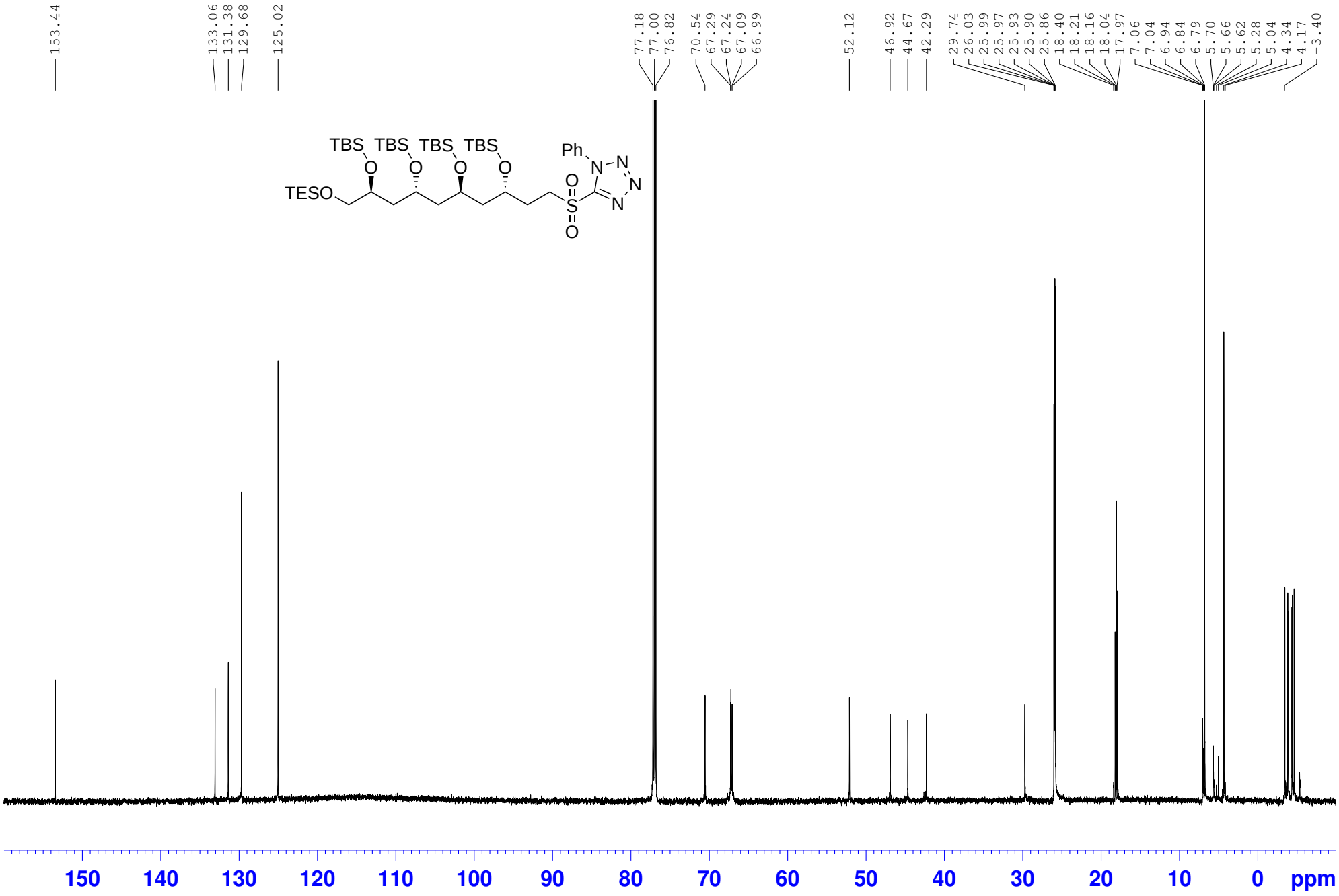

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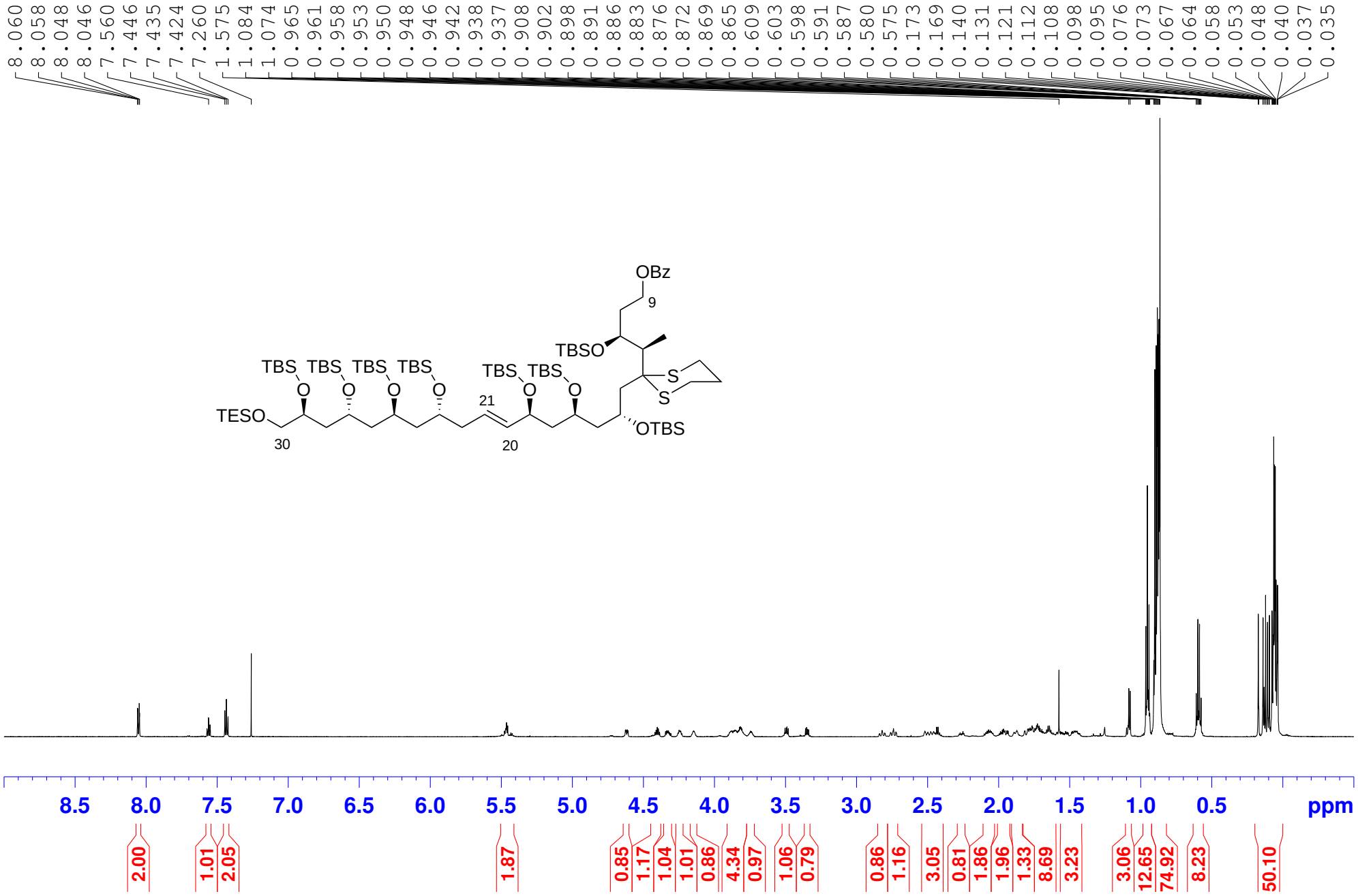
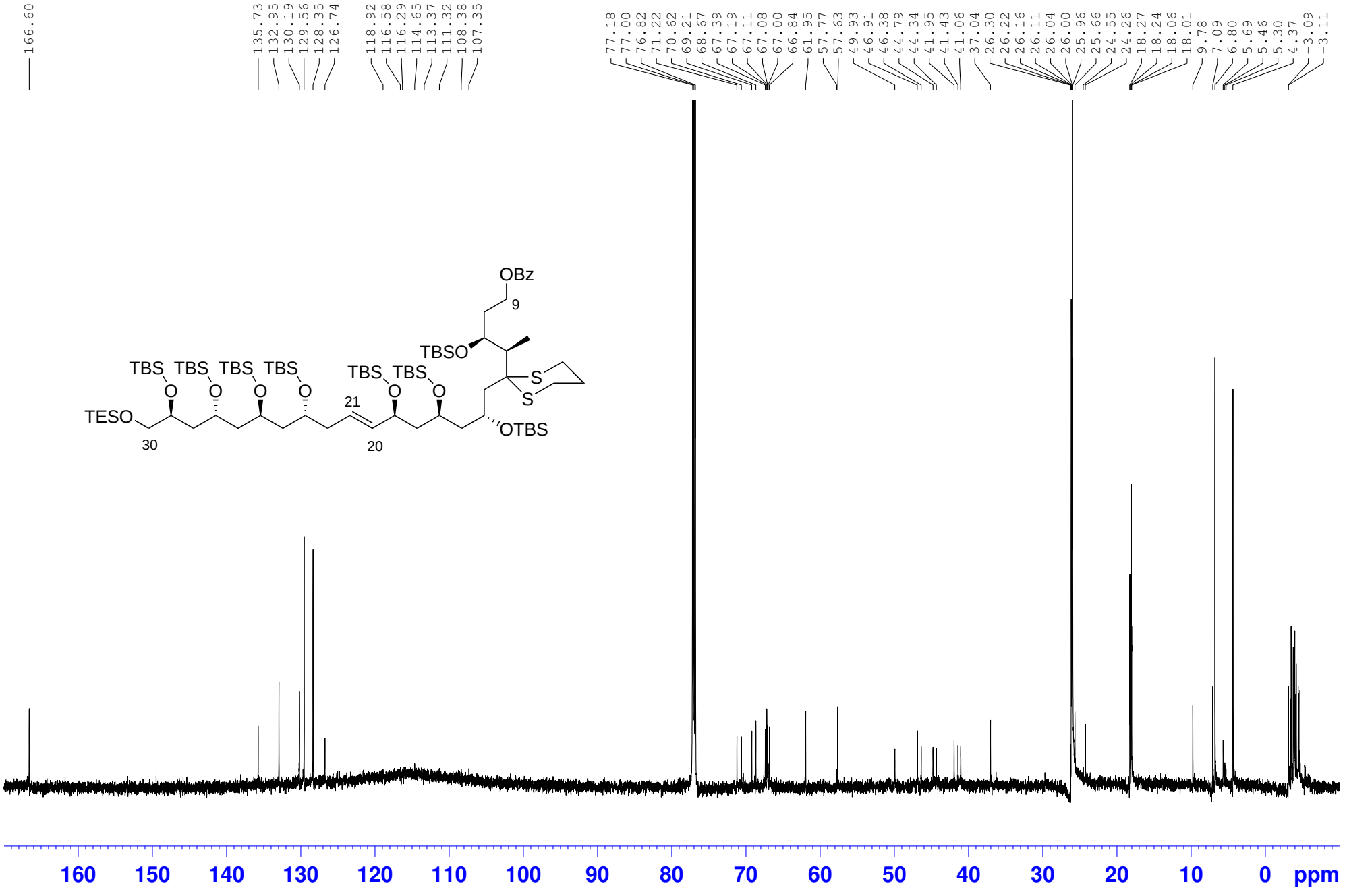
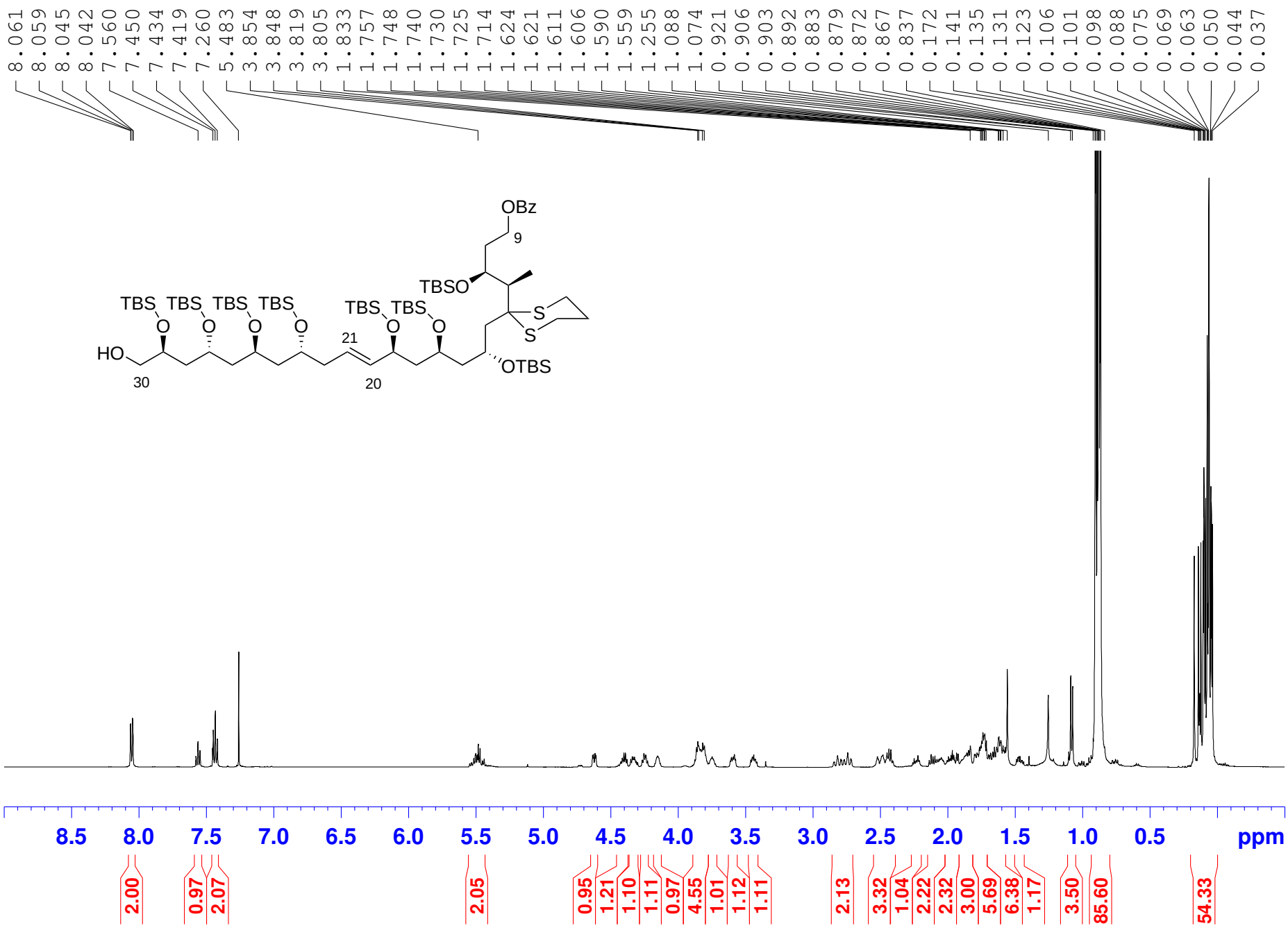


105, 175MHz, CDCl3

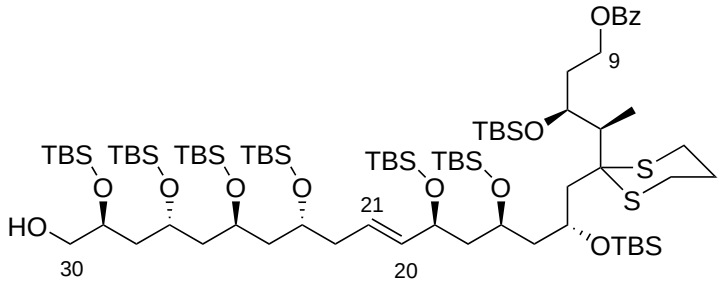


97, 500MHz, CDCl3



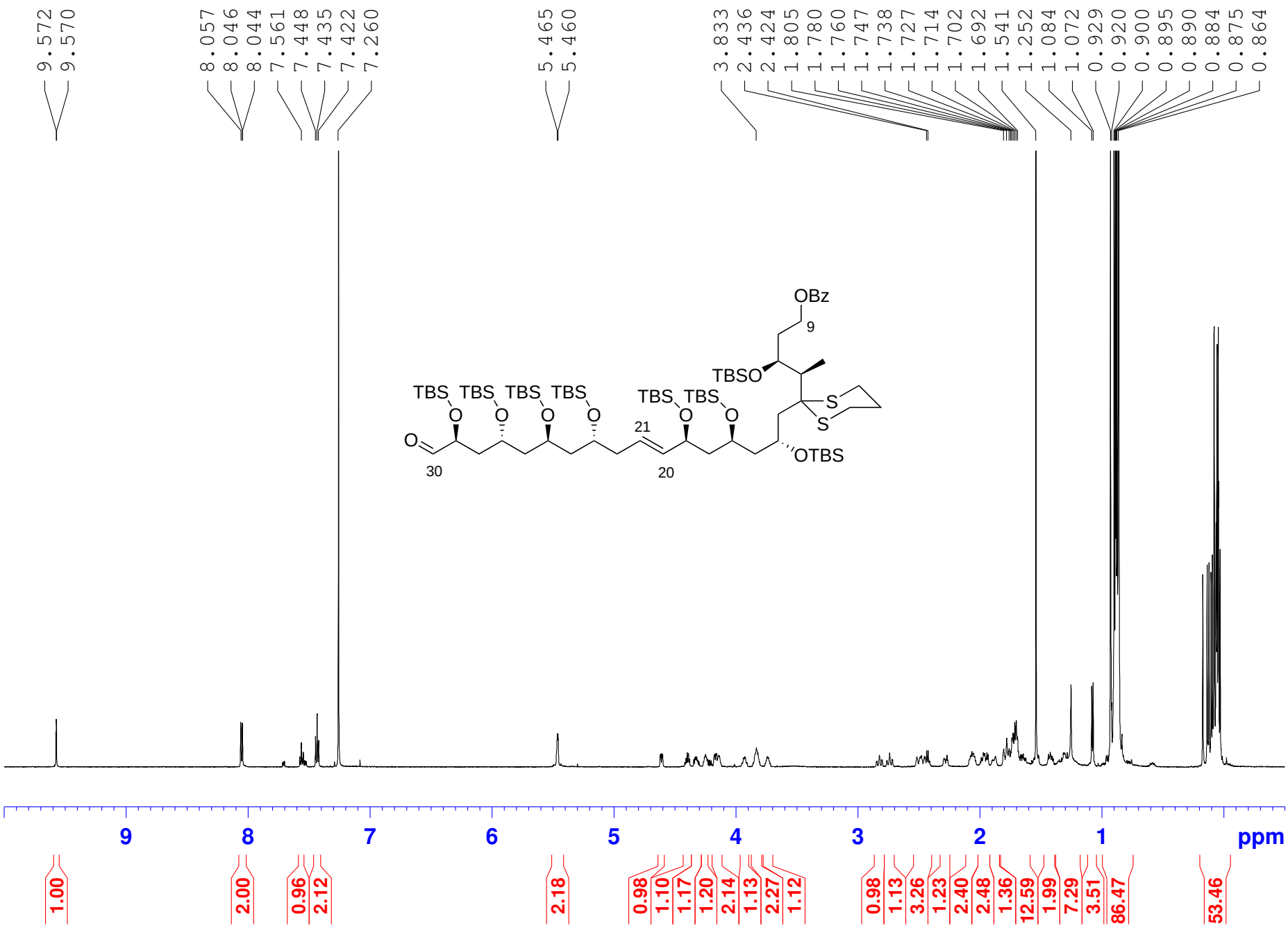
97, 75MHz, CDCl3

166.595
135.815
132.955
130.185
129.552
128.352
126.436
78.849
78.296
77.425
77.204
77.001
76.578
71.095
70.293
69.241
68.672
67.184
67.077
66.846
61.954
57.631
49.897
46.712
46.445
44.854
44.767
41.951
41.265
41.051
37.038
29.697
26.302
26.163
26.043
25.962
25.924
25.680
24.272
18.266
18.096
18.041
9.767
-3.096
-3.124
-3.343
-3.491
-3.542
-3.636
-3.754
-3.818
-3.911
-3.963
-4.103
-4.143
-4.329
-4.376
-4.445

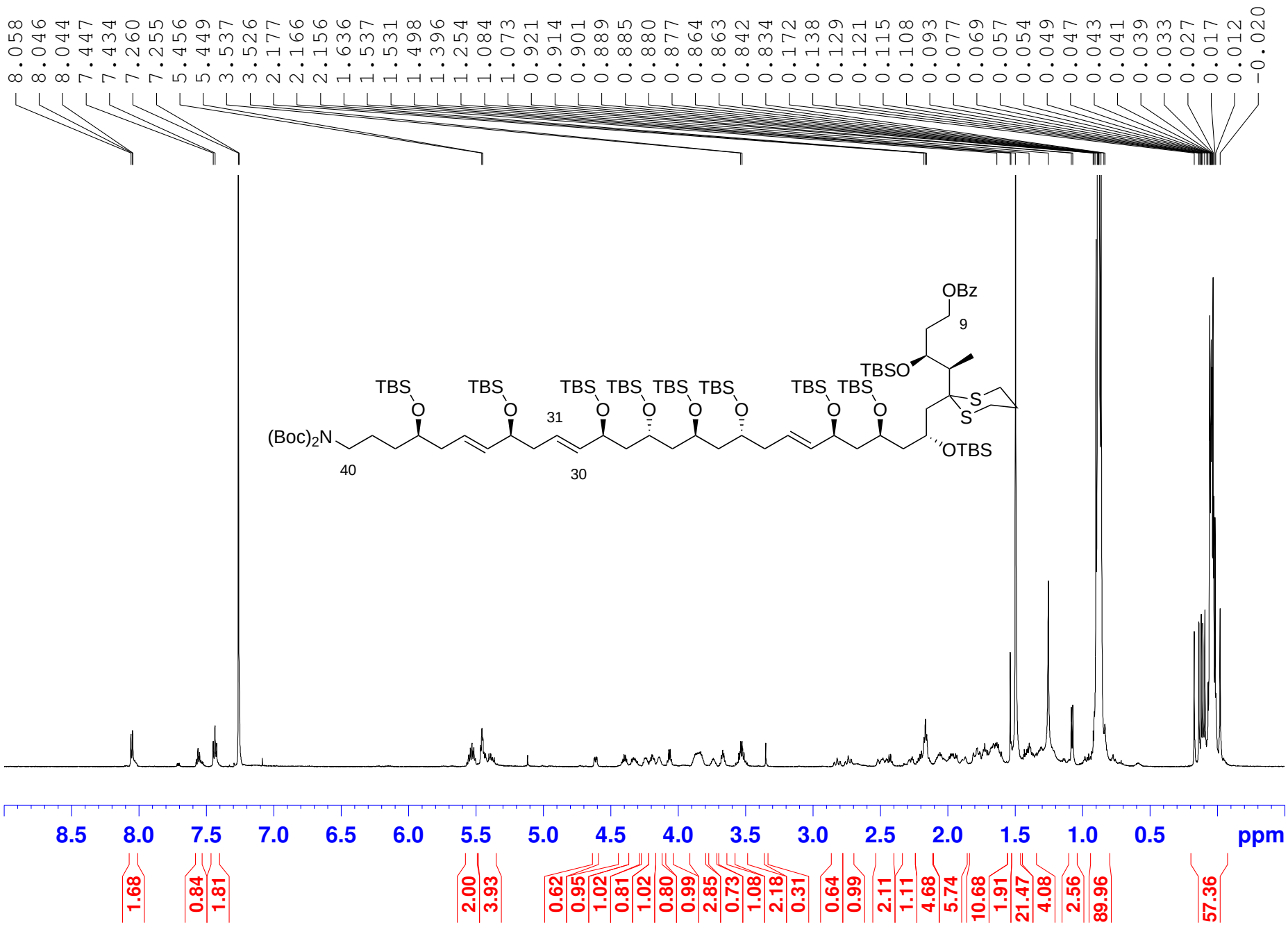



170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

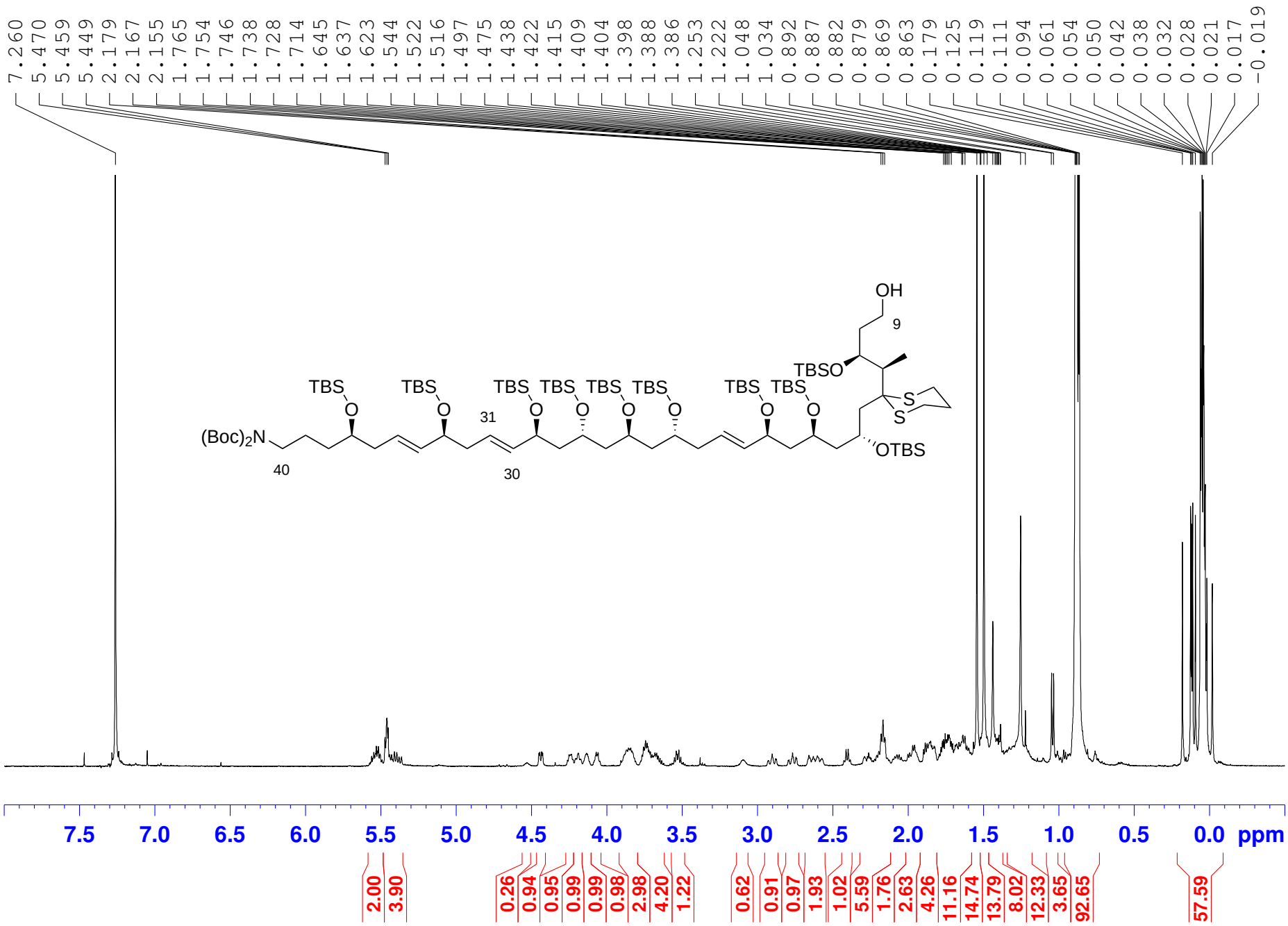
93, 600MHz, CDCl3



88, 600MHz, CDCl3



106, 500MHz, CDCl3



20, 500MHz, CDCl3