Fluorous mixture synthesis of four stereoisomers of the C21-C40 fragment of tetrafibrin
dand efforts towards total synthesis of tetrafibrin

by

Kai Zhang

B.S., University of Science and Technology of China, 2005

Submitted to the Graduate Faculty of
School of Arts and Sciences in partial fulfillment
of the requirements for the degree of Doctor of Philosophy

University of Pittsburgh

2011
UNIVERSITY OF PITTSBURGH

SCHOOL OF ARTS AND SCIENCES

This thesis was presented

by

Kai Zhang

It was defended on

Jan 21st, 2011

and approved by

Paul Floreancig, Professor, Department of Chemistry

Scott Nelson, Professor, Department of Chemistry

Billy W. Day, Professor, Department of Pharmaceutical Sciences

Thesis Director: Dennis P. Curran, Professor, Department of Chemistry
Fluorous mixture synthesis of four stereoisomers of the C21-C40 fragment of tetrafibrin and efforts towards total synthesis of tetrafibrin

Kai Zhang, Ph.D.

University of Pittsburgh, 2011

Efforts towards the synthesis of natural product tetrafibrin and its stereoisomers are described. Retrosynthesis of the framework of tetrafibrin 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 tetrafibrin. 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 tetrafibrin.
## TABLE OF CONTENTS

ABSTRACT.................................................................................................................................. IV  
LIST OF TABLES..................................................................................................................... VIII  
LIST OF FIGURES ...................................................................................................................... IX  
LIST OF SCHEMES ................................................................................................................... X  
LIST OF ABBREVIATIONS ....................................................................................................... XIII  
PREFACE ....................................................................................................................................... XV  

1.0 CHAPTER 1 .................................................................................................................. 1  
1.1 TETRAFIBRICIN ................................................................................................................ 1  
1.2 PREVIOUS WORK ON TETRAFIBRICIN IN CURRAN GROUP ....................... 4  
1.3 FLUOROUS MIXTURE SYNTHESIS (FMS) .............................................................. 9  

2.0 CHAPTER 2 ................................................................................................................ 12  
2.1 PLAN OF FMS OF FOUR STEREOISOMERS OF THE C21-C40 FRAGMENT OF TETRAFIBRICIN ................................................................. 12  
2.2 FRAGMENT SYNTHESSES ......................................................................................... 15  
   2.2.1 Synthesis of the C21-C30 fragment 4 ................................................................. 15  
   2.2.2 Synthesis of the C35-C40 fragment M-2 .......................................................... 19  
   2.2.3 Synthesis of the C31-C34 fragment M-3 .......................................................... 24
2.3 COUPLING OF FRAGMENTS M-2 AND M-3 BY JULIA-KOCIENSKI
   REACTION .................................................................................................................. 27
2.4 SYNTHESIS OF THE C21-C40 FRAGMENT ............................................................. 28
2.5 DEMIXING AND DETAGGING OF FLUOROUS MIXTURE M-23.................. 29
2.6 CONCLUSIONS ...................................................................................................... 38
3.0 CHAPTER 3 .............................................................................................................. 39
3.1 FRAGMENT SYNTHESES OF TETRAFIBRICIN................................................... 39
   3.1.1 Synthesis of the C35-C40 fragment 2............................................................. 39
   3.1.2 Synthesis of the C31-C34 fragment 3............................................................ 41
   3.1.3 Synthesis of the C21-C30 fragment 4............................................................ 42
   3.1.4 Synthesis of the C14-C20 fragment 5............................................................ 43
   3.1.5 Synthesis of the C9-C13 fragment 6.............................................................. 45
   3.1.6 Synthesis of the C1-C8 fragment 7............................................................... 46
3.2 NEW COUPLING ROUTE: FRAGMENTS C1-C8 + C9-C20 + C21-C40........ 48
   3.2.1 Retrosynthesis of tetrafibricin..................................................................... 48
   3.2.2 Synthesis of the C21-C40 fragment.............................................................. 50
   3.2.3 Synthesis of the C9-C20 fragment 87............................................................ 52
   3.2.4 Attempts to couple fragments C9-C20 and C21-C40............................... 53
3.3 FINAL COUPLING ROUTE: FRAGMENTS C1-C8 + C9-C30 + C31-C40 .... 54
   3.3.1 Retrosynthesis of tetrafibricin..................................................................... 54
   3.3.2 Synthesis of the C21-C30 fragment 92........................................................ 56
   3.3.3 Coupling of fragments C9-20 and C21-C30.............................................. 57
   3.3.4 Synthesis of the C9-C30 fragment............................................................... 61
3.3.5 Coupling of fragments C9-C30 and C31-C40 .............................................. 62
3.3.6 Coupling of fragments C1-C8 and C9-C40 .................................................. 65

3.4 CONCLUSIONS .................................................................................................. 66

EXPERIMENTAL .................................................................................................. 68

BIBLIGRAPHY .................................................................................................... 144

APPENDIX .......................................................................................................... 148
LIST OF TABLES

Table 2.1 Synthesis of aldehyde M-45 ......................................................................................... 23
Table 2.2 Synthesis of the C31-C34 fragment M-3 ................................................................ 27
Table 2.3 Coupling of fragments M-2 and M-3 .................................................................... 28
Table 2.4 Model deprotection reactions of M-53 ..................................................................... 32
Table 2.5 $^{13}$C-NMR data of four stereoisomers 24 ................................................................. 37
LIST OF FIGURES

Figure 1.1 Kamiyama’s 2D structure of tetrafibricin ................................................................. 3
Figure 1.2 Kishi’s 3D structure of tetrafibricin ....................................................................... 3
Figure 2.1 Preparative HPLC trace of quasidiastereomers 23 .................................................... 31
LIST OF SCHEMES

Scheme 1.1 Retrosynthesis of tetrafibricin ................................................................. 5

Scheme 1.2 Synthesis of the C21-C40 fragment .......................................................... 7

Scheme 1.3 Synthesis of the C1-C20 fragment ............................................................. 8

Scheme 1.4 Final coupling of fragments C1-C20 and C21-C40 ..................................... 9

Scheme 1.5 Schematic diagram of FMS ........................................................................ 10

Scheme 1.6 Representative natural products and their stereoisomers synthesized with FMS .... 11

Scheme 2.1 Plan of FMS of four stereoisomers of the C21-C40 fragment of tetrafibricin .... 14

Scheme 2.2 Retrosynthesis of the C21-C30 fragment 4 ................................................. 15

Scheme 2.3 Synthesis of epoxide (S,S)-30 ................................................................. 16

Scheme 2.4 Synthesis of dithiane (S,S)-25 ................................................................. 17

Scheme 2.5 Synthesis of epoxide (R)-26 ................................................................. 18

Scheme 2.6 Synthesis of the C21-C30 fragment 4 ...................................................... 19

Scheme 2.7 Synthesis of epoxide (rac)-42 ................................................................. 20

Scheme 2.8 Synthesis of alcohols (R)-43 and (S)-43 .................................................. 21

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

Scheme 2.10 Synthesis of the C35-C40 fragment M-2 ................................................. 24

Scheme 2.11 Synthesis of diols (S)-49 and (R)-49 ...................................................... 25
Scheme 2.12 Synthesis of ethers (S)-22c and (R)-22b .................................................................................................................. 25
Scheme 2.13 Synthesis of the C21-C40 fragment .......................................................................................................................... 29
Scheme 2.14 Deprotection of compound M-23 .......................................................................................................................... 33
Scheme 2.15 Model deprotection reaction of 38 .......................................................................................................................... 34
Scheme 2.16 Deprotection of compound 23 .......................................................................................................................... 35
Scheme 3.1 Synthesis of epoxide (R)-42 .................................................................................................................................... 39
Scheme 3.2 Synthesis of the C35-C40 fragment 2 .......................................................................................................................... 41
Scheme 3.3 Synthesis of the C31-C34 fragment 3 .......................................................................................................................... 42
Scheme 3.4 Synthesis of dithiane 66 .................................................................................................................................... 43
Scheme 3.5 Synthesis of (R)-68 .................................................................................................................................... 44
Scheme 3.6 Synthesis of the C14-C20 fragment 5 .......................................................................................................................... 45
Scheme 3.7 Synthesis of the C9-C13 fragment 6 .......................................................................................................................... 46
Scheme 3.8 Synthesis of the C1-C8 fragment 7 .......................................................................................................................... 47
Scheme 3.9 New coupling route: fragments C1-C8 + C9-C20 + C21-C40 .................................................................................. 49
Scheme 3.10 Synthesis of the C21-C40 fragment .......................................................................................................................... 51
Scheme 3.11 Synthesis of the C9-C20 fragment .......................................................................................................................... 53
Scheme 3.12 Coupling of fragments C9-C20 and C21-C40............................................................................................................... 54
Scheme 3.13 Coupling of fragments C9-C20 and C21-C30 and C31-C40 .................................................................................. 55
Scheme 3.14 Synthesis of the C21-C30 fragment .......................................................................................................................... 56
Scheme 3.15 Coupling of fragments C9-C20 and C21-C30 ............................................................................................................... 57
Scheme 3.16 Deprotection of primary TBS group on C30 ............................................................................................................... 58
Scheme 3.17 Synthesis of the C21-C30 fragment with trityl group .................................................................................................. 59
Scheme 3.18 Synthesis of the C21-C30 fragment with TES group .................................................................................................. 60
Scheme 3.19 Coupling of fragments C9-C20 and C21-C30 .............................................................. 61
Scheme 3.20 Synthesis of the C9-C30 fragment ............................................................................. 62
Scheme 3.21 Coupling of fragments C9-C30 and C31-C40 ............................................................. 64
Scheme 3.22 Final coupling of fragments C1-C8 and C9-C40 ....................................................... 66
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-Borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropylazodicarboxylate</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>FMS</td>
<td>Fluorous mixture synthesis</td>
</tr>
<tr>
<td>HKR</td>
<td>Hydrolytic kinetic resolution</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethyolphosphoramid</td>
</tr>
</tbody>
</table>
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
\textit{m}-CPBA \textit{m}-chloroperbenzoic acid
Me    Methyl
NMR   Nuclear magnetic resonance
Ph    Phenyl
PMB   \textit{p}-Methoxybenzyl
Pr    Propyl
PTSH  1-Phenyl-1\textit{H}-tetrazole-5-thiol
Pyr   Pyridine
Rf    Perfluoroalkyl
TBAF  Tetrabutylammonium fluoride
TBAI  Tetrabutylammonium iodide
TBS   \textit{t}-Butyldimethylsilyl
THF   Tetrahydrofuran
TLC   Thin layer chromatography
I would like to sincerely thank Prof. Dennis Curran for providing me such a wonderful opportunity to pursue graduate studies in his research group. It has been a great experience working under your guidance. I am indebted to you for your support, encouragement and understanding during the critical times in my graduate studies. Thank you very much Prof. Curran for everything.

I would like to thank Profs. Paul Floreancig, Scott Nelson and Billy Day for their immense help by being on my thesis committee. My thanks are also due to the NMR and mass spectrometry groups for their support by providing wonderful facilities. I also would like to thank my co-workers in the Curran research group for helping me a lot with their friendly discussions. My special thanks are due to Dr. Venugopal Gudipati for his previous work on my research studies.

I would also like to take this opportunity to thank my parents (Yongsheng Zhang and Junling Lou) for their encouragement, love and support all the time. Finally, I would like to thank my Wife, Pu Chen, for always being there for me and her understanding and love all the time.

Thank you all again from the bottom of my heart.
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 subendothelial 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 IC₅₀ 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$_2$O solution of tetrafibricin purged with argon was used for the NMR experiments. A combination of the $^1$H NMR, $^{13}$C NMR, $^1$H-$^1$H COSY, HSQC and HMBC experiments were used to deduce partial structures. Additional NMR experiments on a solution of N-acetyldihydrotetrafibricin methyl ester in DMSO-$d_6$ 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.
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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{8}
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.\textsuperscript{9} Roush’s group reported the synthesis of the C1-C19 fragment of tetrafibricin via a highly diastereoselective double allylboration developed in their laboratory.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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

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. Pure (E)-isomer was obtained by preparative chiral HPLC. The
smooth conversion of sulfide to sulfone 9 was accomplished with Mo-catalyst (Mo$_7$O$_{24}$(NH$_4$)$_6$$\cdot$H$_2$O, H$_2$O$_2$) in 92% yield. 14 Another Julia-Kocienski olefination reaction between the sulfone 9 and aldehyde 4 provided the PMB-ether as a sole C(30,31) (E)-olefinic isomer 10 in 94% yield. Removal of PMB protecting group (DDQ, pH 7 buffer, CH$_2$Cl$_2$) gave the primary alcohol 11 in 88% yield. 15 Incorporation of the thiotetrazole via the Mitsunobu reaction, 16 employing commercially available 1-phenyl-1H-tetrazole-5-thiol, followed by oxidation (Mo$_7$O$_{24}$(NH$_4$)$_6$$\cdot$H$_2$O, H$_2$O$_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

1. PTSH, DIAD, PPh₃
2. Mo₇O₂₄(NH₄)₆•H₂O, H₂O₂

11, 89%

12, X = S
13, X = SO₂, 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 SO₃•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 SO₃•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 °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. 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**

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.\textsuperscript{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.

\textbf{Scheme 1.6 Representative natural products and their stereoisomers synthesized by FMS}

\begin{align*}
\text{pyridovericin} & \quad \text{2 enantiomers} \\
\text{mappicine} & \quad \text{2 enantiomers} \\
\text{\((-\text{dictyostatin})\)} & \quad \text{4 diastereomers} \\
\text{lagunapyrone B} & \quad \text{4 diastereomers}
\end{align*}
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-Pr)2C2H4C4F9) to the (R)-alcohol and make (S)-21b by attaching a fluorous tag containing 7 fluorines (TIPS^F7 = Si(i-Pr)2C2H4C3F7) 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. Finally, after detagging, four single diastereomers of the C21-C40 fragment of tetrafibrin will be achieved in the end.
Scheme 2.1 Plan of FMS of four stereoisomers of the C21-C40 fragment of tetrafibricin

(TBSO)O

TIPSF7,9

(R)-21a

Mix

(R)-22a

(S)-21b

M-21

M-2

M-22

M-3

M-2 + M-3

TIPS\textsuperscript{F7} = \text{Si}((\text{Pr})\text{C}_2\text{H}_4\text{C}_3\text{F}_7, \text{TIPS}\textsuperscript{F9} = \text{Si}((\text{Pr})\text{C}_2\text{H}_4\text{C}_4\text{F}_9, \text{TIPS}\textsuperscript{F13} = \text{Si}((\text{Pr})\text{C}_2\text{H}_4\text{C}_6\text{F}_{13}

compounds\n
\begin{tabular}{cccc}
\hline
 & \text{Fluorine content} \\
\hline
 & \text{T1} & \text{T2} & \text{Total F#} \\
(33R,37S)-23a,b & 7 & 9 & 16 \\
(33R,37R)-23a,a & 9 & 9 & 18 \\
(33S,37S)-23b,c & 7 & 13 & 20 \\
(33S,37R)-23a,c & 9 & 13 & 22 \\
\hline
\end{tabular}

Four single diastereomers:
(33R,37S)-24
(33R,37R)-24
(33S,37S)-24
(33S,37R)-24

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. 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

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. Wittig olefination with CH$_3$PPh$_3$Br and t-BuLi in THF gave alkene (S)-29 in 83% yield. 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.
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.
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. 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 PPh₃ in refluxing toluene.
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. 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. Hydroxyl-directed reduction with Me₄NHB(OAc)₃ gave the 1,3-anti diol 37, which was then silylated with TBSOTf to give the compound 38 in 73% yield. 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. 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%.
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 °C for 1 h gave the epoxide (rac)-42.
Scheme 2.7 Synthesis of epoxide \((\text{rac})-42\)

In order to make the quasiracemic fragment M-2, we divided the \((\text{rac})-42\) 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-dithiane to give the secondary alcohol \((R)-43\) in 70% yield. The second portion of \((\text{rac})-42\) 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-dithiane to give the alcohol \((S)-43\) in 60% yield.\(^{23}\)
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 \((^{F9}\text{TIPS} = \text{Si}(i-\text{Pr})_2(\text{CH}_2)_2\text{Rf}, \text{where Rf is perfluoroalkyl})\) in situ. 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.
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\(_3\)I, K\(_2\)CO\(_3\) in ACN-H\(_2\)O (6:1) at 45 °C, which only gave the recovered starting material after 5 h.\(^{30}\) When the reaction mixture was heated up to 65 °C 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\(_2\)O under several different conditions (Table 2.1). A first reaction at 0 °C 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 °C, finally we obtained the desired aldehyde M-45 in 90% yield (Entry 3).
Table 2.1 Synthesis of aldehyde M-45

![Diagram of M-21 to M-45]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hg(ClO₄)₂ • 3H₂O, 2,6-lutidine, THF/H₂O</td>
<td>1 h 0 °C s.m.</td>
</tr>
<tr>
<td>2</td>
<td>Hg(ClO₄)₂ • 3H₂O, 2,6-lutidine, THF/H₂O</td>
<td>36 h r.t. 14% product + 70% s.m.</td>
</tr>
<tr>
<td>3</td>
<td>Hg(ClO₄)₂ • 3H₂O, 2,6-lutidine, THF/H₂O</td>
<td>3 h 45 °C 90%</td>
</tr>
</tbody>
</table>

M-45 is the first quasiracemate product, so this is an appropriate point to briefly summarize the analysis of quasienantiomers mixture by TLC, ¹H-NMR, ¹³C-NMR and ¹⁹F-NMR. The above quasienantiomers have the same Rₚ value on TLC plate and can be purified by column chromatography without separation. In ¹H-NMR spectra, the proton resonances from the quasienantiomers have the identical chemical shifts. For ¹³C-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 ¹⁹F-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.\textsuperscript{16} Oxidation of sulfide M-47 to the corresponding sulfone M-2 was effected with \textit{m}-CPBA (2.2 equiv, 80% yield). Overall, fragment M-2 (750 mg) was synthesized in 9 steps with overall yield 12.6%.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme2_10.png}
\caption{Synthesis of the C35-C40 fragment M-2}
\end{figure}

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 (\textit{S})-27 and (\textit{R})-27 (Scheme 2.11). Mitsunobu reactions as above converted the alcohols to the corresponding sulfides (\textit{S})-48 and (\textit{R})-48 in 79% and 86% yields.\textsuperscript{16} Removal of acetonide protecting group under catalytic acidic conditions gave the two enantiomeric diols (\textit{S})-49 and (\textit{R})-49 each in 93% yield.
Scheme 2.11 Synthesis of diols (S)-49 and (R)-49

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 C₆F₁₃ for (S)-50 and C₄F₉ for (R)-50.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HF•pyr</td>
<td>0 °C 1 h and then r.t. 5 h</td>
<td>M-52 only</td>
</tr>
<tr>
<td>2</td>
<td>HF•pyr</td>
<td>−20 °C 2 h and then r.t. 4 h</td>
<td>M-52 only</td>
</tr>
<tr>
<td>3</td>
<td>CH₃COCl</td>
<td>−10 °C, 2 h</td>
<td>M-52 only</td>
</tr>
<tr>
<td>4</td>
<td>CH₃COCl</td>
<td>−20 °C, 3 h</td>
<td>60% M-36 and 25% M-52</td>
</tr>
</tbody>
</table>

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). First, the sulfone M-2 was reacted with KHMDS solution in toluene as the base in THF at −78 °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 ($J_{	ext{H-H}}$) 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Combined yield</th>
<th>M-53 E/Z ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KHMDS in toluene</td>
<td>THF</td>
<td>85%</td>
<td>7:3</td>
</tr>
<tr>
<td>2</td>
<td>KHMDS in DME</td>
<td>DME</td>
<td>80%</td>
<td>&gt; 9:1</td>
</tr>
</tbody>
</table>

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$_7$O$_{24}$(NH$_4$)$_6$•H$_2$O, H$_2$O$_2$) occurred in 88%
yield.\textsuperscript{14} Another Julia-Kocienski olefination reaction between sulfone M-54 and aldehyde 4 again using KHMDMS 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 (33R,37S)-23a,b, (33R,37R)-23a,a, (33S,37S)-23b,c, (33S,37R)-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) FluoroFlash Column, 100% MeOH, 10 mL/min, 20 mg M-23 in 1 mL MeOH/injection

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

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

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

4th peak, 35.83 min, 22F, (33S,37R)-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%. 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Isolated yield of M-55</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCl</td>
<td>70%</td>
</tr>
<tr>
<td>2</td>
<td>TMSCl</td>
<td>78%</td>
</tr>
<tr>
<td>3</td>
<td>HF•pyr</td>
<td>Complex TLC</td>
</tr>
<tr>
<td>4</td>
<td>TASF</td>
<td>75%</td>
</tr>
</tbody>
</table>
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**

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

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

TASF, DMF

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

(33R,37S)-24

(33R,37R)-24

(33S,37S)-24

(33S,37R)-24
The 700 MHz $^1$H NMR spectra of the four stereoisomers of 24 were substantially identical
(See experimental information). 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

<table>
<thead>
<tr>
<th></th>
<th>(33R,37S)-24</th>
<th>(33R,37R)-24</th>
<th>(33S,37S)-24</th>
<th>(33S,37R)-24</th>
<th>$\delta$ (RR) – RS)</th>
<th>$\delta$ (SS) – RS)</th>
<th>$\delta$ (SR) – RR)</th>
<th>$\delta$ (SS) – RR)</th>
<th>$\delta$ (SR) – SS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C30</td>
<td>160.82</td>
<td>160.81</td>
<td>160.82</td>
<td>160.81</td>
<td>-0.01</td>
<td>0</td>
<td>-0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>C34</td>
<td>136.18</td>
<td>136.19</td>
<td>136.19</td>
<td>136.16</td>
<td>0.01</td>
<td>0.01</td>
<td>-0.02</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>131.70</td>
<td>131.69</td>
<td>131.70</td>
<td>131.69</td>
<td>-0.01</td>
<td>0</td>
<td>-0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>130.54</td>
<td>130.54</td>
<td>130.54</td>
<td>130.54</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C35</td>
<td>128.96</td>
<td>128.80</td>
<td>128.84</td>
<td>129.03</td>
<td>-0.16</td>
<td>-0.12</td>
<td>0.07</td>
<td>0.04</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>127.61</td>
<td>127.64</td>
<td>127.69</td>
<td>127.66</td>
<td>0.03</td>
<td>0.08</td>
<td>0.05</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>114.72</td>
<td>114.71</td>
<td>114.73</td>
<td>114.72</td>
<td>-0.01</td>
<td>0.01</td>
<td>0</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>73.73</td>
<td>73.73</td>
<td>73.73</td>
<td>73.73</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C33</td>
<td>73.34</td>
<td>73.32</td>
<td>73.36</td>
<td>73.37</td>
<td>-0.02</td>
<td>0.02</td>
<td>0.03</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>72.16</td>
<td>72.10</td>
<td>72.12</td>
<td>72.15</td>
<td>-0.06</td>
<td>-0.04</td>
<td>-0.01</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>70.32</td>
<td>70.33</td>
<td>70.34</td>
<td>70.33</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>C21</td>
<td>68.27</td>
<td>68.27</td>
<td>68.28</td>
<td>68.27</td>
<td>0</td>
<td>0.01</td>
<td>0</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>66.90</td>
<td>66.89</td>
<td>66.93</td>
<td>66.90</td>
<td>-0.01</td>
<td>0.03</td>
<td>0</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>66.25</td>
<td>66.24</td>
<td>66.26</td>
<td>66.24</td>
<td>-0.01</td>
<td>0.01</td>
<td>-0.01</td>
<td>0.02</td>
<td>0</td>
</tr>
<tr>
<td>C25</td>
<td>66.20</td>
<td>66.20</td>
<td>66.22</td>
<td>66.19</td>
<td>0</td>
<td>0.02</td>
<td>-0.01</td>
<td>0.02</td>
<td>-0.01</td>
</tr>
<tr>
<td></td>
<td>63.03</td>
<td>63.03</td>
<td>63.03</td>
<td>63.03</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>55.66</td>
<td>55.65</td>
<td>55.67</td>
<td>55.66</td>
<td>-0.01</td>
<td>0.01</td>
<td>0</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>C26</td>
<td>46.64</td>
<td>46.64</td>
<td>46.62</td>
<td>46.64</td>
<td>0</td>
<td>-0.02</td>
<td>0</td>
<td>-0.02</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>46.35</td>
<td>46.35</td>
<td>46.36</td>
<td>46.36</td>
<td>0</td>
<td>0</td>
<td>0.01</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>C28</td>
<td>46.22</td>
<td>46.21</td>
<td>46.16</td>
<td>46.18</td>
<td>-0.01</td>
<td>-0.06</td>
<td>-0.04</td>
<td>-0.05</td>
<td>-0.03</td>
</tr>
<tr>
<td></td>
<td>41.44</td>
<td>41.43</td>
<td>41.45</td>
<td>41.44</td>
<td>-0.01</td>
<td>0.01</td>
<td>0</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>C32</td>
<td>41.41</td>
<td>41.36</td>
<td>41.36</td>
<td>41.41</td>
<td>-0.05</td>
<td>-0.05</td>
<td>0</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>C36</td>
<td>38.86</td>
<td>38.86</td>
<td>38.86</td>
<td>38.86</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C32</td>
<td>34.17</td>
<td>34.13</td>
<td>34.12</td>
<td>34.18</td>
<td>-0.04</td>
<td>-0.05</td>
<td>0.01</td>
<td>-0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>C39</td>
<td>29.86</td>
<td>29.89</td>
<td>29.90</td>
<td>29.86</td>
<td>0.03</td>
<td>0.04</td>
<td>0</td>
<td>0.01</td>
<td>-0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.6 Conclusions

We successfully synthesized four stereoisomers of bottom fragment C21-C40 of tetrafibrin 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.\textsuperscript{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 °C for 1 h gave the epoxide \((racc)-42\) 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.\textsuperscript{23}

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

\[
\begin{align*}
\text{HO-} & \quad \xrightarrow{\text{TBSCl, Imidazole}} \quad \text{TBSO-} \\
40 & \quad \xrightarrow{\text{100\%}} \quad 41 \\
\text{TBSO-} & \quad \xrightarrow{\text{(R,R) Jacobsen catalyst}} \quad \text{TBSO-}
\end{align*}
\]

\[
\begin{align*}
\text{TBSO-} & \quad \xrightarrow{\text{AcOH, H}_2\text{O, THF}} \quad \text{TBSO-} \\
(rac)-42, 88\% & \quad \xrightarrow{\text{(R)-42, 45\%}} \\
\text{m-CPBA, CH}_2\text{Cl}_2
\end{align*}
\]
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 \(\text{CH}_3\text{I}\) and \(\text{K}_2\text{CO}_3\) in ACN-H\(_2\)O (6:1) at 45 °C 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 \(\text{m-CPBA}\) 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-\(\text{tert}\)-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%.
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,\textsuperscript{16} employing commercially available 1-phenyl-1\textit{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 \(\text{SO}_3\cdot\text{pyr}\) in 93% yield (Scheme 3.4). Reaction of aldehyde \((S)-28\) with propane-1,3-dithiol and \(\text{BF}_3\cdot\text{OEt}_2\) 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 Bu₄NI (Scheme 3.5).²⁴

Scheme 3.5 Synthesis of (R)-68

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 °C 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(ClO₄)₂•3H₂O] 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 NaBH₄ 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 CH₂Cl₂/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%. 

Dithiane 66 was treated with t-BuLi at –78 °C 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(ClO₄)₂•3H₂O] 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 NaBH₄ 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 CH₂Cl₂/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%.
### 3.6 Synthesis of the C14-C20 fragment 5

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

- **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 LiBH4 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
MgBr₂•OEt₂ to aldehyde 78 in THF furnished dithiane 6 in 89% yield. 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 (2E,4E)-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 MnO₂ 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 SOBr₂ 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

13, C21-C40

87, C9-C20

88, C9-C40

89

7

53, C1-C40

1

49
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 °C in distilled DME, followed by the addition of aldehyde 3. 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 \([\text{Mo}_7\text{O}_{24}({\text{NH}_4})_6\cdot\text{H}_2\text{O}, \text{H}_2\text{O}_2]\) provided a smooth conversion of sulfide 8 to sulfone 9 in 92% yield. Deprotonation of sulfone 9 with KHMDS at −60 °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\(_2\)Cl\(_2\)) from 10 provided the primary alcohol 11 in 89% yield. Incorporation of the thiotetrazole via the Mitsunobu protocol, employing commercially available 1-phenyl-1\( H \)-tetrazole-5-thiol (PTSH), followed by oxidation (Mo\(_7\)O\(_{24}\)(NH\(_4\))\(_6\)•H\(_2\)O, H\(_2\)O\(_2\)) of the derived sulfide, furnished sulfone 13 (C21-C40 fragment, 65% yield, two steps).
Scheme 3.10 Synthesis of the C21-C40 fragment

2. Mo$_7$O$_{24}$(NH$_4$)$_6$$\cdot$H$_2$O, H$_2$O$_2$

1. PTSH, DIAD, PPh$_3$

12, $X = S$

13, $X = SO_2$, C21-C40, 65%, two steps
3.2.3 Synthesis of the C9-C20 fragment 87

The assembly of C9-C20 carbon framework of tetrafibrin 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 H₂O₂ provided the primary alcohol 15 in 68% yield. Benzoylation of alcohol 15 with BzCl, DMAP and NEt₃ 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.
3.2.4 Attempts to couple fragments C9-C20 and C21-C40

With two major fragments (C9-C20 and C21-C40) of tetrafibrin 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 \(-60^\circ\text{C}\) 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.

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

3.3.1 Retrosynthesis of tetrafibrin

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 \rightarrow 93, C9-C30 \\

9, C31-C40 + 93 \rightarrow 88, C9-C40 \\

Julia-Kocienski reaction

HWE reaction
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,\textsuperscript{15} then the alcohol 94 was converted to alkylthiophenyltetrazole 95 in 98% yield by a Mitsunobu reaction.\textsuperscript{16} Oxidation of sulfide 95 to the corresponding sulfone 92 was achieved with \textit{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 to 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.\(^\text{15}\) Incorporation of the thiotetrazole via the Mitsunobu reaction,\(^\text{16}\) employing commercially available 1-phenyl-1H-tetrazole-5-thiol, followed by oxidation of the derived sulfide furnished sulfone 104 in 83% yield for two steps.
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.
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

105

97, 73%

93, 60%

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 tetrafibrin in hand, Julia-Kocienski olefination reaction was attempted (Scheme 3.21). KHMDS was added to a solution of sulfone 9 in distilled DME at −60 °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 tetrafibrin 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

93, C9-C30

(Boc)$_2$N

OTBS

$\text{S}^\text{O}_2$N

9, C31-C40

KHMDS, DME

88, C9-C40, 45%

(Boc)$_2$N

OTBS

$\text{S}^\text{O}_2$N

10% KOH, MeOH, 24 h

106, 70%

89

around 1.5 mg, crude
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.\textsuperscript{41} LiHMDS was added to a solution of fragment 7 in THF at $-78\,^\circ\text{C}$ 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 $-78\,^\circ\text{C}$ and 0 $^\circ\text{C}$ 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 tetrafibracin. The coupling product was purified by HPLC and characterized by $^1\text{H}$-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.
3.4 Conclusions

A convergent synthesis of the proposed structure of tetrafibrin 1 has been explored. After making six fragments of tetrafibrin 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 Et₂O 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 ¹H NMR, ¹³C NMR, COSY, ¹⁹F 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 CDCl₃ (7.26 ppm), MeOD (4.87 ppm) or central CDCl₃ 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.

\[
\begin{align*}
\text{(S)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)acetaldehyde (S-28): } & \\
\text{To a solution of alcohol (S)-27 (5.00 g, 34.1 mmol) in dichloromethane (200 mL) at 0 °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\text{-pyr (13.6 g, 85.5 mmol) was added and the resulting mixture was stirred for 45 min. Saturated aqueous NaHCO}_3 \text{ 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 \text{ 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); } \\
\text{\( ^1\)H NMR (300 MHz, CDCl}_3) \delta 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); } \\
\text{\( ^{13}\)C NMR (76 MHz, CDCl}_3) \delta 199.9, 109.3, 70.7, 69.2, 47.9, 26.9, 25.5; IR (neat) cm}^{-1} \text{ 2987, 2936, 2735, 1725, 1372, 1217; HRMS for C}_6\text{H}_9\text{O}_3 (M – CH}_3)^{+}: \text{Calcd 129.0552; found 129.0550.}
\end{align*}
\]
(S)-4- Allyl-2,2-dimethyl-1,3-dioxolane ((S)-29): To a solution of CH₃PPh₃Br (15.8 g, 44.2 mmol) in THF (500 mL) at 0 °C 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 °C. 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 °C and then warmed to room temperature and stirred overnight. The reaction mixture was poured into saturated aqueous NH₄Cl. The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over MgSO₄ and concentrated. Purification of the crude product by flash column chromatography (SiO₂, 20% ethyl acetate in hexanes) afforded the alkene (S)-29 (4.0 g, 83%) as a volatile oil: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 NaHCO₃ solution. The layers were separated and the aqueous layer was extracted with dichloromethane and the
combined organic extracts were dried over MgSO₄ and concentrated. Purification by flash column chromatography (SiO₂, 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 °C, 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 °C) gave diastereomerically pure epoxide (S,S)-30 (1.89 g, 11.9 mmol, 45%) as colorless oil. 

1H NMR (500 MHz, CDCl₃) 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); 13C NMR (126 MHz, CDCl₃) 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 C₇H₁₁O₃ (M − CH₃)⁺: Calcd 143.0708; found 143.0706.

(OH)

(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 °C. 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 °C, treated with saturated aqueous NH₄Cl solution. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ 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: [α]$_D$ +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$_3$S$_2$ (M$^+$): Calcd 278.1010; found 278.1006.

$\begin{align*}
\text{TBSO} & \quad \text{O} \\
\text{TBS} & \quad \text{S} \\
\text{TBS} & \quad \text{O} \\
\text{S} & \quad \text{TBS}
\end{align*}$

2-((2S,4S)-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 °C. 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 °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 MgSO₄ and concentrated. Purification by flash column chromatography (SiO₂, 25% ethyl acetate in hexanes) gave the product (R)-33 (1.53 g, 84%) as colorless oil: [α]D +0.87 (c 1.2 CHCl₃); ¹H NMR (500 MHz, CHCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 C₁₅H₂₂O₄ (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 (SiO₂, 80% ethyl acetate in hexanes) to yield the diol \((R)-34\) (1.40 g, 87%) as clear colorless oil: \(\alpha_D -2.6 \ (c \ 1.4 \ \text{CHCl}_3)\); \(^1\)H NMR (300 MHz, CHCl₃) \(\delta\) 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, 2 H), 3.45-3.54 (m, 1 H), 1.60-1.90 (m, 2 H); \(^{13}\)C NMR (126 MHz, CDCl₃) \(\delta\) 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 C₁₂H₁₈O₄ (M⁺): Calcd 226.1205; found 226.1199.

\((R)-2-(2-(4-Methoxybenzyl)oxy)ethyl)oxirane (\((R)-26\)): To a solution of the above diol (800 mg, 3.98 mmol) in toluene (15 mL) were added PPh₃ (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 (SiO₂, 25% ethyl acetate in hexanes) to yield epoxide \((R)-26\) (779 mg, 94%) as oil: \(\alpha_D +12.0 \ (c \ 1.0 \ \text{CHCl}_3)\); \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 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, CDCl₃) \(\delta\) 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 C₁₂H₁₆O₃ (M⁺): Calcd 208.1099; found 208.1094.

\((R)-1-(2-((2S,4S)-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 °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 NH₄Cl solution. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated. The residue was purified by flash column chromatography (SiO₂, 20% ethyl acetate in hexanes) to provide compound 35 (1.1 g, 90%) as an oil: [α]D –5.0 (c 0.9 CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (76 MHz, CDCl₃) 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 C₃₉H₇₆O₆S₂Si₃Na: Calcd 811.4289; found 811.4284.

(3R,7S,9S)-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/H₂O (4:1, 10 mL) was cooled to 0 °C, followed by addition of 2,6-lutidine (662 mg, 6.18 mmol) and Hg(ClO₄)₂•H₂O (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 NH₄Cl. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and
concentrated. Purification by flash column chromatography (20% ethyl acetate in hexanes) provided the ketone 36 (454 mg, 84%) as oil: [α]D −6.53 (c 1.73 CHCl3); 1H NMR (300 MHz, CDCl3) 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); 13C NMR (75 MHz, CHCl3) 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 C36H70O7Si3Na (M + Na)^+: Calcd 721.4327; found 721.4329.

1-(((3R,5S,7R,9S)-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 (CH3)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 MgSO4 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 MgSO4 and concentrated.
crude product was purified by flash column chromatography (SiO₂, 10% ethyl acetate in hexanes) to yield compound 38 (434 mg, 73%) as oil: 

\[ ^1H \text{NMR (600 MHz, } \text{CDCl}_3) \delta 7.26 (d, J = 9.6 \text{ Hz, 2 H}), 6.87 (d, J = 8.8 \text{ Hz, 2 H}), 4.42 (s, 2 H), 3.87-3.92 (m, 2 H), 3.83-3.87 (m, 1 H), 3.81 (s, 3 H), 3.76-3.80 (m, 1 H), 3.49-3.54 (m, 3 H), 3.41 (dd, J = 10.2, 5.5 Hz, 1 H), 1.79-1.84 (m, 1 H), 1.67-1.75 (m, 2 H), 1.59-1.67 (m, 3 H), 1.52-1.58 (m, 1 H), 1.45-1.50 (m, 1 H), 0.90 (s, 9 H), 0.888 (s, 9 H), 0.88 (s, 9 H), 0.877 (s, 9 H), 0.084 (s, 3 H), 0.082 (s, 3 H), 0.08 (s, 3 H), 0.076 (s, 6 H), 0.07 (s, 3 H), 0.063 (s, 3 H), 0.06 (s, 3 H), 0.055 (s, 3 H), 0.04 (s, 3 H); \]

\[ ^{13}C \text{NMR (151 MHz, } \text{CDCl}_3) \delta 159.1, 130.9, 129.2, 113.8, 72.6, 70.8, 67.6, 67.5, 67.4, 67.2, 66.8, 55.3, 46.8, 46.0, 42.6, 37.7, 26.1, 26.1, 26.1, 18.5, 18.3, 18.2, 18.1, -3.4, -3.5, -3.7, -3.8, -4.2, -4.4, -5.2; \]

HRMS for C₄₈H₁₀₀O₇Si₅Na (M + Na)+: Calcd 951.6213; found 951.6311.

(2S,4R,6S,8R)-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 MgSO₄ and concentrated. Purification by flash column chromatography (SiO₂, 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): [α]D +16.5 (c 0.2 CHCl₃); 

\[ ^1H \text{NMR (600 MHz, } \text{CDCl}_3) \delta 7.76 (d, J = 8.5 \text{ Hz, 2 H}), 6.88 (d, J = 8.5 \text{ 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,
1H), 3.50 (t, J = 7.1 Hz, 2H), 3.44 (ddd, J = 11.8, 7.1, 5.2 Hz, 1H), 1.91 (t, J = 6.0 Hz, 1H), 1.80-1.85 (m, 1H), 1.55-1.73 (m, 7H), 0.91 (s, 9H), 0.883 (s, 9H), 0.88 (s, 18H), 0.104 (s, 3H), 0.10 (s, 3H), 0.08 (s, 6H), 0.072 (s, 6H), 0.07 (s, 3H), 0.05 (s, 3H); 13C NMR (151 MHz, CDCl3) 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 C₄₂H₈₆O₇Si₄Na (M + Na)⁺: Calcd 837.5348; found 837.5363.

(2S,4R,6S,8R)-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 NaHCO₃ (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 NaHCO₃ solution. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over MgSO₄ 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: 1H NMR (600 MHz, CD₂Cl₂) δ 8.58 (d, J = 1.7 Hz, 1H), 7.24 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.38 (s, 2H), 4.15-4.18 (m, 1H), 3.95-4.00 (m, 1H), 3.91-3.95 (m, 1H), 3.82-3.86 (m, 1H), 3.79 (s, 3H), 3.47-3.52 (m, 2H), 1.66-1.81 (m, 6H), 1.53-1.60 (m, 2H), 0.97 (s, 9H), 0.93 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.10 (s, 3H), 0.09 (s, 6H), 0.08 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); 13C NMR (151 MHz, CD₂Cl₂) δ 203.8, 159.7, 131.6, 129.7, 114.1, 76.1, 73.1, 68.0, 67.6,
79.6, 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 C₄₂H₈₄O₇Si₄Na (M + Na)+: Calcd 835.5192; found 835.5197.

**TBSO**

*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 °C 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 °C 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 MgSO₄ 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 138.6, 114.6, 62.6, 32.1, 30.1, 26.0, 18.4, −5.2.

**TBSO**

*(rac)-*tert-Butyldimethyl(3-(oxiran-2-yl)propoxy)silane (42): *m*-Chloroperbenzoic acid (75% w/w in H₂O, 16.0 g) was added to a solution of the above alkene (14.0 g, 69.8 mmol) in dichloromethane at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, then warmed to room temperature and stirred for 1 h followed by adding saturated aqueous NaHCO₃ solution. The layers were separated and aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated. Bulb-to-bulb (kugelrohr)
distillation of the crude product under reduced pressure (0.1 mbar, 90-105 °C) gave the epoxide 42 (13.0 g, 88%) as an oil: 1H NMR (300 MHz, CDCl3) 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); 13C NMR (75 MHz, CDCl3) 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 − tBu)+ : 159; HRMS for C7H15O2Si (M − tBu)+ : Calcd 159.0841; found 159.0828.

\[
\text{TBSO} \quad \overset{\text{O}}{\text{O}}
\]

(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 °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 °C) gave diastereomerically pure epoxide (R)-42 (1.42 g, 6.8 mmol, 45%) as colorless oil: 1H NMR (300 MHz, CDCl3) 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); 13C NMR (75 MHz, CDCl3) 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.

\[
\text{TBSO} \quad \overset{\text{O}}{\text{O}}
\]

(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: 1H NMR (300 MHz, CDCl3) 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$_4$Cl 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: [α]$_D$ −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$_2$S$_2$Si (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: $\left[\alpha\right]_D^\circ +7.4$ (c 1.1 CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$S$_2$Si (M$^+$): Calcd 336.161303; found 336.162292.

\[ \text{TBSO} \quad \text{OH} \quad \text{S} \quad \text{S} \]

\[ (\text{R})-8-((1,3\text{-dithian}-2\text{-yl})\text{methyl})-13,13,14,14,15,15,16,16,16\text{-nonafluoro-10,10-diisopropyl}-2,2,3,3\text{-tetramethyl-4,9-dioxo-3,10-disilahexadecane ((R)-21a):} \]

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$_3$SO$_3$H (0.351 mL, 3.9 mmol) dropwise under Ar at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, then warmed to room temperature and stirred for 15 h. Then the homogeneous solution was cooled to 0 °C. A solution of 2,6-lutidine (0.61 mL), alcohol (R)-43 (437 mg, 1.3 mmol) in CH$_2$Cl$_2$ (5 mL) was added slowly and the reaction mixture was stirred for 4 h. The reaction was quenched by adding saturated NH$_4$Cl (10 mL) solution at 0 °C. 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: $\left[\alpha\right]_D^\circ$
−12.0 (c 1.0 CHCl3); 1H NMR (300 MHz, CDCl3) 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); 13C NMR (75 MHz, CDCl3) 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, 17.6, 13.0, 0.8, −5.4; 19F NMR (CDCl3) −126.0 (2 F), −124.2 (2 F), −116.6 (2 F), −81.0 (3 F); HRMS for C_{27}H_{49}F_{9}O_{2}Si_{2}S_{2}K (M + K)^+: Calcd 735.2206; found 735.2278.

(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-heptafluoropentyl)silane 44b (1.71 g, 5.5 mmol) was added to a 10 mL flask followed by adding CF₃SO₃H (0.379 mL, 4.2 mmol) dropwise under Ar at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, then warmed to room temperature and stirred for 15 h. Then the homogeneous solution was cooled to 0 °C. A solution of 2,6-lutidine (0.66 mL), alcohol (S)-43 (470 mg, 1.4 mmol) in CH₂Cl₂ (5 mL) was added slowly and the reaction mixture was stirred for 4 h. The reaction was quenched by adding saturated NH₄Cl (10 mL) solution at 0 °C. The layers were separated and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over MgSO₄ and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) provided (S)-21b (878 mg, 90%) as oil: [α]D +11.3 (c 1.0 CHCl3); 1H NMR (300 MHz, CDCl3) 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, 17.6, 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$_{25}$H$_{49}$F$_7$O$_2$Si$_2$S$_2$K (M + K)$^+$: Calcd 685.2238; found 685.2222.

![Chemical structure](image)

TIPS$^{F7}$ = Si(i-Pr)$_2$C$_2$H$_4$C$_3$F$_7$, TIPS$^{F9}$ = Si(i-Pr)$_2$C$_2$H$_4$C$_4$F$_9$

(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$_2$O (4:1, 28 mL) was cooled to 0 °C followed by addition of 2,6-lutidine (1.9 mL, 16 mmol) at once and Hg(ClO$_4$)$_2$•H$_2$O (2.86 g) in portions. The reaction mixture was stirred at 0 °C 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$_4$Cl. 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).
(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 MgSO₄ 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: ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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; ¹⁹F NMR (CDCl₃) −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-Pr)$_2$C$_2$H$_4$C$_3$F$_7$, TIPS$^{F9}$ = Si(i-Pr)$_2$C$_2$H$_4$C$_4$F$_9$

(Qrac)-5-(6-(tert-Butyldimethylsilyloxy)-3-(perfluoroalkyl(diisopropyl)silyloxy)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 °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$_3$) $\delta$ 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$_3$) $\delta$ 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, 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$_4$O$_2$F$_7$SSi$_2$ (M$^+$): Calcd 719.3081; found 719.3055; HRMS for C$_{31}$H$_{50}$N$_4$O$_2$F$_9$SSi$_2$ (M$^+$): Calcd 769.3096; found 769.3049.
(Qrac)-5-(6-(tert-Butyldimethylsilyloxy)-3-(perfluoroalkyliisopropylsilyloxy)hexylsulfonyl)-1-phenyl-1H-tetrazole (M-2a,b):  
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 °C. The mixture was stirred for 2 h followed by warming to room temperature and stirring overnight. The reaction was quenched by adding saturated NaHCO₃ 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 (SiO₂, 10% ethyl acetate in hexanes) to provide sulfone M-2a,b (562 mg, 85%) as oil: ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CHCl₃) 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; ¹⁹F NMR (CDCl₃) −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 C₃₀H₅₀N₄O₄F₇SSi₂ (M + H)⁺: Calcd 751.2980; found 751.3050; HRMS for C₃₁H₅₀N₄O₄F₉SSi₂ (M + H)⁺: Calcd 801.2948; found 801.3012.
(S)-5-(2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethylthio)-1-phenyl-1H-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-1H-tetrazole-5-thiol (2.60 g, 14.8 mmol) and triphenylphosphine (3.00 g, 11.5 mmol) in THF (20 mL) at 0 °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 MgSO₄ 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: [α]D −1.0 (c 1.0 CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 − CH₃)+ 291; HRMS for C₁₃H₁₅N₄O₂S (M − CH₃): Calcd 291.0916; found 291.0919.

(R)-5-(2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethylthio)-1-phenyl-1H-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: ¹H NMR (300 MHz, CDCl₃) 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-1H-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 (SiO₂, 80% ethyl acetate in hexanes) provided the (S)-diol (S)-49 (650 mg, 2.45 mmol, 93%) as viscous oil: [α]D −7.5 (c 1.82 CHCl₃); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 C₁₀H₁₁N₄O₁S(M – CH₃O): Calcd 235.065358; found 235.065690.

(R)-4-(1-Phenyl-1H-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, CDCl₃) 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-1H-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 °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 MgSO₄ 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: [α]D −3.0 (c 1.0 CHCl₃) ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CHCl₃) 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 C₁₃H₁₉N₄O₂SSi (M − C₄H₉)+ : Calcd 323.099801; found 323.098886.

(R)-1-(tert-butyldimethylsilyloxy)-4-(1-phenyl-1H-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: [α]D +3.1 (c 1.0 CHCl₃) ¹H NMR (300 MHz, CDCl₃) 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 C₁₃H₉₉N₄O₂SSi (M – C₄H₉)⁺: Calcd 323.099801; found 323.099465.

![TIPSF₁³ structure](image)

TIPSF₁³ = Si(i-Pr)₂C₂H₄C₆F₁₃

(S)-5-(4-(tert-Butyldimethylsilyloxy)-3-(diisopropyl(3,3,4,4,5,6,6,7,7,8,8,8-tridecafluoro-octyl)silyloxy)butylthio)-1-phenyl-1H-tetrazole ((S)-22c): Diisopropyl(3,3,4,4,5,6,6,7,7,8,8-tridecafluoro-octyl) silane 44c (540 mg, 1.17 mmol) was added to a 5 mL flask followed by adding CF₃SO₃H (0.081 mL, 0.90 mmol) dropwise under Ar at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, then warmed to room temperature and stirred for 15 h. Then the homogeneous solution was cooled to 0 °C. A solution of 2,6-lutidine (0.144 mL), compound (S)-50 (114 mg, 0.30 mmol) in CH₂Cl₂ (5 mL) was added slowly and the reaction mixture was stirred for 4 h. The reaction was quenched by adding saturated NH₄Cl (10 mL) solution at 0 °C. The organic layer was separated and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over MgSO₄ and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) provided (S)-22c (230 mg, 90%) as oil: [α]₀⁻8.7 (c 1.1 CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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; ¹⁹F NMR (CDCl₃) −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 C₃₁H₄₆F₁₉N₄O₂Si₂S (M + H)⁺: Calcd 841.2672; found 841.2695.
(R)-5-(4-(tert-Butyldimethylsilyloxy)-3-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluoro-hexyl)silyloxy)butylthio)-1-phenyl-1H-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 CF₃SO₃H (0.062 mL, 0.69 mmol) dropwise under Ar at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, then warmed to room temperature and stirred for 15 h. Then the homogeneous solution was cooled to 0 °C. A solution of 2,6-lutidine (0.108 mL), compound (R)-50 (86 mg, 0.23 mmol) in CH₂Cl₂ (5 mL) was added slowly and the reaction mixture was stirred for 4 h. The reaction was quenched by adding saturated NH₄Cl (10 mL) solution at 0 °C. The organic layer was separated and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over MgSO₄ and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) provided (R)-22a (153 mg, 90%) as oil: [α]D +6.6 (c 1.1 CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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, 17.5, 12.8, 12.2, 0.7, −5.3; ¹⁹F NMR (CDCl₃) −126.6 (2 F), −124.8 (2 F), −117.2 (2 F), −81.6 (3 F); HRMS for C₂₉H₄₆F₉N₄O₂Si₂S (M + H)+: Calcd 741.2736; found 741.2677.
(Qrac)-2-(diisopropylperfluoroalkylsilyloxy)-4-(1-phenyl-1H-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 NaHCO₃ (20 mL) solution. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ 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: ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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; ¹⁹F NMR (CDCl₃) −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 C₂₃H₃₂N₄O₂F₉Si (M + H)⁺: Calcd 627.1872; found 627.1858; HRMS for C₂₅H₃₂N₄O₂F₁₃Si (M + H)⁺: Calcd 727.1808; found 727.1820.
**TIPS** = Si(i-Pr)\(_2\)C\(_2\)H\(_4\)C\(_4\)F\(_9\), **TIPS**\(^{13}\) = Si(i-Pr)\(_2\)C\(_2\)H\(_4\)C\(_6\)F\(_{13}\)

*(Qrac)*-2-(diisopropylperfluoroalkysilyloxy)-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\(_3\)) \(\delta\) 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); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 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).

KHMDAS (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 °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 MgSO₄ 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: 

\[ \text{1H NMR (500 MHz, CDCl₃)} \delta 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); 13C NMR (126 MHz, CDCl₃) \delta 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; 19F NMR (CDCl₃) –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 C₄₆H₇₂N₄O₃F₁₆Si₃SNa: Calcd 1171.4275; found 1171.4237. HRMS (M + Na)⁺ for C₄₇H₇₂N₄O₃F₁₈Si₃SNa: Calcd 1221.4243; found 1221.4243. HRMS (M + Na)⁺ for C₄₈H₇₂N₄O₃F₂₀Si₃SNa: Calcd 1271.4211; found 1271.4146. HRMS (M + Na)⁺ for C₄₉H₇₃N₄O₃F₂₂Si₃SNa: Calcd 1321.4179; found 1321.4214.
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 Mo7O24(NH4)6·4H2O in 2.5 mL of 30% w/v aq H2O2). 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 MgSO4 and concentrated. Purification of the crude product by flash column chromatography provided (SiO2, 10% ethyl acetate in hexanes) to yield sulfone M-54a,b/a,c (60 mg, 88%) as an oil: 1H NMR (300 MHz, CDCl3) 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); 13C NMR (126 MHz, CDCl3) 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; 19F NMR (CDCl3) −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 C46H72N4O5F16Si3SNa: Calcd 1203.4147; found 1203.4174. HRMS (M + Na)+ for C47H72N4O5F18Si3SNa: Calcd 1253.4103; found 1253.4142. HRMS (M + Na)+ for C48H72N4O5F20Si3SNa: Calcd 1303.4099; found 1303.4110. HRMS (M + Na)+ for C49H73N4O5F22Si3SNa: Calcd 1353.4044; found 1353.4078.
M-23a,b/a,c:

\[
\begin{align*}
\text{TIPS}^7 &= \text{Si(i-Pr)}_2\text{C}_2\text{H}_4\text{C}_3\text{F}_7, \\
\text{TIPS}^9 &= \text{Si(i-Pr)}_2\text{C}_2\text{H}_4\text{C}_4\text{F}_9, \\
\text{TIPS}^{13} &= \text{Si(i-Pr)}_2\text{C}_2\text{H}_4\text{C}_6\text{F}_{13}
\end{align*}
\]

KHMD (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 MgSO₄ 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 mm, 100% MeOH) to afford four single quasidiastereomers (33R, 37S)-23a,b, (33R, 37R)-23a,a, (33S, 37S)-23b,c, (33S, 37R)-23a,c.

(33R, 37S)-23a,b: \([\alpha]_D^{25} -1.8 \, (c \, 0.5 \, \text{CHCl}_3); \)\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) \( \delta \) 7.25 (d, \( J = 7.8 \, \text{Hz}, 2 \, \text{H} \)), 6.86 (d, \( J = 7.8 \, \text{Hz}, 2 \, \text{H} \)), 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).

(33R, 37R)-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$_3$) −128.2 (4 F), −124.8 (4 F), −117.3 (4 F), −81.6 (6 F).

(33S, 37S)-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, 136.6, 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$_3$) −128.2 (4 F), −124.8 (4 F), −117.3 (4 F), −81.6 (6 F).
CDCl₃) 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, 17.5, 12.8, 12.8, 12.7, 12.7, −3.5, −3.5, −3.6, −3.9, −4.2, −4.3, −4.7, −5.4; ¹⁹F NMR (CDCl₃) −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).

(33S, 37R)-23a,c: [α]D −1.6 (c 0.8 CHCl₃); ¹H NMR (600 MHz, CDCl₃) 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), ¹³C NMR (150 MHz, CDCl₃) 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, 17.5, 12.8, 12.8, 12.7, 12.7, −3.5, −3.5, −3.6, −3.9, −4.2, −4.3, −4.7, −5.4; ¹⁹F NMR (CDCl₃) −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).

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

TASF (15 mg) in DMF (0.2 mL) was added to a solution of (33R, 37S)-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 CH₂Cl₂) to afford compound (33R, 37S)-24 (1.1 mg, 75%) as oil: [α]D +1.0 (c 1.1 CHCl₃); ¹H 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); ¹³C 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.

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

Following the same procedure as above, compound (33R, 37R)-24 was obtained as oil: [α]D +3.2 (c 1.0 CHCl₃); ¹H 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); ¹³C 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.
(4S,6E,8S,10E,12S,14R,16S,18R)-20-(4-methoxybenzyloxy)icos-1,4,8,12,14,16,18-heptaol ((33S, 37S)-24):

Following the same procedure as above, compound (33S, 37S)-24 was obtained as oil: $[\alpha]_D ^{20} +4.4$ (c 1.0 CHCl$_3$); $^1$H NMR (700 MHz, MeOD) $\delta$ 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) $\delta$ 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.

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

Following the same procedure as above, compound (33S, 37R)-24 was obtained as oil: $[\alpha]_D ^{20} +0.8$ (c 0.8 CHCl$_3$); $^1$H NMR (700 MHz, MeOD) $\delta$ 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) $\delta$ 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 \(-78\,^\circ\mathrm{C}\). After 30 min at \(-78\,^\circ\mathrm{C}\), 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 \(-10\,^\circ\mathrm{C}\), the reaction mixture was cooled to \(-78\,^\circ\mathrm{C}\) 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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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 – \(t\)Bu\(^+\)) \(393\); HRMS for C\(_{17}\)H\(_{37}\)O\(_2\)S\(_2\)Si\(_2\) (M – \(t\)Bu\(^+\)) : Calcd 393.1774; found 393.1780.
(R)-3,6-bis(tert-Butyldimethylsilyloxy)hexanal (58): Methyl iodide (0.2 mL) and K₂CO₃ (258 mg, 1.87 mmol) were added to a solution of dithiane 57 (800 mg, 1.77 mmol) in aqueous acetonitrile (MeCN/H₂O, 6:1/2.1 mL). The reaction mixture was stirred for 5 h at 45 °C 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 MgSO₄ and concentrated. The crude product was purified by flash column chromatography (SiO₂, 20% ethyl acetate in hexanes) to give the aldehyde 58 (514 mg, 80%) as an oil: [α]D −3.74 (c 1.15 CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₄H₃₁O₃Si₂ (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 °C and the mixture was stirred for 1 h. The reaction mixture was warmed to 0 °C, 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 MgSO₄ 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: [α]D −21.0 (c 0.2 CHCl3); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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-1H-tetrazole (60):

Diisopropylazodicarboxylate (589 mg, 2.90 mmol) was added to a solution of alcohol 59 (0.65 g, 1.8 mmol), 1-phenyl-1H-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 MgSO₄ 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: [α]D −17.8 (c 0.28 CHCl₃); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 C₂₅H₄₆N₄O₂SSi₂Na (M + Na)⁺: Calcd 545.2778; found 545.2780.
(R)-5-(3,6-bis(tert-Butyldimethylsilyloxy)hexylsulfonyl)-1-phenyl-1H-tetrazole (61):

m-Chloroperbenzoic 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 °C. The mixture was stirred for 2 h at 0 °C followed by overnight stirring at room temperature. The mixture was quenched with saturated NaHCO₃ solution (25 mL) followed by separation of the layers. The aqueous layer was extracted with dichloromethane and combined organic layers were dried over MgSO₄ and concentrated. Purification of the crude product by flash column chromatography (SiO₂, 10% ethyl acetate in hexanes) gave the sulfone 61 (863 mg, 88%) as an oil: [α]D −4.1 (c 1.0 CHCl₃); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 C₂₅H₄₆N₄O₄SSi₂Na (M + Na)⁺: Calcd 577.2676; found 577.2680.

(R)-4-(tert-Butyldimethylsilyloxy)-6-(1-phenyl-1H-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 °C) was added to a solution of sulfone 61 (0.10 g, 0.18 mmol) in THF at 0 °C. The reaction mixture was stirred for 6 h at room temperature. The reaction was slowly quenched with saturated aqueous NaHCO₃ solution, followed by extraction of aqueous layer with ethyl acetate. The combined organic layers were washed with CuSO₄ solution, dried over MgSO₄ and concentrated. The crude product was purified by flash column chromatography to yield the alcohol 62 (81 mg, 76%) as an oil: [α]D −1.1 (c 0.72 CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CHCl₃) 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 C₁₅H₂₃N₄O₄SiS (M – tBu)⁺: 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: [α]D −3,3 (c 1.21 CHCl₃) ¹H NMR (500 MHz, CDCl₃) 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$_3$) $\delta$ 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$_5$O$_7$SiNa: 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 °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 °C for 1 h followed by warming it to 0 °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: [α]$_D$ $−22.6$ (c 0.72 CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_4$O$_2$Si$_2$S (M + Na)$^+$: Calcd 517.2465; found 517.2424.
(S)-2-(tert-Butyldimethylsilyloxy)-4-(1-phenyl-1H-tetrazol-5-yithio)butan-1-ol (64):

To a solution of TBS ether 63 (810 mg, 1.63 mmol) in THF (10 mL) at 0 °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 °C). The mixture was stirred for 1 h at 0 °C and 5 h at room temperature. The reaction mixture was treated with saturated aqueous NaHCO₃ solution (40 mL) and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with sat. aq. CuSO₄, dried over MgSO₄ and concentrated. The crude product was purified by flash column chromatography (SiO₂, 25% ethyl acetate in hexanes) to yield the alcohol 64 (396 mg, 1.04 mmol, 64%) as an oil: [α]D −6.76 (c 4.36 CHCl₃); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 C₁₃H₁₉N₄O₂SiS (M − tBu)⁺: Calcd 323.0998; found 323.0995.

(S)-2-(tert-Butyldimethylsilyloxy)-4-(1-phenyl-1H-tetrazol-5-yithio)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. NaHCO₃ solution (2 mL). The layers were separated
and the aqueous layer was extracted with dichloromethane. Combined organic layers were dried
over MgSO₄ and concentrated. The crude product was purified by flash column chromatography
(SiO₂, 15% ethyl acetate in hexanes) to provide the aldehyde 3 (91 mg, 0.24 mmol, 86%) as an
oil: [α]D −13.1 (c 2.57 CHCl₃); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 C₁₇H₂₇N₄O₂SSi (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 CH₂Cl₂ (130 mL) were added 1,3-propanedithiol (2.60 mL, 37.5 mmol, 3 equiv) and
BF₃•Et₂O (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 NH₄Cl solution, dried over MgSO₄ 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%): [α]D −9.5 (c 0.4 CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C
NMR (75 MHz, CHCl₃) δ 69.1, 66.5, 43.8, 38.5, 30.3, 30.0, 25.8; IR (neat) cm⁻¹ 3386, 2931,
(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 MgSO4 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%): [α]D −28.3 (c 11.9 CHCl3); 1H NMR (300 MHz, CDCl3) 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); 13C NMR (75 MHz, CHCl3) 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 − CH₃)⁺ 407, (M − tBu)⁺ 365; HRMS for C₁₉H₂₂O₂Si₂S₂: 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 °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 °C and stirred for 1 h. The reaction mixture was poured into saturated aqueous NH₄Cl solution (20 mL) and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄, concentrated and the crude product was purified by flash column chromatography (SiO₂, 20% ethyl acetate in hexanes) to provide the product 69 (765 mg, 77%) as an oil: [α]D −1.0 (c 0.24 CHCl₃); ¹H NMR (600 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 – tBu)⁺ 559; HRMS for C₂₆H₄₇O₅Si₂S₂ (M – tBu)⁺: Calcd 559.2404; found 559.2411.
(2R,6S)-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/H₂O (4:1, 45 mL) was cooled to 0 °C followed by addition of 2.6-lutidine (2.9 mL) at once and Hg(ClO₄)₂•3H₂O (3.5 g) in portions. The reaction mixture was stirred at 0 °C for 1.5 h then filtered through a pad of celite and followed by a rinse with ethyl acetate. The filtrate was diluted with ethyl acetate and saturated aqueous NH₄Cl. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄, concentrated and the crude product was purified by flash column chromatography (SiO₂, 25% ethyl acetate in hexanes) to yield the ketone 70 (1.44 g, 85%) as an oil: [α]D −7.36 (c 0.53 CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (151 MHz, CDCl₃) 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 C₂₇H₅₀O₆NaSi₂ (M + Na)⁺: Calcd 549.3044; found 549.3051.
(2R,4S,6S)-1-(4-Methoxybenzoyloxy)-6,7-bis(tert-butyl(dimethyl)silyloxy)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 °C was added diethylmethoxyborane (1.0 M in THF, 4.4 mL, 4.4 mmol) and the reaction mixture was stirred at that temperature for 30 min. Sodium borohydride (181 mg, 4.8 mmol) was added in portions to the above reaction mixture and was stirred for 3 h at –78 °C. The reaction mixture was quenched with H₂O (25 mL) and diluted with Et₂O (100 mL). The layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, 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: [α]D −8.29 (c 1.52 CHCl₃); ¹H NMR (600 MHz, CHCl₃) 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); ¹³C NMR (151 MHz, CDCl₃) 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 C₂₇H₅₂O₆NaSi₂(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 °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 MgSO₄, 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: [α]D 0.41 (c 0.72 CHCl₃); ¹H NMR (601 MHz, CHCl₃) 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); ¹³C NMR (151 MHz, CHCl₃) 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 C₃₉H₈₀O₆Na₂Si₄(M + Na)⁺: Calcd 779.4930; found 551.4893.
(2R,4S,6S)-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 CH₂Cl₂/pH 7 buffer (19 mL/1 mL) was stirred at room temperature for 1 h followed by dilution with CH₂Cl₂ (20 mL) and saturated sodium bicarbonate solution (30 mL). The layers were separated and the aqueous layer was further extracted with CH₂Cl₂ (4 x 10 mL). The combined organic layers were dried over MgSO₄, concentrated and the crude product was purified by flash column chromatography to yield the alcohol 73 (890 mg, 96%) as an oil: [α]D −1.9 (c 0.63 CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CHCl₃) 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 C₃₁H₇₂O₅Si₄Na: Calcd 659.4355; found 659.4352.

(2S,4R,6R)-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
MgSO₄ and concentration provided the iodide 5 (380 mg, 96%) as an oil: [α]₀ = −3.2 (c 0.53 CHCl₃) \( ^1H \) NMR (500 MHz, CHCl₃) \( \delta \) 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, \( J = 3.9, 7.3, 5.4 \) Hz, 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,CDCl₃) \( \delta \) 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 C₂₇H₆₂O₄Si₄I (M − tBu)⁺: Calcd 689.2770; found 689.2789.

(R)-4-Benzyl-3-((2R,3S)-3-hydroxy-2-methylpent-4-enoyl)oxazolidin-2-one (75): Di-n-butyl boryltrifluoromethanesulfonate (1.0 M in CH₂Cl₂, 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 °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 °C and freshly distilled acrolein (1.5 g, 27.4 mmol) was added. After 1 h, the solution was warmed to 0 °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 °C followed by the addition of 80 mL of 2:1 methanol: 30% aqueous H₂O₂ 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. NaHCO₃ solution,
sat. aq. NaCl solution, dried over MgSO₄ and concentrated. The crude product was purified by flash column chromatography (SiO₂, 30% ethyl acetate in hexanes) to provide the product 75 (5.6 g, 78%) as white solid. $\left[\alpha\right]_D^\circ -51$ (c 0.94 CHCl₃); $^1$H NMR (601 MHz, CDCl₃) $\delta$ 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, CDCl₃) $\delta$ 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$_2$Si (M + Na)$^+$: Calcd 312.1212; found 312.1217.

(R)-4-Benzyl-3-((2R,3S)-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 °C. After 15 min, it was warmed to 0 °C and allowed to stir for 2 h. The reaction was quenched with water, organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over MgSO₄, 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: $\left[\alpha\right]_D^\circ -50.8$ (c 0.94 CHCl₃); $^1$H NMR (600 MHz, CDCl₃) $\delta$ 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 − tBu)$^+$ 346; HRMS for C$_{18}$H$_{24}$NO$_4$Si: Calcd 346.1475; found 346.1473.

(2S,3S)-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).
(2R,3S)-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 NaHCO₃ (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. NaHCO₃ solution (20 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over MgSO₄, concentrated and purified by flash column chromatography (SiO₂, 15% ethyl acetate in hexanes) to yield the aldehyde 78 (1.04 g, 88%) as an oil: [α]D −51.6 (c 0.5 CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 − CH₃)+ 213; HRMS for C₈H₁₅O₂Si (M − CH₃)+: Calcd 171.0841; found 171.0842.

((3S,4R)-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 °C were added MgBr₂•OEt₂ (2.3 g, 8.8 mmol) and propane-1,3-dithiol (0.72 g, 6.6 mmol). The reaction mixture was stirred at 0 °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 MgSO₄, and concentrated. The crude product was purified by flash column chromatography (SiO₂, 10% ethyl acetate in hexanes) to yield the dithiane 6 (1.25 g, 89%) as an oil: [α]D −10 (c 0.29 CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (76 MHz, CDCl₃) 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 − tBu)+ 261; HRMS for C₁₅H₃₀OSi₂: Calcd 318.1507; found 318.1497.

(2E,4E)-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 °C 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 white solid which was used in the next step without further purification: ¹H NMR (300 MHz, CDCl₃) δ 7.26-7.38 (m, 2 H), 6.14-6.26 (m, 2 H), 3.78 (s, 6 H); ¹³C NMR (75 MHz, CHCl₃) δ 166.4, 141.0, 128.1, 52.0; HRMS for C₈H₁₀O₄: Calcd 170.0579; found 170.0580.
(2E,4E)-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 °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 °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 MgSO₄ and concentrated to yield the diol 81 (2.05 g, 18.0 mmol, 95%) as white waxy solid: ¹H NMR (300 MHz, CD₃OD) 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); ¹³C NMR (75 MHz, CD₃OD) δ 133.5, 131.4, 63.2; EIMS (M)⁺ 114, (M – H₂O)⁺ 96; HRMS for C₆H₁₀O₂: Calcd 114.0681; found 114.0678.

(2E,4E)-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 MgSO₄, 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: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (76 MHz, CDCl₃)
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.

(2E,4E)-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 MnO₂ (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, CD₂Cl₂) 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); ¹³C NMR (75 MHz, CD₂Cl₂) 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 C₁₆H₁₉NO₄Na: Calcd 226.1389; found 226.1384.

(2E,4E,6E)-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 °C was added methyldiethylphosphonoacetate (857 mg, 4.10 mmol). The reaction mixture was stirred at room temperature for 20 min followed by cooling to −78 °C. The above reaction mixture was added via cannula to a solution of aldehyde 83 (839 mg, 3.71 mmol) in THF (15 mL) at −78 °C. The above reaction mixture was stirred at room temperature for 2 h followed by quenching the reaction with saturated aqueous NaHCO₃ solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaCl solution, dried over MgSO₄ and concentrated.
The crude product was purified by flash column chromatography (SiO₂, 5% ethyl acetate in hexanes) to yield the ester 84 (828 mg, 2.93 mmol, 79%): ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (76 MHz, CDCl₃) 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 C₁₅H₂₆O₃Si₁: Calcd 282.1651; found 282.1641.

\[
\text{MeOOC} \quad \text{OH}
\]

(2E,4E,6E)-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: ¹H NMR (601 MHz, CDCl₃) 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); ¹³C NMR (76 MHz, CDCl₃) δ 167.6, 144.6, 140.1, 137.3, 129.7, 129.6, 120.5, 62.7, 51.6.

\[
\text{MeOOC} \quad \text{Br}
\]

(2E,4E,6E)-Methyl 8-bromooccta-2,4,6-trienoate (86): To a solution of alcohol 85 (470 mg, 2.79 ml) in THF (10 mL) at −20 °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 °C for 40 min followed by 2 h at room temperature. Then the mixture was poured into saturated aqueous NaHCO₃ solution (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The
combined organic extracts were dried over MgSO₄ 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, CHCl₃) 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, CDCl₃) 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 C₉H₁₁O₂Br: Calcd 229.9942; found 229.9935.

![Diagram](image_url)

(2E,4E,6E)-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, CHCl₃) 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, CDCl₃) δ 167.5, 144.4, 139.8 ($J_{C,P} = 6$ Hz), 134.2 ($J_{C,P} = 16$ Hz), 129.6 ($J_{C,P} = 5$ Hz), 127.4 ($J_{C,P} = 13$ Hz), 120.9, 62.2 ($J_{C,P} = 7$ Hz), 51.6, 30.2 ($J_{C,P} = 139$ Hz), 16.1 ($J_{C,P} = 6$ Hz); EIMS (M⁺) 288; HRMS for C₁₃H₂₁O₅P: Calcd 288.1127; found 288.1133.
(4R,8S,E)-4,8-bis(tert-Butyldimethylsilyloxy)-10-(1-phenyl-1H-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 °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 °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 MgSO₄, 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: [α]D +4.3 (c 0.21 CHCl₃); ¹H NMR (600 MHz, CDCl₃) 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); ¹³C NMR (151 MHz, CDCl₃) 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 C₃₉H₆₉N₅O₆Si₂SNa: Calcd 814.4405; found 814.4401.
(4R,8S,E)-4,8-bis(tert-butyldimethylsilyloxy)-10-(1-phenyl-1H-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$_7$O$_{24}$(NH$_4$)$_6$$ullet$4H$_2$O in 2.5 mL of 30% w/v aq H$_2$O$_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, 11 24; HRMS (M + Na)$^+$ for C$_{39}$H$_{69}$N$_5$O$_8$Si$_2$SNa: Calcd 846.4303; found 846.4291.

(4R,6E,8S,10E,12S,14S,18R)-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 MgSO₄, 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: [α]D −1.5 (c 0.6 CHCl₃); ¹H NMR (600 MHz, CDCl₃) 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), 4.07 (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); ¹³C NMR (151 MHz, CDCl₃) 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 C₇₄H₁₄₈NO₁₂Si₆Na: Calcd 1433.9515, found 1433.9498.

(3R,5S,7R,9S,10E,13S,14E,17R)-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 NaHCO₃ (3 mL). Organic layer was separated and aqueous layer was extracted with DCM (3 mL). The combined organic layers were dried over MgSO₄ and concentrated. The crude product was purified by flash column chromatography to yield the alcohol 11 (42 mg, 89%) as an oil. ¹H NMR (600 MHz, CHCl₃) 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); ¹³C NMR (151 MHz, CHCl₃) 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.

(4R,6E,8S,10E,12S,14R,16R,18S)-4,8,12,14,16,18-hexakis(tert-butyldimethylsilyloxy)-20-(1-phenyl-1H-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 MgSO₄ 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 Mo₇O₂₄(NH₄)₆•4H₂O in 2.5 mL of 30% w/v aqueous H₂O₂). 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 MgSO₄ and concentrated. The crude product was purified by flash column chromatography (SiO₂, 10% ethyl acetate in hexanes) to yield the sulfone 13 (30 mg, 65%) as an oil. [α]D −24.1 (c 0.12 CHCl₃); ¹H NMR (600 MHz, CHCl₃) 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), 3.74-3.85 (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); ¹³C NMR (151 MHz, CHCl₃) 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, 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-((2R,4S,6S)-2,4,6,7-tetrakis(tert-Butyldimethylsilyloxy)heptyl)-2-((2R,3S)-3-(tert-butylidimethylsilyloxy)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 °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 °C for 2 h. The reaction mixture was warmed to 0 °C and quenched with saturated aqueous NH₄Cl. The aqueous layer was extracted with ethyl acetate followed by drying of the combined organic extracts over MgSO₄. Concentration and purification of the crude compound by flash column chromatography (SiO₂,
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, $J = 6.9$Hz, 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.

(3S,4R)-4-(2-((2R,4S,6S)-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 °C, followed by the addition of H$_2$O$_2$ 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$_6$S$_2$Si$_5$Na (M + Na): Calcd 977.5862; found 977.5826.

(3S,4R)-4-(2-((2R,4S,6S)-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: [α]$_D$ 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), 1.60-1.21 (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); 13C NMR (151 MHz, CDCl3) 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.

(3S,4R)-4-(2-((2R,4S,6S)-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 MgSO₄ and concentrated. Purification of the crude product by flash column chromatography (SiO₂, 15% ethyl acetate in hexanes) gave the alcohol 91 (16 mg, 39%) as an oil: [α]D 14.3 (c 0.3 CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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$_3$) $\delta$ 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$_7$NaSi$_4$S$_2$(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 $\mu$L, 0.20 mmol) in CH$_2$Cl$_2$ was added slowly a solution of DMSO (21 $\mu$L, 0.30 mmol) in CH$_2$Cl$_2$ at −78 °C. Then the reaction mixture was stirred under −78 °C for 20 min followed by slow addition of alcohol 91 (95mg, 0.10 mmol) in CH$_2$Cl$_2$. The reaction mixture was stirred for another 30 min. NEt$_3$ (70 $\mu$L, 0.50 mmol) was added and the mixture was stirred for 15 min and warmed to 0 °C 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$_3$) $\delta$ 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); 13C NMR (75 MHz, CDCl3) 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 C₄₇H₉₀O₇NaSi₄S₂(M + Na)⁺: Calcd 965.5103; found 965.5110.

(3S,4R)-3-(tert-butyldimethylsilyloxy)-4-(2-((2R,4S,6S,10R,12S,14R,16S,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 MgSO₄, 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: ¹H NMR (700 MHz, CDCl₃) 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); 13C NMR (175 MHz, CDCl₃) 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.

(5R,7S,9R,11S)-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 °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 °C for 3 h followed by warming it to 0 °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 MgSO₄ and concentrated. The crude product was purified by flash column chromatography (SiO₂, 5% ethyl acetate in hexanes) to yield the ether 39 (160 g, 88%) as an oil: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) δ
(3R,5S,7R,9S)-3,5,7,9-tetraakis(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 NaHCO₃. Organic layer was separated and aqueous layer was extracted with DCM. The combined organic layers were dried over MgSO₄ 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); ¹³C NMR (126 MHz, CDCl₃) 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-((3S,5R,7R,9S)-3,5,7,9-tetraakis(tert-butyldimethylsilyloxy)-10-(triethylsilyloxy)decylsulfonyl)-1H-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, 0.209 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 MgSO₄ and concentrated to yield the crude product. To the crude compound in dichloromethane was added m-CPBA (106 mg, 0.430 mmol) and NaHCO₃. The reaction mixture was stirred at room temperature for overnight, quenched with saturated NaHCO₃ and extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated. The crude product was purified by flash column chromatography (SiO₂, 10% ethyl acetate in hexanes) to yield the sulfone 104 (131 mg, 83%) as an oil: ¹H NMR (700 MHz, CDCl₃) 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); ¹³C NMR (175 MHz, CDCl₃) δ 153.4, 133.1, 131.4, 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.

(3S,4R)-3-(tert-butyldimethylsilyloxy)-4-(2-(2R,4S,6S,10R,12S,14R,16S,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 °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 °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 MgSO₄, 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: ¹H NMR (700 MHz, CDCl₃) 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, 1 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); ¹³C NMR (175 MHz, CDCl₃) 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, 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, −3.9, −4.1, −4.2, −4.4, −4.5, −4.6, −4.7, −5.3.

(3S,4R)-3-(tert-butyldimethylsilyloxy)-4-(2-((2R,4S,6S,10R,12S,14R,16S,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 MgSO₄ and concentrated. Purification of the crude product by flash column chromatography (SiO₂, 15% ethyl acetate in hexanes) gave the alcohol (1.6 mg, 10%) as an oil: $^1$H NMR (500 MHz, CDCl₃) 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, CDCl₃) 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, 42.0, 41.3, 41.0, 37.0, 26.2, 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.

(3S,4R)-3-(tert-butyldimethylsilyloxy)-4-(2-((2R,4S,6S,10R,12S,14R,16S,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 NaHCO₃ (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 NaHCO₃ solution. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over MgSO₄ 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: ¹H NMR (600 MHz, CDCl₃) 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).

(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 °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 °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 MgSO₄, 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: ¹H NMR (600 MHz, CDCl₃) 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 (4R,6E,8S,10E,12S,14R,16S,18R,20E,22S,24S,26R)-4,8,12,14,16,18,22,24,26-nonakis(tert-butyldimethylsilyloxy)-27-(2-((2R,3S)-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 °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 MgSO₄, 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: ¹H NMR (600 MHz, CDCl₃) 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).

\[
\text{(Boc)}_2N
\]

\[
\begin{array}{c}
\text{TBS} \\
\text{TBS} \\
\text{TBS} \\
\text{TBS} \\
\text{TBS} \\
\text{TBS} \\
\text{TBS} \\
\text{TBS} \\
\text{TBS} \\
\text{TBS} \\
\text{TBS} \\
\text{TBS} \\
\text{TBS} \\
\text{TBS} \\
\text{TBS} \\
\end{array}
\]

\[
\begin{array}{c}
\text{OTBS} \\
\text{OTBS} \\
\text{OTBS} \\
\text{OTBS} \\
\text{OTBS} \\
\text{OTBS} \\
\text{OTBS} \\
\text{OTBS} \\
\text{OTBS} \\
\text{OTBS} \\
\text{OTBS} \\
\text{OTBS} \\
\text{OTBS} \\
\text{OTBS} \\
\end{array}
\]

di-tert-butyl (4\text{R},6\text{E},8\text{S},10\text{E},12\text{S},14\text{R},16\text{S},18\text{R},20\text{E},22\text{S},24\text{S},26\text{R})-4,8,12,14,16,18,22,24,26-nonakis(tert-butyldimethylsilyloxy)-27-(2-((2\text{R},3\text{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 NaHCO₃ 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 NaHCO₃ solution. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over MgSO₄ 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.\n
\[
\delta 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
(2E,4E,6E,8E,11S,12R)-methyl 12-(2-((2R,4S,6S,7E,10R,12S,14S,16S,17E,20S,21E,24R)-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 °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 °C for 30 min and 0 °C for 30 min. The reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with ethyl acetate. The combined organic extracts were dried over MgSO₄ 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, CDCl₃) 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).
BIBLIOGRAPHY


12. Gudipati, V. *PhD Thesis*; University of Pittsburgh: USA, **2008**;

   http://etd.library.pitt.edu/ETD/available/etd-04212008-115104/.


34. Davidson, M. H.; McDonald, F. E. *Org. Lett.* 2004, 6, 1601.


APPENDIX

NMR spectra of compounds 87, 104, 105, 97, 93, 88, 106 and 20 are listed below.
87, 300MHz, CDCl3
$^{1}H$ NMR spectrum of [compound], recorded at 75 MHz in CDCl$_3$, showing resonances at various ppm values.
104, 700MHz, CDCl3
104, 175MHz, CDCl3

$\text{Ph}$

$\text{TBS TBS TBS TBS}$

$\text{TESO}$

$\text{N-N}$

$\text{O}$

$\text{O}$

$\text{O}$

$\text{O}$

$\text{S}$

$\text{O}$

$\text{O}$
105, 700MHz, CDCl₃
105, 175MHz, CDCl3

160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
97, 500MHz, CDCl3
$97, \text{ 75MHz, CDC}13$
88, 600MHz, CDCl3
106, 500MHz, CDCl3
20, 500MHz, CDC13