FLUOROUS MIXTURE SYNTHESIS AND STRUCTURE ASSIGNMENT OF PETROCORTYNE A AND ITS STEREOISOMERS

by

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Petrocortyne A was isolated from the marine sponge *Petrosia* sp. by Shin and Jung in 1998 and 1999, respectively. Both groups assigned the absolute configuration of the natural product, but the assignments do not consistent with the reported optical rotations. Using the fluorous mixture synthesis (FMS), we have synthesized four stereoisomers of petrocortyne A to determine the absolute configuration. In the FMS, the stereoisomeric starting materials were tagged with different fluorous TIPS groups and mixed together. The resulting mixture was taken through a series of steps to make the fluorous-tagged products, which were separated by fluorous HPLC followed by desilylation to provide four pure products.

Second-generation fluorous TIPS tags were synthesized and used in the FMS. Both Mosher and NMA ester methods were studied during the synthesis. The study showed that NMA ester method is superior to Mosher method for the assignment of absolute configuration of stereocenter C14.

Comparison of optical rotations of the four synthetic and two natural samples showed that both natural samples had the C3-S configuration. Comparison of spectra of Mosher derivatives of the synthetic and natural samples showed that both natural samples had the 3S,14S configuration. At the same time, the use of the Mosher rule has been validated for assigning the challenging C14 stereocenter of petrocortyne A. A “shortcut” variant in which only one Mosher ester is made was developed and can also be used for assignment of this stereocenter.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TABLE OF CONTENTS</td>
<td>V</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>VII</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>IX</td>
</tr>
<tr>
<td>LIST OF SCHEMES</td>
<td>X</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>XII</td>
</tr>
<tr>
<td>PREFACE</td>
<td>XIV</td>
</tr>
<tr>
<td>1.0 FLUOROUS MIXTURE SYNTHESIS AND STRUCTURE ASSIGNMENT OF PETROCORTYNE A AND ITS STEREOISOMERS</td>
<td>1</td>
</tr>
<tr>
<td>1.1 INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.1.1 Fluorous Mixture Synthesis (FMS)</td>
<td>1</td>
</tr>
<tr>
<td>1.1.2 Petrocortyne A</td>
<td>5</td>
</tr>
<tr>
<td>1.2 RESULTS AND DISCUSSION</td>
<td>10</td>
</tr>
<tr>
<td>1.2.1 Retrosynthetic analysis of petrocortyne A</td>
<td>10</td>
</tr>
<tr>
<td>1.2.2 Synthesis of C1–C13 fragment 1.4R</td>
<td>13</td>
</tr>
<tr>
<td>1.2.3 Synthesis of aldehyde 1.5 (C14–C21 fragment)</td>
<td>18</td>
</tr>
<tr>
<td>1.2.4 Model reaction towards the synthesis of fragment M-1.2</td>
<td>19</td>
</tr>
<tr>
<td>1.2.5 Revised synthetic route of C1–C21 fragment M-1.2</td>
<td>20</td>
</tr>
<tr>
<td>1.2.6 Synthesis of iodide M-1.29 (fragment C1–C11)</td>
<td>22</td>
</tr>
</tbody>
</table>
1.2.7 Synthesis of dialkynyl carbinols 1.57R and 1.57S.......................................... 28
1.2.8 Towards the synthesis of fragment M-1.2 with silyl ether rac-1.59 .......... 37
1.2.9 Towards the synthesis of fragment M-1.2 by using dianion strategy ....... 39
1.2.10 Synthesis of the second-generation TIPS$^F$ tags and new iodide M-1.68 .. 42
1.2.11 Unexpected difficulty of removal of PMB group in compound 1.65....... 43
1.2.12 Synthesis of middle fragment MTM ethers 1.74S and 1.74R .............. 45
1.2.13 Successful synthesis of fragment M-1.2 ...................................................... 46
1.2.14 Synthesis of C22–C46 fragment 1.3 ............................................................. 49
1.2.15 Synthesis of four isomers of petrocortyne A ........................................... 50
1.2.16 Structure assignment of petrocortyne A ............................................... 59
1.2.17 “Shortcut” Mosher Ester Method$^50$ .......................................................... 64
1.3 CONCLUSIONS ................................................................................................ 66
1.4 EXPERIMENTAL ........................................................................................... 67
1.5 REFERENCES ................................................................................................. 141
APPENDIX ......................................................................................................... 146
LIST OF TABLES

Table 1.1. $\Delta \delta (\delta_{1.19RS} - \delta_{1.19RR})$ values (ppm) obtained from the MTPA esters of 1.19RS and 1.19RR ........................................................................................................................................... 17

Table 1.2. $\Delta \delta (\delta_{1.39SS} - \delta_{1.39SR})$ values (ppm) obtained from the MTPA esters of 1.39SS and 1.39SR ........................................................................................................................................... 25

Table 1.3. $\Delta \delta (\delta_{1.40RS} - \delta_{1.40SS})$ values (ppm) obtained from the (S)-2-NMA esters of 1.40RS and 1.40SS ........................................................................................................................................... 27

Table 1.4. Yields and ees of reactions of phenylacetylene 1.43 with 2-octynal 1.27 to give propargyl alcohol 1.44S ........................................................................................................................................... 30

Table 1.5. Enantioselective addition of alkynes and aldehyde 1.27 ........................................................................................................................................... 31

Table 1.6. $\Delta \delta (\delta_{1.55RS} - \delta_{1.55SS})$ values (ppm) obtained from the MTPA esters of 1.55RS and 1.55RR ........................................................................................................................................... 36

Table 1.7. $\Delta \delta (\delta_{1.56SS} - \delta_{1.56RS})$ values (ppm) obtained from the MTPA esters of 1.56SS and 1.56RS ........................................................................................................................................... 36

Table 1.8. $^1H$ NMR data of 3R,14R-petrocortyne A, 1.1SS/SR and 1.1Mix (CDCl$_3$) ........................................................................................................................................... 55

Table 1.9. $^{13}C$ NMR data of 3R,14R-petrocortyne A, 1.1SS/SR and 1.1Mix (CD$_3$Cl) ........................................................................................................................................... 56

Table 1.10. $^1H$ NMR data of 3S,14S-petrocortyne A and 1.1SS/SR (CD$_3$OD) ........................................................................................................................................... 57

Table 1.11. $^{13}C$ NMR data of 3S,14S-petrocortyne A and 1.1SS/SR (CD$_3$OD) ........................................................................................................................................... 58
Table 1.12. $^1$H NMR data of reported and synthetic Mosher ester derivatives ......................... 63

Table 1.13. $\Delta \delta_{S\text{-MTPA ester} - R\text{-MTPA ester}}$ value (ppm) of reported and synthetic Mosher ester derivatives ........................................................................................................................................................................... 64

Table 1.14. Selective chemical shifts in Mosher esters and application of the advanced and shortcut Mosher methods ........................................................................................................................................................................................................... 66
LIST OF FIGURES

Figure 1.1. Schematic diagram of the concept of FMS ................................................................. 3
Figure 1.2. Representative polyacetylenes isolated from marine sponge Petrosia sp............... 6
Figure 1.3. Structure of petrocortyne A ......................................................................................... 6
Figure 1.4. Partial structures of petrocortyne A ............................................................................. 8
Figure 1.5. The structure of TIPS\textsuperscript{F} groups used in the following synthesis .................. 10
Figure 1.6. (a) An ideal conformation of an (S)-MTPA ester of a secondary alcohol. (b) Advanced Mosher model for assigning the absolute configuration of a secondary alcohol from $\Delta \delta_H$ values of Mosher ester.$^{20}$ ....................................................................................................... 16
Figure 1.7. Representative HPLC demixing chromatogram........................................................ 52
Figure 1.8. Four isomer of petrocortyne A with optical rotations ............................................... 53
Figure 1.9. $^1$H NMR spectra of mixture 1.1Mix and four pure stereoisomers of 1.1 (CDCl\textsubscript{3}). 54
Figure 1.10. Expansions of the H11/H17 region of the $^1$H NMR spectra of 1.1SS/SR (top) Mosher esters of 1.1SS/SR (middle and bottom). ....................................................................................... 61
Figure 1.11. Expansions of portions of the TOCSY spectra of Mosher esters 1.91SS/SSR .... 62
Figure 1.12. Expansions of portions of the TOCSY spectra of Mosher esters 1.92SRS/SRR .... 62
LIST OF SCHEMES

Scheme 1.1. Representative natural products synthesized by FMS ............................................... 4
Scheme 1.2. The retrosynthesis of petrocortyne A 1.1 ..................................................................... 11
Scheme 1.3. The retrosynthesis of M-1.4 .................................................................................... 12
Scheme 1.4. The retrosynthesis of aldehyde 1.5 ........................................................................... 12
Scheme 1.5. The retrosynthesis of triphenylphosphonium salt 1.3 .................................................. 13
Scheme 1.6. Synthesis of propargylic alcohol 1.18R .................................................................. 14
Scheme 1.7. Midland’s transition state model for the asymmetric reduction of ketone 1.6 with (R)-alpine borane .......................................................................................................................... 15
Scheme 1.8. Synthesis of Mosher esters 1.19RS and 1.19RR .......................................................... 17
Scheme 1.9. Synthesis of fluorous tagged ether 1.4R ................................................................. 18
Scheme 1.10. Synthesis of aldehyde 1.5 ..................................................................................... 19
Scheme 1.11. Carreira’s approach to synthesize dialkynyl methanol 1.25 ..................................... 19
Scheme 1.12. Unsuccessful model reaction between 1-octyne 1.26 with 2-octynal 1.27 ............... 20
Scheme 1.13. Revised retrosynthesis of fragment M-1.2 .............................................................. 21
Scheme 1.14. The retrosynthesis of iodide M-1.29 ....................................................................... 21
Scheme 1.15. The retrosynthesis of fragment M-1.30 ................................................................. 22
Scheme 1.16. Synthesis of ketone 1.31 .......................................................................................... 23
Scheme 1.17. Synthesis of alcohols 1.37R/S by CBS asymmetrical reduction ......................... 23
| Scheme 1.18. | Corey's transition state model for the CBS asymmetric reduction of ketone 1.3124 |
| Scheme 1.20. | Synthesis of (S)-2-NMA esters 1.40SS and 1.40RS ............................................. 26 |
| Scheme 1.21. | Synthesis of iodide M-1.29 ................................................................................... 28 |
| Scheme 1.22. | Proposed synthetic route for 1.57R/S ................................................................. 29 |
| Scheme 1.23. | Enantioselective synthesis of propargyl alcohols reported by Pu and coworkers. 29 |
| Scheme 1.24. | Synthesis of racemic alcohol rac-1.53 ................................................................. 32 |
| Scheme 1.25. | Unsuccessful fragmentation reaction of alcohol rac-1.53 ........................................ 33 |
| Scheme 1.26. | Synthesis of alcohols 1.54R and 1.54S ................................................................. 34 |
| Scheme 1.27. | Synthesis terminal alkynes 1.57S and 1.57R ........................................................ 37 |
| Scheme 1.28. | Synthesis terminal alkyne rac-1.59 ........................................................................ 38 |
| Scheme 1.29. | Model coupling reaction of iodide 1.58 and alkyne rac-1.59 ..................................... 39 |
| Scheme 1.30. | Model reaction of iodide 1.58 and alkyne rac-1.57 ................................................ 40 |
| Scheme 1.31. | Coupling reaction of iodide 1.29S and dialkynol rac-1.57 ....................................... 41 |
| Scheme 1.32. | Coupling reaction of iodide M-1.29 and dialkynol 1.57S ......................................... 42 |
| Scheme 1.33. | Synthesis of the second-generation TIPSf 1.69 and 1.70 ........................................ 42 |
| Scheme 1.34. | Synthesis of new iodide M-1.68 ............................................................................ 43 |
| Scheme 1.35. | Unsuccessful removal of PMB group ..................................................................... 44 |
| Scheme 1.36. | Synthesis of MTM ether 1.74S and 1.74R ............................................................... 46 |
| Scheme 1.37. | Synthesis of fragment M-1.2 ................................................................................. 48 |
| Scheme 1.38. | Synthesis of triphenylphosphonium salt 1.3 ......................................................... 50 |
| Scheme 1.39. | Synthesis of petrocortyne A 1.1 ............................................................................. 52 |
| Scheme 1.40. | Synthesis of Mosher esters of 1.1SS and 1.1SR ..................................................... 60 |
LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BINOL</td>
<td>1,1′-bi-2-naphthol</td>
</tr>
<tr>
<td>‘Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>CAN</td>
<td>ceric ammonium nitrate</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>DCC</td>
<td>1,3-dicyclohexylcarbodiimide</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>DIBAL-H</td>
<td>diisobutyl aluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylamino pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess–Martin periodinane</td>
</tr>
<tr>
<td>DMPS</td>
<td>dimethylphenylsilyl</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>El</td>
<td>electron ionization</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalents</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
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<tr>
<td>FMS</td>
<td>fluorous mixture synthesis</td>
</tr>
<tr>
<td>HETCOR</td>
<td>heteronuclear correlation</td>
</tr>
<tr>
<td>HGF</td>
<td>hepatocyte growth factor</td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond coherence</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HMQC</td>
<td>heteronuclear multiple quantum coherence</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
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<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>INF</td>
<td>interferon</td>
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<tr>
<td>IR</td>
<td>infrared spectrometry</td>
</tr>
<tr>
<td>LPS</td>
<td>lipopolysaccharide</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>MTM</td>
<td>methylthiomethyl</td>
</tr>
<tr>
<td>MTPA</td>
<td>α-methoxytrifluorophenylacetic acid</td>
</tr>
<tr>
<td>2-NMA</td>
<td>α-methoxy-2-naphthylacetic acid</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMA</td>
<td>phorbol 12-myristate 12-acetate</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>'Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-toluenesulfonic acid</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SF</td>
<td>scatter factor</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetrabutylammonium iodide</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyltrimethylsilyl</td>
</tr>
<tr>
<td>TOCSY</td>
<td>total correlation spectroscopy</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TfO</td>
<td>triflate</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
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</tbody>
</table>
I don’t think I would be proud of my degree if I had not worked for a person like Professor Dennis P. Curran, my research advisor. I thank him for his steadfast support, encouragement, and patience. I appreciate all his efforts on my behalf, both in the realm of my graduate studies and in preparation for my life in the future.

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1.0 FLUOROUS MIXTURE SYNTHESIS AND STRUCTURE ASSIGNMENT OF PETROCORTYNE A AND ITS STEREOISOMERS

1.1 INTRODUCTION

1.1.1 Fluorous Mixture Synthesis (FMS)

Natural products are chemical compounds isolated from living organisms, and they usually have pharmacological and biological activities. Natural products play an important role in drug discovery and drug design.\(^1\) Recent reviews showed that natural products and their derivatives are significant sources of new drugs.\(^2,3\) The syntheses of libraries of biologically active natural product stereoisomers are important because they allow the unambiguous structural assignments of natural products whose stereoisomers may have similar or even identical spectra. Establishing the correct stereostructure is a prerequisite for the study of structure-activity relationships (SAR) in drug discovery. Furthermore, the syntheses of stereoisomer libraries provide samples for biological tests that help establish an SAR.

As the complexity of isolated natural products increases, the structure assignment, especially the stereochemistry assignment, becomes more challenging. Total synthesis of all of the stereoisomers can provide enough samples that can be used to prove or disprove the structure assignment by comparison of various physical and spectral data of a natural product with
synthetic products. The recent proof of structure of murisolin by its comparison with a library of its stereoisomers shows the power of having multiple isomers for comparison. The recent proof of structure of murisolin by its comparison with a library of its stereoisomers shows the power of having multiple isomers for comparison.4

Synthetic chemists have always constructed compounds one at a time. It is time-consuming work to synthesize multiple stereoisomers of natural products by traditional solution phase synthesis. For instance, in order to elucidate the structure of khafrefungin, Kobayashi and coworkers had to synthesize five stereoisomers of khafrefungin one by one.5

The situation of synthesizing one stereoisomer at a time began to change in the 1990s as the revolution of solid-phase and combinatorial chemistry spread through synthetic laboratories.6 Recently, Waldmann and coworkers reported the total syntheses of all isomers of cryptocarya diacetate on a polymeric carrier.7 Takahashi and coworkers also reported the combinatorial synthesis of a macrosphelide library on polymer support.8 However, compared to conventional solution-phase methods, solid-phase synthesis sacrifices the reactivity of the supported substrates because of unfavorable kinetics of heterogeneous reaction.9 To date, the scope of reactions developed for solid phase synthesis is still limited.

Fluorous mixture synthesis (FMS), introduced in 2001, is the first solution phase technique that captures the efficiency inherent in mixing compounds yet still allows the reliable separation of the mixtures to provide individual pure target products in the end.10 A typical fluorous mixture synthesis consists of four stages: premix, mixture synthesis, demix, and detag, as shown in Figure 1.1.

During the premix stage, a set of isomeric substrates (S1–Sn) is prepared individually by traditional methods. The configuration of each isomer is encoded with a corresponding set of homologous fluorous tags (F1–Fn) with increasing fluorine content. The fluorous-tagged precursors (S1F1–SnFn) are mixed together (M1) and taken through a multi-step synthesis
(mixture stage) in one-pot reactions or split-parallel fashion. At the end of synthesis, the final mixture (M2) is demixed based on fluorine content by preparative fluorous HPLC. Molecules (F₁P₁–FₙPₙ) with longer fluorous chains have longer retention time on the fluorous HPLC column. The order of elucidation of products can be predicted in advance by the original tag/substrate pairs (SF) based on the fluorine content. In the final stage, detagging is conducted to release the final products (P₁–Pₙ).

![Figure 1.1. Schematic diagram of the concept of FMS](image)

Based on the nature of target, fluorous mixture synthesis has been applied to three different categories of compounds: enantiomers, diastereomers, and analogs (Scheme 1.1). When both enantiomers of a compound are needed, two enantiomeric precursors are tagged with different tags to make quasienantiomers, which are mixed together. The resulting mixture is conducted in the whole synthesis. After the steps of demixing and detagging, the two target enantiomers are obtained as pure compounds. The synthesis of both mappicine enantiomers highlights this application, which is called quasi-racemic synthesis (Scheme 1.1a). The synthesis of diastereomers of natural product is sometimes necessary for elucidation of structure. Fluorous mixture synthesis is a powerful tool to synthesize some or all diastereomers for
comparisons with an isolated natural product. This approach was taken in the synthesis and structure assignment of lagunapyrone B \(^\text{12}\) (Scheme 1.1b) and murisolin. \(^\text{4,13}\) Fluorous mixture synthesis can also be used to generate a library of analogs of a natural product with varying substituents. Recently, the syntheses of a 560-member library of mappicine analogs (Scheme 1.1c) has been reported by Zhang and coworkers. \(^\text{14}\)

**Scheme 1.1. Representative natural products synthesized by FMS**

(a) FMS of enantiomers

\[
\begin{align*}
\text{NOMe} & \quad \text{TMS} \\
\text{Et} & \quad \text{ORf}
\end{align*}
\]

one mixture of 2 quasienantiomers

1. Fluorous HPLC
2. TBAF

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{RfO} \\
\text{Et} & 
\end{align*}
\]

one mixture of 2 quasienantiomers

Mappicine two enantiopure isomers

(b) FMS of diasteromers

\[
\begin{align*}
\text{C}_3\text{H}_7 & \quad \text{O} \\
\text{OH} & \quad \text{Ac}
\end{align*}
\]

RS/SSR isomers

M is a metal suitable for cross-coupling

\[
\begin{align*}
\text{Rf} & \quad \text{ORf} \\
\text{R} & \quad \text{ORf}
\end{align*}
\]

one mixture of 2 SSR/RRS isomers

1. demixing
2. detagging

Lagunapyrone B (6R, 7S, 19S, 20S, 21R) four pure stereoisomers

(c) FMS of analogs of natural product

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{R}^3 & 
\end{align*}
\]

one mixture of 7 analogs

eight mixtures of 7 analogs

eighty mixtures of 7 analogs

1. demixing
2. detagging

Mappicine 560 analogs

\(\text{Rf} = \text{fluorous tag}\)
FMS has been proved to be a powerful tool to synthesize natural products, their isomers, and libraries. We now want to solve more challenging problem of stereocenter assignment for natural products with local symmetry.

1.1.2 Petrocortyne A

Many natural products with unique molecular architectures have been isolated from marine sponges. These natural products often display remarkable biological activities, making them lead structures for the development of new chemotherapeutic agents. Polyacetylenes have been revealed as abundant sources of marine sponge metabolites, which possess great novel and diverse long chain and functionalities. More than 50 biologically active polyacetylenes characterized by unbranched long alkyl chains were isolated from the marine sponge Petrosia sp. Borrowing from the name of the sponge, the compounds were named like petrocortynes, petroformynes, and petrosiacetylenes. One example of each type of substrate is shown in Figure 1.2. Most of these compounds modulate various biological activities such as anti-inflammatory, antimicrobial, antitumor, antiviral, and antifungal effects. The compounds typically consist of a linear carbon skeleton of 30 to 47 carbons interspersed with functional groups including alkynes, E- and Z-alkenes, and hydroxyl groups.
Figure 1.2. Representative polyacetylenes isolated from marine sponge *Petrosia* sp.

Petrocortyne A, a novel lipid compound, was first isolated from the marine sponge *Petrosia* sp. collected in 1994 at Komun Island, Korea by Shin and coworkers in 1998. Approximately 70 mg of a linear tetraacetylene assigned as (3R,14R)-petrocortyne A 1.1RR (Figure 1.3) was isolated. The compound exhibited a modest inhibitory activity against the enzyme phospholipase A2 (PLA2) (31% at 50 μg/mL).

In 1999, Jung and coworkers reported another petrocortyne A, assigned as (3S,14S)-petrocortyne A 1.1SS (Figure 1.3), isolated from sponge *Petrosia* sp. collected in 1995 again off...
Jung’s petrocortyne 1.1SS inhibited the production of tumor necrosis factor (TNF-α) from lipopolysaccharide (LPS)-stimulated murine macrophages RAW264.7 in a concentration-dependent manner with an IC₅₀ of 2.35 μM. Similarly, it inhibited the production of TNF-α from phorbol 12-myristate 13-acetate (PMA)/LPS treated U937 cells at the transcriptional level (46% inhibition at 5 μM). (3S,14S)-Petrocortyne A 1.1SS also blocked NO release from either LPS- or interferon (INF)-γ-treated RAW267.4 cells. It selectively blocked the expression of hepatocyte growth factor/scatter factor (HGF/SF), which plays an important role in regulating infiltration of immune or inflammatory cells into inflamed tissue. Compound 1.1SS also induced U937 homotypic aggregation. Since homotypic aggregation is considered a potential tool for negative modulation of inflammatory cell migration, the pro-aggregative effect of this compound may reinforce its anti-inflammatory function. Therefore, (3S,14S)-petrocortyne A 1.1SS inhibits cellular inflammatory processes and immune cell migration to inflamed tissue, which makes it a potential anti-inflammatory drug.

The constitutions of these two samples 1.1RR and 1.1SS were assigned by a battery of spectroscopic methods. By the combination of HRMS, IR, ¹H NMR, and ¹³C NMR analysis, petrocortyne A 1.1RR or 1.1SS consists of four isolated double bonds and a long alkyl chain without methyl groups or other branches. Several partial structures (Figure 1.4) were identified based on the study of 2D NMR spectra (COSY, HETCOR, HMQC, and HMBC). The COSY data revealed that none of the partial structures was directly connected to another, so the partial structures were considered to be linked by linear alkyl chains. The lengths of alkyl chains and connectivities of partial structures were determined by the combination of chemical degradation, detailed NMR analysis with the addition of Eu(fod)₃, a lanthanide-induced shift reagent, and
EIMS analysis. The geometry of four isolated double bonds was determined by NMR spectroscopy. The double bonds at C4 and C43 were assigned as $E$ and $Z$, based on the coupling constants between the olefinic protons. However, the geometry of those at C21 and C27 were unable to be determined by coupling constants, because signals of the olefinic protons overlapped. However, the geometry of both double bonds was assigned as $Z$ on the basis of chemical shift of allylic carbons in the $^{13}$C NMR spectrum.\textsuperscript{19}

![Figure 1.4. Partial structures of petrocortyne A](image)

The absolute configurations of the two remote stereocenters at C3 and C14 were assigned by the advanced Mosher ester method.\textsuperscript{20} The configurations were assigned as $3R,14R$ for Shin’s petrocortyne A \textbf{1.1RR}, and $3S,14S$ for Jung’s petrocortyne A \textbf{1.1SS}, respectively. Thus, these two natural products are enantiomers. However, the values of optical rotations of petrocortyne A \textbf{1.1RR} (+ 6.4, MeOH, $c = 0.25$) and ($3S,14S$)-petrocortyne A \textbf{1.1SS} (+ 10.8, MeOH, $c = 1.9$) do not meet the expectation that enantiomers should give optical rotations with opposite sign and equal magnitude. Accordingly, the assignment of the absolute configuration of one or even both of these two natural products may be incorrect.

In the murisolin family of acetogenins with very remote stereocenters, we have found the diastereomers exhibit substantially identical spectra.\textsuperscript{4} Similarly, petrocortynes also have remote stereocenters. Would the ($3S,14S$)/($3R,14R$) pair of enantiomers ($\textit{syn}$ diastereomer) exhibit the same spectra as the ($3R,14S$)/($3S,14R$) pair ($\textit{anti}$ diastereomer)? If the spectra are the same, then how can the diastereomers be differentiated? The configuration of the stereocenter at C3 can be
assigned by making a pair of diastereomeric Mosher esters and analyzing their $^1$H NMR spectra by the advanced Mosher method. But, is the application of the advanced Mosher analysis a reliable tactic for assigning the configuration of the stereocenter at C14 of petrocortyne A? This center is difficult to assign because there is a local symmetry plane at C14 and because there are no protons directly attached to the carbons adjacent to the stereocenter.

Despite the novel skeleton and uncertain configuration, there have not been any reports of synthetic efforts toward the petrocortynes and similar compounds. Our goals of this project are to prepare all four individual pure stereoisomers of petrocortyne A by fluorous mixture synthesis, to compare the data of synthetic and natural samples and their Mosher derivatives, and thereby to prove the assignment of absolute configuration of these natural products.
1.2 RESULTS AND DISCUSSION

1.2.1 Retrosynthetic analysis of petrocortyne A

In the fluorous mixture synthesis, diisopropyl(perfluoroalkylethyl)silyl groups (TIPS$^F$) and triisopropylsilyl group are used as tags because they are stable under most reaction conditions and easily deprotected.\textsuperscript{12,21} TIPS$^F$ group is not a “true” TIPS group because it has a $1^\circ$-alkyl(diisopropyl)silyl group while TIPS group has a triisopropylsilyl group. In the following schemes, TIPS$^{Fn}$ is used as an abbreviation of fluorous TIPS group; $n$ is the number of certain fluorine content (the regular TIPS group is displayed as TIPS$^{F0}$). The structures of TIPS$^{F0}$ group and two fluorous tags, $C_3F_7(CH_2)_2(\text{iPr})_2Si$– (TIPS$^{F7}$) and $C_4F_9(CH_2)_2(\text{iPr})_2Si$– (TIPS$^{F9}$), used in the following synthesis are shown in Figure 1.5. Compounds bearing different TIPS$^F$ groups will be mixed, and in the numbering the following text, all samples bearing the “M” prefix are mixtures of fluorous-tagged quasiisomers.

\[ \text{Si} \quad \text{Rf} \]
\[ \text{Si} \quad \text{Si} \]

\begin{align*}
\text{TIPS}^{F7} \quad (\text{Rf} = \text{C}_3\text{F}_7): & \text{diisopropyl(3,3,4,4,5,5,5-heptafluoropentyl)silyl} \\
\text{TIPS}^{F9} \quad (\text{Rf} = \text{C}_4\text{F}_9): & \text{diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyl}
\end{align*}

\text{Figure 1.5. The structure of TIPS}^F \text{ groups used in the following synthesis}
The retrosynthesis and tagging strategy of FMS to assemble the backbone of the target structure 1.1 are shown in Scheme 1.2. Petrocortyne A 1.1 can be constructed from the two large fragments, aldehyde M-1.2 and triphenylphosphonium salt 1.3, by Wittig reaction followed by demixing over fluorous HPLC and desilylation. Because fragment M-1.2 has two stereocenters, we planned to make M-1.2 as quasiisomer mixture of four stereoisomers with configurations encoded by fluorous tags in the protecting group (TIPS\textsuperscript{10}). Fragment M-1.2 can be assembled from alkyne M-1.4 and aldehyde 1.5 by asymmetric alkynylation under Carreira’s condition.\textsuperscript{23}

As shown in Scheme 1.3, both enantiomers of fragment M-1.4 at C3 can be formed by enantioselective reduction of α,β-unsaturated ketone 1.6 using Alpine–Borane,\textsuperscript{24} followed by silylation with different fluorous tags. Ketone 1.6 can be constructed from aldehyde 1.7 by alkynylation followed by oxidation. Aldehyde 1.7 can be synthesized from aldehyde 1.8 by
Wittig olefination$^{22}$ followed by reduction of ester to alcohol and oxidation of alcohol to corresponding aldehyde. Finally, we plan to prepare aldehyde 1.8 from commercially available 3-nonyl-1-ol 1.9 by a zipper reaction,$^{25}$ followed by Swern oxidation.$^{26}$

![Scheme 1.3. The retrosynthesis of M-1.4](image)

Aldehyde 1.5 can be constructed from the reaction between DMF and alkyne 1.10, which can be derived from commercially available 3-heptyl-1-ol 1.11 by another zipper reaction followed by PMB protection (Scheme 1.4).

![Scheme 1.4. The retrosynthesis of aldehyde 1.5](image)

The synthesis of triphenylphosphonium salt 1.3 can start from a smaller triphenylphosphonium salt 1.12 and aldehyde 1.13 by Wittig reaction followed by deprotection, halogenation, and reaction with triphenylphosphine (Scheme 3). Aldehyde 1.13 can be obtained from a Sonagashira coupling reaction$^{27}$ between commercially available tert-
butyldimethylsilylacetylene and vinyl bromide 1.14, which will be synthesized from 16-hydroxyhexadecanoic acid 1.15.

Scheme 1.5. The retrosynthesis of triphenylphosphonium salt 1.3

\[
\begin{align*}
\text{PMBO} & \rightarrow \text{Ph}_3\text{P} \\
1.12 & + 1.13 \\
\text{MeO} & \rightarrow \text{HO} \\
1.14 & \rightarrow 1.15 \text{ 16-hydroxyhexadecanoic acid}
\end{align*}
\]

1.2.2 Synthesis of C1–C13 fragment 1.4R

Prior to starting the FMS of petrocortyne A, the partial synthesis of one isomer was performed. The first aim for this synthesis was to validate that every step could work for FMS. The second aim was to provide some fragments of petrocortynes with known configurations to validate that the Mosher method is a reliable tactic for assigning the absolute configurations at C3 and C14 of petrocortynes.

The work began with the preparation of propargylic alcohol 1.18R (C1–C13), as summarized in Scheme 1.6. Internal alkyne 1.9 was first subjected to an acetylene zipper reaction with sodium hydride in warm ethylene diamine to provide a terminal alkyne\(^{28}\) in 68% yield. Subsequent Swern oxidation of the primary alcohol of the above alkynol afforded aldehyde 1.8\(^{29}\) in 90% yield. This intermediate is unstable toward oxygen and can only be stored for prolonged periods when kept under argon. Aldehyde 1.8 was reacted with commercially

13
available Wittig reagent 1.16 to give (E)-α,β-unsaturated ester 1.17 as a single isomer in 80% isolated yield after flash chromatography. Reduction of ester 1.17 with DIBAL-H cleanly provided the alcohol in 87% yield. This was oxidized to α,β-unsaturated aldehyde 1.7 in 90% yield by Swern oxidation.

Trimethylsilylacetylene was treated with n-BuLi to generate ((trimethylsilyl)ethynyl)lithium, which was reacted with aldehyde 1.7 to give the racemic alcohol in 88% yield. Swern oxidation of this alcohol provided ketone 1.6, which was isolated as yellow oil in 88% yield after rapid chromatographic purification. This ketone could only be stored for a short time; hence, it was used as quickly as possible. Ketone 1.6 was treated with neat (R)-Alpine–Borane at room temperature overnight to generate (R)-propargylic alcohol 1.18R in 58% yield. The ee of compound 1.18R was determined by 19F NMR analysis of the crude Mosher esters (see following text for synthesis). Each crude Mosher ester exhibited three peaks in its 19F NMR spectrum, one from excess MTPA acid (α-methoxytrifluorophenylacetic acid) (−71.0
ppm), and the others from two diastereomeric MTPA esters of −72.1 (major peak for \textbf{1.19RR} and minor peak for \textbf{1.19RS}) and −72.3 ppm (minor peak for \textbf{1.19RR} and major peak in \textbf{1.19RS}). Integration of the latter pair of peaks provided the ee of alcohol \textbf{1.18R} as 93%.

The absolute configuration of major compound \textbf{1.18R} could be predicted based on the model provided by Midland and coworkers (Scheme 1.7).\textsuperscript{30} They proposed that the high enantioselectivity in this reduction originated from a cyclic, boat-like transition state due to the preferential \textit{syn}-1,3-steric interaction between 2-methyl group of Alpine-Borane and the smaller group of the approaching ketone. In the case of reduction of ketone \textbf{1.6}, the acetylene acts as the smaller group, and the alcohol \textbf{1.18R} is predicted to form through the favored transition state. The configuration of compound \textbf{1.18R} can be confidently assigned from Midland model, so alcohol \textbf{1.18R} is a suitable substrate to validate the advanced Mosher method.

\textbf{Scheme 1.7. Midland’s transition state model for the asymmetric reduction of ketone 1.6 with (R)-alpine borane}
The advanced Mosher method was developed by Kusumi and Kakisawa in 1991. They proposed that the carbinyl proton, ester carbonyl and trifluoromethyl groups of MTPA moiety lie in the same plane. This idealized conformation is depicted in Figure 1.6a. Due to the anisotropic effect of the benzene ring, the resonances of protons H^A, H^B, H^C of the (R)-MTPA ester should appear upfield relative to those of the (S)-MTPA ester. The reverse should be true for protons H^X, H^Y, H^Z. Therefore, for the differences in chemical shifts as defined $\Delta\delta_H = \delta_S - \delta_R$, protons on the right side of the MTPA plane (Figure 1.6b) will have positive values ($\Delta\delta_H > 0$) and protons on the left side of the MTPA plane will have negative values ($\Delta\delta_H < 0$). The magnitude of $\Delta\delta_H$ will be proportional to the distance of the protons from MTPA moiety, with closer protons exhibit bigger $\Delta\delta_H$. Consequently, based on this model, the absolute configuration of the compound can be assigned.

Figure 1.6. (a) An ideal conformation of an (S)-MTPA ester of a secondary alcohol. (b) Advanced Mosher model for assigning the absolute configuration of a secondary alcohol from $\Delta\delta_H$ values of Mosher ester.

The Mosher esters of alcohol 1.18R were then synthesized by treatment with (S)- and (R)-MTPA acid in CH$_2$Cl$_2$ in the presence of DCC and DMAP (Scheme 1.8). After removing the
solid byproducts by filtration, the corresponding crude esters 1.19RS and 1.19RR were obtained by solvent evaporation. These crude esters were used for assignment of absolute configuration of 1.18R without further purification. Relevant chemical shifts of protons of esters 1.19RS, 1.19RR and their differences are listed in Table 1.1 in parts per million (ppm). The remote protons (H1’) of the TMS group on one side of the stereocenter exhibited a small negative Δδ, while the protons H4, H5 and H6 on the other side exhibited a substantial positive Δδ. According to the advanced Mosher rule, the absolute configuration of C3 is R, as expected from the Midland transition state model.

![Scheme 1.8. Synthesis of Mosher esters 1.19RS and 1.19RR](image)

<table>
<thead>
<tr>
<th>Table 1.1. Δδ (δ_{1.19RS} − δ_{1.19RR}) values (ppm) obtained from the MTPA esters of 1.19RS and 1.19RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>proton (H)</td>
</tr>
<tr>
<td>δ_{1.19RS}</td>
</tr>
<tr>
<td>δ_{1.19RR}</td>
</tr>
<tr>
<td>Δδ (δ_{1.19RS} − δ_{1.19RR})</td>
</tr>
</tbody>
</table>

Alcohol 1.18R was then tagged with fluorous tag 1.21 bearing a C_{3}F_{7} group. The tag was synthesized from the corresponding perfluoroalkyl iodide 1.20 and chlorodiisopropylsilane in
77% yield.\textsuperscript{11} Fluorous silane 1.21 was reacted with trifluoromethansulfonic acid at 0 °C to generate the fluorous TIPSOTf reagent in situ,\textsuperscript{14} then alcohol 1.18R in the solution of CH\textsubscript{2}Cl\textsubscript{2} and 2,6-lutidine was slowly added at 0 °C. After stirring 2 h at room temperature followed by aqueous work up and flash chromatography, the desired product 1.4R was obtained in 82% yield (Scheme 1.9).

1.2.3 Synthesis of aldehyde 1.5 (C14–C21 fragment)

Aldehyde 1.5 was readily made in three steps (Scheme 1.10). Commercially available 3-heptyn-1-ol 1.11 was treated with sodium hydride in warm ethylenediamine to provide alkynol 1.22\textsuperscript{28} by a zipper reaction in 64% yield. Alkynol 1.22 was protected by para-methoxybenzyl chloride (PMBCl) in the presence of NaH and tetrabutylammonium iodide (TBAI) in DMF to generate the alkyne 1.10 in 92% yield. According to the procedure of Journet and Cai,\textsuperscript{32} alkyne 1.10 was metallated with n-BuLi in THF, and the resulting lithium acetylide was formylated by DMF. Workup under mild acidic conditions (10% aqueous KHPO\textsubscript{4}) followed by flash
chromatography provided aldehyde 1.5 in 88% yield. Thus, about 2.5 g of aldehyde 1.5 was made by this sequence.

Scheme 1.10. Synthesis of aldehyde 1.5

\[ \text{Scheme 1.10. Synthesis of aldehyde 1.5} \]

1.2.4 Model reaction towards the synthesis of fragment M-1.2

Assorted methods have been described to make enantioenriched secondary alcohols with one alkynyl and one alkyl, vinyl or aryl substituent. However, very few methods to make enantioenriched dialkynyl carbinols have been reported. Carreira and co-workers reported one example of synthesizing enantioenriched dialkynyl methanol 1.25 by the asymmetric alkynylation of aldehyde 1.23 using chiral ligand (+)-N-methyl-ephedrine 1.24 (Scheme 1.10). The product was obtained in 89% ee, but its configuration was not assigned.

Scheme 1.11. Carreira’s approach to synthesize dialkynyl methanol 1.25

\[ \text{Scheme 1.11. Carreira’s approach to synthesize dialkynyl methanol 1.25} \]
With the alkyne 1.4 and aldehyde 1.5 in hand, we initially investigated the Carreria method for asymmetric addition of alkynlides to alkynals by studying the reaction of 1-octyne 1.26 with 2-octynal 1.27 (Scheme 1.12). Following the general procedure reported by Carreira and coworkers, a mixture of dried Zn(OTf)$_2$, (+)-N-methyl-ephedrine 1.24 and Et$_3$N in toluene was stirred at 23 °C for 2 h. The alkyne 1.26 was then added in one portion, and the resulting mixture was stirred at 23 °C for 15 min. A solution of aldehyde 1.27 in toluene was then added by syringe pump over 2.5 h, followed by stirring at 75 °C for 20 h. Unfortunately, no product 1.28 was detected by $^1$H NMR spectroscopy.

Scheme 1.12. Unsuccessful model reaction between 1-octyne 1.26 with 2-octynal 1.27

We also found several other examples of failed Carreira reactions on aliphatic aldehydes, which suggested that this type of chiral zinc acetylide addition reaction is sensitive to substrate structure. Due to the failure of Carreira asymmetric alkynylation, we had to revise the synthetic route for fragment M-1.2.

1.2.5 Revised synthetic route of C1–C21 fragment M-1.2

The revised retrosynthetic analysis of C1–C21 fragment M-1.2 is shown in Scheme 1.13. We divide fragment M-1.2 into two parts, iodide M-1.29 and dialkynyl methanol M-1.30, which can be made as quasiracemic mixtures with configurations encoded by fluorous tags in the
protecting groups (TIPS\(^{R}\)). These two fragments then can be connected by a \(S_N2\) reaction to provide a mixture of four fluorous-tagged quasiisomers. This kind of double tagging strategy was recently reported in the synthesis of passifloricin A\(^{21}\) and lagunapyrone B.\(^{12}\)

**Scheme 1.13. Revised retrosynthesis of fragment M-1.2**

Iodide M-1.29 can be constructed from ketone 1.31 by performing enantioselective reduction of \(\alpha,\beta\)-unsaturated ketone 1.31 with chiral oxazaborolidine (CBS) catalyst (Scheme 1.14).\(^{35}\) Ketone 1.31 can be synthesized from the addition of commercially available tert-butyldimethylsilylacetylene to Weinreb amide 1.32, which can be obtained from aldehyde 1.33 by Horner-Wadsworth-Emmons (HWE) olefination.\(^{36}\) Aldehyde 1.33 can be prepared from commercially available 1,7-heptanediol 1.34.

**Scheme 1.14. The retrosynthesis of iodide M-1.29**
Dialkynyl methanol **M-1.30** can be synthesized by enantioselective addition of terminal alkyne to aldehyde **1.5** followed by protection and encoding with TIPS$^F$ groups.

![Scheme 1.15. The retrosynthesis of fragment M-1.30](image)

### 1.2.6 Synthesis of iodide M-1.29 (fragment C1–C11)

The synthesis of iodide **M-1.29** begins with the preparation of common intermediate ketone **1.31** (Scheme 1.16). Commercially available 1,7-heptanediol **1.34** was treated with sodium hydride (1.0 equiv) and PMBCl (1.0 equiv) in THF to provide the mono-PMB ether$^{37}$ in 49% yield after isolation by flash chromatography. Swern oxidation of the remaining primary alcohol afforded aldehyde **1.33$^{37}$** in 98% yield. Weinreb amide **1.32** was accessed by a Horner-Wadsworth-Emmons (HWE) olefination of aldehyde **1.33** with commercially available phosphonate **1.35** in THF with 91% yield. Nucleophilic addition of tert-butyl dimethylsilylacetylene **1.36** to Weinreb amide **1.32** gave the ketone **1.31** in 89% yield. Conveniently, ketone **1.31** is stable and could be stored in refrigerator for 2 weeks without any decomposition.
Scheme 1.16. Synthesis of ketone 1.31

The sample of ketone 1.31 was split into half and each portion was subjected to CBS asymmetric reduction (Scheme 1.17).\textsuperscript{35} Reduction with BH\textsubscript{3} in the presence of the catalyst (R)-CBS was proceeded to provide (R)-alcohol 1.37\textsubscript{R} in 70% yield. Similarly, (S)-alcohol 1.37\textsubscript{S} was generated by the reduction of alkynyl ketone 1.31 using (S)-CBS in 73% yield.

Scheme 1.17. Synthesis of alcohols 1.37R/S by CBS asymmetrical reduction

According to the mechanism proposed by Corey and coworkers for analogous oxazaborolidine-mediated reactions,\textsuperscript{35b} the absolute configurations of alcohols 1.37\textsubscript{R} and 1.37\textsubscript{S} were confidently assigned based on the transition state models in which the acetylenic moiety acts as the smaller group (scheme 1.18).
The corresponding Mosher esters of alcohols 1.37R and 1.37S were then synthesized for three reasons: 1) to determine the ees for the two alcohols; 2) to validate the Mosher method again, although we have done it using alcohol 1.18; 3) to compare the Mosher method and NMA (α-methoxy-2-naphthylacetic acid) ester method in the configuration assignment of secondary alcohol. After removal of the TBS group by TBAF in DCM, the corresponding alcohols 1.38R and 1.38S were obtained. Alcohol 1.38S was reacted with the R- and S-Mosher acid chloride (MTPACl = α-methoxy-α-trifluoromethylphenylacetic acid chloride) in dry pyridine to give the corresponding crude esters 1.39SS and 1.39SR after removing organic solvent under reduced pressure. Integration of the respective signals in ¹H and ¹⁹F NMR spectra of the resulting crude samples provides the indicated ees (93% for 1.37R and 94% for 1.37S) for the CBS asymmetric reduction. After flash chromatography, the pure esters 1.39SS and 1.39SR were obtained and used in NMR experiments. All of the key protons of both compounds were assigned by a combination of ¹H NMR and COSY data. Relevant chemical shifts of protons of esters 1.39SS/SR and the differences of resonances of corresponding pairs (δS − δR) are listed in Table 2. The proton (H1) on the left side of stereocenter exhibited a positive Δδ, while the protons H4—
H10 on the other side showed the substantial negative Δδs. According to the advanced Mosher rule, the absolute configuration of C3 is S, as expected from the Corey transition state model.

**Scheme 1.19. Synthesis of Mosher esters 1.39SS and 1.39SR**

Table 1.2. Δδ (δ_{1.39SS} − δ_{1.39SR}) values (ppm) obtained from the MTPA esters of 1.39SS and 1.39SR

<table>
<thead>
<tr>
<th>position</th>
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<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ_{1.39SS}</td>
<td>2.629</td>
<td>5.496</td>
<td>6.002</td>
<td>2.044</td>
<td>1.368</td>
<td>1.260</td>
<td>1.338</td>
<td>1.578</td>
</tr>
<tr>
<td>δ_{1.39SR}</td>
<td>2.589</td>
<td>5.606</td>
<td>6.063</td>
<td>2.085</td>
<td>1.400</td>
<td>1.312</td>
<td>1.364</td>
<td>1.589</td>
</tr>
<tr>
<td>Δδ (δ_{1.39SS} − δ_{1.39SR})</td>
<td>0.040</td>
<td>−0.110</td>
<td>−0.061</td>
<td>−0.041</td>
<td>−0.032</td>
<td>−0.052</td>
<td>−0.026</td>
<td>−0.011</td>
</tr>
</tbody>
</table>

During the model studies for the C14 stereocenter (see below), we needed to make α-methoxy-2-naphthylacetic acid (2-NMA) esters to validate the Mosher results, so we also made the NMA ester with alcohols 1.38S and 1.38R. The use of α-methoxy-2-naphthylacetic acid as a chiral anisotropic reagent for determining the absolute configuration of long chain secondary alcohols was developed simultaneously by several groups in mid-1990s. Because the
anisotropic effect of 2-NMA is much greater than that of MTPA, Δδ values of 2-NMA esters are larger than those of MTPA esters. This makes assignment of absolute configuration both easier and more reliable.39

Since we only had (S)-2-NMA in hand, our strategy was to synthesize the corresponding (S)-2-NMA esters 1.40SS and 1.40RS by the reaction of two enantiomers 1.38S and 1.38R with (S)-2-NMA in the presence of DCC and DMAP (Scheme 1.20). Ester 1.40RS is the enantiomer of ester 1.40SR obtained from the reaction of 1.38S with (R)-2-NMA acid. Consequently, ΔδH between esters 1.40SR and 1.40SS were obtained from 1H NMR data of esters 1.40RS and 1.40SS. For NMA ester, the subtraction formula is reversed,39 ΔδH = δR − δS, due to the inverted CIP (Cahn–Ingold–Prelog) priority order of NMA ester compared to MTPA ester (δR is the 1H chemical shift of (R)-2-NMA ester, δS is the 1H chemical shift of (S)-2-NMA ester.). After purification by flash chromatography, esters 1.40SS and 1.40RS were studied by 1H NMR spectroscopy. All of the key protons of both compounds were unambiguously assigned by a combination of 1H NMR and COSY data. Relevant chemical shifts of protons of esters 1.40SS, 1.40RS and their differences are listed in Table 1.3. For comparison, the Δδ values for the Mosher esters were also listed in the last row in Table 1.3.

Scheme 1.20. Synthesis of (S)-2-NMA esters 1.40SS and 1.40RS
First, the results showed that the NMA ester method works for configuration assignment of secondary alcohol. The results also showed that the differences of chemical shifts obtained with NMA esters are much larger than those obtained with MTPA esters. For instance, the difference of chemical shift of NMA esters at H6 is −0.152, but that of MTPA esters is only −0.041. The large Δδ allowed us to confirm the C3 absolute configuration of alcohol 1.38S without ambiguity. The results also showed the long-range anisotropic effect of NMA. For NMA esters, the difference of chemical shift for H11 (nine atoms away from the stereocenter) is −0.027, but for MTPA esters, there is no measurable difference for this proton. Taken together, the results show that NMA esters are superior to MTPA esters for the assignment of absolute configuration.

Alcohols 1.37R and 1.37S were then individually tagged with two different tags (Scheme 1.21). The hydroxyl group of 1.37R was protected by silylation with in situ generated fluorous TIPS triflate bearing the C₄F₉ (F9) group to encode the 3R configuration in 1.41R. Likewise,
silylation of \textbf{1.37S} with fluorous TIPS trflate bearing the C$_3$F$_7$ (F7) provided the quasienantiomer \textbf{1.41S} with the 3$S$ configuration encoded. Quasienantiomers \textbf{1.41R} and \textbf{1.41S} were weighed and mixed with 1:1 molar ratio to generate the first quasiracemate. Although not true racemates, the components of quasiracemates usually have nearly identical physical and spectroscopic properties and chemical reactivities toward achiral reagents.$^{40}$ The quasiracemic mixture was deprotected by DDQ to afford alcohol \textbf{M-1.42}, which was then converted to iodide \textbf{M-1.29} with iodine in the presence of triphenylphosphine and imidazole in CH$_2$Cl$_2$ with 49% yield over two steps.

\textbf{1.2.7 Synthesis of dialkynyl carbinols 1.57R and 1.57S}

The precursors for synthesis of fragment \textbf{M-1.30}, dialkynyl carbinols \textbf{1.54R} and \textbf{1.54S}, can be synthesized from aldehyde \textbf{1.5} and terminal alkyne by asymmetric alkynylation (Scheme 1.22).
The key reaction in this transformation is constructing the stereocenter C14 enantioselectively. After the failure of Carreira’s asymmetric alkynylation, we were attracted by a literature report published by Pu and co-workers. They described the asymmetric alkynylation of aldehydes (aromatic, alkyl and vinyl, but no alkynyl aldehyde) using chiral ligand (S)-BINOL with Ti(OiPr)₄ in excellent yields and enantioselectivities. In Pu’s reaction (Scheme 1.23), a terminal alkyne is first reacted with Et₂Zn to generate an alkynylzinc intermediate. This is then added to the aldehyde and the catalyst to form the chiral propargyl alcohol.

We set out to find whether Pu’s asymmetric addition was applicable to alkynals. We first studied the asymmetric reaction of phenylacetylene 1.43 with 2-octynal 1.27. A solution of phenylacetylene 1.43 and diethylzinc in toluene was heated under argon atmosphere at reflux for
1 h. After the solution had cooled to room temperature, (R)-BINOL, Et$_2$O, and Ti(OiPr)$_4$ were added sequentially, and the resulting mixture was stirred for 1 h. 2-Octynal 1.27 was added and stirring was continued for an additional 4 h. After purification on silica gel, alcohol 1.44S was obtained (90–96% yield, Table 1.4). The absolute configuration of this alcohol was tentatively assigned as S by analogy to Pu’s results with other types of aldehydes.\textsuperscript{41}

Table 1.4. Yields and ees of reactions of phenylacetylene 1.43 with 2-octynal 1.27 to give propargyl alcohol 1.44S

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne (equiv)</th>
<th>Et$_2$Zn (equiv)</th>
<th>[Et$_2$Zn] (mol/L)</th>
<th>Ti(OiPr)$_4$ (equiv)</th>
<th>BINOL (equiv)</th>
<th>yield\textsuperscript{a} (%)</th>
<th>ee\textsuperscript{b} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.0</td>
<td>4.0\textsuperscript{c}</td>
<td>1.1</td>
<td>1.0</td>
<td>0.4</td>
<td>96</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>4.0\textsuperscript{d}</td>
<td>3.0</td>
<td>1.0</td>
<td>0.4</td>
<td>94</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>6.0</td>
<td>6.0\textsuperscript{d}</td>
<td>4.5</td>
<td>2.5</td>
<td>1.0</td>
<td>90</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>8.0</td>
<td>8.0\textsuperscript{d}</td>
<td>6.0</td>
<td>2.5</td>
<td>1.0</td>
<td>92</td>
<td>67</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Isolated yield. \textsuperscript{b}ee determined by chiral HPLC (Chiralcel OD column, 4.6 \times 200 mm, hexane/iPrOH = 9:1, 1.0 mL/min). \textsuperscript{c}15 % wt Et$_2$Zn (1.1 M) in toluene was used. \textsuperscript{d}95 % Et$_2$Zn was used.

Various conditions were explored for the reaction to optimizing enantioselectivity (Table 1.4). The ee of propargyl alcohol 1.44S was determined by chiral HPLC. We first used commercially available Et$_2$Zn solution (15 wt% in toluene ≈ 1.1 M) as source of zinc, but the ee of alcohol 1.44S was only 57% (entry 1). When 95% Et$_2$Zn was used, the ee improved to 63% (entry 2). To further increase the ee, we increased the amount of all reagents. This increased the ee to 78% and provided a high yield (90%) (entry 3). In entry 4, we further increased the
amounts of diethylzinc and phenylacetylene 1.43 compared to the aldehyde 1.27. This decreased the ee to 67%, but still gave an excellent yield (92%). Finally, we chose the conditions of entry 3 as the optimized conditions for this reaction.

The optimized procedure was then applied to the reactions of several terminal alkynes with 2-octynal 1.27, and the results of this series of reactions are shown in Table 1.5. The ees of the products were again measured by chiral HPLC. Silylacetylenes generate products that can be easily converted to terminal alkynes by desilylation, so these were tested first. Reaction of dimethylphenylsilylacetylene 1.45 with aldehyde 1.27 gave alcohol 1.48S in 90% yield and 78% ee (entry 1). When methyldiphenylsilylacetylene 1.46 was used, the yield was 85% and the ee of product 1.49S was only increased to 80%. We rationalized this small increase due to the relatively long bond length of carbon-silicon bond (1.86 Å). Increasing the size of the silyl group had little impact on enantioselectivity. If an alkyne with shorter bond length between carbon and
R group is used in the reaction, then the enantioselectivity should be improved. 2-Methyl-3-butyn-2-ol 1.47 is a suitable alkyne, because the bond length of carbon-carbon bonds (1.46 Å) is shorter than carbon-silicon bonds. The addition reaction followed by a facile fragmentation reaction provides an access to the enantioenriched terminal acetylene that could be a useful building block for synthesis of petrocortyne A. When alkyne 1.47 was subjected to this asymmetric addition reaction (entry 3), the product 1.50S was isolated in 90% ee and 86% yield.

The next goal was to convert the compound 1.50S to the corresponding terminal acetylene. As a prelude, the model reaction using racemic alcohol rac-1.53 was performed. Compound rac-1.53 was prepared in three steps (Scheme 1.24). Alkyne 1.47 was treated with n-BuLi to generate lithium acetylene in situ. This was reacted with aldehyde 1.27 to afford racemic propargylic alcohol rac-1.51 in 82% yield. Alcohol rac-1.51 was then converted to diol rac-1.52 with acetyl chloride in MeOH in 91% yield. TIPS protection of the secondary alcohol of diol rac-1.52 afforded alcohol rac-1.53 in 87% yield.

The fragmentation reaction of alcohol rac-1.53 was conducted under a variety of conditions (Scheme 1.25). Reaction with 40 mol % of 18-crown-6 and K₂CO₃ in refluxing...
toluene\textsuperscript{42} or under microwave irradiation resulted in decomposition. When the base was changed
to KOH, no desired product was detected by TLC analysis and starting material was recovered.
This reaction was then carried out in the KH solution of toluene with or without 18-crown-6 at
room temperature, but only starting material was obtained.

Scheme 1.25. Unsuccessful fragmentation reaction of alcohol rac-1.53

1. 40 mol % 18-crown-6, K\textsubscript{2}CO\textsubscript{3}, toluene reflux, decomposition
2. 40 mol % 18-crown-6, K\textsubscript{2}CO\textsubscript{3}, toluene microwave (30 min, 150 °C), decomposition
3. 40 mol % 18-crown-6, KOH, toluene reflux, recovered starting material
4. 40 mol % 18-crown-6, KH, toluene rt, recovered starting material
5. KH, toluene rt, recovered starting material

Because of the difficulty of performing a fragmentation reaction of rac-1.53, the product
generated from dimethylphenylsilylacetylene 1.45 was chosen as the precursor to synthesize
fragment M-1.30. Alcohol 1.54R was synthesized according to the optimized version of Pu’s
procedure (Table 1.4 entry 3). Commercially available dimethylphenylsilylacetylene 1.45 was
treated with Et\textsubscript{2}Zn in refluxing toluene for 1 h to afford the alkynylzinc intermediate. Aldehyde
1.5 was then added with (S)-BINOL and Ti(O\textsuperscript{i}Pr\textsubscript{4})\textsubscript{4} to form (R)-dialkynyl methanol 1.54R
(Scheme 1.26). Alcohol 1.54R was contaminated with residual (S)-BINOL, which was difficult
to remove by flash chromatography. Furthermore the ee of alcohol 1.54R, while a substantial
(83% determined by chiral HPLC: Chiralcel OD column, 4.6 × 200 mm hexane:\textsuperscript{i}PrOH = 9:1, 1.0
mL/min), did not meet our target level of ee >90%. Enantiomeric impurities at this stage would
produce diastereomeric impurities downstream, and we did not know whether or how the impurities could be either separated or identified.

In order to increase the ee and get rid of BINOL in alcohol 1.54R, purification by preparative HPLC was undertaken. The enantiomerically pure (>99% ee) alcohol 1.54R was obtained in 64% yield (269.3 mg) by using semi-preparative Chiralcel OD column (20 × 250 mm, hexane:iPrOH = 19 : 1, 8.0 mL/min, 1.0 mL (0.1 M in hexane)/injection, 320 mg of crude product). Similarly, (S)-dialkynyl methanol 1.54S (not shown) was obtained by addition of alkynylzinc to aldehyde 1.5 in the presence of (R)-BINOL and Ti(OiPr)4 in 83% ee too. After purification by HPLC (350 mg of crude product), the enantiomerically pure alcohol (>99% ee) 1.54S was obtained in 70% yield (294.6 mg).

![Scheme 1.26. Synthesis of alcohols 1.54R and 1.54S](image)

With alcohols 1.54R/S in hand, we next used them as models to validate the Mosher method for assigning the configuration at C14. It is more difficult to assign the C14 stereocenter than C3 for two reasons. First, there are no protons directly attached to the carbons adjacent to the C14 stereocenter. Second, because there is a local plane symmetry, the peaks of protons at C10 and C17 in ¹H NMR are overlap. Making the Mosher esters breaks this local symmetry and differentiates the protons at C10 and C17. It is essential to correctly assign the resonances for protons at C10 and C17 before applying the Mosher method. If the resonances are mis-assigned, then the stereocenter configuration will be mis-assigned.
To unambiguously assign pairs of propargylic methylene protons, we chose dialkynyl carbinol 1.54R and/or 1.54S as a model system with only one propargylic methylene group. We then made both MTPA and 2-NMA esters of alcohol 1.54. Each of the pair of enantiomeric MTPA acid chlorides was reacted with 1.54R in dry pyridine to provide the pair of Mosher esters 1.55RS and 1.55RR, while the single (S)-2-NMA acid was reacted with the pair of enantiomers 1.54R and 1.54S to give the NMA esters pair 1.56RS and 1.56SS. All of key protons of two pairs of esters were assigned by a combination of 1H NMR and COSY spectra. The relevant chemical shifts of protons of Mosher esters 1.55RS/RR and NMA esters 1.56RS/SS and the differences of resonances of corresponding pairs (δS − δR for Mosher esters and δR − δS for NMA esters) are listed in Table 1.6 and 1.7, respectively. The configuration of stereocenter C14 at alcohol 1.54R was assigned as R by applying either the Mosher method or NMA ester method.

Although the differences of proton resonances of both Mosher ester pairs and NMA ester pairs have negative sign on one side of the stereocenter and positive sign on the other side, the magnitudes are very different. For example, the largest chemical shift difference in the Mosher esters is only 0.029 ppm for the protons at the C17, while in NMA esters, this difference is 0.158 ppm. The large ΔδH allowed us to confirm the C14 absolute configuration of alcohol 1.54S without ambiguity. Besides the larger chemical shift differences, the NMA esters have a longer anistropic effect. No difference was measured for the benzylic protons H1" (10 atoms away from the stereocenter) in Mosher esters, but the difference of 0.022 ppm was measured in NMA esters. Taken together, NMA esters are superior to MTPA esters for the assignment of configuration of stereocenters with local symmetry.
Table 1.6. Δδ (δ_{1.55RS} − δ_{1.55RR}) values (ppm) obtained from the MTPA esters of 1.55RS and 1.55RR

<table>
<thead>
<tr>
<th>position</th>
<th>1'</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>1''</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ_{1.55RS}</td>
<td>0.405</td>
<td>2.242</td>
<td>1.534</td>
<td>1.444</td>
<td>1.598</td>
<td>3.415</td>
<td>4.410</td>
</tr>
<tr>
<td>δ_{1.55RR}</td>
<td>0.428</td>
<td>2.213</td>
<td>1.511</td>
<td>1.420</td>
<td>1.587</td>
<td>3.413</td>
<td>4.410</td>
</tr>
<tr>
<td>Δδ (δ_{1.55RS} − δ_{1.55RR})</td>
<td>−0.023</td>
<td>0.029</td>
<td>0.023</td>
<td>0.024</td>
<td>0.011</td>
<td>0.002</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 1.7. Δδ (δ_{1.56SS} − δ_{1.56RS}) values (ppm) obtained from the MTPA esters of 1.56SS and 1.56RS

<table>
<thead>
<tr>
<th>position</th>
<th>1'</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>1''</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ_{1.56SS}</td>
<td>0.249</td>
<td>2.212</td>
<td>1.510</td>
<td>1.429</td>
<td>1.587</td>
<td>3.413</td>
<td>4.414</td>
</tr>
<tr>
<td>δ_{1.56RS}</td>
<td>0.400</td>
<td>2.054</td>
<td>1.335</td>
<td>1.277</td>
<td>1.484</td>
<td>3.349</td>
<td>4.392</td>
</tr>
<tr>
<td>Δδ (δ_{1.56SS} − δ_{1.56RS})</td>
<td>−0.151</td>
<td>0.158</td>
<td>0.175</td>
<td>0.152</td>
<td>0.103</td>
<td>0.064</td>
<td>0.022</td>
</tr>
</tbody>
</table>

From the above results, we validated the use of the Mosher method and the NMA ester method to assign the configuration at C14. Because of larger and longer anistropic effect of the NMA group, the NMA ester method is easier and more reliable to assign the configuration of the stereocenter, especially in a compound with local symmetry, such as petrocortyne A.
Continuing the synthesis of $\text{1.57S/R}$, silylacetylenes $\text{1.54R}$ and $\text{1.54S}$ were then treated with TBAF to generate terminal alkynes $\text{1.57S}$ and $\text{1.57R}$ in 85% and 89% yield, respectively (Scheme 1.27).

Before the alcohols $\text{1.57S}$ and $\text{1.57R}$ were individually tagged with different fluorous tags, several model reactions were carried out to make sure that every step could work for the synthesis of fragment $\text{M-1.2}$.

### 1.2.8 Towards the synthesis of fragment M-1.2 with silyl ether rac-1.59

After completing the syntheses of iodide $\text{M-1.29}$ and alcohols $\text{1.57R/S}$, we initiated our task for the coupling reaction of iodide $\text{M-1.29}$ with alkyne $\text{M-1.30}$ derived from alcohols $\text{1.57R}$ and $\text{1.57S}$. A model coupling reaction between commercially available iodide $\text{1.58}$ and alkyne $\text{rac-1.59}$ was first conducted before the iodide $\text{M-1.29}$ and alcohol $\text{1.57R/S}$ were used in the coupling reaction.

Terminal alkyne $\text{rac-1.59}$ was easily prepared in a three-step procedure (Scheme 1.28). Trimethylsilylacetylene was treated with $n$-BuLi to generate ((trimethylsilyl)ethynyl)lithium, which was reacted with aldehyde $\text{1.5}$ to give a racemic alcohol in 89% yield. After removal of
the TMS group with TBAF, the secondary alcohol \textit{rac-1.57} was protected with TIPS group to afford alkyne \textit{rac-1.59} in 90% yield.

Scheme 1.28. Synthesis terminal alkyne \textit{rac-1.59}

\[
\begin{array}{ccc}
\text{TMS} & + & \text{H} \begin{array}{c} \text{O} \\ \text{OPMB} \end{array} \\ \text{1. n-BuLi, THF, 89\%} \\ \text{2. TBAF, THF, 91\%} \\ \text{TIPSOTf} & \rightarrow & \begin{array}{c} \text{OH} \\ \text{OPMB} \end{array} \\ \text{\textit{rac-1.59}, 90\%} \\
\end{array}
\]

The results of the model coupling reaction of iodide \textit{1.58} (model for C1–C10 fragment) and alkyne \textit{rac-1.59} were shown in Scheme 1.29. After treatment of \textit{rac-1.59} with \textit{n}-BuLi in THF at \(-78^\circ\text{C}\) for 1 h, a solution of iodide \textit{1.58} in THF and HMPA was added. After workup and flash chromatography purification, three major products were isolated. The desired coupling product \textit{1.60} was isolated in 16.5% yield along with the two undesired products \textit{1.61} (2.5%) and \textit{1.62} (9.1%) (Structures were determined by \textit{\textsuperscript{1}H NMR}). The side products arrived from the deprotonation of the protected dialkynylcarbonol proton (proton at C14). Even if the alkylation at C14 could be prevented, this deprotonation still cause epimerization at C14 of substrates (\textit{rac-1.59}).
Scheme 1.29. Model coupling reaction of iodide 1.58 and alkyne rac-1.59

To suppress the undesired products and avoid the epimerization at the C14 stereocenter, we decided to conduct the coupling reaction on a dianion derived from free alcohol rac-1.57. Under the conditions for formation of dianion of rac-1.57 by its treatment with n-BuLi, there should be no anion formation at C14 to give a trianion.43

1.2.9 Towards the synthesis of fragment M-1.2 by using dianion strategy

The model dianion alkylation was performed between iodide 1.58 and free alcohol rac-1.57 (Scheme 1.30). Alcohol rac-1.57 was treated with 2 equiv of n-BuLi to generate dianion in situ, which was then reacted with 2 equiv of iodide 1.58. In addition to the desired product rac-1.63 (26% yield), O-alkylated product rac-1.64 was also isolated in 25% yield and its structure was confirmed by ¹H NMR. The 19% of alcohol rac-1.57 was recovered (entry 1). In entry 2, 1:1 ratio of alkyne and iodide were subjected to the reaction also gave byproduct rac-1.64 (10%) in addition to desired product rac-1.63 (13%). The starting material rac-1.57 was recovered in 51%.
When a 2:1 ratio of alkyne and iodide were used, only product \textit{rac-1.63} was obtained in 59% yield with 65% recovered \textit{rac-1.57} (entry 3).

We then carried out the coupling reaction of iodide 1.29 with dialkynol \textit{rac-1.57} (Scheme 1.31). Dialkynol \textit{rac-1.57} was treated with 2 equiv of \textit{n-BuLi} to generate dianion in situ, then iodide 1.29 was added. Standard workup and chromatography provided coupled product 1.65 in 35% yield. Substantial starting material \textit{rac-1.57} remained, and 1.65 was the only new product of the reaction.
The coupling reaction of the iodide \textbf{M-1.29} and dialkynol \textbf{1.57S} was then performed (Scheme 1.32). The quasiracemate \textbf{M-1.29} was added to the dianion derived from \textbf{1.57S}. Again, a single new spot appeared on TLC analysis. However, this time the chromatographically isolated product (30\% yield) was not the pure quasiracemate \textbf{M-1.66}. Instead, this was contaminated by a substantial amount (about 50\%) of a second component \textbf{1.67} resulting from transfer of the fluorous TIPS groups of \textbf{M-1.29} to the terminal acetylide of \textbf{1.57S}. These compounds were not separable, but the structure of \textbf{1.67} was secured by MS ($m/z = 596.7$ and 646.7) and NMR analysis of mixture. In particular, the $^1$H NMR spectrum of the mixture exhibited no terminal acetylide proton resonance, so the TIPS\textsuperscript{F} group in alcohol \textbf{1.67} must be connected to the terminal acetylide and not to the alcohol.

Suspecting that this reaction provided the byproduct because of liability of the TIPS\textsuperscript{F} under the nucleophilic environment, we conspired to block this side reaction by applying the new second-generation TIPS\textsuperscript{F} tags with a propylene spacer, Rf(CH\textsubscript{2})\textsubscript{3}Si(iPr)\textsubscript{2}, to reduce the electrophilic reactivity of TIPS\textsuperscript{F} tags.\textsuperscript{44}
1.2.10 Synthesis of the second-generation TIPS\textsuperscript{F} tags and new iodide M-1.68

The second-generation TIPS\textsuperscript{F} tags 1.69 and 1.70 were synthesized from the corresponding perfluoroalkyl iodides and chlorodiisopropylsilane (Scheme 1.33).\textsuperscript{44} The perfluoro carbon units in the two fluorous tags are C\textsubscript{3}F\textsubscript{7} (TIPS\textsuperscript{F7'}) and C\textsubscript{4}F\textsubscript{9} (TIPS\textsuperscript{F9'}). The “prime(‘)” in the formula represents the propylene spacer.

The synthesis of new iodide M-1.68 starts from the common intermediate ketone 1.31 (Scheme 1.34). Asymmetric reduction of ketone 1.31 using BH\textsubscript{3} in the presence of the catalyst (R)-CBS proceeded in 70% yield with high enantiomeric selectivity (93%) to provide (R)-alcohol 1.37R. Similarly, (S)-alcohol 1.37S was generated by the reduction of alkynyl ketone 1.31 using (S)-CBS in 73% yield with 94% ee. Fluorosilane 1.70 bearing C\textsubscript{4}F\textsubscript{9} (TIPS\textsuperscript{F9'}) group was treated
trifluoromethansulfonic acid at −78 °C to generate TIPS\textsubscript{F9}\textsuperscript{OTf} in situ. This was then reacted with the hydroxy group of 1.37\textsuperscript{R} to encode the 3\textit{R} configuration in 1.71\textsuperscript{R}. Likewise, silylation of 1.37\textsuperscript{S} with general TIPS triflate provided the quasienantiomer 1.71\textsuperscript{S} with the 3\textit{S} configuration encoded by TIPS (TIPS\textsubscript{F0}) group. Quasienantiomers 1.71\textsuperscript{R} and 1.71\textsuperscript{S} were weighed and mixed with 1:1 molar ratio to generate the starting mixture. The mixture was deprotected by DDQ to afford alcohol, which was then converted to iodide M-1.68 with iodine in the presence of triphenylphosphine and imidazole in CH\textsubscript{2}Cl\textsubscript{2} with 42% yield (5.62 g) over two steps.

\textbf{Scheme 1.34. Synthesis of new iodide M-1.68}

\begin{center}
\begin{tikzpicture}
  \node (1.31) at (0,0) {1.31};
  \node (1.32) at (2,0) {1. \((R)\text{-CBS, BH}_3\cdot \text{SM}e_2 \\
\begin{tabular}{l} 1. TIPS\textsubscript{F9}OTf \\
2. TIPS\textsubscript{F0}OTf \end{tabular}
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tikzpicture}
  \node (1.33) at (0,0) {1. \((S)\text{-CBS, BH}_3\cdot \text{SM}e_2 \\
\begin{tabular}{l} 1. TIPS\textsubscript{F0}OTf \\
2. TIPS\textsubscript{F9}OTf \end{tabular}
\end{center}

\begin{center}
\begin{tikzpicture}
  \node (1.34) at (0,0) {\textcolor{red}{1} mixture of 2 quasienantiomers};
\end{center}

1.2.11 \textbf{Unexpected difficulty of removal of PMB group in compound 1.65}

In parallel with the syntheses of the second-generation TIPS\textsuperscript{F} tags and new iodide M-1.68, we also continued the pilot synthesis from compound 1.65. After protection of the hydroxyl group by TIPS, the resulting TIPS ether 1.72 was subjected to various conditions to remove the
PMB group (Scheme 1.35). We first tried DDQ deprotection in DCM with the pH 7 buffer, but many spots appeared on TLC analysis (entry 1). When the 3 equiv of ceric ammonium nitrate (CAN) was used in acetonitrile with pH 7 buffer, only 28% of desired alcohol 1.73 was obtained and 50% starting material was recovered (entry 2). When the amount of CAN was increased to 5 equiv, the yield of product 1.73 did not change, but the recovered PMB ether 1.72 decreased to 37% (entry 3). We suspected that the substrate, especially the alkynyl alkenyl carbinol unit, was not stable under oxidative cleavage conditions. We then turned to Lewis acids. When MgBr₂·Et₂O and Me₂S were used, only starting material was recovered (room temperature) or decomposition occurred (refluxing) (entry 4). Sonication of a solution of PMB ether 1.72 in DCM at rt for 5 min also gave nothing but starting material (entry 5).

### Scheme 1.35. Unsuccessful removal of PMB group

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>yield</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DDQ (1.2 + 0.3 equiv), pH7 buffer, DCM, rt</td>
<td>/</td>
<td>complex TLC</td>
</tr>
<tr>
<td>2</td>
<td>CAN (3.0 equiv), pH7 buffer, CH₃CN, rt</td>
<td>28%</td>
<td>recovered SM 50%</td>
</tr>
<tr>
<td>3</td>
<td>CAN (5.0 equiv), pH7 buffer, CH₃CN, rt</td>
<td>27%</td>
<td>recovered SM 37%</td>
</tr>
<tr>
<td>4</td>
<td>MgBr₂·Et₂O, Me₂S, DCM, rt/reflux</td>
<td>/</td>
<td>NR (rt), decomposition (reflux)</td>
</tr>
<tr>
<td>5</td>
<td>Sonication 5 min, DCM, rt</td>
<td>/</td>
<td>NR</td>
</tr>
</tbody>
</table>
Faced with difficulty of removal of the PMB group in compound 1.72, we considered other protecting group options. The protecting group should be easily removed after the precursor of fragment M-1.2 was obtained. In order to circumvent this issue, we chose to protect the hydroxyl group as MTM (methylthiomethyl) ether. So it was necessary to synthesize the new middle fragment as an MTM ether.

1.2.12 Synthesis of middle fragment MTM ethers 1.74S and 1.74R

The synthesis of alcohol 1.74S and 1.74R started from the commercially available 3-heptyn-1-ol 1.11 (Scheme 1.36), which was treated with sodium hydride in warm ethylenediamine to provide alkynol 1.22 by a zipper reaction in 68% yield. Alcohol 1.22 was protected by reacting with DSMO in the presence of AcOH in Ac₂O to generate MTM ether 1.75. This was used directly in next step. According to the procedure of Journet and Cai, MTM ether 1.75 was metallated with \( n \)-BuLi in THF, and resulting lithium acetylide was formylated by DMF. Workup under mild acidic conditions (10% aqueous KHPO₄) provided aldehyde 1.76 in 71% yield over two steps. Treatment of aldehyde 1.76 with the lithium (dimethylphenylsilyl)alkynide 1.45 afforded racemic alcohol rac-1.77 in 97% yield.

In analyzing the ees from Pu reactions, we have found that the enantiomers of products like rac-1.77 were well separated on a Chiralcel OD chiral column. Thus, instead doing two asymmetric alkyne additions and upgrading the ees of those enantiomeric products, we simply made racemic rac-1.77 on gram scale and resolved it. The racemic alcohol rac-1.77 was preparatively resolved by chiral HPLC to provide two enantiomerically pure alcohols 1.77R in
49% yield and 1.77S in 48% yield. Both samples had ees ≥ 99% by chiral HPLC analysis. The absolute configurations of two alcohols were assigned by advanced Mosher method. The terminal dimethylphenylsilyl group in 1.75R was removed by TBAF in THF to afford 1.74S in 78% yield. Likewise, alcohol 1.74R was obtained in 95% yield from 1.75S.

1.2.13 Successful synthesis of fragment M-1.2

We envisioned an S_N2 nucleophilic addition to an iodide as the key coupling step to combine fragments M-1.68 and 1.74S/R (Scheme 1.37). In order to avoid racemization at C14 of 1.74S/R, we decided to employ the dianion derived from 1.74S/R for its alkylation with iodide M-1.68 based on the results of the model reaction in Scheme 1.30. Formation of dianion of
1.74S/R by its treatment with n-BuLi should be clean and there should be no deprotonation at C14 of 1.74S/R to give a trianion. We therefore prepared two quasi-diastereomeric compounds by dianion alkylation. Treatment of alcohol 1.74R in THF/HMPA with 2.2 equiv of n-BuLi generated the dinaion. This was alkylated with M-1.68 to provide the first quasi-diastereomeric product M-1.78R in 34% yield. The sample of M-1.78R was then tagged with a second-generation fluorous TIPS triflate bearing the C4F9 group (TIPSF9′) to afford M-1.79R in 99% yield. Similarly, we prepared M-1.79S by alkylation of 1.74S with M-1.68 in 33% yield and tagged this with C3F7 variant of second-generation fluorous TIPS group (TIPSF7′) in 85% yield. Although the yields of alkylations were moderate, there was no evidence of silyl transfer from the M-1.68 to terminal acetylide of 1.74R/S. Thus, the propylene spacer did its job.

Quasidiastereomers M-1.79R and M-1.79S were then mixed in a 1/1 ratio to provide the mixtures of four quasiisomers. MTM deprotection was accomplished under mild alkylation conditions (MeI, NaHCO3, aqueous acetone)46a to give alcohol M-1.80 in 90% yield, and subsequent treatment with Dess-Martin periodinane gave the aldehyde M-1.2 (338.5 mg) in 74% yield.
Scheme 1.37. Synthesis of fragment M-1.2

**Synthesis of M-1.79R**

\[
\text{M-1.68} + \text{1.74R} \xrightarrow{n-\text{BuLi, THF/HMPA}} \text{M-1.79R, 99%}
\]

\[
\text{M-1.68} + \text{1.74R} \xrightarrow{\text{OTIPS}^\text{F} \text{OTf, 2,6-lutidine}} \text{M-1.79R, 99%}
\]

**Synthesis of M-1.79S**

\[
\text{M-1.68} + \text{1.74S} \xrightarrow{n-\text{BuLi, THF/HMPA}} \text{M-1.79S, 85%}
\]

**Synthesis of M-1.2**

\[
\text{M-1.79R} + \text{M-1.79S} \xrightarrow{\text{mix, aqueous acetone, MeI, NaHCO}_3} \text{M-1.80, 90%}
\]

\[
\text{M-1.2, 74%}
\]
1.2.14 Synthesis of C22–C46 fragment 1.3

The synthesis of fragment 1.3 is summarized in Scheme 1.38. Commercially available 1,6-hexanediol 1.81 was treated with sodium hydride (1.0 equiv) and PMBCl (1.0 equiv) in the presence of TBAI in THF to provide the mono-PMB ether 1.82 in 54% yield. Alcohol 1.82 was converted to bromide 1.83 with CBr₄ in 89% yield. The corresponding phosphonium salt 1.12 was derived from bromide 1.83 with triphenylphosphine in refluxing acetonitrile for 2 days. Ester 1.84 was obtained from 16-hydroxyhexadecanoic acid 1.15 by the reaction with MeOH in the presence of p-toluenesulfonic acid with quantitative yield. Swern oxidation of ester 1.84 provided aldehyde 1.85 in 98% yield. The gem-dibromoalkene 1.86 was obtained, in excellent yield (92%) by Wittig homologation of aldehyde 1.85 in the presence of PPh₃ and CBr₄.

Stereoselective palladium-catalyzed hydrogenolysis of 1.86 with n-Bu₃SnH was then performed, yielding the desired Z-vinyl bromide 1.14 quantitatively. Sonogashira cross-coupling reaction of 1.14 with tert-butyldimethylsilylacetylene 1.35 was successfully carried out with Pd(PPh₃)₂Cl₂ and CuI in piperidine to furnish ester 1.87 in 87% yield. Conversion of ester 1.87 to aldehyde 1.13 was effected by DIBAL reduction in 94% yield. Wittig olefination reaction of 1.13 with the ylide derived from triphenylphosphonium salt 1.12 (NaHMDS, THF, −78 °C to rt) afforded olefin 1.88 in 99% yield with complete Z-selectivity. Deprotection of PMB ether 1.88 with DDQ in DCM/H₂O provided alcohol, which was directly brominated by CBr₄ in the presence of PPh₃ to furnish bromide 1.89 in 60% yield over two steps. The bromide 1.89 was then treated with excess PPh₃ in refluxing acetonitrile for 2 days to provide corresponding triphenylphosphonium salt 1.3 (6.8 g).
1.2.15 Synthesis of four isomers of petrocortyne A

With the two large fragments M-1.2 and 1.3 in hand, we finished the synthesis of four isomers of petrocortyne A as shown in Scheme 1.39. The mixture of four aldehydes M-1.2 was subjected to Wittig olefination with phosphonium salt 1.3 to afford final mixture M-1.90 in 44% isolated yield. The low yield of this reaction was caused by instability of M-1.90, which slowly
decomposed during the purification. The 1H NMR of M-1.90 showed that about 50% of the compound M-1.90 decomposed in one week at −20 °C.

The mixture M-1.90 was quickly demixed into four individual quasiisomers by preparative fluorous HPLC. Demixing was conducted on a Waters high-performance liquid chromatograph by fluorous chromatography over a FluoroFlash™ PFC8 column (10 mL/min) with the following gradient: 0 to 45 min, 100% CH3CN up to 85% CH3CN/15% THF; 45 to 65 min, keep 85% CH3CN/15% THF. A representative preparative HPLC demixing chromatogram of mixture M-1.90 is shown in Figure 1.7. The four mixture compounds (137.2 mg) were well separated and eluted in order of increasing fluorine content to give the four quasiisomers 1.90[F0,7′] (41.3 mg) (represents the quasiisomer bearing TIPS^F0 and TIPS^F7′ groups), 1.90[F0,9′] (39.5 mg), 1.90[F9′,7′] (16.0 mg) and 1.90[F9′,9′] (19.7 mg). The combined recovery of demixing was 85%. All four quasiisomers decomposed slightly during the demixing, so the compounds were subjected to the next step immediately.

All four quasiisomers were then deprotected individually by exposure to TBAF in THF to provide four final products 1.1SS (11.4 mg), 1.1SR (10.4 mg), 1.1RS (2.1 mg) and 1.1RR (5.1 mg) in 59%, 59%, 41% and 65% yields, respectively. The complete structures of these final products are shown in Figure 1.8 along with their optical rotations and the fluorous tagging scheme for reference.
Scheme 1.39. Synthesis of petrocortyne A 1.1

1. Demix
2. TBAF, THF

1.1RR, 59%; 1.1RS, 59%; 1.1SR, 41%; 1.1SS, 65% (not shown)

Conditions: FluoroFlash™ PFC8 column, 10 mL/min, 0 to 45 min, 100% CH₃CN up to 85% CH₃CN/15% THF; 45 to 65 min, keep 85% CH₃CN/15% THF.

Figure 1.7. Representative HPLC demixing chromatogram
In a parallel, Mr. Edmund Yeh in our lab also finished the non-selective synthesis of a mixture of all four petrocortyne A isomers 1.1Mix. He used a strategy that somewhat similar to that outlined here, but there were no fluorous protecting groups and the stereocenters were generated non-selectively.

We then compared four pure isomers of 1.1 with mixture 1.1Mix. $^1$H and $^{13}$C NMR spectra (600 and 151 MHz) of all four stereoisomers of 1.1 and mixture 1.1Mix were identical (Figure 1.9, only differences come from the peaks of free alcohols). This is expected for two pairs of compounds, 1.1SS/1.1RR and 1.1SR/1.1RS, because they are enantiomers. However, the spectra of the diastereomeric compounds were also identical, indicating that the long spacer between the two remote stereocenters C3 and C14 prohibits their communication, at least under these standard NMR recording conditions. This phenomenon was also observed in the syntheses
of libraries of murisolin\textsuperscript{4b} and lagunapyrone B.\textsuperscript{12} Importantly, all of the spectra also matched very well with spectra for \((3R,14R)\)-petrocortyne A (The \(^1\text{H}\) and \(^{13}\text{C}\) NMR data (CDCl\textsubscript{3}) were listed in Table 1.8 and 1.9, respectively) and \((3S,14S)\)-petrocortyne A (The \(^1\text{H}\) and \(^{13}\text{C}\) NMR data (CD\textsubscript{3}OD) were listed in Table 1.10 and 1.11, respectively). Thus, based on the NMR spectra, we cannot assign the relative configuration of the natural products.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9.jpg}
\caption{\(^1\text{H}\) NMR spectra of mixture 1.1Mix and four pure stereoisomers of 1.1 (CDCl\textsubscript{3})}
\end{figure}
Table 1.8. $^1$H NMR data of 3R,14R-petrocortyne A, 1.1SS/SR and 1.1Mix (CDCl3)

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<sup>a</sup>Reported by Shin (500MHz), <sup>b</sup>This work (600 MHz), <sup>c</sup>Mr. Yeh's work (600 MHz).
Table 1.9. $^{13}$C NMR data of $3R,14R$-petrocortyne A, 1.1SS/SR and 1.1Mix (CDCl$_3$)

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$^a$Reported by Shin (125MHz), $^{16a}$This work (151 MHz), $^b$Mr. Yeh’s work (151 MHz), $^{d–j}$Assignments with the same superscript in the same column may be interchanged.
Table 1.10. $^1$H NMR data of 3S,14S-petrocortyne A and 1.1SS/SR (CD$_3$OD)

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<th>1.1SR&lt;sup&gt;b&lt;/sup&gt;</th>
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<sup>a</sup>Reported by Jung (200 MHz),<sup>16c</sup> <sup>b</sup>This work (600 MHz).
Table 1.1. $^{13}$C NMR data of 3S,14S-petrocortyne A and 1.1SS/SR (CD$_3$OD)

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$^a$Reported by Jung (50 MHz), $^b$c–i Assignments with the same superscript in the same column may be interchanged.
Furthermore, we could not obtain a natural sample of (3R,14R)- or (3S,14S)-petrocortyne A to do chiral HPLC analysis to assign the structure of the natural product. Accordingly, chiral HPLC analysis, such as used to assign the murisolin, was not possible.

### 1.2.16 Structure assignment of petrocortyne A

In order to assign the stereo structure of petrocortyne A, we first looked at optical rotations. The optical rotations of these isomers are shown in Figure 1.8. Two pairs of diastereomer, **1.1RR/1.1RS** and **1.1SS/1.1SR**, have rotations that are too close to be differentiated in practice. So for the structure assignment purposes, the sign of the optical rotation can be used to assign the configuration of C3, but no information is provided about C14. Contributions to rotation from remote stereocenters are often approximately additive, so at this wavelength the C14 stereocenter apparently contributes an almost negligible amount to the total rotation. Thus, the four isomers could be partly differentiated by optical rotation.

The optical rotations of Shin’s petrocortyne A (+6.4, \(c = 0.25\) MeOH) and Jung’s sample (+10.8, \(c = 1.9\) MeOH) match the measure optical rotations of either (3S,14R)-petrocortyne A **1.1SR** (+9.5, \(c = 0.25\) MeOH) or (3S,14S)-petrocortyne A **1.1SS** (+10.5, \(c = 0.30\) MeOH). The optical rotation of Jung’s sample happens to match that of the (3S,14S)-petrocortyne A very well, but as mentioned above, the magnitudes of the rotations of the two diastereomers **1.1SR/1.1SS** are too close to be differentiated. So after the comparison of optical rotations, we can only assign the configuration of C3 as S. Accordingly, Jung’s assignment of this stereocenter is correct and Shin’s is incorrect. But we still cannot assign the absolute configuration of stereocenter at C14.
Since we have individual samples of all four isomers and have validated the Mosher ester analysis, in order to assign the absolute configuration of petrocortyne A, we turned to advanced Mosher ester derivatives. This was possible because Shin reported full $^1$H NMR data for Mosher esters of his samples and Jung did not report the full Mosher esters’ spectra, but he did report the differences of chemical shifts of the corresponding Mosher ester derivatives. After comparison of the reported and synthetic Mosher esters, we will confirm the assignment of the natural product. We then converted the pair of petrocortyne A diastereomers with the 3S configuration $1.1S$, $1.1S$ to both the bis-(R)- and bis-(S)-Mosher esters $1.91S$, $1.91S$, $1.92R$, and $1.92S$, respectively (Scheme 1.40).

Scheme 1.40. Synthesis of Mosher esters of $1.1S$ and $1.1S$
A set of 1D and 2D $^1$H NMR spectra of these esters were recorded for assignment and analysis. The expansions of the spectra of $1.91\text{SSR/SSS}$ and $1.92\text{SRR/SRS}$ along with their precursors $1.1\text{SS}$ and $1.1\text{SR}$ are shown in Figure 1.10. Our expectations that all the 1D Mosher esters’ spectra might be substantially identical in the region of the C14 stereocenter (H11 and H17) proved to be wrong; there were small yet clear differences.

![Figure 1.10. Expansions of the H11/H17 region of the $^1$H NMR spectra of 1.1SS/SR (top) Mosher esters of 1.1SS/SR (middle and bottom)](image)

Although the differences of the 1D $^1$H NMR spectra of each pair of Mosher esters, $1.91\text{SSR/SSS}$ and $1.92\text{SRR/SRS}$, were observed in Figure 1.10, how can we assign H11 and H17? The proper assignments of H11 and H17 are crucial for comparison of $^1$H NMR data of reported and synthetic Mosher esters. These assignments were made by TOCSY experiments. The expansions of the TOCSY spectra of $1.91\text{SSS/SSR}$ and $1.92\text{SRS/SRR}$ are shown in Figure
1.12 and 1.13, respectively. Accordingly, H11, H17 and related protons were assigned unambiguously. Only one cross-coupling peak between H21 and one of the two resonances in the H11 and H17 region was observed. H11 is too far away to communicate with H21, so this cross peak must be the result of interaction between protons H21 and H17.

![Figure 1.11. Expansions of portions of the TOCSY spectra of Mosher esters 1.91SSS/SSR](image1.png)

![Figure 1.12. Expansions of portions of the TOCSY spectra of Mosher esters 1.92SRS/SRR](image2.png)
All four Mosher esters spectra of the petrocortyne A isomers were unique. To assign the natural product configuration, we do not need to apply the Mosher rule and just simply compared the 1D $^1$H NMR spectra of the synthetic Mosher esters with those reported by Shin and the differences of chemical shifts of the Mosher ester derivatives reported by Jung. The data of the Mosher esters $^{1.91SSSS/SSR}$ of synthetic product $^{1.1SS}$, $^{3S,14S}$-petrocortyne A, uniquely matched the data reported by both groups (Table 1.12, 1.13). We also disproved the compound $^{1.1SR}$ is the natural product by comparison of the data obtained from the Mosher ester $^{1.92SRS/SRR}$ with the reported data (Table 1.12, 1.13). All results showed that Shin’s and Jung’s samples are identical, not enantiomers, and that Jung’s assignment of the $^{3S,14S}$ configuration is correct. Jung assigned H11 and H17 in the Mosher esters and applied the advanced Mosher method to assign the natural product correctly. Shin also assigned H11 and H17 correctly, but unfortunately, Shin and coworker forgot to reverse CIP priority of order of Mosher esters when using Mosher chlorides to synthesize Mosher esters. So their assignment of natural product is reversed.

### Table 1.12. $^1$H NMR data of reported and synthetic Mosher ester derivatives

<table>
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<tr>
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<th>$^{1.91SSR}$$^b$</th>
<th>$^{1.92SRR}$$^b$</th>
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<td>2.59 (d, 2.1)</td>
<td>2.59 (d, 2.1)</td>
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<td>6.01 (m)</td>
<td>6.01 (m)</td>
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<td>5.60 (ddt, 15.4, 7.0, 1.4)</td>
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<tr>
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<td>2.08 (q, 7.0)</td>
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<td>$^{2.22}$ (td, 7.0, 2.1)</td>
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<td>6.21 (t, 2.1)</td>
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<td>2.32 (qd, 7.7, 1.4)</td>
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<td>6.01 (m)</td>
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<td>3.06 (d, 2.1)</td>
<td>3.07 (d, 1.8)</td>
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$^a$Reported by Shin (500 MHz), $^b$This is work (700 MHz)
Table 1.13. \( \Delta \delta_{S-MTPA \text{ ester} - R-MTPA \text{ ester}} \) value (ppm) of reported and synthetic Mosher ester derivatives

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<th>6</th>
<th>11</th>
<th>17</th>
<th>18</th>
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<td>-0.04</td>
<td>-0.03</td>
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</tr>
<tr>
<td>( \Delta \delta_{1.91\text{SSS}/1.91\text{SSR}} )</td>
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<td>-0.10</td>
<td>-0.06</td>
<td>-0.04</td>
<td>-0.03</td>
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<td>0.02</td>
</tr>
<tr>
<td>( \Delta \delta_{1.92\text{SRS}/1.92\text{SRR}} )</td>
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<td>-0.04</td>
<td>0.02</td>
<td>-0.03</td>
<td>-0.03</td>
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</table>

*Reported by Jung 16c

With the optical rotations and Mosher esters spectra, we can confirm that the 3\( S \),14\( S \) configuration of petrocortyne A is correct. This assignment of the 3\( S \),14\( S \)-petrocortyne A is rigorous and is based solely on comparison of data derived from natural and synthetic samples and Mosher ester derivatives; it does not depend on applying Mosher rules.

1.2.17 “Shortcut” Mosher Ester Method

Because the local symmetry at C14, the pairs of methylene protons (H11, H17) in the alcohols 1.1\( SS/\text{SR} \) are chemical equivalent but can be differentiated in the Mosher ester derivatives 1.91\( \text{SSS/SSR} \) and 1.92\( \text{SRS/SRR} \). Subtraction of the pair of resonances from each other in one Mosher ester (rather than from the corresponding resonances in the two Mosher esters as advanced Mosher method mentioned) will provide the absolute configuration of the alcohol. We call this “shortcut” Mosher ester method.

Since we have synthesized and unambiguously assigned Mosher esters 1.91\( \text{SSS/SSR} \) for alcohol 1.1\( SS \) and Mosher esters 1.92\( \text{SRS/SRR} \) for 1.1\( SR \). We next analyzed the Mosher esters spectra by applying the standard advanced method and the shortcut method. In the advanced Mosher method, the differences of chemical shifts of corresponding protons (\( \delta_S - \delta_R \)) in (\( R \)- and
(S)-Mosher esters need to be used. The chemical shift of key protons and their differences between two Mosher esters are listed in Table 1.4. The differences of chemical shift of protons at both sides of the stereocenters have the opposite sign, based on the advanced Mosher method, and the absolute configurations of stereocenters at C3 and C14 were assigned as 3S,14S for **1.1SS** and 3S,14R for **1.1SR**, respectively.

In the shortcut Mosher method, we only use the difference of a symmetry-related pairs of protons ($\delta_{H11} - \delta_{H17}$ or $\delta_{H17} - \delta_{H11}$) in one single Mosher ester. Here we use subtraction ($\delta_{H11} - \delta_{H17}$) to assign the absolute configuration of stereocenter at C14. The subtraction data of Mosher esters of **1.1SS** and **1.1SR** are listed in Table 1.4. The signs of the subtractions are the opposite for stereocenters 14R and 14S, so both analyses correctly indicate the known configuration of the compounds. This validates the applicability of the shortcut Mosher method.

The shortcut Mosher method can be used to assign the petrocortyne A like natural products with local symmetry dialkynyl carbinol unit (other petrocortynes). Only one Mosher ester derivative is needed, after comparison of the natural product derivative with our results, the absolute configuration of the carbinol can be assigned. The shortcut method can also be generally applicable to assign any stereocenters with local symmetry. The method conserves valuable natural product, especially when only small amounts of natural product are isolated.
Table 1.14. Selective chemical shifts in Mosher esters and application of the advanced and shortcut Mosher methods

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<td>2.204</td>
<td>+0.026</td>
<td></td>
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</table>

\( ^{a}\)The standard advanced Mosher method. \( ^{b}\)The shortcut Mosher method with the \( R \)-MTPA ester. \( ^{c}\)Indicates 3S. \( ^{d}\)Indicates 14R. \( ^{e}\)Indicates 14S.

1.3 CONCLUSIONS

Fluorous mixture synthesis was applied to the total synthesis of petrocortyne A and its isomers. This technique features the tagging and mixing of enantiomers of the chiral starting material with different fluorous TIPS groups. The resulting mixture is taken through a series of steps to make the fluorous-tagged products, which are separated by fluorous HPLC in the demixing stage to provide the final enantiomerically pure products. The extra effort in making precursors in enantiopure form and tagging them with fluorous tags paid dividends in the end with easy separation and identification by fluorous dimixing.

The second-generation fluorous TIPS tags were synthesized and used in the synthesis. Both Mosher and NMA derivatization methods were developed during the synthesis. Because the Mosher esters of petrocortyne A are known, we used Mosher method to assign the absolute
configuration of the natural product. However, the study showed that NMA ester method is superior to Mosher method for the assignment of absolute configuration of stereocenter C17. NMA ester method should be a better choice for future natural product isolation work.

Comparison of optical rotations of the four synthetic and two natural samples showed that both natural samples had the C3-S configuration. Comparison of spectra of Mosher derivatives of the synthetic and natural samples showed that both natural samples had the 3S,14S configuration. At the same time, the use of the Mosher rule has been validated for assigning the challenging C14 stereocenter of petrocortyne A. As we showed above, a “shortcut” variant in which only one Mosher ester is made can also be used for assignment of this stereocenter.

In summary, the petrocortyne A and its isomers were synthesized and the two natural products were proved to be the same compound, 3S,14S-petrocortyne A.

1.4 EXPERIMENTAL

General Information:

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 according to literature. All other reagents were purchased commercially and used without further purification unless stated otherwise. Reaction mixtures were magnetically stirred and reaction 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 and reactions were analyzed by $^1$H NMR, $^{13}$C NMR, COSY, $^{19}$F NMR, FT-IR, high and low resolution mass spectroscopy, and HPLC. NMR spectra were taken on a Bruker WH-300, IBM AF-300, a Bruker Avance™ 500 NMR, a Bruker Avance™ 600 NMR, and a Bruker Avance™ 700 NMR spectrometer. Spectra were recorded at room temperature in the indicated deuteriated solvents and chemical shifts were reported in parts per million (ppm) downfield relative to TMS using the residual solvent proton resonance of CDCl$_3$ (7.26 ppm) or central CDCl$_3$ carbon peak (77.0 ppm) as the internal standard. In reporting spectral data, the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, m = multiplet, dd = doublet doublet, dt = doublet triplet, td = triplet doublet, qd = quartet doublet, ddt = doublet doublet triplet, dtd = doublet triplet double. Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film on NaCl plate. Peaks are reported in wavenumbers (cm$^{-1}$). Low resolution mass spectra were obtained on Fision Autospec. High resolution mass spectra were obtained on a V/G 70/70 double focusing machine and were reported in units of $m/e$. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the Na D-line ($\lambda = 589$ nm) using a 1 dm cell. HPLC analyses were performed on a Waters 600 E system with a Waters 2487 dual $\lambda$ absorption detector.

Non-8-yn-1-ol: 39

NaH (2.85 g, 60 wt% in mineral oil, 71.3 mmol) was added to a 250 ml of three-neck flask containing ethylenediamine (35 mL) at 0 °C. The resulting suspension was stirred at room
temperature for 1 h and then warmed to 60 °C. After being stirred at 60 °C for 1 h, the deep blue-black mixture was cooled to 45 °C and 3-nonyl-1-ol 1.9 (2.5 g, 17.8 mmol) was added dropwise. After complete addition, the resulting mixture was warmed back to 60 °C and was stirred for further 1 h. Upon slowly cooling to 0 °C, 1 M HCl (15 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et2O (3 × 40 mL). The combined organic layers were dried over MgSO4 and concentrated under reduced pressure. The crude product was purified by column chromatography (pentane/Et2O = 1:3 followed by 1:1) to afford title compound (1.71 g, 68%) as the colorless oil: 1H NMR (300 MHz, CDCl3) δ 3.63 (t, J = 6.5 Hz, 2 H), 2.18 (td, J = 6.8, 2.6 Hz, 2 H), 1.92 (t, J = 2.6 Hz, 1 H), 1.63–1.48 (m, 4 H), 1.45–1.28 (m, 6 H).

Non-8-ynal (1.8):30

A solution of DMSO (2.13 mL, 30 mmol) in CH2Cl2 (17 mL) was slowly added to a solution of oxalyl chloride (1.72 mL, 20 mmol) in CH2Cl2 (85 mL) at –78 °C. After 15 min at the same temperature, a solution of non-8-yn-1-ol (1.40 g, 10 mmol) in CH2Cl2 (17 mL) was then added dropwise. The resulting mixture was stirred for 15 min and Et3N (6.97 mL, 50 mmol) was added slowly. The reaction was maintained at –78 °C for 15 min, then allowed to warm to 0 °C, the stirring continued for further 30 min. Water was added and the mixture was diluted with Et2O. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with Et2O (3 × 30 mL). The combined organic layers were dried over MgSO4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (pentane/Et2O = 9:1) to afford the title compound 1.8 (1.24 g, 90%) as colorless oil: 1H NMR
(300 MHz, CDCl₃) δ 9.75 (t, J = 1.8 Hz, 1 H), 2.42 (td, J = 7.3, 1.8 Hz, 2 H), 2.17 (td, J = 6.8, 2.6 Hz, 2 H), 1.93 (t, J = 2.6 Hz, 1 H), 1.68–1.27 (m, 8 H).

(E)-Ethyl undec-2-en-10-ynoate (1.17):

Ethyl (triphenylphosphoranylidene)acetate 1.16 (3.21 g, 9.2 mmol) was added to a solution of aldehyde 1.8 (1.06 g, 7.7 mmol) in CH₂Cl₂ (20 mL) at room temperature. After being stirred overnight, the organic solvent was removed in vacuo, the residue was washed with petane and filtered through Celite®. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (pentane/Et₂O = 30:1) to afford the title compound 1.17 as (1.27 g, 80%) colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 6.95 (dt, J = 15.6, 6.9 Hz, 1 H), 5.80 (dt, J = 15.6, 1.6 Hz, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 2.23–2.14 (m, 4 H), 1.93 (t, J = 2.6 Hz, 1 H), 1.56–1.23 (m, 8 H) 1.28 (t, J = 7.1 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 166.7, 149.2, 121.3, 84.5, 68.2, 60.1, 32.1, 28.5, 28.4, 28.3, 18.3, 14.2.

(E)-Undec-2-en-10-yn-1-ol:

DIABL-H (12.5 mL, 1.0 M solution in hexane, 12.5 mmol) was added to a solution of ester 1.17 (1.04 g, 5.0 mmol) in CH₂Cl₂ (50 mL) over 10 min at −78 °C. After 30 min at the same temperature, the mixture was poured into a solution of saturated aqueous sodium potassium tartrate (125 mL) and Et₂O (125 mL), the resultant cloudy mixture was then vigorously stirred for 1 h, at which time the organic layer cleared. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with Et₂O (2 × 25 mL). Then the
combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (pentane/Et₂O = 3:1) to afford the title compound (0.82 g, 99%) as colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 5.71–5.55 (m, 2 H), 4.05 (t, J = 5.1, 2 H), 2.16 (td, J = 6.9, 2.6 Hz, 2 H), 2.02 (q, J = 6.3 Hz, 2 H), 1.92 (t, J = 2.6 Hz, 1 H), 1.65 (t, J = 5.7 Hz, 1 H), 1.57–1.23 (m, 8 H); ¹³C NMR (75 MHz, CDCl₃) δ 133.1, 128.9, 84.6, 68.1, 63.6, 32.0, 28.9, 28.5, 28.4, 28.3, 18.3.

(E)-Undec-2-en-10-yunal (1.7):

A solution of DMSO (0.96 mL, 13.5 mmol) in CH₂Cl₂ (7.5 mL) was slowly added to a solution of oxalyl chloride (0.77 mL, 9 mmol) in CH₂Cl₂ (42 mL) at −78 °C. After 15 min at the same temperature, a solution of (E)-undec-2-en-10-yn-1-ol (0.75 g, 4.5 mmol) in CH₂Cl₂ (7.5 mL) was then added dropwise. The resulting mixture was stirred for 15 min and Et₃N (3.14 mL, 22.5 mmol) was added slowly. The reaction was maintained at −78 °C for 15 min, then allowed to warm to 0 °C, the stirring continued for further 30 min. Water was added and the mixture was diluted with Et₂O. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with Et₂O (3 × 15 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (pentane/Et₂O = 9:1) to afford the title compound 1.7 (0.66 g, 90%): ¹H NMR (300 MHz, CDCl₃) δ 9.48 (d, J = 7.9 Hz, 1 H), 6.83 (dt, J = 15.6, 6.8 Hz, 1 H), 6.09 (ddt, J = 15.6, 7.9, 1.4 Hz, 1 H), 2.33 (qd, J = 7.1, 1.4 Hz, 2 H), 2.17 (td, J = 6.8, 2.6 Hz, 2 H), 1.93 (t, J = 2.6 Hz, 1 H), 1.56–1.28 (m, 8 H); ¹³C NMR (75 MHz, CDCl₃) δ 193.9, 158.5, 133.0, 84.4, 68.2, 32.5, 28.5, 28.3, 28.3, 27.6, 18.3.
\((E)-1-(\text{trimethylsilyl})\text{trideca-4-en-1,12-diyn-3-ol}\):

A solution of \(n\)-BuLi (3.15 mL, 1.6 M solution in hexane, 5.0 mmol) was added to a solution of trimethylsilylacetylene (0.8 mL, 5.5 mmol) in THF (20 mL) at \(-78^\circ\text{C}\). After 10 min, a solution of aldehyde 1.7 (554 mg, 3.4 mmol) in THF (5 mL) was added dropwise. The resulting mixture was stirred for further 10 min at this temperature and allowed to warm to room temperature. The mixture was poured into pH 7 phosphate buffer (20 mL) and extracted with Et\(_2\)O (3 × 20mL). The organic layer was washed with brine, dried over MgSO\(_4\) and concentrated \textit{in vacuo}. The residue was purified by column chromatography (hexane/CH\(_2\)Cl\(_2\) = 1:2) to afford the title compound as pale yellow oil (775 mg, 88%): \(^1\text{H NMR (300 MHz, CDCl}_3\) \(\delta 5.87\ (\text{dtd } J = 15.2, 6.7, 1.0 \text{ Hz, } 1 \text{ H}), 5.59\ (\text{ddt, } J = 15.3, 6.2, 1.4 \text{ Hz, } 1 \text{ H}), 4.82\ (t, J = 6.1 \text{ Hz, } 1 \text{ H}), 2.19\ (\text{td, } J = 6.9, 2.6 \text{ Hz, } 2 \text{ H}), 2.07\ (q, J = 7.0 \text{ Hz, } 2 \text{ H}), 1.94\ (t, J = 2.6 \text{ Hz, } 1 \text{ H}), 1.79\ (d, J = 6.0 \text{ Hz, } 1 \text{ H}), 1.55\text{–}1.26\ (m, 8\text{H}), 0.17\ (s, 9\text{H}); \(^{13}\text{C NMR (75 MHz, CDCl}_3\) \(\delta 134.3, 129.1, 105.3, 90.9, 84.9, 68.4, 63.6, 32.1, 29.0, 28.9, 28.8, 28.7, 18.7, 0.14.\)

\((E)-1-(\text{trimethylsilyl})\text{trideca-4-en-1,12-diyn-3-one (1.6)}:\)

To a solution of oxalyl chloride (0.26 mL, 3 mmol) in CH\(_2\)Cl\(_2\) (14 mL) was slowly added a solution of DMSO (0.32 mL, 4.5 mmol) in CH\(_2\)Cl\(_2\) (2.5 mL) at \(-78^\circ\text{C}\). After 15 min at the same temperature, a solution of \((E)-1-(\text{trimethylsilyl})\text{trideca-4-en-1,12-diyn-3-ol}\ (0.40\text{ g, } 1.5\text{ mmol}) in CH\(_2\)Cl\(_2\) (2.5 mL) was then added dropwise. The resulting mixture was stirred for 15
min and Et3N (1.05 mL, 7.5 mmol) was added slowly. The reaction was maintained at −78 °C for 15 min, then allowed to warm to 0 °C, the stirring continued for further 30 min. Water was added and the mixture was diluted with Et2O. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with Et2O (3 × 5 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/CH₂Cl₂ = 1:1) to afford the title compound 1.6 (347.8 mg, 88%) as pale yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 7.18 (dt, J = 15.7, 6.8 Hz, 1H), 6.15, (dt, J = 15.7, 1.4 Hz, 1H), 2.30 (qd, J = 6.6, 1.4 Hz, 2H), 2.19 (td, J = 6.8, 2.6 Hz, 2H), 1.95 (t, J = 2.6 Hz, 1H), 1.55–1.36 (m, 8H), 0.26 (s, 9H).

(R,E)-1-(Trimethylsilyl)trideca-4-en-1,12-diyn-3-ol (1.18R):

(R)-Alpine borane (7.2 mL, 0.5 M solution in THF, 3.6 mmol) was placed in a round bottle flask, the solvent was removed under vacuum and the flask was refilled with Ar. To it ketone 1.6 (315.0 mg, 1.2 mmol) was added slowly at 0 °C. After stirring at room temperature for 15 h, a solution of acetaldehyde (1.15 mL, 20 mmol)) in THF (2.4 mL) was added and the mixture was then stirred at room temperature for 6 h before removing the solvent in vacuo. To the residue a solution of ethanolamine (0.16 mL) in Et₂O (2.4 mL) was added. After 1 h, the white precipitate was filtered and washed with Et₂O. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The crude compound was purified by column chromatography (hexane/CH₂Cl₂ = 1:2) to afford the title compound 1.18R (183.6 mg, 58%, 93% ee): ¹H NMR (500 MHz, CDCl₃) δ 5.87 (dtd, J = 15.3, 7.4, 0.9 Hz, 1H), 5.58, (dd, J = 15.3, 6.2 Hz, 1H), 4.82 (t, J = 5.9 Hz, 1H), 2.18 (td, J = 7.0, 2.6 Hz, 2H), 2.07 (q, J = 7.2 Hz, 2H), 1.94
(S-(R,E)-1-(Trimethylsilyl)trideca-4-en-1,12-diyn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenyl propanoate (1.19RS):

(S)-MTPA acid (23.5 mg, 0.10 mmol), DCC (24.8 mg, 0.12 mmol), and DMAP (0.6 mg, 0.005 mmol) was added to a solution of alcohol 1.18R (13.1 mg, 0.05 mmol) in CH$_2$Cl$_2$ (0.7 ml) at room temperature. The resulting mixture was stirred at the same temperature overnight. The mixture was then filtered through a pad of Celite®, the filtrate was concentrated in vacuo. The crude product 1.19RS was obtained: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.54-7.51 (m, 2H), 7.43-7.36 (m, 3H), 6.02 (dtd, $J = 15.7$, 7.1, 0.7 Hz, 1H), 6.00 (d, $J = 6.8$ Hz, 1H), 5.57 (ddt, $J = 15.3$, 6.9, 1.2 Hz, 1H), 3.54 (s, 3H), 2.17 (td, $J = 6.8$, 2.6 Hz, 2H), 2.08 (q, $J = 6.6$ Hz, 2H), 1.93 (t, $J = 2.6$ Hz, 1H), 1.58–1.23 (m, 8H), 0.15 (s, 9H).
(R)-(R,E)-1-(Trimethylsilyl)trideca-4-en-1,12-diyln-3-yl)3,3,3-trifluoro-2-methoxy-2-phenyl propanoate (1.19RR):

Following the same procedure as above, except for using (R)-MTPA acid rather than (S)-MTPA acid, the title compound 1.19RR was obtained: $^1$H NMR (300 MHz, CDCl$_3$) δ 7.54-7.51 (m, 2H), 7.43-7.36 (m, 3H), 6.02 (dtd, $J$ = 15.7, 7.1, 0.7 Hz, 1H), 6.00 (d, $J$ = 6.8 Hz, 1H), 5.57 (ddt, $J$ = 15.3, 6.9, 1.2 Hz, 1H), 3.54 (s, 3H), 2.17 (td, $J$ = 6.8, 2.6 Hz, 2H), 2.08 (q, $J$ = 6.6 Hz, 2H), 1.93 (t, $J$ = 2.6 Hz, 1H), 1.58–1.23 (m, 8H), 0.15 (s, 9H).

(3,3,4,4,5,5,5-Heptafluoropentyl)diisopropylsilane (1.21):

t-BuLi (10.4 mL, 1.7 M solution in pentane, 17.6 mmol) was added by syringe pump in 40 min to a solution of iodide 1.20 (3.80 g, 11.7 mmol) in Et$_2$O (20 mL) at −78 °C. After 10 min at the same temperature, the mixture was warmed to −15 °C and stirred for further 10 min. The mixture was recooled to −78 °C. Chlorodisopropylsilane (1.10 mL, 6.5 mmol) was added to the above solution in 15 min. The resulting mixture was then warmed to room temperature and stirred overnight. Water (2 mL) was added at 0 °C, followed by 1 M HCl (20 mL). The mixture was extracted with Et$_2$O (3 × 30 mL). The organic layer was washed with water (2 × 20 mL), dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (100% hexane) to afford the title compound 25 (1.56 g, 77%): $^1$H NMR (300 MHz, CDCl$_3$) δ 3.49 (s, 1H), 2.20–2.04 (m, 2H), 1.05 (s, 14H), 0.88–0.82 (m, 2H).
(R,E)-(3,3,4,5,5,5-Heptafluoropentyl)diisopropyl(1-(trimethylsilyl)trideca-4-en-1,12-diyn-3-yloxy)silane (1.4R):

Trifluoromethanesulfonic acid (neat, 75.0 mg, 0.50 mmol) was slowly added to silane 25 (neat, 203.0 mg, 0.65 mmol) at 0 °C. After being stirred for 5 min at the same temperature, the mixture was warmed to room temperature and stirred for 15 h. To it a solution of alcohol 23 (131.2 mg, 0.50 mmol) in CH$_2$Cl$_2$ and 2,6-lutidine (116.0 μL, 1.00 mmol) were added at 0 °C. The resulting mixture was warmed to room temperature and stirred for further 2 h. Saturated aqueous NH$_4$Cl (1 mL) was then added to quench the reaction at 0 °C. The mixture was extracted with Et$_2$O (3 × 10 mL), the organic layers were combined and washed with water, dried over MgSO$_4$, and concentrated in vacuo. The crude product was purified by column chromatography (100% hexane) to afford the title compound 1.4R (135.9 mg, 82%): $^1$H NMR (300 MHz, CDCl$_3$) δ 5.77 (dtd, $J$ = 15.2, 6.7, 1.1 Hz, 1H), 5.34 (ddt, $J$ = 15.2, 5.7, 1.3 Hz, 1H), 4.88 (dd, $J$ = 5.7, 1.0 Hz, 1H), 2.18 (td, $J$ = 6.9, 2.6 Hz, 2H), 2.05 (q, $J$ = 6.9 Hz, 2H), 1.93 (t, $J$ = 2.6 Hz, 1H), 1.55-1.25 (m, 10H), 1.10–1.03 (m, 12H), 0.93–0.87 (m, 2H), 0.15 (s, 9H); MS (EI) m/z 572 (M$^+$); HRMS (EI) m/z (M$^+$) calcd for C$_{27}$H$_{43}$F$_7$OSi$_2$ 572.2741, found 572.2744.

Hept-6-yn-1-ol (1.22):$^{29}$

NaH (3.75g, 60 wt% in mineral oil, 93.8 mmol) was added to a 250 ml of three-neck flask containing ethylenediamine (37.5 mL) at 0 °C. The resulting suspension was stirred at room temperature for 1 h and then warmed to 60 °C. After being stirred at 60 °C for 1 h, the deep blue-black mixture was cooled to 45 °C and 3-heptyn-1-ol 1.10 (2.1 g, 18.8 mmol) was added dropwise. After complete addition, the resulting mixture was warmed back to 60 °C and was
stirred for further 1 h. Upon slowly cooling to 0 °C, 1 M HCl (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et₂O (3 × 50 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (pentane/Et₂O = 1:3) to afford compound 1.22 (1.35 g, 64%) as the colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 3.64 (t, J = 6.2 Hz, 2H), 2.20 (td, J = 6.7, 2.6 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.63–1.41 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 84.3, 68.2, 62.4, 32.0, 28.1, 24.8, 18.2.

OPMB

1-((Hept-6-ynyloxy)methyl)-4-methoxybenzene (1.10)

Alcohol 1.22 (1.34 g, 12 mmol) was added dropwise to a suspension of NaH (0.60 g, 60 wt% in mineral oil, 15 mmol) in DMF (25 mL) at 0 °C. After being stirred for 30 min at the same temperature, PMBCl (2.06 g, 13 mmol) was slowly added followed by addition of TBAI (44 mg, 0.12 mmol). The resulting mixture was stirred at room temperature for 18 h. Cold water (20 mL) was added to quench the reaction. The resulting mixture was extracted with Et₂O (3 × 30 mL). The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/Et₂O = 9:1) to afford the title compound 1.10 (2.55 g, 92%) as colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.46 (s,2H), 3.80 (s, 3H), 3.44 (t, J = 6.4 Hz, 2H), 2.19 (td, J = 6.8, 2.6 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.66–1.41 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 159.1, 130.7, 129.2, 113.7, 84.5, 72.5, 69.9, 68.2, 55.2, 29.2, 28.3, 25.4, 18.4.
8-(4-Methoxybenzyloxy)oct-2-ynal (1.5)

\(n\)-BuLi (6.8 mL, 1.6 M solution in hexane, 10.8 mmol) was slowly added to a solution of alkyne 1.10 (2.50 g, 10.8 mmol) in THF (27 mL) at \(-40^\circ\)C. After completion of addition, DMF (1.67 mL, 21.6 mmol) was added. The mixture was then warmed to room temperature. After being stirred for 30 min at the same temperature, the resulting mixture was poured into a solution of 10% acuos solution KH\(_2\)PO\(_4\) (58 mL) and methyl tert-butyl ether (MTBE) (54 mL) at 0°C. The organic layer was separated and the aqueous layer was extracted with MTBE (3 \(\times\) 40 mL). The combined organic layers was washed with water, dried over MgSO\(_4\), and concentrated in vacuo. The residue was purified by column chromatography (hexane/Et\(_2\)O = 3:1) to afford the title compound 1.5 (2.46 g, 88%) as pale yellow oil: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 9.17\) (s, 1H), 7.26 (d, \(J = 8.6\) Hz, 2H), 6.88 (d, \(J = 8.7\) Hz, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.45 (t, \(J = 6.2\) Hz, 2H), 2.42 (t, \(J = 6.5\) Hz, 2H), 1.67–1.46 (m, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 177.1, 159.0, 130.5, 129.1, 113.7, 99.0, 81.6, 72.5, 69.6, 55.2, 29.1, 27.3, 25.5, 19.0\); IR (film) 2935, 2858, 2279, 1667, 1612, 1512, 1462, 1246, 1173, 1095, 1033, 817 cm\(^{-1}\); MS (EI) \(m/z\) 260 (M\(^+\)); HRMS (EI) \(m/z\) (M\(^+\)) calcd for C\(_{16}\)H\(_{20}\)O\(_3\) 260.1412, found 260.1410.

7-(4-Methoxybenzyloxy)heptan-1-ol: \(^{37}\)

1,7-Heptanediol 1.34 (17.00 g, 128.6 mmol) was added dropwise to a suspension of NaH (5.15 g, 60 wt% in mineral oil, 128.8 mmol) in THF (490 mL) at 0°C. PMBCl (17.50 mL, 128.9 mmol) was then added dropwise followed by addition of TBAI (5.22 g, 14.1 mmol). After warm to room temperature and stirring for 1 h, the reaction mixture was heated to 60°C for 15 h. After being cooled to room temperature, the resulting mixture was poured into a solution of...
saturated NaHCO₃ and vigorously stirred. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were dried over MgSO₄ and concentrated \textit{in vacuo}. The residue was purified by flash chromatography (hexane/EtOAc = 7:3) to afford the title compound (15.93 g, 49%) as colorless oil: \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.26 (d, \(J = 8.6\) Hz, 2 H), 6.87 (d, \(J = 8.6\) Hz, 2 H), 4.42 (s, 2 H), 3.80 (s, 3 H), 3.61 (t, \(J = 6.6\) Hz, 2 H), 3.43 (t, \(J = 6.6\) Hz, 2 H), 1.62–1.50 (m, 4 H), 1.40–1.33 (m, 6 H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 159.0, 130.7, 129.2, 113.7, 72.5, 70.1, 62.9, 55.2, 32.6, 29.6, 29.2, 26.1, 25.6; IR (film) 3428, 2935, 2859, 1612, 1513, 1465, 1247, 1092, 908, 734, 650 cm\(^{-1}\); MS (EI) \(m/z\) 252 (M\(^+\)); HRMS (ESI) \(m/z\) (M\(^+\)) calcd for C\(_{15}\)H\(_{24}\)O\(_3\) 252.1725, found 252.1730.

\textbf{7-(4-Methoxybenzylloxy)heptanal (1.33):}\(^{37}\)

A solution of DMSO (13.0 mL, 183.0 mmol) in CH\(_2\)Cl\(_2\) (76 mL) was slowly added to a solution of oxalyl chloride (10.5 mL, 122.0 mmol) in CH\(_2\)Cl\(_2\) (350 ml) at –78 °C. After 15 min at the same temperature, a solution of 7-(4-Methoxybenzylloxy)heptan-1-ol (15.40 g, 61.0 mmol) in CH\(_2\)Cl\(_2\) (76 mL) was then added dropwise. The resulting mixture was stirred for 15 min and Et\(_3\)N (42.6 mL, 305.6 mmol) was added slowly. The reaction was maintained at –78 °C for 15 min, then allowed to warm to 0 °C, the stirring continued for further 30 min. Water was added and the mixture was diluted with Et\(_2\)O. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with Et\(_2\)O (3 × 120 mL). The combined organic layers were dried over MgSO\(_4\) and concentrated under reduced pressure. The crude product was purified by flash chromatography (Hexane/EtOAc = 5:1) to afford the title compound 1.33 (15.01 g, 98%) as colorless oil: \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 9.76 (t, \(J = 1.8\) Hz, 1 H) 7.26 (d, \(J\)
= 8.5 Hz, 2 H), 6.88 (d, J = 8.6 Hz, 2 H), 4.42 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, J = 6.5 Hz, 2 H), 2.42 (td, J = 7.3, 1.7 Hz, 2 H), 1.67–1.55 (m, 4 H), 1.44–1.28 (m, 6 H); 13C NMR (75 MHz, CDCl3) δ 202.7, 159.0, 130.6, 129.1, 113.6, 72.4, 69.8, 55.1, 43.7, 29.4, 28.8, 25.9, 21.9; IR (film) 2937, 2860, 1722, 1612, 1512, 1464, 1248, 1093, 1036, 908, 731, 650 cm⁻¹; MS (EI) m/z 250 (M⁺); HRMS (ESI) m/z (M⁺) calcd for C15H22O3 250.1569, found 250.1572.

(E)-N-Methoxy-9-(4-methoxybenzyl)-N-methylnon-2-enamide (1.32):

The diethyl N-methoxy-N-methylphosphonoacetamide 1.35 (15.1 mL, 73.2 mmol) was added to a suspension of NaH (3.30 g, 60 wt% in mineral oil, 82.5 mmol) in THF (400 mL) at 0 °C. The resulting mixture was stirred for 30 min, then a solution of aldehyde 1.33 (15.01 g, 60.0 mmol) in THF (100 mL) was added dropwise. The mixture was stirred for 1 h at room temperature before saturated aqueous NH₄Cl solution (120 mL) and Et₂O (120 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et₂O (3 × 120 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/EtOAc = 6:4) to afford the title compound 1.32 (18.30 g, 91%) as colorless oil: 1H NMR (300 MHz, CDCl3) δ 7.26 (d, J = 8.6 Hz, 2 H), 6.97 (dt, J = 15.4, 7.0 Hz, 1 H), 6.88 (d, J = 8.7 Hz, 2 H), 6.38 (dt, J = 15.4, 1.3 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.69 (s, 3 H), 3.43 (t, J = 6.6 Hz, 2 H), 3.23 (s, 3 H), 2.23 (qd, J = 7.0, 1.3 Hz, 2 H), 1.64–1.55 (m, 4 H), 1.50–1.25 (m, 6 H); 13C NMR (75 MHz, CDCl3) δ 167.0, 159.0, 147.8, 130.7, 129.1, 118.6, 113.7, 72.4, 70.0, 61.6, 55.2, 32.3, 32.2, 29.6, 28.9, 28.2, 25.9; IR (film) 2932, 2855, 1664, 1633, 1613, 1513, 1463, 1442, 1413, 1380, 1247,
1173, 1097, 1053, 998, 820 cm$^{-1}$; MS (EI) m/z 335 (M$^+$); HRMS (ESI) m/z (M$^+$) calcd for C$_{19}$H$_{29}$NO$_4$ 335.2097, found 335.2099.

(E)-1-(tert-Butyldimethylsilyl)-11-(4-methoxybenzyloxy)undec-4-en-1-yn-3-one (1.31):

$n$-BuLi (72.0 mL, 1.6 M solution in hexane, 115.2 mmol) was added to a solution of tert-butylidimethylsilylacetylene 1.36 (20.5 mL, 109.8 mmol) in THF (300 mL) at −78 °C. After 20 min, the solution of amide 1.32 (18.3 g, 54.6 mmol) in THF (100 mL) was added. The resulting mixture was stirred for further 1 h at −78 °C. The mixture was poured into a saturated aqueous NH$_4$Cl solution and extracted with Et$_2$O (3 × 150 mL). The combined organic extracts were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 10:1) to afford the title compounds 1.31 (20.17 g, 89%) as pale yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.26 (d, J = 8.5 Hz, 2 H), 7.19 (dt, J = 15.5, 7.0 Hz, 1 H), 6.88 (d, J = 8.5 Hz, 2 H), 6.15 (dt, J = 15.5, 1.3 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, J = 6.5 Hz, 2 H), 2.29 (qd, J = 7.0, 1.0 Hz, 2 H), 1.60 (quin, J = 6.9 Hz, 2 H), 1.50 (quin, J = 7.4 Hz, 2 H), 1.4–1.34 (m, 4 H), 0.98 (s, 9 H), 0.20 (s, 6 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 178.0, 159.0, 154.6, 132.1, 130.6, 129.1, 113.6, 101.1, 96.7, 72.4, 69.9, 55.1, 32.4, 29.5, 28.9, 27.8, 25.9, 25.8, 16.5, −5.2; IR (film) 2933, 2859, 1641, 1620, 1513, 1465, 1363, 1301, 1248, 1174, 1095, 1037, 1008, 976, 910, 841, 780, 734 cm$^{-1}$; MS (EI) m/z 437 (M$^+$ + Na); HRMS (ESI) m/z (M$^+$) calcd for C$_{25}$H$_{39}$O$_3$Si 415.2668, found 415.2669.
\((R,E)\)-1-(tert-Butyldimethylsilyl)-11-(4-methoxybenzyloxy)undec-4-en-1-yn-3-ol (1.37R):

A solution of compound 1.31 (10.62 g, 25.6 mmol) in THF (90 ml) was added dropwise in 10 min to a solution of \((R)\)-CBS (7.10 g, 25.6 mmol) and BH\(_3\)SMe\(_2\) (2.8 mL, 29.5 mmol) in THF (30 mL) at 0 °C under Ar. Upon completion of addition, reaction was cautiously quenched by slow addition of MeOH (30 mL) at 0 °C. The resulting solution was stirred for 15 min at room temperature and most organic solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 17:3) to afford the title compound 1.37R (7.48 g, 70%, 93% ee), \([\alpha]_D^{25} = -21.7 \ (c = 1.30, \text{CHCl}_3)\), \(\text{^1H NMR (300 MHz, CDCl}_3)\) \(\delta\) 7.26 (d, \(J = 8.4\) Hz, 2 H), 6.88 (d, \(J = 8.7\) Hz, 2 H), 5.90 (ddt, \(J = 15.3, 6.6, 0.9\) Hz, 1 H), 5.59 (ddt, \(J = 15.3, 5.7, 1.4\) Hz, 1 H), 4.82 (t, \(J = 6.0\) Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, \(J = 6.6\) Hz, 2 H), 2.06 (q, \(J = 6.6\) Hz, 2 H), 1.80 (d, \(J = 6.3\) Hz, 1 H), 1.63–1.55 (m, 2 H), 1.45–1.28 (m, 6 H), 0.94 (s, 9 H), 0.12 (s, 6 H); \(\text{^13C NMR (75 MHz, CDCl}_3)\) \(\delta\) 158.9, 133.7, 130.6, 129.1, 128.8, 113.6, 105.8, 88.4, 72.3, 69.9, 63.0, 55.1, 31.7, 29.5, 28.8, 28.7, 26.0, 25.9, 16.4, −4.8; IR (film) 3593, 3419, 2932, 2858, 1612, 1513, 1465, 1363, 1301, 1249, 1091, 1034, 909, 827, 777, 734 cm\(^{-1}\); HRMS (ESI) \(m/z\) (M\(^+\) + Na) calcd for C\(_{25}\)H\(_{40}\)O\(_3\)NaSi 439.2644, found 439.2620.

\((S,E)\)-1-(tert-Butyldimethylsilyl)-11-(4-methoxybenzyloxy)undec-4-en-1-yn-3-ol (1.37S):

Following the same procedure for 1.37R, ketone 1.31 (9.50 g, 22.9 mmol) was reacted with \((S)\)-CBS (6.35 g, 22.9 mmol), BH\(_3\)SMe\(_2\) (2.5 mL, 26.4 mmol), the title compound 1.37S (6.99 g, 73%, 94% ee) was obtained. \([\alpha]_D^{25} = +22.1 \ (c = 1.17, \text{CHCl}_3)\), \(\text{^1H NMR (300 MHz, CDCl}_3)\) \(\delta\) 7.26 (d, \(J = 8.1\) Hz, 2 H), 6.88 (d, \(J = 8.4\) Hz, 2 H), 5.89 (dt, \(J = 15.0, 6.9\) Hz, 1 H),
5.59 (dd, $J = 15.0, 5.7$ Hz, 1 H), 4.82 (t, $J = 6.0$ Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, $J = 6.6$ Hz, 2 H), 2.05 (q, $J = 6.6$ Hz, 2 H), 1.86 (d, $J = 6.3$ Hz, 1 H), 1.63–1.54 (m, 2 H), 1.45–1.28 (m, 6 H), 0.94 (s, 9 H), 0.12 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.0, 133.9, 130.7, 129.2, 128.8, 113.7, 105.7, 88.7, 72.4, 70.0, 63.2, 55.2, 31.8, 29.6, 28.9, 28.7, 26.0(2C), 16.4, –4.7; IR (film) 3405, 2931, 2857, 1613, 1513, 1464, 1362, 1302, 1249, 1091, 1035, 910, 828, 776, 733 cm$^{-1}$; MS (EI) $m/z$ 439 (M$^+$ + Na); HRMS (ESI) $m/z$ (M$^+$ + Na) calcd for C$_{25}$H$_{40}$O$_3$NaSi 439.2644, found 439.2640.

(S,E)-11-(4-methoxybenzyloxy)undec-4-en-1-yn-3-ol (1.38S):

TBAF (0.77 mL, 1.0 M solution in THF, 0.77 mmol) was added to a solution of 43b (216.3 mg, 0.52 mmol) in THF (10 mL) at –20 °C. The mixture then was stirred for 30 min at this temperature and quenched with saturated aqueous NH$_4$Cl. The resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic layers were washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 9 : 1) to give compound 1.38S (149.1 mg, 95%) as pale yellow oil. $[\alpha]_D^{25} = +17.9$ (c = 1.14, CHCl$_3$). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 5.90 (dt, $J = 15.3, 6.7, 1.1$ Hz, 1H), 5.60 (ddt, $J = 15.3, 6.1, 1.4$ Hz), 4.83 (m, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, $J = 6.5$ Hz, 2H), 2.56 (d, $J = 2.2$ Hz, 1H), 2.06 (q, $J = 6.5$ Hz, 2H), 1.89 (d, $J = 6.2$ Hz, 1H), 1.64–1.54 (m, 2H), 1.45–1.23 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.0, 134.1, 130.6, 129.2, 128.5, 113.7, 83.4, 73.8, 72.4, 69.9, 62.5, 55.2, 31.7, 29.5, 28.9, 28.6, 25.9; IR (film) 3591, 3416, 3306, 3004, 2935, 2858, 1613, 1513,
1465, 1248, 1090, 908, 732, 650 cm\(^{-1}\); MS (EI) \(m/z\) 302 (M\(^+\)); HRMS (EI) \(m/z\) (M\(^+\)) calcd for C\(_{19}\)H\(_{26}\)O\(_3\) 302.1882, found 302.1872.

\[(R,E)-11-(4\text{-methoxybenzyloxy})\text{undec-4-en-1-yn-3-ol (1.38R)}:\]

Following the same procedure for 1.38S, alcohol 1.37R (207.6 mg, 0.50 mmol) was reacted with TBAF (0.75 mL, 1.0 M solution in THF, 0.75 mmol), the title compound 1.38R (150.2 mg, 95%) was obtained. \([\alpha]_D^{25} = -18.1 (c = 1.37, \text{CHCl}_3)\), \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.26 (d, \(J = 8.7\) Hz, 2H), 6.88 (d, \(J = 8.7\) Hz, 2H), 5.90 (dtd, \(J = 15.2, 6.7, 1.1\) Hz, 1H), 5.60 (ddt, \(J = 15.3, 6.1, 1.4\) Hz), 4.83 (m, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, \(J = 6.6\) Hz, 2H), 2.56 (d, \(J = 2.2\) Hz, 1H), 2.06 (q, \(J = 6.7\) Hz, 2H), 1.89 (d, \(J = 6.2\) Hz, 1H), 1.63–1.55 (m, 2H), 1.45–1.23 (m, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 158.9, 133.9, 130.5, 129.1, 128.5, 113.6, 83.4, 73.7, 72.3, 69.9, 62.4, 55.1, 31.7, 29.4, 28.8, 28.6, 25.8; IR (film) 3591, 3417, 3306, 3004, 2934, 2858, 1613, 1513, 1465, 1248, 1090, 905, 731, 650 cm\(^{-1}\); MS (EI) \(m/z\) 302 (M\(^+\)); HRMS (EI) \(m/z\) (M\(^+\)) calcd for C\(_{19}\)H\(_{26}\)O\(_3\) 302.1882, found 302.1871.

\[(S,E)-11-(4\text{-methoxybenzyloxy})\text{undec-4-en-1-yn-3-yl)3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (1.39SS)}:\]

Alcohol 1.38S (11.0 mg, 0.04 mmol) was added to a solution of (R)-MTPA-Cl (20.4 \(\mu\)L, 0.11 mmol) in pyridine (0.4 mL) at room temperature. After 4 h, the organic solvent was
removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound **1.39SS** (14.5 mg, 78%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.54-7.51 (m, 2H), 7.41-7.36 (m, 3H), 7.26 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 6.00 (d, $J = 6.8$ Hz, 1H), 6.03 (dt, $J = 15.3$, 6.9, 0.9 Hz, 1H), 5.49 (ddt, $J = 15.1$, 6.9, 1.4 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.59 (s, 3H), 3.42 (t, $J = 6.6$ Hz, 2H), 2.63 (d, $J = 2.2$ Hz, 1H), 2.04 (q, $J = 7.0$ Hz, 2H), 1.63–1.53 (m, 2H), 1.41–1.23 (m, 6H).

![Chemical Structure](image)

**OPMB**

**(R)**-**((S,E))**-11-(4-Methoxybenzyloxy)undec-4-en-1-yn-3-yl)3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**1.39SR**)

Following the same procedure as above, except for using **(S)**-MTPA-Cl rather than **(R)**-MTPA-Cl, the title compound **1.39SR** (15.0 mg, 80%) was obtained. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.54-7.52 (m, 2H), 7.43-7.37 (m, 3H), 7.26 (d, $J = 8.6$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 6.07 (dt, $J = 15.3$, 6.9 Hz, 1H), 6.00 (d, $J = 6.8$ Hz, 1H), 5.60 (ddt, $J = 15.4$, 6.9, 1.2 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.55 (s, 3H), 3.43 (t, $J = 6.5$ Hz, 2H), 2.59 (d, $J = 2.2$ Hz, 1H), 2.09 (q, $J = 6.9$ Hz, 2H), 1.64–1.54 (m, 2H), 1.45–1.23 (m, 6H).

![Chemical Structure](image)

**(S)**-**((S,E))**-11-(4-Methoxybenzyloxy)undec-4-en-1-yn-3-yl)2-methoxy-2-(naphthalen-2-yl)acetate (**1.40SS**):
(S)-NMA acid (16.0 mg, 0.07 mmol), DCC (18.3, 0.09 mmol), and DMAP (0.9 mg, 0.007 mmol) was added to a solution of alcohol 43a (11.2 mg, 0.04 mmol) in CH$_2$Cl$_2$ (0.7 ml) at room temperature. The resulting mixture was stirred at the same temperature overnight. The mixture was then filtered through a pad of Celite, the filtrate was concentrated in vacuo. The crude product was purified by column chromatography (hexane/EtOAc = 17:3) to afford the title compound 1.40SS (14.2 mg, 77%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.93 (s, 1H), 7.86-7.82 (m, 3H), 7.56 (dd, $J$ = 8.5, 1.5 Hz, 1H), 7.51-7.47 (m, 2H), 7.26 (d, $J$ = 8.5 Hz, 2H), 6.88 (d, $J$ = 8.5 Hz, 2H), 5.98 (dtd, $J$ = 15.0, 7.0, 1.0 Hz, 1H), 5.34 (dd, $J$ = 6.5, 1.0 Hz, 1H), 5.39 (dtd, $J$ = 15.0, 6.5, 1.5 Hz, 1H), 4.96 (s, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.46 (s, 3H), 3.42 (t, $J$ = 6.5 Hz, 2H), 2.45 (d, $J$ = 2.0 Hz, 1H), 2.04 (q, $J$ = 7.0 Hz, 2H), 1.61–1.55 (m, 2H), 1.39–1.23 (m, 6H).

1.40SS (S)-(R,E)-11-(4-Methoxybenzyloxy)undec-4-en-1-yn-3-yl 2-methoxy-2-(naphthalen-2-yl) acetate (1.40RS):

Following the same procedure as above, except for using alcohol 1.38R rather than 1.38S, the title compound 1.40RS (15.7 mg, 85%) was obtained. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.92 (s, 1H), 7.86-7.81 (m, 3H), 7.54 (dd, $J$ = 8.5, 1.5 Hz, 1H), 7.50-7.47 (m, 2H), 7.26 (d, $J$ = 8.5 Hz, 2H), 6.88 (d, $J$ = 8.5 Hz, 2H), 5.89 (dd, $J$ = 6.5, 1.0 Hz, 1H), 5.79 (dtd, $J$ = 15.0, 7.0, 1.0 Hz, 1H), 5.34 (ddt, $J$ = 15.0, 6.5, 1.5 Hz, 1H), 4.97 (s, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.47 (s, 3H), 3.42 (t, $J$ = 6.5 Hz, 2H), 2.56 (d, $J$ = 2.5 Hz, 1H), 1.89 (q, $J$ = 6.5 Hz, 2H), 1.52 (m, 2H), 1.27–1.12 (m, 6H).
(R,E)-tert-Butyl(3-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-11-(4-
methoxybenzyloxy)undec-4-en-1-ynyl)dimethylsilane (1.41R):

Trifluoromethanesulfonic acid (neat, 2.9 mL, 33.2 mmol) was slowly added to silane
C₄F₉(CH₂)₂(Pr)₂SiH (neat, 15.1 g, 41.5 mmol) at 0 °C. After being stirred for 20 min at the same
temperature, the mixture was warmed to room temperature and stirred for 15 h. CH₂Cl₂ (30 mL)
was added to above mixture at −60 °C, followed by a solution of alcohol 1.37R (6.92 g, 16.6
mmol) in CH₂Cl₂ (42 mL) and 2,6-lutidine (5.8 mL, 49.8 mmol). The resulting mixture was
warmed to room temperature and stirred for further 2 h. Saturated aqueous NH₄Cl (100 mL) was
then added to quench the reaction at 0 °C. The mixture was extracted with Et₂O (3 × 150 mL),
the organic layers were combined and washed with water, dried over MgSO₄, and concentrated
in vacuo. The crude product was purified by column chromatography (hexane/EtOAc = 19:1) to
afford the title compound 1.41R (11.23 g, 87%) as colorless oil. [α]D²⁵ = +1.13 (c = 1.20,
CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 5.79
(dtd, J = 15.3, 6.6, 0.9 Hz, 1 H), 5.51 (dd, J = 15.0, 5.7 Hz, 1 H), 4.89 (d, J = 5.4 Hz, 1 H), 4.43
(s, 2 H), 3.80 (s, 3 H), 3.43 (t, J = 6.3 Hz, 2 H), 2.23–2.01 (m, 4 H), 1.61–1.54 (m, 2 H), 1.43–
1.28 (m, 6 H), 1.06 (br s, 14 H), 0.93–0.86 (m, 11 H), 0.09 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃)
δ 159.1, 132.5, 130.8, 129.4, 129.2, 113.8, 106.0, 88.4, 72.5, 70.2, 64.1, 55.3, 31.7, 29.7, 29.0,
28.9, 26.0, 25.9, 25.4 (t, JₐCF = 23.2 Hz, 1 C), 17.5 (2 C), 17.4 (2 C) 16.5, 12.7, 12.6, 0.3 –4.9; IR
(film) 3020, 2934, 1640, 1514, 1474, 1424, 1216, 1133, 1036, 929, 755 cm⁻¹; HRMS (ESI) m/z
(M⁺ + H) calcd for C₃₇H₅₈O₃Si₂F₉ 777.3793, found 777.3781.
(S,E)-tert-Butyl(3-(3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-11-(4-methoxybenzyloxy)undec-4-en-1-ynyl)dimethylsilane (1.41S):

Trifluoromethanesulfonic acid (neat, 2.7 mL, 30.8 mmol) was slowly added to silane C₃F₇(CH₂)₂(Pr)₂SiH (neat, 12.1 g, 39.5 mmol) at 0 °C. After being stirred for 20 min at the same temperature, the mixture was warmed to room temperature and stirred for 15 h. CH₂Cl₂ (23 mL) was added to above mixture at –60 °C, followed by a solution of alcohol 1.37R (6.44 g, 15.4 mmol) in CH₂Cl₂ (39 mL) and 2,6-lutidine (5.4 mL, 46.2 mmol). The resulting mixture was warmed to room temperature and stirred for further 2 h. Saturated aqueous NH₄Cl (90 mL) was then added to quench the reaction at 0 °C. The mixture was extracted with Et₂O (3 × 150 mL), the organic layers were combined and washed with water, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound 1.41S (10.11 g, 90%) as colorless oil. [α]D²⁵ = −1.09 (c = 0.92, CHCl₃),

¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 5.79 (dtd, J = 15.3, 6.9, 0.6 Hz, 1 H), 5.51 (dd, J = 15.3, 5.7 Hz, 1 H), 4.89 (d, J = 5.7 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, J = 6.6 Hz, 2 H), 2.23–2.01 (m, 4 H), 1.61–1.53 (m, 2 H), 1.43–1.28 (m, 6 H), 1.06 (br s, 14 H), 0.93–0.86 (m, 11 H), 0.09 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 159.1, 132.5, 130.8, 129.4, 129.2, 113.8, 106.0, 88.4, 72.5, 70.2, 64.1, 55.2, 31.7, 29.7, 29.0, 28.9, 26.0, 25.9, 25.3 (t, JCF = 23.2 Hz, 1 C), 17.5 (2 C), 17.4 (2 C) 16.5, 12.7, 12.6, 0.3–4.9; IR (film) 3020, 2934, 1640, 1514, 1474, 1424, 1216, 1133, 1037, 929, 755 cm⁻¹; HRMS (ESI) m/z (M⁺ + Na + H) calcd for C₃₇H₅₈O₃NaSi₄F₇: 749.3634, found 749.3632.
(R/S,E)-11-(tert-Butyldimethylsilyl)-9-((perfluoroalkylethyl)diisopropylsilyloxy)undec-7-en-10-yn-1-ol (M-1.42):

DDQ (5.90 g, 26.0 mmol) was added to the mixture of compound 1.41R (7.77 g, 10.0 mmol) and compound 1.41S (7.25 g, 10.0 mmol) in CH₂Cl₂ (200 mL) and H₂O (22.3 mL) at room temperature. The reaction was monitored by TLC until completion, and then saturated NaHCO₃ aqueous solution was added. The mixture was extracted with CH₂Cl₂ (3 × 150 mL), the organic layers were combined, washed with saturated NaHCO₃ aqueous solution, brine, dried over MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography (hexane/Et₂O = 85:15) to afford the title compound M-41, which was contaminated with tiny 4-(methoxymethyl)benzaldehyde and was used in the following step without further purification. ¹H NMR (300 MHz, CDCl₃) δ 5.79 (dtd, J = 15.3, 7.8, 0.9 Hz, 1H), 5.54 (dd, J = 15.3, 5.7, 1H), 4.89 (d, J = 5.7 Hz, 1H), 3.64 (q, J = 6.2 Hz, 2H), 2.23–2.03 (m, 2H), 2.06 (q, J = 6.6 Hz, 2H), 1.61–1.52 (m, 2H), 1.45–1.33 (m, 6H), 1.18 (t, J = 5.4 Hz, 1H), 1.08–1.06 (m, 14H), 0.95–0.85 (m, 11H), 0.09 (s, 6H).

(R/S,E)-tert-Butyl(3-(perfluoroalkylethyl)diisopropylsilyloxy)-11-iodoundec-4-en-1-ynyl)dimethylsilane (M-1.29):

A solution of iodine (5.74 g, 22.6 mmol) in CH₂Cl₂ (85 mL) was slowly added to a solution of triphenylphosphine (5.93 g, 22.6 mmol) in CH₂Cl₂ (28 mL), followed by a mixture of imidazole (1.69 g, 24.8 mmol) and alcohol M-1.42 (crude, 7.14 g, 11.3 mmol) in CH₂Cl₂ (28 mL)
at room temperature. After 2 h, the reaction was quenched with saturated aqueous NaHCO₃ (150 mL). The mixture was extracted with Et₂O (3 × 100 mL) and organic layer was washed with saturated aqueous Na₂S₂O₃ (100 mL), water, brine, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/Et₂O = 99.5:0.5) to afford the title compound **M-40** (7.33 g, 49%) as yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 5.79 (dtd, J = 15.3, 7.5, 0.9 Hz, 1H), 5.52 (dd, J = 15.3, 5.7 Hz, 1H), 4.90 (d, J = 5.7 Hz, 1H), 3.18 (t, J = 6.9 Hz, 2H), 2.28–2.06 (m, 2H), 2.06 (q, J = 6.6 Hz, 2H), 1.86–1.77 (m, 2H), 1.43–1.26 (m, 6H), 1.19–1.02 (m, 14H), 1.06 (m, 11H), 0.09 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 132.2, 129.6, 105.9, 88.4, 87.6, 64.1, 33.5, 31.6, 30.3, 28.7, 28.0, 26.0, 17.5 (2C), 17.4 (2C), 16.5, 12.7, 12.6, 7.0, 0.3, −4.9.

**General procedure: asymmetric alkynylation to alkynyl aldehyde.**

In a 25mL round bottle flask, a solution of alkyne (3.0 mmol) and diethylzinc (323.4 μL, 3.0 mmol) in toluene (1.0 mL) was heated under argon atmosphere to reflux for 1 h. After the solution cooled to room temperature, (R)-BINOL (143.2 mg, 0.5 mmol), Et₂O (8.0 mL), and Ti(OiPr)₄ (370.0 μL, 1.25 mmol) were added sequentially, the resulting mixture was stirred for 1 h. Aldehyde (0.5 mmol) was added to the above mixture and stirring continued for additional 4 h. Saturated aqueous NH₄Cl was added to quench the reaction. The mixture was extracted with CH₂Cl₂, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography to afford the corresponding propargylic alcohol. The ee of product was determined by chiral HPLC (Chiralcel OD column, 4.6 × 200 mm, hexane/iPrOH = 9:1, 1.0 mL/min)
**OH**

**(S)-1-Phenyldeca-1,4-diyn-3-ol (1.44S):**

General procedure was followed employing phenylacetylene 1.43 (336.2 μL, 3.0 mmol), diethylzinc (323.4 μL, 3.0 mmol), (R)-BINOL (143.2 mg, 0.5 mmol), Ti(OiPr)₄ (370.0 μL, 1.25 mmol), and 2-octynal 1.27 (73.5 μL, 0.5 mmol). Purification by column chromatography (hexane/EtOAc = 19:1) afforded the title compound 1.44S (102.1 mg, 90%). 78% ee determined by HPLC analysis (t_{minor} = 6.16 min, t_{major} = 11.03 min). ¹H NMR (300 MHz, CDCl₃) δ 7.49–7.45 (m, 2H), 7.34–7.28 (m, 3H), 5.35 (dt, J = 6.9, 1.8 Hz, 1H), 2.35 (d, J = 7.0, 1H), 2.25 (td, J = 7.1 Hz, 2.0 Hz, 2H), 1.60–1.50 (m, 2H), 1.43–1.26 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 131.8, 128.7, 128.2, 122.1, 86.7, 86.0, 83.9, 77.4, 52.9, 31.0, 28.0, 22.1, 18.7, 13.9; IR (film) 3336, 3032, 2917, 1855, 2230, 1599, 1499, 1443, 1378, 1071, 1010, 996, 963, 942, 756, 691 cm⁻¹.

**Si**

**(S)-1-(Dimethyl(phenyl)silyl)deca-1,4-diyn-3-ol (1.48S):**

General procedure was followed employing dimethylphenylsilylacetylene 1.45 (540.1 μL, 3.0 mmol), diethylzinc (323.4 μL, 3.0 mmol), (R)-BINOL (143.2 mg, 0.5 mmol), Ti(OiPr)₄ (370.0 μL, 1.25 mmol), and 2-octynal 1.27 (73.5 μL, 0.5 mmol). Purification by column chromatography (hexane/EtOAc = 19:1) afforded the title compound 1.48S (127.1 mg, 90%) as yellow oil. 78% ee determined by HPLC analysis (hexane/iPrOH = 49:1, 1 mL/min, t_{minor} = 11.01 min, t_{major} = 13.25 min). ¹H NMR (300 MHz, CDCl₃) δ 7.64–7.61 (m, 2H), 7.39–7.35 (m, 3H), 5.14 (dt, J = 7.4, 1.9 Hz, 1H), 2.23 (td, J = 7.0, 1.9 Hz, 2H), 2.15 (d, J = 7.4 Hz, 1H), 1.58–1.49
(m, 2H), 1.42–1.26 (m, 4H), 0.90 (t, \( J =7.1 \) Hz, 3H), 0.44 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 136.4, 133.7, 129.5, 127.9, 104.3, 86.9, 86.0, 77.2, 52.9, 31.0, 28.0, 22.2, 18.7, 13.9, –1.1; IR (film) 3368, 3070, 2958, 2932, 2860, 2178, 1466, 1429, 1298, 1250, 1115, 1034, 964, 838, 782, 732, 698; MS (EI) \( m/z \) 283 (\( M^+ - H \)); HRMS (EI) \( m/z \) (\( M^+ - H \)) calcd for C\(_{18}\)H\(_{23}\)OSi 283.1518, found 283.1520.

![Chemical Structure](image)

(S)-1-(Methyldiphenylsilyl)deca-1,4-diyn-3-ol (1.49S):

General procedure was followed employing methyldiphenylsilylacetylene \( 1.46 \) (660.5 \( \mu \)L, 3.0 mmol), diethylzinc (323.4 \( \mu \)L, 3.0 mmol), (R)-BINOL (143.2 mg, 0.5 mmol), Ti(O\(^{i}\)Pr)\(_4\) (370.0 \( \mu \)L, 1.25 mmol), and 2-octynal \( 1.27 \) (73.5 \( \mu \)L, 0.5 mmol). Purification by column chromatography (hexane/EtOAc = 33:1) afforded the title compound \( 1.49S \) (147.3 mg, 85%) as a yellow oil. 80% ee determined by HPLC analysis (hexane/\(^{i}\)PrOH = 49:1, 1 mL/min, \( t_{\text{minor}} \) = 15.55 min, \( t_{\text{major}} \) = 20.78 min), \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.66–7.63 (m, 4H), 7.45–7.34 (m, 6H), 5.19 (dt, \( J = 7.6, 2.1 \) Hz, 1H), 2.24 (td, \( J = 7.0, 2.1 \) Hz, 2H), 2.20 (d, \( J = 7.5 \) Hz, 1H), 1.59-1.50 (m, 2H), 1.43–1.26 (m, 4H), 0.90 (t, \( J =6.9 \) Hz, 3H), 0.71 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 134.7 134.5, 129.8, 128.0, 105.9, 86.2, 85.3, 77.1, 53.0, 31.0, 28.0, 22.2, 18.7, 13.9, –2.3; IR (film) 3398, 3069, 2957, 2930, 2859, 2178, 1466, 1429, 1298, 1252, 1114, 1034, 964, 793, 728, 698; MS (EI) \( m/z \) 346 (\( M^+ \)); HRMS (EI) \( m/z \) (\( M^+ \)) calcd for C\(_{23}\)H\(_{26}\)OSi 346.1753, found 346.1736.
(S)-2-(tert-Butyldimethylsilyloxy)-2-methyldodeca-3,6-diyn-5-ol (1.50S):

General procedure was followed employing alkyne 1.47 (679.2 mg, 3.0 mmol), diethylzinc (323.4 μL, 3.0 mmol), (R)-BINOL (143.2 mg, 0.5 mmol), Ti(O"Pr)₄ (370.0 μL, 1.25 mmol), and 2-octynal 1.27 (73.5 μL, 0.5 mmol). Purification by column chromatography (hexane/EtOAc = 33:1) afforded the title compound 1.50S (150.6 mg, 86%) as a yellow oil. 90% ee determined by HPLC analysis (hexane/PrOH = 49:1, 0.6 mL/min, t_minor = 15.55 min, t_major = 20.78 min), ¹H NMR (300 MHz, CDCl₃) δ 5.10 (dt, J = 7.4, 2.1 Hz, 1H), 2.22 (td, J = 7.0, 2.0 Hz, 2H), 1.99 (d, J = 7.3 Hz, 1H), 1.57–1.50 (m, 2H), 1.46 (s, 6H), 1.39-1.25 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 89.3, 85.8, 80.1, 77.2, 66.2, 52.5, 32.7, 31.0, 28.0, 25.7, 22.2, 18.6, 17.9, 13.9, −3.0; IR (film) 3053, 2986, 2254, 1422, 1265, 1162, 1037, 909, 735, 650; MS (EI) m/z 307 (M⁺ - CH₃); HRMS (EI) m/z (M⁺ - CH₃) calcd for C₁₈H₃₁O₂Si 307.2093, found 307.2089.

2-(tert-Butyldimethylsilyloxy)-2-methyldodeca-3,6-diyn-5-ol (rac-1.51):

n-BuLi (4.1 mL, 1.6 M solution in hexane, 6.5 mmol) was slowly added to a solution of alkyne 1.47 (1.29 g, 6.5 mmol) in THF (30 mL) at −78 °C. The mixture was then warmed to room temperature and stirred for 1 h. 2-Octynal 1.27 (0.74 mL, 5.0 mmol) was added and the resulting mixture was then stirred overnight. Ice was added to quench reaction; the mixture was extracted with CH₂Cl₂ (3 × 30 mL). The organic layers were combined, dried over MgSO₄, and
concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 97:3) to afford the racemic compound \textit{rac-1.51} (1.32 g, 82%) as yellow oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.10 (dt, $J$ = 7.3, 2.0 Hz, 1H), 2.21 (td, $J$ = 7.0, 2.1 Hz, 2H), 2.12 (d, $J$ = 7.4 Hz, 1H), 1.56–1.48 (m, 2H), 1.45 (s, 6H), 1.39–1.27 (m, 4H), 0.90 (t, $J$ = 6.9 Hz, 3H), 0.86 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 89.2, 85.7, 80.0, 77.3, 66.1, 52.4, 32.6, 31.0, 28.0, 25.7, 22.2, 18.6, 17.9, 13.9, −3.1.

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

2-Methyldodeca-3,6-diyne-2,5-diol \textit{(rac-1.52)}:

Acetyl chloride (1 mL) was added to a solution of compound 37 (1.28 g, 4.0 mmol) in MeOH (40 mL) at room temperature. The mixture was then stirred for 10 min at the same temperature. The organic solvents were then removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 7:3) to afford the title compound 38 (0.75 g, 91%) as pale yellow oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.10 (br s, 1H), 3.06 (d, $J$ = 6.7 Hz, 1H), 2.80 (s, 1H), 2.21 (td, $J$ = 7.1, 2.0 Hz, 2H), 1.58–1.45 (m, 2H), 1.52 (s, 6H), 1.39–1.24 (m, 4H), 0.89 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 88.4, 85.6, 80.0, 77.0, 65.1, 52.1, 31.0 (3C), 28.0, 22.1, 18.6, 13.9.

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

2-Methyl-5-(triisopropylsilyloxy)dodeca-3,6-diyn-2-ol \textit{(rac-1.53)}:
TIPSCI (0.66 mL, 3.1 mmol) and imidazole (279 mg, 4.1 mmol) was added to a solution of diol rac-1.52 (533 mg, 2.6 mmol) in DMF (13 mL) at room temperature. The mixture was stirred overnight at the same temperature. Water (20 mL) was added to quench reaction. The organic layer was separated; the aqueous layer was extracted with Et₂O (3 × 15 mL). The organic layers were combined, dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc = 97:3) to afford title compound 39 (813 mg, 87%) as pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 5.25 (t, J = 2.1 Hz, 1H), 2.20 (td, J = 6.9, 2.0 Hz, 2H), 1.96 (br s, 1H), 1.55-1.44 (m, 2H), 1.50 (s, 6H), 1.39–1.26 (m, 4H), 1.17–1.04 (m, 21H), 0.88 (t, J = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 87.3, 84.4, 80.9, 78.2, 65.1, 53.3, 31.2, 31.1, 31.0, 28.0, 22.1, 18.6, 17.8, 13.9, 12.2.

(R)-1-(Dimethyl(phenyl)silyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-ol (1.54R):

In a 50 mL round bottle flask, a solution of dimethylphenylsilylacetylene 1.45 (6.0 mmol) and diethylzinc (646.8 μL, 6.0 mmol) in toluene (2.0 mL) was heated under argon atmosphere to reflux for 1 h. After the solution cooled to room temperature, (S)-BINOL (286.4 mg, 1.0 mmol), Et₂O (16.0 mL), and Ti(OiPr)₄ (540.0 μL, 2.5 mmol) were added sequentially, the resulting mixture was stirred for 1 h. Aldehyde 1.5 (260.1 mg, 1.0 mmol) was added to the above mixture and stirring continued for additional 4 h. Saturated aqueous NH₄Cl (20 mL) was added to quench the reaction. The mixture was extracted with CH₂Cl₂ (3 × 35 mL), dried over MgSO₄, and concentrated in vacuo. The crude product was purified by chiral HPLC (semi-preparation Chiracel OD column, hexane/iPrOH = 19:1, 8.0 mL/min) to afford the optical pure compound

95
1.54R (269.3 mg, 64%), followed by 1.54S (25.8 mg, 6%). [α]D25 = +4.3 (c = 1.09, CHCl3). 1H NMR (300 MHz, CDCl3) δ 7.64–7.61 (m, 2H), 7.39–7.37 (m, 3H), 7.26 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.12 (dt, J = 7.5, 2.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.44 (t, J = 6.3 Hz, 2H), 2.24 (td, J = 6.9, 1.8 Hz, 2H), 2.22 (d, J = 7.5 Hz, 1H), 1.64–1.46 (m, 6H), 0.43 (s, 6H); 13C NMR (75 MHz, CDCl3) δ 158.9, 136.2, 133.6, 130.4, 129.4, 129.2, 127.8, 113.6, 104.5, 86.4, 85.2, 77.4, 72.3, 69.6, 55.1, 52.5, 29.0, 27.9, 25.3, 18.5, –1.2; IR (film) 3585, 3019, 2986, 2400, 1613, 1513, 1429, 1215, 1114, 1033, 929, 755; MS (EI) m/z 420 (M+); HRMS (EI) m/z (M+) calcd for C26H32SiO3 420.2121, found 420.2109.

(S)-1-(Dimethyl(phenyl)silyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-ol (1.54S):

In a 50 mL round bottle flask, a solution of dimethylphenylsilylacetylene 1.45 (6.0 mmol) and diethylzinc (646.8 μL, 6.0 mmol) in toluene (2.0 mL) was heated under argon atmosphere to reflux for 1 h. After the solution cooled to room temperature, (R)-BINOL (286.4 mg, 1.0 mmol), Et2O (16.0 mL), and Ti(OiPr)4 (540.0 μL, 2.5 mmol) were added sequentially, the resulting mixture was stirred for 1 h. Aldehyde 1.5 (260.1 mg, 1.0 mmol) was added to the above mixture and stirring continued for additional 4 h. Saturated aqueous NH4Cl (20 mL) was added to quench the reaction. The mixture was extracted with CH2Cl2 (3 × 35 mL), dried over MgSO4, and concentrated in vacuo. The crude product was purified by chiral HPLC (semi-preparation Chiracel OD column, hexane/iPrOH = 19:1, 8.0 mL/min) to afford the optical pure compound 1.54R (23.4 mg, 5%), followed by 1.54S (294.6 mg, 70%). [α]D25 = −4.2 (c = 0.96, CHCl3). 1H NMR (300 MHz, CDCl3) δ 7.65–7.61 (m, 2H), 7.40–7.35 (m, 3H), 7.26 (d, J = 8.7 Hz, 2H), 6.88
(d, $J = 8.7$ Hz, 2H), 5.12 (dt, $J = 7.2$, 2.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.44 (t, $J = 6.3$ Hz, 2H), 2.28 (d, $J = 7.5$ Hz, 1H), 2.24 (td, $J = 6.9$, 2.1 Hz, 2H), 1.66–1.43 (m, 6H), 0.44 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.0, 136.3, 133.6, 130.5, 129.4, 129.2, 127.8, 113.7, 104.4, 86.5, 85.4, 77.4, 72.4, 69.7, 55.2, 52.6, 29.1, 27.9, 25.3, 18.6, –1.2; IR (film) 3585, 3019, 2400, 1613, 1514, 1429, 1215, 1114, 1034, 929, 755; MS (EI) $m/z$ 420 (M$^+$); HRMS (EI) $m/z$ (M$^+$) calcd for C$_{26}$H$_{32}$SiO$_3$ 420.2121, found 420.2121.

\[\text{(S)-(R)-1-(Dimethyl(phenyl)silyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-yl)3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (1.55RS):}\]

Alcohol 1.54R (11.0 mg, 0.04 mmol) was added to a solution of (R)-MTPA-Cl (20.4 $\mu$L, 0.11 mmol) in pyridine (0.4 mL) at room temperature. After 4 h, the organic solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound 1.55RS (15.1 mg, 80%): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.59–7.56 (m, 2H), 7.53 (d, $J = 7.3$ Hz, 2H), 7.41–7.30 (m, 6H), 7.25 (d, $J = 8.1$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 6.27 (t, $J = 2.1$ Hz, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.57 (s, 3H), 3.41 (t, $J = 6.4$ Hz, 2H), 2.24 (td, $J = 7.0$, 2.1 Hz, 2H), 1.62–1.41 (m, 6H), 0.41 (s, 6H).
(R)-(R)-1-(Dimethyl(phenyl)silyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-yl)3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (1.55RR):

Following the same procedure as above, except for using (S)-MTPA-Cl rather than (R)-MTPA-Cl, the title compound 1.55RR (14.5 mg, 78%) was obtained: 1H NMR (300 MHz, CDCl3) δ 7.61–7.58 (m, 2H), 7.53 (d, J = 7.0 Hz, 2H), 7.42–7.31 (m, 6H), 7.25 (d, J = 7.5 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.29 (t, J = 2.1 Hz, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.56 (s, 3H), 3.41 (t, J = 6.5 Hz, 2H), 2.21 (td, J = 6.8, 2.0 Hz, 2H), 1.64–1.33 (m, 6H), 0.43 (s, 6H).

(5)-(R)-1-(Dimethyl(phenyl)silyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-yl) 2-methoxy-2-(naphthalen-2-yl)acetate (1.56RS):

(S)-NMA acid (7.8 mg, 0.04 mmol), DCC (8.9, 0.04 mmol), and DMAP (0.4 mg, 0.004 mmol) was added to a solution of alcohol 1.54R (7.6 mg, 0.02 mmol) in CH2Cl2 (0.3 ml) at room temperature. The resulting mixture was stirred at the same temperature overnight. The mixture was then filtered through a pad of Celite®, the filtrate was concentrated in vacuo. The crude product was purified by column chromatography (hexane/EtOAc = 17:3) to afford the title compound 1.56RS (8.7 mg, 78%): 1H NMR (300 MHz, CDCl3) δ 7.93 (s, 1H), 7.85–7.80 (m, 3H), 7.60–7.55 (m, 3H), 7.49–7.46 (m, 2H), 7.37–7.32 (m, 3H), 7.24 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.13 (t, J = 2.1 Hz, 1H), 4.99 (s, 1H), 4.39 (s, 2H), 3.80 (s, 3H), 3.46 (s, 3H), 3.35 (t, J = 6.5 Hz, 2H), 2.05 (td, J = 6.8, 2.1 Hz, 2H), 1.51–1.44 (m, 2H), 1.38–1.23 (m, 4H), 0.40 (s, 6H).
(S)-(S)-1-(Dimethyl(phenyl)silyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-yl 2- methoxy-2-(naphthalen-2-yl)acetate (1.56SS):

Following the same procedure as above, except for using alcohol 1.54S rather than 1.54R, the title compound 1.56SS (8.2 mg, 74%) was obtained: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.94 (s, 1H), 7.85–7.76 (m, 3H), 7.60–7.45 (m, 4H), 7.37–7.24 (m, 6H), 6.88 (d, $J = 8.6$ Hz, 2H), 6.13 (t, $J = 2.0$ Hz, 1H), 5.00 (s, 1H), 4.41 (s, 2H), 3.79 (s, 3H), 3.47 (s, 3H), 3.41 (t, $J = 6.4$ Hz, 2H), 2.21 (td, $J = 6.6$, 2.0 Hz, 2H), 1.70–1.37 (m, 6H), 0.25 (s, 6H).

(S)-10-(4-Methoxybenzyloxy)deca-1,4-diyn-3-ol (1.57S):

TBAF (9.2 mL, 1.0 M solution in THF, 9.2 mmol) was added to a solution of alcohol 1.54R (1.93 g, 4.6 mmol) in THF (45 mL) at room temperature. The mixture then was stirred for 1 h at this temperature and quenched with saturated aqueous NH$_4$Cl. The resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 70 mL). The organic layers were washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 4 : 1) to give compound 1.57S (1.12 g, 85%) as a pale yellow oil. $[\alpha]_D^{25} = +3.71$ (c = 1.09, CHCl$_3$), $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 5.09 (dq, $J = 7.5$, 2.1 Hz, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.44 (t, $J = 6.6$ Hz, 2H).
Hz, 2H), 2.53 (d, $J = 2.1$ Hz, 1H), 2.30–2.25 (m, 1H), 2.24 (td, $J = 6.6$, 2.1 Hz, 2H), 1.66–1.40 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.1, 130.6, 129.3, 113.8, 85.8, 81.5, 77.2, 72.5, 72.2, 69.8, 55.3, 52.1, 29.1, 28.0, 25.5, 18.6; IR (film) 3422, 3020, 1642, 1514, 1425, 1216, 1089, 1015, 928, 757.

(R)-10-(4-Methoxybenzyloxy)deca-1,4-diyn-3-ol (1.57R):

TBAF (9.1 mL, 1.0 M solution in THF, 9.1 mmol) was added to a solution of alcohol 1.54R (1.91 g, 4.5 mmol) in THF (45 mL) at room temperature. The mixture then was stirred for 1 h at this temperature and quenched with saturated aqueous NH$_4$Cl. The resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 70 mL). The organic layers were washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 4 : 1) to give compound 1.57S (1.15 g, 85%) as a pale yellow oil. $[\alpha]_D^{25} = -3.29$ (c = 1.25, CHCl$_3$), $^1$H NMR (300 MHz, CDCl$_3$) δ 7.26 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 5.09 (dq, $J = 7.5$, 2.1 Hz, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.44 (t, $J = 6.6$ Hz, 2H), 2.53 (d, $J = 2.1$ Hz, 1H), 2.30–2.25 (m, 1H), 2.24 (td, $J = 6.6$, 2.1 Hz, 2H), 1.66–1.40 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.1, 130.6, 129.3, 113.8, 85.8, 81.5, 77.2, 72.5, 72.2, 69.8, 55.3, 52.1, 29.1, 28.0, 25.5, 18.6; IR (film) 3422, 3020, 1642, 1514, 1425, 1216, 1089, 1015, 928, 757.

10-(4-Methoxybenzyloxy)-1-(trimethylsilyl)deca-1,4-diyn-3-ol:
n-BuLi (7.5 mL, 1.6 M in hexane, 12.0 mmol) was added dropwise to a solution of trimethylsilylacetylene (1.70 mL, 12.0 mmol) in THF (50 mL) at −78 °C. After 30 min, a solution of aldehyde 1.5 (2.09 g, 8.0 mmol) in THF (14 mL) was added slowly. The resulting mixture was stirred for 45 min, and then allowed to warm to rt. The solution was poured into pH 7 phosphate buffer and extracted with Et₂O (3 × 50 mL). The organic layer was washed with brine. The aqueous layer was extracted with Et₂O (50 mL) again. The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 85 : 15) to give the title compound (2.55 g, 89%) as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.08 (dq, J = 7.2, 2.1 Hz, 1H), 4.30 (s, 2H), 3.81 (s, 3H), 3.44 (t, J = 6.3 Hz, 2H), 2.23 (td, J = 6.9, 2.1 Hz, 2H), 2.21 (d, J = 7.5 Hz, 1H), 1.66–1.40 (m, 6H), 0.19 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 159.1, 130.6, 129.2, 113.8, 102.7, 88.7, 85.4, 77.5, 72.5, 69.8, 55.2, 52.7, 29.2, 28.0, 25.4, 18.7, −0.3; IR (film) 3419, 2941, 1612, 1513, 1464, 1373, 1302, 1251, 1174, 1093, 1034, 907, 846, 732; MS (EI) m/z 358 (M⁺)

10-(4-Methoxybenzyl)deca-1,4-diyn-3-ol (rac-1.57):

TBAF (14.4 mL, 1.0 M in THF, 14.4 mmol) was added to a solution of 10-(4-Methoxybenzyl)deca-1,4-diyn-3-ol (2.50 g, 7.2 mmol) in THF (70 mL). The resulting mixture was stirred for 2 h at rt. The mixture was diluted with Et₂O (50 mL), washed with brine (3 × 50 mL), dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 3:1) to give the compound rac-1.57 (1.88 g, 91%) as pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, J =
8.7 Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 5.08 (dq, $J = 7.5$, 2.1 Hz, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.44 (t, $J = 6.3$ Hz, 2H), 2.54 (d, $J = 2.4$ Hz, 1H), 2.26 (d, $J = 7.5$ Hz, 1H), 2.23 (td, $J = 6.6$, 2.1 Hz, 2H), 1.66–1.40 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.1, 130.6, 129.2, 113.8, 85.7, 81.6, 77.2, 72.5, 72.1, 69.8, 55.3, 52.1, 29.1, 28.0, 25.4, 18.6; IR (film) 3416, 2941, 1615, 1514, 1464, 1378, 1302, 1248, 1174, 1095, 1014, 907, 731; MS (EI) m/z 286 (M$^+$).

Triisopropyl(10-(4-methoxybenzylloxy)deca-1,4-diyn-3-yloxy)silane (rac-1.59):

2,6-Lutidine (1.5 mL, 13.1 mmol) and TIPSOTf (3.6 mL, 13.1 mmol) were sequentially added to a solution of alcohol rac-1.57 (1.85 g, 6.5 mmol) in CH$_2$Cl$_2$ (65 mL) at 0 °C. The reaction was monitored by TLC until completion. Saturated NH$_4$Cl (aq) (50 mL) was then added to quench reaction. The reaction mixture was poured in a separatory funnel containing CH$_2$Cl$_2$ (50 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 92:8) to afford the product rac-1.59 (2.59 g, 90%) as pale yellow oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.26 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 5.23 (q, $J = 2.1$ Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.43 (t, $J = 6.3$ Hz, 2H), 2.47 (d, $J = 2.4$ Hz, 1H), 2.22 (td, $J = 6.9$, 2.1 Hz, 2H), 1.66–1.40 (m, 6H), 1.18–1.04 (m, 21H).
n-BuLi (0.15 mL, 1.6 M in hexane, 0.24 mmol) was added to a solution of alkyne rac-1.59 (88.5 mg, 0.2 mmol) in THF (2 mL) at −30 °C. After stirring at the same temperature for 1 h, the reaction mixture was cooled to −78 °C. HMPA (0.2 mL) was added to above solution, followed by a solution of iodide 1.58 (64.6 μL, 0.4 mmol) in THF (1 mL). The mixture was stirred at −78 °C for another 3 h and allowed to warm to rt for overnight stirring. The reaction was quenched with saturated NH₄Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (3 × 15 mL). The combined organic layers were washed with H₂O and brine, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/Et₂O = 98:2) to give three products shown below.

**Triisopropyl(1-(4-methoxybenzyl)oxy)octadeca-6,9-diyn-8-oloxysilane (1.60):**
Yield: 18.3 mg, 16.5%. ¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.22 (quint, J = 2.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.43 (t, J = 6.6 Hz, 2H), 2.25–2.16 (m, 2H), 1.62–1.41 (m, 8H), 1.26 (br s, 12H), 1.18–1.08 (m, 21H), 0.88 (t, J = 6.3 Hz, 3H).
(8-Ethynyl-1-(4-methoxybenzyloxy)hexadec-6-yn-8-yl)triisopropylsilane (1.61):

Yield: 2.8 mg, 2.5%. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.43 (t, $J = 6.6$ Hz, 2H), 2.44 (s, 1H), 2.24–2.16 (m, 2H), 1.89–1.84 (m, 2H), 1.62–1.41 (m, 8H), 1.26 (br s, 12H), 1.10–1.06 (m, 21H), 0.88 (t, $J = 6.3$ Hz, 3H).

Triisopropyl(9-(7-(4-methoxybenzyloxy)hept-1-ynyl)nonadec-10-yn-9-yloxy)silane (1.62):

Yield: 12.2 mg, 9.1%. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.43 (t, $J = 6.6$ Hz, 2H), 2.44 (s, 1H), 2.24–2.16 (m, 2H), 1.89–1.84 (m, 2H), 1.62–1.41 (m, 8H), 1.26 (br s, 12H), 1.10–1.06 (m, 21H), 0.88 (t, $J = 6.3$ Hz, 3H).

$^1$-(4-Methoxybenzyloxy)octadeca-6,9-diyn-8-ol (rac-1.63):

$n$-BuLi (0.28 mL, 1.6 M in hexane, 0.44 mmol) was added to a solution of alkyne rac-1.57 (57.3 mg, 0.2 mmol) in THF (1 mL) at $-30$ °C. After stirring at the same temperature for 1 h, the reaction mixture was cooled to $-78$ °C. HMPA (0.1 mL) was added to above solution, followed by a solution of iodide 1.58 (16.2 μL, 0.1 mmol) in THF (0.5 mL). The mixture was stirred at $-78$ °C for another 3 h and allowed to warm to rt for overnight stirring. The reaction was quenched with saturated NH$_4$Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et$_2$O (3 × 10 mL). The combined organic layers were washed with H$_2$O and brine, dried over MgSO$_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 95:5) to give the product rac-1.63 (23.3
mg, 59%) as pale yellow oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 5.09 (dt, $J = 3.0$, 2.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.43 (t, $J = 6.3$ Hz, 2H), 2.25–2.19 (m, 2H), 2.14 (d, $J = 7.2$ Hz, 1H), 1.65–1.45 (m, 8H), 1.26 (br s, 12H), 0.88 (t, $J = 6.3$ Hz, 3H).

![1-Methoxy-4-((8-(octyloxy)octadeca-6,9-diylyoxy)methyl)benzene (rac-1.64):](image)

$n$-BuLi (0.28 mL, 1.6 M in hexane, 0.44 mmol) was added to a solution of alkyne $rac$-1.57 (57.3 mg, 0.2 mmol) in THF (2 mL) at $-30$ °C. After stirring at the same temperature for 1 h, the reaction mixture was cooled to $-78$ °C. HMPA (0.2 mL) was added to above solution, followed by a solution of iodide 1.58 (64.6 µL, 0.4 mmol) in THF (1 mL). The mixture was stirred at $-78$ °C for another 3 h and allowed to warm to rt for overnight stirring. The reaction was quenched with saturated NH$_4$Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et$_2$O (3 × 10 mL). The combined organic layers were washed with H$_2$O and brine, dried over MgSO$_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 95:5) to give the products $rac$-1.64 (26.3 mg, 26%) and $rac$-1.63 (20.0 mg, 25%) as pale yellow oils. $rac$-1.64: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 4.92 (t, $J = 2.1$ Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.56 (t, $J = 6.6$ Hz, 2H), 3.43 (t, $J = 6.3$ Hz, 2H), 2.25–2.19 (m, 2H), 1.65–1.45 (m, 8H), 1.26 (br s, 24H), 0.88 (t, $J = 6.3$ Hz, 6H).
(19S,E)-21-((tert-Butyldimethylsilyl)-1-(4-methoxybenzyloxy)-19-(triisopropylsilyloxy)henicosa-17-en-6,9,20-triyn-8-ol (1.65):

\[ n\text{-BuLi} (0.28 \text{ mL, 1.6 M in hexane, 0.44 mmol}) \text{ was added to a solution of alkyne } rac-1.57 (57.3 \text{ mg, 0.2 mmol}) \text{ in THF (0.35 mL) at } -30^\circ C. \text{ After stirring at the same temperature for 1 h, the reaction mixture was cooled to } -78^\circ C. \text{ HMPA (0.1 mL) was added to above solution, followed by a solution of iodide } 1.29S (56.3 \text{ mg, 0.1 mmol}) \text{ in THF (0.05 mL). The mixture was stirred at } -78^\circ C \text{ for another 3 h and allowed to warm to rt for overnight stirring. The reaction was quenched with saturated NH}_4\text{Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et}_2\text{O (3 } \times 10 \text{ mL). The combined organic layers were washed with H}_2\text{O and brine, dried over MgSO}_4, \text{ and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 95:5) to give the products 1.65 (25.1 mg, 35%). \text{ }^1\text{H NMR (300 MHz, CDCl}_3) \delta 7.26 (d, J = 8.4 \text{ Hz, 2H}), 6.88 (d, J = 8.4 \text{ Hz, 2H}), 5.79 (dtd, J = 15.0, 7.8, 0.9 \text{ Hz, 1H}), 5.53 (dd, J = 15.3, 5.4 \text{ Hz, 1H}), 5.08 (br s, 1H), 4.92 (d, J = 5.1 \text{ Hz, 1H}), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, J = 6.6 \text{ Hz, 2H}), 2.25–2.16 (m, 4H), 2.04 (q, J = 6.6 \text{ Hz, 2H}), 1.65–1.28 (m, 16H), 1.13–1.02 (m, 21H), 0.92 (s, 9H), 0.09 (s, 6H). \]

(8S,E)-21-((tert-butyldimethylsilyl)-19-((purfluoroethyl)diisopropylsilyloxy)-1-(4-methoxybenzyloxy)henicosa-17-en-6,9,20-triyn-8-ol (M-1.66) and (R)-1-((3,3,4,4,5,5,5-perfluoroethyl)diisopropylsilyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-ol (1.67):
n-BuLi (0.27 mL, 1.6 M in hexane, 0.42 mmol) was added to a solution of alkyne 1.57S (57.3 mg, 0.2 mmol) in THF (1.0 mL) at −30 °C. After stirring at the same temperature for 1 h, the reaction mixture was cooled to −78 °C. HMPA (0.1 mL) was added to above solution, followed by a solution of iodide M-1.29 (74.2 mg, 0.1 mmol) in THF (0.5 mL). The mixture was stirred at −78 °C for another 3 h and allowed to warm to rt for overnight stirring. The reaction was quenched with saturated NH₄Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with H₂O and brine, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 95:5) to give the inseparable products M-1.66 and 1.67 (24.7 mg, 30%). ¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, J = 8.4 Hz, 4H), 6.88 (d, J = 8.4 Hz, 4H), 5.79 (dt, J = 15.0, 7.8, 0.9 Hz, 1H), 5.52 (dd, J = 15.3, 5.4 Hz, 1H), 5.08 (m, 2H), 4.89 (d, J = 6.0 Hz, 1H), 4.43 (s, 4H), 3.80 (s, 6H), 3.43 (td, J = 6.0, 0.9 Hz, 4H), 2.25–2.04 (m, 8H), 1.65–1.28 (m, 28H), 1.13–1.02 (m, 28H), 0.92 (s, 11H), 0.09 (s, 6H); MS (ESI) for M-1.66-C₃F₇ m/z 913.3 (M⁺ + K); M-1.66-C₄F₉ m/z 963.4 (M⁺ + K); 1.63-C₃F₇ m/z 635.2 (M⁺ + K); 1.67-C₄F₉ m/z 685.2 (M⁺ + K).

(4,4,5,5,6,6,6-Heptafluorohexyl)diisopropylsilane (1.69):

To a three-neck flask equipped with addition funnel, thermometer, and Ar gas inlet, t-BuLi (14.7 mL, 1.7 M in hexane, 25.0 mmol) was added while cooling with −78 °C bath (a precipitate was observed). A solution of 1,1,1,2,2,3,3-heptafluoro-6-iodohexane (3.72 g, 11.0 mmol) in Et₂O (25 mL) was added dropwise, keeping the internal temperature below −50 °C. The mixture was
stirred for 45 min and allowed to warm to \(-25\) °C (internal temperature) and maintained at this temperature until the solution became clear. After everything were into solution, the solution was cooled to \(-50\) °C, chlorodiisopropylsilane (1.71 mL, 10.0 mmol) was added slowly. The mixture was stirred for overnight, during which time it was warmed to rt. The mixture was cooled to 0 °C, H$_2$O (12.5 mL) was added quickly and the mixture was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with Et$_2$O (3 × 30 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane 100%) to afford the title compound 1.69 (2.94 g, 90%) as colorless oil. 1H NMR (300 MHz, CDCl$_3$) 3.46 (s, 1H), 2.20–2.02 (m, 2H), 1.78–1.66 (m, 2H), 0.72–0.66 (m, 2H).

Diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silane (1.70):

Following the same procedure for 1.69, 1,1,1,2,2,3,3,4,4-nonafluoro-7-iodoheptane (4.27 g, 11.0 mmol) was reacted with chlorodiisopropylsilane (1.71 mL, 10.0 mmol), the title compound 1.70 (3.34 g, 89%) was obtained as colorless oil. 1H NMR (300 MHz, CDCl$_3$) 3.46 (s, 1H), 2.20–2.02 (m, 2H), 1.78–1.66 (m, 2H), 0.72–0.66 (m, 2H).

(R,E)-tert-Butyl(3-(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)-11-(4-methoxybenzyloxy)undec-4-en-1-ynyl)dimethylsilane (1.71R):
Trifluoromethanesulfonic acid (neat, 1.9 mL, 21.7 mmol) was slowly added to silane 1.70 (neat, 8.67 g, 23.0 mmol) at 0 °C. After being stirred for 20 min at the same temperature, the mixture was warmed to room temperature and stirred for 15 h. To it CH₂Cl₂ (24 mL) was added at –60 °C, followed by a solution of alcohol 1.37R (6.00 g, 14.4 mmol) in CH₂Cl₂ (36 mL) and 2,6-lutidine (3.3 mL, 28.7 mmol). The resulting mixture was warmed to room temperature and stirred for further 2 h. Saturated aqueous NH₄Cl (75 mL) was then added to quench the reaction at 0 °C. The mixture was extracted with Et₂O (3 × 150 mL), the organic layers were combined and washed with water, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound 1.71R (9.94 g, 87%). [α]D²⁵ = +1.1 (c = 1.20, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, J = 8.4 Hz, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 5.79 (dt, J = 15.0, 6.9, 0.9 Hz, 1 H), 5.51 (dd, J = 15.3, 5.7 Hz, 1 H), 4.88 (d, J = 6.0 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, J = 6.6 Hz, 2 H), 2.19–2.00 (m, 4 H), 1.76–1.69 (m, 2 H), 1.61–1.53 (m, 2 H), 1.43–1.28 (m, 6 H), 1.06 (br s, 14 H), 0.93 (s, 9 H), 0.79–0.73 (m, 2 H), 0.09 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 159.1, 132.2, 130.8, 129.6, 129.2, 113.8, 106.3, 88.0, 72.5, 70.2, 64.0, 55.3, 34.5 (t, JHCF = 21.8 Hz, 1 C), 31.8, 29.7, 29.0, 28.9, 26.0 (2 C), 17.6 (2 C), 17.5 (2 C) 16.5, 14.6, 12.7, 12.6, 11.0, –4.8; IR (film) 3020, 2933, 1514, 1423, 1215, 1133, 1044, 928, 755 cm⁻¹; HRMS (ESI) m/z (M⁺ + Na) calcd for C₃₈H₅₉O₃NaSi₂F₉ 813.3757, found 813.3793.

(S,E)-tert-Butyl(11-(4-methoxybenzyloxy)-3-(triisopropylsilyloxy)undec-4-en-1-ynyl)dimethylsilane (1.71S):
2,6-Lutidine (3.5 mL, 30.1 mmol) and TIPSOTf (7.9 mL, 29.4 mmol) were sequentially added to the solution of alcohol 1.37S (6.90 g, 16.6 mmol) in CH₂Cl₂ (160 mL) at 0 °C. The resulting mixture was stirred for 2 h at the same temperature. Saturated aqueous NH₄Cl (80 mL) was then added to quench the reaction. The mixture was extracted with Et₂O (3 × 150 mL), the organic layers were combined and washed with water, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound 1.71S (8.53 g, 90%). [α]D²⁵ = -1.0 (c = 0.92, CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 5.80 (dtd, J = 15.3, 6.6, 0.9 Hz, 1 H), 5.52 (dd, J = 15.0, 5.4 Hz, 1 H), 4.92 (dd, J = 5.1, 0.6 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, J = 6.6 Hz, 2 H), 2.04 (q, J = 6.6 Hz, 2 H), 1.61–1.54 (m, 2 H), 1.43–1.28 (m, 6 H), 1.15–1.06 (m, 21 H), 0.92 (s, 9 H), 0.09 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 159.1, 131.7, 130.8, 129.9, 129.2, 113.7, 106.8, 87.5, 72.5, 70.2, 63.9, 55.3, 31.8, 29.7, 28.9 (2 C), 26.1 (2 C), 18.0, 16.5, 12.2, –4.7; IR (film) 3019, 2934, 2864, 1514, 1424, 1216, 1039, 928, 756 cm⁻¹; HRMS (ESI) m/z (M⁺ + Na) calcd for C₃₄H₆₀O₃NaSi₂ 595.3979, found 595.3959.

(R,E)-11-(tert-Butyldimethylsilyl)-9-(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy) undec-7-en-10-yn-1-ol and (S,E)-11-(tert-butyldimethylsilyl)-9-(triisopropylsilyloxy) undec-7-en-10-yn-1-ol:

DDQ (7.88 g, 34.7 mmol) was added to the mixture of compound 1.71R (7.89 g, 10.0 mmol) and compound 1.71S (5.75 g, 10.0 mmol) in CH₂Cl₂ (250 mL) and H₂O (13 mL) at room temperature. The reaction was monitored by TLC until completion, and then saturated NaHCO₃...
aqueous solution was added. The mixture was extracted with CH₂Cl₂ (3 × 150 mL), the organic layers were combined, washed with saturated NaHCO₃ aqueous solution, brine, dried over MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography (hexane/Et₂O = 4:1) to afford the title mixture, which was contaminated with tiny 4-(methoxymethyl)benzaldehyde and was used in the following step without further purification.

(R,E)-tert-Butyl(3-(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)-11-iodoundec-4-en-1-ynyl)dimethylsilane and (S,E)-tert-butyl(11-iodo-3-(triisopropylsilyloxy)undec-4-en-1-ynyl)dimethylsilane (M-1.68):

To a solution of triphenylphosphine (5.44 g, 20.7 mmol) in CH₂Cl₂ (27 mL) was slowly added a solution of iodine (5.26 g, 20.7 mmol) in CH₂Cl₂ (27 mL), followed by a mixture of imidazole (1.55 g, 22.8 mmol) and above alcohol (5.74 g, 10.2 mmol) in CH₂Cl₂ (80 mL) at room temperature. After 2 h, the reaction was quenched with saturated aqueous NaHCO₃ (100 mL). The mixture was extracted with Et₂O (3 × 100 mL) and organic layer was washed with saturated aqueous Na₂S₂O₃ (100 mL), water, brine, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/EtOAc = 99:1) to afford the title compound M-1.68 (5.62 g, 82%): ¹H NMR (300 MHz, CDCl₃) δ 5.83–5.74 (m, 1 H), 5.52 (dd, J = 15.0, 5.1 Hz, 1 H), 4.94–4.88 (m, 1 H), 3.18 (t, J = 6.9 Hz, 2 H), 2.19–2.04 (m, 4H), 1.88–1.70 (m, 4H), 1.47–1.27 (m, 8 H), 1.19–1.02 (m, 17.5 H), 1.06 (s, 9 H), 0.79–0.73 (m, 2 H), 0.09 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 131.9, 131.4, 130.1, 129.8, 106.8, 106.2, 88.1, 87.6, 64.0, 63.8, 34.5 (t, Jₐₙₛ = 21.8 Hz), 33.5, 31.6, 30.3, 28.7, 28.0, 26.0, 18.0, 17.6, 17.5, 16.5,
14.6, 12.7, 12.6, 12.2, 10.9, 7.1; IR (film) 2932, 2862, 1464, 1384, 1236, 1133, 1057, 908, 826, 733; MS (EI) for **M-1.68-C₄F₉** m/z 737 (M⁺ - C₅H₇); **M-1.68-TIPS** m/z 519 (M⁺ - C₃H₇); HRMS (ESI) **M-1.68-C₄F₉** m/z (M⁺ - C₅H₇) calcd for C₂₇H₄₃OF₉Si₂I 737.1753, found 737.1748; . **M-1.68-TIPS** m/z (M⁺ - C₃H₇) calcd for C₂₃H₄₄OSi₂I 519.1976, found 519. 1993.

(5S,E)-5-((tert-butyldimethylsilyl)ethynyl)-3,3,18,18-tetraisopropyl-16-(7-(4-methoxy benzyl oxy)hept-1-ynyl)-2,19-dimethyl-4,17-dioxa-3,18-disilaicos-6-en-14-yne (1.72):

2,6-Lutidine (27.2 μL, 0.24 mmol) and TIPSOTf (62.9 μL, 0.24 mmol) were sequentially added to the solution of alcohol **1.65** (84.4 mg, 0.12 mmol) in CH₂Cl₂ (1.2 mL) at 0 °C. The resulting mixture was stirred for 2 h at the same temperature. Saturated aqueous NH₄Cl (5 mL) was then added to quench the reaction. The mixture was extracted with Et₂O (3 × 10 mL), the organic layers were combined and washed with water, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound **1.72** (95.6 mg, 93%). **¹H** NMR (500 MHz, CDCl₃) 7.26 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2 H), 5.79 (dt, J = 15.0, 6.5 Hz, 1H), 5.53 (dd, J = 15.5, 5.5 Hz, 1H), 5.22 (d, J = 2.0 Hz, 1H), 4.92 (d, J = 5.5 Hz, 1H), 4.42 (s, 2H), 3.82 (s, 3H), 3.42 (t, J = 6.5 Hz, 2H), 2.21 (q, J = 7.5 Hz, 4H), 2.06 (q, J = 7.0 Hz, 2H), 1.63–1.21 (m, 14H), 1.20–1.10 (m, 42H), 0.93 (s, 9H), 0.09 (s, 6H).
(19S,E)-21-(tert-Butyldimethylsilyl)-8,19-bis(triisopropylsilyloxy)henicosa-17-en-6,9,20-triyn-1-ol (1.73):

Ceric ammonium nitrate (CAN, 16.5 mg, 0.03 mmol) was added to a solution of PMB ether 1.72 (8.6 mg, 0.01 mmol) in CH$_2$Cl$_2$ (0.4 mL) and pH 7 phosphate buffer (0.04 mL) at rt. The orange mixture was stirred at rt for 30 min, CH$_2$Cl$_2$ (5 mL) was added to dilute the mixture. The organic layer was washed with saturated NaHCO$_3$ (10 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/Et$_2$O = 7:3) to give the title compound 1.73 (2.1 mg, 28%) and strating material 1.72 (4.4 mg, 50%). $^1$H NMR (300 MHz, CDCl$_3$) 5.80 (dt, $J = 15.0$, 6.9 Hz, 1H), 5.52 (dd, $J = 15.0$, 4.5 Hz, 1H), 5.22 (m, 1H), 4.92 (d, $J = 5.1$ Hz, 1H) 3.64 (t, $J = 6.0$ Hz, 2H), 2.27–2.21 (m, 4H), 2.05–2.03 (m, 2H), 1.63–1.21 (m, 14H), 1.20–1.10 (m, 42H), 0.93 (s, 9H), 0.09 (s, 6H).

\[
\text{OMTM} \quad \text{[(Hept-6-ynyloxy)methyl]sulfane (1.75):}
\]

A mixture of Ac$_2$O (71 mL) and AcOH (12.7 mL) was added to a solution of alcohol 1.22 (3.70 g, 33.0 mmol) in DMSO (102 mL) at room temperature. The resulting mixture was stirred at same temperature for 24 h. The mixture was poured into cold saturated NaHCO$_3$ aqueous solution. The mixture was extracted with CH$_2$Cl$_2$ (3 × 100 mL). The organic layer was washed with saturated NaHCO$_3$ aqueous solution, water, brine, dried over MgSO$_4$ concentrated in vacuo. The curde product was used in next step without further purification.
8-(Methylthiomethoxy)oct-2-ynal (1.76):

To a solution of alkyne 1.75 (4.98 g, 28.9 mmol) in THF (67 mL) was slowly added n-BuLi (21.7 mL, 1.6 M solution in hexane, 34.7 mmol) at −40 °C. After completion of addition, DMF (4.5 mL, 57.9 mmol) was added. The mixture was then warmed to room temperature. After being stirred for 30 min at the same temperature, the resulting mixture was poured into a solution of 10% aqueous solution KH2PO4 (145 mL) and methyl tert-butyl ether (MTBE) (135 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with MTBE (3 × 120 mL). The combined organic layers was washed with water, dried over MgSO4, and concentrated in vacuo. The residue was purified by column chromatography (hexane/Et2O = 17:3) to afford the title compound 1.76 (4.11 g, 71%) as pale yellow oil. 1H NMR (300 MHz, CDCl3) δ 9.17 (s, 1H), 4.62 (s, 2H), 3.53 (t, J = 6.0 Hz, 2H), 2.43 (t, J = 6.6 Hz, 2H), 2.15 (s, 3H), 1.69–1.47 (m, 6H); 13C NMR (75 MHz, CDCl3) δ 177.2, 99.9, 81.7, 75.2, 67.6, 28.8, 27.3, 25.5, 19.1, 13.9; IR (film) 3054, 2987, 1666, 1423, 1265, 1139, 1077, 896, 740 cm⁻¹; MS (EI) m/z 185 (M⁺ – CH3); HRMS (EI) m/z (M⁺ – CH3) calcd for C9H13O2S 185.0636, found 185.0629.

1-(Dimethyl(phenyl)silyl)-10-(methylthiomethoxy)deca-1,4-diyn-3-ol (rac-1.77):

n-BuLi (18.5 mL, 1.6 M solution in hexane, 29.7 mmol) was added to a solution of (dimethylphenylsilyl)acetylene 1.45 (5.2 mL, 29.7 mmol) in the THF (125 mL) at −78 °C. After stirring at same temperature for 30 min, a solution of aldehyde 1.76 (3.96 g, 19.8 mmol) in THF
(30 mL) was added slowly. The resulting mixture was stirred for additional 45 min at –78 °C, then allowed to warm to room temperature. The mixture was poured into pH 7 phosphate buffer (100 mL) and extracted with Et2O (3× 100 mL). The organic layer was washed with brine, dried over MgSO4, and concentrated in vacuo. The residue was purified by column chromatography (hexane/Et2O = 4:1) to afford the title compound rac-1.77 (6.25 g, 97%) as pale yellow oil. 1H NMR (300 MHz, CDCl3) $\delta$ 7.64 – 7.61 (m, 2H), 7.39 – 7.35 (m, 3H), 5.13 (dt, $J = 7.5, 1.8$ Hz, 1H), 4.62 (s, 2H), 3.52 (t, $J = 6.3$ Hz, 2H), 2.25 (td, $J = 6.9, 2.1$ Hz, 2H), 2.23 (d, $J = 7.5$ Hz, 1H), 2.14 (s, 3H), 1.66–1.43 (m, 6H), 0.44 (s, 6H); 13C NMR (75 MHz, CDCl3) $\delta$ 136.3, 133.7, 129.5, 127.9, 104.2, 86.9, 85.6, 77.2, 75.2, 67.9, 52.8, 28.8, 28.0, 25.5, 18.7, 14.0, –1.1; IR (film) 3585, 3399, 3070, 2942, 2864, 1644, 1429, 1300, 1253, 1113, 1077, 1033, 909, 820, 733; HRMS (ESI) m/z (M+ + K) calcd for C20H28O2SiSK 399.1216, found 399.1215.

![Chemical structure of rac-1.77](image)

(R)-1-(Dimethyl(phenyl)silyl)-10-(methylthiomethoxy)deca-1,4-diyn-3-ol (1.77R):

(S)-1-(Dimethyl(phenyl)silyl)-10-(methylthiomethoxy)deca-1,4-diyn-3-ol (1.77S):

The racemic alcohol rac-1.77 (6.25 g, 17.3 mmol) was separated by chiral HPLC (Chiralcel OD semi-preparative column, hexane/PrOH = 93:7, 10.0 mL/min) to afford two optical pure compounds 1.77R (3.04 g, 49%) and 1.77S (2.99 g, 48%) as pale yellow oils.

1.77R: $[\alpha]_D^{25} = +5.0$ (c = 1.03, CHCl3), 1H NMR (300 MHz, CDCl3) $\delta$ 7.64–7.61 (m, 2H), 7.39–7.35 (m, 3H), 5.13 (dt, $J = 7.5, 2.1$ Hz, 1H), 4.62 (s, 2H), 3.52 (t, $J = 6.3$ Hz, 2H), 2.25 (td, $J = 7.5, 1.8$ Hz, 2H), 2.14 (s, 3H), 1.66–1.43 (m, 6H), 0.44 (s, 6H); 13C NMR (75 MHz, CDCl3) $\delta$ 136.3, 133.7, 129.5, 127.9, 104.2, 86.9, 85.6, 77.2, 75.2, 67.9, 52.8, 28.8, 28.0, 25.5, 18.7, 14.0, –1.1; IR (film) 3585, 3399, 3070, 2942, 2864, 1644, 1429, 1300, 1253, 1113, 1077, 1033, 909, 820, 733; HRMS (ESI) m/z (M+ + K) calcd for C20H28O2SiSK 399.1216, found 399.1215.
6.9, 2.1 Hz, 2H), 2.22 (d, J = 7.5 Hz, 1H), 2.14 (s, 3H), 1.66–1.43 (m, 6H), 0.44 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 136.3, 133.7, 129.5, 127.9, 104.3, 86.8, 85.5, 77.2, 75.2, 67.9, 52.8, 28.8, 28.0, 25.4, 18.7, 13.9, -1.1; IR (film) 3420, 3019, 2942, 2865, 1640, 1429, 1300, 1216, 1113, 1076, 1031, 956, 756; HRMS (ESI) \(m/z\) (M\(^+\) + Na) calcd for C\(_{20}\)H\(_{28}\)O\(_2\)NaSiS 383.1477, found 383.1461.

**1.77S:** \([\alpha]_D^{25} = -4.5\) (c = 0.99, CHCl\(_3\)), \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.64–7.61 (m, 2H), 7.39–7.35 (m, 3H), 5.13 (dt, J = 7.2, 2.1 Hz, 1H), 4.62 (s, 2H), 3.52 (t, J = 6.3 Hz, 2H), 2.25 (td, J = 6.6, 1.8 Hz, 2H), 2.24 (d, J = 7.5 Hz, 1H), 2.14 (s, 3H), 1.66–1.43 (m, 6H), 0.44 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 136.3, 133.7, 129.5, 127.9, 104.3, 86.8, 85.5, 77.2, 75.2, 67.9, 52.7, 28.8, 27.9, 25.4, 18.6, 13.9, -1.1; IR (film) 3440, 3019, 2973, 1637, 1427, 1382, 1216, 1159, 1076, 946, 755; HRMS (ESI) \(m/z\) (M\(^+\) + Na) calcd for C\(_{20}\)H\(_{28}\)O\(_2\)NaSiS 383.1477, found 383.1460.

**OMTM**

(\(S\)-10-(Methylthiomethoxy)deca-1,4-diyn-3-ol (1.74S):

TBAF (12.5 mL, 1.0 M solution in THF, 12.5 mmol) was added to a solution of alcohol **1.77R** (3.00 g, 8.3 mmol) in THF (80 mL) at room temperature. The mixture then was stirred for 1 h at this temperature and quenched with saturated aqueous NH\(_4\)Cl. The resulting mixture was extracted with CH\(_2\)Cl\(_2\) (3 × 50 mL). The organic layers were washed with brine, dried over MgSO\(_4\), and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/Et\(_2\)O = 4:1) to give compound **1.74S** (1.47 g, 78%) as pale yellow oil. \([\alpha]_D^{25} = +5.0\) (c = 1.20, CHCl\(_3\)), \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.10 (dq, J = 7.5, 2.1 Hz, 1H),
4.62 (s, 2H), 3.53 (t, $J = 6.0$ Hz, 2H), 2.54 (d, $J = 2.4$ Hz, 1H), 2.25 (td, $J = 6.9$, 2.1 Hz, 2H), 2.22 (d, $J = 7.2$ Hz, 1H), 2.15 (s, 3H), 1.66–1.43 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 85.7, 81.5, 77.3, 75.2, 72.1, 67.9, 52.1, 28.8, 27.9, 25.4, 18.6, 13.9; IR (film) 3422, 3020, 1647, 1429, 1216, 1015, 929, 757; MS (EI) m/z 249 (M$^+$ + Na); HRMS (ESI) m/z (M$^+$ + Na) calcd for C$_{12}$H$_{18}$O$_2$NaS 249.0925, found 249.0945.

(R)-10-(Methylthiomethoxy)deca-1,4-diyn-3-ol (1.74R):

Following the same procedure for 1.74S, alcohol 1.77R (2.99 g, 8.3 mmol) was reacted with TBAF (12.5 mL, 1.0 M solution in THF, 12.5 mmol), the title compound 1.74R (1.78 g, 95%) was obtained as pale yellow oil. [α]$_D^{25}$ = −4.4 (c = 1.37, CHCl$_3$), $^1$H NMR (300 MHz, CDCl$_3$) δ 5.10 (dq, $J = 7.5$, 2.1 Hz, 1H), 4.63 (s, 2 H), 3.53 (t, $J = 6.3$ Hz, 2H), 2.54 (d, $J = 2.1$ Hz, 1H), 2.25 (td, $J = 6.6$, 1.8 Hz, 2H), 2.24 (d, $J = 7.5$ Hz, 1H), 2.15 (s, 3H), 1.66–1.42 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 85.3, 81.5, 77.3, 75.0, 71.9, 67.8, 51.8, 28.6, 27.8, 25.3, 18.5, 13.8; IR (film) 3420, 3307, 3020, 2943, 1641, 1430, 1216, 1076, 1015, 928, 755; MS (EI) m/z 249 (M$^+$ + Na); HRMS (ESI) m/z (M$^+$ + Na) calcd for C$_{12}$H$_{18}$O$_2$NaS 249.0925, found 249.0945.

\[ \text{n-BuLi (4.0 mL, 1.6 M solution in THF, 6.4 mmol) was slowly added to the solution of alkyne 1.74R (679.0 mg, 3.0 mmol) in THF (15 mL) at } -30^\circ C \text{. After stirring at the same temperature for 1 h, the mixture was cooled to } -78^\circ C \text{, HMPA (1.5 mL) was added followed by a solution of iodide M-1.68 (1.01 g, 1.5 mmol) in THF (7.5 mL). The resulting mixture was stirred for 2 h at } -78^\circ C \text{ and warmed to room temperature. After stirring at room temperature for overnight, saturated NH}_4\text{Cl aqueous solution (20 mL) was added, the organic layer was separated and the aqueous layer was extracted with Et}_2\text{O (3 } \times \text{ 20 mL). The combined organic layers were washed with water, brine, dried over MgSO}_4 \text{, and concentrated } \text{in vacuo. The crude product was purified by column chromatography (hexane/Et}_2\text{O = 4:1) to afford the mixture M-1.78R (370.7 mg, 34%), which was contaminated with some inseparable impurities and was used in the following step without further purification.} \]

\[ \text{ } ^1\text{H NMR (500 MHz, CDCl}_3 \text{) } \delta 5.80-5.76 (m, 1H), 5.55-5.49 (m, 1H), 5.10-5.08 (m, 1H), 4.93-4.88 (m, 1H), 4.63 (s, 2H), 3.52 (t, } J = 6.5 \text{ Hz, 2H), 2.23 (quind, } J = 7.0, 1.5 \text{ Hz, 4H), 2.15 (s, 3H), 2.12-2.06 (m, 1H), 2.05 (q, } J = 6.5 \text{ Hz, 2H), 1.78-1.69 (m, 1H), 1.64-1.45 (m, 8H), 1.40-1.25 (m, 6H), 1.10-1.05 (m, 17.5H), 0.93 (s, 9H), 0.78-0.74 (m, 1H), 0.09 (s, 6H); HRMS (ESI) M-1.78R-C}_4\text{F}_9 \text{ m/z (M}^+ + \text{Na) caleld for C}_{42}\text{H}_{67}\text{O}_3\text{F}_9\text{NaSi}_2\text{S 901.4103, found 901.4134; M-1.78R-TIPS m/z (M}^+ + \text{Na) caleld for C}_{38}\text{H}_{68}\text{O}_3\text{NaSi}_2\text{S 683.4325, found 683.4340.} \]

Following the same procedure for M-1.78R, alkyne 1.74S (679.0 mg, 3.0 mmol) was reacted with n-BuLi (4.0 mL, 1.6 M solution in THF, 6.4 mmol), HMPA (1.5 mL), and iodide M-1.68 (1.01 g, 1.5 mmol), the title mixture M-1.78S (356.2 mg, 33%) was obtained, which was contaminated with some inseparable impurities and was used in the following step without further purification. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 5.82–5.77 (m, 1H), 5.55–5.49 (m, 1H), 5.10–5.08 (m, 1H), 4.92–4.88 (m, 1H), 4.63 (s, 2H), 3.52 (t, $J = 6.6$ Hz, 2H), 2.23–2.20 (m, 4H), 2.15 (s, 3H), 2.14–2.09 (m, 1H), 2.05 (q, $J = 6.6$ Hz, 2H), 1.76–1.70 (m, 1H), 1.63–1.43 (m, 8H), 1.40–1.25 (m, 6H), 1.11–1.03 (m, 17H), 0.92 (s, 9H), 0.77–0.74 (m, 1H), 0.09 (s, 6H); HRMS (ESI) M-1.78S-C$_4$F$_9$ m/z (M$^+$ + Na) calcd for C$_{42}$H$_{67}$O$_3$F$_9$NaSi$_2$S 901.4103, found 901.4072; M-1.78S-TIPS m/z (M$^+$ + Na) calcd for C$_{38}$H$_{68}$O$_3$NaSi$_2$S 683.4325, found 683.4296.

Trifluoromethanesulfonic acid (neat, 72.4 μL, 0.82 mmol) was slowly added to silane 1.70 (neat, 359.0 mg, 0.95 mmol) at 0 °C. After being stirred for 20 min at the same temperature, the mixture was warmed to room temperature and stirred for 15 h. To it CH₂Cl₂ (0.8 mL) was added at –60 °C, followed by a solution of alcohol M-1.78R (200.0 mg, 0.27 mmol) in CH₂Cl₂ (1.2 mL) and 2,6-lutidine (0.13 mL, 1.09 mmol). The resulting mixture was warmed to room temperature and stirred for further 2 h. Saturated aqueous NH₄Cl (10 mL) was then added to quench the reaction at 0 °C. The mixture was extracted with Et₂O (3 × 10 mL), the organic layers were combined and washed with water, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/Et₂O = 97:3) to afford the title mixture M-1.79R (272.5 g, 99%). ¹H NMR (600 MHz, CDCl₃) δ 5.81–5.77 (m, 1H), 5.54–5.49 (m, 1H), 5.21 (s, 1H), 4.92–4.87 (m, 1H), 4.62 (s, 2H), 3.50 (t, J = 6.6 Hz, 2H), 2.23–2.18 (m, 4H), 2.14 (s, 3H), 2.12–2.03 (m, 5H), 1.80–1.73 (m, 3H), 1.62–1.41 (m, 8H), 1.40–1.33 (m, 4H), 1.31–1.25 (m, 2H), 1.12–1.05 (m, 31.5H), 0.92 (s, 9H), 0.79–0.75 (m, 3H), 0.09 (s, 6H); MS (EI) M-1.79R-
\( \text{C}_4\text{F}_9, \text{C}_4\text{F}_9 \text{ m/z 1275 (M}^+ + \text{Na)}; \text{ M-1.79R-TIPS, C}_4\text{F}_9 \text{ m/z 1057 (M}^+ + \text{Na); HRMS (ESI) M-1.79R-C}_4\text{F}_9, \text{C}_4\text{F}_9 \text{ m/z (M}^+ + \text{Na) calcd for C}_{55}\text{H}_{86}\text{O}_3\text{F}_{18}\text{NaSi}_3\text{S 1275.5216, found 1275.5110; M-1.79R-TIPS, C}_4\text{F}_9 \text{ m/z (M}^+ + \text{Na) calcd for C}_{51}\text{H}_{87}\text{O}_3\text{F}_{9}\text{NaSi}_3\text{S 1057.5438, found 1057.5507.} \)

(12\text{S},23\text{R},\text{E})-23-((\text{ tert-Butyldimethylsilyl})\text{ethynyl})-29,29,30,31,32,32,32-\text{nonafluoro-12-}((4,4,5,5,6,6,6-\text{heptafluorohexyl})\text{diisopropylsilyloxy})-25,25-\text{diisopropyl-4,24-dioxa-2-thia-25-siladotriaconta-21-en-10,13-diyn}e \text{ and (12\text{S},23\text{S},\text{E})-23-((\text{ tert-butyldimethylsilyl})\text{ethynyl})-12-}((4,4,5,5,6,6,6-\text{heptafluorohexyl})\text{diisopropylsilyloxy})-25,25-\text{diisopropyl-26-methyl-4,24-dioxa-2-thia-25-silaheptacosa-21-en-10,13-diyn}e \text{ (M-1.79S)}:

Following the same procedure for \text{M-1.79R}, the mixture \text{M-1.78S} (250.0 mg, 0.34 mmol) was reacted with Trifluoromethanesulfonic acid (neat, 79.6 \mu L, 0.90 mmol), silane 1.69 (neat, 333.6 mg, 1.02 mmol), and 2,6–lutidine (0.14 mL, 1.19 mmol), the title mixture \text{M-1.79S} (277.7 mg, 85%) was obtained. \(^1\text{H NMR} (600 \text{ MHz, CDCl}_3) \delta 5.80–5.77 \text{ (m, 1 H), 5.54–5.50 \text{ (m, 1 H), 5.21 \text{ (s, 1 H), 4.92–4.87 \text{ (m, 1 H), 4.62 \text{ (s, 2 H), 3.50 \text{ (t, J = 6.6 Hz, 2 H), 2.23–2.18 \text{ (m, 4 H), 2.14 \text{ (s, 3 H), 2.12–2.03 \text{ (m, 5 H), 1.80–1.73 \text{ (m, 3 H), 1.62–1.43 \text{ (m, 8 H), 1.40–1.33 \text{ (m, 4 H), 1.31–1.25 \text{ (m, 2 H), 1.12–1.05 \text{ (m, 31.5 H), 0.92 \text{ (s, 9 H), 0.79–0.75 \text{ (m, 3 H), 0.09 \text{ (s, 6 H); MS (EI) M-1.79S-C}_4\text{F}_9, C}_3\text{F}_7 \text{ m/z 1225 (M}^+ + \text{Na); M-1.79S-TIPS, C}_3\text{F}_7 \text{ m/z 1008 (M}^+ + \text{Na + H); HRMS (ESI) M-1.79S-C}_4\text{F}_9, C}_3\text{F}_7 \text{ m/z (M}^+ + \text{Na) calcd for C}_{54}\text{H}_{88}\text{O}_3\text{F}_{16}\text{NaSi}_3\text{S 1225.5248,}} \)
found 1225.5331; **M-1.79S-TIPS, C₃F₇** m/z (M⁺ + Na) calcd for C₅₀H₈₇O₃F₇NaSi₃S 1007.5470, found 1007.5438.

(8R,19R,E)-21-(tert-Butyldimethylsilyl)-8,19-bis(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)henicosa-17-en-6,9,20-triyn-1-ol, (8R,19S,E)-21-(tert-butyl dimethylsilyl)-8-(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)-19-(triisopropyl silyloxy)henicosa-17-en-6,9,20-triyn-1-ol, (8S,19R,E)-21-(tert-butyldimethylsilyl)-19-(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)-8-(diisopropyl(4,4,5,5,6,6,6-heptafluorohexyl)diisopropylsilyloxy)henicosa-17-en-6,9,20-triyn-1-ol, and (8S,19S,E)-21-(tert-butyldimethyl silyl)-8-((4,4,5,5,6,6,6-heptafluorohexyl)diisopropylsilyloxy)-19-(triisopropylsilyloxy) henicosa-17-en-6,9,20-triyn-1-ol (M-1.80):

Solid NaHCO₃ (324.4 mg, 3.86 mmol) and MeI (9.0 mL) were added to the solution of mixture **M-1.79R** (270.0 mg, 0.27 mmol) and **M-1.79S** (259.4 mg, 0.27 mmol) in mixture of acetone (16.0 mL) and water (0.86 mL). The resulting suspension was stirred in a sealed tube at 45 °C for 14 h. The mixture was diluted with water (20 mL) and EtOAc (30 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated in vacuo.
The crude product was purified by column chromatography (hexane/Et₂O = 3:1) to afford the mixture **M-1.80** (451.0 mg, 90%). ¹H NMR (600 MHz, CDCl₃) δ 5.82–5.76 (m, 1H), 5.54–5.49 (m, 1H), 5.20 (s, 1H), 4.92–4.87 (m, 1H), 3.64 (t, J = 6.6 Hz, 2H), 2.24–2.18 (m, 4H), 2.14–2.03 (m, 5H), 1.78–1.73 (m, 3H), 1.62–1.43 (m, 8H), 1.40–1.24 (m, 6H), 1.13–1.05 (m, 31.5H), 0.92 (s, 9H), 0.79–0.75 (m, 3H), 0.09 (s, 6H); MS (EI) **M-1.80-C₄F₉**, **C₄F₉** m/z 1215 (M⁺ + Na); **M-1.80-TIPS**, **C₃F₇** m/z 998 (M⁺ + Na + H); **M-1.80-C₄F₉**, **C₃F₇** m/z 1165 (M⁺ + Na); **M-1.80-TIPS**, **C₃F₇** m/z 948 (M⁺ + Na + H) HRMS (ESI) **M-1.80-C₄F₉**, **C₄F₉** m/z (M⁺ + Na) calcd for C₅₃H₈₂O₃F₁₈NaSi₃ 1215.5182, found 1215.5067; **M-1.80-TIPS**, **C₃F₇** m/z (M⁺ + Na) calcd for C₄₉H₈₃O₃F₉NaSi₃ 997.5404, found 997.5370; **M-1.80-C₄F₉**, **C₃F₇** m/z (M⁺ + Na) calcd for C₄₉H₈₃O₃F₉NaSi₃ 1165.5214, found 1165.5240; **M-1.80-TIPS**, **C₃F₇** m/z (M⁺ + Na) calcd for C₄₈H₈₃O₃F₇NaSi₃ 947.5436, found 947.5422.

(8R,19R,E)-21-(tert-Butyldimethylsilyl)-8,19-bis(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)henicosa-17-en-6,9,20-triynal, (8R,19S,E)-21-(tert-butyldimethylsilyl)-8-(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)-19-(triisopropylsilyloxy)henicosa-17-en-6,9,20-triynal, (8S,19R,E)-21-(tert-butyldimethylsilyl)-19-(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)-8-((4,4,5,5,6,6,6-heptafluorohexyl)diisopropylsilyloxy)henicosa-
17-en-6,9,20-triynal, and (85S,19S,E)-21-((tert-butyldimethylsilyl)-8-((4,4,5,5,6,6,6-heptafluorohexyl)diisopropylsilyloxy)-19-(triisopropylsilyloxy)henicosa-17-en-6,9,20-triynal (M-1.2):

NaHCO3 (196.2 mg, 2.34 mmol) was added followed by DMP (371.5 mg, 0.88 mmol) to the solution of mixture M-1.80 (270.0 mg, 0.29 mmol) in CH2Cl2 (4.5 mL) at room temperature. The resulting mixture was stirred at the same temperature for 2 h. Saturated NH4Cl aqueous solution (15 mL) was added. The organic phase was separated and the aqueous phase was extracted with CH2Cl2 (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO4, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/Et2O = 9:1) to afford the mixture M-1.2 (200.3 mg, 74%). 1H NMR (600 MHz, CDCl3) δ 9.76 (s, 1H), 5.82–5.76 (m, 1H), 5.54–5.49 (m, 1H), 5.20 (s, 1H), 4.92–4.87 (m, 1H), 2.44 (t, J = 7.2 Hz, 2H), 2.24 (t, J = 6.6 Hz, 2H), 2.19 (t, J = 7.2 Hz, 2H), 2.14–2.02 (m, 5H), 1.79–1.70 (m, 5H), 1.57–1.46 (m, 6H), 1.38–1.33 (m, 4H), 1.31–1.25 (m, 2H), 1.13–1.05 (m, 31.5H), 0.92 (s, 9H), 0.79–0.75 (m, 3H), 0.09 (s, 6H); HRMS (ESI) M-1.2-C4F9, C4F9 m/z (M+ + Na) calcd for C53H80O3F18NaSi3 1213.5026, found 1213.5062; M-1.2-TIPS, C4F9 m/z (M+ + Na) calcd for C49H81O3F9NaSi3 995.5248, found 995.5237; M-1.2-C4F9, C3F7 m/z (M+ + Na) calcd for C52H80O3F16NaSi3 1163.5058, found 1163.5133; M-1.2-TIPS, C3F7 m/z (M+ + Na) calcd for C48H81O3F7NaSi3 945.5279, found 945.5218.

PMBO

6-(4-Methoxybenzyloxy)hexan-1-ol (1.82):47

1,6-Hexanediol 1.81 (14.19 g, 120 mmol) was added dropwise to a suspension of NaH (4.80 g, 60 wt% in mineral oil, 120 mmol) in THF (400 mL) at 0 °C. PMBCl (16.4 mL, 120
mmol) was then added dropwise followed by addition of TBAI (4.88 g, 13.2 mmol). After stirring at room temperature for 1 h, the reaction mixture was heated to 60 °C for 15 h. After being cooled to room temperature, the resulting mixture was poured into a solution of saturated NaHCO₃ and vigorously stirred. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc = 3:2) to afford the title compound 1.82 (15.45 g, 54%). ¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.63 (q, J = 5.5 Hz, 2H), 3.44 (t, J = 6.5 Hz, 2H), 1.64–1.52 (m, 4 H), 1.39–1.36 (m, 4H), 1.23 (t, J = 5.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 158.9, 130.4, 129.0, 113.5, 72.3, 69.8, 62.3, 55.0, 32.4, 29.5, 25.8, 25.4; IR (film) 3425, 2937, 2861, 1613, 1513, 1464, 1302, 1248, 1174, 1090, 1036, 907, 731, 650; MS (EI) m/z 238 (M⁺); HRMS (ESI) m/z (M⁺) calcd for C₁₄H₂₂O₃ 238.1569, found 238.1575.

1-((6-Bromohexyloxy)methyl)-4-methoxybenzene (1.83):

A solution of triphenylphosphine (18.5 g, 70.7 mmol) was added to a solution of alcohol 1.82 (11.23 g, 47.1 mmol) and CBr₄ (18.8 g, 56.5 mmol) in CH₂Cl₂ (175 mL) at 0 °C. After stirring at room temperature for 1 h, the organic solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound 1.83 (12.65 g, 89%). ¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.44 (t, J = 6.5 Hz, 2H), 3.40 (t, J = 6.8 Hz, 2H), 1.86 (quin, J = 6.8 Hz, 2H), 1.66–1.57 (m, 2H), 1.50–1.37 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 159.1, 130.7, 129.2, 113.8, 72.5, 69.9, 55.3, 33.8, 32.7, 29.6, 28.0, 25.4; IR (film) 3015, 2938,
(6-(4-Methoxybenzyloxy)hexyl)triphenylphosphonium bromide (1.12):\(^{47}\)

A mixture of bromide 1.83 (12.62 g, 41.9 mmol) and triphenylphosphine (22.03 g, 84.0 mmol) in CH\(_3\)CN (310 mL) was stirred at 90 °C for 2 days. The organic solvent was removed under reduced pressure, the residue was purified by column chromatography (CHCl\(_3\)/MeOH = 19:1) to afford the title compound 1.12 with tiny triphenylphosphine (21.23 g, 90%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.81–7.73 (m, 9H), 7.68–7.59 (m, 6H), 7.17 (d, \(J = 8.7\) Hz, 2H), 6.78 (d, \(J = 8.7\) Hz, 2H), 4.33 (s, 2H), 3.73 (s, 3H), 3.68 (m, 2H), 3.34 (t, \(J = 6.3\) Hz, 2H), 1.60 (br s, 4H), 1.52–1.43 (m, 2H), 1.33–1.29 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 158.3, 134.4 (d, \(J_{CP} = 2.2\) Hz, 1C), 132.8 (d, \(J_{CP} = 9.8\) Hz, 1C), 129.8 (d, \(J_{CP} = 12.8\) Hz, 1C), 128.5, 127.6, 117.4 (d, \(J_{CP} = 85.5\) Hz, 1C), 113.0, 71.7, 69.1, 54.6, 29.4 (d, \(J_{CP} = 15.8\) Hz, 1C), 28.5, 25.0, 22.0 (d, \(J_{CP} = 49.5\) Hz, 1C), 21.8 (d, \(J_{CP} = 3.8\) Hz, 1C); IR (film) 3010, 2937, 2863, 2193, 1702, 1610, 1513, 1462, 1439, 1302, 1250, 1170, 1113, 1033, 910, 732; MS (EI) m/z 483 (M\(^+\) – Br); HRMS (ESI) m/z (M\(^+\)) calcd for C\(_{32}\)H\(_{36}\)O\(_2\)P 483.2453, found 483.2418.

Methyl 16-hydroxyhexadecanoate (1.84):\(^{48}\)

16-Hydroxyhexadecanoic acid 1.15 (5.60 g, 20.6 mmol) and p-toluenesulfonic acid monohydrate (1.25 g, 6.6 mmol) were dried under vacuum for 2 h. MeOH (300 mL) was added and the mixture was stirred at room temperature for 16 h. Solid NaHCO\(_3\) (1.25 g) was added and
the resulting mixture was stirred for further 30 min, then filtered through a pad of Celite. The organic solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 3:1) to afford the title compound 1.84 (5.89 g, 100%) as colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.66 (s, 3H), 3.64 (q, $J = 6.5$ Hz, 2H), 2.30 (t, $J = 7.5$ Hz, 2H), 1.64–1.54 (m, 4H), 1.25 (br s, 22H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 174.3, 62.6, 51.3, 39.9, 32.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 25.6, 24.8; IR (film) 3435, 2927, 2855, 1731, 1465, 1438, 1202, 1175, 1054, 908, 735, 650; MS (EI) $m/z$ 287 (M$^+$); HRMS (ESI) $m/z$ (M$^+$) calcd for C$_{17}$H$_{35}$O$_3$ 287.2586, found 287.2594.

**Methyl 16-oxohexadecanoate (1.85):**

To a solution of oxalyl chloride (3.50 mL, 40.8 mmol) in CH$_2$Cl$_2$ (145 mL) was slowly added a solution of DMSO (4.35 mL, 61.2 mmol) in CH$_2$Cl$_2$ (30 mL) at –78 °C. After 15 min at the same temperature, a solution of alcohol 1.84 (5.85 g, 20.4 mmol) in CH$_2$Cl$_2$ (30 mL) was then added dropwise. The resulting mixture was stirred for 15 min and Et$_3$N (14.2 mL, 102.0 mmol) was added slowly. The reaction was maintained at –78 °C for 15 min, then allowed to warm to 0 °C, the stirring continued for further 30 min. Water was added and the mixture was diluted with Et$_2$O. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with Et$_2$O (3 × 90 mL). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc = 9:1) to afford the title compound 1.85 (5.70 g, 98%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.76 (t, $J = 2.0$ Hz, 1H), 3.66 (s, 3H), 2.41 (td, $J = 7.5, 2.0$ Hz, 2H), 2.30 (t, $J = 7.5$ Hz, 2H), 1.69–1.58 (m, 4H), 1.25 (br s, 20H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 202.7,
Methyl 17, 17-dibromoheptadec-16-enoate (1.86):

To a solution of triphenylphosphine (23.6 g, 90 mmol) in CH₂Cl₂ (60 mL) at 0 °C was slowly added a solution of CBr₄ (13.9 g, 42 mmol) in CH₂Cl₂ (12 mL) at a rate to maintain the temperature below 15 °C. Then a solution of aldehyde 1.85 (5.7 g, 20 mmol) and Et₃N (8.4 mL, 60 mmol) in CH₂Cl₂ (12 mL) was added dropwise at 0 °C. After stirring for 35 min at the same temperature, the mixture was poured into hexane (120 mL) and filtered through a pad of Celite. The solid was washed with hexane (2 × 50 mL) and the filtrate was concentrated under reduced pressure. Hexane (40 mL) was added and the mixture was filtered again. The combined organic layers were dried over MgSO₄ and concentrated \textit{in vacuo}. The residue was purified by flash chromatography (hexane/EtOAc = 49:1) to afford the title compound 1.86 (8.10 g, 92%): £H NMR (300 MHz, CDCl₃) δ 6.38 (t, $J = 7.2$ Hz, 1 H), 3.66 (s, 3H), 2.30 (t, $J = 7.5$ Hz, 2H), 2.08 (q, $J = 7.2$ Hz, 2H), 1.66–1.56 (m, 2H), 1.46–1.35 (m, 2H), 1.25 (br. s, 20H); £C NMR (75 MHz, CDCl₃) δ 174.2, 138.8, 88.4, 51.3, 34.0, 33.0, 29.5, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 27.7, 24.9; IR (film) 2925, 2853, 1741, 1462, 1436, 1361, 1249, 1197, 1170, 1112, 1016, 911, 799; MS (EI) $m/z$ 439 (M⁺ + H); HRMS (ESI) $m/z$ (M⁺) calcd for C₁₈H₃₂O₂Br₂ 438.0769, found 438.0782.

(Z)-Methyl 17-bromoheptadec-16-enoate (1.14):
A mixture of triphenylphosphine (2.42 g, 9.2 mmol) and Pd(OAc)$_2$ (0.42 g, 1.9 mmol) in CH$_2$Cl$_2$ (95 mL) was stirred for 15 min at room temperature to generate a light yellow solution. Dibromide 1.86 (8.10 g, 18.4 mmol) and tributyltin hydride (12.9 mL, 47.8 mmol) were sequentially added and the mixture was stirred for 45 min at room temperature. After the reaction was completed, the mixture was diluted with Et$_2$O and washed with water (3 × 75 mL), brine (3 × 75 mL). The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography (hexane/Et$_2$O = 49:1) to afford the title compound 1.14 (6.66 g, 100%). $^1$H NMR (300 MHz, CDCl$_3$) δ 6.15–6.04 (m, 2H), 3.65 (s, 3H), 2.29 (t, $J$ = 7.5 Hz, 2H), 2.18 (q, $J$ = 6.9 Hz, 2H), 1.66–1.56 (m, 2H), 1.44–1.33 (m, 2H), 1.25 (br. s, 20H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 174.2, 134.9, 107.5, 51.3, 34.0, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.1, 24.9; IR (film) 2928, 2855, 1731, 1463, 1439, 1201, 1174, 908, 734; MS (EI) m/z 329 (M$^+$ - CH$_3$O); HRMS (ESI) m/z (M$^+$ - CH$_3$O) calcd for C$_{17}$H$_{30}$OBr 329.1480, found 329.1480.

(Z)-Methyl 19-(tert-butyldimethylsilyl)nonadec-16-en-18-ynoate (1.87):

tert-Butyldimethylsilylacetylene 1.35 (8.4 mL, 45 mmol) was added to a solution of vinyl bormide 1.14 (6.60 g, 18.3 mmol), PdCl$_2$(PPh$_3$)$_2$ (1.52 g, 2.2 mmol), and CuI (0.34 g, 1.8 mmol) in degassed piperidine (180 mL) at room temperature. After stirring at the same temperature for 2 h, saturated NH$_4$Cl aqueous solution (90 mL) was added and extracted with Et$_2$O (3 × 75 mL). The organic layer was washed with brine (3 × 75 mL), dried over MgSO$_4$, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/Et$_2$O = 49:1) to afford the title compound 1.87 (6.86 g, 87%). $^1$H NMR (300 MHz, CDCl$_3$) δ 5.95 (dt, $J$ = 10.8,
7.8 Hz, 1H), 5.48 (d, J = 10.8 Hz, 1H), 3.66 (s, 3H), 2.31 (q, J = 7.1 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.64–1.56 (m, 2H), 1.43–1.35 (m, 2H), 1.25 (br. s, 20H), 0.96 (s, 9H), 0.13 (s, 6H); 13C NMR (75 MHz, CDCl₃) δ 174.2, 145.5, 109.2, 102.7, 96.6, 51.3, 34.1, 30.3, 29.6, 29.6, 29.4, 29.4, 29.2, 29.2, 29.1, 28.7, 26.1, 24.9, 16.6, –4.6; IR (film) 2928, 2855, 1731, 1465, 1439, 1251, 1201, 1174, 909, 838, 735; MS (EI) m/z 443 (M⁺ + Na); HRMS (ESI) m/z (M⁺ + Na) calcd for C₂₆H₄₈O₂NaSi 443.3321, found 443.3309.

(Z)-19-(tert-Butyldimethylsilyl)nonadec-16-en-18-ynal (1.13):

DIBAL-H (22 mL, 1.0 M solution in hexane, 22 mmol) was added to a solution of ester 1.87 (6.85 g, 16.3 mmol) in CH₂Cl₂ (85 mL) at –78 °C. After stirring for 30 min at the same temperature, the mixture was poured into a rapidly stirred mixture of saturated aqueous sodium potassium tartrate (240 mL) and Et₂O (160 mL). The resulting mixture was stirred vigorously for 1 h, at which time the organic layer cleared. The organic layer was washed with brine (150 mL) and the combined aqueous layers were extracted with Et₂O (150 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography (hexane/Et₂O = 49:1) to afford the title compound 1.13 (5.98 g, 94%).

1H NMR (300 MHz, CDCl₃) δ 9.76 (t, J = 1.8 Hz, 1H), 5.95 (dt, J = 10.8, 7.5 Hz, 1H), 5.48 (d, J = 10.8 Hz, 1H), 2.42 (td, J = 7.5, 2.1 Hz, 2H), 2.32 (qd, J = 6.9, 0.6 Hz, 2H), 1.68–1.57 (m, 2H), 1.44–1.35 (m, 2H), 1.25 (br. s, 20H), 0.96 (s, 9H), 0.13 (s, 6H); 13C NMR (75 MHz, CDCl₃) δ 202.8, 145.5, 109.2, 102.8, 96.7, 43.9, 30.4, 29.6, 29.3, 29.2, 28.7, 26.1,
22.1, 16.6, ~4.6; IR (film) 2928, 2855, 1721, 1646, 1389, 1251, 908, 810, 733; MS (EI) m/z 390 (M⁺); HRMS (ESI) m/z (M⁺) calcd for C₂₅H₄₆OSi 390.3318, found 390.3316.

tert-Butyl((3Z,19Z)-25-(4-methoxybenzyloxy)pentacosa-3,19-dien-1-ynyl)dimethylsilane (1.88):

NaHMDS (30 mL, 1.0 M solution in THF, 30 mmol) was added to the solution of phosphonium bromide 1.12 (19.86 g, 35 mmol) in THF (120 mL) at 0 °C. The resulting orange solution was stirred at the same temperature for 30 min and then cooled to −78 °C. The solution of aldehyde 1.13 (5.86 g, 15 mmol) in THF (55 mL) was then added. The mixture was stirred at −78 °C for 2 h and warmed to room temperature for further 2 h stirring. Saturated NH₄Cl aqueous solution (75 mL) was added, the organic phase was separated and aqueous phase was extracted with Et₂O (3 × 75 mL). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography (hexane/Et₂O = 49:1) to afford the title compound 1.88 (8.85 g, 99%). ¹H NMR (300 MHz, CDCl₃) δ 7.26 (m, 2H), 6.88 (m, 2H), 5.96 (dt, J = 10.8, 7.5 Hz, 1H), 5.47 (d, J = 10.8 Hz, 1H), 5.37–5.28 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, J = 6.6 Hz, 2H), 2.32 (qd, J = 6.6, 0.6 Hz, 2H), 2.07–1.95 (m, 4H), 1.64–1.56 (m, 2H), 1.44–1.33 (m, 6H), 1.25 (br. s, 22H), 0.96 (s, 9H), 0.13 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 159.1, 145.6, 130.8, 130.1, 129.6, 129.2, 113.7, 109.2, 102.8, 96.7, 72.5, 70.2, 55.2, 30.4, 29.8, 29.7, 29.6, 29.4, 29.3, 29.2, 28.8, 27.2, 27.1, 26.1, 25.9, 16.6, ~4.5; IR (film) 3054, 2928, 2855, 1612, 1513, 1463, 1423, 1361, 1265,
1096, 1035, 895, 826, 740, 706; MS (EI) m/z 595 (M$^+$ + H); HRMS (ESI) m/z (M$^+$ + H) calcd for C$_{39}$H$_{47}$O$_2$Si 595.4910, found 595.4912.

**HO**

(6Z,22Z)-25-(tert-Butyldimethylsilyl)pentacosa-6,22-dien-24-yn-1-ol:

DDQ (5.03 g, 22.2 mmol) was added to the solution of compound 1.88 (8.80 g, 14.8 mmol) in CH$_2$Cl$_2$ (150 mL) and H$_2$O (16 mL) at room temperature. The reaction was monitored by TLC until completion, and then saturated NaHCO$_3$ aqueous solution was added. The mixture was extracted with CH$_2$Cl$_2$ (3 × 100 mL), the organic layers were combined, washed with saturated NaHCO$_3$ aqueous solution, brine, dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography (hexane/Et$_2$O = 3:1) to afford the title compound, which was contaminated with tiny 4-(methoxymethyl)benzaldehyde and was used in the following step without further purification.

**Br**


A solution of triphenylphosphine (14.0 g, 53.4 mmol) was added to a solution of (6Z,22Z)-25-(tert-Butyldimethylsilyl)pentacosa-6,22-dien-24-yn-1-ol (14.8 mmol) and CBr$_4$ (14.2 g, 42.8 mmol) in CH$_2$Cl$_2$ (70 mL) at 0 °C. After stirring at room temperature for 1 h, the organic solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 99:1) to afford the title compound 1.89 (4.77 g, 60% for 2 steps). $^1$H NMR (300 MHz, CDCl$_3$) δ 5.96 (dt, $J = 10.8, 7.5$ Hz, 1H), 5.48 (d, $J = 10.8$ Hz, 1H), 5.48 (d, $J = 10.8$ Hz, 1H),...
5.43–5.28 (m, 2H), 3.41 (t, \( J = 6.9 \) Hz, 2H), 2.32 (q, \( J = 7.2 \) Hz, 2H), 2.07–1.96 (m, 4H), 1.87 (quin, \( J = 6.9 \) Hz, 2H), 1.50–1.37 (m, 6H), 1.26 (br. s, 22H), 0.96 (s, 9H), 0.13 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 145.6, 130.4, 129.2, 109.2, 102.8, 96.7, 33.9, 32.8, 30.4, 29.7, 29.7, 29.7, 29.6, 29.4, 29.3, 29.2, 28.9, 28.8, 27.8, 27.2, 27.0, 26.1, 16.6, −4.5; IR (film) 2926, 2854, 1650, 1558, 1459, 1251, 1022, 910, 736; MS (EI) \( m/z \) 536 (M\(^+\)); HRMS (ESI) \( m/z \) (M\(^+\)) calcd for C\(_{31}\)H\(_{57}\)OSi 536.3413, found 536.3401.

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\text{((6Z,22Z)-25-(tert-butyldimethylsilyl)pentacosa-6,22-dien-24-ynyl)triphenylphosphonium bromide (1.3):}
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A mixture of bromide 1.89 (4.77 g, 8.9 mmol) and triphenylphosphine (5.82 g, 22.2 mmol) in CH\(_3\)CN (90 mL) was stirred at 90 °C for 2 days. The organic solvent was removed under reduced pressure, the residue was purified by column chromatography (CHCl\(_3\)/MeOH = 19:1) to afford the title compound 1.3 (6.78 g, 96%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.87–7.82 (m, 6H), 7.79–7.74 (m, 3H), 7.71–7.67 (m, 6H), 5.95 (dtd, \( J = 10.5, 7.5, 2.0 \) Hz, 1H), 5.46 (dt, \( J = 11.0, 1.3 \) Hz, 1H), 5.31–5.20 (m, 2H), 3.87–3.77 (m, 2H), 2.30 (q, \( J = 6.5 \) Hz, 2H), 1.96–1.89 (m, 4H), 1.68–1.58 (m, 4H), 1.43–1.35 (m, 4H), 1.23 (br. s, 22H), 0.94 (d, \( J = 2.0 \) Hz, 9H), 0.11 (d, \( J = 2.5 \) Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 145.6, 134.9 (d, \( J_{CP} = 2.5 \) Hz), 133.6 (d, \( J_{CP} = 10.0 \) Hz), 133.4 (d, \( J_{CP} = 12.5 \) Hz), 130.3, 129.0, 118.3 (d, \( J_{CP} = 86.3 \) Hz), 109.1, 102.7, 96.6, 30.3, 30.0, 29.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 27.2, 26.7, 26.0, 22.7 (d, \( J_{CP} = 45 \) Hz), 22.5, 16.5, −4.5; IR (film) 2925, 2854, 1650, 1558, 1458, 1437, 1112, 914; HRMS (ESI) \( m/z \) (M\(^+\) − Br) calcd for C\(_{49}\)H\(_{72}\)SiP 719.5141, found 719.5121.

NaHMDS (0.63 mL, 1.0 M solution in THF, 0.63 mmol) was added to the solution of phosphonium bromide 1.3 (658.9 mg, 0.82 mmol) in THF (2.1 mL) at 0 °C. The resulting orange solution was stirred at the same temperature for 10 min and then cooled to −78 °C. The solution of aldehyde M-1.2 (190.0 mg, 0.21 mmol) in THF (1.4 mL) was then added. The mixture was
stirred at −78 °C for 2 h. Saturated NH₄Cl aqueous solution (10 mL) was added, the organic phase was separated and aqueous phase was extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography (hexane/CH₂Cl₂ = 9:1) to afford the title compound M-1.90 (137.2 mg, 44%). ¹H NMR (600 MHz, CDCl₃) δ 5.96 (dt, J = 10.8, 7.8 Hz, 1H), 5.83–5.76 (m, 1H), 5.54–5.47 (m, 2H), 5.38–5.30 (m, 4H), 5.21 (s, 1H), 4.92–4.87 (m, 1H), 2.32 (q, J = 7.2 Hz, 2H), 2.20 (q, J = 7.8 Hz, 2H), 2.15–2.08 (m, 3H), 2.06–1.98 (m, 10H), 1.79–1.72 (m, 3H), 1.53–1.47 (m, 4H), 1.44–1.25 (m, 36H), 1.13–1.05 (m, 31.5H), 0.96 (s, 9H), 0.92 (s, 9H), 0.79–0.75 (m, 3H), 0.13 (s, 6H), 0.09 (s, 6H).

Demix the mixture M-1.90:

The mixture M-1.90 (137.2 mg, 0.09 mmol) was dissolved in CH₃CN/THF (3:2) (6 mL) and demixed by semi-preparative fluorous HPLC (FluorosFlash™ PFC8 column, CH₃CN:THF = 100:0 to 85:15 in 45 min, then 85:15 for further 20 min). The four desired compounds were obtained.

1.90SS: 41.3 mg, t = 20.3 min
1.90SR: 39.5 mg, t = 25.5 min
1.90RS: 16.0 mg, t = 42.2 min
1.90RR: 19.7 mg, t = 52.7 min
TBAF (0.24 mL, 1.0 M solution in THF, 0.24 mmol) was added to a solution of compound 1.90SS (40.0 mg, 0.29 mmol) in THF (0.6 mL) at room temperature. The mixture then was stirred for 1 h at this temperature and quenched with saturated aqueous NH₄Cl. The resulting mixture was extracted with CH₂Cl₂ (3 × 5 mL). The organic layers were washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/Et₂O = 4:1) to give compound 1.1SS (11.4 mg, 59%). [α]D²⁵ = +10.5 (c = 0.30, CH₃OH), ¹H NMR (600 MHz, CDCl₃) δ 6.00 (dt, J = 10.8, 7.2 Hz, 1H), 5.91 (dt, J = 15.0, 7.0 Hz, 1H), 5.62 (dd, J = 15.0, 6.0 Hz, 1H), 5.44 (dd, J = 10.8, 1.2 Hz, 1H), 5.39–5.31 (m, 4H), 5.09 (dt, J = 7.2, 1.8 Hz, 1H), 4.84 (t, J = 6.0 Hz, 1H), 3.07 (d, J = 1.8 Hz, 1H), 2.57 (d, J = 2.4 Hz, 1H), 2.32 (q, J = 7.2 Hz, 2H), 2.23 (qd, J = 6.0, 1.2 Hz, 4H), 2.13 (d, J = 7.2 Hz, 1H), 2.08 (q, J = 7.2 Hz, 2H), 2.06–1.99 (m, 8H), 1.88 (d, J = 6.0 Hz, 1H), 1.55–1.49 (m, 4H), 1.46–1.25 (m, 36H); ¹³C NMR (200 MHz, CDCl₃) δ 146.31, 134.32, 130.21, 130.07, 129.65, 129.31, 128.52, 107.88, 85.02, 84.97, 83.26, 81.13, 80.58, 78.10, 78.10, 74.01, 62.77, 52.54, 31.76, 30.26, 29.76, 29.68 (3 C), 29.65 (3 C), 29.57, 29.44, 29.37, 29.33 (2 C), 29.17, 28.87, 28.72, 28.56, 28.54, 28.49, 28.19, 27.92, 27.23, 27.13, 27.09, 26.65, 18.64, 18.63; IR (film) 3054, 2986, 2929, 2855, 1422, 1265, 909, 740; MS (EI) m/z 678 (M⁺ + Na + H); HRMS (ESI) m/z (M⁺ + Na) calcd for C₄₆H₇₀O₂Na 677.5274, found 677.5321.
(3S,4E,14R,21Z,27Z,43Z)-Hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diol (1.1SR):

Following the same procedure for 1.1SS, the compound 1.90SR (38.0 mg, 0.027 mmol) was reacted with TBAF (0.22 mL, 1.0 M solution in THF, 0.22 mmol), the title compound 1.1SR (10.4 mg, 59%) was obtained. \([\alpha]_D^{25} = +9.5\) (c = 0.25, CH₃OH), \(^1\)H NMR (600 MHz, CDCl₃) \(\delta\) 6.00 (dt, \(J = 10.8, 7.2\) Hz, 1H), 5.91 (dt, \(J = 15.6, 7.2\) Hz, 1H), 5.62 (ddd, \(J = 15.6, 6.0, 0.6\) Hz, 1H), 5.44 (dd, \(J = 10.8, 1.2\) Hz, 1H), 5.39–5.31 (m, 4H), 5.09 (dt, \(J = 6.6, 1.2\) Hz, 1H), 4.84 (t, \(J = 6.0\) Hz, 1H), 3.07 (d, \(J = 1.8\) Hz, 1H), 2.57 (d, \(J = 1.8\) Hz, 1H), 2.32 (q, \(J = 7.2\) Hz, 2H), 2.23 (qd, \(J = 6.5, 1.2\) Hz, 4H), 2.11 (d, \(J = 7.2\) Hz, 1H), 2.08 (q, \(J = 7.2\) Hz, 2H), 2.06–1.99 (m, 8H), 1.87 (d, \(J = 6.0\) Hz, 1H), 1.56–1.49 (m, 4H), 1.46–1.25 (m, 36H); \(^13\)C NMR (200 MHz, CDCl₃) \(\delta\) 146.32, 134.33, 130.21, 130.07, 129.65, 129.31, 128.51, 107.87, 85.03, 84.98, 83.26, 81.12, 80.58, 78.09, 78.08, 74.02, 62.78, 52.54, 31.77, 30.26, 29.76, 29.68 (3 C), 29.66 (3 C), 29.58, 29.44, 29.37, 29.33 (2 C), 29.17, 28.87, 28.72, 28.56, 28.54, 28.50, 28.20, 27.91, 27.23, 27.13, 27.09, 26.65, 18.65, 18.63; IR (film) 3054, 2986, 2929, 2855, 1423, 1265, 909, 736; MS (EI) m/z 678 (M⁺ + Na + H); HRMS (ESI) m/z (M⁺ + Na) calcd for C₄₆H₇₀O₂Na 677.5274, found 677.5267.

(3R,4E,14S,21Z,27Z,43Z)-Hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diol (1.1RS):

Following the same procedure for 1.1SS, the compound 1.90RS (12.5 mg, 0.008 mmol) was reacted with TBAF (0.07 mL, 1.0 M solution in THF, 0.07 mmol), the title compound 1.1RS
(2.1 mg, 41%) was obtained. \([\alpha]_D^{25} = -9.0\) \((c = 0.16, \text{CH}_3\text{OH})\), \(^1\text{H} \text{NMR (600 MHz, CDCl}_3\) \(\delta 6.00 \) \((dt, J = 10.8, 7.2 \text{ Hz, 1H})\), 5.91 \((dt, J = 15.0, 7.2 \text{ Hz, 1H})\), 5.62 \((ddd, J = 15.6, 6.0 \text{ Hz, 1H})\), 5.44 \((dd, J = 10.8, 1.2 \text{ Hz, 1H})\), 5.39–5.31 \((m, 4H)\), 5.09 \((dt, J = 7.2, 1.8 \text{ Hz, 1H})\), 4.84 \((t, J = 6.0 \text{ Hz, 1H})\), 3.07 \((d, J = 1.8 \text{ Hz, 1H})\), 2.57 \((d, J = 1.8 \text{ Hz, 1H})\), 2.32 \((q, J = 7.2 \text{ Hz, 2H})\), 2.23 \((qd, J = 6.9, 1.8 \text{ Hz, 4H})\), 2.10 \((d, J = 6.6 \text{ Hz, 1H})\), 2.08 \((q, J = 7.2 \text{ Hz, 2H})\), 2.06–1.99 \((m, 8H)\), 1.85 \((d, J = 6.0 \text{ Hz, 1H})\), 1.56–1.49 \((m, 4H)\), 1.46–1.25 \((m, 36H)\); \(^{13}\text{C} \text{NMR (200 MHz, CDCl}_3\) \(\delta 146.33, 134.35, 130.22, 130.08, 129.66, 129.31, 128.52, 107.88, 85.05, 85.00, 83.26, 81.12, 80.58, 78.08 \((2 \text{ C})\), 74.02, 62.80, 52.55, 31.77, 30.27, 29.77, 29.68 \((3 \text{ C})\), 29.66 \((3 \text{ C})\), 29.59, 29.45, 29.38, 29.34 \((2 \text{ C})\), 29.18, 28.88, 28.73, 28.57, 28.55, 28.51, 28.21, 27.92, 27.24, 27.14, 27.09, 26.66, 18.65, 18.63; IR (film) 3053, 2986, 2929, 1423, 1265, 909, 736, 706; MS (EI) \(m/\ell 678 \) \((M^+ + \text{Na} + \text{H})\); HRMS (ESI) \(m/\ell (M^+ + \text{Na})\) calcd for C\text{46}H\text{70}O\text{2}Na 677.5274, found 677.5307.

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\text{(3RAE,14R,21Z,27Z,43Z)-Hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diol (1.1RR):}\]

Following the same procedure for 1.1SS, the compound 1.90RR \((18.5 \text{ mg, 0.011 mmol})\) was reacted with TBAF \((0.09 \text{ mL, 1.0 M solution in THF, 0.09 mmol})\), the title compound 1.1RR \((5.1 \text{ mg, 69%})\) was obtained. \([\alpha]_D^{25} = -11.2\) \((c = 0.20, \text{CH}_3\text{OH})\), \(^1\text{H} \text{NMR (600 MHz, CDCl}_3\) \(\delta 6.00 \) \((dt, J = 10.8, 7.2 \text{ Hz, 1H})\), 5.91 \((dt, J = 15.0, 6.6 \text{ Hz, 1H})\), 5.62 \((ddd, J = 15.0, 6.0, 1.2 \text{ Hz, 1H})\), 5.44 \((d, J = 10.8, 1.5 \text{ Hz, 1H})\), 5.39–5.31 \((m, 4H)\), 5.09 \((dt, J = 7.2, 1.8 \text{ Hz, 1H})\), 4.84 \((t, J = 6.0 \text{ Hz, 1H})\), 3.07 \((d, J = 1.2 \text{ Hz, 1H})\), 2.57 \((d, J = 1.8 \text{ Hz, 1H})\), 2.32 \((q, J = 7.2 \text{ Hz, 2H})\), 2.23 \((qd, J = 7.2, 1.8 \text{ Hz, 4H})\), 2.11 \((d, J = 7.2 \text{ Hz, 1H})\), 2.08 \((q, J = 7.2 \text{ Hz, 2H})\), 2.06–1.99 \((m, 8H)\), 1.86
(d, J = 6.0 Hz, 1H), 1.56–1.49 (m, 4H), 1.46–1.25 (m, 36H); 13C NMR (200 MHz, CDCl3) δ 146.33, 134.35, 130.22, 130.08, 129.66, 129.31, 128.52, 107.88, 85.04, 84.99, 83.26, 81.13, 80.58, 78.09 (2 C), 74.03, 62.79, 52.55, 31.77, 30.28, 29.77, 29.69 (3 C), 29.66 (3 C), 29.59, 29.45, 29.38, 29.34 (2 C), 29.18, 28.88, 28.73, 28.56, 28.54, 28.50, 28.20, 27.92, 27.24, 27.14, 27.09, 26.66, 18.65, 18.63; IR (film) 3054, 2986, 1423, 1265, 909, 735, 705; MS (EI) m/z 678 (M⁺ + Na + H); HRMS (ESI) m/z (M⁺ + Na) calcd for C₄₆H₇₀O₂Na 677.5274, found 677.5295.

(2R,2'R)-(3S,4E,14S,21Z,27Z,43Z)-hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diyl) bis(3,3,3-trifluoro-2-methoxy-2-phenylpropanoate) (1.91SSR):

To a solution of alcohol 1.1SS (1.0 mg, 1.5×10⁻³ mmol) in CH₂Cl₂ (0.5 ml) was added (R)-MTPA acid (1.8 mg, 7.6×10⁻³ mmol), DCC (1.9 mg, 9.2×10⁻³ mmol), and DMAP (0.2 mg, 1.5×10⁻³ mmol) at room temperature. The resulting mixture was stirred at the same temperature overnight. The mixture was then filtered through a pad of Celite®, the filtrate was concentrated in vacuo. The crude product 1.191SSR was obtained: ¹H NMR (700 MHz, CDCl3) δ 7.55 (d, J = 7.0 Hz, 2H), 7.52 (d, J = 7.0 Hz, 2H), 7.43–7.39 (m, 6H), 6.21 (t, J = 2.1 Hz, 1H), 6.05 (ddt, J = 15.4, 7.0, 1.4 Hz, 1H), 6.02–5.98 (m, 2H), 5.60 (ddt, J = 15.4, 7.0, 1.4 Hz, 1H), 5.44 (ddt, J = 10.5, 2.8, 1.4 Hz, 1H), 5.39–5.29 (m, 4H), 3.59 (s, 3H), 3.55 (s, 3H), 3.06 (d, J = 2.1 Hz, 1H), 2.59 (d, J = 2.1 Hz, 1H), 2.32 (qd, J = 7.7, 1.4 Hz, 2H), 2.22 (td, J = 7.0, 2.1 Hz, 2H), 2.20 (td, J = 7.0, 2.1 Hz, 2H), 2.07 (q, J = 7.0 Hz, 2H), 2.03–1.99 (m, 8H), 1.52–1.46 (m, 4H), 1.42–1.38 (m, 4H), 1.36–1.25 (m, 32H).
(2S,2'S)-((3S,4E,14S,21Z,27Z,43Z)-hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diyl) bis(3,3,3-trifluoro-2-methoxy-2-phenylpropanoate) (1.91SSS):

Following the same procedure for 1.91SSR, the compound 1.1SS (1.0 mg, 0.027 mmol) was reacted with (S)-MTPA acid (1.8 mg, 7.6×10⁻³ mmol), DCC (1.9 mg, 9.2×10⁻³ mmol), and DMAP (0.2 mg, 1.5×10⁻³ mmol), the title compound 1.91SSS (10.4 mg, 59%) was obtained. ¹H NMR (700 MHz, CDCl₃) δ7.55 (d, J = 7.0 Hz, 2H), 7.52 (d, J = 7.0 Hz, 2H), 7.43–7.39 (m, 6H), 6.21 (t, J = 2.1 Hz, 1H), 6.03 (m, 1H), 6.00 (m, 1H), 5.99 (m, 1H), 5.49 (dd, J = 15.4, 7.0 Hz, 1H), 5.44 (d, J = 10.5 Hz, 1H), 5.37–5.29 (m, 4H), 3.59 (s, 3H), 3.58 (s, 3H), 3.06 (d, J = 1.4 Hz, 1H), 2.63 (d, J = 2.1 Hz, 1H), 2.32 (q, J = 7.0 Hz, 2H), 2.23 (td, J = 7.0, 2.1 Hz, 2H), 2.22 (td, J = 7.0, 2.1 Hz, 2H), 2.04 (m, 2H), 2.03–1.99 (m, 8H), 1.53–1.50 (m, 2H), 1.48–1.44 (m, 2H), 1.43–1.38 (m, 4H), 1.36–1.25 (m, 32H).

(2R,2'R)-((3S,4E,14R,21Z,27Z,43Z)-hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diyl) bis(3,3,3-trifluoro-2-methoxy-2-phenylpropanoate) (1.92SRR):

Following the same procedure for 1.91SSR, the compound 1.1SR (1.0 mg, 0.027 mmol) was reacted with (R)-MTPA acid (1.8 mg, 7.6×10⁻³ mmol), DCC (1.9 mg, 9.2×10⁻³ mmol), and DMAP (0.2 mg, 1.5×10⁻³ mmol), the title compound 1.92SRR (10.4 mg, 59%) was obtained. ¹H NMR (600 MHz, CDCl₃) δ7.55 (d, J = 7.0 Hz, 2H), 7.52 (d, J = 7.0 Hz, 2H), 7.43–7.39 (m, 6H), 6.21 (t, J = 2.1 Hz, 1H), 6.06 (dt, J = 15.4, 7.0, 1.4 Hz, 1H), 6.01 (m, 1H), 6.00 (m, 2H), 5.60
(ddt, $J = 15.4, 7.0, 1.4$ Hz, 1H), 5.44 (ddt, $J = 10.5, 2.8, 1.4$ Hz, 1H), 5.38–5.29 (m, 4H), 3.59 (s, 3H), 3.55 (s, 3H), 3.07 (d, $J = 1.4$ Hz, 1H), 2.59 (d, $J = 2.1$ Hz, 1H), 2.32 (q, $J = 7.0$ Hz, 2H), 2.23 (td, $J = 7.0, 2.1$ Hz, 2H), 2.19 (td, $J = 7.0, 2.1$ Hz, 2H), 2.08 (q, $J = 7.0$ Hz, 2H), 2.04–2.00 (m, 8H), 1.53–1.50 (m, 2H), 1.48–1.44 (m, 2H), 1.43–1.38 (m, 4H), 1.36–1.25 (m, 32H).

(2S,2'S)-((3S,4E,14R,21Z,27Z,43Z)-hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diyl) bis(3,3,3-trifluoro-2-methoxy-2-phenylpropanoate) (1.92SRS):

Following the same procedure for 1.91SSR, the compound 1.1SR (1.0 mg, 0.027 mmol) was reacted with (S)-MTPA acid (1.8 mg, $7.6 \times 10^{-3}$ mmol), DCC (1.9 mg, $9.2 \times 10^{-3}$ mmol), and DMAP (0.2 mg, $1.5 \times 10^{-3}$ mmol), the title compound 1.92SRS (10.4 mg, 59%) was obtained. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.55 (d, $J = 7.0$ Hz, 2H), 7.52 (d, $J = 7.0$ Hz, 2H), 7.43–7.39 (m, 6H), 6.21 (t, $J = 2.1$ Hz, 1H), 6.02 (m, 1H), 6.00 (m, 1H), 5.99 (m, 1H), 5.49 (ddt, $J = 15.4, 7.0, 1.4$ Hz, 1H), 5.44 (ddt, $J = 10.5, 2.8, 1.4$ Hz, 1H), 5.38–5.29 (m, 4H), 3.59 (s, 3H), 3.58 (s, 3H), 3.07 (d, $J = 0.7$ Hz, 1H), 2.63 (d, $J = 1.4$ Hz, 1H), 2.32 (qd, $J = 7.0, 1.4$ Hz, 2H), 2.21 (td, $J = 7.7, 2.1$ Hz, 2H), 2.20 (td, $J = 7.0, 2.1$ Hz, 2H), 2.04 (m, 2H), 2.03–1.99 (m, 8H), 1.52–1.46 (m, 4H), 1.42–1.38 (m, 4H), 1.36–1.25 (m, 32H).

1.5 REFERENCES


APPENDIX

NMR SPECTRA

1. $^1$H and $^{13}$C NMR spectra of M-1.68, 1.74R/S, M-1.78–M-1.80, M-1.2, 1.3, and M-1.90.

2. $^1$H and $^{13}$C NMR spectra of petrocortyne A four isomers 1.1 and COSY, HMQC, and HMBC spectra of 1.1SS

3. $^1$H, and TOCSY spectra of Mosher esters 1.91SSR/SSS and 1.92SRS/SRR
BS5P35 CDCl3 600 MHz 01/31/08
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190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

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BS5P40 peak 3 Rf(4, 3) After deprotection 13C NMR CDCl3 600 Bins 02/17/08
BS5P40 peak 1 Rf(0.3) After deprotection HMBC CDCl3 600 Buns 02/16/08
BSPP40 peak 2 Rf (0.4) After deprotection 13C NMR MeOD 600 BINS 01/24/09
BS5P151 SS+S 700 CDCl3