Bio-inspired acetal induced polyene cyclization : the development and applications

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**NANYANG
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**BIO-INSPIRED ACETAL INDUCED POLYENE CYCLIZATION: THE
DEVELOPMENT AND APPLICATIONS**

**LI BIN
SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES
2012**

**BIO-INSPIRED ACETAL INDUCED POLYENE CYCLIZATION: THE
DEVELOPMENT AND APPLICATIONS**

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Abstract

The development of a bio-inspired acetal induced intermolecular polyene cyclization is described. This process has been successfully applied to construct terpenoids skeletons and the core structure of Cortistatin A between chiral acetals and silyl enol ethers. On the other hand, a direct method to construct 2-functionalized terpenoids was developed by using isobutene as the other component. In addition, this strategy was further extended to construct 7-6-6 fused rings. Interestingly, TiCl_4 and SnCl_4 gave different diastereomers.

Another InBr_3 catalyzed Prins reaction initiated polyene cyclization also has been developed, which allowed for the rapid synthesis of 3-oxaterpenoids. The first total synthesis of ($\pm$)-moluccanic acid methyl ester has been achieved using the current method as the key step.

By exploiting the acetal induced intermolecular polyene cyclization, a highly efficient method to construct 8-oxabicyclo[3,2,1]octanes was discovered. Interestingly, an opposite diastereoselectivity product was obtained, which depended on whether aldehydes or corresponding acetals were used.

The investigation of the reaction of acetal with relatively stable (TIPS-, TBS-, Me-) enol ethers disclosed that the reaction undertook another pathway compared with classical Mukaiyama-aldol reaction. Switching the protecting group of acetal, mono and double Mukaiyama-aldol/[1,5]-H shift cascade products were obtained. The reaction mechanism was studied in great detail through deuterium labelling experiments. Based on this method, a novel synthetic route for the synthesis of commercial analgesics drug Sufentanil also has been developed.

Index of Abbreviations

δ	chemical shift
$^{\circ}\text{C}$	degree centigrade
Ac	acetyl
Ar	aryl
aq	aqueous
Bn	benzyl
Bz	benzoyl
calcd	calculated
cm^{-1}	inverse centimeter
d	doublet
DIBAl-H	diisobutylaluminium hydride
dd	doublet of doublets
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
FTIR	fourier transform infrared spectrometry
g	gram
h	hour(s)
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
<i>i</i> -Pr	isopropyl
M	molar concentration
m	multiplet
m/z	mass per charge ratio
M^{+}	parent ion peak (mass spectrum)
Me	methyl

MHz	mega hertz
min	minute(s)
mL	milliliter(s)
mmol	millimole
mol%	mole percent
<i>t</i> -Bu	<i>n</i> -butyl
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
<i>p</i> -TSA	<i>p</i> -toluenesulfonic acid
Py	pyridine
q	quartet
s	singlet
sat	saturated
t	triplet
TBDPS	<i>tert</i> -butyldiphenyl silyl
TBS	<i>tert</i> -butyldimethyl silyl
<i>t</i> Bu	<i>tert</i> -butyl
THF	tetrahydrofuran
TES	Triethylsilyl
TIP	Triisopropyl silyl
TMS	trimethylsilyl
TLC	thin layer chromatography
UV	ultraviolet
vol	volume

Chapter 1. Development of Biomimetic Polyene Cyclization

1.1 Introduction

In the history of organic chemistry, nature is the best supplier because it fascinated organic chemists with vast interesting organic substances of complex components, structures, and properties. On the other hand, nature is the best teacher as well. Despite tremendous advancement of technologies in the 21st century, organic chemists are still passionate about nature's high efficient, atom economic, chirality specific and environmental-friendly strategies to produce compounds.

One of such strategies is the biosynthesis of terpenoids. First of all, they are a ubiquitous subject of molecules which are related to life closely. Terpenoids have been found in all classes of livings, and engaged in many activities, such as cell-wall and glycoprotein biosynthesis, antibacterial, antineoplastic and other pharmaceutical functions.¹ They are also widely applied as flavors, hormones and drugs.² At the same time, enzymatic cyclizations of squalene (**1**) and 2,3-oxidosqualene (**5**) to build terpenoids has captivated chemist try to reproduce this powerful and bewitched method in laboratories. As shown in Scheme 1.1, squalene **1** undergoes polyene cyclization adopting all chair conformation (**2**) to give hopan-22-ol (**4**),³ while 2,3-oxidosqualenes **5** cyclizes stereoselectively through a chair-boat-chair (**6**) transition state and sequentially rearranged in a single enzyme-catalyzed process to

1 (a) Derek, D.; Nakanishi, K.; Methcohen, O.; Cane, D. E., eds. *Comprehensive Natural Products Chemistry*, Vol. 2: *Isoprenoids Including Carotenoids and Steroids*. Elsevier Science Ltd.: Oxford, **1999**. (b) Leeper, F. J.; Vederas, J. C., eds. *Top. Curr. Chem.* **2000**, 209, 53.

2 (a) Nicolaou, K. C.; Montagnon, T. *Molecules That Changed the World*, Wiley-VCH, **2008**. (b) Chen, K.; Baran, P. S. *Nature*, **2009**, 459, 824.

3 (a) Poralla, K. in *Cycloartenol and other triterpene cyclases*, ed. Barton, D. H. R.; Nakanishi, K. Elsevier, Oxford, UK, **1999**. (b) Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, 93, 2189. (c) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem. Int. Ed.* **2000**, 39, 2812.

furnish corresponding terpenoids.^{2,4} In one step, four or five fused rings, more than eight chiral carbon centers were formed with excellent selectivity (Scheme 1.1).

Scheme 1.1 Mechanism of enzymatic polyene cyclization

Stimulated by pharmaceutical properties and fantastic structures, terpenoids have stimulated the interest of organic chemists more than half a century. As the result, many of elegant biomimetic processes have been developed.⁵ These include cationic biomimetic polyene cyclization, radical initiate polyene cyclization and enzyme or antibody catalyzed polyene cyclization. The subject of our studies focuses on the chemical simulated reactions.

1.2 Biomimetic Polyene Cyclization Reactions

1.2.1 Brønsted Acid Promoted Polyene Cyclization

In order to promote the polyene substrate to cyclize, a proper electrophile or

4 Corey, E. J.; Virgil, S. C.; Sarshar, S. *J. Am. Chem. Soc.* **1991**, *113*, 8171.

5 Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730.

initiator is the key point. Considering nature's wisdom, proton is the trigger either for squalene or 2,3-oxidosqualene cyclization. Undoubtedly, proton was firstly chosen as the initiator in the biomimetic process. As early as 1950s, Stork⁶ and Eschenmoser's⁷ group has indicated the probability of biomimetic polyene cyclization under acid conditions (Scheme 1.2). They found the diene, even triene **9** cyclized and provided the desired product **10** in 69% yield.

Scheme 1.2

Eschenmoser and Stork's researches not only opened a window for us to understand biomimetic polyene cyclization, they also set up the general principles for polyene cyclization, which known as *Stork-Eschenmoser* principles:⁸

(1): The cyclization proceeds *via* chair-like folding conformations of the nascent rings, *Z* olefin to *cis*-decalin ring while *E* olefin to *trans*-decalin ring (Scheme 1.3);

(2): Antiparallel addition (*anti* addition) of initiator and terminator to the alkene acceptor (*center* alkene).

6 (a) Stork, G.; Conroy, H. *J. Am. Chem. Soc.* **1951**, 73, 4748. (b) Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, 40, 2191.

7 (a) Stadler, P. A.; Nechvatal, A.; Frey, A. J.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, 40, 1373. (b) Gamboni, G.; Schinz, H.; Eschenmoser, A. *Helv. Chim. Acta* **1954**, 37, 964.

8 (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, 77, 5068. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, 38, 1890.

Scheme 1.3

Stand on the shoulder of Eschenmoser and Stork, tremendous progresses have been achieved for biomimetic polyene cyclization in the following years. Another important acid catalyzed polyene cyclization is developed by Johnson's group. The allylic alcohol (**11**) could generate a carbon cation through dehydroxylation under acidic condition. In the polyene system, this cation intermediate was trapped by the alkene spontaneously and provided the cyclization product. This strategy also allowed the construction of tetra-cyclic products **12** in 60% yield (Scheme 1.4).⁹ The case also indicated that fluorine atom could be an effective cation stabilizing auxiliary in polyene cyclization.

Scheme 1.4

Although proton is the simplest and most common source for polyene cyclization, how to manipulate it under the asymmetric way disturbed chemists for many years. After about 40 years since the first example of acid induced biomimetic polyene cyclization, Yamamoto group reported an enantioselective cyclization using their

⁹ (a) Johnson, W. S.; Plummer, M. S.; Reddy, S. P.; Bartlett, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 515. (b) Johnson, W. S.; Buchanan, R. A.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 504. (c) Johnson, W. S.; Fletcher, V. R.; Chenera, B.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 497. (d) Johnson, W. S.; Chenera, B.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 493. (e) Bartlett, W. R.; Johnson, W. S.; Plummer, M. S.; Small, Jr. V. R. *J. Org. Chem.* **1990**, *55*, 2215. (f) Guay, D.; Johnson, W. S.; Schubert, U. *J. Org. Chem.* **1989**, *54*, 4731. (g) Johnson, W. S.; Lindell, S. D.; Steele, J. *J. Am. Chem. Soc.* **1987**, *109*, 5852. (h) Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517. (i) Johnson, W. S.; Elliott, J. D.; Hanson, G. *J. Am. Chem. Soc.* **1984**, *106*, 1138. (j) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (k) Johnson, W. S.; Dumas, J. D.; Berner, D. *J. Am. Chem. Soc.* **1982**, *104*, 3510. (l) Johnson, W. S.; Berner, D.; Dumas, D. J.; Nederlof, P. J. R.; Welch, J. *J. Am. Chem. Soc.* **1982**, *104*, 3508.

designed artificial cyclase LAB (Lewis acid and chiral Brønsted acid coordinated acid) (Scheme 1.5).¹⁰ Although two equivalents of LAB were required, the reaction achieved the asymmetric version for the first time.

Scheme 1.5

Very recently, Corey group found that the reaction yield and enantioselectivity was dramatically improved by using *o,o'*-dichloro-BINOL as the ligand and SbCl₅ as the Lewis acid (Scheme 1.6).¹¹

Scheme 1.6

10 (a) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505-1506. (b) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647. (c) Uyanik, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 5649. (d) Yamamoto, H.; Ishihara, K.; Ishibashi, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122. (e) Uyanik, M.; Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1601. (f) Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551. (g) Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131. (h) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906.

11 Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2012**, *134*, 11992.

1.2.2 Epoxide (Aziridine) Induced Polyene Cyclization Mediated by Lewis Acid

The initial results reported by Eschenmoser enlightened the passion of chemists, and many elegant methods have been developed ever since. Among them, acid catalyzed cyclization of terminal epoxide of polyenes which reported by E. J. Corey hold a place of great mark in the history.¹² The methodology was also deeply studied by E. E. van Tamelen's group.¹³ The asymmetric version of this process also made a great progress with the development of asymmetric epoxidation. Considering its utility in natural product synthesis, epoxide was one of the best triggers for polyene cyclization (Scheme 1.7).

Scheme 1.7

Aziridines, which have the same intrigue three membered rings, yet draw few attentions from organic chemists. Only until 2009, Loh's group demonstrated that aziridine was a promising initiator for the polyene cyclization (Scheme 1.8).¹⁴ Interestingly, catalytic amount of Lewis acid is enough to furnish the reaction in good

12 (a) Behenna, D. C.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 6720. (b) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2009**, *131*, 13928. (c) Surenda, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865. (d) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999. (e) Corey, E. J.; Wood, Jr., H. B. *J. Am. Chem. Soc.* **1996**, *118*, 11982. (f) Zhang, J.-H.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215. (g) Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526. (h) Corey, E. J.; Staas, D. D. *Angew. Chem., Int. Ed.* **1998**, *37*, 1126. (i) Corey, E. J.; Liu, K. *J. Am. Chem. Soc.* **1998**, *119*, 9929. (j) Corey, E. J.; Luo, G.-L.; Lin, S.-Z. *J. Am. Chem. Soc.* **1997**, *119*, 9927. (k) Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873. (l) Corey, E. J.; Reid, J. G.; Myers, A. G.; Hahl, R. W. *J. Am. Chem. Soc.* **1998**, *109*, 918. (m) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742. (n) Corey, E. J.; Yi, K. Y.; Matsuda, S. P. *Tetrahedron Lett.* **1992**, *17*, 2319. (o) Corey, E. J.; Burk, R. M. *Tetrahedron Lett.* **1987**, *28*, 6413.

13 (a) van Tamelen, E. E.; Hwu, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2490. (b) van Tamelen, E. E.; Zawacky, S. R.; Russell, R. K.; Carlson, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 142. (c) van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 2061. (d) van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 1785. (e) van Tamelen, E. E.; Nadeau, R. G. *Bioorg. Chem.* **1982**, *11*, 197. (f) van Tamelen, E. E.; Carlson, J. G.; Russell, R. K.; Zawacky, S. R. *J. Am. Chem. Soc.* **1981**, *103*, 4615. (g) van Tamelen, E. E.; Loughhead, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 869. (h) van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152.

14 Zhao, Y. J.; Tan, L. S.; Li, B.; Li, S. M.; Loh, T. P. *Chem. Commun.* **2009**, 3738.

yield at room temperature, and the chirality retained in the cyclization. It provided an efficient method to construct terpenoid alkaloids in one step.

Scheme 1.8

1.2.3 Halogenium Induced Polyene Cyclization

Inspired by epoxide or aziridine induced biomimetic polyene cyclization, Halogeniums might be another suitable candidate for its ability to form halonium three member rings. Initially, the reaction was limited to a few of electron rich terpenes in racemic version.¹⁵ In 2007, Ishihara group made a breakthrough.¹⁶ They found that the reactivity of N-iodosuccinimide (NIS) or N-bromosuccinimide (NBS) could be highly improved by adding nucleophilic promoters like phosphine (Scheme 1.9). More importantly, very high enantioselectivity product was achieved when chiral phosphine (**27**) was chosen as the promoter.

15 (a) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 3416. (b) Barluenga, J.; Alvarez-Pérez, M.; Rodríguez, F.; Fañanás, F. J.; Cuesta, J. A.; García-Granda, S. *J. Org. Chem.* **2003**, *68*, 6583. (c) van Tamelen, E. E.; Hessler, J. *Chem. Commun.* **1966**, 411. (d) Kato, T.; Ichinose, I.; Kumazawa, S.; Kitahara, Y. *Bioorg. Chem.* **1975**, *4*, 188. (e) Kato, T.; Ichinose, I.; Kamoshida, A.; Kitahara, Y. *J. Chem. Soc., Chem. Commun.* **1976**, 518. (f) Wolinsky, L. E.; Faulkner, D. J. *J. Org. Chem.* **1976**, *41*, 597. (g) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1978**, *43*, 3693. (h) Kato, T.; Ichinose, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1051. (i) Shieh, H. M.; Prestwich, G. D. *Tetrahedron Lett.* **1982**, *23*, 4643. (j) Kato, T.; Mochizuki, M.; Hirano, T.; Fujiwara, S.; Uyehara, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1077. (k) Yamaguchi, Y.; Uyehara, T.; Kato, T. *Tetrahedron Lett.* **1985**, *26*, 343. (l) Fujiwara, S.; Takeda, K.; Uyehara, T.; Kato, T. *Chem. Lett.* **1986**, 1763.

16 Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900.

Scheme 1.9

In 2009, Snyder group produced a stable bromonium salt, which also induced polyene cyclization very productively.¹⁷ Furthermore, they even could apply chloronium salt to promote this transformation, which was difficult to achieved previously (Scheme 1.10).¹⁸

Scheme 1.10

1.2.4 Oxocarbenium (Iminium) Induced Polyene Cyclization

Beside proton, epoxide and halogenium, another important initiator, oxocarbenium, was announced by Johnson group. Oxocarbenium and iminium, which can be easily generated from acetal, have been widely used in organic synthesis. The potential in polyene cyclization was keenly awared by Johnson.

¹⁷ Snyder, S. A.; Treitler, D. S. *Angew. Chem., Int. Ed.* **2009**, 48, 7899.

¹⁸ Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, 132, 14303.

In 1966, Johnson's group first applied oxocarbenium in polyene cyclization.¹⁹ They found that acetal tethering polyene substrate cyclized smoothly upon treating with tin *tetra*-chloride. Chiral alcohol protected acetal led to the desired product in moderated enantioselectivity (Scheme 1.11).

Scheme 1.11

In view of the complexity of installing an acetal group to the polyene cyclization precursor, an intermolecular acetal initiated polyene cyclization was proposed from Loh's group (Scheme 1.12).²⁰ The reaction simplifies mostly for polyene substrates, but it also introduces a bothersome side chain to the product.

- 19 (a) Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324. (b) Schmid, R.; Huesmann, P. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1980**, *102*, 5122. (c) Gravestock, M. B.; Morton, D. R.; Boots, S. G.; Johnson, W. S. *J. Am. Chem. Soc.* **1980**, *102*, 800. (d) Johnson, W. S.; McCarry, B. E.; Markezich, R. L.; Boots, S. G. *J. Am. Chem. Soc.* **1980**, *102*, 352. (e) Garst, M. E.; Cheung, Y.-F.; Johnson, W. S. *J. Am. Chem. Soc.* **1979**, *101*, 4404. (f) Gravestock, M. B.; Johnson, W. S.; Myers, R. F.; Bryson, T. A.; Miles, D. H.; Racliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4268. (g) Johnson, W. S.; Hughes, L. R.; Carlson, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 1281. (h) Johnson, W. S.; Hughes, L. R.; Kloek, J. A.; Niemi, T.; Shenvi, A. *J. Am. Chem. Soc.* **1979**, *101*, 1279. (i) Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *100*, 8341. (j) Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *99*, 6188. (k) Bunes, L. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1976**, *99*, 5597. (l) Johnson, W. S.; Lunn, W. H.; Fitz, K. *J. Am. Chem. Soc.* **1973**, *86*, 1972. (m) Johnson, W. S.; Frel, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1512. (n) Johnson, W. S.; Ward, C. E.; Boots, S. G.; Gravestock, M. B.; Markezich, R. L.; McCarry, B. E.; Okorie, D. A.; Parry, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 88.
- 20 (a) Zhao, Y. J.; Chng, S. S.; Loh, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 492. (b) Zhao, Y. J.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 10024.

Scheme 1.12

Similar as oxocarbenium, iminium also has been applied in polyene cyclization successfully. The first example of iminium promoted polyene cyclization was reported by Speckamp group in 1977 (Scheme 1.13).²¹ Under acidic condition, the reaction furnished products in almost quantitative. The asymmetric version of this reaction was achieved in Jacobsen group by using anion binding thiourea catalysis **40** (Scheme 1.14).²²

Scheme 1.13

Scheme 1.14

1.2.5 Metal Induced Polyene Cyclization

Nonmetal Cation- π cyclizations constitutes an important strategy for the terpenoid synthesis. On the other hand, colorful organometallic chemistry also contributed a lot to the polyene cyclization, especially for Hg(II), Pd(II), Pt(II), Au(I), In(III) and so on.

²¹ Dijkink, J.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, 18, 935.

²² Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, 132, 5030.

Replacement of the proton by Hg^{2+} constitutes a classical solution to polyene cyclization since the front stage of this area.²³ Recently, this reaction was further extended to asymmetric version.²⁴ In this reaction, the resulting $\text{C}(\text{sp}^3)\text{-Hg}$ bond is kinetically stable and could be further functionalized (Scheme 1.15). However, it also means that stoichiometric mercury salts is needed for this transformation. Considering the toxicity of mercury compounds, some alternative approaches should be proposed.

Scheme 1.15

Palladium(II) catalyzed Cope rearrangement has been well studied by Overman et al.²⁵ The carbon cation intermediate **47** goes through a fragmentation to form a new diene-palladium(II) complex **48**. On the other hand, the cationic intermediate **47** might be trapped by a nucleophile as well. Gagné group realized it and applied such design in polyene cyclization (Scheme 1.16).²⁶

23 (a) Kurbanov, M.; Semenovskiy, A. V.; Smit, W. A.; Shmelev, L. V.; Kuchero, V. F. *Tetrahedron Lett.* **1972**, 13, 2175. (b) Skeean, R. W.; Trammell, G. L.; White, J. D. *Tetrahedron Lett.* **1976**, 17, 525. (c) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, 102, 1742. (d) Corey, E. J.; Reid, J. G.; Myers, A. G.; Hahl, R. W. *J. Am. Chem. Soc.* **1987**, 109, 918. (e) Hoye, T. R.; Caruso, A. J.; Kurth, M. J. *J. Org. Chem.* **1981**, 46, 3550. (f) Gopalan, A. S.; Prieto, R.; Mueller, B.; Peters, D. *Tetrahedron Lett.* **1992**, 33, 1679. (g) Takao, H.; Wakabayashi, A.; Takahashi, K.; Imagawa, H.; Sugihara, T.; Nishizawa, M. *Tetrahedron Lett.* **2004**, 45, 1079. (h) Nishizawa, M.; Morikuni, E.; Asoh, K.; Kan, Y.; Uenoyama, K.; Imagawa, H. *Synlett* **1995**, 169. (i) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, 7, 451.

24 Snyder, S. A.; Treitler, D. S.; Schall, A. *Tetrahedron* **2010**, 66, 4796.

25 (a) Overman, L. E.; Knoll, F. M. *J. Am. Chem. Soc.* **1980**, 102, 865. (b) Overman, L. E. *Angew. Chem. Int. Ed.* **1984**, 23, 579. (c) Overman, L. E.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1982**, 104, 7225.

26 (a) Koh, J. H.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2004**, 43, 3459. (b) Sokol, J. G.; Korapala, C. S.; White, P. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2011**, 50, 5658.

Scheme 1.16

In 2008, Gagné reported an enantioselective oxidative cationic polyolefin cyclization (Scheme 1.17). Although the reaction scope was limited, it enriched the chemistry of asymmetric polyene cyclization.²⁷

Scheme 1.17

Gold catalyst has been well known for its ability to catalyze ring formation reaction, as well as in polyene cyclization.²⁸ In 2010, Toste group disclosed a gold(I) promoted highly enantioselective polyene cyclization (Scheme 1.18).²⁹ In this context, a series of nucleophiles, such as acid, amide, phenol etc. can be used to terminate the reaction

27 Mullen, C. A.; Campbell, A. N.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2008**, *47*, 6011.

28 (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (b) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167.

29 Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276.

Scheme 1.18

Very recently, Corey group developed another metal catalyzed cationic cascade cyclization.³⁰ Given that InBr_3 and InI_3 are more soluble in solutions of 1-heptyne and CH_2Cl_2 mixture than in CH_2Cl_2 alone, they hypothesized that the C-C triple bond should play a role. Indeed, the soluble indium(III) salt might serve to activate the acetylenic subunit of a propargylic alcohol or ether by the coordination with the C-C triple bond and the oxygen. With this idea in mind, Corey et. al. treated propargylic alcohol-polyene with indium salt and the cascade polyene cyclization proceeded well as expected. They also found that the stereochemistry of the product was predominantly controlled by the chirality of alcohol (Scheme 1.19).

Scheme 1.19

1.2.6 Biomimetic Polyene Cyclization Reaction Initiated by Radicals

Besides cationic polyene cyclization, another branch of polyene cyclization consisted of radicals. In 1968, Breslow demonstrated that oxygen radical was also a promising initiator for biomimetic polyene cyclization (Scheme 1.20). Although the preliminary studies gave products in relatively low yields (20-30%), it reached a basis

30 (a) Surendra, K.; Qiu, W. W.; Corey, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 9724. (b) Qiu, W. W.; Surendra, K.; Yin, L.; Corey, E. J. *Org. Lett.* **2011**, *13*, 5893.

for this remarkable transformation.³¹

Scheme 1.20

The success of oxygen radical initiated polyene cyclization stimulates the further efforts. One of the best studied radicals for polyene cyclization is carbon radical, which can be generated from β -Keto ester under oxidation condition (Mn(OAc)_3 , Cu(OAc)_2 etc). In 1985, Zoretic group reported a carbon radical initiated cascade annulation using β -keto ester as the tail. As shown in Scheme 1.21, the desired product was obtained in 31% yield.³² Other radical, such as acyl radical generated from selenyl ester **65** has been applied as well (Scheme 1.22).³³

Scheme 1.21

31 Breslow, R.; Barrett, E.; Mohaosi, E. *Tetrahedron Lett.* **1962**, 3, 1207.

32 (a) Zoretic, P. A.; Weng, X.-Y.; Caspar, M. L. *Tetrahedron Lett.* **1991**, 37, 4819. (b) Zoretic, P. A.; Weng, X.-Y.; Biggers, C. K.; Biggers, M. S.; Caspar, M. L. *Tetrahedron Lett.* **1992**, 33, 2637.

33 (a) Pattenden, G.; Gonzalez, M. A.; McCulloch, S.; Walter, A.; Woodhead, S. J. *Proc. Natl. Acad. Sci.* **2004**, 101, 12024. (b) Boehm, H. M.; Handa, S.; Pattenden, G.; Roberts, L.; Blake, J. A.; Li, W. S. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3522. (c) Pattenden, G.; Roberts, L.; Blake, J. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 863. (d) Chen, L.-G.; Gill, B.; Pattenden, G. *Tetrahedron Lett.* **1994**, 35, 2593.

Scheme 1.22

In order to grant the continuous requirement of chirality interest of this area, asymmetrical radical polyene cyclization has also well developed. In 1997, Demuth reported the first substrate controlled hydroxyl radical initiated biomimetic polyene cyclization. Even the chirality was far away from the reaction centre, tricyclic product **68** was obtained in >99% ee despite the relative low yield (Scheme 1.23).³⁴

Scheme 1.23

In 2000, Yang's group reported a Lewis acid promoted atom-transfer cascade radical cyclization reaction. Moderate enantioselective product **70** was formed when chiral ligand **71** (PyBox) was added (Scheme 1.24).³⁵

Scheme 1.24

Another asymmetric radical polyene cyclization came from MacMillan group in 2010.³⁶ They showed a powerful organo-catalytic strategy to construct terpenoidal architecture by the SOMO activation (Scheme 1.25). There were many advantages:

³⁴ Heinemann, C.; Demuth, M. *J. Am. Chem. Soc.* **1997**, *119*, 1129.

³⁵ (a) Yang, D.; Gu, S.; Yan, Y.-L.; Zhao, H.-W.; Zhu, N. Y. *Angew. Chem. Int. Ed.* **2002**, *41*, 3014.

³⁶ Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027.

First, the desired product was produced in high yield with excellent enantioselectivity. Second, the substrates scope was extremely wide. Third, catalytic organo-catalyst was used. Fourth, the reaction proceeded in mild condition.

Scheme 1.25

1.3 Summary of Biomimetic Polyene Cyclization

Biomimetic polyene cyclization has made great progress in the past 70 years, but chemists are still far from reproducing enzymatic cyclization in laboratories. There are several challenges waiting to be solved.

The current method focused on building fused six member rings, and the functional group mostly limited at 3- and 4-position. However, the structures of terpenoids that created by nature are not restricted to that. For example, Salviol (**75**) and Stemodin (**77**) have a hydroxyl group at 2-position. Cyathane (**78**) diterpenoids have 7-6-5 fused rings, while icetexane (**79**) have 6-7-6 core structure.³⁷ Hence, invent new strategies to construct multifarious skeletons is one of the challenges.

37 Simmons, E. M.; Sarpong, R. *Nat. Prod. Rep.* **2009**, 26, 1195.

Figure 1.1

Another challenge is to manipulate the reaction conformation. Although tremendous progress has been achieved in mimicking enzyme catalyzed 2,3-oxasqualene cyclization. So far, there is no method to control the reaction go through enzymatic chair-boat-chair conformation (Scheme 1.1). In 1996, E. J. Corey tried to solve the problem by introducing a trifluoroethoxymethylene group to the B ring (Scheme 1.26). It resulted *A/B-trans* (9,10-*syn*) product, while the introducing group also induced the *B/C-syn* (8,9-*syn*) instead of *B/C-trans* (8,9-*trans*) at the same time.³⁸

Scheme 1.26

The third challenge is to manipulate the back bone rearrangement like enzymatic polyene cyclization (Scheme 1.1). It has yet to be resolved by the following organic chemists and biochemists.

38 Corey, E. J.; Jr. Wood, H. B. *J. Am. Chem. Soc.* **1996**, *118*, 11982.

The last challenge is to make the laboratory method more efficient, more reliable, more environmental-friendly, and benefit to the pharmaceutical industry and daily life.

1.4 Summary of This Thesis

In this thesis, we designed two intermolecular strategies to construct poly-functionalized steroids:

1. Intermolecular Mukaiyama-aldol-Prins cascade reaction. When silyl enol ether was one of the reaction partners, an asymmetric method to construct steroids skeletons has been developed and applied to construct the core structure of Cortistatin A. If isobutene was involved in the reaction, a direct method to build 2-functionalized tepernoids backbones was developed. In addition, a strategy to synthesize 7-6-6 fused rings was created for the first time.
2. Another Prins reaction initiated polyene cyclization also has been developed and applied in the total synthesis of ($\pm$)-moluccanic acid methyl ester.

Among the study of intermolecular Mukaiyama-aldol-Prins cascade reaction, some new cascade reactions were found.

3. A highly efficient method to construct 8-Oxabicyclo[3,2,1]octanes was discovered. Interestingly, an opposite diastereoselectivity product was obtained, which depended on whether aldehydes or corresponding acetals were used.
4. Two types of Mukaiyama-aldol / [1,5] H-shift cascade reaction were found in the reaction of acetals with enol ethers.

Chapter 2. Acetal Initiated Intermolecular Polyene Cyclization

2.1 Introduction

In the past 70 years, tremendous efforts have been put in the biomimetic polyene cyclization, but progress continues unabated.³⁹ Main challenges are to install the functional group onto the carbon framework and to meet the diversity of scaffolds. Considering current methods, polyene cyclization substrates generally carry all atoms comprising the cyclic core of the cyclization product, whereas the initiator eventually bonds to the cyclic core and provided 3-or 4-functionalized terpenoids. However, natural products present us with functional groups that can be at any position. Such as Salviol has a hydroxy group at 2-position;⁴⁰ Lucensimycin A has functional groups at 2- and 4- position (Figure 2.1).⁴¹

Figure 2.1

On the other hand, nature also presents us many kinds of fused terpenoids not

39 (a) Corey, E. J.; Virgil, S. C.; Sarshar, S. *J. Am. Chem. Soc.* **1991**, *113*, 8171. (b) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730.

40 Hayashi, T.; Handa, T.; Ohashi, M.; Kakisawa, H. *Chem. Comm.* **1971**, 541.

41 Singh, S. B.; Zink, D. L.; Huber, J.; Genilloud, O.; Salazar, O.; Diez, M. T.; Basilio, A.; Vicente, F.; Byrne, K. *M. Org. Lett.* **2006**, *8*, 5449.

only with six or five member rings. For example, icetexanes have 6-7-6 core structure,⁴² while Cyathane diterpenoids have 7-6-5 fused rings.⁴³ To the best of our knowledge, there was no efficient method to construct 2-functionalized or seven membered fused terpenoids skeletons directly.

In this chapter, we will try to probe the problem.

2.2 The Origin of This Project

Inspired by Johnson's strategy, recently our group developed an acetal initiated intermolecular polyene cyclization (Scheme 2.1).⁴⁴ Although it has been applied in the total synthesis of Hydroxyabietatetraenoic acid successfully, removing the bothersome side chain took up more than one third of steps in this work.⁴⁵

Scheme 2.1

Drawing lessons from the Mukaiyama-aldol-Prins cascade reaction that was developed in our group,⁴⁶ we were interested in constructing terpenoids structures by the same tactics. As showing in scheme 2.2, we estimated that six membered ring could be formed by using the tri-substituted alkenyl acetal instead of previous substrate. In addition, incorporation of phenyl ring in the substrate might make the reaction to go through a Friedel-Crafts cascade, leading to the desired steroids core structure (Scheme 2.2). Compared with traditional strategies, the current approach

42 Simmons, E. M.; Sarpong, R. *Nat. Prod. Rep.*, **2009**, 26, 1195.

43 Krzyczkowski, W.; Malinowska, E.; Herold, F. *Biotechnologia* **2008**, 146.

44 (a) Zhao, Y. J.; Chng, S. S.; Loh, T. P. *J. Am. Chem. Soc.* **2007**, 129, 492. (b) Zhao, Y. J.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, 130, 10024.

45 Zhao, Y. J.; Loh, T. P. *Org. Lett.* **2008**, 10, 2143.

46 (a) Li, H.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, 130, 7194. (b) Li, H.; Loh, T. P. *Org. Lett.* **2010**, 12, 2679.

shall provide diverse 2-position functionalized fused rings. Furthermore, product diversity should be much easier to be achieved thanks to the combination of versatility not only in the polyolefin substrates but also in the nucleophiles.

Scheme 2.2 Our proposal

2.3 Results and Discussion

2.3.1 Acetal Initiated Polyene Cyclization with Silyl Enol Ether

With this idea in mind, the first step was to prepare the starting material. As shown in Scheme 2.3, the alkenyl-acetal was easily prepared from commercially available aldehyde (**1**). The Wittig reaction gave (*E*)- α,β -unsaturated ester (**2**) in high yield. Homo-elongation to one more carbon is achieved by introduction a cyanide group through S_N2 reaction (**3**).⁴⁷ The cyanide group can be smoothly converted to the aldehyde **4** through a sequential DIBAL-H reduction. However, since the aldehyde was not so stable towards purification by chromatography, it must be protected by alcohol directly in one pot to provide the raw material for the next step.

⁴⁷ Uyanik, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, 8, 5649.

Scheme 2.3 Strategy for substrate synthesis

Having established a facile method for substrate synthesis, the reaction of 1,3-propandiol protected acetal (**5a**) with silyl enol ether (**9a**) was chosen to be the model reaction (Scheme 2.4). To our delight, the reaction proceeded very well and gave the desired product **10a/10a'** in 89% yield with moderate diastereoselectivity (67:33) by using SnCl_4 as the promoter at -78°C in CH_2Cl_2 . TiCl_4 gave similar result (83% yield with 65:35 dr), but other Lewis acids (including $\text{BF}_3\cdot\text{OEt}_2$, InBr_3 and AlClMe_2) were unreactive under the given conditions. Solvent effect was studied as well. Interestingly, **10a'** was obtained as the major product when the solvent was switched from dichloromethane to toluene. According to H. Yamamoto's model,⁴⁸ the addition of silyl enol ether to cyclic acetals normally undergoes $\text{S}_{\text{N}}1$ mechanism and gives **10a** as the major products in CH_2Cl_2 . On the other hand, the 30:70 ratio of diastereomer resulting from this reaction in nonpolar solvent toluene suggests that the reaction follows $\text{S}_{\text{N}}2$ or via oxocarbenium ion pair mechanism for six membered cyclic acetals. The reaction did not work in other solvents (such as CH_3CN , THF and Et_2O). The diastereomers can be separated by silica gel chromatography and structures of these two isomers have been confirmed by X-ray analyses of their alcohol derivatives (Scheme 2.5).

48 Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, 55, 6107.

Scheme 2.4 Preliminary results

Scheme 2.5 Determination of structures

With the knowledge of Lewis acid and solvent effects, a series of different alcohol protected acetals were evaluated for their reactivity (Table 2.1). When 1,2-glycol protected acetal (**6a**) was subjected to the reaction, the desired product also was obtained in 90% yield with moderate diastereoselectivity at the 2-position (dr: 64/36, entry 1). Similar result was obtained in toluene as the solvent (entry 2). In the quest to improve the diastereoselectivity and to explore the asymmetric version, chiral diol protected substrates were tested. When six-membered cyclic chiral acetal (**7a**) was used and SnCl₄ as the promoter, the reaction gave the desired product in good yield with moderate distereoselectivity (entry 3). Surprisingly, five-membered acetal cannot proceed at all under the reaction conditions (entry 5). In contrast, both good yield (72%) and excellent distereoselectivity (91:9) was obtained (entry 8) when TiCl₄ was applied as the Lewis acid. Solvent had no effect on diastereoselectivity in this case and

this condition was selected for further study.

Table 2.1 Preliminary studies^a

Entry	Substrate	LA	Solvent		Yield (%) ^b	Dr ^c
1		SnCl ₄	CH ₂ Cl ₂	11a	90	64:36
2		SnCl ₄	Toluene	11a	83	68:32
3		SnCl ₄	CH ₂ Cl ₂	12a	76	82:18
4		TiCl ₄	CH ₂ Cl ₂	12a	messy	messy
5		SnCl ₄	CH ₂ Cl ₂	13a	- ^d	-
6		TiCl ₄	CH ₂ Cl ₂	13a	72	91:9

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b Isolated yield. ^c Dr value (7:7') determined by ¹H NMR. ^d No reaction.

With the refined reaction conditions in hand, a series of silyl enol ethers were evaluated (Table 2.2). Silyl enol ethers, whether generated from aldehyde or ketones, the reactions proceeded well. For the methyl and ethyl substituted silyl enol ethers (entry 1-2), both of them gave high yields with excellent diastereoselectivity. While the silyl enol ether tethering a bromo-substituent (entry 3), the desired product was obtained in good yield, but the diastereoselectivity dropped dramatically as a result of the newly created surplus chiral center. Acetone derived enol ether also performed well (entry 4). Five- (entry 5) as well as six-membered (entry 6) cyclic silyl enol ethers were effective partners, although the yield were a little bit lower, it provided an valuable way to construct the steroids skeletons bearing a quaternary chiral alcohol.

Table 2.2 Substrate scope of enol ethers^a

Entry	Substrate	Product	Yield (%) ^b	Dr ^c
1	 9a	 13a	72	91:9
2	 9b	 13b	70	89:11
3	 9c	 13c	54	60:40
4	 9d	 13d	52	79:21
5	 9e	 13e	45	86:14
6	 9f	 13f	58	75:25

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b Isolated yield. ^c Dr value (7:7') determined by $^1\text{H NMR}$.

To further demonstrate the substrate scope of this cascade reaction, a variety of alkenyl acetals were synthesized and subjected to the optimized reaction conditions (Table 2.3). To our delight, most of them gave desired products in high yields and good diastereoselectivities. Electron rich substituents at various positions, for example, *ortho*-(entries 1 and 2), *para*-(entry 3) and 2,3,4-tri-substituted (entry 4), have little effect in the yield. When the phenyl group was attached with an electron-withdrawing group (Cl, entry 5), the reaction proceeded smoothly but with slightly compromised yield. The substrate (entry 6) tethering an indole group was tolerated as well. Interestingly, the generation of **16i** proves that disubstituted *E*-alkene **8i** is a good candidate for this reaction as well (entry 7). Furthermore, the reaction not only can construct 6-6-6 member rings, it also can build 6-5-6 fused rings. Deducting a carbon from the normal aromatic terminated substrate, provided an efficient way to generate 6-5-6 ring system, which is an exceptional example in polyene cyclization (entry 8). Incorporation of an internal alkyne as the terminate group provided 6-5 ring system **16k** in 74% yield with good selectivity (entry 9).

Table 2.3 Substrate scope of alkenyl acetal^a

Entry	Substrate	Product	Yield (%) ^b	Dr ^c	
1	8b	16b	62	89:11	

2		8c		16c	67	91:9
3		8d		16d	73	91:9
4		8e		16e	76	89:11
5		8g		16g	50	88:12
6		8h		16h	57	88:12
7		8i		16i	64	85:15
8		8j		16j	59	84:16
9		8k		16k	74	91:9

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b Isolated yield. ^c Dr value (7:7') determined by ¹H NMR.

Encouraged by the results shown in Table 2.3, we extended the strategy to more complicated system. As the result shown in scheme 2.6, this method can be applied to construct 6-6-6-6 fused skeleton as well. However, dimethyl substituted silyl enol ether **9a** was not suitable for this reaction because some unknown rearrangements occurred. While **9f** was applied to this reaction, desired pentacyclic product **17** was obtained in 58% yield with good distereoselectivity (82:18).

Scheme 2.6 Tricyclization between a polyolefin and an enol ether

Encouraged by the success of this intermolecular Mukaiyama-aldol-polyene cyclization reaction, we were confident to apply this method to construct the skeleton of natural products. Satisfyingly, **8k** reacted with **9g** smoothly leading to the desired product **20** in 53% yield with excellent distereoselectivity (Scheme 2.7 I), which has the same skeleton with Cortistatin A,⁴⁹ a potential candidate for medicinal purpose. Another application is to synthesize the core structure of steroids. Subjected the silyl enol ether **9f** and acetal **8m** to the standard conditions, the core structure **22** was obtained in 61% yield with good diastereoselectivity (Scheme 2.7 II).

49 Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setia-wan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148.

Scheme 2.7 Access to useful skeletons

The following issue we tackled was the removal of the chiral auxiliary from the product. As depicted in Scheme 2.7, the chiral auxiliary can be removed by two independent methods. First step is to oxidize the alcohol to ketone for both of the methods. If the ketone (**23**) was treated with Li/Et₂NH, the side chain can be removed by birch reduction smoothly. However, the phenyl ring was reduced at the same time (Scheme 2.8, method a). On the other hand, under oxidative condition, the ketone could convert to ester by Baeyer-Villiger rearrangement, followed with TsOH provided the alcohol **26** in 54% yield (Scheme 2.8, method b). The absolute stereochemistry of product was confirmed via X-ray analyses of the diol **27**.

Scheme 2.8 Methods to remove the chiral auxiliary

2.3.2 Acetal Initiated Polyene Cyclization with Alkene

Having established the intermolecular Mukaiyama-aldol-Prins reaction to construct variety steroids skeletons, we also interested in the reaction that employed simple alkene (like isobutene) as the component (Scheme 2.9), which would provide an efficient method to construct 2-functionalized terpenoids.

Scheme 2.9 Proposed reaction of acetal with alkene

Our proposed strategy was first evaluated by **5a** and isobutene. As the results shown in Table 2.4, treated the reaction with TiCl_4 , the desired product **29a'** was obtained in 38% yield with moderate diastereoselectivity (75:25). At the same time,

another 3-oxaterpenoid **30** was generated. To our delight, when **6a** was applied, the reaction yielded 85% **29a** with moderate distereoselectivity (77:23), and 3-oxaterpenoid was not observed. Other Lewis acid, such as SnCl_4 caused relatively poor yield (17%) and chloro trapped product **31** was the major product. A series of solvent also was screened. Toluene gave similar yield with much lower distereoselectivity (58:42). 2-Nitropropane gave very poor yield (21%). So CH_2Cl_2 and TiCl_4 were selected for further study.

Table 2.4 Preliminary studies of acetal with isobutene^a

Entry	Substrate	L.A.	solvent	product	Yield (%) ^b	Dr ^c
1	5a	TiCl_4	CH_2Cl_2	29a'	38	75:25
2	6a	TiCl_4	CH_2Cl_2	29a	85	77:23
3	6a	TiCl_4	Toluene	29a	76	58:42
4	6a	TiCl_4	$\text{CH}_3\text{CH}(\text{NO}_2)\text{CH}_3$	29a	21	- ^d
5	6a	SnCl_4	CH_2Cl_2	29a	17	-

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b Isolated yield. ^c Dr value was determined by ^1H NMR. ^d Dr values did not test.

With this optimized reaction condition in hand, we next turned our attention to the substrate scope of acetal component. A series of acetal was investigated (Table 2.5). Generally, the reaction proceeded very well for electron-donating group substituted substrate. When the terminated phenyl ring tethering a chloro group, the reaction went through another way that *tert*-cation was trapped by a chloro instead of Friedel-Craft

reaction. For entry 5, it should have two possible regio isomers, the reaction only occurred at the less steric hindrance position. Entry 6 fully indicated that indole is a suitable terminating group. While an alkyne was incorporated to the substrate, it gave a 6-5 fused structure. At current stage, the reaction was unfit to tricyclic reaction precursors.

Table 2.5 Polyene cyclization of various acetal with isobutene^a

Entry	Substrate	Product	Yield (%) ^b	Dr ^c	
1			85	77:23	
2			81	89:11	
3			77	75:25	
4			85	75:25	
5			53	78:22	

6		6f		29f	68	80:20
7		6g		29g	74	78:22
8		6h		29h	71	67:33
9		6i		29i	76	77:23

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b Isolated yield. ^c Dr value was determined by ¹H NMR.

Having established an intermolecular polyene cyclization of acetal with alkene to construct 2-functionalized terpenoids skeletons, we are fully expected to apply it in natural product synthesis. Considering the structure of Salviol **35**, we envisioned that it could be synthesized from **27e**. The glycol ether of **27e** was converted to the iodo product **32** in 93% yield. Compound **32** was treated with Zn powder in benzyl alcohol yielded the benzyl ether **33** in 78%. The benzyl group of **33** could be cleaved by hydrogenation to give the free alcohol **34**, which was the key intermediate to synthesize Salviol, Abietatriene and 2-oxoferruginol.⁵⁰

50 (a) Matsumoto, T.; Usui, S.; Kawashima, H.; Mitsuki, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 581. (b) Ajoy, K. B.; Héctor, H. S.; Manuel, L. M.; Julio, C. A.; Jaime, A. G. *J. Chem. Soc. Perkin Trans. I* **1988**, 931.

Scheme 2.10 Application to the formal synthesis of 2-oxoferruginol

2.3.3 Acetal Initiated Polyene Cyclization with TBDPS-Protected 2-Methyl Allyl Alcohol

Stimulated by previous results, isobutene derivatives, TBDPS-protected 2-methyl allyl alcohol **36a** was investigated in the next section. Surprisingly, the reaction provided a 7-6-6 fused product **37a** instead of the proposed product in 56% yield with 89:11 diastereoselectivity. More interestingly, a different isomer **38a** was produced when SnCl_4 was employed as the promoter (Scheme 2.11). The relative stereochemistry of **37a** and **38a** were ascertained by reference to an X-ray diffraction analysis of relative compound **40** and **42** (Scheme 2.12).

Scheme 2.11 Acetal initiated polyene cyclization with TBDPS-protected 2-methyl allyl alcohol

Scheme 2.12 Determination of relative stereochemistry of **37** and **38**

Intrigued by the behavior of TBDPS-protected 2-methyl allyl alcohol, the effect of a range of protecting groups were explored (Table 2.6). As representative examples, TBDPS-group gave the highest yield and diastereoselectivity (entry 1). TIPS-protected substrate also could be incorporated in this manner, but the yield and the diastereoselectivity were observed much lower (entries 2-3). PhMe₂Si- was not so stable in the standard condition, only 21% desired product was obtained. Other protecting groups, such as Bz-, Bn- and p-OMe-Ph-, were not fit to the reaction (entries 4-6).

Table 2.6 Polyene cyclization of acetal with various protected 2-methyl allyl alcohol^a

Entry	Substrate	PG-		Yield (%) ^b	Dr ^c
1	36a	TBDPS-	37e	49	92:8
2	36b	TIPS-	37eb	44	72:28
3	36c	PhMe ₂ Si-	37ec	21	86:14

4	36d	Bn-	37ed	- ^d	-
5	36e	<i>p</i> -OMe-Ph-	37ee	- ^d	-
6	36f	Bz-	37ef	- ^d	-

^a Reactions were carried out on a 0.1 mmol scale with 0.1 M of substrate. ^b Isolated yield. ^c Dr value was determined by ¹H NMR. ^d The reaction was too messy to analyze.

Based on the result showed in Table 2.6, TBDPS-protected 2-methyl allyl alcohol was selected for other substrates study. Only electron-donating group can be tolerated in the phenyl ring. For most of cases, the reaction worked well and gave the desired product in good yield with good diastereoselectivity. If the methoxy group was introduced to the *ortho*-position, SnCl₄ promoted reaction gave the messy result. The entry 6 indicated that the reaction prefer to occur at the less steric hindrance position. If the acetal without a phenyl group as the terminating group, an ene-type product was obtained in good yield. However, the same major product was obtained whether SnCl₄ or TiCl₄ was applied (Scheme 2.13).

Table 2.7 Polyene cyclization to construct 7-6-6 fused rings^a

Entry	Substrate	LA	Product	Yield (%) ^b	Dr ^c
1	5a	TiCl ₄	37a	56	89:11
		SnCl ₄	38a	54	80:20
2	5b	TiCl ₄	37b	51	90:10
		SnCl ₄	38b	47	87:13

3		5c	TiCl ₄	37c	46	91:9
			SnCl ₄	38c	-	-
4		5d	TiCl ₄	37d	58	92:8
			SnCl ₄	38d	53	86:14
5		5e	TiCl ₄	37e	49	92:8
			SnCl ₄	38e	63	89:11
6		5f	TiCl ₄	37f	55	90:10
			SnCl ₄	38f	63	85:15

^a Reactions were carried out on a 0.1 mmol scale with 0.1 M of substrate. ^b Isolated yield. ^c Dr value was determined by ¹H NMR.

Scheme 2.13

In light of the previous results, a possible reaction mechanism was proposed as shown in Scheme 2.14. The initial step involved an allyl alkene attacked the oxocarbenium to generate a tert-carbon cation II. Followed by 1,2-hydride shift to form a more stable oxocarbenium. If TiCl₄ was chosen as the promoter, oxocarbenium

IV was generated and gave the product **37**. On the other hand, when SnCl_4 was used as the Lewis acid, the reaction preferred to form intermediate III leading to product **38**.

Scheme 2.14 Proposed reaction mechanism

2.4 Conclusion

We have developed an acetal-induced intermolecular polyene cyclization reaction for constructing many kinds of terpenoids skeletons. It provides the first example of polyene cyclization to incorporate both polyene substrate and initiators into the backbone of terpenoids. Furthermore, this approach provides diverse structures of cyclization products because of a possibly wider combination of the versatile polyolefin substrates and the initiators (such as silyl enol ether, isobutene and allyl alcohol).

When enol ethers and chiral acetals were applied as the reaction components, the strategy provided an asymmetric method to construct polyfunctionalized terpenoids skeletons. Especially for the ketene silyl enol ethers, diverse complex fused ring systems with a quaternary alcohol were formed, which are widely featured in natural

products. The core structure of Cortistatin A and steroids can be easily built by this strategy.

On the other hand, when isobutene was applied in the reaction, it provided an efficient method to build 2-functionalized terpenes which could not be prepared by the reported methods directly. The usefulness of this method has been certificated by the total synthesis of Salviol in four steps from the cyclization product.

In addition, it presented the first example to synthesize 7-6-6 fused rings by using TBDPS-protected 2-methyl allyl alcohol. More interestingly, different diastereoselectives were generated by employing different Lewis acid (TiCl_4 or SnCl_4). To the best of our knowledge, this is the first example to provide seven membered terpenoids core structure through 1,2-H shift reaction. This should inspire chemist to develop new biomimetic strategies for other type of terpene skeletons (such as cyathane and icetexanes).

2.5 Experimental Section

General Information

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Columns were typically packed as slurry and equilibrated with hexane prior to use. Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on Bruker Advance 300, 400 and 500 NMR spectrometers. Chemical shifts of ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 ($\delta = 0.0$) and relative to the signal of chloroform-*d* ($\delta = 7.264$, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); ddd (doublet of doublets of doublets); m (multiplets) and etc. The number of protons for a given resonance is indicated by nH. Coupling constants are reported as *J* values in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 ($\delta = 0.0$) and relative to the signal of chloroform-*d* ($\delta = 77.23$, triplet). High-resolution mass spectral analysis (HRMS) was performed on Q-ToF Premier mass spectrometer (Waters Corporation).

To an oven-dried round bottom flask (100 mL) equipped with a magnetic stir bar, aldehyde (10 mmol) and wittg reagent (12 mmol, 1.2 equiv) was dissolved in THF (50 mL). After the reaction was stirred at 60 °C for 10h, solvent was removed under reduce pressure. The crude product was purified by flash column chromatography on silica gel using appropriate solvents (hexane/EtOAc mixture) to provide the title compounds.

(*E*)-Methyl 2-methyl-5-phenylpent-2-enoate

Yield: 92%, yellow oil. ^1H NMR (500 MHz, CDCl_3): δ 1.78 (s, 3H), 2.49 (q, $J = 7.6$ Hz, 2H), 2.75 (t, $J = 7.8$ Hz, 2H), 3.73 (s, 3H), 6.81 (t, $J = 7.4$ Hz, 1H), 7.18-7.22 (m,

3H), 7.26-7.31 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 12.37, 30.57, 34.71, 51.75, 126.11, 128.19, 128.36, 128.47, 141.20, 141.28, 168.63. HRMS (ESI^+) exact mass calcd for $\text{C}_{13}\text{H}_{17}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 205.1229, found m/z 205.1232.

(E)-Methyl 2-methyl-5-o-tolylpent-2-enoate

Yield: 85%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.79 (s, 3H), 2.31 (s, 3H), 2.45 (q, $J = 7.6$ Hz, 2H), 2.72 (t, $J = 7.6$ Hz, 2H), 3.73 (s, 3H), 6.84 (t, $J = 7.4$ Hz, 1H), 7.10-7.23 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.33, 19.30, 29.34, 32.02, 51.75, 126.10, 126.28, 128.12, 128.68, 130.28, 135.86, 139.35, 141.39, 168.62. HRMS (ESI^+) exact mass calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 219.1385, found m/z 219.1376.

(E)-Methyl 5-(2-methoxyphenyl)-2-methylpent-2-enoate

Yield: 95%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.78 (s, 3H), 2.47 (q, $J = 7.6$ Hz, 2H), 2.73 (t, $J = 7.6$ Hz, 2H), 3.73 (s, 3H), 3.83 (s, 3H), 6.83-6.90 (m, 3H), 7.12 (d, $J = 7.6$ Hz, 1H), 7.19 (t, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.26, 28.98, 29.39, 51.67, 55.20, 110.23, 120.42, 127.39, 127.78, 129.60, 129.82, 142.11, 157.47, 168.76. HRMS (ESI^+) exact mass calcd for $\text{C}_{14}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires m/z 235.1334, found m/z 235.1325.

(E)-Methyl 2-methyl-5-p-tolylpent-2-enoate

Yield: 89%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.78 (s, 3H), 2.30 (s, 3H), 2.47 (q, $J = 7.6$ Hz, 2H), 2.71 (t, $J = 7.8$ Hz, 2H), 3.72 (s, 3H), 6.81 (t, $J = 7.4$ Hz, 1H), 7.09 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.38, 21.02, 30.70, 34.26, 51.73, 128.07, 128.21, 129.13, 135.56, 138.12, 141.45, 168.63. HRMS (ESI^+) exact mass calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 219.1385, found m/z 219.1396.

(E)-Methyl 5-(4-methoxyphenyl)-2-methylpent-2-enoate

Yield: 93%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.55 (s, 3H), 1.95-2.04 (m, 2H), 2.69 (t, $J = 7.6$ Hz, 2H), 3.78 (s, 3H), 3.84 (s, 3H), 4.78 (t, $J = 5.3$ Hz, 1H), 6.82 (d, $J = 8.6$ Hz, 2H), 7.10 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.39, 30.82, 33.80, 51.74, 55.27, 113.86, 128.09, 129.27, 133.28, 141.41, 157.96,

168.64. HRMS (ESI⁺) exact mass calcd for C₁₄H₁₉O₃ [M+Na]⁺ requires *m/z* 257.1154, found *m/z* 257.1143.

(E)-Methyl 2-methyl-5-(3,4,5-trimethoxyphenyl)pent-2-enoate

Yield: 79%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.81 (s, 3H), 2.49 (q, *J* = 7.5 Hz, 2H), 2.70 (t, *J* = 7.7 Hz, 2H), 3.74 (s, 3H), 3.83 (s, 3H), 3.85 (s, 6H), 6.40 (s, 2H), 6.80 (t, *J* = 7.4 Hz, 1H); ¹³C NMR (100

MHz, CDCl₃): δ 12.44, 30.55, 35.10, 51.76, 56.08, 60.88, 105.27, 128.21, 136.33, 136.93, 141.17, 153.16, 168.59. HRMS (ESI⁺) exact mass calcd for C₁₆H₂₂O₅Na [M+Na]⁺ requires *m/z* 317.1365, found *m/z* 317.1363.

(E)-Methyl 5-(3-isopropyl-4-methoxyphenyl)-2-methylpent-2-enoate

Yield: 85%, yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 1.20 (d, *J* = 6.9 Hz, 6H), 1.77 (s, 3H), 2.46 (q, *J* = 7.5 Hz, 2H), 2.69 (t, *J* = 7.5 Hz, 2H), 3.25-3.47 (m, 1H), 3.72 (s, 3H), 3.80 (s, 3H),

6.75-6.88 (m, 2H), 6.95-7.01 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 12.4, 22.6, 22.7, 26.7, 30.9, 34.1, 51.7, 55.5, 110.4, 126.2, 133.0, 136.9, 139.3, 141.6, 155.2, 168.7. HRMS (ESI⁺) exact mass calcd for C₁₇H₂₄O₃Na [M+Na]⁺ requires *m/z* 299.1623, found *m/z* 299.1618.

(E)-Methyl 5-(4-chlorophenyl)-2-methylpent-2-enoate

Yield: 84%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.77 (s, 3H), 2.47 (q, *J* = 7.6 Hz, 2H), 2.72 (t, *J* = 7.7 Hz, 2H), 3.73 (s, 3H), 6.76 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 12.39, 30.34,

34.02, 51.77, 128.54, 129.71, 130.90, 131.86, 139.56, 140.69, 168.50. HRMS (ESI⁺) exact mass calcd for C₁₃H₁₆ClO₂ [M+H]⁺ requires *m/z* 239.0839, found *m/z* 239.0848.

(E)-Methyl 2-methyl-5-(1-tosyl-1*H*-indol-3-yl)pent-2-enoate

Yield: 85%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.76 (s, 3H), 2.33 (s, 3H), 2.55 (q, *J* = 7.5 Hz, 2H), 2.80 (t, *J* = 7.6 Hz, 2H), 3.75 (s, 3H), 6.79 (t, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz,

1H), 7.33 (s, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 7.4 Hz, 2H), 7.97 (d, *J* = 8.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 12.48, 21.56, 23.91, 28.00, 51.79, 113.82,

119.27, 122.06, 122.86, 123.06, 124.74, 126.74, 128.56, 129.83, 130.79, 135.26, 135.32, 140.89, 144.77, 168.42. HRMS (ESI⁺) exact mass calcd for C₂₂H₂₄NO₄S [M+H]⁺ requires *m/z* 398.1426, found *m/z* 398.1424.

(E)-Methyl 5-phenylpent-2-enoate

Yield: 93%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 2.53 (q, *J* = 7.0 Hz, 2H), 2.76-2.79 (m, 2H), 3.72 (s, 3H), 5.85 (td, *J*₁ = 1.5 Hz, *J*₂ = 15.7 Hz, 1H), 7.01 (td, *J*₁ = 6.9 Hz, *J*₂ = 15.6 Hz, 1H), 7.17-7.22 (m, 3H), 7.28-7.31 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 33.90, 34.33, 51.45, 121.45, 126.19, 128.34, 128.50, 140.75, 148.38, 167.02. HRMS (ESI⁺) exact mass calcd for C₁₂H₁₄O₂Na [M+Na]⁺ requires *m/z* 237.0891, found *m/z* 237.0890.

(E)-Methyl 2-methylnon-2-en-6-ynoate

Yield: 85%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.11 (t, *J* = 7.5 Hz, 3H), 1.86 (s, 3H), 2.15 (tq, *J*₁ = 2.2 Hz, *J*₂ = 7.5 Hz, 2H), 2.26-2.30 (m, 2H), 2.37 (q, *J* = 7.0 Hz, 2H), 3.74 (s, 3H), 6.78 (t, *J* = 7.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.38, 12.53, 14.20, 18.12, 28.45, 51.74, 78.14, 82.50, 128.55, 140.54, 168.54. HRMS (ESI⁺) exact mass calcd for C₁₁H₁₆O₂Na [M+Na]⁺ requires *m/z* 203.1048, found *m/z* 203.1047.

(2E,6E)-Methyl 9-(2-methoxyphenyl)-2,6-dimethylnona-2,6-dienoate

Yield: 89%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.57 (s, 3H), 1.83 (s, 3H), 2.05-2.11 (m, 2H), 2.23-2.30 (m, 4H), 2.61-2.65 (m, 2H), 3.73 (s, 3H), 3.82 (s, 3H), 5.24 (t, *J* = 7.1 Hz, 1H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.85 (t, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.3 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.42, 15.86, 27.36, 28.18, 30.50, 38.23, 51.69, 55.22, 110.14, 120.27, 124.97, 126.96, 127.44, 129.88, 130.60, 134.37, 142.40, 157.49, 168.73. HRMS (ESI⁺) exact mass calcd for C₁₉H₂₆O₃Na [M+Na]⁺ requires *m/z* 325.1780, found *m/z* 325.1778.

(2E,6E)-Methyl 2,6-dimethyltrideca-2,6-dien-10-ynoate

Yield: 80%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.11 (t, *J* = 7.7 Hz, 3H), 1.63 (s, 3H), 1.83 (s, 3H), 2.09-2.20 (m, 8H), 2.28 (q, *J* =

7.6 Hz, 2H), 3.73 (s, 3H), 5.21 (t, $J = 5.6$ Hz, 1H), 6.74 (t, $J = 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.41, 14.32, 16.09, 19.14, 27.28, 27.82, 38.18, 51.67, 79.22, 81.71, 123.83, 127.51, 135.15, 142.16, 168.67. HRMS (ESI^+) exact mass calcd for $\text{C}_{16}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 249.1855, found m/z 249.1859.

(E)-Methyl 2-methyloct-2-enoate

Yield: 94%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 0.89 (t, $J = 6.7$ Hz, 3H), 1.27-1.35 (m, 5H), 1.40-1.46 (m, 2H), 1.83 (s, 3H), 2.16 (q, $J = 7.2$ Hz, 1H), 3.73 (s, 3H), 6.77 (t, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.34, 13.99, 22.49, 28.24, 28.63, 31.53, 51.66, 127.36, 142.85, 168.79. HRMS (ESI^+) exact mass calcd for $\text{C}_{10}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 171.1385, found m/z 171.1376.

An oven-dried round bottom flask (100 mL) equipped with a magnetic stir bar, ester was dissolved in 40 mL CH_2Cl_2 and cooled to 0°C . DIBAL-H (1.0M solution in heptane, 2.2 equiv) was added dropwisely. Then the reaction was allowed to stir at ambient temperature for 10 h. The reaction mixture was poured into cool sat. NH_4Cl , filtered through celight and extracted the filtrated with EtOAc (3 x 50 mL). The combined organic phase was washed with brine (100 mL), dried with Na_2SO_4 and concentrated *in vacuo* to give the alcohol. The product was used for the next step without further purification.

An oven-dried round bottom flask (100 mL) equipped with a magnetic stir bar, alcohol, pyridine (1.2 equiv) and LiCl (0.2 equiv) were dissolved in DMF (50 mL). Cooled the solution to 0°C , MsCl (1.2 equiv) was added. The reaction was allowed to stir at ambient temperature overnight. Poured the mixture to water, extracted with diethyl ether (3 x 50 mL) and washed with brine. Dried with Na_2SO_4 and concentrated *in vacuo* to give the chloro-product.

The crude chloro product was dissolved in CH_3CN , NaCN (2.0 equiv) and 18-crown-6 (1.0 equiv) were added. The mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with H_2O (2 x 100 mL) and brine (2 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was

purified by flash column chromatography on silica gel using appropriate solvents (hexane/EtOAc mixture) to provide the title compounds.

(E)-3-Methyl-6-phenylhex-3-enenitrile

Yield: 87%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.64 (s, 3H), 2.36 (q, $J = 7.6$ Hz, 2H), 2.67 (t, $J = 7.7$ Hz, 2H), 3.00 (s, 2H), 5.53 (t, $J = 7.2$ Hz, 1H), 7.16-7.21 (m, 3H), 7.27-7.30 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 15.97, 27.22, 29.94, 35.41, 117.74, 124.96, 125.99, 128.39, 128.45, 128.81, 141.48. HRMS (ESI^+) exact mass calcd for $\text{C}_{13}\text{H}_{16}\text{N}$ $[\text{M}+\text{H}]^+$ requires m/z 186.1283, found m/z 186.1287.

(E)-3-Methyl-6-o-tolylhex-3-enenitrile

Yield: 88%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.65 (s, 3H), 2.33 (s, 3H), 2.29-2.35 (m, 2H), 2.66 (t, $J = 7.5$ Hz, 2H), 3.01 (s, 2H), 5.57 (t, $J = 7.3$ Hz, 1H), 7.11-7.14 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.93, 19.31, 27.21, 28.69, 32.69, 117.73, 124.91, 126.00, 128.82, 128.90, 130.23, 135.85, 139.63. HRMS (ESI^+) exact mass calcd for $\text{C}_{14}\text{H}_{18}\text{N}$ $[\text{M}+\text{H}]^+$ requires m/z 200.1439, found m/z 200.1435.

(E)-6-(2-Methoxyphenyl)-3-methylhex-3-enenitrile

Yield: 93%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.65 (s, 3H), 2.32 (q, $J = 7.5$ Hz, 2H), 2.66 (t, $J = 7.2$ Hz, 2H), 2.99 (s, 2H), 3.82 (s, 3H), 5.55 (t, $J = 7.3$ Hz, 1H), 6.84 (d, $J = 8.2$ Hz, 1H), 6.88 (t, $J = 7.7$ Hz, 1H), 7.10 (d, $J = 7.4$ Hz, 1H), 7.19 (t, $J = 7.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.85, 27.21, 28.29, 30.00, 55.22, 110.20, 117.88, 120.36, 124.53, 127.27, 129.40, 129.86, 129.90, 157.46. HRMS (ESI^+) exact mass calcd for $\text{C}_{14}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$ requires m/z 216.1388, found m/z 216.1383.

(E)-3-Methyl-6-p-tolylhex-3-enenitrile

Yield: 79%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.66 (s, 3H), 2.32 (s, 3H), 2.34 (q, $J = 7.2$ Hz, 2H), 2.63 (t, $J = 7.6$ Hz, 2H), 3.01 (s, 2H), 5.53 (t, $J = 7.2$ Hz, 1H), 7.05-7.12 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.97, 21.01, 27.21, 30.04, 34.95, 117.76, 124.81, 128.28, 128.96, 129.06, 135.43, 138.40. HRMS (ESI^+) exact mass calcd for $\text{C}_{14}\text{H}_{18}\text{N}$ $[\text{M}+\text{H}]^+$ requires m/z 200.1439, found m/z 200.1430.

(E)-6-(4-Methoxyphenyl)-3-methylhex-3-enenitrile

Yield: 64%, yellow oil. ^1H NMR (500 MHz, CDCl_3): δ 1.67 (s, 3H), 2.35 (q, $J = 7.5$

Hz, 2H), 2.64 (t, $J = 7.6$ Hz, 2H), 3.03 (s, 2H), 3.82 (s, 3H), 5.55 (t, $J = 7.8$ Hz, 1H), 6.86 (d, $J = 8.6$ Hz, 2H), 7.12 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 15.99, 27.22, 30.18, 34.49, 55.28, 113.79, 117.77, 124.86, 128.89, 129.33, 133.57, 157.89. HRMS (ESI^+) exact mass calcd for $\text{C}_{14}\text{H}_{18}\text{NO}$ [$\text{M}+\text{H}$] $^+$ requires m/z 216.1388, found m/z 216.1379.

(E)-3-Methyl-6-(3,4,5-trimethoxyphenyl)hex-3-enenitrile

Yield: 79%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.69 (s, 3H), 2.36 (q, $J = 7.4$ Hz, 2H), 2.62 (t, $J = 7.7$ Hz, 2H), 3.02 (s, 2H), 3.83 (s, 3H), 3.86 (s, 6H), 5.55 (t, $J = 6.5$ Hz, 1H), 6.40 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.10, 27.16, 29.93, 35.77, 56.08, 60.87, 105.28, 117.72, 125.01, 128.66, 136.17, 137.31, 153.11. HRMS (ESI^+) exact mass calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3\text{Na}$ [$\text{M}+\text{Na}$] $^+$ requires m/z 298.1419, found m/z 298.1418.

(E)-6-(3-Isopropyl-4-methoxyphenyl)-3-methylhex-3-enenitrile

Yield: 69%, yellow oil. ^1H NMR (300 MHz, CDCl_3): δ 1.20 (d, $J = 6.9$ Hz, 6H), 1.65 (s, 3H), 2.33 (q, $J = 7.5$ Hz, 2H), 2.61 (t, $J = 7.5$ Hz, 2H), 3.00 (s, 2H), 3.20-3.32 (m, 1H), 3.80 (s, 3H), 5.53 (dt, $J_1 = 1.2$, $J_2 = 7.2$ Hz, 1H), 6.76 (d, $J = 8.1$ Hz, 1H), 6.95 (dd, $J_1 = 2.1$ Hz, $J_2 = 8.4$ Hz, 1H), 7.00 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 16.0, 22.7, 22.8, 26.7, 27.2, 30.2, 34.8, 55.5, 110.3, 117.8, 124.7, 126.1, 126.2, 129.1, 133.4, 136.9, 155.1. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{23}\text{NONa}$ [$\text{M}+\text{Na}$] $^+$ requires m/z 280.1677, found m/z 280.1680.

(E)-6-(4-Chlorophenyl)-3-methylhex-3-enenitrile

Yield: 86%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.64 (s, 3H), 2.33 (q, $J = 7.5$ Hz, 2H), 2.64 (t, $J = 7.6$ Hz, 2H), 3.00 (s, 2H), 5.50 (t, $J = 7.2$ Hz, 1H), 7.10 (d, $J = 8.3$ Hz, 2H), 7.25 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.02, 27.16, 29.76, 34.72, 117.64, 125.32, 128.31, 128.46, 129.79, 131.72, 139.87. HRMS (ESI^+) exact mass calcd for $\text{C}_{13}\text{H}_{15}\text{ClN}$ [$\text{M}+\text{H}$] $^+$ requires m/z 220.0893, found m/z 220.0891.

(E)-3-Methyl-6-(1-tosyl-1H-indol-3-yl)hex-3-enenitrile

Yield: 78%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.64 (s, 3H), 2.33 (s, 3H), 2.44 (q, $J = 7.2$ Hz, 2H), 2.71 (t, $J = 7.6$ Hz, 2H), 2.99 (s, 2H), 5.55 (t, $J = 5.6$ Hz, 1H), 7.20-7.25 (m, 3H), 7.29-7.33 (m, 2H), 7.46 (d, $J = 7.4$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.98 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.11, 21.56, 24.51, 27.13, 27.50, 113.77, 119.35, 122.35, 122.71, 123.02, 124.69, 125.39, 126.77, 128.48, 129.85, 130.90, 135.28, 135.36, 144.80. HRMS (ESI^+) exact mass calcd for $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ requires m/z 379.1480, found m/z 379.1469.

(E)-6-Phenylhex-3-enenitrile

Yield: 75%. ^1H NMR (400 MHz, CDCl_3): δ 2.38 (q, $J = 7.6$ Hz, 2H), 2.69-2.72 (m, 2H), 3.04 (ddd, $J_1 = 1.3$ Hz, $J_2 = 2.8$ Hz, $J_3 = 5.6$ Hz, 2H), 5.36 (ttd, $J_1 = 1.4$ Hz, $J_2 = 5.5$ Hz, $J_3 = 15.3$ Hz, 1H), 5.86 (ttd, $J_1 = 1.6$ Hz, $J_2 = 6.8$ Hz, $J_3 = 15.2$ Hz, 1H), 7.16-7.19 (m, 3H), 7.25-7.31 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.41, 33.94, 35.25, 117.75, 117.91, 126.03, 128.41, 135.28, 141.23. HRMS (ESI^+) exact mass calcd for $\text{C}_{12}\text{H}_{13}\text{NNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 194.0946, found m/z 194.0946.

(E)-3-Methyl-5-phenylpent-3-enenitrile

Yield: 73%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.85 (s, 3H), 3.07 (s, 2H), 3.40 (d, $J = 7.4$ Hz, 2H), 5.69 (t, $J = 7.4$ Hz, 1H), 7.15-7.22 (m, 3H), 7.28-7.31 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.16, 27.29, 34.25, 117.64, 125.24, 126.23, 128.31, 128.44, 128.60, 139.98. HRMS (ESI^+) exact mass calcd for $\text{C}_{12}\text{H}_{13}\text{NNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 194.0946, found m/z 194.0952.

(E)-3-Methyldec-3-en-7-ynenitrile

Yield: 75%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.14 (t, $J = 7.6$ Hz, 3H), 1.76 (s, 3H), 2.13-2.26 (m, 6H), 3.05 (s, 2H), 5.54 (t, $J = 7.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.38, 14.25, 16.13, 18.69, 27.25, 27.75, 78.45, 82.30, 117.69, 125.40, 128.30. HRMS (ESI^+) exact mass calcd for $\text{C}_{11}\text{H}_{15}\text{NNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 184.1102, found m/z 184.1098.

(3E,7E)-10-(2-methoxyphenyl)-3,7-dimethyldeca-3,7-dienenitrile

Yield: 79%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.56 (s, 3H), 1.72 (s, 3H), 1.99-2.03 (m, 2H), 2.12 (q, $J = 7.3$ Hz, 2H), 2.27 (q, $J = 7.4$ Hz,

2H), 2.61-2.65 (m, 2H), 3.00 (s, 2H), 3.83 (s, 3H), 5.20 (t, $J = 7.1$ Hz, 1H), 5.44 (t, $J = 7.1$ Hz, 1H), 6.84 (d, $J = 8.3$ Hz, 1H), 6.87 (t, $J = 7.4$ Hz, 1H), 7.12 (d, $J = 7.4$ Hz, 1H), 7.17 (t, $J = 7.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.88, 16.00, 26.63, 27.25, 28.13, 30.50, 38.96, 55.25, 110.16, 117.91, 120.27, 124.02, 124.78, 126.96, 129.68, 129.84, 130.63, 134.63, 157.51. HRMS (ESI^+) exact mass calcd for $\text{C}_{19}\text{H}_{26}\text{NO}$ $[\text{M}+\text{H}]^+$ requires m/z 284.2014, found m/z 284.2018.

(3E,7E)-3,7-Dimethyltetradeca-3,7-dien-11-ynenitrile

Yield: 70%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.12 (t, $J = 7.4$ Hz, 3H), 1.62 (s, 3H), 1.73 (s, 3H), 2.02-2.05 (m, 2H), 2.12-2.19 (m, 8H), 3.02 (s, 2H), 5.18 (t, $J = 7.0$ Hz, 1H), 5.54 (t, $J = 7.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.43, 14.34, 16.00, 16.07, 19.19, 26.54, 27.24, 27.81, 38.92, 79.29, 81.68, 117.83, 123.66, 124.09, 129.55, 135.41. HRMS (ESI^+) exact mass calcd for $\text{C}_{16}\text{H}_{25}\text{N}$ $[\text{M}+\text{H}]^+$ requires m/z 230.1909, found m/z 230.1907.

(E)-3-Methylnon-3-enenitrile

Yield: 86%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 0.89 (t, $J = 6.6$ Hz, 3H), 1.25-1.38 (m, 6H), 1.72 (s, 3H), 2.03 (q, $J = 7.1$ Hz, 2H), 3.02 (s, 2H), 5.48 (t, $J = 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.04, 15.98, 22.53, 27.25, 27.97, 28.90, 31.44, 117.92, 123.85, 130.13. HRMS (ESI^+) exact mass calcd for $\text{C}_{10}\text{H}_{17}\text{NNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 174.1259, found m/z 174.1262.

To an oven-dried round bottom flask (50 mL) equipped with a magnetic stir bar, the cyanide (5.0 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to -78°C . DIBAL-H (5.5 mL of a 1.0M solution in heptane, 5.5 mmol, 1.1 equiv) was added dropwisely. The solution was allowed to stir at -78°C for 1h and then EtOH (0.5 mL) was added, the reaction mixture was diluted with EtOAc (20 mL) and poured into Sat. NH_4Cl (30 mL). After stirred for 10 mins, potassium sodium tartrate (2.0 equiv) was added and stirred for 2h. Separated the organic layer, and extracted the aqueous with EtOAc (2 x 30mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , and concentrated under reduce pressure gave the crude product for next step directly.

The crude product was dissolved in toluene (30 mL), then ethanol (3.0 equiv) and

TsOH (0.10 equiv) were added cooled the reaction to 0 °C. Triethyl orthoformate was added dropwisely, after that the reaction mixture was stirred overnight at room temperature. The reaction was quenched with triethyl amine (0.2 equiv) and concentrated under reduce pressure. The crude product was purified by chromatography afford the ethonal protected acetal.

(E)-(6,6-Diethoxy-4-methylhex-3-enyl)benzene

Yield: 73%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ

1.18 (t, $J = 7.1$ Hz, 6H), 1.61 (s, 3H), 2.29-2.35 (m, 4H), 2.63-2.67 (m, 2H), 3.47 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.3$ Hz, 2H),

3.63 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.3$ Hz, 2H), 4.56 (t, $J = 5.8$ Hz, 1H), 5.28 (t, $J = 6.6$ Hz, 1H), 7.16-7.20 (m, 3H), 7.26-7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.32, 16.66, 29.93, 35.93, 43.78, 61.00, 102.25, 125.70, 126.65, 128.23, 128.45, 131.59, 142.26. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{26}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 285.1831, found m/z 285.1828.

(E)-1-(6,6-Diethoxy-4-methylhex-3-enyl)-2-methylbenzene

Yield: 79%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ

1.19 (t, $J = 7.1$ Hz, 6H), 1.63 (s, 3H), 2.25-2.31 (m, 4H), 2.31 (s, 3H), 2.61-2.64 (m, 2H), 3.48 (qd, $J_1 = 7.1$ Hz, J_2

= 9.4 Hz, 2H), 3.65 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.4$ Hz, 2H), 4.57 (t, $J = 5.8$ Hz, 1H), 5.31 (t, $J = 7.1$ Hz, 1H), 7.08-7.25 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.32, 16.61, 19.32, 28.69, 33.23, 43.81, 61.04, 102.27, 125.86, 126.80, 128.81, 130.08, 131.55, 135.88, 140.39. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{28}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 299.1987, found m/z 299.1984.

(E)-1-(6,6-Diethoxy-4-methylhex-3-enyl)-2-methoxybenzene

Yield: 81%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ

1.19 (t, $J = 7.1$ Hz, 6H), 1.63 (s, 3H), 2.26-2.30 (m, 4H), 2.62-2.66 (m, 2H), 3.48 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.4$ Hz, 2H),

3.64 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.4$ Hz, 2H), 3.82 (s, 3H), 4.56 (t, $J = 5.8$ Hz, 1H), 5.31 (t, $J = 6.9$ Hz, 1H), 6.84 (d, $J = 8.3$ Hz, 1H), 6.87 (t, $J = 7.4$ Hz, 1H), 7.12 (d, $J = 7.3$ Hz, 1H), 7.17 (t, $J = 7.9$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.33, 16.57, 28.21, 30.40, 43.80, 55.22, 61.00, 102.36, 110.14, 120.27, 126.94, 127.24, 129.84, 130.62, 131.25, 157.49. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{29}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires m/z 293.2117, found m/z 293.2115.

(E)-1-(6,6-Diethoxy-4-methylhex-3-enyl)-4-methylbenzene

Yield: 74%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.18 (t, $J = 7.1$ Hz, 6H), 1.61 (s, 3H), 2.29-2.32 (m, 4H), 2.31 (s, 3H), 2.58-2.62 (m, 2H), 3.47 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.4$ Hz, 2H), 3.63 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.4$ Hz, 2H), 4.56 (t, $J = 5.8$ Hz, 1H), 5.27 (t, $J = 7.1$ Hz, 1H), 7.08 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.31, 16.68, 21.00, 30.07, 35.48, 43.79, 61.00, 102.29, 126.80, 128.31, 128.92, 131.47, 135.10, 139.19. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{28}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 299.1987, found m/z 299.1984.

(E)-5-(6,6-Diethoxy-4-methylhex-3-enyl)-1,2,3-trimethoxybenzene

Yield: 78%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.19 (t, $J = 7.1$ Hz, 6H), 1.65 (s, 3H), 2.30-2.35 (m, 4H), 2.56-2.61 (m, 2H), 3.48 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.4$ Hz, 2H), 3.64 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.4$ Hz, 2H), 3.82 (s, 3H), 3.85 (s, 6H), 4.56 (t, $J = 5.6$ Hz, 1H), 5.28 (t, $J = 6.8$ Hz, 1H), 6.41 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.31, 16.74, 29.93, 36.29, 43.75, 56.04, 60.86, 60.01, 102.20, 105.26, 126.58, 131.65, 136.02, 138.07, 153.02. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{32}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 375.2147, found m/z 375.2149.

(E)-4-(6,6-diethoxy-4-methylhex-3-enyl)-2-isopropyl-1-methoxybenzene

Yield: 57%, colorless oil. ^1H NMR (300 MHz, CDCl_3): δ 1.19-1.21 (m, 12H), 1.63 (s, 3H), 2.30 (q, $J = 7.5$ Hz, 4H), 2.56 (t, $J = 7.8$ Hz, 2H), 3.27-3.31 (m, 1H), 3.42-3.52 (m, 2H), 3.59-3.69 (m, 2H), 3.80 (s, 3H), 4.56 (t, $J = 5.7$ Hz, 1H), 5.28 (t, $J = 6.6$ Hz, 1H), 6.75 (d, $J = 8.4$ Hz, 1H), 6.97 (dd, $J_1 = 2.1$ Hz, $J_2 = 8.0$ Hz, 1H), 7.02 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 15.3, 16.7, 22.8, 26.7, 30.3, 35.3, 43.8, 55.5, 61.0, 102.3, 110.3, 126.1, 126.2, 127.0, 131.3, 134.2, 136.7, 154.9, 162.3. HRMS (ESI^+) exact mass calcd for $\text{C}_{21}\text{H}_{34}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 357.2406, found m/z 357.2409.

(E)-1-Chloro-4-(6,6-diethoxy-4-methylhex-3-enyl)benzene

Yield: 65%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.18 (t, $J = 7.1$ Hz, 6H), 1.59 (s, 3H), 2.28-2.32 (m, 4H), 2.59-2.63 (m, 2H), 3.46 (qd, $J_1 =$

7.1 Hz, $J_2 = 9.4$ Hz, 2H), 3.63 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.4$ Hz, 2H), 4.54 (t, $J = 5.8$ Hz, 1H), 5.23 (t, $J = 6.6$ Hz, 1H), 7.11 (d, $J = 8.4$ Hz, 2H) 7.23 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.31, 16.67, 29.72, 35.21, 43.76, 61.00, 102.20, 126.18, 128.28, 129.83, 131.40, 131.98, 140.63. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{25}\text{ClO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 319.1441, found m/z 319.1444.

(E)-3-(6,6-Diethoxy-4-methylhex-3-enyl)-1-tosyl-1H-indole

Yield: 69%, colorless oil. ^1H NMR (400 MHz, CDCl_3):

δ 1.18 (t, $J = 7.1$ Hz, 6H), 1.62 (s, 3H), 2.29 (d, $J = 5.7$ Hz, 2H), 2.37 (s, 3H), 2.38 (q, $J = 7.4$ Hz, 2H), 2.66-2.68 (m, 2H), 3.45-3.50 (m, 2H), 3.60-3.64 (m,

2H), 4.56 (t, $J = 5.8$ Hz, 1H), 5.27 (t, $J = 7.3$ Hz, 1H), 7.19-7.24 (m, 3H), 7.26-7.31 (m, 2H), 7.47 (d, $J = 7.8$ Hz, 1H), 7.74 (d, $J = 7.8$ Hz, 2H), 7.97 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.32, 16.74, 21.54, 24.94, 27.42, 43.81, 54.15, 61.12, 102.24, 113.74, 119.45, 122.68, 122.94, 123.09, 124.54, 126.42, 126.74, 129.78, 131.16, 132.06, 135.32, 135.40, 144.66. HRMS (ESI^+) exact mass calcd for $\text{C}_{26}\text{H}_{33}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 478.2028, found m/z 478.2027.

(E)-(6,6-Diethoxyhex-3-enyl)benzene

Yield: 73%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ

1.19 (t, $J = 7.1$ Hz, 6H), 2.31-2.36 (m, 4H), 2.66-2.70 (m, 2H), 3.48 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.4$ Hz, 2H), 3.63 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.4$ Hz, 2H), 4.44 (t, $J = 5.7$ Hz, 1H), 5.44 (td, $J_1 = 6.8$ Hz, $J_2 = 15.4$ Hz, 1H), 5.56 (td, $J_1 = 6.8$ Hz, $J_2 = 15.4$ Hz, 1H), 7.15-7.19 (m, 3H), 7.25-7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.32, 34.46, 35.90, 37.32, 61.09, 102.74, 125.39, 125.73, 128.24, 128.45, 132.43, 142.02. HRMS (ESI^+) exact mass calcd for $\text{C}_{16}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 249.1855, found m/z 249.1858.

(E)-(5,5-Diethoxy-3-methylpent-2-enyl)benzene

Yield: 75%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.19

(t, $J = 7.1$ Hz, 6H), 1.77 (s, 3H), 2.37 (d, $J = 5.8$ Hz, 2H), 3.38 (d, $J = 7.4$ Hz, 2H), 3.49 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.3$ Hz, 2H), 3.65 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.3$ Hz, 2H), 4.63 (t, $J = 5.8$ Hz, 1H), 5.44 (t, $J = 7.4$ Hz, 1H), 7.15-7.19 (m, 3H), 7.25-7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.30, 16.77, 34.17, 43.80, 61.02, 102.06, 125.74, 126.00, 128.33, 132.11, 141.41. HRMS (ESI^+) exact mass calcd for $\text{C}_{16}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 249.1855, found m/z 249.1849.

(E)-1,1-Diethoxy-3-methyldec-3-en-7-yne

Yield: 76%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.11 (t, $J = 7.4$ Hz, 3H), 1.19 (t, $J = 7.1$ Hz, 6H), 1.67 (s, 3H), 2.12-2.21 (m, 6H), 2.31 (d, $J = 5.8$ Hz, 2H), 3.49 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.3$ Hz, 2H), 3.65 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.3$ Hz, 2H), 4.58 (t, $J = 5.3$ Hz, 1H), 5.28 (t, $J = 6.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.42, 14.32, 15.30, 16.78, 19.08, 27.87, 43.78, 61.07, 79.23, 81.67, 102.23, 126.05, 132.05. HRMS (ESI^+) exact mass calcd for $\text{C}_{15}\text{H}_{26}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 261.1831, found m/z 261.1818.

1-((3E,7E)-10,10-Diethoxy-4,8-dimethyldeca-3,7-dienyl)-2-methoxybenzene

Yield: 81%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.19 (t, $J = 7.1$ Hz, 6H), 1.57 (s, 3H), 1.66 (s, 3H), 1.97-2.01 (m, 2H), 2.06-2.10 (m, 2H), 2.23-2.30 (m, 4H), 2.62 (t, $J = 6.1$ Hz, 2H), 3.49 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.3$ Hz, 2H), 3.64 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.3$ Hz, 2H), 3.82 (s, 3H), 4.57 (t, $J = 5.7$ Hz, 1H), 5.21-5.24 (m, 2H), 6.84 (d, $J = 8.3$ Hz, 1H), 6.87 (t, $J = 6.7$ Hz, 1H), 7.13 (d, $J = 7.2$ Hz, 1H), 7.17 (t, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.33, 15.89, 16.68, 26.70, 28.21, 30.56, 39.53, 43.79, 55.22, 61.00, 102.32, 110.13, 120.26, 124.19, 126.90, 127.40, 129.84, 130.70, 130.75, 135.38, 157.49. HRMS (ESI^+) exact mass calcd for $\text{C}_{23}\text{H}_{36}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 383.2562, found m/z 383.2577.

(3E,7E)-1,1-diethoxy-3,7-dimethyltetradeca-3,7-dien-11-yne

Yield: 77%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.11 (t, $J = 7.0$ Hz, 3H), 1.19 (t, $J = 7.0$ Hz, 6H), 1.62 (s, 3H), 1.65 (s, 3H), 1.99-2.19 (m, 10H), 2.29 (d, $J = 5.7$ Hz, 2H), 3.49 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.3$ Hz, 2H), 3.63 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.3$ Hz, 2H), 4.57 (t, $J = 5.8$ Hz, 1H), 5.16-5.23 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.43, 14.33, 15.31, 16.09, 16.67, 19.23, 26.62, 27.85, 39.50, 43.77, 60.98, 79.36, 81.65, 102.30, 123.05, 127.24, 130.79, 136.17. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{35}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 307.2637, found m/z 307.2638.

(E)-1,1-Diethoxy-3-methylnon-3-ene

Yield: 66%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.88 (t, $J = 7.1$ Hz, 3H), 1.19 (t, $J = 7.2$ Hz, 6H), 1.25-1.35 (m, 6H), 1.65 (s, 3H), 1.99 (q, $J = 6.8$ Hz, 2H), 2.30 (d, $J = 6.2$ Hz, 2H),

3.49 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.3$ Hz, 2H), 3.65 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.3$ Hz, 2H), 4.58 (t, $J = 5.8$ Hz, 1H), 5.23 (t, $J = 7.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.09, 15.30, 16.60, 22.60, 27.90, 29.37, 31.49, 43.84, 60.98, 102.23, 127.95, 130.49. HRMS (ESI^+) exact mass calcd for $\text{C}_{14}\text{H}_{29}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 229.2168, found m/z 229.2163.

To a round bottom flask equipped with a magnetic stir, diethoxy acetal (1.0 mmol), *p*-toluenesulfonic acid monohydrate (0.1 mmol) and chiral diol (1.2 mmol) were dissolved in CH_2Cl_2 (10 mL). After stirring for 8h at room temperature, the reaction was quenched with triethylamine (0.2 mL). The reaction mixture was purified by flash chromatography on silica gel using diethyl ether/hexane to provide the title compound.

(4*R*,5*R*)-4,5-Dimethyl-2-((*E*)-2-methyl-5-phenylpent-2-enyl)-1,3-dioxolane (8a)

Yield: 95%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.23 (d, $J = 5.2$ Hz, 3H), 1.29 (d, $J = 5.2$ Hz, 3H), 1.63 (s, 3H), 2.30-2.36 (m, 4H), 2.63-2.67 (m, 2H), 3.58-3.62

(m, 2H), 5.09 (t, $J = 4.8$ Hz, 1H), 5.32 (t, $J = 6.8$ Hz, 1H), 7.16-7.20 (m, 3H), 7.25-7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.87, 17.11, 17.30, 30.08, 35.93, 44.91, 77.95, 79.71, 102.70, 125.69, 127.06, 128.23, 128.49, 130.96, 142.30. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 261.1855, found m/z 261.1850.

(4*R*,6*R*)-4,6-dimethyl-2-((*E*)-2-methyl-5-phenylpent-2-enyl)-1,3-dioxane (7a)

Yield: 93%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.20 (d, $J = 6.0$ Hz, 3H), 1.32 (d, $J = 9.6$ Hz, 1H), 1.32 (d, $J = 8.0$ Hz, 3H), 1.59 (s, 3H), 1.83 (dt, $J_1 = 6.0$

Hz, $J_2 = 13.2$ Hz, 1H), 2.20-2.33 (m, 2H), 2.63 (q, $J = 7.6$ Hz, 2H), 2.65 (t, $J = 7.8$ Hz, 2H), 3.92-3.97 (m, 1H), 4.27-4.33 (m, 1H), 4.91 (t, $J = 5.6$ Hz, 1H), 5.28 (t, $J = 7.2$ Hz, 1H), 7.15-7.25 (m, 3H), 7.26-7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.62, 17.14, 21.91, 29.97, 35.94, 36.74, 45.32, 67.56, 67.99, 93.75, 125.66, 126.42, 128.20, 128.51, 131.35, 142.36. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{27}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 275.2011, found m/z 275.2011.

(4*R*,5*R*)-4,5-Dimethyl-2-((*E*)-2-methyl-5-*o*-tolylpent-2-enyl)-1,3-dioxolane (8b)

Yield: 95%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.23 (d, $J = 5.8$ Hz, 3H), 1.29 (d, $J = 5.8$ Hz, 3H), 1.65 (s, 3H), 2.26-2.33 (m, 4H), 2.31 (s, 3H), 2.61-2.65 (m,

2H), 3.57-3.65 (m, 2H), 5.10 (t, $J = 5.0$ Hz, 1H), 5.35 (t, $J = 6.4$ Hz, 1H), 7.08-7.13 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.83, 17.11, 17.30, 19.33, 28.80, 33.21, 44.94, 77.97, 79.71, 102.71, 125.86, 127.16, 128.87, 130.06, 130.92, 135.90, 140.43. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{26}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 297.1831, found m/z 297.1835.

(4R,5R)-2-((E)-5-(2-Methoxyphenyl)-2-methylpent-2-enyl)-4,5-dimethyl-1,3-dioxolane (8c)

Yield: 91%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.22 (d, $J = 5.6$ Hz, 3H), 1.29 (d, $J = 5.6$ Hz, 3H), 1.64 (s, 3H), 2.27-2.32 (m, 4H), 2.64 (t, $J = 8.0$ Hz, 2H), 3.58-3.63 (m, 2H), 3.82 (s, 3H), 5.09 (t, $J = 5.0$ Hz, 1H), 5.34 (t, $J = 6.9$ Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 6.88 (t, $J = 7.6$ Hz, 1H), 7.13 (d, $J = 7.4$ Hz, 1H), 7.16 (t, $J = 7.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.78, 17.12, 17.30, 28.33, 30.36, 44.95, 55.22, 77.94, 79.69, 102.82, 110.15, 120.27, 126.92, 127.62, 129.88, 130.61, 130.67, 157.50. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{26}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 313.1780, found m/z 313.1766.

(4R,5R)-4,5-Dimethyl-2-((E)-2-methyl-5-p-tolylpent-2-enyl)-1,3-dioxolane (8d)

Yield: 89%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.22 (d, $J = 5.8$ Hz, 3H), 1.28 (d, $J = 5.8$ Hz, 3H), 1.64 (s, 3H), 2.28-2.33 (m, 4H), 2.31 (s, 3H), 2.61 (t, $J = 7.2$ Hz, 2H), 3.58-3.62 (m, 2H), 5.09 (t, $J = 5.0$ Hz, 1H), 5.31 (t, $J = 6.8$ Hz, 1H), 7.08 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.90, 17.11, 17.30, 21.01, 30.22, 35.49, 44.92, 77.95, 79.70, 102.75, 127.20, 128.34, 128.92, 130.83, 135.09, 139.24. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{26}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 297.1831, found m/z 297.1828.

(4R,5R)-4,5-Dimethyl-2-((E)-2-methyl-5-(3,4,5-trimethoxyphenyl)pent-2-enyl)-1,3-dioxolane (8e)

Yield: 85%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.22 (d, $J = 5.6$ Hz, 3H), 1.29 (d, $J = 5.6$ Hz, 3H), 1.66 (s, 3H), 2.31-2.36 (m, 4H), 2.60 (t, $J = 7.2$ Hz, 2H), 3.58-3.62 (m, 2H), 3.82 (s, 3H), 3.85 (s, 6H), 5.09 (t, $J = 5.2$ Hz, 1H), 5.32 (t, $J = 7.2$ Hz, 1H), 6.41 (s, 2H);

^{13}C NMR (100 MHz, CDCl_3): δ 16.95, 17.09, 17.27, 30.02, 36.25, 44.94, 56.04, 60.86, 79.96, 79.71, 102.71, 105.32, 126.96, 131.06, 138.09, 153.01. HRMS (ESI $^+$) exact mass calcd for $\text{C}_{20}\text{H}_{30}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 373.1991, found m/z 373.2009.

(4*R*,5*R*)-2-((*E*)-5-(4-Chlorophenyl)-2-methylpent-2-enyl)-4,5-dimethyl-1,3-dioxolane (8g)

Yield: 89%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.22 (d, $J = 5.8$ Hz, 3H), 1.28 (d, $J = 5.8$ Hz, 3H), 1.61 (s, 3H), 2.27-2.33 (m, 4H), 2.62 (t, $J = 7.7$ Hz, 2H), 3.56-3.63 (m, 2H), 5.07 (t, $J = 5.0$ Hz, 1H), 5.27 (t, $J = 6.6$ Hz, 1H), 7.11 (d, $J = 8.5$ Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.88, 17.10, 17.29, 29.85, 35.21, 44.89, 77.95, 79.70, 102.63, 126.58, 128.27, 129.88, 131.34, 131.38, 140.65. HRMS (ESI $^+$) exact mass calcd for $\text{C}_{17}\text{H}_{24}\text{ClO}_2$ $[\text{M}+\text{H}]^+$ requires m/z 295.1465, found m/z 295.1458.

3-((*E*)-5-((4*R*,5*R*)-4,5-Dimethyl-1,3-dioxolan-2-yl)-4-methylpent-3-enyl)-1-tosyl-1*H*-indole (8h)

Yield: 85%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.22 (d, $J = 5.8$ Hz, 3H), 1.28 (d, $J = 5.7$ Hz, 3H), 1.62 (s, 3H), 2.28 (s, 3H), 2.30 (d, $J = 5.0$ Hz, 2H), 2.38 (q, $J = 7.3$ Hz, 2H), 2.69 (t, $J = 7.4$ Hz, 2H), 3.57-3.65 (m, 2H), 5.09 (t, $J = 5.0$ Hz, 1H), .30 (t, $J = 6.5$ Hz, 1H), 7.15-7.22 (m, 3H), 7.26-7.30 (m, 1H), 7.32 (s, 1H), 7.46 (d, $J = 7.7$ Hz, 1H), 7.72 (d, $J = 8.4$ Hz, 2H), 7.97 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.98, 17.14, 17.33, 21.52, 24.87, 27.46, 44.92, 78.02, 79.75, 102.61, 113.75, 119.49, 122.82, 122.97, 123.08, 124.53, 126.73, 126.82, 129.77, 131.20, 131.43, 135.33, 135.37, 144.66. HRMS (ESI $^+$) exact mass calcd for $\text{C}_{26}\text{H}_{32}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ requires m/z 454.2052, found m/z 454.2047.

(4*R*,5*R*)-4,5-Dimethyl-2-((*E*)-5-phenylpent-2-enyl)-1,3-dioxolane (8i)

Yield: 95%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.22 (d, $J = 5.7$ Hz, 3H), 1.28 (d, $J = 5.7$ Hz, 3H), 2.32-2.37 (m, 4H), 2.66-2.70 (m, 2H), 3.55-3.64 (m, 2H), 5.03 (t, $J = 4.7$ Hz, 1H), 5.48 (td, $J_1 = 6.5$ Hz, $J_2 = 15.4$ Hz, 1H), 5.61 (td, $J_1 = 6.5$ Hz, $J_2 = 15.4$ Hz, 1H), 7.15-7.19 (m, 3H), 7.25-7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.95, 17.24, 34.51, 35.82, 38.30, 78.17, 79.77, 102.95, 124.24, 125.73,

128.26, 128.44, 133.25, 142.05. HRMS (ESI⁺) exact mass calcd for C₁₆H₂₃O₂ [M+H]⁺ requires m/z 247.1698, found m/z 247.1704.

(4*R*,5*R*)-4,5-Dimethyl-2-((*E*)-2-methyl-4-phenylbut-2-enyl)-1,3-dioxolane (8j)

Yield: 88%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.22 (d, J = 5.8 Hz, 3H), 1.28

(d, J = 5.8 Hz, 3H), 1.79 (s, 3H), 2.37 (d, J = 4.8 Hz, 2H), 3.39 (d, J = 7.3 Hz, 2H), 3.59-3.62 (m, 2H), 5.14 (t, J = 5.0 Hz, 1H), 5.48 (t, J = 7.3 Hz, 1H), 7.15-7.20 (m, 3H),

7.26-7.29 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 17.07, 17.27, 34.25, 44.93, 77.96, 79.72, 102.69, 125.74, 126.40, 128.34, 128.38, 131.46, 141.42. HRMS (ESI⁺) exact mass calcd for C₁₆H₂₃O₂ [M+H]⁺ requires m/z 247.1698, found m/z 247.1686.

(4*R*,5*R*)-4,5-Dimethyl-2-((*E*)-2-methylnon-2-en-6-ynyl)-1,3-dioxolane (8k)

Yield: 89%, yellow oil. ¹H NMR (400 MHz, CDCl₃):

δ 1.11 (t, J = 7.4 Hz, 3H), 1.22 (d, J = 5.8 Hz, 3H), 1.29 (d, J = 5.8 Hz, 3H), 1.70 (s, 3H), 2.13-2.32 (m,

6H), 2.32 (d, J = 4.8 Hz, 2H), 3.56-3.65 (m, 2H), 5.10 (t, J = 5.0 Hz, 1H), 5.30 (t, J = 6.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.42, 14.31, 17.02, 17.08, 17.27, 19.04, 27.92, 44.88, 77.95, 79.25, 79.69, 81.72, 102.77, 126.40, 131.48. HRMS (ESI⁺) exact mass calcd for C₁₅H₂₅O₂ [M+H]⁺ requires m/z 237.1855, found m/z 237.1851.

(4*R*,5*R*)-2-((2*E*,6*E*)-9-(2-Methoxyphenyl)-2,6-dimethylnona-2,6-dienyl)-4,5-dimethyl-1,3-dioxolane (8l)

Yield: 91%, yellow oil. ¹H NMR (400 MHz,

CDCl₃): δ 1.22 (d, J = 5.3 Hz, 3H), 1.28 (d, J = 5.3 Hz, 3H), 1.56 (s, 3H), 1.68 (s, 3H),

1.98-2.01 (m, 2H), 2.08 (q, J = 6.4 Hz, 2H), 2.26 (q, J = 7.3 Hz, 2H), 2.31 (d, J = 4.8 Hz, 2H), 2.62 (t, J = 8.3 Hz, 2H), 3.58-3.63 (m, 2H), 3.82 (s, 3H), 5.09 (t, J = 5.2 Hz, 1H), 5.22 (t, J = 7.2 Hz, 1H), 5.24 (t, J = 6.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.87 (t, J = 7.3 Hz, 1H), 7.12 (d, J = 7.3 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 15.90, 16.91, 17.11, 17.29, 26.79, 28.21, 30.54, 39.50, 44.95, 55.23, 77.93, 79.69, 102.86, 110.14, 120.26, 124.19, 126.88, 127.79, 129.87, 130.11, 130.78, 135.37, 157.50. HRMS (ESI⁺) exact mass calcd for C₂₃H₃₅O₃ [M+H]⁺ requires m/z 359.2586, found m/z 359.2592.

(4*R*,5*R*)-2-((2*E*,6*E*)-2,6-dimethyltrideca-2,6-dien-10-ynyl)-4,5-dimethyl-1,3-dioxolane (8m)

 Yield: 88%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.11 (t, $J = 7.4$ Hz, 3H), 1.22 (d, $J = 5.6$ Hz, 3H), 1.29 (d, $J = 5.6$ Hz, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 1.99-2.05 (m, 2H), 2.09-2.19 (m, 8H), 2.30 (d, $J = 4.9$ Hz, 2H), 3.58-3.62 (m, 2H), 5.09 (t, $J = 5.1$ Hz, 1H), 5.17 (t, $J = 6.8$ Hz, 1H), 5.24 (t, $J = 6.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.43, 14.34, 16.11, 16.90, 17.10, 17.29, 19.22, 26.70, 27.86, 39.5, 44.94, 77.93, 79.39, 79.68, 81.62, 102.83, 123.08, 127.64, 130.20, 131.14. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{33}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 305.2481, found m/z 305.2481.

In a round bottom flask equipped with a magnetic stirring bar, aldehyde (5.0 mmol) and triethyl amine (9.0 mmol) were dissolved in CH_2Cl_2 (25 mL). The reaction was cooled to 0°C prior to the addition of triisopropylsilyl trifluoromethanesulfonate (5.5 mmol) via syringe. The reaction solution was allowed to stir at room temperature for 1 hour before diluting with CH_2Cl_2 (25 mL). The organic solution was washed with NaHCO_3 (2×30 mL, saturated aqueous solution) and brine (2×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel using appropriate solvents (hexane/EtOAc mixture) to provide the title compounds.⁵¹

Triisopropyl((2-methylprop-1-en-1-yl)oxy)silane (9a)

 ^1H NMR (400 MHz, CDCl_3): δ 1.05-1.16 (m, 21H), 1.52 (s, 3H), 1.61 (s, 3H), 6.12 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.99, 14.69, 17.78, 19.27, 112.42, 133.99. HRMS (ESI^+) exact mass calcd for $\text{C}_{13}\text{H}_{29}\text{OSi}$ $[\text{M}+\text{H}]^+$ requires m/z 229.1988, found m/z 229.1983.

((2-Ethylbut-1-en-1-yl)oxy)triisopropylsilane (9b)

 ^1H NMR (400 MHz, CDCl_3): δ 0.98 (t, $J = 7.5$ Hz, 6H), 1.06-1.19 (m, 21H), 1.90 (q, $J = 7.4$ Hz, 2H), 2.13 (q, $J = 7.5$ Hz, 2H), 6.15 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.02, 12.34, 13.40, 17.80, 19.61, 24.11, 123.71, 133.47. HRMS (ESI^+) exact mass calcd for $\text{C}_{15}\text{H}_{32}\text{OSiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 279.2120, found m/z 279.2107.

(E)-(2-Bromoprop-1-enyloxy)triisopropylsilane (9c)

⁵¹ Yu, J. Q.; Wu, H. C.; Corey, E. J. *Org. Lett.* **2005**, 7, 1415.

^1H NMR (400 MHz, CDCl_3): δ 1.05-1.16 (m, 21H), 1.52 (s, 3H), 1.61 (s, 3H), 6.12 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.99, 14.69, 17.78, 19.27, 112.42, 133.99. HRMS (ESI^+) exact mass calcd for $\text{C}_{12}\text{H}_{25}\text{BrOSiNa}$ $[\text{M}+\text{H}]^+$ requires m/z 315.0756, found m/z 315.0771.

Triisopropyl(prop-1-en-2-yloxy)silane (9d)

^1H NMR (400 MHz, CDCl_3): δ 1.06-1.23 (m, 21H), 1.81 (s, 3H), 4.02 (s, 1H), 4.05 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.59, 17.97, 22.76, 90.48, 156.38. HRMS (ESI^+) exact mass calcd for $\text{C}_{12}\text{H}_{27}\text{OSi}$ $[\text{M}+\text{H}]^+$ requires m/z 215.1831, found m/z 215.1830.

Cyclopentenylxytriisopropylsilane (9e)

^1H NMR (400 MHz, CDCl_3): δ 1.07-1.21 (m, 21H), 1.81-1.89 (m, 2H), 2.24-2.29 (m, 4H), 4.63 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.48, 17.89, 21.48, 28.69, 33.57, 102.18, 155.54. HRMS (ESI^+) exact mass calcd for $\text{C}_{14}\text{H}_{29}\text{OSi}$ $[\text{M}+\text{H}]^+$ requires m/z 241.1988, found m/z 241.1979.

Cyclohexenylxytriisopropylsilane (9f)

^1H NMR (400 MHz, CDCl_3): δ 1.05-1.16 (m, 21H), 1.48-1.56 (m, 2H), 1.63-1.69 (m, 2H), 1.98-2.07 (m, 4H), 4.88 (t, $J = 4.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.64, 18.01, 22.37, 23.26, 23.87, 29.93, 103.63, 150.63. HRMS (ESI^+) exact mass calcd for $\text{C}_{15}\text{H}_{31}\text{OSi}$ $[\text{M}+\text{H}]^+$ requires m/z 255.2144, found m/z 255.2133.

(6,9-Dihydro-5H-benzo[7]annulen-7-yloxy)triisopropylsilane (9g)

^1H NMR (400 MHz, CDCl_3): δ 1.00-1.16 (m, 21H), 2.36-2.40 (m, 3H), 2.92 (t, $J = 6.2$ Hz, 2H), 3.27 (dt, $J_1 = 1.9$ Hz, $J_2 = 6.2$ Hz, 2H), 7.06-7.16 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.58, 17.97, 29.93, 30.70, 34.33, 104.00, 126.06, 126.32, 127.43, 128.00, 140.99, 142.20, 151.65. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{33}\text{OSi}$ $[\text{M}+\text{H}]^+$ requires m/z 317.2301, found m/z 317.2299.

An oven-dried round bottom flask (10 mL) equipped with a magnetic stir bar was charged with 4Å molecular sieves (200 mg), and sealed with a rubber septum. Then

acetal (0.20 mmol) and silyl enol ether (0.3 mmol, 1.5 equiv) were dissolved in dry CH_2Cl_2 (2 mL) and added via syringe. After cooling the solution to -78°C , TiCl_4 (0.24 mL of a 1.0M solution in CH_2Cl_2 , 0.24 mmol, 1.2 equiv) was added dropwisely. The solution was allowed to stir at -78°C for 2 h and then quenched with sat. NaHCO_3 (5 mL). The reaction mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel using appropriate solvents (hexane/ EtOAc mixture) to provide the title compound.

3-(2,2,4a-Trimethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)propan-1-ol (10a)

Yield: 60%. ^1H NMR (400 MHz, CDCl_3): δ 0.91 (s, 3H), 1.12 (s, 3H), 1.13-1.19 (m, 21H), 1.25 (s, 3H), 1.61-1.69 (m, 1H), 1.72-1.81 (m, 2H), 1.83-1.88 (m, 2H), 2.05-2.10 (m, 1H), 2.21 (brs, 1H), 2.46 (dd, $J_1 = 2.6$ Hz, $J_2 = 14.5$ Hz, 1H), 2.85-2.91 (m, 2H), 3.27 (t, $J = 2.8$ Hz, 1H), 3.41-3.45 (m, 1H), 3.80 (t, $J = 5.7$ Hz, 2H), 3.91 (td, $J_1 = 5.2$ Hz, $J_2 = 9.0$ Hz, 1H), 3.96 (d, $J = 10.7$ Hz, 1H), 7.06-7.13 (m, 3H), 7.25 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.12, 18.52, 19.62, 20.12, 25.70, 25.93, 29.54, 32.51, 34.16, 38.59, 41.49, 44.10, 62.15, 68.84, 75.82, 86.40, 124.23, 125.42, 125.51, 129.42, 134.97, 148.61. HRMS (ESI^+) exact mass calcd for $\text{C}_{29}\text{H}_{50}\text{O}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 497.3427, found m/z 497.3416.

3-(2,2,4a-Trimethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)propan-1-ol (10a')

Yield: 28%. ^1H NMR (400 MHz, CDCl_3): δ 0.84 (s, 3H), 0.86-0.88 (m, 1H), 1.11(s, 3H), 1.13-1.26 (m, 21H), 1.17 (s, 3H), 1.51-1.60 (m, 2H), 1.71 (t, $J = 11.6$ Hz, 1H), 1.86-1.90 (m, 2H), 2.03-2.08 (m, 1H), 2.40 (dd, $J_1 = 4.2$ Hz, $J_2 = 12.6$ Hz, 1H), 2.58 (t, $J = 5.4$ Hz, 1H), 2.81-2.96 (m, 2H), 3.18 (dd, $J_1 = 4.3$ Hz, $J_2 = 12.0$ Hz, 1H), 3.58 (d, $J = 10.6$ Hz, 1H), 3.59-3.61 (m, 1H), 3.82 (q, $J = 5.4$ Hz, 1H), 3.89-3.94 (m, 1H), 7.08-7.14 (m, 3H), 7.28 (d, $J = 7.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.96, 14.20, 18.54, 20.75, 22.67, 24.38, 26.19, 29.52, 32.37, 36.31, 37.72, 43.18, 43.63, 62.66, 70.27, 78.45, 82.56, 124.35, 125.72, 129.34, 135.19, 147.25. HRMS (ESI^+) exact mass calcd for

$C_{29}H_{50}O_3SiNa$ $[M+Na]^+$ requires m/z 497.3427, found m/z 497.3421.

2-(2,2,4a-Trimethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)ethanol (11a)

Yield: 57%, colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.09-1.25 (m, 24H), 1.29 (s, 3H), 1.60-1.71 (m, 1H), 1.75-1.82 (m, 2H), 1.99 (brs, 1H), 2.06-2.11 (m, 1H), 2.43 (dd, $J_1 = 2.4$ Hz, $J_2 = 12.3$ Hz, 1H), 2.86-2.96 (m, 2H), 3.33 (t, $J = 2.7$ Hz, 1H), 3.41-3.45 (m, 1H), 3.74-3.83 (m, 3H), 4.01 (d, $J = 10.7$ Hz, 1H), 7.06-7.14 (m, 3H), 7.24-7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.13, 18.53, 18.55, 19.58, 20.12, 25.59, 26.03, 29.55, 34.64, 38.68, 41.69, 44.06, 62.29, 70.93, 75.75, 86.23, 124.26, 125.46, 125.56, 129.43, 134.96, 148.44. HRMS (ESI^+) exact mass calcd for $C_{28}H_{49}O_3Si$ $[M+H]^+$ requires m/z 461.3451, found m/z 461.3444.

2-(2,2,4a-Trimethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)ethanol (11a')

Yield: 32%, colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ 0.86 (s, 3H), 1.10-1.19 (m, 27H), 1.52-1.61 (m, 2H), 1.69-1.75 (m, 1H), 2.03-2.08 (m, 2H), 2.38 (dd, $J_1 = 4.4$ Hz, $J_2 = 12.8$ Hz, 1H), 2.81-2.96 (m, 2H), 3.23 (dd, $J_1 = 4.4$ Hz, $J_2 = 12.4$ Hz, 1H), 3.52-3.56 (m, 1H), 3.58 (d, $J = 10.6$ Hz, 1H), 3.71-3.84 (m, 3H), 7.07-7.16 (m, 3H), 7.26-7.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.93, 14.14, 14.21, 18.54, 18.68, 18.89, 20.75, 24.41, 26.22, 29.53, 36.30, 37.90, 43.35, 43.61, 62.28, 71.28, 78.43, 82.15, 124.35, 125.72, 129.34, 135.20, 147.27. HRMS (ESI^+) exact mass calcd for $C_{28}H_{48}O_3SiNa$ $[M+Na]^+$ requires m/z 483.3270, found m/z 483.3270.

(2R,4R)-4-(((1R,3R,4aR,10aS)-2,2,4a-Trimethyl-1-((triisopropylsilyl)oxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yl)oxy)pentan-2-ol (12a)

Yield: 76%, dr: 82/18. 1H NMR (400 MHz, $CDCl_3$): δ 0.82 (s, 3H), 1.10-1.17 (m, 27H), 1.20 (d, $J = 6.6$ Hz, 3H), 1.22 (d, $J = 6.6$ Hz, 3H), 1.52-1.73 (m, 5H), 2.03-2.08 (m, 1H), 2.38 (dd, $J_1 = 3.9$ Hz, $J_2 = 12.7$ Hz, 1H), 2.80-2.95 (m, 2H), 3.30 (dd, $J_1 = 3.6$ Hz, $J_2 = 12.7$ Hz, 1H), 3.36 (s, 1H), 3.58 (d, $J = 10.1$ Hz, 1H), 3.97-4.00 (m, 1H), 4.15 (brs, 1H), 7.06-7.15 (m, 3H), 7.27 (d, $J = 7.6$ Hz,

1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.94, 14.20, 18.54, 18.56, 19.09, 20.74, 23.52, 24.32, 26.36, 29.54, 36.29, 37.82, 42.63, 43.63, 44.65, 64.52, 70.90, 78.48, 78.59, 124.30, 125.71, 125.74, 129.34, 135.20, 147.22. HRMS (ESI^+) exact mass calcd for $\text{C}_{31}\text{H}_{54}\text{O}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 525.3740, found m/z 525.3758.

(2R,3R)-3-((1R,3R,4aR,10aS)-2,2,4a-Trimethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)butan-2-ol (13a)

Yield: 72%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.92 (s, 3H), 1.10 (s, 3H), 1.11-1.26 (m, 24H), 1.19 (d, J = 6.4 Hz, 3H), 1.29 (s, 3H), 1.62-1.68 (m, 1H), 1.76-1.81 (m, 2H), 2.07-2.10 (m, 1H), 2.36 (dd, J_1 = 2.2 Hz, J_2 = 14.6 Hz, 1H), 2.53 (brs, 1H), 2.85-2.92 (m, 2H), 3.44-3.47 (m, 2H), 3.69 (p, J = 6.3 Hz, 1H), 3.98 (d, J = 10.8 Hz, 1H), 7.07-7.13 (m, 3H), 7.26 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.12, 14.75, 18.52, 18.54, 19.95, 20.06, 25.72, 26.61, 29.58, 35.18, 38.56, 41.25, 43.81, 71.21, 75.63, 77.26, 81.21, 124.48, 125.49, 125.59, 129.38, 134.95, 148.25. HRMS (ESI^+) exact mass calcd for $\text{C}_{30}\text{H}_{52}\text{O}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 511.3583, found m/z 511.3570.

(2R,3R)-3-((1R,3R,4aR,10aS)-2,2-Diethyl-4a-methyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)butan-2-ol (13b)

Yield: 75%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.86 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.6 Hz, 3H), 1.13-1.20 (m, 27H), 1.26 (s, 3H), 1.61-1.78 (m, 5H), 1.82-1.91 (m, 1H), 2.03-2.10 (m, 2H), 2.31 (brs, 1H), 2.38 (dd, J_1 = 2.1 Hz, J_2 = 14.9 Hz, 1H), 2.85-2.98 (m, 2H), 3.65-3.71 (m, 3H), 4.13 (d, J = 10.9 Hz, 1H), 7.06-7.14 (m, 3H), 7.23-7.25 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.51, 10.00, 13.57, 14.26, 18.61, 18.78, 18.91, 20.08, 23.56, 23.61, 26.41, 29.44, 32.75, 38.53, 43.25, 45.53, 71.54, 73.56, 74.70, 76.79, 124.14, 125.50, 125.53, 129.41, 134.96, 148.73. HRMS (ESI^+) exact mass calcd for $\text{C}_{32}\text{H}_{57}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 517.4077, found m/z 517.4081.

(2R,3R)-3-((1R,3R,4aR,10aS)-2-Bromo-2,4a-dimethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)butan-2-ol (13c)

Yield: 54%, dr: 60/40, colorless Oil. ^1H NMR (400 MHz, CDCl_3): δ 1.07-1.18 (m, 21H), 1.23 (d, J = 6.4 Hz, 3H), 1.29 (d, J = 6.1 Hz, 3H), 1.32 (s, 3H), 1.36-1.42 (m, 1H),

1.70-1.79 (m, 1H), 1.82 (s, 3H), 1.87-1.91 (m, 1H), 2.14-2.18 (m, 1H), 2.38 (d, $J = 6.1$ Hz, 1H), 2.44 (dd, $J_1 = 2.8$ Hz, $J_2 = 14.4$ Hz, 1H), 2.81-2.98 (m, 2H), 3.72-3.79 (m, 2H), 3.96 (t, $J = 2.9$ Hz, 1H), 4.40 (d, $J = 10.2$ Hz, 1H), 7.07-7.13 (m, 3H), 7.20-7.26 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.11, 15.01, 18.61, 19.59, 20.52, 24.15, 26.85, 29.28, 36.24, 38.19, 46.15, 71.34, 75.85, 76.93, 78.37, 79.87, 124.07, 125.69, 125.77, 129.51, 134.53, 147.67. HRMS (ESI^+) exact mass calcd for $\text{C}_{29}\text{H}_{50}\text{BrO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 553.2713, found m/z 553.2720.

(2R,3R)-3-((4bR,6R,10aR,10bS)-4b-Methyl-10a-(triisopropylsilyloxy)-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysen-6-yloxy)butan-2-ol (13f)

Yield: 58%, dr: 75/25, colorless Oil. ^1H NMR (400 MHz, CDCl_3): δ 1.13-1.20 (m, 24H), 1.35-1.43 (m, 6H), 1.58-1.75 (m, 4H), 1.85-2.04 (m, 6H), 2.19-2.39 (m, 2H), 2.77-3.04 (m, 3H), 2.85-2.92 (m, 2H), 3.33-3.37 (m, 0.25H) for the minor, 3.39-3.46 (m, 0.75H) for the major, 3.52-3.58 (m, 1H), 4.28-4.35 (m, 1H), 7.05-7.15 (m, 3H), 7.26-7.28 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.12, 14.75, 18.52, 18.54, 19.95, 20.06, 25.72, 26.61, 29.58, 35.18, 38.56, 41.25, 43.81, 71.21, 75.63, 77.26, 81.21, 124.48, 125.49, 125.59, 129.38, 134.95, 148.25. HRMS (ESI^+) exact mass calcd for $\text{C}_{32}\text{H}_{54}\text{O}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 537.3740, found m/z 537.3748.

(2R,3R)-3-((8S,9R,12R,14R)-9-Methyl-14-(triisopropylsilyloxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-12-yloxy)butan-2-ol (13e)

Yield: 45%, dr: 86/14, colorless Oil. ^1H NMR (400 MHz, CDCl_3): δ 1.11-1.15 (m, 21H), 1.14 (d, $J = 6.3$ Hz, 3H), 1.19 (d, $J = 6.4$ Hz, 3H), 1.34 (s, 3H), 1.41-1.51 (m, 2H), 1.54-1.62 (m, 2H), 1.70-1.73 (m, 3H), 1.93-1.98 (m, 2H), 2.09-2.14 (m, 1H), 2.39-2.48 (m, 2H), 2.81 (brs, 1H), 2.84-2.93 (m, 1H), 2.97-3.04 (m, 1H), 3.39 (p, $J = 6.3$ Hz, 1H), 3.52 (p, $J = 6.3$ Hz, 1H), 4.15 (td, $J_1 = 4.5$ Hz, $J_2 = 12.4$ Hz, 1H), 7.06-7.18 (m, 3H), 7.31 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.02, 16.71, 18.50, 18.61, 19.20, 19.78, 21.90, 25.98, 30.11, 37.32, 38.41, 39.23, 43.71, 51.41, 71.15, 72.64, 78.08, 86.32, 124.27, 125.55, 125.75, 129.20, 134.87, 148.57. HRMS (ESI^+) exact mass calcd for $\text{C}_{31}\text{H}_{52}\text{O}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 523.3583, found m/z 523.3599.

(2R,3R)-3-((1R,3R,4aR,10aS)-2,2,4a,8-Tetramethyl-1-(triisopropylsilyloxy)-1,2,3,

4,4a,9,10,10a-octahydrophenanthren-3-yloxy)butan-2-ol (16b)

Yield: 62%, colorless Oil. ^1H NMR (400 MHz, CDCl_3): δ 0.92 (s, 3H), 1.05-1.20 (m, 27H), 1.19 (d, $J = 6.3$ Hz, 3H), 1.21 (s, 3H), 1.59-1.70 (m, 1H), 1.74-1.82 (m, 2H), 2.12-2.20 (m, 1H), 2.20 (s, 3H), 2.36 (dd, $J_1 = 2.2$ Hz, $J_2 = 14.6$ Hz, 1H), 2.56-2.65 (m, 1H), 2.80 (dd, $J_1 = 6.3$ Hz, $J_2 = 17.7$ Hz, 1H), 3.44 (brs, 1H), 3.46 (p, $J = 6.3$ Hz, 1H), 3.69 (p, $J = 6.3$ Hz, 1H), 3.98 (d, $J = 10.7$ Hz, 1H), 6.98 (d, $J = 7.2$ Hz, 1H), 7.06 (t, $J = 7.6$ Hz, 1H), 7.16 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.14, 14.73, 18.52, 18.55, 19.92, 20.02, 25.71, 26.71, 27.28, 35.49, 38.62, 41.10, 43.24, 71.23, 75.70, 77.21, 81.28, 122.24, 125.34, 127.13, 133.50, 136.68, 148.27. HRMS (ESI^+) exact mass calcd for $\text{C}_{31}\text{H}_{54}\text{O}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 525.3740, found m/z 525.3751.

(2R,3R)-3-((1R,3R,4aR,10aS)-8-Methoxy-2,2,4a-trimethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)butan-2-ol (16c)

Yield: 67%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.92 (s, 3H), 1.10-1.19 (m, 27H), 1.18 (d, $J = 6.3$ Hz, 3H), 1.29 (s, 3H), 1.49-1.62 (m, 1H), 1.74-1.81 (m, 2H), 2.11-2.16 (m, 1H), 2.35 (dd, $J_1 = 2.2$ Hz, $J_2 = 14.6$ Hz, 1H), 2.52 (d, $J = 2.8$ Hz, 1H), 2.55-2.62 (m, 1H), 2.89 (dd, $J_1 = 6.4$ Hz, $J_2 = 18.3$ Hz, 1H), 3.44 (brs, 1H), 3.45 (p, $J = 6.4$ Hz, 1H), 3.69 (dt, $J_1 = 2.8$ Hz, $J_2 = 6.3$ Hz, 1H), 3.81 (s, 3H), 3.96 (d, $J = 10.8$ Hz, 1H), 6.66 (d, $J = 7.9$ Hz, 1H), 6.91 (d, $J = 7.8$ Hz, 1H), 7.12 (t, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.13, 14.73, 18.53, 18.55, 19.42, 19.94, 23.65, 25.72, 26.49, 35.37, 38.51, 41.14, 43.38, 55.23, 71.20, 75.66, 77.22, 81.27, 106.68, 116.63, 123.93, 125.97, 149.65, 157.27. HRMS (ESI^+) exact mass calcd for $\text{C}_{31}\text{H}_{54}\text{O}_4\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 541.3689, found m/z 541.3701.

(2R,3R)-3-((1R,3R,4aR,10aS)-2,2,4a,6-Tetramethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)butan-2-ol (16d)

Yield: 73%, colorless Oil. ^1H NMR (400 MHz, CDCl_3): δ 0.92 (s, 3H), 1.05-1.20 (m, 27H), 1.20 (d, $J = 6.3$ Hz, 3H), 1.28 (s, 3H), 1.56-1.67 (m, 1H), 1.72-1.82 (m, 2H), 2.05-2.10 (m, 1H), 2.30 (s, 3H), 2.35 (dd, $J_1 = 2.2$ Hz, $J_2 = 14.6$ Hz, 1H), 2.76-2.91 (m, 2H), 3.45 (brs, 1H), 3.46 (p, $J =$

6.4 Hz, 1H), 3.69 (p, $J = 6.4$ Hz, 1H), 3.97 (d, $J = 10.8$ Hz, 1H), 6.98 (dd, $J_1 = 1.0$ Hz, $J_2 = 7.7$ Hz, 1H), 7.06 (d, $J = 7.7$ Hz, 1H), 7.06 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.11, 14.78, 18.52, 18.54, 19.94, 20.11, 21.22, 25.73, 26.60, 29.21, 35.23, 38.51, 41.22, 43.90, 71.26, 75.64, 77.35, 81.27, 125.05, 126.38, 129.27, 131.77, 134.90, 148.08. HRMS (ESI^+) exact mass calcd for $\text{C}_{31}\text{H}_{55}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 503.3920, found m/z 503.3932.

(2R,3R)-3-((1R,3R,4aR,10aS)-5,6,7-Trimethoxy-2,2,4a-trimethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)butan-2-ol (16e)

Yield: 76%, colorless Oil. ^1H NMR (400 MHz, CDCl_3): δ 0.92 (s, 3H), 1.03-1.21 (m, 27H), 1.20 (d, $J = 6.4$ Hz, 3H), 1.39 (s, 3H), 1.43-1.52 (m, 1H), 1.59 (dd, $J_1 = 3.5$ Hz, $J_2 = 14.9$ Hz, 1H), 1.69-1.75 (m, 1H), 1.99-2.02 (m, 1H), 2.73-2.85 (m, 2H), 3.14 (dd, $J_1 = 2.2$ Hz, $J_2 = 14.9$ Hz, 1H), 3.37 (t, $J = 2.8$ Hz, 1H), 3.45 (p, $J = 6.1$ Hz, 1H), 3.69 (p, $J = 6.1$ Hz, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 3.92 (s, 3H), 4.01 (d, $J = 10.9$ Hz, 1H), 6.36 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.05, 14.93, 18.46, 18.51, 18.77, 19.63, 20.06, 22.43, 25.70, 32.06, 33.89, 39.94, 41.28, 46.13, 55.70, 60.45, 60.54, 71.28, 75.31, 77.35, 81.95, 107.48, 131.80, 133.17, 140.57, 151.26, 153.13. HRMS (ESI^+) exact mass calcd for $\text{C}_{33}\text{H}_{58}\text{O}_6\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 601.3900, found m/z 601.3896.

(2R,3R)-3-((1R,3R,4aR,10aS)-6-Chloro-2,2,4a-trimethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)butan-2-ol (16g)

Yield: 50%, colorless Oil. ^1H NMR (400 MHz, CDCl_3): δ 0.92 (s, 3H), 1.08-1.16 (m, 27H), 1.19 (d, $J = 6.3$ Hz, 3H), 1.27 (s, 3H), 1.58-1.66 (m, 1H), 1.73-1.79 (m, 2H), 2.06-2.13 (m, 1H), 2.29 (dd, $J_1 = 2.2$ Hz, $J_2 = 14.5$ Hz, 1H), 2.72-2.95 (m, 2H), 3.43-3.52 (m, 2H), 3.70 (p, $J = 6.4$ Hz, 1H), 3.96 (d, $J = 10.7$ Hz, 1H), 6.98 (d, $J = 8.2$ Hz, 1H), 7.05 (dd, $J_1 = 2.1$ Hz, $J_2 = 8.2$ Hz, 1H), 7.24 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.29, 14.09, 14.64, 17.70, 18.41, 18.51, 18.71, 19.86, 25.66, 26.52, 28.95, 35.00, 38.70, 41.20, 43.52, 71.17, 75.46, 77.03, 80.92, 124.59, 125.59, 130.70, 131.13, 133.35, 150.08. HRMS (ESI^+) exact mass calcd for $\text{C}_{30}\text{H}_{52}\text{ClO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 523.3374, found m/z 523.3388.

(2R,3R)-3-((2R,4R,4aS,11bR)-3,3,11b-Trimethyl-11-tosyl-4-(triisopropylsilyloxy)-2,3,4,4a,5,6,11,11b-octahydro-1H-benzo[a]carbazol-2-yloxy)butan-2-ol (16h) Yield: 57%, colorless Oil. ^1H NMR (400 MHz, CDCl_3):

δ 0.86 (s, 3H), 1.10-1.22 (m, 27H), 1.62 (s, 3H),
1.72-1.76 (m, 2H), 1.87 (s, 3H), 2.11-2.19 (m, 1H),
2.27 (s, 3H), 2.58-2.69 (m, 2H), 2.75 (dd, $J_1 = 6.1$ Hz,

$J_2 = 17.0$ Hz, 1H), 3.34-3.50 (m, 2H), 3.54-3.57 (m, 1H), 3.77 (dd, $J_1 = 3.7$ Hz, $J_2 = 11.9$ Hz, 1H), 3.81 (d, $J = 2.4$ Hz, 1H), 7.07 (d, $J = 8.1$ Hz, 2H), 7.14-7.25 (m, 3H), 7.45 (d, $J = 8.4$ Hz, 2H), 8.05 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.17, 15.76, 18.75, 18.88, 19.15, 20.69, 21.47, 22.75, 22.87, 24.41, 24.68, 35.98, 40.28, 40.94, 45.92, 71.33, 74.11, 75.86, 84.54, 116.86, 118.05, 121.40, 123.82, 124.40, 126.52, 129.25, 131.00, 135.61, 138.69, 143.90, 147.03. HRMS (ESI^+) exact mass calcd for $\text{C}_{39}\text{H}_{60}\text{NO}_5\text{SSi}$ $[\text{M}+\text{H}]^+$ requires m/z 682.3961, found m/z 682.3958.

(2R,3R)-3-((1R,3R,4aR,10aS)-2,2-Dimethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)butan-2-ol (16i) Yield: 64%, colorless Oil. ^1H NMR (400 MHz, CDCl_3): δ

0.88 (s, 3H), 1.10-1.19 (m, 30H), 1.31 (q, $J = 12.2$ Hz, 1H),
1.66-1.84 (m, 3H), 2.62 (td, $J_1 = 4.2$ Hz, $J_2 = 12.4$ Hz, 1H),
2.84-2.94 (m, 4H), 3.35-3.41 (m, 1H), 3.50-3.56 (m, 1H),

3.69 (dd, $J_1 = 4.5$ Hz, $J_2 = 11.4$ Hz, 1H), 3.75 (d, $J = 1.3$ Hz, 1H), 7.07-7.17 (m, 3H), 7.36 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.30, 14.07, 15.83, 17.72, 18.66, 18.70, 19.93, 24.91, 26.86, 30.43, 32.17, 34.52, 40.27, 41.05, 71.17, 77.28, 77.39, 83.31, 125.54, 125.73, 126.36, 128.97, 136.52, 140.19. HRMS (ESI^+) exact mass calcd for $\text{C}_{29}\text{H}_{50}\text{O}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 497.3427, found m/z 497.3445.

(2R,3R)-3-((1R,3R,4aR,9aS)-2,2,4a-Trimethyl-1-(triisopropylsilyloxy)-2,3,4,4a,9,9a-hexahydro-1H-fluoren-3-yloxy)butan-2-ol (16j) Yield: 59%, colorless Oil. ^1H NMR (400 MHz, CDCl_3): δ

0.96 (s, 3H), 1.09-1.20 (m, 34H), 1.63 (dd, $J_1 = 11.3$ Hz, $J_2 = 13.9$ Hz, 1H), 2.06 (t, $J = 8.9$ Hz, 1H), 2.13 (dd, $J_1 = 4.1$ Hz, $J_2 = 14.0$ Hz, 1H), 2.77 (dd, $J_1 = 9.1$ Hz, $J_2 = 15.0$ Hz,

1H), 3.20 (p, $J = 6.3$ Hz, 1H), 3.27 (d, $J = 14.5$ Hz, 1H), 3.45 (dd, $J_1 = 4.2$ Hz, $J_2 = 11.3$ Hz, 1H), 3.52 (p, $J = 6.3$ Hz, 1H), 3.74 (d, $J = 10.1$ Hz, 1H), 7.13-7.17 (m, 1H), 7.21-7.28 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.29, 13.16, 13.64, 14.21, 15.76,

17.71, 18.55, 18.63, 25.81, 33.63, 34.22, 42.39, 43.09, 51.73, 71.08, 75.38, 76.55, 79.44, 125.62, 127.94, 128.34, 128.80, 129.11, 143.27. HRMS (ESI⁺) exact mass calcd for C₂₉H₅₁O₃Si [M+H]⁺ requires *m/z* 475.3607, found *m/z* 475.3596.

(2*R*,3*R*)-3-((3*aR*,5*R*,7*R*,7*aS*)-3-(1-Chloropropylidene)-3*a*,6,6-trimethyl-7-(triisopropylsilyloxy)octahydro-1*H*-inden-5-yloxy)butan-2-ol (16k)

Yield: 74%, colorless Oil, Dr: 1/1. ¹H NMR (400 MHz, CDCl₃): δ 0.94 (s, 6H), 1.05-1.17 (m, 74H), 1.47-1.69 (m, 5H), 1.76-1.82 (m, 2H), 1.89-1.96 (m, 3H), 2.06-2.10 (m, 1H), 2.16 (d, *J* = 12.3 Hz, 1H), 2.26-2.56 (m, 7H), 3.31-3.38 (m, 4H), 3.65 (t, *J* = 6.4 Hz, 1H), 3.84 (d, *J* = 10.7 Hz, 1H), 3.92 (d, *J* = 10.7 Hz, 1H);

¹³C NMR (100 MHz, CDCl₃): δ 13.41, 13.74, 13.86, 14.02, 14.62, 14.70, 17.69, 18.44, 18.48, 20.03, 20.08, 20.12, 21.04, 22.15, 22.21, 23.91, 24.87, 25.53, 29.01, 32.36, 33.14, 34.58, 35.26, 41.21, 41.75, 42.27, 44.28, 47.47, 51.65, 71.13, 74.73, 75.23, 77.63, 81.05, 82.60, 128.38, 128.60, 143.58, 145.63. HRMS (ESI⁺) exact mass calcd for C₂₈H₅₃ClO₃SiK [M+K]⁺ requires *m/z* 539.3090, found *m/z* 539.3096.

(2*R*,3*R*)-3-((5*R*,6*aS*,6*bS*,12*bS*,14*aS*,14*bR*)-9-Methoxy-6*a*,12*b*-dimethyl-14*b*-(triisopropylsilyloxy)-1,2,3,4,4*a*,5,6,6*a*,6*b*,7,8,12*b*,13,14,14*a*,14*b*-hexadecahydropicen-5-yloxy)butan-2-ol (17)

Yield: 58%, dr: 82/18, colorless Oil. ¹H NMR (400 MHz, CDCl₃): δ 1.05-1.18 (m, 33H), 1.24 (s, 3H), 1.33-1.38 (m, 3H), 1.48-1.71 (m, 8H), 1.90-1.98 (m, 3H), 2.22 (d, *J* = 12.6 Hz, 1H), 2.45 (d, *J* = 12.8 Hz, 1H), 2.53-2.62 (m, 1H), 2.78 (brs, 1H), 2.89 (dd, *J*₁ = 6.4 Hz, *J*₂ = 18.7 Hz, 1H),

3.27-3.35 (m, 1H), 3.47-3.56 (m, 1H), 3.80 (s, 3H), 4.11-4.24 (m, 1H), 6.64 (d, *J* = 8.0 Hz, 0.82H) for the major, 6.67 (d, *J* = 8.0 Hz, 0.18H) for the minor, 6.89 (d, *J* = 8.0 Hz, 0.82H), 6.93 (d, *J* = 8.0 Hz, 0.18H), 7.12 (t, *J* = 7.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.48, 16.60, 17.25, 18.49, 18.57, 18.76, 18.86, 23.19, 23.68, 24.67, 25.33, 26.23, 36.64, 38.07, 38.14, 38.75, 39.00, 40.77, 45.30, 49.81, 54.65, 55.23, 71.24, 71.66, 78.30, 79.48, 106.41, 116.46, 124.15, 126.13, 151.70, 157.04. HRMS (ESI⁺) exact mass calcd for C₃₈H₆₄O₄SiNa [M+Na]⁺ requires *m/z* 635.4472, found *m/z* 635.4472.

(2*R*,3*R*)-3-((6*R*,8*S*,9*S*,1*R*,13*S*,14*S*)-17-(1-Chloropropylidene)-8,13-dimethyl-10-(triisopropylsilyloxy)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-6-yloxy)butan-2-

ol (22)

Yield: 61%, dr: 78/22, colorless Oil. ^1H NMR (400 MHz, CDCl_3): δ 1.04-1.14 (m, 37H), 1.32-1.84 (m, 15H), 1.91-2.03 (m, 2H), 2.15-2.55 (m, 5H), 2.75 (brs, 1H), 3.22-3.29 (m, 1H), 3.45-3.51 (m, 1H), 4.13-4.18 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.29, 13.34, 13.72, 14.46, 16.50, 17.70, 18.38, 18.55, 18.71, 18.77, 18.85, 18.93, 19.77, 21.24, 21.33, 21.99, 23.16, 23.25, 23.66, 25.32, 28.69, 32.08, 38.08, 38.29, 38.35, 38.59, 39.19, 39.29, 41.29, 45.71, 46.49, 50.19, 55.64, 63.30, 71.05, 71.20, 79.19, 79.45, 127.97, 144.18, 146.48. HRMS (ESI^+) exact mass calcd for $\text{C}_{35}\text{H}_{64}\text{ClO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 595.4313, found m/z 595.4315.

(2R,3R)-3-(((3aR,5R,12aR,12bS)-3-(1-Chloropropylidene)-3a-methyl-12a-((triisopropylsilyl)oxy)-1,2,3,3a,4,5,5a,6,11,12,12a,12b-dodecahydrobenzo[4,5]cyclohepta[1,2-e]inden-5-yl)oxy)butan-2-ol (20)

Yield: 53%, colorless Oil. ^1H NMR (400 MHz, CDCl_3): δ 0.96-1.13 (m, 21H), 1.15 (t, $J = 7.3$ Hz, 3H), 1.19 (d, $J = 6.1$ Hz, 3H), 1.20 (d, $J = 6.1$ Hz, 3H), 1.23 (s, 3H), 1.56 (t, $J = 12.3$ Hz, 2H), 1.68-1.78 (m, 3H), 2.00 (dd, $J_1 = 4.4$ Hz, $J_2 = 11.6$ Hz, 1H), 2.22-2.28 (m, 3H), 2.43-2.67 (m, 7H), 3.02 (d, $J = 14.3$ Hz, 1H), 3.35 (p, $J = 6.3$ Hz, 1H), 3.62 (p, $J = 6.3$ Hz, 1H), 4.23 (td, $J_1 = 4.1$ Hz, $J_2 = 12.0$ Hz, 1H), 7.06-7.13 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.49, 14.35, 17.50, 18.58, 18.82, 19.76, 21.75, 28.64, 29.76, 30.09, 31.57, 38.87, 39.64, 46.24, 48.61, 50.54, 71.27, 74.87, 79.36, 79.95, 126.36, 126.43, 127.66, 128.12, 128.97, 140.71, 142.83, 144.91. HRMS (ESI^+) exact mass calcd for $\text{C}_{35}\text{H}_{57}\text{OCl}_3\text{Si}$ $[\text{M}+\text{Na}]^+$ requires m/z 611.3663, found m/z 611.3668.

(3aR,5R,12aR,12bS)-5-(((2R,3R)-3-Hydroxybutan-2-yl)oxy)-3a-methyl-12a-((triisopropylsilyl)oxy)-1,3a,4,5,5a,6,11,12,12a,12b-decahydrobenzo[4,5]cyclohepta[1,2-e]inden-3(2H)-one (21)

The crude product was dissolved in CH_2Cl_2 and cooled to -78°C . O_3 was inlet into the reaction mixture until the color turned to blue. Me_2S (0.5 mL) was added and stirred for 0.5 h. The reaction mixture was concentrated and purified by flash chromatography on silica gel to provide the title compound.

Yield: 75%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.89-1.05 (m, 21H), 1.16 (d, $J = 6.2$ Hz, 3H), 1.19 (d, $J = 6.2$ Hz, 3H), 1.23 (s, 3H), 1.46 (t, $J = 12.5$ Hz, 1H), 1.57-1.62 (m, 1H), 1.94-2.07 (m, 4H), 2.17-2.36 (m, 3H), 2.50-2.72 (m, 5H), 3.04 (d, $J = 14.2$ Hz, 1H), 3.37 (p, $J = 6.2$ Hz, 1H), 3.61 (p, $J = 6.2$ Hz, 1H), 4.21-4.26 (m, 1H), 7.06-7.13 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.35, 17.11, 17.31, 18.23, 18.56, 18.67, 18.92, 29.73, 30.13, 32.83, 35.47, 38.51, 44.16, 48.24, 51.32, 71.24, 73.71, 78.65, 80.37, 126.49, 126.63, 129.06, 140.58, 142.40, 218.24. HRMS (ESI^+) exact mass calcd for $\text{C}_{32}\text{H}_{52}\text{O}_4\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 551.3533, found m/z 551.3529.

To a round bottom flask equipped with a magnetic stir, the alcohol (1.0 equiv.) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0°C . PCC (1.2 equiv) were added and then the reaction mixture was allowed to stirred for 2 h at room temperature. The reaction mixture was diluted with Et_2O and filtered through silicone gel (3 cm). The filtrate was concentrated under reduce pressure gave the aldehyde, yield: 87%.

The aldehyde was dissolved in 3 M KOH/MeOH solution. Then reaction mixture was stirred at room temperature for 10 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with brine and dried over Na_2SO_4 . Concentrated under reduce pressure gave the crude product, yield: 70%.

The crude product was dissolved in THF (2 mL), then TBAF (2.0 equiv) was added and the reaction mixture was stirred for 4 h at 60°C . The reaction mixture was concentrated and purified by flash chromatography to give the 1,3-diol, yield: 87%.

2,2,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1,3-diol (15a)

for $C_{17}H_{24}O_2Na$ $[M+Na]^+$ requires m/z 283.1674, found m/z 283.1678.

2,2,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1,3-diol (15a')

1H NMR (400 MHz, $CDCl_3$): δ 0.83 (s, 3H), 1.11 (s, 3H), 1.20 (s, 3H), 1.46 (brs, 2H), 1.60-1.71 (m, 3H), 2.14-2.19 (m, 1H), 2.33 (dd, $J_1 = 4.3$ Hz, $J_2 = 12.5$ Hz, 1H), 2.86-2.98 (m, 2H), 3.30 (d, $J = 10.3$ Hz, 1H), 3.70 (d, $J = 12.1$ Hz, 1H), 7.08-7.16 (m, 3H), 7.25-7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.47, 20.02, 24.23, 25.26, 28.64, 36.59, 41.61, 42.30, 42.63, 73.45, 76.28, 123.99, 125.78, 125.85, 129.43, 135.13, 146.94. HRMS (ESI $^+$) exact mass calcd for $C_{17}H_{25}O_2$ $[M+H]^+$ requires m/z 261.1855, found m/z 261.1862.

The ketone was dissolved in CH_2Cl_2 and then *m*-CPBA (1.2 equiv) was added. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with Sat. Na_2CO_3 . The organic layer was dried over Na_2SO_4 and concentrated under reduce pressure to give the crude Baeyer-Villiger rearrangement product.

The crude Baeyer-Villiger rearrangement product and TsOH (100 mg) were dissolved in MeOH (10 mL). The reaction was stirred for 4 h at 60 $^{\circ}C$. After cooling to room temperature, the reaction mixture was concentrated under reduce pressure and purified by flash chromatography to give **26**.

(1R,3R,4aR,10aS)-6-Chloro-2,2,4a-trimethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-ol (26)

1H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 3H), 1.13-1.25 (m, 24H), 1.29 (s, 3H), 1.58 (brs, 1H), 1.60-1.69 (m, 1H), 1.75 (q, $J = 10.2$ Hz, 1H), 1.95 (dd, $J_1 = 3.5$ Hz, $J_2 = 14.4$ Hz, 1H), 2.09 (dd, $J_1 = 7.3$ Hz,

$J_2 = 12.4$ Hz, 1H), 2.25 (dd, $J_1 = 2.5$ Hz, $J_2 = 14.4$ Hz, 1H), 2.79-2.91 (m, 2H), 3.80 (t, $J = 2.9$ Hz, 1H), 4.05 (d, $J = 10.4$ Hz, 1H), 6.99 (d, $J = 8.2$ Hz, 1H), 7.05 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.2$ Hz, 1H), 7.20 (d, $J = 1.9$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.12, 18.51, 18.54, 19.98, 25.17, 26.71, 28.97, 38.80, 39.59, 41.37, 43.90, 75.32, 77.73, 124.60, 125.48, 130.68, 131.10, 133.27, 150.41.

(1R,3R,4aR,10aS)-6-Chloro-2,2,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1,3-diol (27)

^1H NMR (400 MHz, CDCl_3): δ 0.89 (s, 3H), 1.19 (s, 3H), 1.28 (s, 3H), 1.57 (brs, 2H), 1.64-1.76 (m, 2H), 1.97 (dd, $J_1 = 3.3$ Hz, $J_2 = 14.4$ Hz, 1H), 2.18-2.21 (m, 1H), 2.28 (dd, $J_1 = 2.7$ Hz, $J_2 = 14.4$ Hz, 1H), 2.57-2.95 (m, 2H), 3.75 (d, $J = 10.3$ Hz, 1H), 3.84 (t, $J = 3.0$ Hz, 1H), 7.01 (d, $J = 8.2$ Hz, 1H), 7.06 (dd, $J_1 = 2.1$ Hz, $J_2 = 8.2$ Hz, 1H), 7.20 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 18.94, 19.26, 24.16, 26.49, 27.98, 38.48, 39.33, 40.27, 42.81, 73.42, 77.33, 124.17, 125.59, 130.79, 131.11, 133.24, 150.22.

(R)-3-((1R,3R,4aR,10aS)-2,2,4a-Trimethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)butan-2-one (23)

Yield: 88%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.84 (s, 3H), 1.07-1.11 (m, 24H), 1.15 (s, 3H), 1.22 (d, $J = 6.8$ Hz, 3H), 1.53-1.61 (m, 1H), 1.66-1.76 (m, 2H), 1.97-2.04 (m, 1H), 2.14 (s, 3H), 2.28 (dd, $J_1 = 2.4$ Hz, $J_2 = 14.6$ Hz, 1H), 2.74-2.87 (m, 2H), 3.37 (t, $J = 2.8$ Hz, 1H), 3.93 (q, $J = 6.8$ Hz, 1H), 3.98 (d, $J = 10.7$ Hz, 1H), 7.01-7.05 (m, 3H), 7.14 (d, $J = 7.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.14, 16.50, 18.51, 18.52, 19.55, 20.10, 25.13, 25.76, 26.27, 29.52, 34.86, 38.52, 41.49, 43.95, 75.55, 79.60, 82.48, 124.26, 125.47, 125.60, 129.40, 148.39, 210.89.

(1R,3R,4aR,10aS)-2,2,4a-Trimethyl-1-(triisopropylsilyloxy)-1,2,3,4,4a,5,6,7,8,9,10,10a-dodecahydrophenanthren-3-ol (24)

To a round bottom flask equipped with a magnetic stir, compound was dissolved in Et₂NH. Li was added and the reaction mixture was refluxed for 4h. NH₄Cl solution was added slowly to quench the reaction. The aqueous solution was extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduce pressure. The crude product was purified by flash chromatography to give the title compound. Yield: 79%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.91 (s, 3H), 1.11-1.18 (m, 30H), 1.33-1.46 (m, 4H), 1.56-1.67 (m, 2H), 1.69-1.77 (m, 2H), 1.81-1.99 (m, 5H), 3.68 (t, *J* = 3.0 Hz, 1H), 3.95 (d, *J* = 10.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.10, 18.50, 18.53, 19.55, 19.99, 21.79, 22.89, 23.72, 23.87, 25.19, 30.66, 31.58, 37.80, 38.74, 41.62, 45.19, 75.56, 78.12, 125.71, 137.80.

To a round bottom flask equipped with a magnetic stir, diethoxy acetal (1.0 mmol), *p*-toluenesulfonic acid monohydrate (0.1 mmol) and ethane-1,2-diol (2.0 mmol) were dissolved in CH₂Cl₂ (10 mL). After stirring for 8h at room temperature, the reaction was quenched with triethylamine (0.2 mL). The reaction mixture was purified by flash chromatography on silica gel using diethyl ether/hexane to provide the title compound.

(*E*)-2-(2-Methyl-5-phenylpent-2-enyl)-1,3-dioxolane (6a)

Yield: 92%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.60 (s, 3H), 2.31-2.37 (m, 4H), 2.66 (t, *J* = 7.9 Hz, 2H), 3.83-3.89 (m, 2H), 3.93-3.99 (m, 2H), 4.91 (t, *J* = 4.8 Hz, 1H), 5.33 (dt, *J*₁ = 1.2 Hz, *J*₂ = 7.2 Hz, 1H), 7.16-7.20 (m, 3H), 7.25-7.29 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 16.75, 30.06, 35.92, 44.09, 64.80, 103.95, 125.72, 127.22, 128.25, 128.47, 130.88, 142.25. HRMS (ESI⁺) exact mass calcd for C₁₅H₂₀O₂Na [M+Na]⁺ requires *m/z* 255.1361, found *m/z* 255.1372.

(*E*)-2-(2-Methyl-5-*o*-tolylpent-2-enyl)-1,3-dioxolane (6c)

Yield: 89%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.66 (s, 3H), 2.29-2.35 (m, 7H), 2.62-2.66 (m, 2H), 3.83-3.89 (m, 2H), 3.94-4.00 (m, 2H), 4.91 (dt, *J*₁ = 1.6 Hz, *J*₂ = 5.2 Hz, 1H), 5.37 (t, *J* = 6.8 Hz, 1H), 7.11-7.14 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 16.71, 19.33, 28.79, 33.21, 44.11, 64.80, 103.94, 125.88, 127.33, 128.86, 130.08, 130.83, 135.90, 140.38. HRMS (ESI⁺) exact mass calcd for C₁₆H₂₃O₂ [M+H]⁺

requires m/z 247.1698, found m/z 247.1701.

(E)-2-(5-(4-Methoxyphenyl)-2-methylpent-2-enyl)-1,3-dioxolane (6b)

Yield: 94%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.63 (s, 3H), 2.27-2.33 (m, 4H), 2.59 (dd, $J_1 = 7.4$ Hz, $J_2 = 8.3$ Hz, 2H), 3.77 (s, 3H), 3.81-3.85 (m, 2H), 3.94-3.98 (m, 2H), 4.90 (t, $J = 5.1$ Hz, 1H), 5.31 (t, $J = 6.8$ Hz, 1H), 6.81 (d, $J = 8.5$ Hz, 2H), 7.09 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.78, 30.31, 34.99, 44.11, 55.24, 64.79, 103.97, 113.65, 127.30, 129.34, 130.80, 134.35, 157.72. HRMS (ESI^+) exact mass calcd for $\text{C}_{16}\text{H}_{23}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires m/z 263.1647, found m/z 263.1641.

(E)-2-(2-Methyl-5-p-tolylpent-2-enyl)-1,3-dioxolane (6d)

Yield: 88%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.65 (s, 3H), 2.31-2.34 (m, 7H), 2.61 (t, $J = 7.6$ Hz, 2H), 3.83-3.89 (m, 2H), 3.93-3.99 (m, 2H), 4.92 (t, $J = 5.2$ Hz, 1H), 5.33 (t, $J = 6.8$ Hz, 1H), 7.08 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.77, 21.02, 30.20, 35.47, 44.09, 64.79, 103.98, 127.37, 128.32, 128.94, 130.75, 135.13, 139.19. HRMS (ESI^+) exact mass calcd for $\text{C}_{16}\text{H}_{22}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 269.1517, found m/z 269.1506.

(E)-2-(5-(3-Isopropyl-4-methoxyphenyl)-2-methylpent-2-enyl)-1,3-dioxolane (6e)

Yield: 93%, colorless oil. ^1H NMR (300 MHz, CDCl_3): δ 1.20 (d, $J = 6.9$ Hz, 6H), 1.64 (s, 3H), 2.27-2.34 (m, 4H), 2.60 (t, $J = 7.8$ Hz, 2H), 3.29 (sept, $J = 6.9$ Hz, 1H), 3.80 (s, 3H), 3.82-3.86 (m, 2H), 3.90-4.00 (m, 2H), 4.92 (t, $J = 5.1$ Hz, 1H), 5.33 (t, $J = 6.3$ Hz, 1H), 6.76 (d, $J = 6.3$ Hz, 1H), 6.96 (dd, $J_1 = 2.1$, $J_2 = 8.1$ Hz, 1H), 7.02 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 16.77, 22.76, 26.70, 30.37, 35.27, 44.12, 55.50, 64.79, 104.01, 110.29, 126.10, 126.22, 127.51, 130.62, 134.18, 136.69, 154.93. ^1H HRMS (ESI^+) exact mass calcd for $\text{C}_{19}\text{H}_{28}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 327.1936, found m/z 327.1938.

(E)-3-(5-(1,3-Dioxolan-2-yl)-4-methylpent-3-enyl)-1-tosyl-1H-indole (6f)

Yield: 79%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.62 (s, 3H), 2.29 (s, 3H), 2.32 (d, $J = 5.2$ Hz, 2H), 2.39 (q, $J = 7.2$ Hz, 2H), 2.69 (t, $J = 7.2$ Hz, 2H), 3.82-3.88 (m, 2H), 3.93-3.99 (m, 2H), 4.91 (t, $J = 5.2$ Hz, 1H), 5.30 (t, $J = 6.0$ Hz,

1H), 7.18 (dd, $J_1 = 8.0$, $J_2 = 11.2$ Hz, 3H), 7.22-7.33 (m, 2H), 7.46 (d, $J = 7.6$ Hz, 1H), 7.73 (d, $J = 8.0$ Hz, 2H), 7.97 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.84, 21.52, 24.83, 27.40, 44.10, 64.81, 103.79, 113.74, 119.47, 122.87, 122.97, 124.53, 126.73, 126.99, 129.78, 131.19, 131.35, 135.31, 135.37, 144.68. HRMS (ESI⁺) exact mass calcd for $\text{C}_{24}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ requires m/z 426.1739, found m/z 426.1740.

(E)-2-(5-(4-Chlorophenyl)-2-methylpent-2-enyl)-1,3-dioxolane (6h)

Yield: 85%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.62 (s, 3H), 2.28-2.33 (m, 4H), 2.62 (t, $J = 7.8$ Hz, 2H), 3.82-3.89 (m, 2H), 3.93-3.99 (m, 2H),

4.90 (t, $J = 5.0$ Hz, 1H), 5.29 (dt, $J_1 = 1.2$ Hz, $J_2 = 7.0$ Hz, 1H), 7.11 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.76, 29.84, 35.19, 44.07, 64.79, 103.87, 126.74, 128.28, 129.85, 131.24, 131.41, 140.60. HRMS (ESI⁺) exact mass calcd for $\text{C}_{15}\text{H}_{20}\text{ClO}_2$ $[\text{M}+\text{H}]^+$ requires m/z 267.1152, found m/z 267.1142.

(E)-2-(2-Methyl-4-phenylbut-2-enyl)-1,3-dioxolane (6i)

Yield: 88%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.80 (s, 3H), 2.39 (d, $J = 5.0$ Hz, 2H), 3.40 (d, $J = 7.3$ Hz, 2H), 3.83-3.89 (m, 2H), 3.96-4.00 (m, 2H), 4.97 (t, $J = 5.0$ Hz, 1H), 5.49 (t, $J = 7.3$ Hz, 1H), 7.16-7.20 (m, 3H), 7.25-7.30 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.95, 34.26, 44.13, 64.81, 103.95, 125.79, 126.56, 128.36, 128.38, 131.34, 141.33. HRMS (ESI⁺) exact mass calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 219.1385, found m/z 219.1379.

(E)-2-(2-Methylnon-2-en-6-ynyl)-1,3-dioxolane (6g)

Yield: 85%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.1 (t, $J = 7.2$ Hz, 3H), 1.70 (s, 3H), 2.13-2.25 (m, 6H), 2.35 (d, $J = 4.8$ Hz, 2H), 3.83-3.89 (m, 2H), 3.94-4.00 (m, 2H), 4.93 (t, $J = 5.0$ Hz, 1H), 5.32 (t, $J = 6.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.42, 14.30, 16.88, 19.03, 27.89, 44.09, 64.78, 79.19, 81.75, 103.98, 126.56, 131.39. HRMS (ESI⁺) exact mass calcd for $\text{C}_{13}\text{H}_{20}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 209.3046, found m/z 209.3048.

An oven-dried round bottom flask (10 mL) equipped with a magnetic stir bar was charged with 4Å molecular sieves (200 mg), and sealed with a rubber septum. Then acetal (0.20 mmol) was dissolved in dry CH_2Cl_2 (2 mL) and added via syringe. After

cooling the solution to $-78\text{ }^{\circ}\text{C}$, 20 mL isobutene (S. T. P.) was added. TiCl_4 (0.24 mL of a 1.0M solution in CH_2Cl_2 , 0.24 mmol, 1.2 equiv) was added dropwisely. The solution was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 10 h and then quenched with sat. NaHCO_3 (5 mL). The reaction mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel using appropriate solvents (hexane/EtOAc mixture) to provide the title compound.

3-((1,1,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yl)oxy)propan-1-ol (29a')

^1H NMR (400 MHz, CDCl_3): δ 0.97 (s, 3H), 1.01 (s, 3H), 1.21 (s, 3H), 1.30-1.43 (m, 2H), 1.68-1.73 (m, 2H), 1.84-1.94 (m, 3H), 2.62-2.69 (m, 2H), 2.85-3.00 (m, 2H), 3.60-3.73 (m, 2H), 3.78 (t, $J = 5.6$ Hz, 2H), 3.82 (t, $J = 5.3$ Hz, 2H), 7.04-7.15 (m, 3H), 7.28-7.30 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 18.80, 22.61, 25.74, 30.10, 32.29, 33.42, 34.55, 39.16, 44.47, 47.30, 49.79, 62.66, 67.86, 73.68, 124.09, 125.51, 125.75, 129.10, 134.87, 149.09. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{31}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 303.2324, found m/z 303.2309.

2-(2-Isobutyl-10b-methyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromen-4-yl)ethanol (30)

^1H NMR (400 MHz, CDCl_3): δ 0.95-1.04 (m, 4H), 1.17 (s, 3H), 1.23-1.38 (m, 3H), 1.42-1.57 (m, 4H), 1.61-1.79 (m, 1H), 1.82-1.87 (m, 2H), 1.95-2.00 (m, 1H), 2.13 (d, $J = 12.8$ Hz, 1H), 2.94-2.97 (m, 2H), 3.20 (brs, 1H), 3.75 (t, $J = 8.2$ Hz, 1H), 3.87 (s, 3H), 7.09-7.29 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 19.25, 22.22, 23.36, 24.62, 27.84, 31.24, 34.73, 35.67, 38.16, 43.91, 45.18, 45.75, 61.87, 71.06, 123.67, 125.73, 125.77, 129.20, 134.80, 147.03. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{31}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 303.2324, found m/z 303.2328.

2-(1,1,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)ethanol (29a)

Yield: 85%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.32-1.35 (m, 3H), 1.59-1.63 (m, 6H), 1.79-2.03 (m, 7H), 2.14 (dd, $J_1 = 6.4$ Hz, $J_2 = 15.2$ Hz, 1H), 2.76-2.80 (m, 2H), 3.31-3.33 (m, 1H), 3.41-3.50 (m, 3H), 3.71-3.74 (m, 1H), 7.06-7.16 (m,

3H), 7.31-7.33 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 19.52, 30.69, 31.21, 33.14, 33.66, 35.96, 36.54, 49.36, 51.60, 62.05, 69.03, 69.92, 74.81, 125.43, 125.54, 127.26, 129.22, 136.49, 144.63. HRMS (ESI^+) exact mass calcd for $\text{C}_{19}\text{H}_{28}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 311.1987, found m/z 311.1981.

(E)-2-(2-Chloro-2,6-dimethyl-9-phenylnon-6-en-4-yloxy)ethanol (31)

^1H NMR (400 MHz, CDCl_3): δ 1.55-1.70 (m, 9H), 1.90-1.94 (m, 2H), 2.03-2.08 (m, 2H), 2.31-2.38 (m, 3H), 2.66 (t, J = 8.0 Hz, 2H), 3.48-3.52 (m, 1H), 3.64-3.76 (m, 4H), 5.25 (t, J = 6.8 Hz, 1H), 7.16-7.20 (m, 3H), 7.26-7.29 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 16.46, 29.81, 32.55, 34.09, 35.81, 45.03, 49.52, 62.13, 69.50, 70.28, 75.98, 125.77, 127.42, 128.29, 128.43, 132.24, 142.08.

2-(1,1,4a,8-Tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)ethane (29c)

Yield: 77%. ^1H NMR (400 MHz, CDCl_3): δ 1.14-1.17 (m, 9H), 1.26 (s, 3H), 1.64-1.76 (m, 3H), 1.85 (q, J = 5.6 Hz, 2H), 2.15-2.21 (m, 5H), 2.46 (dd, J_1 = 2.4 Hz, J_2 = 14.4 Hz, 1H), 2.52-2.66 (m, 1H), 2.80 (dd, J_1 = 6.4 Hz, J_2 = 17.6 Hz), 3.26 (t, J = 2.8 Hz, 1H), 3.42-3.44 (m, 1H), 6.98 (d, J = 7.2 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 18.54, 19.61, 19.94, 25.69, 26.07, 27.28, 32.51, 34.47, 38.65, 41.36, 43.55, 62.17, 68.86, 75.89, 122.00, 125.28, 127.07, 133.51, 136.73, 148.62. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{30}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 325.2144, found m/z 325.2142.

2-((6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yl)oxy)ethanol (29b)

Yield: 81%. ^1H NMR (400 MHz, CDCl_3): δ 1.31 (s, 3H), 1.40 (d, J = 9.4 Hz, 1H), 1.57 (s, 3H), 1.59 (s, 3H), 1.76-1.85 (m, 2H), 1.88-1.95 (m, 2H), 2.00 (dd, J_1 = 4.9 Hz, J_2 = 14.9 Hz, 1H), 2.09 (dd, J_1 = 6.2 Hz, J_2 = 14.9 Hz, 1H), 2.69-2.72 (m, 2H), 3.33-3.36 (m, 1H), 3.42-3.47 (m, 1H), 3.53-3.54 (m, 2H), 3.69-3.74 (m, 2H), 3.78 (s, 3H), 6.67 (dd, J_1 = 2.6 Hz, J_2 = 8.4 Hz, 1H), 6.85 (d, J = 2.7 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.62, 29.78, 30.89, 33.10, 33.70, 35.91, 36.79, 49.24, 51.64, 55.28, 62.08, 68.97, 69.96, 74.82, 110.89, 113.04, 128.75, 129.95, 145.94, 157.46. HRMS (ESI^+)

exact mass calcd for $C_{20}H_{31}O_3$ $[M+H]^+$ requires m/z 319.2273, found m/z 319.2270.

2-(1,1,4a,6-Tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)ethane (29d)

Yield: 85%. 1H NMR (400 MHz, $CDCl_3$): δ 1.31-1.33 (m, 3H), 1.56 (s, 3H), 1.58 (s, 3H), 1.77-2.04 (m, 7H), 2.09 (dd, $J_1 = 6.0$ Hz, $J_2 = 14.8$ Hz, 1H), 2.30 (s, 3H), 2.71-2.72 (m, 2H), 3.33-3.35 (m, 1H), 3.41-3.44 (m, 1H), 3.52-3.54 (m, 2H), 3.70-3.73 (m, 1H), 6.88-6.95 (m, 2H), 7.10 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.57, 21.25, 30.24, 30.93, 33.11, 33.72, 36.17, 36.46, 49.24, 51.71, 62.08, 68.97, 69.99, 74.87, 126.37, 127.75, 129.12, 133.38, 134.74, 144.33. HRMS (ESI^+) exact mass calcd for $C_{20}H_{31}O_2$ $[M+H]^+$ requires m/z 303.2324, found m/z 303.2321.

2-(7-Isopropyl-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yloxy)ethanol (29e)

Yield: 53%, colorless oil. 1H NMR (300 MHz, $CDCl_3$): δ 1.16-1.18 (m, 6H), 1.33 (s, 3H), 1.55 (s, 3H), 1.57 (s, 3H), 1.74-1.84 (m, 3H), 1.86-1.88 (m, 2H), 1.92-1.99 (m, 2H), 2.03-2.09 (m, 1H), 2.69 (t, $J = 6.3$ Hz, 2H), 3.20-3.24 (m, 1H), 3.33-3.37 (m, 1H),

3.41-3.47 (m, 1H), 3.55 (t, $J = 4.5$ Hz, 2H), 3.74 (t, $J = 5.1$ Hz, 1H), 3.80 (s, 3H), 6.75 (s, 1H), 6.84 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.68, 22.61, 22.91, 26.48, 29.85, 30.52, 33.06, 33.76, 36.22, 36.55, 49.18, 51.68, 55.64, 62.09, 68.99, 70.02, 74.91, 109.24, 126.56, 128.25, 134.67, 142.48, 154.84. HRMS (ESI^+) exact mass calcd for $C_{23}H_{37}O_3$ $[M+H]^+$ requires m/z 361.2743, found m/z 361.2735.

2-(4,4,11b-Trimethyl-11-tosyl-2,3,4,4a,5,6,11,11b-octahydro-1H-benzo[a]carbazol-2-yloxy)ethanol (29f)

Yield: 68%. 1H NMR (400 MHz, $CDCl_3$): δ 1.55-1.64 (m, 9H), 1.83-2.14 (m, 8H), 2.33 (s, 3H), 2.67-2.70 (m, 2H), 3.56 (t, $J = 4.4$ Hz, 2H), 3.67-3.69 (m, 2H), 3.91 (t, $J = 4.8$ Hz, 1H), 7.20-7.35 (m, 4H), 7.48 (d, $J = 7.6$

Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.98 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.56, 24.17, 24.88, 30.46, 32.88, 33.83, 44.51, 49.93, 51.66, 62.05, 69.01, 69.79, 73.23, 74.64, 113.79, 119.42, 122.71, 122.77, 123.04, 124.67, 126.76, 129.83,

130.95, 135.32, 135.35, 144.75. HRMS (ESI⁺) exact mass calcd for C₂₈H₃₆NO₄S [M+H]⁺ requires *m/z* 482.2365, found *m/z* 482.2356.

2-(4-(4-Chlorophenethyl)-3-chloro-3,5,5-trimethylcyclohexyloxy)ethanol (29h)

Yield: 71%. ¹H NMR (400 MHz, CDCl₃): δ 1.46 (s, 3H), 1.61 (s, 3H), 1.64 (s, 3H), 1.79-1.84 (m, 3H), 1.94 (dt, *J*₁ = 7.2 Hz, *J*₂ = 15.2 Hz, 3H), 2.03-2.14 (m, 2H), 2.61 (t, *J* = 6.8 Hz, 2H), 3.57 (t, *J* = 4.4 Hz, 2H), 3.66-3.76 (m, 2H), 3.91 (q, *J* = 4.8 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J*

= 8.4 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 26.44, 30.44, 32.88, 33.81, 35.14, 44.19, 49.92, 51.66, 62.07, 68.97, 69.77, 73.21, 74.64, 128.48, 129.75, 131.63, 140.32. HRMS (ESI⁺) exact mass calcd for C₁₉H₂₉Cl₂O₂ [M+H]⁺ requires *m/z* 359.1545, found *m/z* 359.1549.

2-((-4-Benzyl-3-chloro-3,5,5-trimethylcyclohexyl)oxy)ethanol(29i)

Yield: 76%. ¹H NMR (400 MHz, CDCl₃): δ 1.64 (s, 3H), 1.65 (s, 3H), 1.66 (s, 3H), 1.99-2.24 (m, 5H), 2.80-2.85 (m, 2H), 3.59-3.75 (m, 5H), 3.97-4.00 (m, 2H), 7.20-7.21

(m, 2H), 7.28-7.31 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 30.45, 31.21, 32.88, 33.88, 46.73, 49.87, 51.68, 62.05, 69.10, 72.98, 74.71, 126.04, 128.35, 128.53, 141.55.

2-(3-(1-Chloropropylidene)-3a,7,7-trimethyl-octahydro-1*H*-inden-5-yloxy)ethanol (29g)

Yield: 74%. ¹H NMR (400 MHz, CDCl₃): δ 0.92-0.97 (m, 2H), 1.03-1.08 (m, 2H), 1.13-1.19 (m, 7H), 1.24-1.43 (m, 3H), 1.58-1.66 (m, 4H), 1.87-1.90 (m, 1H), 1.93-2.07 (m, 1H), 2.37-2.53 (m, 4H), 3.57-3.75 (m, 5H). HRMS (ESI⁺)

exact mass calcd for C₁₇H₃₀ClO₂ [M+H]⁺ requires *m/z* 301.1934, found *m/z* 301.1932.

3-(2-Iodoethoxy)-7-isopropyl-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (32)

Alcohol **27e** (0.16 g, 0.43 mmol, 1.0 equiv.), triphenylphosphine (0.12 g, 0.46 mmol, 1.05 equiv.), iodine (0.12 g, 0.48 mmol, 1.1 equiv.) and imidazole (0.04 g, 0.52 mmol, 1.2 equiv.) were dissolved in toluene (2 mL) and the reaction mixture was heated at 80 °C for 2 hours. The crude

product was then directly purified by column chromatography to afford the desired iodinated compound **32** as colorless oil. Yield: 93%. ¹H NMR (400 MHz, CDCl₃): δ 1.20-1.23 (m, 7H), 1.36 (s, 3H), 1.58-1.63 (m, 6H), 1.74-2.10 (m, 7H), 2.72 (s, 2H), 3.02 (t, *J* = 6.4 Hz, 1H), 3.26-3.27 (m, 1H), 3.47-3.51 (m, 1H), 3.56-3.59 (m, 1H), 3.76-3.77 (m, 1H), 3.83 (s, 3H), 6.76 (s, 1H), 6.87 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 2.98, 19.75, 22.67, 23.01, 26.49, 29.94, 30.48, 32.98, 34.06, 36.33, 36.66, 49.15, 52.01, 55.63, 68.83, 70.28, 74.91, 109.23, 126.54, 128.40, 134.62, 142.24, 154.84. HRMS (ESI⁺) exact mass calcd for C₂₃H₃₅IO₂Na [M+Na]⁺ requires *m/z* 493.1580, found *m/z* 493.1591.

7-Isopropyl-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-3,6-diol (33)

Compound **32** (100 mg, 0.21 mmol) was dissolved in BnOH (1.5 mL), then Zn powder (100 mg) and ZnCl₂ (3 mg) was added and the reaction mixture was heated at 110 °C for 4 hours. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and extracted with

EtOAc (3 x 20 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduce pressure. The crude product was purified by flash column chromatography to give the title compound. Yield: 78%, white solid. ¹H NMR (400 MHz, CDCl₃): δ 1.17 (d, *J* = 2.5 Hz, 3H), 1.19 (d, *J* = 2.5 Hz, 3H), 1.27 (s, 3H), 1.33 (s, 3H), 1.34 (s, 3H), 1.39 (d, *J* = 14.6 Hz, 1H), 1.53-1.62 (m, 2H), 1.72-1.76 (m, 1H), 1.80-1.90 (m, 3H), 1.95 (ddd, *J*₁ = 2.9 Hz, *J*₂ = 7.6 Hz, *J*₃ = 13.0 Hz, 1H), 2.67 (t, *J* = 6.4 Hz, 1H), 3.18-3.25 (m, 1H), 3.78 (s, 3H), 4.18 (t, *J* = 6.4 Hz, 1H), 4.41 (d, *J* = 11.0 Hz, 1H), 4.48 (d, *J* = 11.0 Hz, 1H), 6.82 (s, 1H), 6.84 (s, 1H), 7.25-7.33 (m, 5H). ¹³C NMR (100 MHz, CDCl₃): δ 19.61, 22.79, 23.88, 26.47, 26.79, 29.85, 29.93, 36.69, 36.90, 49.69, 50.69, 55.61, 64.06, 66.54, 77.12, 109.29, 126.54, 127.44, 127.46,

128.43, 134.38, 138.78, 142.72, 154.85. HRMS (ESI⁺) exact mass calcd for C₂₈H₃₈O₂Na [M+Na]⁺ requires *m/z* 429.2770, found *m/z* 429.2781.

7-Isopropyl-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-3-ol (34)

To a solution of compound **33** (35 mg, 0.21 mmol) MeOH (1.5 mL) solution, Pd/C (10 mg) was added. The reaction mixture was stirred for 4 hours under H₂, then filtered through celite and the filtration was concentrated in vacuo to give the title compound. Yield: 98%. ¹H NMR (400

MHz, CDCl₃): δ 1.17 (d, *J* = 1.9 Hz, 3H), 1.19 (d, *J* = 2.1 Hz, 3H), 1.24 (s, 3H), 1.30 (s, 3H), 1.38 (d, *J* = 14.4 Hz, 1H), 1.53-1.60 (m, 2H), 1.67-1.95 (m, 5H), 2.08 (dd, *J*₁ = 8.6 Hz, *J*₂ = 14.8 Hz, 1H), 2.17 (s, 1H), 2.63-2.75 (m, 2H), 3.16-3.25 (m, 1H), 3.46 (s, 1H), 3.80 (s, 3H), 4.24 (t, *J* = 9.6 Hz, 1H), 6.78 (s, 1H), 6.88 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 20.03, 22.67, 22.74, 26.46, 27.74, 30.10, 31.66, 32.07, 36.34, 36.48, 49.43, 51.44, 55.57, 67.64, 71.01, 108.76, 127.21, 129.04, 135.11, 140.75, 155.10. HRMS (ESI⁺) exact mass calcd for C₂₁H₃₃O₂ [M+H]⁺ requires *m/z* 317.2481, found *m/z* 317.2482.

To a round bottom flask equipped with a magnetic stir, diethoxy acetal (1.0 mmol), *p*-toluenesulfonic acid monohydrate (0.1 mmol) and 1,3-propanediol (2.0 mmol) were dissolved in CH₂Cl₂ (10 mL). After stirring for 8h at room temperature, the reaction was quenched with triethylamine (0.2 mL). The reaction mixture was purified by flash chromatography on silica gel using diethyl ether/hexane to provide the title compound.

(E)-2-(2-Methyl-5-phenylpent-2-enyl)-1,3-dioxane (5a)

Yield: 93%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.33 (d, *J* = 13.4 Hz, 1H), 1.59 (s, 3H), 2.04-2.17 (m, 1H), 2.28 (d, *J* = 5.5 Hz, 2H), 2.33-2.36 (m, 2H), 2.65-2.70 (m, 2H), 3.75 (dt, *J*₁ = 2.3 Hz, *J*₂ = 12.4 Hz, 2H), 4.11 (dd, *J*₁ = 4.9 Hz, *J*₂ = 10.9 Hz, 2H), 4.59 (t, *J* = 5.3 Hz, 1H), 5.29 (t, *J* = 6.8 Hz, 1H), 7.16-7.19 (m, 3H), 7.25-7.29 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 16.59, 25.76, 30.02, 35.91, 45.41, 66.99, 101.62, 125.67, 126.91, 128.19, 128.51, 130.94, 142.29. HRMS (ESI⁺) exact mass calcd for C₁₆H₂₃O₂ [M+H]⁺ requires *m/z* 247.1698, found *m/z* 247.1692.

(E)-2-(2-Methyl-5-o-tolylpent-2-enyl)-1,3-dioxane (5b)

Yield: 92%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.33 (d, $J = 13.5$ Hz, 1H), 1.61 (s, 3H), 2.04-2.14 (m, 1H), 2.25-2.32 (m, 7H), 2.63 (t, $J = 8.6$ Hz, 2H), 3.76 (t, $J =$ Hz, 2H), 4.11 (dd, $J_1 = 4.8$ Hz, $J_2 = 11.8$ Hz, 2H), 4.60 (t, $J = 7.6$ Hz, 1H), 5.32 (t, $J = 6.5$ Hz, 1H), 7.09-7.13 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.54, 19.33, 25.77, 28.74, 33.19, 45.45, 64.53, 67.00, 101.59, 125.84, 127.03, 128.90, 130.05, 130.90, 135.91, 140.42. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 261.1855, found m/z 261.1850.

(E)-2-(5-(2-Methoxyphenyl)-2-methylpent-2-enyl)-1,3-dioxane (5c)

Yield: 89%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.33 (d, $J = 13.4$ Hz, 1H), 1.60 (s, 3H), 2.03-2.13 (m, 1H), 2.26-2.32 (m, 4H), 2.62-2.66 (m, 2H), 3.75 (t, $J = 11.0$ Hz, 2H), 3.82 (s, 3H), 4.11 (dd, $J_1 = 5.0$ Hz, $J_2 = 10.6$ Hz, 2H), 4.59 (t, $J = 5.3$ Hz, 1H), 5.31 (t, $J = 6.6$ Hz, 1H), 6.83 (d, $J = 8.2$ Hz, 1H), 6.86 (t, $J = 7.5$ Hz, 1H), 7.12 (d, $J = 7.4$ Hz, 1H), 7.16 (t, $J = 7.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.50, 25.77, 28.25, 30.36, 45.45, 55.22, 67.00, 101.71, 110.13, 120.24, 126.93, 127.49, 129.92, 130.60, 130.64, 157.50. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{24}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 299.1623, found m/z 299.1635.

(E)-2-(2-Methyl-5-p-tolylpent-2-enyl)-1,3-dioxane (5d)

Yield: 90%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.33 (d, $J = 13.5$ Hz, 1H), 1.60 (s, 3H), 2.02-2.15 (m, 1H), 2.29 (d, $J = 5.6$ Hz, 3H), 2.31 (s, 4H), 2.58-2.62 (m, 2H), 3.75 (t, $J = 11.0$ Hz, 2H), 4.11 (dd, $J_1 = 5.0$ Hz, $J_2 = 10.7$ Hz, 2H), 4.59 (t, $J = 5.3$ Hz, 1H), 5.28 (t, $J = 7.0$ Hz, 1H), 7.08 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.61, 21.01, 25.76, 30.17, 35.46, 45.41, 66.99, 101.64, 127.07, 128.35, 128.89, 130.81, 135.08, 139.24. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{24}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 283.1674, found m/z 283.1679.

(E)-2-(5-(4-Methoxyphenyl)-2-methylpent-2-enyl)-1,3-dioxane (5e)

Yield: 83%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.33 (d, $J = 13.6$ Hz, 1H), 1.58 (s, 3H), 2.02-2.14 (m, 1H), 2.25-2.31 (m, 4H), 2.58 (t, $J = 7.8$ Hz, 2H), 3.75 (t, $J = 11.0$ Hz, 2H), 3.78 (s, 3H), 4.11 (dd, $J_1 = 5.0$ Hz, $J_2 = 10.7$ Hz,

2H), 4.58 (t, $J = 5.3$ Hz, 1H), 5.27 (t, $J = 6.9$ Hz, 1H), 6.81 (d, $J = 8.4$ Hz, 2H), 7.09 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.60, 25.76, 30.26, 34.97, 45.42, 55.26, 66.99, 101.62, 113.61, 127.01, 129.37, 130.84, 134.43, 157.68. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{25}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires m/z 277.1804, found m/z 277.1809.

(E)-2-(5-(4-Chlorophenyl)-2-methylpent-2-enyl)-1,3-dioxane (5h)

Yield: 85%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.33 (d, $J = 13.5$ Hz, 1H), 1.56 (s, 3H), 2.02-2.14 (m, 1H), 2.16-2.32 (m, 4H), 2.61 (t, $J = 7.7$ Hz, 2H), 3.75 (t, $J = 11.0$ Hz, 2H), 4.11 (dd, $J_1 = 5.0$ Hz, $J_2 = 10.6$ Hz, 2H), 4.57 (t, $J = 5.3$ Hz, 1H), 5.24 (t, $J = 7.1$ Hz, 1H), 7.10 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.59, 25.74, 29.80, 35.17, 45.39, 66.99, 101.51, 126.47, 128.23, 129.90, 131.29, 131.36, 140.66. HRMS (ESI^+) exact mass calcd for $\text{C}_{16}\text{H}_{21}\text{ClO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 303.1128, found m/z 303.1124.

(E)-2-(5-(3-Isopropyl-4-methoxyphenyl)-2-methylpent-2-enyl)-1,3-dioxane (5f)

Yield: 92%, colorless oil. ^1H NMR (300 MHz, CDCl_3): δ 1.18 (d, $J = 6.9$ Hz, 6H), 1.33 (d, $J = 13.6$ Hz, 1H), 1.59 (s, 3H), 2.00-2.17 (m, 1H), 2.28-2.33 (m, 4H), 2.59 (t, $J = 8.7$ Hz, 2H), 3.21-3.33 (m, 1H), 3.75 (t, $J = 12.4$ Hz, 2H), 3.82 (s, 3H), 4.10 (dd, $J_1 = 5.1$ Hz, $J_2 = 10.8$ Hz, 2H), 4.60 (t, $J = 5.4$ Hz, 1H), 5.29 (t, $J = 7.8$ Hz, 1H), 6.75 (d, $J = 8.1$ Hz, 1H), 6.96 (d, $J = 8.4$ Hz, 1H), 7.02 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 16.61, 22.77, 25.77, 26.70, 30.34, 35.27, 45.45, 55.50, 66.99, 101.68, 110.27, 126.12, 126.21, 127.25, 130.69, 134.24, 136.68, 154.91. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{30}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 341.2093, found m/z 341.2094.

(E)-2-(2-Methyloct-2-enyl)-1,3-dioxane (5g)

Yield: 94%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.88 (t, $J = 6.3$ Hz, 3H), 1.25-1.35 (m, 7H), 1.64 (s, 3H), 1.99 (q, $J = 7.4$ Hz, 2H), 2.03-2.13 (m, 1H), 2.29 (d, $J = 5.3$ Hz, 2H), 3.75 (t, $J = 12.1$ Hz, 2H), 4.11 (dd, $J_1 = 8.9$ Hz, $J_2 = 11.7$ Hz, 2H), 4.61 (t, $J = 5.4$ Hz, 1H), 5.23 (t, $J = 7.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.10, 16.57, 22.59, 25.76, 27.94, 29.35, 31.56, 45.50, 66.99, 101.69, 128.22, 129.86. HRMS (ESI^+) exact mass calcd for $\text{C}_{13}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 213.1855, found m/z 213.1850.

To a round bottom flask equipped with a magnetic stirring bar, 2-methylprop-2-en-1-ol (5.0 mmol) and triethyl amine (6.0 mmol) were dissolved in CH_2Cl_2 (25 mL). The flask was cooled to 0 °C prior to the addition of RCl (5.5 mmol) via syringe. The reaction solution was allowed to stir at room temperature for 4 hour before diluting with CH_2Cl_2 (25 mL). The organic solution was washed with H_2O (2×30 mL) and brine (2×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel using appropriate solvents (hexane/EtOAc mixture) to provide the title compounds.

***tert*-Butyl((2-methylallyl)oxy)diphenylsilane (36a)**

^1H NMR (400 MHz, CDCl_3): δ 1.08 (s, 9H), 1.69 (s, 3H), 4.08 (s, 2H), 4.86 (s, 1H), 5.14 (s, 1H), 7.26-7.45 (m, 6H), 7.68-7.71 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.04, 19.31, 26.82, 67.26, 109.12, 127.66, 129.61, 133.73, 135.53, 144.24. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{26}\text{OSiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 333.1651, found m/z 333.1642.

2-Methylallyl benzoate (36f)

Yield: 97%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.84 (s, 3H), 4.75 (s, 2H), 4.99 (s, 1H), 5.08 (s, 1H), 7.43-7.47 (m, 2H), 7.54-7.59 (m, 1H), 8.07-8.09 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.60, 68.13, 112.95, 128.39, 129.64, 130.21, 132.99, 140.01, 166.26. HRMS (ESI^+) exact mass calcd for $\text{C}_{11}\text{H}_{13}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 177.0916, found m/z 177.0908.

Triisopropyl((2-methylallyl)oxy)silane (36b)

Yield: 95%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.05-1.19 (m, 21H), 1.73 (s, 3H), 4.14 (s, 2H), 4.84 (s, 1H), 5.07 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.04, 18.01, 18.94, 66.86, 108.76, 144.65. HRMS (ESI^+) exact mass calcd for $\text{C}_{13}\text{H}_{28}\text{OSiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 251.1807, found m/z 251.1809.

Dimethyl((2-methylallyl)oxy)(phenyl)silane (36c)

Yield: 95%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.39 (s, 6H), 1.69 (s, 3H), 4.02 (s, 2H), 4.82 (s, 1H), 4.99 (s, 1H), 7.34-7.40 (m, 3H), 7.57-7.59 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ -1.74, -0.88, 19.06, 66.78, 109.83, 127.86, 129.63, 133.51, 137.76, 144.19. HRMS (ESI^+) exact mass calcd for $\text{C}_{12}\text{H}_{18}\text{OSiK}$ $[\text{M}+\text{K}]^+$ requires m/z 245.0764, found m/z 245.0767.

(((2-Methylallyl)oxy)methyl)benzene (36d)

To a round bottom flask equipped with a magnetic stirring bar, NaH (60%, 6.0 mmol) was dissolved in anhydrous THF (25 mL) and cooled to 0 °C. 2-Methylprop-2-en-1-ol (5.0 mmol) was dissolved in 10 mL THF and added to the reaction mixture via syringe. The reaction mixture was allowed to stir at room temperature for 30min, then BnBr (5.5 mmol) was added slowly and the reaction was stirred for another 2 h. The reaction mixture was poured into ice/H₂O and extracted with EtOAc (3 x 40 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to provide the title compounds. Yield: 84%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.77 (s, 3H), 3.94 (s, 2H), 4.50 (s, 2H), 4.93 (s, 1H), 5.01 (s, 1H), 7.25-7.35 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 19.57, 71.83, 74.13, 112.34, 127.55, 127.69, 128.38, 138.45, 142.22. HRMS (ESI⁺) exact mass calcd for C₁₁H₁₄ONa [M+Na]⁺ requires *m/z* 185.0942, found *m/z* 185.0934.

1-Methoxy-4-(2-methylallyloxy)benzene (36e)

In a round bottom flask equipped with a magnetic stirring bar, 4-methoxyphenol (5.0 mmol) and K₂CO₃ (6.0 mmol) were dissolved in THF (25 mL). The flask was cooled to 0 °C prior to the addition of 3-bromo-2-methylprop-1-ene (5.0 mmol) via syringe. After stirring at room temperature for 8 hour, the reaction mixture was poured into H₂O and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with H₂O (2 x 30 mL) and brine (30 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to provide the title compounds. Yield: 82%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.82 (s, 3H), 3.76 (s, 3H), 4.38 (s, 2H), 4.97 (s, 1H), 5.08 (s, 1H), 6.80-6.87 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 19.44, 55.70, 72.44, 112.59, 114.57, 115.73, 141.24, 152.94, 153.85. HRMS (ESI⁺) exact mass calcd for C₁₁H₁₅O₂ [M+H]⁺ requires *m/z* 179.1072, found *m/z* 179.1070.

3-(7-(*tert*-Butyldiphenylsilyloxy)-8,11a-dimethyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[*a*]naphthalen-10-yloxy)propan-1-ol (37a)

Yield: 56%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.64 (d, *J* = 7.2 Hz, 3H), 1.10 (s, 9H), 1.30-1.32 (m, 1H), 1.50 (t, *J* = 12.8 Hz, 2H), 1.57 (s, 3H), 1.75 (dd, *J*_I

= 10.8 Hz, $J_2 = 13.8$ Hz, 1H), 1.84-1.90 (m, 3H), 2.06-2.14 (m, 1H), 2.52 (ddd, $J_1 = 6.7$ Hz, $J_2 = 10.9$ Hz, $J_3 = 14.7$ Hz, 1H), 2.68 (dd, $J_1 = 4.2$ Hz, $J_2 = 14.1$ Hz, 1H), 2.77 (dd, $J_1 = 4.2$ Hz, $J_2 = 8.8$ Hz, 3H), 3.74-3.83 (m, 5H), 4.11-4.13 (m, 1H), 7.01 (d, $J = 7.6$ Hz, 1H), 7.07 (t, $J = 7.3$ Hz, 1H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.34-7.44 (m, 7H), 7.71-7.73 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.08, 22.31, 25.82, 26.12, 27.74, 31.15, 32.19, 34.59, 34.94, 40.09, 45.59, 54.03, 62.83, 68.32, 76.17, 84.17, 125.46, 125.72, 125.75, 127.24, 127.29, 129.30, 129.47, 129.64, 133.57, 134.29, 135.91, 136.76, 136.89, 148.58. HRMS (ESI^+) exact mass calcd for $\text{C}_{36}\text{H}_{49}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 557.3451, found m/z 557.3454.

3-(7-(*tert*-Butyldiphenylsilyloxy)-8,11a-dimethyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[*a*]naphthalen-10-yloxy)propan-1-ol (38a)

Yield: 54%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.79 (s, 3H), 0.99 (d, $J = 8.4$ Hz, 3H), 1.10 (s, 9H), 1.32-1.35 (m, 1H), 1.55-1.59 (m, 2H), 1.71-1.80 (m, 3H), 1.92-1.98 (m, 3H), 2.18-2.23 (m, 1H), 2.41 (d, $J = 13.2$ Hz, 1H), 2.72-2.75 (m, 2H), 3.17 (t, $J = 10.3$ Hz, 1H), 3.52-3.56 (m, 2H), 3.73 (t, $J = 5.5$ Hz, 2H), 3.94 (dd, $J_1 = 5.2$ Hz, $J_2 = 7.4$ Hz, 1H), 7.00 (d, $J = 7.4$ Hz, 1H), 7.03 (t, $J = 5.8$ Hz, 1H), 7.10 (t, $J = 7.0$ Hz, 1H), 7.33-7.43 (m, 7H), 7.70-7.73 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.30, 19.76, 21.94, 24.22, 27.39, 31.15, 32.15, 34.32, 38.85, 39.59, 42.90, 51.99, 62.46, 67.70, 72.50, 75.46, 125.33, 125.90, 127.13, 127.46, 127.49, 128.82, 129.65, 134.03, 134.62, 135.77, 136.25, 136.34, 147.39. HRMS (ESI^+) exact mass calcd for $\text{C}_{36}\text{H}_{49}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 557.3451, found m/z 557.3447.

3-(7-(*tert*-Butyldiphenylsilyloxy)-4,8,11a-trimethyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[*a*]naphthalen-10-yloxy)propan-1-ol (37b)

Yield: 51%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.64 (d, $J = 7.2$ Hz, 3H), 1.10 (s, 9H), 1.35-1.40 (m, 1H), 1.49 (d, $J = 12.8$ Hz, 1H), 1.54 (td, $J_1 = 4.2$ Hz, $J_2 = 14.1$ Hz, 1H), 1.59 (s, 3H), 1.73 (dd, $J_1 = 10.7$ Hz, $J_2 = 13.9$ Hz, 1H), 1.81-1.91 (m, 3H), 2.01-2.13 (m, 1H), 2.17 (s, 3H), 2.46-2.58 (m, 2H), 2.64-2.70 (m, 2H), 3.72-3.83 (m, 5H), 4.09-4.14 (m, 1H), 6.96 (d, $J = 7.2$ Hz, 1H), 7.08 (t, $J = 7.8$ Hz, 1H), 7.31-7.46 (m, 7H), 7.71-7.73 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.01, 20.09, 22.29, 25.94, 26.00, 27.75, 28.54, 32.21,

34.59, 35.10, 40.15, 45.87, 53.40, 62.82, 68.29, 76.16, 84.28, 123.56, 125.37, 127.11, 127.24, 127.29, 129.48, 129.64, 133.59, 134.31, 134.56, 136.40, 136.77, 136.91, 148.64. HRMS (ESI⁺) exact mass calcd for C₃₇H₅₁O₃Si [M+H]⁺ requires *m/z* 571.3607, found *m/z* 571.3611.

3-(-7-(*tert*-Butyldiphenylsilyloxy)-4,8,11a-trimethyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[*a*]naphthalen-10-yloxy)propan-1-ol (38b)

Yield: 47%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.81 (s, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 1.10 (s, 9H), 1.26-1.34 (m, 3H), 1.73-1.79 (m, 2H), 1.90-2.01 (m, 3H), 2.19 (s, 3H), 2.24-2.29 (m, 1H), 2.39-2.50 (m, 2H), 2.69 (dd, *J*₁ = 3.8 Hz, *J*₂ = 17.0 Hz, 1H), 3.17 (t, *J* = 10.5 Hz,

1H), 3.73 (t, *J* = 5.5 Hz, 2H), 3.68-3.74 (m, 1H), 3.96 (dd, *J*₁ = 5.2 Hz, *J*₂ = 7.4 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 7.01 (t, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.33-7.43 (m, 6H), 7.70-7.73 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 15.29, 19.78, 19.95, 21.67, 24.19, 27.41, 28.30, 32.15, 34.33, 39.00, 39.61, 42.21, 52.44, 62.45, 67.66, 72.50, 75.46, 124.91, 125.49, 126.84, 127.46, 127.50, 129.63, 134.07, 134.52, 134.64, 135.88, 136.26, 136.35, 147.48. HRMS (ESI⁺) exact mass calcd for C₃₇H₅₁O₃Si [M+H]⁺ requires *m/z* 571.3607, found *m/z* 571.3603.

3-(4-Methoxy-8,11a-dimethyl-7-(*tert*-butyldiphenylsilyloxy)-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[*a*]naphthalen-10-yloxy)propan-1-ol (37c)

Yield: 46%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.64 (d, *J* = 7.2 Hz, 3H), 1.10 (s, 9H), 1.30-1.36 (m, 1H), 1.47 (d, *J* = 12.8 Hz, 1H), 1.57 (s, 3H), 1.54-1.63 (m, 2H), 1.73 (dd, *J*₁ = 10.7 Hz, *J*₂ =

13.9 Hz, 1H), 1.84-1.92 (m, 1H), 1.98-2.09 (m, 3H), 2.41-2.54 (m, 1H), 2.68 (dd, *J*₁ = 4.0 Hz, *J*₂ = 14.1 Hz, 1H), 2.80 (dd, *J*₁ = 5.6 Hz, *J*₂ = 17.8 Hz, 1H), 3.78 (s, 3H), 3.72-3.83 (m, 5H), 4.07-4.13 (m, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.34-7.44 (m, 6H), 7.71-7.73 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 20.07, 22.28, 24.76, 25.55, 25.75, 27.73, 29.71, 32.17, 34.58, 35.04, 40.06, 45.61, 53.47, 55.28, 62.88, 68.33, 76.14, 84.30, 106.57, 117.83, 125.08, 125.91, 127.21, 127.27, 129.44, 129.63, 133.53, 134.36, 136.76, 136.90, 149.96, 156.99. HRMS (ESI⁺) exact mass calcd for C₃₇H₅₁O₄Si [M+H]⁺ requires *m/z* 587.3557, found *m/z* 587.3547.

3-(2,8,11a-Trimethyl-7-(*tert*-butyldiphenylsilyloxy)-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[a]naphthalen-10-yloxy)propan-1-ol (37d)

Yield: 58%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.63 (d, $J = 7.2$ Hz, 3H), 1.10 (s, 9H), 1.28-1.34 (m, 1H), 1.48 (d, $J = 12.6$ Hz, 1H), 1.56 (s, 3H), 1.75 (dd, $J_1 = 10.6$ Hz, $J_2 = 13.9$ Hz, 1H), 1.85-1.91 (m, 3H), 2.05-2.14 (m, 1H), 2.28-2.32 (m, 1H), 2.32 (s, 3H), 2.50 (ddd, $J_1 = 6.6$ Hz, $J_2 = 10.9$ Hz, $J_3 = 14.6$ Hz, 1H), 2.67 (dd, $J_1 = 4.0$ Hz, $J_2 = 14.1$ Hz, 1H), 2.72-2.74 (m, 2H), 3.73-3.80 (m, 3H), 3.83 (t, $J = 5.6$ Hz, 2H), 4.08-4.13 (m, 1H), 6.90 (s, 2H), 7.21 (s, 1H), 7.34-7.43 (m, 6H), 7.71-7.73 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.08, 21.39, 22.32, 25.78, 26.24, 27.75, 30.70, 32.24, 34.61, 34.97, 40.03, 45.63, 54.11, 62.80, 68.25, 76.16, 84.22, 126.20, 126.41, 127.25, 127.28, 129.23, 129.48, 129.64, 132.78, 133.60, 134.31, 134.98, 136.77, 136.90, 148.43. HRMS (ESI^+) exact mass calcd for $\text{C}_{37}\text{H}_{51}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 571.3607, found m/z 571.3594.

3-(2,8,11a-Trimethyl-7-(*tert*-butyldiphenylsilyloxy)-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[a]naphthalen-10-yloxy)propan-1-ol (38d)

Yield: 53%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.79 (s, 3H), 0.98 (d, $J = 6.2$ Hz, 3H), 1.10 (s, 9H), 1.29-1.33 (m, 2H), 1.74-1.80 (m, 3H), 1.91-1.95 (m, 3H), 2.17-2.21 (m, 1H), 2.25 (s, 3H), 2.28-2.33 (m, 1H), 2.40 (d, $J = 13.1$ Hz, 1H), 2.67-2.71 (m, 2H), 3.16 (t, $J = 10.2$ Hz, 1H), 3.51-3.57 (m, 2H), 3.74 (t, $J = 5.6$ Hz, 2H), 3.94 (dd, $J_1 = 5.0$ Hz, $J_2 = 7.4$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 6.89 (d, $J = 7.6$ Hz, 1H), 7.04 (s, 1H), 7.33-7.44 (m, 6H), 7.69-7.72 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.27, 19.76, 21.28, 22.04, 24.31, 27.40, 30.77, 32.17, 34.34, 38.81, 39.53, 42.95, 52.13, 62.42, 67.65, 72.47, 75.50, 126.33, 127.48, 127.58, 128.72, 129.63, 132.67, 134.06, 134.65, 135.13, 136.26, 136.35, 147.21. HRMS (ESI^+) exact mass calcd for $\text{C}_{37}\text{H}_{51}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 571.3607, found m/z 571.3600.

3-(2-Methoxy-8,11a-dimethyl-7-(*tert*-butyldiphenylsilyloxy)-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[a]naphthalen-10-yloxy)propan-1-ol (37e)

Yield: 49%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.63 (d, $J = 7.2$ Hz, 3H), 1.10 (s, 9H), 1.29-1.33 (m, 2H), 1.47 (d, $J = 12.6$ Hz, 1H), 1.56 (s, 3H), 1.76 (dd, $J_1 = 10.7$

Hz, $J_2 = 14.0$ Hz, 1H), 1.84-1.91 (m, 3H), 2.05-2.14 (m, 1H), 2.50 (ddd, $J_1 = 6.7$ Hz, $J_2 = 11.0$ Hz, $J_3 = 14.7$ Hz, 1H), 2.63 (dd, $J_1 = 4.2$ Hz, $J_2 = 14.1$ Hz, 1H), 2.65-2.72 (m, 3H), 3.74-3.81 (m, 5H), 3.79 (s, 3H), 4.10 (dt, $J_1 = 4.2$ Hz, $J_2 = 10.5$ Hz, 1H), 6.66 (dd, $J_1 = 2.6$ Hz, $J_2 = 8.3$ Hz, 1H), 6.94 (d, $J = 8.4$ Hz, 1H), 6.96 (d, $J = 2.5$ Hz, 1H), 7.34-7.43 (m, 6H), 7.70-7.73 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.03, 22.25, 25.68, 26.24, 27.69, 30.18, 32.18, 34.57, 35.05, 40.20, 45.49, 53.90, 55.36, 62.73, 68.23, 76.01, 84.09, 110.62, 111.87, 127.19, 127.24, 128.10, 129.43, 129.60, 130.00, 133.50, 134.25, 136.71, 136.84, 149.93, 157.57. HRMS (ESI^+) exact mass calcd for $\text{C}_{37}\text{H}_{51}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 587.3557, found m/z 587.3552.

3-((2-Methoxy-8,11a-dimethyl-7-((triisopropylsilyl)oxy)-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[a]naphthalen-10-yl)oxy)propan-1-ol (38eb)

Yield: 44%, colorless oil, dr: 72/28. ^1H NMR (400 MHz, CDCl_3): δ 0.95-1.18 (m, 24H), 1.31-1.54 (m, 5H), 1.64-1.67 (m, 2H), 1.77-2.05 (m, 6H), 2.50-2.54 (m, 2H), 2.73-2.77 (m, 2H), 3.65-3.93 (m, 9H), 6.65-6.69 (m, 1H), 6.89-6.94 (m, 1H), 6.95-6.98 (m, 1H). HRMS (ESI^+) exact mass calcd for $\text{C}_{33}\text{H}_{53}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 541.3713, found m/z 541.3705.

3-((7-((Dimethyl(phenyl)silyl)oxy)-2-methoxy-8,11a-dimethyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[a]naphthalen-10-yl)oxy)propan-1-ol (37ec)

^1H NMR (400 MHz, CDCl_3): δ 0.41 (s, 3H), 0.42 (s, 3H), 0.88 (d, $J = 6.9$ Hz, 3H), 1.31 (s, 3H), 1.45-1.55 (m, 2H), 1.72-2.03 (m, 6H), 2.21-2.28 (m, 1H), 2.60 (dd, $J_1 = 4.6$

Hz, $J_2 = 13.8$ Hz, 1H), 2.78-2.82 (m, 3H), 3.67-3.72 (m, 2H), 3.78 (s, 3H), 3.78-3.83 (m, 3H), 3.93-3.97 (m, 1H), 6.66 (dd, $J_1 = 2.6$ Hz, $J_2 = 8.4$ Hz, 1H), 6.93 (d, $J = 2.5$ Hz, 1H), 6.95 (d, $J = 8.5$ Hz, 1H), 7.35-7.38 (m, 3H), 7.59-7.61 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ -1.10, -0.24, 22.53, 25.05, 26.33, 30.11, 32.17, 34.09, 34.79, 40.04, 45.21, 52.88, 55.37, 62.81, 68.24, 76.18, 83.73, 110.63, 111.89, 127.70, 127.97, 129.40, 129.98, 133.57, 138.56, 150.03, 157.58. HRMS (ESI^+) exact mass calcd for $\text{C}_{29}\text{H}_{43}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 483.2931, found m/z 483.2939.

3-(2-Methoxy-8,11a-dimethyl-7-(tert-butylidiphenylsilyloxy)-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[a]naphthalen-10-yloxy)propan-1-ol (38e)

Yield: 63%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 0.78 (s, 3H), 0.98 (d, $J = 6.2$

Hz, 3H), 1.09 (s, 9H), 1.24-1.44 (m, 3H), 1.71-1.80 (m, 3H), 1.89-1.97 (m, 3H), 2.19 (d, $J = 13.4$ Hz, 1H), 2.36 (d, $J = 13.2$ Hz, 1H), 2.61-2.72 (m, 2H), 3.15 (t, $J = 10.2$ Hz, 1H), 3.53 (t, $J = 5.7$ Hz, 2H), 3.72-3.77 (m, 2H), 3.74 (s, 3H), 3.93 (dd, $J_1 = 5.1$ Hz, $J_2 = 7.3$ Hz, 1H), 6.64 (dd, $J_1 = 2.5$ Hz, $J_2 = 8.4$ Hz, 1H), 6.78 (d, $J = 2.5$ Hz, 1H), 6.93 (d, $J = 8.4$ Hz, 1H), 7.33-7.45 (m, 6H), 7.69-7.72 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.25, 19.76, 22.11, 24.25, 27.39, 30.33, 32.15, 34.32, 39.07, 39.67, 42.83, 51.96, 55.32, 62.35, 67.59, 72.43, 75.38, 111.05, 112.85, 127.46, 127.49, 128.16, 129.57, 129.63, 129.65, 134.01, 134.61, 136.25, 136.35, 148.65, 157.69. HRMS (ESI^+) exact mass calcd for $\text{C}_{37}\text{H}_{51}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 587.3557, found m/z 587.3546.

3-(3-Isopropyl-2-methoxy-8,11a-dimethyl-7-(*tert*-butyldiphenylsilyloxy)-6,6a,7,8,9,10,11,11a-octahydro-5*H*-cyclohepta[*a*]naphthalen-10-yloxy)propan-1-ol (37f)

Yield: 55%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.63 (d, $J = 7.2$ Hz, 3H), 1.10 (s, 9H), 1.16 (d, $J = 6.9$ Hz, 3H), 1.19 (d, $J = 6.9$ Hz, 3H), 1.25-1.33 (m, 2H), 1.46-1.52 (m, 2H), 1.58 (s, 3H), 1.77-1.91 (m, 5H), 2.03-2.11 (m, 1H), 2.41-2.55 (m, 1H), 2.62 (dd, $J_1 = 4.1$ Hz, $J_2 = 14.1$ Hz, 1H), 2.69 (dd, $J_1 = 4.2$ Hz, $J_2 = 8.9$ Hz, 1H), 3.18-3.25 (m, 1H), 3.71-3.82 (m, 5H), 3.83 (s, 3H), 4.08-4.14 (m, 1H), 6.81 (s, 1H), 6.85 (s, 1H), 7.35-7.44 (m, 6H), 7.67-7.73 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.07, 22.32, 22.64, 22.86, 25.78, 26.43, 27.74, 30.50, 32.20, 34.61, 34.87, 40.14, 45.81, 54.12, 55.88, 62.76, 68.13, 76.13, 84.26, 107.97, 126.70, 127.23, 127.27, 127.66, 127.73, 129.46, 129.63, 130.10, 133.58, 134.33, 134.65, 136.76, 136.89, 146.47, 154.97. HRMS (ESI^+) exact mass calcd for $\text{C}_{40}\text{H}_{57}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 629.4026, found m/z 629.4021.

3-(3-Isopropyl-2-methoxy-8,11a-dimethyl-7-(*tert*-butyldiphenylsilyloxy)-6,6a,7,8,9,10,11,11a-octahydro-5*H*-cyclohepta[*a*]naphthalen-10-yloxy)propan-1-ol (38f)

Yield: 63%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 0.80 (s, 3H), 0.98 (d, $J = 6.0$ Hz, 3H), 1.10 (s, 9H), 1.16 (d, $J = 6.9$ Hz, 3H), 1.18 (d, $J = 6.9$ Hz, 3H), 1.34-1.42 (m, 3H), 1.77 (q, $J = 5.6$ Hz, 2H), 1.90-1.95 (m, 3H), 2.17-2.22 (m, 1H), 2.35 (d, $J = 13.1$ Hz, 1H),

2.67-2.69 (m, 3H), 3.12-3.22 (m, 2H), 3.47-3.58 (m, 2H), 3.72-3.75 (m, 5H), 3.93 (dd, $J_1 = 5.0$ Hz, $J_2 = 7.3$ Hz, 1H), 6.67 (s, 1H), 6.80 (s, 1H), 7.24-7.43 (m, 6H), 7.69-7.73 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.21, 19.76, 22.15, 22.63, 22.87, 24.28, 26.43, 27.41, 30.47, 32.16, 34.35, 38.90, 39.52, 42.73, 52.29, 55.71, 62.38, 67.54, 72.35, 75.39, 109.00, 126.12, 127.46, 127.50, 127.62, 129.63, 129.65, 134.05, 134.71, 136.27, 136.39, 145.26, 155.16. HRMS (ESI^+) exact mass calcd for $\text{C}_{40}\text{H}_{57}\text{O}_4\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 629.4026, found m/z 629.4037.

3-(4-(*tert*-Butyldiphenylsilyloxy)-3-methyl-6-methylene-5-pentylcycloheptyloxy)propan-1-ol (37g)

Yield: 50%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.79 (t, $J = 7.3$ Hz, 3H), 0.87 (d, $J = 7.2$ Hz, 3H), 0.95-1.02 (m, 4H), 1.06-1.16 (m, 12H), 1.45 (dd, $J_1 = 4.8$ Hz, $J_2 = 13.6$ Hz, 1H), 1.58-1.65 (m, 2H), 1.82-1.87 (m, 2H), 2.07 (td, $J_1 = 9.8$ Hz, $J_2 = 13.6$ Hz, 1H), 2.24-2.29 (m, 1H), 2.33-2.43 (m, 2H), 2.81 (brs, 1H), 3.41 (qd, $J_1 = 5.2$ Hz, $J_2 = 10.2$ Hz, 1H), 3.51 (d, $J = 3.2$ Hz, 1H), 3.63 (td, $J_1 = 5.4$ Hz, $J_2 = 9.0$ Hz, 1H), 3.69 (td, $J_1 = 5.4$ Hz, $J_2 = 9.0$ Hz, 1H), 3.81 (t, $J = 5.4$ Hz, 2H), 4.69 (d, $J = 1.9$ Hz, 1H), 4.85 (d, $J = 1.9$ Hz, 1H), 7.34-7.43 (m, 6H), 7.68-7.72 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.04, 19.73, 21.29, 22.49, 26.90, 27.27, 31.71, 32.06, 32.18, 34.83, 38.87, 52.19, 62.90, 68.36, 78.60, 79.85, 116.01, 127.31, 127.38, 129.47, 129.48, 134.22, 134.52, 136.29, 136.32, 144.42. HRMS (ESI^+) exact mass calcd for $\text{C}_{33}\text{H}_{50}\text{O}_3\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 545.3427, found m/z 545.3444.

8,11a-Dimethyl-6,6a,7,8,9,10,11,11a-octahydro-5*H*-cyclohepta[*a*]naphthalene-7,10-diol (40)

^1H NMR (400 MHz, CDCl_3): δ 1.12 (d, $J = 7.0$ Hz, 3H), 1.38 (s, 3H), 1.45-1.51 (m, 3H), 1.61 (brs, 2H), 1.69-1.73 (m, 1H), 1.79 (dd, $J_1 = 10.7$ Hz, $J_2 = 14.1$ Hz, 1H), 2.10 (ddd, $J_1 = 6.4$ Hz, $J_2 = 12.7$ Hz, $J_3 = 18.9$ Hz, 1H), 2.16-2.23 (m, 1H), 2.49 (ddd, $J_1 = 6.4$ Hz, $J_2 = 11.6$ Hz, $J_3 = 15.4$ Hz, 1H), 2.75 (dd, $J_1 = 5.6$ Hz, $J_2 = 14.1$ Hz, 1H), 2.92 (dd, $J_1 = 6.4$ Hz, $J_2 = 17.0$ Hz, 1H), 2.98-3.04 (m, 1H), 3.88 (s, 1H),

4.37-4.43 (m, 1H), 7.06-7.13 (m, 2H), 7.18 (t, $J = 7.4$ Hz, 1H), 7.44 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 22.09, 25.08, 25.31, 31.35, 32.63, 36.96, 40.08, 48.57, 52.97, 68.13, 81.67, 125.47, 125.81, 126.30, 129.29, 135.72, 148.13. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 261.1855, found m/z 261.1847.

2-Methoxy-8,11a-dimethyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[*a*]naphthalene-7,10-diol (42)

^1H NMR (400 MHz, CDCl_3): δ 1.08 (d, $J = 7.0$ Hz, 3H), 1.33 (s, 3H), 1.42-1.60 (m, 3H), 1.64-1.70 (m, 1H), 1.72-1.80 (m, 2H), 2.13-2.18 (m, 1H), 2.25 (d, $J = 14.1$ Hz, 1H), 2.63 (dd, $J_1 = 2.7$ Hz, $J_2 = 13.4$ Hz, 1H), 2.73-2.77 (m, 2H), 3.51-3.55 (m, 1H), 3.78 (s, 3H), 3.98 (ddt, $J_1 = 3.1$ Hz, $J_2 = 4.3$ Hz, $J_3 = 11.1$ Hz, 1H), 6.68 (dd, $J_1 = 2.6$ Hz, $J_2 = 8.4$ Hz, 1H), 6.91 (d, $J = 2.5$ Hz, 1H), 6.97 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 18.86, 23.38, 25.48, 30.70, 33.12, 39.08, 39.39, 51.45, 55.32, 55.55, 71.53, 76.47, 111.47, 113.15, 128.71, 129.70, 148.22, 157.79. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{27}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires m/z 291.1960, found m/z 291.1953.

Chapter 3. Prins Polyene Cyclization for the Synthesis of Oxaterpenoid Skeleton and Its Application in Total Synthesis of ($\pm$)-Moluccanic Acid Methyl Ester

3.1 Introduction

Nature presents us with large amount of terpenoids that are not only diverse in size and functional groups, but also varied in the structural backbone. Most of the terpenoids have exclusive carbon skeletons, but oxygenated derivatives of terpenoids (oxaterpenoids) also have been found in many natural products (Figure 3.1). Moreover, oxaterpenoids are one of the important classes of plant-based compounds for pharmaceutical use and have promising medicinal potential. Salvinorin A, which is a selective κ -opioid receptor agonist, isolated from Mexican hallucinogenic plant *Salvia divinorum*. Compound **B** shows toxicity to brine shrimp. Oxandrin, a synthetic anabolic steroid derived from dihydrotestosterone has been clinically used to treat alcoholic hepatitis, Turner syndrome, and HIV-induced weight loss, also has an oxygen tethering skeleton.

Figure 3.1 Selected examples of oxaterpenoids

In the course of efforts towards the development of cationic polyene

cyclization,⁵² iminium induced intermolecular polyene cyclization has been well established for constructing *N*-tethering terpenoids skeletons as early as 1977 (Scheme 3.1, I).⁵³ Recently, Jacobsen group successfully extended the reaction to organo-catalyzed asymmetric version (Scheme 3.1, II).⁵⁴ However, there was no efficient method for azaterpenoids synthesis reported until now.

Scheme 3.1

In this chapter, we present a novel Prins reaction initiated polyene cyclization reaction for the synthesis of oxaterpenoids. We also have applied this strategy to the total synthesis of ($\pm$)-moluccanic acid methyl ester successfully.

3.2 Result and Discussion

As the due course of building variety of terpenoid skeletons by intermolecular way,⁵⁵ also captivated by the oxaterpenoids featuring polycyclic structure, potent bio-activity and efficient ways to be synthesized in organisms, we are interested in developing a direct method to construct this unique polycyclic structure featuring a

⁵² Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730.

⁵³ Dijkink, J.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, *18*, 935.

⁵⁴ Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030.

⁵⁵ (a) Zhao, Y. J.; Chng, S. S.; Loh, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 492. (b) Zhao, Y. J.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 10024.

tetrahydropyran ring fused to trans-decalin. As we know, Prins reaction has been widely investigated for its ability to construct THP rings. Considering the mechanism of Prins reaction, we hypothesized that the cation intermediate **3** might be trapped by an alkene or aromatic ring through intramolecular reaction at the last stage. As a result, *O*-tethering terpenoids **4** could be synthesized by the Prins initiated polyene cyclization (Scheme 3.2).

Scheme 3.2 Proposed reaction mechanism

With this idea in mind, a suitable substrate was designed and prepared as shown in Scheme 3.3. It was noteworthy that the reaction precursor could be easily prepared from the same aldehyde intermediate **8**, which was applied for acetal synthesis in previous chapter.

Scheme 3.3 Synthetic route to substrates

The Prins reaction initiated polyene cyclization was first evaluated by (E)-3-methyl-6-phenylhex-3-en-1-ol **1a** and benzaldehyde **2a**. To our delight, the Prins-polyene cyclization reaction proceeded smoothly in the presence of InBr_3 (30

mol%) using CH₂Cl₂ as the solvent. A single isomer **4a** was obtained in 88% yield.

Using this condition, the scope of the carbonyl component was investigated. As shown in Table 3.1, a wide range of aldehydes readily participated in this Prins-polyene cyclization. Both aryl (**2a**) and hetero aryl (furan, **2b** and thiophene, **2c**) aldehydes gave the desired product in high yields (>71%). α,β -Unsaturated aldehydes (**2d** and **2e**) can also be applied for this Prins-polyene cyclization to construct oxaterpenoids (87% and 97%). Furthermore, aliphatic aldehydes also work well (**2f-k**). Sterically demanding aliphatic aldehydes (**2h**, **2i** and **2k**) did not show retarded reactivity and the desired products are obtained in high yield. In case of functionalized aliphatic aldehyde, benzyloxyacetaldehyde gave **4j** with slightly compromised yield (66%). It is worthy of note that 2-chloro-1,1-diethoxyethane (**2m**) and 2-bromo-1,1-diethoxyethane (**2n**), acetal protected form of aldehyde, were also reactive substrates for the reaction. The alkyl halide moiety of cyclization products could be readily functionalized. Interestingly, acetone which generally considered as less reactive carbonyl compound was good substrate for this reaction providing cyclization product **4l** in 73% yield.

Table 3.1 InBr₃-catalyzed Cyclization by Different Carbonyl Compounds^a

Entry	Substrate	Product	Yield (%) ^b
-------	-----------	---------	------------------------

7		2g		4g	81
8		2h		4h	88
9		2i		4i	79
10		2j		4j	66
11		2k		4k	84 ^c
12		2l		4l	73
13		2m		4m	69

Figure 3.2 Steroidal aldehyde **2o** induced cyclization and Crystal Structure of **4o**

Having identified that both aldehydes and acetone are suitable substrate for the titled Prins-polyene cyclization, we directed our attention to the activity of various olefin-alcohols towards benzaldehyde. As summarized in Table 3.2, substrates with both electron-donating (entries 1 to 3) and electron-withdrawing (entry 4) groups provided desired products in high yield (>80%). Satisfying results were also obtained when furan (entry 5) and indole (entry 6) tethering substrates were used. When internal alkyne (entry 7) acted as the terminating group, six-five ring compounds **4h** was obtained in 68% yield. Not only the primary alcohols, but also the secondary alcohol (entry 8) worked well and gave the desired product in 75% yield with excellent diastereoselectivity (single isomer).

Table 3.2 InBr₃-Catalyzed Prins-Polyene Cyclization^a

Entry	Substrate	Product	Yield (%) ^b
1			94
2			82
3			86
4			81
5			63

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b Isolated yield. ^c The stereochemistry of alkene was 3/1, which determined by ¹H NMR.

In view of the cationic character of Prins reaction initiated polyene cyclization, we envisioned that tetracyclic and pentacyclic compounds may be constructed based on our experiences of bio-inspired polyene cyclization. To our delight, further elongation of the 1,3-olefin-alcohol substrates to be diene, tetracyclic products (**10j-n**) were obtained in good yield (>66%) as single isomers (entries 1 to 4). The relative stereochemistry of the tetra-cyclic product was elucidated by a single-crystal X-ray analysis of **10j** as depicted in Figure 3.3. When substrate was **1m**, a diene with indole as the terminating group, the reaction proceeded well and pentacycle **10m** was obtained in 66% yield as a single isomer. It is noteworthy that four out of the five cyclohexane rings of **10n** formed in single step with 59% yield as a single isomer when triene **1n** was used as the substrate.

Table 3.3 InBr₃-Catalyzed Prins-Polyene Cyclization

Entry	Substrate	Product	Yield (%) ^a
1	1j	10j	81
2	1k	10k	87
3	1l	10l	82
4	1m	10m	66
5	1n	10n	59

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b Isolated yield.

Figure 3.3 Crystal X-ray Structure (50% ellipsoids) of **10j**

Since an efficient Prins polyene cyclization has been developed successfully, we next turned our attention to the applications of the current method. As the structure shown in Figure 3.4, moluccanic acid methyl ester **11** consists of a highly functionalized hexane core with similar side chains adopting the same relative stereochemistry.⁵⁶ We envisioned that **11** might be synthesized from **12** through elimination and elongation one more carbon through S_N2 reaction. In addition, compound **12** can be traced back to **13** with proper modification of the THP rings.

Figure 3.4 Retrosynthetic analysis

With this idea in mind, compound **13** was prepared by our prins-polyene cyclization successfully in 74% yield. In order to get the intermediate **12**, we first attempted to open the THP ring under acid condition. However, the THP ring was so stable that even refluxing in 40% HBr/acetic acid or treatment **12** with 1.0 M $TiCl_4$ in CH_2Cl_2 at room temperature did not yield any product (Scheme 3.4).

⁵⁶ Li, Y. X.; Liu, J.; Yu, S. J.; Proksch, P.; Gu, J.; Lin, W. H. *Phytochemistry* **2010**, 71, 2124.

Scheme 3.4 Synthesis **12** under acid condition

An alternative method to get intermediate **12** is to oxidize the THP ring of **13** to lactone **14**, followed by ring opening reaction. Unfortunately, the benzylic position oxidized product was formed much easier than the desired lactone **14** (Scheme 3.5).

Scheme 3.5 Oxidation of oxaterpenoids

Considering the difficulty to open the THP ring of compound **13**, we changed the strategy again. The double bond of the target molecular also could be introduced by Wittig reaction or Tebbe reaction from the ketone **16**. This ketone may be synthesized from compound **17** (Scheme 3.6).

Scheme 3.6 Retrosynthetic analysis

The key intermediate **17** was obtained in 64% yield by using 2-chloro-1,1-dimethoxyethane as the aldehyde counterpart. The chloro-substituted

oxaterpenoid **17** was then treated with sodium hydride to promote S_N2 elimination reaction. The crude enol ether **18** was subjected to HBr acetone solution affording bromo-substituted ketone **19** in 55% yield over two steps. Installation of a terminal alkene group on **19** through Wittig reaction was unsuccessful. On the other hand, the desired product **20** was obtained in 71% yield by Tebbe reaction. One carbon elongation was established in 67% yield by replacing bromide with a cyanide group. The nitrile **21** was hydrolyzed followed by esterification leading to ester **22** in 58% yield. Deprotection of ester **22** was achieved in 71% yield in the presence of trichloroborane and tetrabutyl ammonium iodide. The total synthesis of (±)-moluccanic acid methyl ester was completed in seven steps. The obtained ¹H NMR and ¹³C NMR spectrum of **11** were consistent with the reported data.

Scheme 3.7 Total synthesis of (±) Moluccanic acid methyl ester

3.3 Conclusion

In summary, a novel and efficient intermolecular Prins-polyene cyclization cascade reaction has been demonstrated to be compatible with various aldehyde,

acetone and polyolefin-alcohol substrates. Catalytic amount of InBr_3 (30 mol%) was used and excellent diastereoselectivity was observed with chiral and achiral substrates, mostly single isomers was obtained. This reaction provides an alternative and concise way to synthesize derivatives of oxaterpenoids and oxasteroids, which are widely appeared in natural products and drugs. It also yields versatile useful intermediates for natural product synthesis as shown in the total synthesis of (±)-moluccanic acid methyl ester.

3.4 Experimental Section

To an oven-dried round bottom flask (100 mL) equipped with a magnetic stir bar, aldehyde (10 mmol) and wittg reagent (12 mmol, 1.2 equiv) was dissolved in THF (50 mL). After the reaction was stirred at 60 °C for 10h, solvent was removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel using appropriate solvents (hexane/EtOAc mixture) to provide the title compounds.

(E)-Methyl 5-(furan-2-yl)-2-methylpent-2-enoate

Yield: 76%, yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 1.80 (s, 3H), 2.51 (q, *J* = 7.4 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 3.71 (s, 3H), 5.99 (d, *J* = 3.1 Hz, 1H), 6.26 (dd, *J*₁ = 1.9 Hz, *J*₂ = 3.1 Hz, 1H), 6.75 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 1.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 12.35, 26.93, 27.23, 51.74, 105.33, 110.19, 128.51, 140.68, 141.13, 154.76, 168.50. HRMS (ESI⁺) exact mass calcd for C₁₁H₁₄O₃ [M+Na]⁺ requires *m/z* 217.0841, found *m/z* 217.0843.

(E)-Methyl 5-(1-benzyl-1*H*-indol-3-yl)-2-methylpent-2-enoate

Yield: 85%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.79 (s, 3H), 2.59 (q, *J* = 7.5 Hz, 2H), 2.90 (t, *J* = 7.6 Hz, 2H), 3.72 (s, 3H), 5.27 (s, 2H), 6.87 (t, *J* = 7.3 Hz, 1H), 6.91 (s, 1H), 7.08-7.10 (m, 3H), 7.17 (t, *J* = 7.5 Hz, 2H), 7.23-7.31 (m, 3H), 7.60 (d, *J* = 7.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.48, 24.19, 29.41, 49.86, 51.72, 109.71, 114.79, 118.95, 118.99, 121.81, 125.54, 126.76, 127.55, 127.90, 127.98, 128.74, 136.73, 137.73, 142.18, 168.69. HRMS (ESI⁺) exact mass calcd for C₂₂H₂₃NO₂ [M+H]⁺ requires *m/z* 334.1807, found *m/z* 334.1805.

(2*E*,6*E*)-Methyl 2,6-dimethyl-9-phenylnona-2,6-dienoate

Yield: 99%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.55 (s, 3H), 1.83 (s, 3H), 2.07-2.10 (m, 2H), 2.26 (q, *J* = 8.6 Hz, 2H), 2.31 (q, *J* = 7.6 Hz, 2H), 2.62-2.65 (m, 2H), 3.73 (s, 3H), 5.20 (t, *J* = 7.1 Hz, 1H), 6.74 (t, *J* = 7.3 Hz, 1H), 7.16-7.19 (m, 3H), 7.25-7.28 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 12.43,

15.92, 27.28, 29.96, 36.04, 38.23, 51.70, 124.45, 125.72, 127.51, 128.24, 128.49, 134.67, 142.27, 168.70. HRMS (ESI⁺) exact mass calcd for C₁₈H₂₅O₂ [M+H]⁺ requires m/z 273.1855, found m/z 273.1844.

(2E,6E)-Methyl 2,6-dimethyl-9-(3,4,5-trimethoxyphenyl)nona-2,6-dienoate

Yield: 83%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.60 (s, 3H), 1.83 (s, 3H), 2.11 (t, J = 7.6 Hz, 2H), 2.24-2.33 (m, 4H), 2.56-2.60 (m, 2H), 3.73 (s, 3H), 3.83 (s,

3H), 3.86 (s, 6H), 5.21 (t, J = 7.0 Hz, 1H), 6.41 (s, 2H), 6.75 (t, J = 7.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.42, 16.02, 27.30, 29.99, 36.41, 38.22, 51.72, 56.05, 60.88, 105.29, 124.39, 127.54, 134.74, 136.05, 138.09, 142.15, 153.03, 168.70. HRMS (ESI⁺) exact mass calcd for C₂₁H₃₀O₅ [M+Na]⁺ requires m/z 385.1991, found m/z 385.2006.

(2E,6E,10E)-Methyl 2,6,10-trimethyl-13-phenyltrideca-2,6,10-trienoate

Yield: 98%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.58 (s, 3H), 1.64 (s, 3H), 1.86 (s, 3H), 2.00-2.03

(m, 2H), 2.08-2.13 (m, 4H), 2.27-2.35 (m, 4H), 2.65-2.68 (m, 2H), 3.76 (s, 3H), 5.16 (t, J = 6.5 Hz, 1H), 5.22 (t, J = 6.7 Hz, 1H), 6.78 (t, J = 7.3 Hz, 1H), 7.19-7.23 (m, 3H), 7.29-7.32 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 12.43, 15.99, 26.60, 27.37, 29.96, 36.15, 38.23, 39.60, 51.69, 123.71, 125.10, 125.67, 127.46, 128.22, 128.47, 133.86, 135.65, 142.32, 142.39, 168.77. HRMS (ESI⁺) exact mass calcd for C₂₃H₃₂O₂ [M+Na]⁺ requires m/z 363.2300, found m/z 363.205.

An oven-dried round bottom flask (100 mL) equipped with a magnetic stir bar, ester was dissolved in 40 mL CH₂Cl₂ and cooled to 0 °C. DIBAL-H (1.0M solution in heptane, 2.2 equiv) was added dropwisely. Then the reaction was allowed to stir at ambient temperature for 10 h. The reaction mixture was poured into cool sat. NH₄Cl, filtered through celight and extracted the filtrate with EtOAc (3 x 50 mL). The combined organic phase was washed with brine (100 mL), dried with Na₂SO₄ and concentrated *in vacuo* to give the alcohol. The product was used for the next step

without further purification.

An oven-dried round bottom flask (100 mL) equipped with a magnetic stir bar, alcohol, pyridine (1.2 equiv) and LiCl (0.2 equiv) were dissolved in DMF (50 mL). Cooled the solution to 0 °C, MsCl (1.2 equiv) was added. The reaction was allowed to stir at ambient temperature overnight. Poured the mixture to water, extracted with diethyl ether (3 x 50 mL) and washed with brine. Dried with Na₂SO₄ and concentrated *in vacuo* to give the chloro-product.

The crude chloro product was dissolved in CH₃CN, NaCN (2.0 equiv) and 18-crown-6 (1.0 equiv) were added. The mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with H₂O (2 x 100 mL) and brine (2 x 100 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel using appropriate solvents (hexane/EtOAc mixture) to provide the title compounds.

(E)-6-(Furan-2-yl)-3-methylhex-3-enenitrile

Yield: 67%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.69 (s, 3H), 2.38 (q, J = 7.3 Hz, 2H), 2.68 (t, J = 7.5 Hz, 2H), 3.01 (s, 2H), 5.50 (t, J = 7.2 Hz, 1H), 5.98 (d, J = 3.0 Hz, 1H), 6.27 (s, 1H), 7.30 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 15.94, 26.63, 27.22, 27.55, 105.24, 110.18, 117.68, 125.35, 128.34, 141.02, 155.12. HRMS (ESI⁺) exact mass calcd for C₁₁H₁₃NO [M+H]⁺ requires m/z 176.1075, found m/z 176.1075.

(E)-6-(1-Benzyl-1H-indol-3-yl)-3-methylhex-3-enenitrile

Yield: 77%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.64 (s, 3H), 2.44 (q, J = 7.2 Hz, 2H), 2.82 (t, J = 7.6 Hz, 2H), 2.98 (s, 2H), 5.27 (s, 2H), 5.59 (t, J = 7.2 Hz, 1H), 6.90 (s, 1H), 7.09-7.12 (m, 3H), 7.17 (t, J = 7.6 Hz, 2H), 7.25-7.32 (m, 3H), 7.60 (d, J = 7.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 16.06, 24.77, 27.23, 28.81, 49.85, 109.66, 115.05, 117.85, 118.92, 118.99, 121.74, 124.60, 125.51, 126.82, 127.56, 128.06, 128.74, 129.60, 136.70, 137.79. HRMS (ESI⁺) exact mass calcd for C₂₂H₂₂N₂Na [M+Na]⁺ requires m/z 337.1681, found m/z 337.1685.

(3E,7E)-3,7-Dimethyl-10-phenyldeca-3,7-dienenitrile

Yield: 87%, yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 1.55 (s, 3H), 1.71 (s, 3H), 2.00-2.03 (m,

2H), 2.12 (q, $J = 7.3$ Hz, 2H), 2.31 (q, $J = 7.4$ Hz, 2H), 2.63-2.66 (m, 2H), 2.99 (s, 2H), 5.18 (t, $J = 7.2$ Hz, 1H), 5.43 (t, $J = 7.0$ Hz, 1H), 7.18-7.19 (m, 3H), 7.25-7.29 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 15.95, 16.01, 26.55, 27.25, 29.86, 36.04, 38.94, 117.87, 124.08, 124.28, 125.71, 128.24, 128.48, 129.57, 134.92, 142.29. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{23}\text{N}$ $[\text{M}+\text{H}]^+$ requires m/z 254.1909, found m/z 254.1913.

(3E,7E)-3,7-Dimethyl-10-(3,4,5-trimethoxyphenyl)deca-3,7-dienenitrile

Yield: 60%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.59 (s, 3H), 1.72 (s, 3H), 2.01-2.05 (m, 2H), 2.13 (q, $J = 7.3$ Hz, 2H), 2.31 (q, $J = 7.4$ Hz, 2H), 2.57-2.61 (m, 2H), 3.01 (s, 2H), 3.83 (s, 3H), 3.85 (s, 6H), 5.19 (t, $J = 7.0$ Hz, 1H), 5.45 (t, $J = 7.0$ Hz, 1H), 6.41 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.03, 26.58, 27.21, 29.90, 36.39, 38.95, 56.07, 60.88, 105.31, 117.85, 124.15, 124.21, 129.44, 134.99, 136.03, 138.12, 153.01. HRMS (ESI^+) exact mass calcd for $\text{C}_{21}\text{H}_{29}\text{NO}_3$ $[\text{M}+\text{Na}]^+$ requires m/z 366.2054, found m/z 366.2052.

(3E,7E)-10-(1-Benzyl-1H-indol-3-yl)-3,7-dimethyldeca-3,7-dienenitrile

Yield: 75%. ^1H NMR (400 MHz, CDCl_3): δ 1.52 (s, 3H), 1.66 (s, 3H), 1.95-1.98 (m, 2H), 2.06 (q, $J = 7.3$ Hz, 2H), 2.37 (q, $J = 7.3$ Hz, 2H), 2.81 (t, $J = 7.6$ Hz, 2H), 2.92 (s, 2H), 5.24 (t, $J = 7.6$ Hz, 1H), 5.34 (s, 2H), 5.39 (t, $J = 7.0$ Hz, 1H), 7.04-7.15 (m, 5H), 7.17-7.27 (m, 4H), 7.55 (d, $J = 6.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.00, 16.06, 24.43, 26.56, 27.22, 28.37, 38.99, 46.86, 109.62, 111.94, 117.95, 118.53, 119.80, 121.92, 123.30, 124.09, 124.31, 126.46, 127.05, 127.48, 128.74, 129.64, 135.06, 135.44, 137.37. HRMS (ESI^+) exact mass calcd for $\text{C}_{27}\text{H}_{30}\text{N}_2$ $[\text{M}+\text{K}]^+$ requires m/z 421.2046, found m/z 421.2044.

(3E,7E,11E)-3,7,11-Trimethyl-14-phenyltetradeca-3,7,11-trienenitrile

Yield: 80%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.56 (s, 3H), 1.60 (s, 3H), 1.72 (s, 3H), 1.97-2.08 (m, 6H), 2.13 (q, $J = 7.2$ Hz, 2H), 2.31 (q, $J = 7.6$ Hz, 2H), 2.62-2.66 (m, 2H), 3.01 (s, 2H), 5.11 (t, $J = 6.7$ Hz, 1H), 5.19 (t, $J = 7.0$ Hz, 1H), 5.46 (t, $J = 7.0$ Hz, 1H), 7.18-7.20 (m, 3H), 7.26-7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.98, 26.61, 26.67, 27.26, 29.97, 36.16, 38.97, 39.65, 117.85, 123.66, 124.03, 124.89, 125.68, 128.22, 128.48, 129.66, 134.14, 135.71, 142.39. HRMS (ESI^+)

exact mass calcd for $C_{23}H_{31}N$ $[M+H]^+$ requires m/z 322.2535, found m/z 322.2542.

To an oven-dried round bottom flask (50 mL) equipped with a magnetic stir bar, the cyanide (1.0 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and cooled to $-78\text{ }^\circ\text{C}$. DIBAL-H (1.1 mL of a 1.0M solution in heptane, 1.1 mmol, 1.1 equiv) was added dropwisely. The solution was allowed to stir at $-78\text{ }^\circ\text{C}$ for 1h and then EtOH (0.1 mL) was added, the reaction mixture was diluted with EtOAc (10 mL) and poured into Sat. NH_4Cl (10 mL). After stirred for 10 mins, potassium sodium tartrate (2.0 equiv) was added and stirred for 2h. Separated the organic layer, and exacted the aquous with EtOAc (2 x 30mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The crude product was dissolved in 10 mL MeOH/THF (1/4) and cooled to $0\text{ }^\circ\text{C}$. $NaBH_4$ (1.0 equiv.) was added and the mixture was stirred for 1 h at $0\text{ }^\circ\text{C}$. The reaction was quenched with 1 M HCl solution and extracted with EtOAc (3 x 20 mL). the combined organic layer was washed with brine (30 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using EtOAc in hexane to provide the title compound.

(E)-3-Methyl-6-phenylhex-3-en-1-ol (1a)

Yield: 84%, colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ 1.55 (s, 3H), 2.22 (t, $J = 6.0$ Hz, 2H), 2.36 (q, $J = 7.2$ Hz, 2H), 2.68 (t, $J = 7.2$ Hz, 2H), 3.58-3.63 (m, 2H), 5.27 (t, $J = 7.2$ Hz, 1H), 7.17-7.20 (m, 3H), 7.26-7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.62, 29.88, 35.87, 42.66, 59.93, 125.86, 127.19, 128.32, 128.45, 132.04, 142.01. HRMS (ESI $^+$) exact mass calcd for $C_{13}H_{18}ONa$ $[M+Na]^+$ requires m/z 213.1255, found m/z 213.1260.

(E)-6-(2-Methoxyphenyl)-3-methylhex-3-en-1-ol (1b)

Yield: 80%, colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ 1.53 (s, 3H), 2.20 (t, $J = 6.1$ Hz, 2H), 2.33 (q, $J = 7.4$ Hz, 2H), 2.67 (t, $J = 7.6$ Hz, 2H), 3.59 (t, $J = 6.2$ Hz, 2H), 3.81 (s, 3H), 5.29 (t, $J = 7.2$ Hz, 1H), 6.83 (d, $J = 8.2$ Hz, 1H), 6.87 (t, $J = 7.4$ Hz, 1H), 7.10 (d, $J = 7.4$ Hz, 1H), 7.17 (t, $J = 7.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.52,

28.26, 30.34, 42.66, 55.32, 59.96, 110.36, 120.38, 127.13, 127.66, 129.96, 130.40, 131.71, 157.51. HRMS (ESI⁺) exact mass calcd for C₁₄H₂₀O₂Na [M+Na]⁺ requires *m/z* 243.1361, found *m/z* 243.1358.

(E)-6-(4-Methoxyphenyl)-3-methylhex-3-en-1-ol (1c)

Yield: 87%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.55 (s, 3H), 2.22 (t, *J* = 6.2 Hz, 2H), 2.31 (q, *J* = 7.4 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 3.60 (t, *J* = 6.2 Hz, 2H), 3.78 (s, 3H), 5.26 (t, *J* = 7.1 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 15.68, 30.14, 34.97, 42.67, 55.26, 60.02, 113.72, 127.19, 129.31, 131.96, 134.12, 157.77. HRMS (ESI⁺) exact mass calcd for C₁₄H₂₀O₂Na [M+Na]⁺ requires *m/z* 243.1361, found *m/z* 243.1364.

(E)-3-Methyl-6-(3,4,5-trimethoxyphenyl)hex-3-en-1-ol (1d)

Yield: 88%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.59 (s, 3H), 2.24 (t, *J* = 6.2 Hz, 2H), 2.35 (q, *J* = 7.4 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 3.63 (t, *J* = 6.3 Hz, 2H), 3.82 (s, 3H), 3.85 (s, 6H), 5.27 (t, *J* = 6.5 Hz, 1H), 6.40 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 15.79, 29.94, 36.29, 42.65, 56.05, 60.06, 60.85, 105.32, 126.86, 132.20, 136.11, 137.87, 153.05. HRMS (ESI⁺) exact mass calcd for C₁₆H₂₄O₄Na [M+Na]⁺ requires *m/z* 303.1572, found *m/z* 303.1571.

(E)-6-(4-Chlorophenyl)-3-methylhex-3-en-1-ol (1e)

Yield: 79%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.55 (s, 3H), 2.22 (t, *J* = 6.2 Hz, 2H), 2.32 (q, *J* = 7.3 Hz, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 3.62 (t, *J* = 6.2 Hz, 2H), 5.24 (t, *J* = 7.1 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 15.70, 29.77, 35.22, 42.63, 60.05, 126.61, 128.37, 129.80, 131.53, 132.44, 140.43. HRMS (ESI⁺) exact mass calcd for C₁₃H₁₇ClONa [M+Na]⁺ requires *m/z* 247.0866, found *m/z* 247.0870.

(E)-6-(Furan-2-yl)-3-methylhex-3-en-1-ol (1f)

Yield: 76%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.58 (s, 3H), 2.23 (t, *J* = 6.1 Hz, 2H), 2.38 (q, *J* = 7.3 Hz, 2H), 2.68 (t, *J* = 7.3 Hz, 2H), 3.62 (t, *J* = 6.1 Hz, 2H), 5.26 (t, *J* = 7.2 Hz, 1H), 5.98 (d, *J* = 2.7 Hz, 1H), 6.28 (dd, *J*₁ = 1.9 Hz, *J*₂ = 2.9 Hz, 1H), 7.30 (s, 1H); ¹³C NMR (100

MHz, CDCl₃): δ 15.51, 26.74, 28.00, 42.62, 59.87, 105.08, 110.14, 126.70, 132.47, 140.96, 155.80. HRMS (ESI⁺) exact mass calcd for C₁₁H₁₆O₂Na [M+Na]⁺ requires m/z 203.1048, found m/z 203.1040.

(E)-6-(1-Benzyl-1H-indol-2-yl)-3-methylhex-3-en-1-ol (1g)

Yield: 83%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.56 (s, 3H), 2.21 (t, J = 6.2 Hz, 2H), 2.44 (q, J = 7.3 Hz, 2H), 2.81 (t, J = 7.5 Hz, 2H), 3.59 (t, J = 6.2 Hz, 2H), 5.24 (s, 2H), 5.33 (t, J = 7.0 Hz, 1H), 6.88 (s, 1H), 7.08-7.11 (m, 3H), 7.15 (t, J = 7.6 Hz, 1H), 7.22-7.30 (m, 4H), 7.61 (d, J = 7.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 15.83, 25.28, 28.85, 42.70, 49.85, 60.05, 109.67, 115.63, 118.90, 119.13, 121.72, 125.45, 126.84, 127.54, 127.93, 128.23, 128.75, 131.75, 136.76, 137.90. HRMS (ESI⁺) exact mass calcd for C₂₂H₂₅NONa [M+Na]⁺ requires m/z 342.1834, found m/z 342.1845.

(E)-3-Methyldec-3-en-7-yn-1-ol (1h)

Yield: 68%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.10 (t, J = 7.5 Hz, 3H), 1.66 (s, 3H), 2.12-2.18 (m, 2H), 2.21-2.23 (m, 4H), 2.27 (t, J = 6.1 Hz, 2H), 3.65 (t, J = 6.1 Hz, 2H), 5.28 (t, J = 6.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.35, 14.23, 15.78, 19.13, 27.56, 42.61, 59.76, 79.03, 82.04, 126.64, 132.61. HRMS (ESI⁺) exact mass calcd for C₁₁H₁₈ONa [M+Na]⁺ requires m/z 189.1255, found m/z 189.1250.

(E)-5-Methyl-8-phenyloct-5-en-3-ol (1i)

Yield: 75%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.87 (t, J = 7.5 Hz, 3H), 1.34-1.42 (m, 2H), 1.47 (s, 3H), 1.88 (dd, J_1 = 9.5 Hz, J_2 = 13.4 Hz, 1H), 2.10 (d, J = 13.4 Hz, 1H), 2.29 (q, J = 7.5 Hz, 2H), 2.54-2.64 (m, 2H), 3.43-3.49 (m, 1H), 5.19 (t, J = 7.1 Hz, 1H), 7.09-7.12 (m, 3H), 7.17-7.22 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): 10.03, 16.02, 29.71, 29.89, 35.87, 47.55, 69.78, 125.88, 127.61, 128.34, 128.44, 132.92, 141.97. HRMS (ESI⁺) exact mass calcd for C₁₅H₂₂ONa [M+Na]⁺ requires m/z 241.1568, found m/z 241.1567.

(3E,7E)-3,7-Dimethyl-10-phenyldeca-3,7-dien-1-ol (1j)

Yield: 81%. ¹H NMR (400 MHz, CDCl₃): δ 1.55 (s, 3H), 1.62 (s, 3H), 2.01 (t, J = 7.1 Hz, 2H), 2.12 (q, J = 7.3 Hz, 2H), 2.23 (t, J = 6.1 Hz,

2H), 2.30 (q, $J = 7.3$ Hz, 2H), 2.63 (t, $J = 7.6$ Hz, 2H), 3.63 (t, $J = 6.2$ Hz, 2H), 5.16-5.21 (m, 2H), 7.15-7.19 (m, 2H), 7.25-7.29 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.73, 15.88, 26.49, 29.95, 36.10, 39.56, 42.63, 59.93, 124.03, 125.69, 127.85, 128.23, 128.49, 131.22, 135.51, 142.36. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{26}\text{ONa}$ $[\text{M}+\text{Na}]^+$ requires m/z 281.1881, found m/z 281.1888.

(3E,7E)-10-(2-Methoxyphenyl)-3,7-dimethyldeca-3,7-dien-1-ol (1k)

Yield: 88%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.56 (s, 3H), 1.63 (s, 3H), 2.03 (t, $J = 7.4$ Hz, 2H), 2.12 (q, $J = 7.3$ Hz, 2H), 2.22-2.27

(m, 4H), 2.63 (t, $J = 7.5$ Hz, 2H), 3.64 (t, $J = 6.0$ Hz, 2H), 3.82 (s, 3H), 5.21 (t, $J = 7.0$ Hz, 2H), 6.84 (d, $J = 8.2$ Hz, 1H), 6.87 (t, $J = 7.4$ Hz, 1H), 7.12 (d, $J = 7.4$ Hz, 1H), 7.16 (t, $J = 7.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.74, 15.81, 26.56, 28.21, 30.54, 39.59, 42.67, 55.24, 59.96, 110.16, 120.29, 124.55, 126.93, 127.91, 129.86, 130.72, 131.18, 135.19, 157.51. HRMS (ESI^+) exact mass calcd for $\text{C}_{19}\text{H}_{28}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 311.1987, found m/z 311.1984.

(3E,7E)-3,7-Dimethyl-10-(3,4,5-trimethoxyphenyl)deca-3,7-dien-1-ol (1l)

Yield: 86%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.57 (s, 3H), 1.62 (s, 3H), 2.01-2.05 (m, 2H), 2.11-2.16 (m, 2H), 2.23 (t, $J = 6.2$ Hz, 2H), 2.30 (q, $J = 7.3$ Hz, 2H),

2.57-2.61 (m, 2H), 3.63 (t, $J = 6.2$ Hz, 2H), 3.82 (s, 3H), 3.85 (s, 6H), 5.18 (t, $J = 7.5$ Hz, 2H), 6.41 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.70, 15.93, 26.41, 29.86, 36.39, 39.52, 42.62, 56.04, 59.90, 60.86, 105.31, 123.96, 127.65, 131.28, 135.56, 135.97, 138.17, 152.97. HRMS (ESI^+) exact mass calcd for $\text{C}_{21}\text{H}_{32}\text{O}_4$ $[\text{M}+\text{Na}]^+$ requires m/z 371.2198, found m/z 371.2201.

(3E,7E)-10-(1-Benzyl-1H-indol-3-yl)-3,7-dimethyldeca-3,7-dien-1-ol (1m)

Yield: 79%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.50 (s, 3H), 1.60 (s, 3H), 1.97-2.00 (m, 2H), 2.06-2.10 (m, 2H), 2.22 (t, $J = 6.1$ Hz,

2H), 2.37 (q, $J = 7.4$ Hz, 2H), 2.81 (t, $J = 7.4$ Hz, 2H), 3.62 (t, $J = 6.2$ Hz, 2H), 5.19 (t, $J = 7.1$ Hz, 1H), 5.25 (t, $J = 7.2$ Hz, 1H), 5.36 (s, 2H), 7.05-7.09 (m, 2H), 7.10-7.15 (m, 3H), 7.18-7.28 (m, 4H), 7.54-7.57 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.71,

15.93, 24.45, 26.48, 28.39, 39.58, 42.64, 46.84, 59.91, 109.55, 111.99, 118.52, 121.85, 123.27, 124.10, 126.43, 127.01, 127.42, 127.97, 128.71, 131.17, 135.41, 135.59, 137.35. HRMS (ESI⁺) exact mass calcd for C₂₇H₃₃NO [M+H]⁺ requires *m/z* 388.2640, found *m/z* 388.2642.

(3*E*,7*E*,11*E*)-3,7,11-Trimethyl-14-phenyltetradeca-3,7,11-trien-1-ol (1n)

Yield: 83%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.55 (s, 3H), 1.59 (s, 3H), 1.63 (s, 3H), 1.96-2.16 (m, 8H), 2.24 (t, *J* = 6.0 Hz, 2H), 2.30 (q, *J* = 7.6 Hz, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 3.64 (q, *J* = 6.0 Hz, 2H), 5.11 (t, *J* = 6.8 Hz, 1H), 5.17-5.23 (m, 2H), 7.18-7.20 (m, 3H), 7.25-7.29 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 15.69, 15.89, 15.98, 26.52, 26.61, 29.98, 36.16, 39.57, 39.67, 42.64, 59.84, 123.64, 124.67, 125.66, 127.98, 128.21, 128.47, 131.13, 134.70, 135.74, 142.43. HRMS (ESI⁺) exact mass calcd for C₂₃H₃₄O [M+Na]⁺ requires *m/z* 349.2507, found *m/z* 349.2510.

Experimental Data for InBr₃ Catalyzed Prins Cascade Reaction Products

An oven-dried round bottom flask (10 mL) equipped with a magnetic stir bar was charged with 4Å molecular sieves (100 mg), indium bromide (0.03 mmol, 0.3 equiv) and sealed with a rubber septum. Then alcohol (0.10 mmol) and aldehyde (0.12 mmol, 1.2 equiv) were dissolved in dry CH₂Cl₂ (2 mL) and added via syringe. The solution was allowed to stir at room temperature for 48 h and then quenched with sat. NaHCO₃ (5mL), and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using appropriate solvents (hexane/EtOAc mixture) to provide the title compounds.

10b-Methyl-4-phenyl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (4a)

Yield: 88%, white solid, mp: 83.9-84.8 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.16-1.22 (m, 1H), 1.33 (s, 3H), 1.51 (ddt, *J*₁ = 8.1 Hz, *J*₂ = 10.1 Hz, *J*₃ = 13.3 Hz, 1H), 1.89 (ddd, *J*₁ = 3.3 Hz, *J*₂ = 10.3 Hz, *J*₃ = 13.3 Hz, 1H), 2.04 (dt, *J*₁ = 5.1 Hz, *J*₂ = 12.8 Hz, 1H), 2.14 (d, *J* =

13.1 Hz, 1H), 2.70-2.77 (m, 2H), 4.03 (dt, $J_1 = 2.5$ Hz, $J_2 = 12.2$ Hz, 1H), 4.12 (dd, $J_1 = 5.1$ Hz, $J_2 = 11.9$ Hz, 1H), 4.36 (d, $J = 10.3$ Hz, 1H), 7.02 (d, $J = 7.4$ Hz, 1H), 7.10 (t, $J = 7.3$ Hz, 1H), 7.16 (t, $J = 7.4$ Hz, 1H), 7.24 (d, $J = 7.7$ Hz, 1H), 7.25-7.33 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.70, 21.89, 27.91, 35.72, 37.97, 46.74, 64.38, 80.38, 123.92, 125.82, 125.87, 127.46, 127.94, 128.43, 129.36, 135.13, 141.21, 147.02. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{22}\text{ONa}$ [$\text{M}+\text{Na}$] $^+$ requires m/z 301.1568, found m/z 301.1564.

4-(Furan-2-yl)-10b-methyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene

(4b)

Yield: 79%, yellow solid, mp: 75.4-76.2 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.26-1.33 (m, 1H), 1.29 (s, 3H), 1.47-1.58 (m, 1H), 2.01 (dt, $J_1 = 5.2$ Hz, $J_2 = 12.8$ Hz, 1H), 2.11 (d, $J = 13.1$ Hz, 1H), 2.18 (ddd, $J_1 = 3.3$ Hz, $J_2 = 10.8$ Hz, $J_3 = 13.7$ Hz, 1H), 2.83-2.87 (m, 2H), 4.02 (dt, $J_1 = 2.5$ Hz, $J_2 = 12.2$ Hz, 1H), 4.10 (ddd, $J_1 = 1.6$ Hz, $J_2 = 5.2$ Hz, $J_3 = 12.0$ Hz, 1H), 4.49 (d, $J = 10.7$ Hz, 1H), 6.32-6.35 (m, 2H), 7.06 (d, $J = 7.3$ Hz, 1H), 7.12 (t, $J = 7.1$ Hz, 1H), 7.17 (t, $J = 1.5$ Hz, 1H), 7.23 (d, $J = 7.5$ Hz, 1H), 7.39 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.66, 21.68, 27.97, 35.55, 37.57, 44.15, 64.39, 72.88, 108.19, 110.06, 123.88, 125.80, 125.89, 129.35, 134.98, 142.31, 146.63, 153.78. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{21}\text{O}_2$ [$\text{M}+\text{H}$] $^+$ requires m/z 269.1542, found m/z 269.1533.

10b-Methyl-4-(thiophen-2-yl)-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene

(4c)

Yield: 71%, yellow solid, mp: 84.0-85.2 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.32 (s, 3H), 1.37 (tdd, $J_1 = 3.3$ Hz, $J_2 = 6.9$ Hz, $J_3 = 13.6$ Hz, 1H), 1.47-1.58 (m, 1H), 1.90 (ddd, $J_1 = 3.3$ Hz, $J_2 = 10.4$ Hz, $J_3 = 13.5$ Hz, 1H), 2.03 (dt, $J_1 = 5.2$ Hz, $J_2 = 12.8$ Hz, 1H), 2.13 (d, $J = 13.1$ Hz, 1H), 2.75-2.87 (m, 2H), 4.04 (dt, $J_1 = 2.5$ Hz, $J_2 = 12.2$ Hz, 1H), 4.12 (ddd, $J_1 = 1.7$ Hz, $J_2 = 5.2$ Hz, $J_3 = 12.0$ Hz, 1H), 4.70 (d, $J = 10.4$ Hz, 1H), 6.97 (dd, $J_1 = 3.5$ Hz, $J_2 = 5.0$ Hz, 1H), 7.01 (dd, $J_1 = 1.1$ Hz, $J_2 = 3.4$ Hz, 1H), 7.05 (d, $J = 7.3$ Hz, 1H), 7.12 (dt, $J_1 = 1.5$ Hz, $J_2 = 7.3$ Hz, 1H), 7.17 (t, $J = 7.3$ Hz, 1H), 7.24 (d, $J = 8.3$ Hz, 1H), 7.27 (d, $J = 5.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.79, 21.93, 27.98, 35.86, 37.68, 47.97, 64.45, 75.59, 123.90, 125.13, 125.49, 125.83, 125.90, 126.16, 129.34, 135.05, 144.59, 146.65. HRMS (ESI^+) exact mass calcd for

$C_{18}H_{20}OSNa$ $[M+Na]^+$ requires m/z 307.1133, found m/z 307.1126.

10b-Methyl-4-((*E*)-styryl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (4d)

Yield: 87%, colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, 3H), 1.55-1.61 (m, 1H), 1.69-1.79 (m, 2H), 1.94 (dt, $J_1 = 5.2$ Hz, $J_2 = 12.8$ Hz, 1H), 2.10 (d, $J = 13.1$ Hz, 1H), 2.88 (dd, $J_1 = 4.8$ Hz, $J_2 = 8.8$ Hz, 2H), 3.98 (dt, $J_1 = 2.3$ Hz, $J_2 = 12.3$ Hz, 1H), 4.03-4.09 (m, 2H), 6.17 (dd, $J_1 = 7.8$ Hz, $J_2 = 15.9$ Hz, 1H), 6.65 (d, $J = 15.9$ Hz, 1H), 7.06 (d, $J = 7.3$ Hz, 1H), 7.10-7.18 (m, 2H), 7.21-7.26 (m, 2H), 7.31 (t, $J = 7.5$ Hz, 2H), 7.41 (d, $J = 7.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.83, 21.95, 28.06, 35.30, 37.77, 45.65, 63.79, 78.29, 123.89, 125.78, 125.83, 126.60, 127.75, 128.57, 1229.25, 129.35, 133.25, 135.04, 136.75, 146.87. HRMS (ESI^+) exact mass calcd for $C_{22}H_{25}O$ $[M+H]^+$ requires m/z 305.1905, found m/z 305.1920.

10b-Methyl-4-((*E*)-prop-1-en-1-yl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (4e)

Yield: 90%, colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.50 (ddt, $J_1 = 8.0$ Hz, $J_2 = 10.1$ Hz, $J_3 = 13.3$ Hz, 1H), 1.54-1.62 (m, 1H), 1.68-1.73 (m, 3H), 1.74 (dd, $J_1 = 1.6$ Hz, $J_2 = 6.5$ Hz, 1H), 1.88 (dt, $J_1 = 5.2$ Hz, $J_2 = 12.8$ Hz, 1H), 2.05 (d, $J = 13.1$ Hz, 1H), 2.88 (dd, $J_1 = 5.0$ Hz, $J_2 = 8.7$ Hz, 2H), 3.82 (t, $J_1 = 9.2$ Hz, 1H), 3.92 (dt, $J_1 = 2.3$ Hz, $J_2 = 12.3$ Hz, 1H), 4.00 (ddd, $J_1 = 1.6$ Hz, $J_2 = 5.3$ Hz, $J_3 = 11.8$ Hz, 1H), 5.43 (dd, $J_1 = 8.1$ Hz, $J_2 = 15.3$ Hz, 1H), 5.76 (qd, $J_1 = 6.5$ Hz, $J_2 = 15.1$ Hz, 1H), 7.08 (t, $J = 7.4$ Hz, 1H), 7.12 (dd, $J_1 = 1.8$ Hz, $J_2 = 7.3$ Hz, 1H), 7.16 (d, $J = 5.5$ Hz, 1H), 7.20 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.89, 19.77, 21.94, 28.14, 35.17, 37.76, 45.25, 63.63, 78.30, 123.88, 125.70, 125.73, 129.31, 130.11, 131.15, 135.11, 147.03. HRMS (ESI^+) exact mass calcd for $C_{17}H_{22}ONa$ $[M+Na]^+$ requires m/z 265.1568, found m/z 265.1566.

10b-Methyl-4-phenethyl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (4f)

Yield: 94%, colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 3H), 1.46-1.55 (m, 1H), 1.56-1.61 (m, 1H), 1.65-1.75 (m, 1H), 1.77-1.82 (m, 1H), 1.85-1.93 (dt, $J_1 = 5.1$ Hz, $J_2 = 13.0$ Hz, 1H), 1.93-2.01 (m, 1H), 2.06 (d, $J = 13.0$ Hz, 1H), 2.66 (ddd, $J_1 = 6.2$ Hz, $J_2 = 10.6$ Hz, $J_3 = 13.6$ Hz, 1H), 2.83-2.91 (m, 3H), 3.45 (dt, $J_1 = 2.7$ Hz, $J_2 = 9.2$ Hz, 1H), 3.87 (dt, $J_1 = 2.3$ Hz, $J_2 = 12.6$ Hz, 1H), 4.04

(ddd, $J_1 = 1.4$ Hz, $J_2 = 5.0$ Hz, $J_3 = 11.8$ Hz, 1H), 7.06 (d, $J = 7.0$ Hz, 1H), 7.11 (dt, $J_1 = 1.5$ Hz, $J_2 = 7.0$ Hz, 1H), 7.15-7.30 (m, 7H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.39, 21.83, 27.96, 31.58, 35.37, 35.44, 38.10, 45.29, 63.87, 75.40, 123.86, 125.70, 125.75, 128.36, 128.54, 129.19, 134.91, 142.79, 147.24. HRMS (ESI^+) exact mass calcd for $\text{C}_{22}\text{H}_{26}\text{ONa}$ [$\text{M}+\text{Na}$] $^+$ requires m/z 329.1881, found m/z 329.1869.

4-Isobutyl-10b-methyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene (4g)

Yield: 81%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.92 (t, $J = 6.6$ Hz, 6H), 1.22 (s, 3H), 1.35-1.38 (m, 2H), 1.49-1.55 (m, 2H), 1.79-1.93 (m, 3H), 2.04 (d, $J = 13.0$ Hz, 1H), 2.89-2.92 (m, 2H), 3.45 (dd, $J_1 = 9.0$ Hz, $J_2 = 12.8$ Hz, 1H), 3.83 (dt, $J_1 = 2.2$ Hz, $J_2 = 12.4$ Hz, 1H), 3.98 (ddd, $J_1 = 1.5$ Hz, $J_2 = 5.0$ Hz, $J_3 = 11.8$ Hz, 1H), 7.07 (d, $J = 7.1$ Hz, 1H), 7.11 (t, $J = 7.0$ Hz, 1H), 7.16 (t, $J = 7.0$ Hz, 1H), 7.19 (d, $J = 7.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.42, 21.56, 21.93, 24.12, 24.17, 28.02, 35.40, 38.08, 42.69, 46.06, 63.80, 74.12, 123.83, 125.69, 125.70, 129.16, 134.97, 147.37. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{26}\text{ONa}$ [$\text{M}+\text{Na}$] $^+$ requires m/z 281.1881, found m/z 281.1871.

4-Cyclohexyl-10b-methyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene (4h)

Yield: 88%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.16-1.26 (m, 3H), 1.20 (s, 3H), 1.47-1.58 (m, 6H), 1.63-1.65 (m, 1H), 1.70-1.86 (m, 5H), 2.01 (d, $J = 13.0$ Hz, 1H), 2.90 (dd, $J_1 = 5.0$ Hz, $J_2 = 8.9$ Hz, 2H), 3.27 (d, $J = 10.0$ Hz, 1H), 3.79 (dt, $J_1 = 2.3$ Hz, $J_2 = 12.4$ Hz, 1H), 3.98 (ddd, $J_1 = 1.5$ Hz, $J_2 = 5.0$ Hz, $J_3 = 11.8$ Hz, 1H), 7.06 (d, $J = 7.0$ Hz, 1H), 7.10 (t, $J = 6.9$ Hz, 1H), 7.15 (t, $J = 7.0$ Hz, 1H), 7.19 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 18.90, 21.62, 24.71, 26.64, 26.69, 27.06, 27.96, 30.87, 35.41, 38.20, 38.79, 41.57, 64.15, 79.93, 123.92, 125.66, 125.68, 129.13, 135.00, 147.64. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{28}\text{ONa}$ [$\text{M}+\text{Na}$] $^+$ requires m/z 307.2038, found m/z 307.2029.

4-(tert-Butyl)-10b-methyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene (4i)

Yield: 79%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.00 (s, 9H), 1.25 (s, 3H), 1.56-1.66 (m, 1H), 1.77 (ddd, $J_1 = 3.4$ Hz, $J_2 = 9.6$ Hz, $J_3 = 12.8$ Hz, 1H), 1.83 (dd, $J_1 = 5.3$ Hz, $J_2 = 12.9$ Hz, 1H), 2.02 (d, $J = 12.9$ Hz, 1H), 2.06-2.08 (m, 1H), 2.86-2.90 (m, 2H), 3.05 (d, $J = 9.5$ Hz, 1H), 3.78 (dt, $J_1 = 2.3$ Hz, $J_2 = 12.8$ Hz, 1H), 3.99 (dd, $J_1 = 5.2$ Hz,

$J_2 = 11.8$ Hz, 1H), 7.05 (d, $J = 7.0$ Hz, 1H), 7.10 (t, $J = 7.1$ Hz, 1H), 7.16 (t, $J = 7.0$ Hz, 1H), 7.21 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.85, 22.21, 27.79, 28.31, 35.10, 36.36, 38.60, 44.24, 64.60, 83.54, 124.38, 125.64, 125.73, 128.90, 134.65, 147.52. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{26}\text{ONa}$ $[\text{M}+\text{Na}]^+$ requires m/z 281.1881, found m/z 281.1875.

4-((Benzyloxy)methyl)-10b-methyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene (4h)

Yield: 66%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.21 (s, 3H), 1.48-1.59 (m, 1H), 1.63-1.70 (m, 1H), 1.83-1.94 (m, 2H), 2.04 (d, $J = 13.1$ Hz, 1H), 2.86-2.90 (m, 2H), 3.55 (dd, $J_1 = 4.8$ Hz, $J_2 = 10.1$ Hz, 1H), 3.60-3.64 (m, 1H), 3.68 (dd, $J_1 = 2.3$ Hz, $J_2 = 10.1$ Hz, 1H), 3.91 (dt, $J_1 = 2.4$ Hz, $J_2 = 12.4$ Hz, 1H), 4.06 (ddd, $J_1 = 1.6$ Hz, $J_2 = 5.1$ Hz, $J_3 = 11.8$ Hz, 1H), 4.53 (d, $J = 12.3$ Hz, 1H), 4.65 (d, $J = 12.3$ Hz, 1H), 7.07 (d, $J = 6.9$ Hz, 1H), 7.10 (dt, $J_1 = 1.7$ Hz, $J_2 = 7.0$ Hz, 1H), 7.16 (t, $J = 7.0$ Hz, 1H), 7.19 (d, $J = 7.4$ Hz, 1H), 7.26-7.35 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.18, 21.71, 27.88, 35.07, 37.70, 41.89, 63.98, 71.46, 73.54, 75.83, 123.87, 125.72, 125.74, 127.61, 127.83, 128.34, 129.19, 134.83, 138.30, 146.97. HRMS (ESI^+) exact mass calcd for $\text{C}_{22}\text{H}_{26}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 345.1831, found m/z 345.1842.

10b-Methyl-4-(1-phenylethyl)-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene (4k)

Yield: 84%, colorless oil, dr: 50:50. ^1H NMR (400 MHz, CDCl_3): δ 1.19 (s, 3H), 1.21 (s, 3H), 1.24 (s, 1.5H), 1.25 (s, 1.5H), 1.27-1.31 (m, 1H), 1.38 (s, 1.5H), 1.40 (s, 1.5H), 1.49-1.56 (m, 1H), 1.60-1.74 (m, 2H), 1.78-2.03 (m, 7H), 2.56-2.65 (m, 1H), 2.79 (dd, $J_1 = 6.3$ Hz, $J_2 = 17.4$ Hz, 1H), 2.96 (dd, $J_1 = 5.4$ Hz, $J_2 = 8.9$ Hz, 2H), 3.00-3.07 (m, 2H), 3.57 (ddd, $J_1 = 2.5$ Hz, $J_2 = 5.8$ Hz, $J_3 = 9.9$ Hz, 2H), 3.68 (dt, $J_1 = 2.3$ Hz, $J_2 = 12.5$ Hz, 1H), 3.84 (t, $J = 12.3$ Hz, 1H), 3.93 (ddd, $J_1 = 1.5$ Hz, $J_2 = 5.0$ Hz, $J_3 = 11.8$ Hz, 1H), 4.05 (ddd, $J_1 = 1.6$ Hz, $J_2 = 5.0$ Hz, $J_3 = 11.7$ Hz, 1H), 6.95 (d, $J = 7.2$ Hz, 1H), 7.01-7.06 (m, 1.5H), 7.08-7.16 (m, 5.5H), 7.17-7.23 (m, 4H), 7.30-7.37 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.73, 19.07, 19.36, 20.50, 21.59, 21.95, 27.79, 27.89, 35.24, 35.61, 37.88, 38.09, 39.92, 41.27, 42.54, 63.85, 79.64, 79.87, 123.76, 123.88, 125.57, 125.59, 125.77, 125.79, 125.96, 126.01, 127.85, 128.00, 128.25, 129.10, 129.15, 129.22, 134.92, 135.00, 143.33, 146.31, 147.42, 147.55. HRMS (ESI^+) exact mass calcd for

C₂₂H₂₆O [M+H]⁺ requires m/z 307.2062, found m/z 307.2060.

4-(Chloromethyl)-10b-methyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene (4m)

Yield: 69%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.23 (s, 3H), 1.55-1.66 (m, 1H), 1.75-1.82 (m, 1H), 1.90 (ddd, $J_1 = 4.3$ Hz, $J_2 = 11.6$ Hz, $J_3 = 13.3$ Hz, 2H), 2.07 (d, $J = 13.1$ Hz, 1H), 2.93-2.97 (m, 2H), 3.65-3.70 (m, 2H), 3.81-3.84 (m, 1H), 3.93 (dt, $J_1 = 2.4$ Hz, $J_2 = 12.4$ Hz, 1H), 4.08 (ddd, $J_1 = 1.6$ Hz, $J_2 = 5.1$ Hz, $J_3 = 11.9$ Hz, 1H), 7.08 (d, $J = 6.8$ Hz, 1H), 7.12 (dd, $J_1 = 1.8$ Hz, $J_2 = 6.9$ Hz, 1H), 7.15 (d, $J = 5.9$ Hz, 1H), 7.19 (t, $J = 6.2$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 19.14, 21.74, 27.59, 35.08, 37.51, 42.34, 47.02, 64.02, 75.48, 123.83, 125.85, 125.92, 129.23, 134.62, 146.54. HRMS (ESI⁺) exact mass calcd for C₁₅H₁₉ClONa [M+Na]⁺ requires m/z 273.1022, found m/z 273.1016.

4-(Bromomethyl)-10b-methyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene (4n)

Yield: 58%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.24 (s, 3H), 1.56-1.62 (m, 1H), 1.7 (ddd, $J_1 = 3.4$ Hz, $J_2 = 7.0$ Hz, $J_3 = 13.8$ Hz, 1H), 1.81-1.89 (m, 1H), 1.93 (dd, $J_1 = 5.1$ Hz, $J_2 = 12.9$ Hz, 1H), 2.06 (d, $J = 13.2$ Hz, 1H), 2.93-2.97 (m, 2H), 3.52 (dd, $J_1 = 4.9$ Hz, $J_2 = 10.9$ Hz, 1H), 3.61 (ddd, $J_1 = 2.2$ Hz, $J_2 = 4.9$ Hz, $J_3 = 9.7$ Hz, 1H), 3.70 (dd, $J_1 = 2.2$ Hz, $J_2 = 10.9$ Hz, 1H), 3.93 (dt, $J_1 = 2.4$ Hz, $J_2 = 12.4$ Hz, 1H), 4.08 (ddd, $J_1 = 1.5$ Hz, $J_2 = 5.1$ Hz, $J_3 = 11.9$ Hz, 1H), 7.08 (d, $J = 6.9$ Hz, 1H), 7.13 (dd, $J_1 = 2.0$ Hz, $J_2 = 7.0$ Hz, 1H), 7.15 (d, $J = 5.9$ Hz, 1H), 7.19 (d, $J = 7.3$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 19.18, 21.92, 27.61, 35.12, 36.29, 37.55, 43.61, 64.02, 74.84, 123.84, 125.87, 125.94, 129.24, 134.64, 146.52. HRMS (ESI⁺) exact mass calcd for C₁₅H₁₉BrONa [M+Na]⁺ requires m/z 317.0517, found m/z 317.0526.

4,4,10b-Trimethyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene (4l)

Yield: 73%, white solid, mp: 73.2-74.5 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.24 (s, 3H), 1.26 (s, 3H), 1.29 (s, 3H), 1.67-1.78 (m, 3H), 1.83 (dt, $J_1 = 4.9$ Hz, $J_2 = 12.7$ Hz, 1H), 2.07 (td, $J_1 = 2.2$ Hz, $J_2 = 13.0$ Hz, 1H), 2.91-2.95 (m, 2H), 3.82 (ddd, $J_1 = 2.2$ Hz, $J_2 = 4.9$ Hz, $J_3 = 12.3$ Hz, 1H), 3.96 (dt, $J_1 = 2.3$ Hz, $J_2 = 12.3$ Hz, 1H), 7.05 (d, $J = 7.3$ Hz, 1H), 7.09 (dt, $J_1 = 1.7$ Hz, $J_2 = 6.7$ Hz, 1H), 7.14 (t, $J = 6.4$ Hz, 1H), 7.17 (d, $J = 7.8$ Hz,

1H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.04, 20.47, 24.26, 29.34, 31.67, 35.49, 38.20, 49.11, 58.45, 74.88, 123.91, 125.56, 125.85, 129.12, 134.62, 148.78. HRMS (ESI^+) exact mass calcd for $\text{C}_{16}\text{H}_{22}\text{O}$ $[\text{M}+\text{Na}]^+$ requires m/z 253.1568, found m/z 253.1567.

(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-17-((*S*)-1-((4*R*,4*aS*,10*bR*)-10*b*-methyl-2,4,4*a*,5,6,10*b*-hexahydro-1*H*-benzo[*f*]isochromen-4-yl)ethyl)-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*)-one (4o)

Yield: 74%, white solid, mp: 149.5-151.0 °C.

^1H NMR (400 MHz, CDCl_3): δ 0.73 (s, 3H), 0.90 (d, $J = 6.1$ Hz, 3H), 0.93-0.97 (m, 1H), 1.18 (s, 3H), 1.20 (s, 3H), 1.01-1.27 (m, 5H), 1.38-1.72 (m, 10H), 1.77-1.86 (m, 2H), 1.93-2.04 (m, 4H), 2.24-2.46 (m, 4H), 2.91 (dd, $J_1 = 5.2$ Hz, $J_2 = 8.7$ Hz, 2H), 3.42 (d, $J = 9.8$ Hz, 1H), 3.76 (t, $J = 11.3$ Hz, 1H), 3.98 (dd, $J_1 = 3.9$ Hz, $J_2 = 11.7$ Hz, 1H), 5.72 (s, 1H), 7.07 (d, $J = 7.0$ Hz, 1H), 7.11 (t, $J = 6.8$ Hz, 1H), 7.14 (t, $J = 6.8$ Hz, 1H), 7.19 (d, $J = 7.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.92, 11.96, 17.41, 18.86, 21.09, 21.64, 24.04, 27.56, 27.80, 32.02, 32.96, 34.00, 35.52, 35.67, 35.73, 36.14, 38.16, 38.61, 39.64, 41.46, 42.20, 52.13, 53.76, 55.73, 64.23, 123.80, 123.86, 125.69, 125.71, 129.13, 134.94, 147.66, 171.63, 199.64. HRMS (ESI^+) exact mass calcd for $\text{C}_{35}\text{H}_{49}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 501.3733, found m/z 501.3719.

7-Methoxy-10*b*-methyl-4-phenyl-2,4,4*a*,5,6,10*b*-hexahydro-1*H*-benzo[*f*]isochromene (10b)

Yield: 94%, white solid, mp: 96.5-97.8 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.22-1.26 (m, 1H), 1.34 (s, 3H), 1.46 (ddt, $J_1 = 7.8$ Hz, $J_2 = 10.6$ Hz, $J_3 = 13.3$ Hz, 1H), 1.88 (ddd, $J_1 = 3.0$ Hz, $J_2 = 10.3$ Hz, $J_3 = 13.3$ Hz, 1H), 2.03 (dt, $J_1 = 5.2$ Hz, $J_2 = 12.8$ Hz, 1H), 2.13 (d, $J = 13.1$ Hz, 1H), 2.45-2.54 (m, 1H), 2.68 (dd, $J_1 = 7.5$ Hz, $J_2 = 18.5$ Hz, 1H), 3.77 (s, 3H), 4.02 (dt, $J_1 = 2.5$ Hz, $J_2 = 12.2$ Hz, 1H), 4.11 (ddd, $J_1 = 1.6$ Hz, $J_2 = 5.1$ Hz, $J_3 = 11.9$ Hz, 1H), 4.36 (d, $J = 10.3$ Hz, 1H), 6.68 (d, $J = 8.0$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 1H), 7.17 (t, $J = 8.0$ Hz, 1H), 7.26-7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.05, 21.95, 22.06, 35.63, 38.15, 46.29, 55.23, 64.37, 80.37, 107.07, 116.05, 123.99, 126.20, 127.46, 127.89, 128.39, 141.21, 148.26, 157.29. HRMS (ESI^+) exact mass calcd for $\text{C}_{21}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 309.1855, found m/z 309.1859.

9-Methoxy-10b-methyl-4-phenyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene (10c)

Yield: 82%, white solid, mp: 89.0-91.2 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.14-1.21 (m, 1H), 1.34 (s, 3H), 1.49 (ddt, $J_1 = 8.1$ Hz, $J_2 = 10.2$ Hz, $J_3 = 13.2$ Hz, 1H), 1.87 (ddd, $J_1 = 3.3$ Hz, $J_2 = 10.3$ Hz, $J_3 = 13.3$ Hz, 1H), 2.04-2.09 (m, 2H), 2.64-2.70 (m, 1H), 2.73 (dd, $J_1 = 7.1$ Hz, $J_2 = 16.4$ Hz, 1H), 3.80 (s, 3H), 4.03 (dt, $J_1 = 3.2$ Hz, $J_2 = 11.9$ Hz, 1H), 4.12 (ddd, $J_1 = 1.9$ Hz, $J_2 = 4.8$ Hz, $J_3 = 11.9$ Hz, 1H), 4.36 (d, $J = 10.3$ Hz, 1H), 6.69 (dd, $J_1 = 2.6$ Hz, $J_2 = 8.4$ Hz, 1H), 6.80 (d, $J = 2.6$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 7.26-7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.76, 21.76, 27.06, 35.90, 37.91, 46.70, 55.32, 64.33, 80.35, 109.92, 111.08, 127.18, 127.42, 127.90, 128.39, 130.11, 141.16, 148.25, 157.76. HRMS (ESI^+) exact mass calcd for $\text{C}_{21}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 261.1855, found m/z 309.1854.

8,9,10-Trimethoxy-10b-methyl-4-phenyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene (10d)

Yield: 86%, white solid, mp: 131.8-133.3 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.05-1.10 (m, 1H), 1.38 (t, $J = 5.8$ Hz, 1H), 1.46 (s, 3H), 1.88 (ddd, $J_1 = 2.1$ Hz, $J_2 = 10.4$ Hz, $J_3 = 12.6$ Hz, 1H), 1.98 (td, $J_1 = 9.2$ Hz, $J_2 = 13.4$ Hz, 1H), 2.58-2.72 (m, 2H), 2.83 (d, $J = 13.4$ Hz, 1H), 3.80 (s, 3H), 3.83 (s, 3H), 3.92 (s, 3H), 4.03 (d, $J = 7.9$ Hz, 2H), 4.46 (d, $J = 10.3$ Hz, 1H), 6.32 (s, 1H), 7.25-7.35 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.29, 19.77, 30.67, 36.74, 38.04, 49.05, 55.73, 60.50, 60.60, 64.35, 79.76, 107.59, 127.46, 127.82, 128.39, 131.73, 131.90, 140.60, 141.51, 151.50, 153.29. HRMS (ESI^+) exact mass calcd for $\text{C}_{23}\text{H}_{29}\text{O}_4$ $[\text{M}+\text{H}]^+$ requires m/z 369.2066, found m/z 369.2061.

9-Chloro-10b-methyl-4-phenyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene (10e)

Yield: 81%, white solid, mp: 123.6-125.0 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.16-1.23 (m, 1H), 1.32 (s, 3H), 1.49 (ddt, $J_1 = 8.0$ Hz, $J_2 = 10.1$ Hz, $J_3 = 13.3$ Hz, 1H), 1.84 (ddd, $J_1 = 3.3$ Hz, $J_2 = 10.3$ Hz, $J_3 = 13.3$ Hz, 1H), 1.99-2.11 (m, 2H), 2.67 (dd, $J_1 = 9.2$ Hz, $J_2 = 14.0$ Hz, 1H), 2.75 (ddd, $J_1 = 2.1$ Hz, $J_2 = 10.4$ Hz, $J_3 = 12.6$ Hz, 1H), 4.02 (dt, $J_1 = 3.0$ Hz, $J_2 = 12.0$ Hz, 1H), 4.13 (ddd, $J_1 = 1.9$ Hz, $J_2 = 4.9$ Hz, $J_3 = 12.0$ Hz, 1H),

4.35 (d, $J = 10.3$ Hz, 1H), 6.95 (d, $J = 8.2$ Hz, 1H), 7.07 (dd, $J_1 = 2.2$ Hz, $J_2 = 8.2$ Hz, 1H), 7.20 (d, $J = 2.2$ Hz, 1H), 7.25-7.35 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.46, 21.75, 27.30, 35.90, 37.77, 46.42, 64.19, 80.21, 124.15, 125.93, 127.37, 127.98, 128.42, 130.66, 131.36, 133.51, 140.91, 148.80. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{21}\text{OClNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 335.1179, found m/z 335.1177.

9a-Methyl-6-phenyl-5,5a,6,8,9,9a-hexahydro-4H-furo[3,2-f]isochromene (10f)

Yield: 75%, yellow solid, mp: 73.5-75.5 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.19-1.26 (m, 1H), 1.33 (s, 3H), 1.48-1.57 (m, 1H), 1.82-1.89 (m, 2H), 1.93-2.01 (m, 1H), 2.41-2.57 (m, 2H), 4.01-4.05 (m, 2H), 4.40 (d, $J = 10.4$ Hz, 1H), 6.24 (d, $J = 1.8$ Hz, 1H), 7.24 (s, 1H), 7.27-7.37 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.87, 20.82, 23.08, 32.55, 37.81, 49.00, 63.79, 79.35, 106.78, 127.22, 127.78, 127.91, 128.44, 140.91, 141.17, 149.01. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{20}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 291.1361, found m/z 291.1365.

11-Benzyl-11b-methyl-4-phenyl-1,2,4,4a,5,6,11,11b-octahydropyrano[4,3-a]carbazole (10g)

Yield: 82%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 1.20-1.27 (m, 1H), 1.47-1.56 (m, 1H), 1.50 (s, 3H), 2.01-2.05 (m, 2H), 2.18 (t, $J = 11.6$ Hz, 1H), 2.60 (ddd, $J_1 = 6.7$ Hz, $J_2 = 11.5$ Hz, $J_3 = 16.0$ Hz, 1H), 2.73 (dd, $J_1 = 5.6$ Hz, $J_2 = 16.0$ Hz, 1H), 3.89-3.95 (m, 2H), 4.48 (d, $J = 10.5$ Hz, 1H), 5.49 (s, 2H), 6.97 (d, $J = 7.1$ Hz, 2H), 7.05-7.10 (m, 3H), 7.21-7.38 (m, 8H), 7.45 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.30, 20.08, 21.41, 35.61, 37.49, 48.46, 50.28, 63.27, 79.32, 109.40, 109.43, 118.07, 119.30, 121.63, 125.67, 127.01, 127.13, 127.43, 128.02, 128.50, 128.76, 137.76, 138.23, 141.23, 142.61. HRMS (ESI^+) exact mass calcd for $\text{C}_{29}\text{H}_{30}\text{NO}$ $[\text{M}+\text{H}]^+$ requires m/z 408.2327, found m/z 408.2331.

2-Ethyl-10b-methyl-4-phenyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene (10i)

Yield: 75%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.98 (t, $J = 7.5$ Hz, 3H), 1.16-1.22 (m, 1H), 1.32 (s, 3H), 1.45-1.54 (m, 1H), 1.56-1.69 (m, 3H), 1.77 (ddd, $J_1 = 3.2$ Hz, $J_2 = 10.3$ Hz, $J_3 = 13.3$ Hz, 1H), 2.21 (dd, $J_1 = 1.9$ Hz, $J_2 = 12.9$ Hz, 1H), 2.69-2.77 (m, 2H), 3.84 (dtd, $J_1 = 1.9$ Hz, $J_2 = 5.9$ Hz, $J_3 = 7.8$ Hz, 1H), 4.40 (d, $J = 10.2$ Hz, 1H),

7.02 (d, $J = 7.4$ Hz, 1H), 7.10 (t, $J = 7.4$ Hz, 1H), 7.16 (t, $J = 7.2$ Hz, 1H), 7.26 (d, $J = 6.2$ Hz, 1H), 7.25-7.33 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 9.87, 19.62, 22.71, 27.98, 29.51, 36.09, 42.79, 46.85, 74.20, 80.09, 123.88, 125.72, 125.77, 127.54, 127.68, 128.30, 129.33, 135.19, 141.71, 147.29. HRMS (ESI^+) exact mass calcd for $\text{C}_{22}\text{H}_{26}\text{ONa}$ [$\text{M}+\text{Na}$] $^+$ requires m/z 329.1881, found m/z 329.1827.

5-(1-Bromopropylidene)-4a-methyl-1-phenyloctahydrocyclopenta[*c*]pyran (10h)

Yield: 68%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.16 (t, $J = 7.3$ Hz, 3H), 1.16 (s, 3H), 1.29-1.36 (m, 1H), 1.73-1.90 (m, 2H), 2.01-2.14 (m, 2H), 2.17-2.27 (m, 1H), 2.37 (d, $J = 9.0$ Hz, 1H), 2.49 (q, $J = 7.3$ Hz, 1H), 2.67 (q, $J = 7.3$ Hz, 1H), 3.88 (dt, $J_1 = 3.3$ Hz, $J_2 = 12.1$ Hz, 1H), 4.05 (ddd, $J_1 = 1.8$ Hz, $J_2 = 5.0$ Hz, $J_3 = 12.2$ Hz, 1H), 4.41 (d, $J = 10.3$ Hz, 1H), 7.27-7.35 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.31, 16.74, 23.03, 30.90, 34.42, 39.04, 44.89, 55.71, 63.66, 78.92, 123.11, 126.34, 127.28, 127.77, 128.37, 140.94, 147.38. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{23}\text{BrO}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$ requires m/z 357.0830, found m/z 357.0823.

4a,10b-Dimethyl-1-phenyl-3,4,4a,4b,5,6,10b,11,12,12a-decahydro-1*H*-naphtho[2,1-*f*]isochromene (10j)

Yield: 81%, white solid, mp: 184.5-186.2 $^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3): δ 0.92-0.96 (m, 1H), 1.12 (s, 3H), 1.21 (s, 3H), 1.35-1.43 (m, 3H), 1.47-1.55 (m, 2H), 1.70 (d, $J = 13.0$ Hz, 1H), 1.74-1.82 (m, 1H), 1.85-1.90 (m, 1H), 2.19-2.25 (m, 1H), 2.84-3.01 (m, 2H), 3.99-4.03 (m, 2H), 4.27 (d, $J = 10.1$ Hz, 1H), 7.02-7.11 (m, 3H), 7.14-7.16 (m, 1H), 7.27-7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.55, 17.71, 20.28, 26.03, 30.28, 35.91, 37.74, 39.07, 39.67, 52.68, 52.97, 63.90, 79.23, 124.21, 125.33, 125.78, 127.23, 127.70, 128.33, 128.92, 134.87, 141.37, 149.96. HRMS (ESI^+) exact mass calcd for $\text{C}_{25}\text{H}_{31}\text{O}$ [$\text{M}+\text{H}$] $^+$ requires m/z 347.2375, found m/z 347.2368.

7-Methoxy-4a,10b-dimethyl-1-phenyl-3,4,4a,4b,5,6,10b,11,12,12a-decahydro-1*H*-naphtho[2,1-*f*]isochromene (10k)

Yield: 87%, white solid, mp: 198.3-200.5 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ 0.93 (d, $J = 7.8$ Hz, 1H), 1.14 (s, 3H), 1.21 (s, 3H), 1.31-1.41 (m, 3H), 1.46-1.56 (m, 2H), 1.64-1.73 (m, 2H), 1.88-1.93 (m, 1H), 2.19 (dd, $J_1 = 3.0$ Hz, $J_2 = 9.7$ Hz, 1H), 2.57-2.69 (m, 1H), 2.92 (dd, $J_1 = 6.5$ Hz, $J_2 = 18.2$ Hz, 1H),

3.80 (s, 3H), 3.93-4.06 (m, 2H), 4.26 (d, $J = 10.1$ Hz, 1H), 6.63 (d, $J = 8.0$ Hz, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 7.09 (t, $J = 8.0$ Hz, 1H), 7.26-7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.52, 17.09, 20.33, 24.47, 25.93, 35.84, 37.72, 39.29, 39.66, 52.30, 52.90, 55.23, 63.93, 79.22, 106.44, 116.38, 123.95, 126.17, 127.23, 127.68, 128.32, 141.40, 151.36, 156.99. HRMS (ESI^+) exact mass calcd for $\text{C}_{26}\text{H}_{33}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 377.2481, found m/z 377.2488.

8,9,10-Trimethoxy-4a,10b-dimethyl-1-phenyl-3,4,4a,4b,5,6,10b,11,12,12a-decahydro-1H-naphtho[2,1-f]isochromene (10l)

Yield: 82%, white solid, mp: 208.5-210.9. ^1H NMR (400 MHz, CDCl_3): δ 0.84-0.97 (m, 1H), 1.13 (s, 3H), 1.30 (s, 3H), 1.26-1.36 (m, 2H), 1.46-1.64 (m, 5H), 1.69 (d, $J = 13.2$ Hz, 1H), 1.78-1.81 (m, 1H), 2.83-2.86 (m, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 3.98-4.05 (m, 2H), 4.23 (d, $J = 10.1$ Hz, 1H), 6.34 (s, 1H), 7.24-7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.83, 17.73, 20.53, 22.82, 32.89, 36.20, 37.86, 39.56, 39.80, 53.06, 55.05, 55.68, 60.32, 60.44, 63.89, 79.14, 107.28, 127.19, 127.62, 128.27, 131.72, 134.71, 140.78, 141.39, 151.14, 153.14. HRMS (ESI^+) exact mass calcd for $\text{C}_{28}\text{H}_{36}\text{O}_4$ $[\text{M}+\text{H}]^+$ requires m/z 437.2692, found m/z 437.2689.

13-Benzyl-6a,13b-dimethyl-3-phenyl-1,2,2a,3,5,6,6a,6b,7,8,13,13b-dodecahydroiso chromeno[6,5-a]carbazole (10m)

Yield: 66%, yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 0.74 (dd, $J_1 = 3.1$ Hz, $J_2 = 13.5$ Hz, 1H), 1.15 (s, 3H), 1.34 (s, 3H), 1.39-1.62 (m, 4H), 1.68-1.75 (m, 3H), 1.97-2.01 (m, 1H), 2.14 (td, $J_1 = 3.1$ Hz, $J_2 = 12.6$ Hz, 1H), 2.69-2.77 (m, 1H), 2.94 (dd, $J_1 = 4.8$ Hz, $J_2 = 15.0$ Hz, 1H), 4.02-4.05 (m, 2H), 4.21 (d, $J = 10.0$ Hz, 1H), 5.34 (d, $J = 17.7$ Hz, 1H), 5.46 (d, $J = 17.7$ Hz, 1H), 6.89 (d, $J = 6.8$ Hz, 2H), 6.95-6.97 (m, 1H), 7.03-7.09 (m, 2H), 7.14-7.30 (m, 8H), 7.48-7.50 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.77, 18.11, 19.88, 22.32, 22.89, 36.13, 37.46, 38.22, 39.73, 48.68, 53.04, 56.09, 63.80, 78.92, 109.19, 109.50, 117.87, 119.12, 121.34, 125.59, 126.89, 127.11, 127.65, 128.28, 128.61, 138.18, 141.17, 144.53. HRMS (ESI^+) exact mass calcd for $\text{C}_{34}\text{H}_{37}\text{NO}$ $[\text{M}+\text{H}]^+$ requires m/z 476.2953, found m/z 476.2948.

6a,12b,14b-Trimethyl-4-phenyl-2,4,4a,5,6,6a,6b,7,8,12b,13,14,14a,14b-tetradecah

hydro-1*H*-phenanthro[2,1-*f*]isochromene (10n)

Yield: 59%, white solid, mp: 134.0-136.1 °C. ¹H NMR (400 MHz, CDCl₃): δ 0.75-0.90 (m, 3H), 0.95 (s, 3H), 1.07 (s, 3H), 1.20 (s, 3H), 1.26-1.34 (m, 2H), 1.36-1.47 (m, 3H), 1.56-1.77 (m, 6H), 2.40-2.44 (m, 1H), 2.77 (ddd, *J*₁ = 7.4 Hz, *J*₂ = 11.6 Hz, *J*₃ = 16.8 Hz, 1H), 2.89 (dd, *J*₁ = 4.9 Hz, *J*₂ = 17.2 Hz, 1H), 3.96-4.00 (m, 2H), 4.21 (d, *J* = 10.2 Hz, 1H), 7.00 (d, *J* = 7.3 Hz, 1H), 7.05 (dt, *J*₁ = 1.3 Hz, *J*₂ = 7.0 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.24-7.33 (m, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 13.39, 17.70, 17.76, 17.90, 19.52, 26.18, 30.87, 35.73, 37.63, 38.16, 39.59, 40.27, 40.54, 53.32, 55.51, 58.64, 63.91, 79.23, 124.66, 125.20, 125.73, 127.20, 127.62, 128.85, 135.03, 141.45, 150.08. HRMS (ESI⁺) exact mass calcd for C₃₀H₃₈O [M+Na]⁺ requires *m/z* 437.2820, found *m/z* 437.2803.

Experimental Data for (±)-Moluccanic Acid Methyl Ester Synthesis

9-Methoxy-4,4,10b-trimethyl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (13)

Yield: 74%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.24 (s, 3H), 1.26 (s, 3H), 1.29 (s, 3H), 1.65-1.75 (m, 3H), 1.83 (dt, *J*₁ = 4.8 Hz, *J*₂ = 12.8 Hz, 1H), 2.02 (d, *J* = 13.2 Hz, 1H), 2.79-2.92 (m, 2H), 3.78 (s, 3H), 3.78-3.84 (m, 1H), 3.95 (t, *J* = 12.2 Hz, 1H), 6.68 (dd, *J*₁ = 2.8 Hz, *J*₂ = 8.4 Hz, 1H), 6.72 (s, 1H), 6.98 (d, *J* = 8.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 20.04, 20.58, 24.14, 28.53, 31.68, 35.69, 38.18, 49.13, 55.28, 58.43, 74.89, 109.73, 110.99, 126.77, 129.90, 150.04, 157.78. HRMS (ESI⁺) exact mass calcd for C₁₇H₂₅O₂ [M+H]⁺ requires *m/z* 261.1855, found *m/z* 261.1864.

9-Methoxy-4,4,10b-trimethyl-4,4a,5,10b-tetrahydro-1*H*-benzo[*f*]isochromen-6(2*H*)-one (15)

Yield: 51%, yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.24 (s, 3H), 1.30 (s, 3H), 1.35 (s, 3H), 1.93-2.06 (m, 2H), 2.20 (dd, *J*₁ = 7.1 Hz, *J*₂ = 11.1 Hz, 1H), 2.57 (d, *J* = 4.6 Hz, 1H), 2.59 (s, 1H), 3.87 (s, 3H), 3.87-3.90 (m, 1H), 4.00 (t, *J* = 12.1 Hz, 1H), 6.76 (s, 1H), 6.83 (d, *J* = 6.9 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 19.68, 22.75, 31.27, 36.18, 37.06, 48.49, 55.46, 58.17, 73.80, 108.73, 111.58, 124.38, 130.30, 157.28, 164.35, 196.52. HRMS (ESI⁺) exact mass calcd for C₁₇H₂₃O₃ [M+H]⁺ requires *m/z* 275.1647, found *m/z* 275.1648.

4-(Chloromethyl)-9-methoxy-10b-methyl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]is

ochromene (17)

Yield: 64%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.23 (s, 3H), 1.55-1.61 (m, 1H), 1.73-1.80 (m, 1H), 1.83-1.89 (m, 1H), 1.93 (dd, $J_1 = 5.0$ Hz, $J_2 = 12.8$ Hz, 1H), 2.02 (d, $J = 13.1$ Hz, 1H), 2.86-2.90 (m, 2H), 3.64-3.70 (m, 2H), 3.79 (s, 3H), 3.78-3.84 (m, 1H), 3.91 (dt, $J_1 = 2.5$ Hz, $J_2 = 12.3$ Hz, 1H), 4.07 (ddd, $J_1 = 1.6$ Hz, $J_2 = 5.0$ Hz, $J_3 = 11.9$ Hz, 1H), 6.71 (dd, $J_1 = 2.6$ Hz, $J_2 = 8.3$ Hz, 1H), 6.74 (d, $J = 2.6$ Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.26, 21.65, 26.79, 35.30, 37.51, 42.40, 47.02, 55.30, 64.00, 75.52, 109.92, 111.14, 126.71, 130.03, 147.81, 157.79. HRMS (ESI^+) exact mass calcd for $\text{C}_{16}\text{H}_{21}\text{ClO}_2$ $[\text{M}+\text{Na}]^+$ requires m/z 303.1128, found m/z 303.1133.

1-(1-(2-Bromoethyl)-7-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-2-yl)ethanone (19)

Prepared by the following procedure: To a round bottom flask equipped with a magnetic stir, sodium hydride (0.16 g, 60% dispersion in mineral oil, 4.0 mmol) was dissolved in N,N-dimethylformamide (5 mL). Aftering cooling to 0 $^\circ\text{C}$, compound **19** (0.28 g, 1.0 mmol) was added slowly, the mixture was stirred for 10 h at 130 $^\circ\text{C}$. Then the reaction mixture was poured into ice-water, extracted with diethyl ether (3 x 20 mL). The combined organic layer was washed with water (2 x 30 mL) and brine (30 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The crude product was dissolved in 10 mL acetone and followed 1mL 40% HBr acetic solution was added. The reaction mixture was stirred for 1 h at room temperature. After that, the reaction mixture was poured into ice-water, extracted with diethyl ether (3 x 20 mL). The combined organic layer was washed with water (2 x 30 mL) and brine (30 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 5% EtOAc in hexane to provide the title compound as colorless oil. Yield: 55%. ^1H NMR (400 MHz, CDCl_3): δ 1.30 (s, 3H), 1.96-2.03 (m, 2H), 2.22 (s, 3H), 2.33-2.42 (m, 2H), 2.67-2.82 (m, 3H), 3.04 (ddd, $J_1 = 5.5$ Hz, $J_2 = 9.7$ Hz, $J_3 = 11.3$ Hz, 1H), 3.36 ($J_1 = 6.1$ Hz, $J_2 = 9.7$ Hz, $J_3 = 10.7$ Hz, 1H), 3.78 (s, 3H), 6.70 (dd, $J_1 = 2.6$ Hz, $J_2 = 8.4$ Hz, 1H), 6.78 (d, $J = 2.5$ Hz, 1H), 6.98 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 22.24, 27.09, 28.13, 28.20, 29.70, 30.98, 41.55, 44.29, 53.62, 55.30, 111.29, 111.81, 127.97, 130.13, 142.76,

158.30, 210.84. HRMS (ESI⁺) exact mass calcd for C₁₆H₂₁BrO₂ [M+H]⁺ requires *m/z* 325.0803, found *m/z* 325.0797.

1-(2-Bromoethyl)-7-methoxy-1-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydronaphthalene (20)

Prepared by the following procedure: To a round bottom flask equipped with a magnetic stir, compound **19** (240 mg, 0.74 mmol) and pyridine (0.06 mL, 0.22 mmol) were dissolved in toluene (6 mL) and cooled to -55 °C. Tebbe reagent (4.4 mL, 0.5M in toluene, 2.2 mmol) was added dropwisely and the reaction mixture was stirred for 1 h at -55 °C. Then the reaction mixture was quenched with Sat. NaHCO₃. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with Sat. NaHCO₃ (2 x 30 mL) and brine (30 mL), dried over Na₂SO₄ and concentrated under reduce pressure. The crude product was purified by flash chromatography on silica gel using 5% EtOAc in hexane to provide the title compound as colorless oil. Yield: 71%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.21 (s, 3H), 1.79 (s, 3H), 1.84-1.92 (m, 2H), 2.25-2.48 (m, 3H), 2.71-2.76 (m, 2H), 3.00 (ddd, *J*₁ = 5.1 Hz, *J*₂ = 9.6 Hz, *J*₃ = 12.0 Hz, 1H), 3.28 (*J*₁ = 4.9 Hz, *J*₂ = 9.6 Hz, *J*₃ = 12.6 Hz, 1H), 3.79 (s, 3H), 4.72 (s, 1H), 4.99 (s, 1H), 6.69 (dd, *J*₁ = 2.7 Hz, *J*₂ = 8.4 Hz, 1H), 6.81 (d, *J* = 2.5 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 22.85, 24.63, 27.73, 29.04, 29.33, 42.85, 43.70, 47.41, 55.30, 111.52, 111.89, 114.62, 129.06, 130.05, 143.74, 146.35, 158.13. HRMS (ESI⁺) exact mass calcd for C₁₇H₂₃BrO₂ [M+H]⁺ requires *m/z* 323.1011, found *m/z* 323.1007.

3-(7-Methoxy-1-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanenitrile (21)

Prepared by the following procedure: To a round bottom flask equipped with a magnetic stir, sodium cyanide (47 mg, 0.96 mmol), 18-crown-6 (127 mg, 0.048 mmol) and compound **20** (155 mg, 0.48 mmol) were dissolved in acetonitrile (5 mL). The mixture was stirred at room temperature and TLC. Then the reaction mixture was poured into water, extracted with diethyl ether (3 x 20 mL). The combined organic layer was washed with brine (2 x 30 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 5% EtOAc in hexane to provide the title compound as colorless oil.

Yield: 67%. ^1H NMR (400 MHz, CDCl_3): δ 1.23 (s, 3H), 1.79 (s, 3H), 1.81-1.85 (m, 1H), 1.87-2.00 (m, 2H), 2.05-2.13 (m, 2H), 2.17-2.37 (m, 2H), 2.70-2.80 (m, 2H), 3.79 (s, 3H), 4.72 (s, 1H), 4.99 (s, 1H), 6.68-6.73 (m, 2H), 6.98 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.51, 22.50, 24.52, 27.54, 29.32, 35.42, 41.42, 47.08, 55.30, 111.70, 111.82, 114.93, 120.21, 129.38, 130.28, 142.94, 146.04, 158.26. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{23}\text{NO}$ $[\text{M}+\text{Na}]^+$ requires m/z 292.1677, found m/z 292.1682.

Methyl-3-(7-hydroxy-1-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanoate (22)

Prepared by the following procedure: To a round bottom flask equipped with a magnetic stir, compound **21** (46 mg, 0.17 mmol) was dissolved in MeOH/ H_2O (10 mL, MeOH/ H_2O : 4/1). Then KOH (224 mg, 4 mmol) was added and the mixture was stirred overnight at 60 $^\circ\text{C}$. The reaction mixture was

poured into water and adjusted the pH value to 2 with 1M HCl, extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine (2 x 30 mL), dried over Na_2SO_4 , and concentrated under reduce pressure. The crude product was dissolved in 5 mL THF, DCC and MeOH (0.1 mL) were added. The mixture was attired for 10 h. The solvent was removed *in vacuo* and purified by flash chromatography on silica gel using 5% EtOAc in hexane to provide the title compound as colorless oil. Yield: 58% over two steps. ^1H NMR (400 MHz, CDCl_3): δ 1.22 (s, 3H), 1.78 (s, 3H), 1.80-1.83 (m, 1H), 1.86-1.98 (m, 2H), 2.04-2.14 (m, 2H), 2.18-2.28 (m, 1H), 2.41 (dd, $J_1 = 2.8$ Hz, $J_2 = 11.2$ Hz, 1H), 2.72-2.75 (m, 2H), 3.60 (s, 3H), 3.78 (s, 3H), 4.70 (s, 1H), 4.95 (s, 1H), 6.67 (d, $J = 8.4$ Hz, 1H), 6.79 (s, 1H), 6.96 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 22.86, 24.74, 27.79, 29.43, 29.52, 34.67, 41.16, 47.12, 51.51, 55.24, 111.48, 111.89, 114.31, 129.30, 129.84, 144.40, 146.65, 158.00, 174.42. HRMS (ESI^+) exact mass calcd for $\text{C}_{19}\text{H}_{26}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires m/z 303.1960, found m/z 303.1964.

(±)Moluccanic acid methyl ester (23)

Prepared by the following procedure: To a round bottom flask equipped with a magnetic stir, compound **22** (22.2 mg, 0.074 mmol) and tetra-butyl ammonium iodide (35.5 mg, 0.096 mmol) were dissolved in 5 mL CH₂Cl₂. Then BCl₃ (0.19 mL, 1.0 M in CH₂Cl₂, 0.19 mmol) was added to the mixture slowly at 0 °C. After 2 h, the reaction mixture was poured into sat. NaHCO₃, extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layer was washed with brine (2 x 30 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 5% EtOAc in hexane to provide the title compound as colorless oil. Yield: 71%. ¹H NMR (400 MHz, CDCl₃): δ 1.21 (s, 3H), 1.78 (s, 3H), 1.80-1.83 (m, 1H), 1.84-1.99 (m, 2H), 2.00-2.16 (m, 2H), 2.21-2.29 (m, 1H), 2.40 (dd, *J*₁ = 3.1 Hz, *J*₂ = 11.3 Hz, 1H), 2.70-2.75 (m, 2H), 3.61 (s, 3H), 4.70 (s, 1H), 4.82 (brs, 1H), 4.95 (s, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.79 (s, 1H), 6.96 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 22.84, 24.74, 27.79, 29.46, 29.50, 34.64, 41.06, 47.05, 51.58, 112.92, 113.25, 114.34, 129.29, 130.12, 144.61, 146.61, 153.90, 174.60. HRMS (ESI⁺) exact mass calcd for C₁₈H₂₄O₃ [M+H]⁺ requires *m/z* 289.1804, found *m/z* 289.1805.

Chapter 4. Stereoselective Syntheses of 8-Oxatropane via Cationic Cascade Cyclization: Different Initiators, Opposite Diastereoselectivity

4.1 Overview of 8-Oxabicyclo[3.2.1]octane Synthesis

8-Oxabicyclo[3.2.1]octane, has similar structure of tropane, featured in many types of polycyclic natural products, such as cortistatin A,⁵⁷ englerin A,⁵⁸ hedyosumin C⁵⁹ and (+)-antheclarin⁶⁰ (Figure 4.1). Attractively, most of them show very interesting biological activities. Cortistatin A, isolated from the sponge of *Corticium simplex*, selectively inhibits the proliferation of umbilical vein endothelial cells and has no adverse effect on normal cells.¹ Englerin A, a guaiane sesquiterpene, selectively inhibits the growth of renal cancer cells.² Furthermore, as an analogue of tropane, 8-oxabicyclo[3.2.1]octane (or 8-oxatropane) derivatives have the potential for the treatment of cocaine abuse.⁶¹

57 Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setia-wan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148.

58 Ratnayake, R.; Covell, D.; Ransom, T. T.; Gustafson, K. R.; Beutler, J. A. *Org. Lett.* **2008**, *11*, 57.

59 Yin, Su, S.; Zhou, Z. W.; Wu, Y.; Ding, J.; Yue, J. M. *J. Nat. Prod.* **2008**, *71*, 1410.

60 Karioti, A.; Skaltsa, H.; Linden, A.; Perozzo, R.; Brun, R.; Tasdemir, D. *J. Org. Chem.* **2007**, *72*, 8103.

61 Meltzer, P. C.; Kryatova, O.; Pham-Huu, D. P.; Donovan, P.; Janowsky, A. *Bioorg. Med. Chem.* **2008**, *16*, 1832-1841

Figure 4.1 Examples of natural products containing 8-oxatropane core and the core structure of a tropane alkaloid

Stimulated by the bioactivities and pharmacological properties of 8-oxatropanes, many research groups have involved in the development of new methodologies to create this typical bicyclic structure. Among the strategies reported, Lewis acid and transition metal catalyzed annulation reactions are emerged as the most powerful methods.

4.1.1 Lewis Acid Promoted Cascade Reactions

[4+3] annulation reaction has been widely applied in constructing 8-oxatropanes. Twenty five years ago, Molander and his coworkers reported an intramolecular [4+3] annulation of 1,4-dicarbonyl compounds and the special trimethylenemethane dianionic synthon to construct 8-oxatropanes (Scheme 4.1, eq I).⁶² Although the reaction was limited to trimethylenemethane dianionic synthon, it provided an efficient method to make this type of compound. Considering the limitation of the method, the same group later proposed an alternative way by using bis(trimethylsilyl) enol ether as the dianionic component (Scheme 4.1, eq II) and thus expanded the reaction scope.⁶³

⁶² Molander, G. A.; Shubert, D. C. *J. Am. Chem. Soc.* **1987**, 109, 6877.

⁶³ (a) Molander, G. A.; Andrews, S. W. *Tetrahedron Lett.* **1989**, 30, 2351. (b) Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1993**, 58, 5931. (c) Molander, G. A.; Siedem, C. S. *J. Org. Chem.* **1995**, 60, 130.

Scheme 4.1

In 2001, Hsung group reported another Lewis acid catalyzed [4+3] cycloaddition reaction by using their developed allenamides. The allenamide formed an epoxide first under oxidative condition, followed by [4+3] cycloaddition reaction to generate 8-oxatropanes in very high yield with excellent diastereoselectivity.⁶⁴ Later, the same group found that exposed the reaction partner to the chiral Lewis acid and the desired product was obtained in high yield with excellent enantioselectivity (Scheme 4.2).⁶⁵ However, the reaction scope was narrow, and the reaction condition was extremely complicated to handle.

Scheme 4.2

Scheme 4.3

For the interest of developing a different strategy to generate allyl cations, Chiu group developed another [4+3] cycloaddition component, epoxy enol silanes. The

64 (a) Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, 123, 7174. (b) Rameshkumar, C.; Hsung, R. P. *Angew. Chem. Int. Ed.* **2004**, 43, 615.

65 Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, 127, 50.

selectivity of outcomes can be easily controlled by the chirality of epoxide (Scheme 4.3).⁶⁶

Alkynylcyclopropane (ACP) ketone is another type of 1,3-dipole precursor. More recently, Wang group applied it in the [4+3] cyclic addition reaction successfully (Scheme 4.4).⁶⁷ Treating ACP ketone with Lewis acid provided 8-oxabicyclo[3.2.1]octane in high yield.

Scheme 4.4

In recent years, organo-catalysts draw much attention from chemists, including this area. In 2003, Harmata group reported an asymmetric strategy to construct 8-oxabicyclo[3.2.1]octane by organocatalysis of [4+3] cycloaddition reaction (Scheme 4.5).⁶⁸ The reaction gave the desired product in high enantioselectivity with relative moderate yield. However, the substrate scope was strictly limited for terminal diene.

Scheme 4.5

⁶⁶ Chung, W. K.; Lam, S. K.; Lo, B.; Liu, L. L.; Wong, W. T.; Chiu, P. *J. Am. Chem. Soc.* **2009**, *131*, 4556.

⁶⁷ Bai, Y.; Tao, W. J.; Ren, J.; Wang, Z. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 4112.

⁶⁸ Harmata, M.; Ghosh, S. K.; Hong, X. C.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058.

4.1.2 Transition Metal Catalyzed Annulation Reaction to Construct 8-Oxabicyclo[3.2.1]octane

Beside Lewis acid promoted [4+3] annulation reaction, another important method is transition metal catalyzed [3+2] cycloaddition of zwitterionic intermediates with electro-rich olefins. Many metals have been applied for this transformation, such as tungsten(0),⁶⁹ platinum(II),⁷⁰ gold(I)⁷¹ etc. As shown in Scheme 4.6, treatment of the carbonyl tethering alkyne (γ -ynones) with proper catalyst, the carbonyl group could attack the activated alkyne forming a carbonyl ylide, followed by 1,3-dipolar cycloaddition to provide 8-oxabicyclo[3.2.1]octane (Scheme 4.6).

Initially, the success of the reaction was relied on rigid aromatic substrates. Iwasawa group firstly extended the reaction to non-conjugated system. Furthermore, Iwasawa group achieved a catalytic asymmetric version of the reaction by using Walphos as the ligand in 2010 (Scheme 4.7).⁷²

69 (a) Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814. (b) Kusama, H.; Funami, H.; Shido, M.; Hara, Y.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, *127*, 2709.

70 (a) Kusama, H.; Ishida, K.; Funami, H.; Iwasawa, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4903. (b) Ishida, K.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2010**, *132*, 8842.

71 Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echav-arren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5452.

72 Ishida, K.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2010**, *132*, 8842.

Another method to generate 1,3-dipolar precursor is rhodium(II)-catalyzed carbene cyclization reaction from diazodione (Scheme 4.8). Padwa had pioneered this reaction, who extensively investigated the mechanism and the substrate scope for this reaction.⁷³ After that, remarkable progress has been achieved in this area and the method has been successfully applied in many natural products synthesis.⁷⁴ However, the reaction precursors, diazodione, are difficult to synthesize and handle. It inhibits the further application of this reaction.

Scheme 4.8

Despite the tremendous progress made so far for the synthesis of 8-oxatropanes, most of them are restricted to special substrates. On the other hand, harsh reaction condition and expensive catalyst also would suppress the application. Thus, developing the practical and stereoselective methods still are highly sought after.

4.2 The Origin of This Project

Considering the strategy to construct seven-six-six fused ring system through 1,2-hydride shift cascade reaction that described in the first chapter (Scheme 4.9, eq I), we speculated that the seven-six-six ring system might be synthesized by inserting one more carbon between acetal and alkene (Scheme 4.9, eq II).

73 (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998; Chapter 7.

74 (a) Hodgson, D. M.; Avery, T. D.; Donohue, A. C. *Org. Lett.* **2002**, *4*, 1809. (b) Lam, S. K.; Chiu, P. *Chem. Eur. J.* **2007**, *13*, 9589. (c) Shimada, N.; Anada, M.; Nakamura, S.; Nambu, H.; Tsutsui, H.; Hashimoto, S. *Org. Lett.* **2008**, *10*, 3603. (d) Rout, L.; Harned, A. M. *Chem. Eur. J.* **2009**, *15*, 12926.

Chapter 1

Scheme 4.9

4.3 Result and Discussion

In order to achieve the goal, a simple method for the substrate synthesis was developed by Grignard reaction, Claisen rearrangement and DIBAL-H reduction leading to the corresponding aldehyde **3** in high yield.⁷⁵ The aldehyde **3** can be protected with a series of alcohols to provide the raw material **4**.

Scheme 4.10

Our idea was sooner evaluated through employing 1,4-cyclic acetal-olefin **4a** and silyl enol ether **5a** with 1.2 equivalent of TiCl_4 as the promoter. Initial result revealed that this reaction took a different pathway instead of that the proposed one. 8-Oxatropane **6a** was obtained in 91% yield as a single isomer. No trace of 7-6-6 fused ring product (**B**) was observed. Based on our experience in Mukaiyama-aldol-Prins

⁷⁵ Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R.J. *J. Am. Chem. Soc.* **1978**, *100*, 4274.

cascade reaction,⁷⁶ the tert-butyl cation also can be trapped by halogen to form product **A**, but it was not detected at all. The structure of **6a** was elucidated with the aid of X-ray crystal data of its alcohol derivative **7** (Scheme 4.11). Other Lewis acids (such as: TiBr₄, SnCl₄, BF₃·Et₂O, Sc(OTf)₃) were also tested and TiCl₄ gave the highest yield.

Scheme 4.11

With the optimal reaction conditions in hand, we turned our attention to explore the substrate scope. As the result presented in Table 4.1, the desired products were generated in very high yields with excellent diastereoselectivities for most cases (entries 1-16). Altering the tail length did not affect the reaction performance (entry 2-4). When an electron-rich group (**4h** and **4j**) was introduced in the substrate, the desired 8-oxabicyclo[3.2.1]-octanes were obtained in high yields (84% and 71%), and still there was no Friedel-Crafts reaction observed on the phenyl unit. In addition, substrates tethering isolated alkene (entries 11 and 12) and isolated alkyne (entry 13) were also tolerated in this reaction, in spite of the yields were slightly compromised. To understand the reaction mechanism, additional ether group (entries 6 and 7) was introduced to the substrate. It does not affect the reaction pathways, the oxygen which

76 (a) Li, H.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 7194. (b) Li, H.; Loh, T. P. *Org. Lett.* **2010**, *12*, 2679.

trapped the tert-butyl cation still came from the acetal group, and desired products were obtained in high yields. In cases of the terminal alkene (**4n** and **4o**) were tested, di-substituted substrate **4n** gave a better yield (74%) than mono-substituted substrate (**4o**, 46%). We speculated that the methyl group can stabilize the tert-butyl cation, it also inhibited the chlorine to trap the fresh cation. While phenyl substituted terminal alkene (**4q**) were applied, the reaction underwent Mukaiyama-aldol-ene pathway, and a different alkene product (**6q**) was generated in 62% yield. The same phenomena were also found in cyclohexene (**4r**) substrates, moderate yield of Mukaiyama-aldol-ene cascade reaction products were obtained. On the other hand, when a similar cycloheptene substrate (**4p**) was tested, a desired product **6p** was obtained in 54% yield as well as 21% ene-type product.

At present, the reaction has some limitations, such as furan containing substrate could not be tolerated in the in acid reaction condition (entry 19). In addition, the reaction was vigorously effect by the steric factor, any branches appeared at the α -position of alkene (entry 21 and 22) made the reaction messy.

Table 4.1 Cationic cascade cyclization between various cyclic acetals and silyl enol ether **5a**^a

Entry	Substrate	Product ^b	Yield (%) ^c
1			91
2			85
3			90

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4		4d		6d	88
5		4e		6e	92
6		4f		6f	84
7		4g		6g	89
8		4h		6h	84
9		4i		6i	85
10		4j		6j	71
11		4k		6k	66
12		4l		6l	52
13		4m		6m	56
14		4n		6n	74
15		4o		6o	46

16		4p		6p	54
17		4q		6q	62
18		4r		6r	57
19		4s		6s	- ^d
21		4t		6t	- ^d
22		4u		6u	- ^d

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b Single diastereomer (determined by ¹H NMR). ^c Isolated yield. ^d No desired product.

Encouraged by results showed in Table 4.1, we further studied the reactivity of different silyl enol ethers of the reaction, and the results are outlined in Table 4.2. Generally, high yields and excellent diastereoselectivities were obtained when symmetrical trisubstituted silyl enol ethers were used (**5b** to **5d**, yields > 85%). When a disubstituted silyl enol ether **5e** was tested, the yield remained high but the diastereoselectivity was significantly compromised (41:59). Halogenated (entry 6) substrate was not suitable for this reaction. The silyl enol ether tethering a hetero atom (entry 5) also made the reaction complex. For the steric hindrance reason, when silyl enol ether derived from ketone (entry 7) was used, the reaction stopped at the Mukaiyama-aldol stage.

Table 4.2 Cationic cascade cyclization between **4a** and different silyl enol ethers^a

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Entry	Substrate	Product	Yield (%) ^b	Dr ^c
1			85	90:10
2			87	96:4
3			91	93:7
4			96	59:41
5			- ^d	-
6			-	-
7			-	-

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b Isolated yield ^c Determined by ¹H NMR analysis). ^d No desired product.

After established a practical method to construct 8-oxabicyclo[3.2.1]octanes, we next focused on the asymmetric version of the reaction. Three chiral diol were chosen to test the chirality of outcomes. As the results revealed in Table 4.3, acetal **9a** generated from (2*R*,3*R*)-2,3-butanediol gave higher enantioselectivity in the final product than (2*R*,4*R*)-2,4-pentanediol protected acetal **9a'** (97% ee vs 89% ee). While (*R*, *R*)-hydrobenzoin was selected as the protecting group (entry 3), not only yield (66%) and enantioselectivity (56%) were dropped dramatically, but also the diastereoselectivity became much poor (63:37). Compromised by these results,

(2R,3R)-2,3-butanediol was adopted for further investigation of the reaction.

Generally, the desired product was obtained in high yield with very good ee for the simple linear olefin substrates (**9a-e**). Ether functionality (entry 7) did not affect the result. The absolute stereochemistry of the cyclization products was confirmed by X-ray analysis of an alcohol derivative of an enantiomeric-enriched product **6i** (Table 4.3, entry 5 and Figure 4.2). Further, additional alkene (**9f**) or alkyne (**9g**) were proved to be inappropriate choice of substrates in the asymmetric version. When cyclic substrate (**9h**) was utilized and investigated, the reaction provided Mukaiyama-aldol-ene cascade product in high yield with excellent diastereoselectivity (only one isomer was detected).

Table 4.3 Asymmetric cationic cascade cyclization between various chiral cyclic acetals and silyl enol ether **5a**

Entry	Substrate	Product ^b	Yield (%) ^c	Ee (%) ^d
1			91	89
2			66	56
3			88	97
4			91	94
5			80	98

6		9d		6h	74	95
7		9e		6f	79	94
8		9f		10f	- ^e	-
9		9g		10g	- ^e	-
10		9h		10h	70 ^f	-

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b Single diastereomer (determined by ¹H NMR analysis). ^c Isolated yield. ^d Ee value was determined by chiral HPLC. ^e No desired product. ^f dr value > 20:1, was determined by ¹H NMR.

Figure 4.2 Determination of absolute stereochemistry of **11**

As the results shown above, acetals have been certified as the proper initiator for the reaction of 8-oxabicyclo[3.2.1]-octane synthesis. However, compared with acetal, aldehydes drawn much more attention from the chemist. Firstly, it would simplify the substrate synthesis. Secondly, it provided a chance to realize the catalytic asymmetric version of the title reaction.

From these standpoints, we compared the difference of acetals and aldehydes. Surprisingly, the reaction provided another 8-oxabicyclo[3.2.1]-octane diastereomeric product **12a** in good yield (51%) with high diastereoselectivity in the same condition. The structures of compounds **12a-e** were confirmed by reference to an X-ray diffraction analysis of the desilylation compound **13** (Figure 4.3). Interestingly, the

2-alkyl and 3-hydroxyl groups in product **13** were aligned syn to each other. That is contrary to the 2,3-anti relative stereochemistry observed in products **6a-p**, when cyclic acetals were used as substrates (Tables 4.1-4.3).

Figure 4.3 Determination of relative stereochemistry of **14**

To evaluate the synthetic value of this method, ten other substrates were tested at the next stage. Generally, they gave the bicyclic products in moderate to good yield (entry 2-8) with high diastereoselectivities. However, the product **12e** and **12p** were obtained in much poorer diastereoselectivity which could be probably reasoned by the steric factor around alkene. The ether group strongly affected the result; no desired product was obtained for **3f**. If the substrate had one more independent alkene (**3l**), the reaction turned to another path way, 7-6-6-6 fused cyclization product (**12l**) was generated in 38% yield.

Table 4.4 Aldehyde induced cationic cascade cyclization^a

Entry	Substrate	Product	Yield (%) ^b	Dr ^c
1			51	97:3
2			53	93:7

Chapter 4. Stereoselective Syntheses of 8-Oxatropane via Cationic Cascade Cyclization: Different Initiators, Opposite Diastereoselectivity

3		3c		12c	58	93:7
4		3d		12d	50	92:8
5		3e		12e	57	55:45
6		3h		12h	56	95:5
7		3p		12p	55	50:50
8		3n		12n	65	99:1
9		3f		12f	- ^d	-
10		3l		12l	38	99:1

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b Isolated yield. ^c Dr value determined by ¹H NMR analysis. ^d No desired product.

In light of the above results, a reaction mechanism may be proposed to rationalize the impact of the cyclic acetal or aldehyde groups on the stereochemical outcome of the cyclizations. As depicted in Scheme 4.12, the initial step involves a Mukaiyama-aldol reaction between the acetal or aldehyde and the silyl enol ether (**I**).

Scheme 4.12 Proposed mechanism for 8-oxabicyclo[3,2,1]octanes synthesis from cyclic acetal or aldehyde

Subsequently, the olefin attacks the silylated oxocarbenium via the syn-clinal, closed-chain transition state with four possible conformations **II-V**. According to our model, the transition state conformation appears to be critical for defining the relative stereochemistry at the 2 and 3 positions of 8-oxatropane. In the case when an acetal is the substrate, the transition state **II** is favored with the R^1 and OTIPS groups adopting pseudo equatorial position. As a result, the *anti* configuration product **VI** is produced. In comparison, the corresponding conformation of transition state **III** was not favored, presumably due to 1,3-diaxial repulsion of the OTIPS/Me and OTIPS/OR groups. On

the other hand, when an aldehyde is the substrate, the Lewis acid bonds to the oxygen directly. So the transition state has conformation **IV** with the R¹ and OTiCl_n groups taking pseudo equatorial positions and the OTIPS group occupying a pseudo axial position, thereby resulting in the formation of cyclization product **VIII**.

4.4 Conclusion

In conclusion, we have developed a novel and practical diastereoselective cationic cascade cyclization reaction for the synthesis of 8-oxabicyclo[3.2.1]octanes, a common structural motif presents in many natural products. More importantly, the stereochemical outcome of the 2,3-substituents can be readily controlled through employing either an acetal or an aldehyde as the reaction initiator. In addition, a highly enantioselective reaction can also be achieved by using (2*R*,3*R*)-2,3-butanediol derived chiral acetals as the substrate. Moreover, the mild reaction conditions and its compatibility with substrates containing multiple electron-rich functional groups, such as olefins, alkynes and substituted anisole also make the present protocol attractive for organic synthesis.

4.5 Experimental Section

To a solution of 2-propenylmagnesium bromide (1.0 M in THF, 45 mL), corresponding aldehyde (30 mmol) in THF (30 mL) was added dropwise at 0 °C. The mixture was stirred at room temperature for 30 mins, followed by quenching with saturated NH_4Cl solution (50 mL). The reaction mixture was extracted with Et_2O (3×100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous MgSO_4 and concentrated under reduce pressure provided the allylic alcohols, which was used for the next step directly.

A solution of the allylic alcohol (30 mmol) and propanoic acid (1 mL) in triethyl orthoacetate (30 mL) was heated to 145 °C. Heating was continued until ethanol was no longer distilled from the reaction mixture. The reaction was cooled to room temperature and washed with saturated NaHCO_3 solution (100 mL) and brine (100 mL). The organic layer was dried over NaSO_4 and concentrated *in vacuo* to yield the ester as colourless oil in 80-96% yields.

To a solution of the above prepared esters (10 mmol) in 25 mL dry dichloromethane was added DIBAL-H (1 M in heptane, 11 mL, 1.1 equiv) dropwise at -78 °C. The mixture was stirred at that temperature for 2.5 h, then quenched by adding MeOH (5 mL) and saturated aqueous Rochelle's salt (15 mL). The resulting mixture was stirred vigorously until two clear layers were obtained (about 2 h) at room temperature. The two layers were separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layer was washed with brine (40 mL), dried over NaSO_4 and concentrated under reduce pressure to obtain crude aldehydes. The pure compound was obtained by flash chromatography with hexane/ EtOAc as the eluent in 75-86% yields.

(E)-4-Methyl-7-phenylhept-4-enal (3a)

^1H NMR (400 MHz, CDCl_3): δ 1.55 (s, 3H), 2.27-2.32 (m, 4H), 2.49 (t, $J = 7.4$ Hz, 2H), 2.63 (t, $J = 7.7$ Hz, 2H), 5.21 (t, $J = 7.0$ Hz, 1H), 7.16-7.19 (m, 3H), 7.25-7.29 (m, 2H), 9.73 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.05, 29.88,

31.83, 35.91, 42.12, 124.69, 125.77, 128.26, 128.48, 133.79, 142.08, 202.65. HRMS (ESI⁺) exact mass calcd for C₁₄H₁₉O [M+H]⁺ requires *m/z* 203.1436, found *m/z* 203.1434.

(E)-4-Methylhept-4-enal (3b)

¹H NMR (400 MHz, CDCl₃): δ 0.93 (t, *J* = 7.5 Hz, 3H), 1.61 (s, 3H), 1.99 (p, *J* = 7.2 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.52 (t, *J* = 7.5 Hz, 2H), 5.16 (t, *J* = 6.8 Hz, 1H), 9.76 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.21, 15.91, 21.15, 31.78, 42.15, 127.51, 132.25, 202.77. HRMS (ESI⁺) exact mass calcd for C₈H₁₅O [M+H]⁺ requires *m/z* 127.1123, found *m/z* 127.1126.

(E)-4-Methyloct-4-enal (3c)

¹H NMR (400 MHz, CDCl₃): δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.32-1.37 (m, 2H), 1.62 (s, 3H), 1.96 (q, *J* = 7.2 Hz, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.52 (t, *J* = 7.4 Hz, 2H), 5.17 (t, *J* = 7.0 Hz, 1H), 9.76 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 13.76, 16.07, 22.82, 29.96, 31.90, 42.19, 125.73, 132.93, 202.78. HRMS (ESI⁺) exact mass calcd for C₉H₁₇O [M+H]⁺ requires *m/z* 141.1279, found *m/z* 141.1278.

(E)-4-Methyltridec-4-enal (3d)

¹H NMR (400 MHz, CDCl₃): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.26-1.30 (m, 12H), 1.61 (s, 3H), 1.97 (q, *J* = 6.6 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.51 (t, *J* = 7.4 Hz, 2H), 5.16 (t, *J* = 7.1 Hz, 1H), 9.75 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.11, 16.05, 22.68, 27.90, 29.31, 29.52, 29.69, 31.89, 31.90, 42.18, 125.99, 132.67, 202.74. HRMS (ESI⁺) exact mass calcd for C₁₄H₂₇O [M+H]⁺ requires *m/z* 211.2062, found *m/z* 211.2065.

(E)-4-Methyl-6-phenylhex-4-enal (3e)

¹H NMR (400 MHz, CDCl₃): δ 1.73 (s, 3H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.55 (t, *J* = 7.6 Hz, 2H), 3.35 (d, *J* = 7.2 Hz, 2H), 5.38 (t, *J* = 7.3 Hz, 1H), 7.14-7.19 (m, 3H), 7.24-7.29 (m, 2H), 9.76 (t, *J* = 1.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 16.31, 31.81, 34.19, 42.14, 124.16, 125.88, 128.30, 128.44, 134.20, 141.26, 202.43. HRMS (ESI⁺) exact mass calcd for C₁₃H₁₆OK [M+K]⁺ requires *m/z* 227.0838, found *m/z* 227.0842.

(E)-8-(Benzyloxy)-4-methyloct-4-enal (3f)

¹H NMR (400 MHz, CDCl₃): δ 1.61 (s, 3H), 1.66 (q, *J* = 7.0 Hz, 2H), 2.08 (q, *J* = 7.3 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.50 (t, *J* = 7.5 Hz, 2H), 3.45 (t, *J* = 6.4 Hz, 2H), 4.49 (s, 2H), 5.15 (t, *J* = 7.2 Hz, 1H), 7.26-7.34 (m, 5H), 9.74 (t, *J* = 1.7 Hz, 1H);
¹³C NMR (100 MHz, CDCl₃): δ 16.08, 24.48, 29.68, 31.84, 42.16, 69.73, 72.91, 125.02, 127.51, 127.65, 128.36, 133.55, 138.64, 202.64. HRMS (ESI⁺) exact mass calcd for C₁₆H₂₂O₂Na [M+Na]⁺ requires *m/z* 269.1517, found *m/z* 269.1524.

(E)-9-(Benzyloxy)-4-methylnon-4-enal (3g)

¹H NMR (400 MHz, CDCl₃): δ 1.42 (q, *J* = 7.6 Hz, 2H), 1.60 (s, 3H), 1.60-1.64 (m, 2H), 2.00 (q, *J* = 7.3 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.51 (t, *J* = 7.5 Hz, 2H), 3.46 (t, *J* = 6.5 Hz, 2H), 4.50 (s, 2H), 5.16 (t, *J* = 7.5 Hz, 1H), 7.26-7.34 (m, 5H), 9.75 (t, *J* = 1.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 16.11, 26.26, 27.68, 29.38, 31.86, 42.18, 70.34, 72.91, 125.54, 127.50, 127.64, 128.36, 133.13, 138.67, 202.70. HRMS (ESI⁺) exact mass calcd for C₁₇H₂₄O₂Na [M+Na]⁺ requires *m/z* 283.1674, found *m/z* 283.1675.

(E)-7-(4-Methoxyphenyl)-4-methylhept-4-enal (3h)

¹H NMR (400 MHz, CDCl₃): δ 1.55 (s, 3H), 2.26-2.32 (m, 4H), 2.49 (t, *J* = 7.1 Hz, 2H), 2.57 (t, *J* = 7.7 Hz, 2H), 3.78 (s, 3H), 5.19 (t, *J* = 7.0 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 9.73 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 16.06, 30.11, 31.83, 34.98, 42.12, 55.26, 113.66, 124.77, 129.34, 133.68, 134.19, 157.75, 202.69. HRMS (ESI⁺) exact mass calcd for C₁₅H₂₀O₂Na [M+Na]⁺ requires *m/z* 255.1361, found *m/z* 255.1357.

(E)-7-(4-Chlorophenyl)-4-methylhept-4-enal (3i)

¹H NMR (400 MHz, CDCl₃): δ 1.54 (s, 3H), 2.29 (q, *J* = 7.8 Hz, 4H), 2.49 (t, *J* = 7.6 Hz, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 5.17 (t, *J* = 7.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 9.74 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 16.06, 29.69, 31.77, 35.20, 42.08, 124.24, 128.31, 129.83, 131.47, 134.14, 140.46, 202.50. HRMS (ESI⁺) exact mass calcd for C₁₄H₁₇ClO [M+H]⁺ requires *m/z* 237.1046, found *m/z* 237.1042.

(E)-4-Methyl-7-(1-tosyl-1H-indol-3-yl)hept-4-enal (3j)

^1H NMR (400 MHz, CDCl_3): δ 1.54 (s, 3H), 2.28-2.39 (m, 4H), 2.32 (s, 3H), 2.49 (t, $J = 7.4$ Hz, 2H), 2.67 (t, $J = 7.4$ Hz, 2H), 5.20 (t, $J = 7.0$ Hz, 1H), 7.19-7.30 (m, 5H), 7.47 (d, $J = 7.6$ Hz, 1H), 7.74 (d, $J = 8.4$ Hz, 2H), 7.98 (d, $J = 8.3$ Hz, 1H), 9.75 (t, $J = 1.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.14, 21.55, 24.88, 27.38, 31.71, 42.11, 113.74, 119.44, 122.68, 122.89, 122.94, 124.47, 124.58, 126.74, 129.80, 131.11, 134.25, 135.29, 135.41, 144.72, 202.44. HRMS (ESI^+) exact mass calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_3\text{SNa}$ [$\text{M}+\text{Na}$] $^+$ requires m/z 418.1453, found m/z 418.1454.

(4E,8E)-4,8-Dimethyldodeca-4,8-dienal (3k)

^1H NMR (400 MHz, CDCl_3): δ 0.89 (t, $J = 7.4$ Hz, 3H), 1.35 (q, $J = 7.3$ Hz, 2H), 1.59 (s, 3H), 1.62 (s, 3H), 1.93-2.01 (m, 4H), 2.08 (t, $J = 7.2$ Hz, 2H), 2.31 (t, $J = 7.4$ Hz, 2H), 2.51 (t, $J = 7.5$ Hz, 2H), 5.10-5.18 (m, 2H), 9.75 (t, $J = 1.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.80, 15.93, 16.10, 22.98, 26.49, 29.99, 31.85, 39.53, 42.15, 124.84, 125.43, 132.83, 134.63, 202.75. HRMS (ESI^+) exact mass calcd for $\text{C}_{14}\text{H}_{25}\text{O}$ [$\text{M}+\text{H}$] $^+$ requires m/z 209.1905, found m/z 209.1907.

(4E,8E)-4,8-Dimethyl-11-phenylundeca-4,8-dienal (3l)

^1H NMR (400 MHz, CDCl_3): δ 1.55 (s, 3H), 1.61 (s, 3H), 1.96-1.99 (m, 2H), 2.04-2.10 (m, 2H), 2.30 (q, $J = 7.4$ Hz, 4H), 2.49 (t, $J = 7.6$ Hz, 2H), 2.63 (t, $J = 8.1$ Hz, 2H), 5.13 (t, $J = 6.8$ Hz, 1H), 5.17 (t, $J = 6.8$ Hz, 1H), 7.16-7.20 (m, 3H), 7.25-7.29 (m, 2H), 9.74 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.95, 16.10, 26.49, 29.91, 31.85, 36.11, 39.48, 42.15, 123.83, 125.37, 125.68, 128.22, 128.47, 132.93, 135.47, 142.36, 202.72. HRMS (ESI^+) exact mass calcd for $\text{C}_{19}\text{H}_{26}\text{ONa}$ [$\text{M}+\text{Na}$] $^+$ requires m/z 293.1881, found m/z 293.1875.

(E)-4-Methylundec-4-en-8-ynal (3m)

^1H NMR (400 MHz, CDCl_3): δ 1.11 (t, $J = 7.3$ Hz, 3H), 1.64 (s, 3H), 2.13-2.19 (m, 6H), 2.34 (t, $J = 7.5$ Hz, 2H), 2.53 (t, $J = 7.4$ Hz, 2H), 5.22 (t, $J = 6.8$ Hz, 1H), 9.77 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.40, 14.31, 16.21, 19.06, 27.70,

31.82, 42.10, 79.04, 81.83, 124.12, 134.24, 202.59. HRMS (ESI⁺) exact mass calcd for C₁₂H₁₈ONa [M+Na]⁺ requires *m/z* 201.1255, found *m/z* 201.1252.

4-Methylpent-4-enal (3n)

¹H NMR (400 MHz, CDCl₃): δ 1.75 (s, 3H), 2.35 (t, *J* = 7.4 Hz, 2H), 2.58 (dt, *J*₁ = 1.3 Hz, *J*₂ = 7.3 Hz, 2H), 4.69 (s, 1H), 4.77 (s, 1H), 9.78 (t, *J* = 1.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 22.61, 29.82, 41.76, 110.68, 143.75, 202.23.

3-(Cyclohept-1-en-1-yl)propanal (3p)

¹H NMR (400 MHz, CDCl₃): δ 1.41-1.50 (m, 4H), 1.70-1.76 (m, 2H), 2.04-2.11 (m, 4H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.49 (dt, *J*₁ = 1.9 Hz, *J*₂ = 7.4 Hz, 2H), 5.57 (t, *J* = 6.4 Hz, 1H), 9.75 (t, *J* = 1.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 26.66, 27.14, 28.20, 32.43, 32.53, 32.83, 42.17, 127.01, 142.49, 202.90. HRMS (ESI⁺) exact mass calcd for C₁₀H₁₇O [M+H]⁺ requires *m/z* 153.1279, found *m/z* 153.1277.

3-Cyclohexenylpropanal (3r)

¹H NMR (400 MHz, CDCl₃): δ 1.52-1.57 (m, 2H), 1.59-1.65 (m, 2H), 1.91-2.00 (m, 4H), 2.27 (t, *J* = 7.4 Hz, 2H), 2.52 (dt, *J*₁ = 1.99 Hz, *J*₂ = 7.4 Hz, 2H), 5.41-5.43 (m, 1H), 9.76 (t, *J* = 1.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 22.35, 22.82, 25.15, 28.42, 30.18, 41.86, 121.89, 135.71, 202.87. HRMS (ESI⁺) exact mass calcd for C₉H₁₄ONa [M+Na]⁺ requires *m/z* 161.0942, found *m/z* 161.0945.

(E)-7-(Furan-2-yl)-4-methylhept-4-enal (3t)

¹H NMR (400 MHz, CDCl₃): δ 1.59 (s, 3H), 2.33 (q, *J* = 8.1 Hz, 4H), 2.50 (t, *J* = 7.4 Hz, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 5.18 (t, *J* = 7.0 Hz, 1H), 5.96 (d, *J* = 2.9 Hz, 1H), 6.27 (t, *J* = 1.9 Hz, 1H), 7.29 (s, 1H), 9.73 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 16.01, 26.51, 28.00, 31.80, 42.09, 104.95, 110.10, 124.23, 134.17, 140.81, 155.77, 202.58. HRMS (ESI⁺) exact mass calcd for C₁₂H₁₇O₂ [M+H]⁺ requires *m/z* 193.1229, found *m/z* 193.1225.

(E)-4,6-Dimethylhept-4-enal (3u)

¹H NMR (400 MHz, CDCl₃): δ 0.92 (d, *J* = 6.7 Hz, 6H), 1.62 (s, 3H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.44-2.49 (m, 1H), 2.51 (t, *J* = 7.2 Hz, 2H), 4.98 (d, *J* = 9.0 Hz, 1H), 9.75 (s, 1H); ¹³C NMR (100

MHz, CDCl₃): δ 16.04, 23.03, 27.09, 31.79, 42.15, 130.52, 133.56, 202.76. HRMS (ESI⁺) exact mass calcd for C₉H₁₆ONa [M+Na]⁺ requires m/z 163.1099, found m/z 163.1092.

(E)-5-Cyclohexyl-4-methylpent-4-enal (3v)

¹H NMR (400 MHz, CDCl₃): δ 0.96-1.05 (m, 2H), 1.12-1.32 (m, 4H), 1.62 (s, 3H), 1.56-1.75 (m, 4H), 2.12-2.15 (m, 1H), 2.29 (t, J = 7.6 Hz, 2H), 2.50 (t, J = 7.2 Hz, 2H), 4.99 (d, J = 8.9 Hz, 1H), 9.75 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 16.18, 26.02, 26.08, 31.86, 33.21, 36.91, 42.18, 131.01, 132.08, 202.79. HRMS (ESI⁺) exact mass calcd C₁₂H₂₀ONa [M+Na]⁺ requires m/z 203.1412, found m/z 203.1417.

Experimental Data for Reaction Precursors of 1,3-propanediol Protected Acetal

To a solution of aldehyde (2 mmol), TsOH (0.10 equiv) and 1,3-propanediol in 15 mL toluene was added triethylorthoformate (6 mmol, 3.0 equiv) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. The reaction was then quenched with triethyl amine (0.5 mL) and concentrated *in vacuo*. The crude product was purified by flash chromatography with hexane/EA as the eluent provided the desired products as colorless oil in 78-93% yields.

(E)-2-(3-Methyl-6-phenylhex-3-en-1-yl)-1,3-dioxane (4a)

Yield: 89% as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.32 (d, J = 13.4 Hz, 1H), 1.54 (s, 3H), 1.64-1.69 (m, 2H), 2.03-2.13 (m, 3H), 2.30 (q, J = 7.4 Hz, 2H), 2.63 (t, J = 7.7 Hz, 2H), 3.73 (t, J = 12.2 Hz, 2H), 4.09 (dd, J_1 = 5.5 Hz, J_2 = 11.2 Hz, 2H), 4.45 (t, J = 5.2 Hz, 1H), 5.20 (t, J = 7.1 Hz, 1H), 7.15-7.19 (m, 3H), 7.25-7.28 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 15.95, 25.87, 29.84, 33.60, 33.83, 36.04, 66.89, 102.05, 123.85, 125.67, 128.22, 128.49, 135.07, 142.31. HRMS (ESI⁺) exact mass calcd for C₁₇H₂₅O₂ [M+H]⁺ requires m/z 261.1855, found m/z 261.1852.

(E)-2-(3-Methylhex-3-en-1-yl)-1,3-dioxane (4b)

Yield: 93% as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.93 (t, J = 7.5 Hz, 3H), 1.34 (d, J = 13.4 Hz, 1H), 1.59 (s, 3H), 1.65-1.71 (m, 2H), 1.95-2.14 (m, 5H), 3.75 (t, J = 12.2 Hz, 2H), 4.10 (dd, J_1 = 4.9 Hz, J_2 = 11.7 Hz, 2H), 4.49 (t, J = 5.2 Hz, 1H), 5.14 (t, J = 7.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.34, 15.78, 21.15, 25.87, 33.66, 33.78, 66.90,

102.13, 126.66, 133.52. HRMS (ESI⁺) exact mass calcd for C₁₁H₂₁O₂ [M+H]⁺ requires *m/z* 185.1542, found *m/z* 185.1543.

(E)-2-(3-Methylhept-3-en-1-yl)-1,3-dioxane (4c)

Yield: 87% as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.26-1.35 (m, 3H), 1.59 (s, 3H), 1.66-1.71 (m, 2H), 1.96 (q, *J* = 7.0 Hz, 2H), 2.02-2.13 (m, 3H), 3.75 (t, *J* = 12.3 Hz, 2H), 4.10 (dd, *J*₁ = 4.9 Hz, *J*₂ = 11.0 Hz, 2H), 4.49 (t, *J* = 5.2 Hz, 1H), 5.15 (t, *J* = 6.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 13.78, 15.95, 22.95, 25.88, 29.97, 33.69, 33.89, 66.92, 102.14, 124.86, 134.21. HRMS (ESI⁺) exact mass calcd for C₁₂H₂₃O₂ [M+H]⁺ requires *m/z* 199.1698, found *m/z* 199.1696.

(E)-2-(3-Methyldodec-3-enyl)-1,3-dioxane (4d)

Yield: 85% as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.30-1.39 (m, 3H), 1.59 (s, 3H), 1.67-1.72 (m, 2H), 1.95 (q, *J* = 7.2 Hz, 2H), 2.02-2.14 (m, 3H), 3.75 (t, *J* = 12.3 Hz, 2H), 4.10 (dd, *J*₁ = 4.9 Hz, *J*₂ = 11.0 Hz, 2H), 4.49 (t, *J* = 5.2 Hz, 1H), 5.15 (t, *J* = 6.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.11, 15.93, 22.68, 25.88, 27.88, 29.30, 29.36, 29.56, 29.82, 31.91, 33.67, 33.87, 66.91, 102.14, 125.11, 133.96. HRMS (ESI⁺) exact mass calcd for C₁₇H₃₂O₂ [M+H]⁺ requires *m/z* 269.2481, found *m/z* 269.2475.

(E)-2-(3-Methyl-5-phenylpent-3-en-1-yl)-1,3-dioxane (4e)

Yield: 82% as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.32 (d, *J* = 13.4 Hz, 1H), 1.71 (s, 3H), 1.71-1.75 (m, 2H), 2.01-2.11 (m, 1H), 2.13 (t, *J* = 7.2 Hz, 2H), 3.35 (d, *J* = 7.3 Hz, 2H), 3.72 (t, *J* = 12.3 Hz, 2H), 4.08 (dd, *J*₁ = 4.9 Hz, *J*₂ = 11.2 Hz, 2H), 4.49 (t, *J* = 5.2 Hz, 1H), 5.37 (t, *J* = 7.3 Hz, 1H), 7.16-7.17 (m, 3H), 7.25-7.28 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 16.13, 25.87, 33.63, 33.88, 34.17, 66.91, 102.02, 123.29, 125.70, 128.31, 128.33, 135.53, 141.69. HRMS (ESI⁺) exact mass calcd for C₁₆H₂₃O₂ [M+H]⁺ requires *m/z* 247.1698, found *m/z* 247.1692.

(E)-2-(7-(Benzyloxy)-3-methylhept-3-en-1-yl)-1,3-dioxane (4f)

Yield: 83% as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.33 (d, *J* = 13.5 Hz, 1H), 1.60 (s, 3H), 1.65-1.71 (m, 4H), 2.03-2.10 (m, 5H), 3.46 (t, *J* = 6.5 Hz, 2H), 3.74 (t, *J* = 12.0 Hz, 2H), 4.10 (dd, *J*₁ = 4.8 Hz, *J*₂ = 11.4 Hz, 2H),

4.47-4.49 (m, 3H), 5.14 (t, $J = 7.1$ Hz, 1H), 7.26-7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.96, 24.45, 25.87, 29.83, 33.67, 33.84, 66.92, 69.91, 72.93, 102.10, 124.11, 127.48, 127.64, 128.35, 134.86, 138.68. HRMS (ESI^+) exact mass calcd for $\text{C}_{19}\text{H}_{28}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 327.1936, found m/z 327.1940.

(E)-2-(8-(Benzyloxy)-3-methyloct-3-en-1-yl)-1,3-dioxane (4g)

Yield: 84% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.31 (d, $J = 13.4$ Hz, 1H), 1.37-1.44 (m, 2H), 1.58 (s, 3H), 1.59-1.63 (m, 2H), 1.66-1.71 (m, 2H), 1.99 (q, $J = 7.2$ Hz, 2H), 2.02-2.13 (m, 1H), 2.05 (t, $J = 8.0$ Hz, 2H), 3.46 (t, $J = 6.5$ Hz, 2H), 3.74 (t, $J = 12.0$ Hz, 2H), 4.09 (dd, $J_1 = 4.8$ Hz, $J_2 = 11.4$ Hz, 2H), 4.48 (t, $J = 5.2$ Hz, 1H), 4.49 (s, 2H), 5.14 (t, $J = 7.0$ Hz, 1H), 7.25-7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.98, 25.88, 26.36, 27.66, 29.37, 33.67, 33.87, 66.91, 70.41, 72.88, 102.10, 124.66, 127.47, 127.63, 128.35, 134.42, 138.71. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{31}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires m/z 319.2273, found m/z 319.2276.

(E)-2-(6-(4-Methoxyphenyl)-3-methylhex-3-en-1-yl)-1,3-dioxane (4h)

Yield: 87% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.33 (d, $J = 13.4$ Hz, 1H), 1.54 (s, 3H), 1.64-1.70 (m, 2H), 2.01-2.13 (m, 3H), 2.27 (q, $J = 7.4$ Hz, 2H), 2.57 (t, $J = 7.7$ Hz, 2H), 3.73 (t, $J = 12.2$ Hz, 2H), 3.79 (s, 3H), 4.09 (dd, $J_1 = 4.9$ Hz, $J_2 = 11.6$ Hz, 2H), 4.46 (t, $J = 5.2$ Hz, 1H), 5.18 (t, $J = 7.1$ Hz, 1H), 6.81 (d, $J = 8.4$ Hz, 2H), 7.09 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.97, 25.87, 30.07, 33.60, 33.82, 35.10, 55.25, 66.90, 102.06, 113.64, 123.92, 129.34, 134.43, 134.95, 157.67. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{27}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires m/z 291.1960, found m/z 291.1955.

(E)-2-(6-(4-Chlorophenyl)-3-methylhex-3-en-1-yl)-1,3-dioxane (4i)

Yield: 92% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.33 (d, $J = 13.4$ Hz, 1H), 1.52 (s, 3H), 1.63-1.69 (m, 2H), 2.04 (t, $J = 8.0$ Hz, 2H), 2.06-2.13 (m, 1H), 2.27 (q, $J = 7.4$ Hz, 2H), 2.60 (t, $J = 7.6$ Hz, 2H), 3.72 (t, $J = 11.9$ Hz, 2H), 4.09 (dd, $J_1 = 4.8$ Hz, $J_2 = 11.3$ Hz, 2H), 4.44 (t, $J = 5.2$ Hz, 1H), 5.15 (t, $J = 7.0$ Hz, 1H), 7.10 (d, $J = 8.2$ Hz, 2H), 7.22 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.98, 25.86, 29.62, 33.60, 33.78, 35.31,

66.89, 102.00, 123.36, 128.28, 129.85, 131.36, 135.45, 140.68. HRMS (ESI⁺) exact mass calcd for C₁₇H₂₄ClO₂ [M+H]⁺ requires *m/z* 295.1465, found *m/z* 295.1468.

(E)-3-(6-(1,3-Dioxan-2-yl)-4-methylhex-3-enyl)-1-tosyl-1H-indole (4j)

Yield: 86% as yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.31 (d, *J* = 13.4 Hz, 1H), 1.54 (s, 3H), 1.64-1.70 (m, 2H), 2.00-2.10 (m, 3H), 2.29 (s, 3H), 2.36 (q, *J* = 7.4 Hz, 2H), 2.67 (t, *J* = 7.4 Hz, 2H), 3.71 (td, *J*₁ = 2.4, *J*₂ = 2.4 Hz, 2H), 4.08 (dd, *J*₁ = 5.0 Hz, *J*₂ = 10.7 Hz, 2H), 4.46 (t, *J* = 5.2 Hz, 1H), 5.18 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 7.1 Hz, 1H), 7.26-7.30 (m, 2H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 16.12, 21.53, 25.03, 25.88, 27.28, 33.58, 33.77, 66.89, 101.99, 113.75, 119.51, 122.71, 122.99, 123.16, 123.59, 124.56, 126.73, 129.83, 131.23, 135.34, 135.52, 144.69. HRMS (ESI⁺) exact mass calcd for C₂₆H₃₂NO₄S [M+H]⁺ requires *m/z* 454.2052, found *m/z* 454.2062.

2-((3E,7E)-3,7-Dimethylundeca-3,7-dien-1-yl)-1,3-dioxane (4k)

Yield: 91% as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.89 (t, *J* = 7.3 Hz, 3H), 1.30-1.37 (m, 3H), 1.59 (s, 6H), 1.65-1.71 (m, 2H), 1.93-2.11 (m, 9H), 3.75 (t, *J* = 12.4 Hz, 2H), 4.10 (dd, *J*₁ = 4.9 Hz, *J*₂ = 11.0 Hz, 2H), 4.48 (t, *J* = 5.2 Hz, 1H), 5.13 (t, *J* = 6.9 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 13.83, 15.98, 16.00, 23.00, 25.88, 26.63, 30.02, 33.64, 33.84, 33.69, 66.91, 102.13, 124.57, 124.63, 134.12, 134.90. HRMS (ESI⁺) exact mass calcd for C₁₇H₃₀O₂Na [M+Na]⁺ requires *m/z* 289.2143, found *m/z* 289.2145.

2-((3E,7E)-3,7-Dimethyl-10-phenyldeca-3,7-dien-1-yl)-1,3-dioxane (4l)

Yield: 90% as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.33 (d, *J* = 13.4 Hz, 1H), 1.55 (s, 3H), 1.59 (s, 3H), 1.66-1.71 (m, 2H), 1.96-2.14 (m, 7H), 2.30 (q, *J* = 7.4 Hz, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 3.74 (t, *J* = 11.4 Hz, 2H), 4.10 (dd, *J*₁ = 4.8 Hz, *J*₂ = 11.4 Hz, 2H), 4.49 (t, *J* = 5.2 Hz, 1H), 5.12 (t, *J* = 6.5 Hz, 1H), 5.18 (t, *J* = 6.9 Hz, 1H), 7.15-7.20 (m, 3H), 7.25-7.29 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 15.99, 25.88, 26.60, 29.99, 33.70, 33.84, 36.15, 39.65, 66.92, 102.13, 123.64, 124.48, 125.65, 128.22, 128.48, 134.24, 135.73, 142.43. HRMS (ESI⁺) exact mass calcd for C₂₂H₃₃O₂ [M+H]⁺ requires *m/z* 329.2481, found *m/z* 329.2485.

(E)-2-(3-Methyldec-3-en-7-yn-1-yl)-1,3-dioxane (4m)

Yield: 83% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.11 (t, $J = 7.3$ Hz, 3H), 1.34 (d, $J = 13.4$ Hz, 1H), 1.62 (s, 3H), 1.67-1.72 (m, 2H), 2.05-2.20 (m, 9H), 3.76 (t, $J = 12.2$ Hz, 2H), 4.10 (dd, $J_1 = 5.0$ Hz, $J_2 = 10.8$ Hz, 2H), 4.50 (t, $J = 5.2$ Hz, 1H), 5.19 (t, $J = 6.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.43, 14.33, 16.06, 19.20, 25.87, 27.80, 33.52, 33.81, 66.90, 79.32, 81.63, 102.04, 123.29, 135.50. HRMS (ESI^+) exact mass calcd for $\text{C}_{15}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 237.1855, found m/z 237.1865.

2-(3-Methylbut-3-en-1-yl)-1,3-dioxane (4n)

Yield: 68% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.34 (d, $J = 13.5$ Hz, 1H), 1.71-1.76 (m, 2H), 1.73 (s, 3H), 2.02-2.14 (m, 3H), 3.76 (dt, $J_1 = 2.3$ Hz, $J_2 = 12.3$ Hz, 2H), 4.11 (dd, $J_1 = 5.0$ Hz, $J_2 = 10.8$ Hz, 2H), 4.53 (t, $J = 5.2$ Hz, 1H), 4.69 (s, 1H), 4.71 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 22.55, 25.85, 31.92, 33.25, 66.91, 101.96, 109.91, 145.20. HRMS (ESI^+) exact mass calcd for $\text{C}_9\text{H}_{17}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 157.1229, found m/z 157.1223.

2-(But-3-en-1-yl)-1,3-dioxane (4o)

Yield: 59% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.34 (d, $J = 13.4$ Hz, 1H), 1.66-1.72 (m, 2H), 2.02-2.18 (m, 3H), 3.76 (dt, $J_1 = 2.2$ Hz, $J_2 = 12.3$ Hz, 2H), 4.11 (dd, $J_1 = 5.0$ Hz, $J_2 = 10.9$ Hz, 2H), 4.53 (t, $J = 5.2$ Hz, 1H), 4.96 (d, $J = 10.2$ Hz, 1H), 5.03 (d, $J = 17.1$ Hz, 1H), 5.82 (tdd, $J_1 = 6.6$ Hz, $J_2 = 10.2$ Hz, $J_3 = 16.9$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 25.84, 28.15, 34.31, 66.90, 101.73, 114.74, 138.03. HRMS (ESI^+) exact mass calcd for $\text{C}_8\text{H}_{14}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 165.0891, found m/z 165.0896.

2-(2-(Cyclohept-1-en-1-yl)ethyl)-1,3-dioxane (4p)

Yield: 89% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.34 (d, $J = 13.4$ Hz, 1H), 1.41-1.48 (m, 4H), 1.64-1.73 (m, 4H), 2.03-2.10 (m, 7H), 3.75 (dt, $J_1 = 2.4$ Hz, $J_2 = 12.4$ Hz, 2H), 4.10 (dd, $J_1 = 4.8$ Hz, $J_2 = 10.4$ Hz, 2H), 4.50 (t, $J = 5.6$ Hz, 1H), 5.55 (t, $J = 10.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 25.87, 26.83, 27.34, 28.28, 32.71, 32.77, 33.75, 34.38, 66.87, 102.13, 126.02, 143.91. HRMS (ESI^+) exact mass calcd for $\text{C}_{13}\text{H}_{23}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 211.1698, found m/z 211.1701.

2-(3-Phenylbut-3-enyl)-1,3-dioxane (4q)

Yield: 87% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.30 (d, $J = 13.4$ Hz, 1H), 1.73-1.79 (m, 2H), 2.06 (tq, $J_1 = 5.0$ Hz, $J_2 = 12.6$ Hz, 1H), 2.58-2.62 (m, 2H), 3.72 (dt, $J_1 = 2.3$ Hz, $J_2 = 12.3$ Hz, 2H), 4.08 (dd, $J_1 = 5.0$ Hz, $J_2 = 10.9$ Hz, 2H), 4.53 (t, $J = 5.2$ Hz, 1H), 5.07 (s, 1H), 5.29 (s, 1H), 7.22-7.24 (m, 1H), 7.30-7.32 (m, 2H), 7.40-7.42 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 25.86, 29.48, 33.92, 66.90, 101.76, 112.30, 126.11, 127.38, 128.30, 141.08, 147.82. HRMS (ESI^+) exact mass calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 219.1385, found m/z 219.1394.

2-(2-(Cyclohex-1-en-1-yl)ethyl)-1,3-dioxane (4r)

Yield: 76% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.33 (d, $J = 13.4$ Hz, 1H), 1.51-1.71 (m, 6H), 1.89-2.14 (m, 7H), 3.75 (dt, $J_1 = 2.4$ Hz, $J_2 = 12.4$ Hz, 2H), 4.10 (dd, $J_1 = 5.0$ Hz, $J_2 = 10.7$ Hz, 2H), 4.50 (t, $J = 5.2$ Hz, 1H), 5.42 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 22.52, 22.98, 25.22, 25.86, 28.34, 32.15, 33.36, 66.89, 102.20, 120.90, 136.98. HRMS (ESI^+) exact mass calcd for $\text{C}_{12}\text{H}_{21}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 197.1542, found m/z 197.1544.

(E)-2-(6-(Furan-2-yl)-3-methylhex-3-enyl)-1,3-dioxane (4s)

Yield: 79% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.33 (d, $J = 13.4$ Hz, 1H), 1.59 (s, 3H), 1.64-1.70 (s, 2H), 2.03-2.09 (s, 3H), 2.32 (q, $J = 7.4$ Hz, 2H), 2.64 (t, $J = 7.5$ Hz, 2H), 3.73 (dt, $J_1 = 2.5$ Hz, $J_2 = 12.4$ Hz, 2H), 4.09 (dd, $J_1 = 5.0$ Hz, $J_2 = 10.6$ Hz, 2H), 4.46 (t, $J = 5.2$ Hz, 1H), 5.17 (t, $J = 7.1$ Hz, 1H), 5.96 (d, $J = 2.4$ Hz, 1H), 6.26 (dd, $J_1 = 1.9$ Hz, $J_2 = 3.0$ Hz, 1H), 7.29 (d, $J = 1.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.92, 25.87, 26.47, 28.14, 33.56, 33.80, 66.89, 102.01, 104.84, 110.08, 123.39, 135.42, 156.04. HRMS (ESI^+) exact mass calcd for $\text{C}_{15}\text{H}_{23}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 251.1647, found m/z 251.1651.

(E)-2-(3,5-Dimethylhex-3-enyl)-1,3-dioxane (4t)

Yield: 87% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.91 (d, $J = 6.7$ Hz, 6H), 1.33 (d, $J = 13.4$ Hz, 1H), 1.60 (s, 3H), 1.66-1.71 (m, 2H), 2.01-2.14 (m, 3H), 2.43-2.52 (m, 1H), 3.75 (t, $J = 12.2$ Hz, 2H), 4.10 (dd, $J_1 = 4.9$ Hz, $J_2 = 11.6$ Hz, 2H), 4.48 (t, $J = 5.2$

Hz, 1H), 4.97 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.89, 23.14, 25.87, 27.03, 33.61, 33.79, 66.90, 102.11, 131.67, 132.83. HRMS (ESI^+) exact mass calcd for $\text{C}_{12}\text{H}_{22}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 221.1517, found m/z 221.1511.

(E)-2-(4-Cyclohexyl-3-methylbut-3-enyl)-1,3-dioxane (4u)

Yield: 90% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.96-1.05 (m, 2H), 1.13-1.34 (m, 5H), 1.60 (s, 3H), 1.63-1.70 (m, 7H), 2.01-2.18 (m, 4H), 3.74 (t, $J = 8.3$ Hz, 2H), 4.10 (dd, $J_1 = 4.3$ Hz, $J_2 = 11.6$ Hz, 2H), 4.48 (t, $J = 4.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.02, 25.88, 26.08, 26.15, 33.33, 33.60, 33.83, 36.87, 66.90, 102.10, 131.34, 132.15. HRMS (ESI^+) exact mass calcd for $\text{C}_{15}\text{H}_{26}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 261.1831, found m/z 261.1825.

To a solution of corresponding achiral acetal (1 mmol) in DCM (5 mL) was added chiral diol (1.2 mmol, 1.2 equiv) and TsOH (0.1 mmol) at room temperature. The mixture was stirred at room temperature for 5 h, followed by quenching with triethylamine (0.1 mL). The reaction mixture concentrated *in vacuo* and purified by flash chromatography with hexane/EA as the eluent provided the desired products as colorless oil in 85-98% yields.

(4R,6R)-4,6-Dimethyl-2-((E)-3-methyl-6-phenylhex-3-en-1-yl)-1,3-dioxane (9a')

Yield: 94% as colorless oil. $[\alpha]_{\text{D}}^{20} = 16.1^\circ$ ($c = 4.60$ in CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.20 (d, $J = 6.1$ Hz, 3H), 1.33 (d, $J = 7.0$ Hz, 4H), 1.55 (s, 3H), 1.60-1.68 (m, 2H), 1.79-1.87 (m, 1H), 2.05 (t, $J = 7.9$ Hz, 2H), 2.30 (q, $J = 7.4$ Hz, 2H), 2.62 (t, $J = 7.8$ Hz, 2H), 3.91 (dq, $J_1 = 2.4$ Hz, $J_2 = 6.2$ Hz, $J_3 = 12.4$ Hz, 1H), 4.29 (p, $J = 6.8$ Hz, 1H), 4.79 (t, $J = 5.2$ Hz, 1H), 5.20 (t, $J = 7.0$ Hz, 1H), 7.15-7.19 (m, 3H), 7.25-7.28 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.97, 17.24, 21.90, 29.88, 33.56, 34.03, 36.08, 36.86, 67.50, 67.95, 93.98, 123.75, 125.66, 128.22, 128.45, 135.16, 142.34. HRMS (ESI^+) exact mass calcd for $\text{C}_{19}\text{H}_{29}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 289.2168, found m/z 289.2176.

(4R,5R)-2-((E)-3-Methyl-6-phenylhex-3-en-1-yl)-4,5-diphenyl-1,3-dioxolane (9a'')

Yield: 85% as colorless oil. $[\alpha]_D^{20} = 10.0^\circ$ ($c = 1.03$ in CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.62 (s, 3H), 1.97-2.02 (m, 2H), 2.26-2.37 (m, 2H), 2.66 (t, $J = 7.8$ Hz, 2H), 4.73 (d, $J = 7.8$ Hz, 1H), 4.76 (d, $J = 7.6$ Hz, 1H), 5.30 (t, $J = 7.0$ Hz, 1H), 5.50 (t, $J = 4.5$ Hz, 1H), 7.18-7.35 (m, 15H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.07, 29.99, 33.14, 33.66, 36.08, 84.94, 86.81, 124.01, 125.71, 126.35, 126.81, 128.09, 128.25, 128.47, 128.50, 128.54, 128.58, 135.03, 136.95, 138.59, 142.32. HRMS (ESI^+) exact mass calcd for $\text{C}_{28}\text{H}_{30}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 421.2144, found m/z 421.2151.

(4R,5R)-4,5-Dimethyl-2-((E)-3-methyl-6-phenylhex-3-en-1-yl)-1,3-dioxolane (9a)

Yield: 90% as colorless oil. $[\alpha]_D^{20} = 59.8^\circ$ ($c = 0.95$ in CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.22 (d, $J = 5.6$ Hz, 3H), 1.29 (d, $J = 5.6$ Hz, 3H), 1.55 (s, 3H), 1.69-1.74 (m, 2H), 2.06-2.10 (m, 2H), 2.30 (q, $J = 7.6$ Hz, 2H), 2.61-2.65 (m, 2H), 3.58-3.64 (m, 2H), 5.02 (t, $J = 4.7$ Hz, 1H), 5.22 (t, $J = 7.0$ Hz, 1H), 7.15-7.19 (m, 3H), 7.25-7.28 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.03, 16.98, 17.31, 29.94, 33.16, 33.69, 36.06, 78.10, 79.75, 103.03, 123.66, 125.67, 128.21, 128.48, 135.11, 142.33. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{27}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 275.2011, found m/z 275.2013.

(4R,5R)-4,5-Dimethyl-2-((E)-3-methyl-5-phenylpent-3-en-1-yl)-1,3-dioxolane (9b)

Yield: 87% as yellow oil. $[\alpha]_D^{20} = -11.9^\circ$ ($c = 1.54$ in CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.22 (d, $J = 5.6$ Hz, 3H), 1.28 (d, $J = 5.6$ Hz, 3H), 1.72 (s, 3H), 1.75-1.80 (m, 2H), 2.14-2.18 (m, 2H), 3.35 (d, $J = 7.3$ Hz, 2H), 3.57-3.61 (m, 2H), 5.04 (t, $J = 4.7$ Hz, 1H), 5.39 (t, $J = 7.3$ Hz, 1H), 7.16-7.18 (m, 3H), 7.25-7.28 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.26, 16.98, 17.30, 33.19, 33.71, 34.18, 78.12, 79.76, 103.00, 123.07, 125.70, 128.31, 128.34, 135.59, 141.67. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 261.1855, found m/z 261.1866.

(4R,5R)-2-((E)-6-(4-Chlorophenyl)-3-methylhex-3-en-1-yl)-4,5-dimethyl-1,3-dioxolane (9c)

Yield: 88% as colorless oil. $[\alpha]_D^{20} = 29.0^\circ$ ($c = 0.99$ in CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.22 (d, $J = 5.8$ Hz, 3H), 1.28 (d, $J = 5.8$ Hz, 3H), 1.53 (s, 3H), 1.68-1.73 (m,

2H), 2.06-2.10 (m, 2H), 2.27 (q, $J = 7.4$ Hz, 2H), 2.59 (t, $J = 7.6$ Hz, 2H), 3.57-3.63 (m, 2H), 5.00 (t, $J = 4.7$ Hz, 1H), 5.17 (t, $J = 7.1$ Hz, 1H), 7.09 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.06, 16.97, 17.30, 29.71, 33.13, 33.65, 35.34, 78.11, 79.75, 102.97, 123.20, 128.26, 129.85, 131.36, 135.47, 140.69. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{26}\text{O}_2\text{Cl}$ $[\text{M}+\text{H}]^+$ requires m/z 309.1621, found m/z 309.1630.

(4R,5R)-2-((E)-6-(4-Methoxyphenyl)-3-methylhex-3-en-1-yl)-4,5-dimethyl-1,3-dioxolane (9d)

Yield: 92% as colorless oil. $[\alpha]_{\text{D}}^{20} = 8.3^\circ$ ($c = 1.81$ in CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.21 (d, $J = 5.5$ Hz, 3H), 1.28 (d, $J = 5.5$ Hz, 3H), 1.54 (s, 3H), 1.69-1.74 (m, 2H), 2.06-2.10 (m, 2H), 2.26 (q, $J = 7.4$ Hz, 2H), 2.56 (t, $J = 7.7$ Hz, 2H), 3.57-3.61 (m, 2H), 3.76 (s, 3H), 5.01 (t, $J = 4.7$ Hz, 1H), 5.20 (t, $J = 6.9$ Hz, 1H), 6.80 (d, $J = 8.5$ Hz, 2H), 7.08 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.06, 16.99, 17.32, 30.17, 33.18, 33.71, 35.13, 55.19, 78.10, 79.74, 103.03, 113.63, 123.75, 129.34, 134.40, 134.99, 157.69. HRMS (ESI^+) exact mass calcd for $\text{C}_{19}\text{H}_{29}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires m/z 305.2117, found m/z 305.2122.

(4R,5R)-2-((E)-7-(Benzyloxy)-3-methylhept-3-en-1-yl)-4,5-dimethyl-1,3-dioxolane (9e)

Yield: 89%, colorless oil. $[\alpha]_{\text{D}}^{20} = 8.4^\circ$ ($c = 1.14$ in CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.22 (d, $J = 5.5$ Hz, 3H), 1.28 (d, $J = 5.5$ Hz, 3H), 1.60 (s, 3H), 1.60-1.75 (m, 4H), 2.05-2.11 (m, 4H), 3.45 (t, $J = 6.5$ Hz, 2H), 3.57-3.60 (m, 2H), 4.48 (s, 2H), 5.03 (t, $J = 4.7$ Hz, 1H), 5.16 (t, $J = 6.9$ Hz, 1H), 7.25-7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.07, 16.99, 17.31, 24.45, 29.80, 33.24, 33.70, 69.86, 72.90, 78.10, 79.74, 103.04, 123.91, 127.47, 127.63, 128.35, 134.90, 138.68. HRMS (ESI^+) exact mass calcd for $\text{C}_{20}\text{H}_{31}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires m/z 319.2273, found m/z 319.2269.

(4R,5R)-2-((3E,7E)-3,7-Dimethyl-10-phenyldeca-3,7-dienyl)-4,5-dimethyl-1,3-dioxolane (9f)

Yield: 93%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.22 (d, $J = 6.2$ Hz, 3H), 1.27 (d, $J = 6.2$ Hz, 3H), 1.55 (s, 3H), 1.60 (s, 3H), 1.68-1.76 (m, 2H), 1.96-1.99 (m, 2H), 2.04-2.11 (m, 4H), 2.29 (q, $J = 7.8$ Hz, 2H), 2.63 (t, $J = 7.6$ Hz, 2H), 3.56-3.64 (m, 2H), 5.04 (t, $J = 4.8$ Hz, 1H), 5.14 (t, $J = 6.8$ Hz, 1H), 5.18 (t, $J = 6.4$ Hz, 1H), 7.15-7.19 (m, 3H), 7.26-7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.98, 16.09, 16.98, 17.30, 26.59, 29.99, 33.26, 33.69, 36.15, 39.62, 78.09, 79.74, 103.08, 123.64, 124.29, 125.65, 128.21, 128.48, 134.28, 135.72, 142.43. HRMS (ESI^+) exact mass calcd for $\text{C}_{23}\text{H}_{35}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 343.2637, found m/z 343.2645.

(4R,5R)-4,5-Dimethyl-2-((E)-3-methyldec-3-en-7-ynyl)-1,3-dioxolane (9g)

Yield: 91%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.11 (t, $J = 7.2$ Hz, 3H), 1.23 (d, $J = 5.8$ Hz, 3H), 1.29 (d, $J = 5.8$ Hz, 3H), 1.62 (s, 3H), 1.70-1.77 (m, 2H), 2.08-2.18 (m, 8H), 3.56-3.64 (m, 2H), 5.04 (t, $J = 4.6$ Hz, 1H), 5.21 (t, $J = 7.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.40, 14.31, 16.15, 16.95, 17.27, 19.16, 27.81, 33.11, 33.63, 78.08, 79.29, 79.72, 81.61, 102.99, 123.06, 135.55. HRMS (ESI^+) exact mass calcd for $\text{C}_{16}\text{H}_{27}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 251.2011, found m/z 251.2013.

(4R,5R)-2-(2-Cyclohexenylethyl)-4,5-dimethyl-1,3-dioxolane (9h)

Yield: 98%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.23 (d, $J = 5.8$ Hz, 3H), 1.29 (d, $J = 5.8$ Hz, 3H), 1.51-1.64 (m, 4H), 1.71-1.78 (m, 2H), 1.90-1.99 (m, 4H), 2.04 (t, $J = 7.6$ Hz, 2H), 3.56-3.64 (m, 2H), 5.04 (t, $J = 4.8$ Hz, 1H), 5.42 (t, $J = 1.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 16.94, 17.24, 22.52, 22.97, 25.20, 28.41, 32.04, 32.87, 78.04, 79.69, 103.14, 120.76, 136.98. HRMS (ESI^+) exact mass calcd for $\text{C}_{13}\text{H}_{23}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 211.1698, found m/z 211.1698.

An oven-dried round bottom flask (10 mL) equipped with a magnetic stir bar was charged with 4Å molecular sieves (300 mg), and sealed with a rubber septum. Then acetal/aldehyde (0.20 mmol) and silyl enol ether (0.3 mmol, 1.5 equiv) were dissolved in dry CH_2Cl_2 (2 mL) and added via syringe. After cooling the solution to -78°C , TiCl_4 (0.24 mL of a 1.0M solution in CH_2Cl_2 , 0.24 mmol, 1.2 equiv) was added dropwisely. The solution was allowed to stir at -78°C for 10 h and then quenched with sat. NaHCO_3 (5 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel using appropriate solvents (hexane/diethyl ether mixture) to provide the title compound.

Triisopropyl(((1*S*,2*R*,3*R*,5*R*)-1,4,4-trimethyl-2-phenethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)silane (6a)

Yield: 91% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.93 (s, 3H), 1.04 (s, 3H), 1.07-1.10 (m, 21H), 1.38 (s, 3H), 1.51-1.64 (m, 3H), 1.81 (ddt, $J_1 = 5.2$ Hz, $J_2 = 7.6$ Hz, $J_3 = 12.5$ Hz, 1H), 2.11-2.14 (m, 1H), 2.22-2.28 (m, 1H), 2.45 (dt, $J_1 = 5.1$ Hz, $J_2 = 10.0$ Hz, 1H), 2.64-2.73 (m, 2H), 3.67 (d, $J = 7.9$ Hz, 1H), 3.69 (s, 1H), 7.16-7.20 (m, 3H), 7.25-7.30 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.96, 18.55, 23.88, 25.61, 26.27, 26.81, 35.29, 36.69, 37.66, 37.94, 51.23, 80.49, 80.96, 84.47, 125.90, 128.30, 128.41, 142.50. HRMS (ESI⁺) exact mass calcd for $\text{C}_{27}\text{H}_{46}\text{O}_2\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 453.3165, found m/z 453.3164.

The enantiomeric excess was determined by chiral HPLC (Chiralpak OD-H, 0.1% *i*-PrOH/hexanes, flow rate 1.0 mL/min, $\lambda = 220$ nm), 11.62 min (major) and 11.62 min (minor). 97% ee. Yield: 88%. $[\alpha]_{\text{D}}^{20} = 27.9^\circ$ ($c = 1.52$ in CHCl_3).

2-Ethyl-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropylsilane (6b)

Yield: 85% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.93 (s, 3H), 1.00 (t, $J = 7.2$ Hz, 3H), 1.03 (s, 3H), 1.08-1.14 (m, 21H), 1.30 (s, 3H), 1.43 (t, $J = 6.1$ Hz, 1H), 1.51 (dt, $J_1 = 3.8$ Hz, $J_2 = 12.2$ Hz, 1H), 1.75-1.85 (m, 2H), 2.24 (dt, $J_1 = 3.6$ Hz, $J_2 = 11.2$ Hz, 1H), 2.42 (dt, $J_1 = 5.2$ Hz, $J_2 = 10.4$ Hz, 1H), 3.66 (d, $J = 7.8$ Hz, 1H), 3.69 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.92, 15.47, 18.50, 23.92, 25.28, 26.22, 26.70, 36.73, 37.87, 53.13, 79.31, 80.94, 84.43. HRMS (ESI^+) exact mass calcd for $\text{C}_{21}\text{H}_{43}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 355.3032, found m/z 355.3041.

Triisopropyl((1,4,4-trimethyl-2-propyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)silane (6c)

Yield: 90% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.91 (t, $J = 7.2$ Hz, 3H), 0.93 (s, 3H), 1.04 (s, 3H), 1.05-1.14 (m, 21H), 1.18-1.26 (m, 1H), 1.28 (s, 3H), 1.32-1.42 (m, 2H), 1.46-1.54 (m, 2H), 1.64-1.73 (m, 1H), 1.79 (ddt, $J_1 = 4.9$ Hz, $J_2 = 7.7$ Hz, $J_3 = 12.2$ Hz, 1H), 2.24 (dt, $J_1 = 3.8$ Hz, $J_2 = 12.0$ Hz, 1H), 2.41 (dt, $J_1 = 4.2$ Hz, $J_2 = 8.8$ Hz, 1H), 3.65 (d, $J = 6.0$ Hz, 1H), 3.66 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.93, 14.86, 18.51, 23.91, 24.52, 25.34, 26.23, 26.79, 35.53, 36.65, 37.89, 51.62, 80.17, 80.92, 84.47. HRMS (ESI^+) exact mass calcd for $\text{C}_{22}\text{H}_{45}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 369.3189, found m/z 369.3202.

(1,4,4-Trimethyl-2-octyl-8-oxabicyclo[3.2.1]octan-3-yloxy)triisopropylsilane (6d)

Yield: 88%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.88 (t, $J = 6.8$ Hz, 3H), 0.92 (s, 3H), 1.04 (s, 3H), 1.05-1.10 (m, 21H), 1.27-1.36 (m, 16H), 1.45-1.47 (m, 1H), 1.52 (dd, $J_1 = 3.4$ Hz, $J_2 = 12.6$ Hz, 1H), 1.67-1.84 (m, 2H), 2.20-2.27 (m, 1H), 2.37-2.44 (m, 1H), 3.64-3.69 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.94, 14.10, 18.51, 22.69, 23.91, 25.37, 26.22, 26.81, 29.29, 29.43, 30.35, 31.33, 31.86, 33.02, 36.66, 37.88, 51.70, 80.15, 80.94, 84.46. HRMS (ESI^+) exact mass calcd for $\text{C}_{27}\text{H}_{55}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 439.3971, found m/z 439.3978.

(((1S,2R,3R,5R)-2-Benzyl-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropylsilane (6e)

Yield: 92% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.68 (qd, $J_1 = 7.5$ Hz, $J_2 = 15.1$ Hz, 1H), 0.89-0.93 (m, 21H), 1.25 (s, 3H), 1.38 (s, 3H), 1.58 (dt, $J_1 = 3.7$ Hz, $J_2 = 12.2$ Hz, 1H), 1.79-1.85 (m, 1H), 1.89

(dd, $J_1 = 5.2$ Hz, $J_2 = 10.8$ Hz, 1H), 2.24 (dt, $J_1 = 4.0$ Hz, $J_2 = 12.8$ Hz, 1H), 2.46 (dt, $J_1 = 5.2$ Hz, $J_2 = 10.4$ Hz, 1H), 2.64 (dd, $J_1 = 10.9$ Hz, $J_2 = 14.0$ Hz, 1H), 3.08 (dd, $J_1 = 5.1$ Hz, $J_2 = 14.1$ Hz, 1H), 3.59 (s, 1H), 3.73 (d, $J = 7.7$ Hz, 1H), 7.15-7.19 (m, 3H), 7.24-7.28 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.43, 18.37, 18.41, 24.25, 25.83, 26.14, 28.03, 36.77, 37.03, 38.15, 52.90, 75.52, 81.01, 84.43, 125.81, 128.18, 129.62, 141.51. HRMS (ESI^+) exact mass calcd for $\text{C}_{26}\text{H}_{45}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 417.3189, found m/z 417.3204.

The enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H, 0.1% *i*-PrOH/hexanes, flow rate 1.0 mL/min, $t_r = 5.284$ min (major) and 5.68 min (minor). 94% ee. Yield: 91%. $[\alpha]_{\text{D}}^{20} = -16.2^\circ$ ($c = 2.60$ in CHCl_3).

(((1*S*,2*R*,3*R*,5*R*)-2-(3-(Benzyloxy)propyl)-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropylsilane (6f)

Yield: 84% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.92 (s, 3H), 1.03 (s, 3H), 1.06-1.10 (m, 21H), 1.30 (s, 3H), 1.30-1.33 (m, 1H), 1.48-1.55 (m, 2H), 1.66-1.74 (m, 2H), 1.75-1.85 (m, 2H), 2.24 (dt, $J_1 = 3.6$ Hz, $J_2 = 12.4$ Hz, 1H), 2.42 (dt, $J_1 = 5.1$ Hz, $J_2 = 10.7$ Hz, 1H), 3.44 (t, $J = 6.6$ Hz, 2H), 3.66 (s, 2H), 4.50 (s, 2H), 7.27-7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.92, 18.53, 23.90, 25.41, 26.24, 26.79, 29.33, 31.46, 36.64, 37.88, 51.41, 70.73, 72.91, 80.12, 80.92, 84.48, 127.51, 127.60, 128.36, 138.58. HRMS (ESI^+) exact mass calcd for $\text{C}_{29}\text{H}_{51}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 475.3607, found m/z 475.3595.

The enantiomeric excess was determined by chiral HPLC (Chiralpak OD-H, 0.5% *i*-PrOH/hexanes, flow rate 1.0 mL/min, $t_r = 5.240$ min (major) and 9.13 min (minor). 94% ee. Yield: 79%. $[\alpha]_{\text{D}}^{20} = 4.6^\circ$ ($c = 1.68$ in CHCl_3).

((2-(4-(Benzyloxy)butyl)-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropylsilane (6g)

Yield: 89% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.92 (s, 3H), 1.03 (s, 3H), 1.07-1.10 (m, 21H), 1.28 (s, 3H), 1.39-1.54 (m, 4H), 1.59-1.64 (m, 1H), 1.72-1.81 (m, 2H), 1.70-1.84 (m, 2H), 2.23 (dt, $J_1 = 3.2$ Hz, $J_2 = 12.8$ Hz, 1H), 2.41 (dt, $J_1 = 5.1$ Hz, $J_2 = 10.7$ Hz, 1H), 3.47 (t, $J = 6.4$ Hz, 2H), 3.66 (s, 2H), 4.49 (s, 2H), 7.27-7.36 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.94, 18.53, 23.91, 25.38, 26.23, 26.82, 27.89, 30.42, 32.84, 36.64, 37.89, 51.73,

70.12, 72.88, 80.13, 80.91, 84.48, 127.47, 127.58, 128.34, 138.67. HRMS (ESI⁺) exact mass calcd for C₃₀H₅₃O₃Si [M+H]⁺ requires *m/z* 489.3764, found *m/z* 489.3752.

Triisopropyl(((1*S*,2*R*,3*R*,5*R*)-2-(4-methoxyphenethyl)-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy) (6h)

Yield: 84% as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.93 (s, 3H), 1.02-1.10 (m, 24H), 1.38 (s, 3H), 1.50-1.59 (m, 3H), 1.78-1.84 (m, 1H), 2.05-2.11 (m, 1H), 2.25 (td, *J*₁ = 3.6 Hz, *J*₂ = 10.0 Hz, 1H), 2.45 (td, *J*₁ = 4.8

Hz, *J*₂ = 10.0 Hz, 1H), 2.55-2.62 (m, 1H), 2.64-2.72 (m, 1H), 3.67 (d, *J* = 7.2 Hz, 1H), 3.68 (s, 1H), 3.78 (s, 3H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 12.96, 18.55, 23.88, 25.62, 26.27, 26.80, 35.57, 36.68, 36.72, 37.93, 51.09, 55.24, 80.57, 80.96, 84.47, 113.80, 129.19, 134.60, 157.83. HRMS (ESI⁺) exact mass calcd for C₂₈H₄₉O₃Si [M+H]⁺ requires *m/z* 461.3451, found *m/z* 461.3455.

The enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H, 0.5% *i*-PrOH/hexanes, flow rate 1.0 mL/min, $[t_R] = 8.78$ min (minor) and 9.53 min (major). 95% ee. Yield: 74%. $[\alpha]_D^{20} = 29.6^\circ$ (*c* = 1.98 in CHCl₃).

(((1*S*,2*R*,3*R*,5*R*)-2-(4-chlorophenethyl)-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropylsilane (6i)

Yield: 85% as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.93 (s, 3H), 0.99 (s, 3H), 1.10-1.10 (m, 21H), 1.37 (s, 3H), 1.50-1.63 (m, 1H), 1.77-1.86 (m, 1H), 2.04-2.14 (m, 1H), 2.21-2.28 (m, 1H), 2.41-2.48 (m, 1H), 2.58-2.74 (m, 2H),

3.66 (s, 1H), 3.67 (d, *J* = 8.2 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 12.96, 18.54, 23.85, 25.62, 26.26, 26.79, 35.25, 36.63, 36.93, 37.92, 51.00, 80.59, 80.88, 84.47, 128.49, 129.66, 131.63, 140.87. HRMS (ESI⁺) exact mass calcd for C₂₇H₄₆O₂SiCl [M+H]⁺ requires *m/z* 465.2956, found *m/z* 465.2953.

The enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H + OD-H, 0.1% *i*-PrOH/hexanes, flow rate 0.7 mL/min, $[t_R] = 17.82$ min (minor) and 19.13 min (major). 98% ee. Yield: 80%. $[\alpha]_D^{20} = 32.9^\circ$ (*c* = 2.93 in CHCl₃).

1-Tosyl-3-(2-(1,4,4-trimethyl-3-((triisopropylsilyl)oxy)-8-oxabicyclo[3.2.1]octan-2-yl)ethyl)-1*H*-indole (6j)

Yield: 71% as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.94 (s, 3H), 1.02-1.12 (m,

24H), 1.36 (s, 3H), 1.55 (dt, $J_1 = 3.8$ Hz, $J_2 = 12.5$ Hz, 1H), 1.61-1.71 (m, 2H), 1.78-1.87 (m, 1H), 2.10-2.19 (m, 1H), 2.23-2.29 (m, 1H), 2.33 (s, 3H), 2.43-2.50 (m, 1H), 2.71-2.75 (m, 2H), 3.69-3.70 (m, 2H), 7.20 (d, $J = 8.1$ Hz, 2H), 7.23 (d, $J = 7.2$ Hz, 1H), 7.29-7.32 (m, 2H), 7.44 (d, $J = 7.7$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.99 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.96, 18.51, 21.56, 23.87, 25.59, 26.26, 26.56, 26.89, 32.44, 36.63, 37.94, 51.25, 80.39, 80.85, 84.52, 113.80, 119.37, 122.55, 123.01, 123.21, 124.66, 126.78, 129.83, 130.90, 135.33, 135.38, 144.74. HRMS (ESI^+) exact mass calcd for $\text{C}_{36}\text{H}_{54}\text{NO}_4\text{SSi}$ $[\text{M}+\text{H}]^+$ requires m/z 624.3543, found m/z 624.3531.

Triisopropyl((1,4,4-trimethyl-2-((*E*)-3-methylhept-3-en-1-yl)-8-oxabicyclo[3.2.1]octan-3-yl)oxy)silane (6k)

Yield: 66% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.89 (t, $J = 7.4$ Hz, 3H), 0.93 (s, 3H), 1.05 (s, 3H), 1.09-1.11 (m, 21H), 1.28-1.38 (m, 3H), 1.31 (s, 3H), 1.46-1.55 (m, 2H), 1.58-1.59 (m, 2H), 1.75-1.89 (m, 2H), 1.95 (q, $J = 7.2$ Hz, 2H), 2.02-2.06 (m, 2H), 2.21-2.27 (m, 1H), 2.42 (dt, $J_1 = 5.1$ Hz, $J_2 = 10.6$ Hz, 1H), 3.66-3.69 (m, 2H), 5.13 (t, $J = 7.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.95, 13.85, 16.03, 18.52, 22.96, 23.90, 25.43, 26.23, 26.80, 30.02, 31.97, 36.66, 37.90, 41.57, 51.35, 80.31, 80.98, 84.48, 124.57, 135.41. HRMS (ESI^+) exact mass calcd for $\text{C}_{27}\text{H}_{53}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 437.3815, found m/z 437.3812.

Triisopropyl((1,4,4-trimethyl-2-((*E*)-3-methyl-6-phenylhex-3-en-1-yl)-8-oxabicyclo[3.2.1]octan-3-yl)oxy)silane (6l)

Yield: 52% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.93 (s, 3H), 1.02-1.11 (m, 21H), 1.05 (s, 3H), 1.30 (s, 3H), 1.45-1.58 (m, 2H), 1.54 (s, 3H), 1.75-1.88 (m, 2H), 2.05 (t, $J = 8.4$ Hz, 2H), 2.21-2.31 (m, 3H), 2.38-2.45 (m, 1H), 2.63 (t, $J = 7.8$ Hz, 2H), 3.67 (s, 1H), 3.68 (d, $J = 7.9$ Hz, 1H), 5.18 (t, $J = 6.8$ Hz, 1H), 7.15-7.29 (m, 3H), 7.26-7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.97, 16.01, 18.55, 23.90, 25.45, 26.24, 26.82, 30.00, 31.97, 36.11, 36.67, 37.91, 41.53, 51.38, 80.35, 80.98, 84.48, 123.57, 125.69, 128.21, 128.50, 136.27, 142.33. HRMS (ESI^+) exact mass calcd for $\text{C}_{32}\text{H}_{55}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 499.3971, found m/z 499.3975.

((2-(Hex-3-yn-1-yl)-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropylsilane (6m)

Yield: 56% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.93 (s, 3H), 1.05 (s, 3H), 1.10-1.13 (m, 24H), 1.30 (s, 3H), 1.47-1.56 (m, 3H), 1.80 (ddt, $J_1 = 5.2$ Hz, $J_2 = 7.7$ Hz, $J_3 = 12.6$ Hz, 1H), 1.93-2.03 (m, 1H), 2.12-2.27 (m, 5H), 2.43 (ddd, $J_1 = 5.2$ Hz, $J_2 = 9.9$ Hz, $J_3 = 11.6$ Hz, 1H), 3.63 (s, 1H), 3.66 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.43, 12.92, 14.26, 18.53, 19.94, 23.91, 25.38, 26.23, 26.87, 32.36, 36.61, 37.89, 50.63, 79.26, 79.83, 80.77, 81.86, 84.41. HRMS (ESI^+) exact mass calcd for $\text{C}_{25}\text{H}_{47}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 407.3345, found m/z 407.3347.

Triisopropyl((1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)silane (6n)

Yield: 74% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.93 (s, 3H), 1.02 (s, 3H), 1.09-1.12 (m, 21H), 1.29 (s, 3H), 1.47 (ddt, $J_1 = 1.8$ Hz, $J_2 = 4.4$ Hz, $J_3 = 12.8$ Hz, 1H), 1.60 (dd, $J_1 = 1.2$ Hz, $J_2 = 14.3$ Hz, 1H), 1.82 (ddt, $J_1 = 4.2$ Hz, $J_2 = 7.9$ Hz, $J_3 = 12.1$ Hz, 1H), 1.98 (ddd, $J_1 = 1.5$ Hz, $J_2 = 4.5$ Hz, $J_3 = 14.3$ Hz, 1H), 2.22 (ddd, $J_1 = 4.7$ Hz, $J_2 = 9.9$ Hz, $J_3 = 12.1$ Hz, 1H), 2.37 (ddd, $J_1 = 4.5$ Hz, $J_2 = 10.1$ Hz, $J_3 = 12.1$ Hz, 1H), 3.68 (d, $J = 8.1$ Hz, 1H), 3.73 (td, $J_1 = 1.3$ Hz, $J_2 = 4.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.79, 18.36, 22.71, 26.26, 26.88, 26.92, 34.56, 38.16, 42.27, 74.05, 78.59, 83.74. HRMS (ESI^+) exact mass calcd for $\text{C}_{19}\text{H}_{39}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 327.2719, found m/z 327.2722.

((2,2-Dimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropylsilane (6o)

Yield: 46% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.96 (s, 3H), 1.05 (s, 3H), 1.05-1.09 (m, 21H), 1.55 (d, $J = 14.5$ Hz, 1H), 1.72 (ddt, $J_1 = 4.0$ Hz, $J_2 = 7.3$ Hz, $J_3 = 11.2$ Hz, 1H), 1.81 (ddt, $J_1 = 4.0$ Hz, $J_2 = 7.3$ Hz, $J_3 = 11.2$ Hz, 1H), 2.11-2.22 (m, 2H), 2.34-2.40 (m, 1H), 3.69 (s, 1H), 3.69 (d, $J = 11.9$ Hz, 1H), 4.30-4.33 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.78, 18.36, 23.11, 24.85, 26.92, 28.34, 36.31, 39.02, 73.44, 73.79, 82.60. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{37}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 313.2563, found m/z 313.2566.

((2,2-Dimethyldecahydro-1H-3,5a-epoxyheptalen-1-yl)oxy)triisopropylsilane (6p)

Yield: 54% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.92 (s, 3H), 1.00 (s, 3H), 1.06-1.11 (m, 21H), 1.25-1.34 (m, 3H), 1.37-1.38 (m, 1H), 1.46 (dt, $J_1 = 4.0$ Hz, $J_2 = 12.0$ Hz, 1H), 1.65-1.73 (m, 2H), 1.75-1.90 (m, 6H), 2.28 (dt, $J_1 = 4.1$ Hz, $J_2 = 11.2$ Hz, 1H), 2.41 (dt, $J_1 = 4.8$ Hz, $J_2 = 11.2$ Hz, 1H), 3.54 (s, 1H), 3.63 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.94, 18.46, 22.38, 23.48, 26.26, 26.42, 30.59, 30.78, 32.21, 37.39, 37.70, 41.08, 52.91, 82.76, 83.06, 83.39. HRMS (ESI^+) exact mass calcd for $\text{C}_{23}\text{H}_{45}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 381.3189, found m/z 381.3194.

3-(7,7-Dimethyl-4-phenyl-6-(triisopropylsilyloxy)cyclohept-3-enyloxy)propan-1-ol (6q)

Yield: 62% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.00-1.03 (m, 21H), 1.07 (s, 3H), 1.08 (s, 3H), 1.76-1.86 (m, 2H), 2.39 (dd, $J_1 = 7.2$ Hz, $J_2 = 17.1$ Hz, 1H), 2.46-2.54 (m, 2H), 2.67 (brs, 1H), 2.96-3.03 (m, 1H), 3.22 (dd, $J_1 = 1.7$ Hz, $J_2 = 9.6$ Hz, 1H), 3.48-3.53 (m, 1H), 3.74-3.83 (m, 3H), 3.98 (dd, $J_1 = 1.6$ Hz, $J_2 = 10.4$ Hz, 1H), 5.86-5.89 (m, 1H), 7.18-7.32 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.82, 13.03, 18.26, 19.34, 21.63, 28.03, 32.19, 37.54, 43.91, 62.70, 69.80, 75.61, 84.81, 125.38, 125.67, 126.62, 128.20, 128.30, 140.15, 144.24. HRMS (ESI^+) exact mass calcd for $\text{C}_{27}\text{H}_{46}\text{O}_3\text{SiK}$ $[\text{M}+\text{K}]^+$ requires m/z 485.2853, found m/z 485.2873.

3-((8,8-Dimethyl-9-((triisopropylsilyl)oxy)-2,3,5,6,7,8,9,9a-octahydro-1H-benzo[7]annulen-7-yl)oxy)propan-1-ol (6r)

Yield: 57% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.84 (s, 3H), 1.11-1.16 (m, 21H), 1.16 (s, 3H), 1.36-1.57 (m, 3H), 1.70-1.91 (m, 4H), 1.97 (s, 2H), 2.05-2.15 (m, 2H), 2.25 (t, $J = 12.0$ Hz, 1H), 2.49 (d, $J = 11.9$ Hz, 1H), 2.92 (brs, 1H), 3.53-3.60 (m, 2H), 3.68 (s, 1H), 3.72-3.78 (m, 3H), 5.37 (d, $J = 3.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.02, 18.19, 18.51, 23.75, 25.51, 29.10, 30.90, 31.47, 32.23, 32.79, 44.79, 48.60, 63.07, 70.95, 82.79, 84.68, 122.52, 140.90. HRMS (ESI^+) exact mass calcd for $\text{C}_{25}\text{H}_{49}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 425.3451, found m/z 425.3452.

((4,4-Diethyl-1-methyl-2-phenethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropyl silane (8b)

Yield: 85% as colorless oil. Dr: 10:90. ^1H NMR (400 MHz, CDCl_3): δ 0.73 (t, $J = 7.6$ Hz, 3H), 0.80 (t, $J = 7.6$ Hz, 3H), 1.03-1.14 (m, 21H), 1.38 (s, 3H), 1.30-1.47 (m, 2H), 1.50-1.69 (m, 5H), 1.76-1.86 (m, 1H), 2.06-2.15 (m, 1H), 2.21-2.27 (m, 1H), 2.41-2.48 (m, 1H), 2.60-2.77 (m, 2H), 3.70 (s, 0.10H for minor isomer), 3.80 (s, 0.90H for major isomer), 3.88 (d, $J = 7.77$ Hz, 1H), 7.16-7.20 (m, 3H), 7.25-7.30 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 6.73, 8.37, 13.09, 18.60, 22.30, 24.20, 25.64, 25.79, 35.20, 37.94, 41.90, 51.65, 76.82, 80.87, 81.84, 125.91, 128.31, 128.42, 142.44. HRMS (ESI^+) exact mass calcd for $\text{C}_{29}\text{H}_{51}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 459.3658, found m/z 459.3673.

Triisopropyl((5-methyl-4-phenethyl-8-oxaspiro[bicyclo[3.2.1]octane-2,1'-cyclopentane]-3-yl)oxy)silane (8c)

Yield: 87% as colorless oil. Dr: 4:96. ^1H NMR (400 MHz, CDCl_3): δ 1.02-1.13 (m, 21H), 1.36 (s, 3H), 1.26-1.41 (m, 2H), 1.48-1.66 (m, 7H), 1.77-1.91 (m, 2H), 1.97-2.11 (m, 2H), 2.22-2.29 (m, 1H), 2.52 (ddd, $J_1 = 4.9$ Hz, $J_2 = 10.0$ Hz, $J_3 = 11.5$ Hz, 1H), 2.63-2.73 (m, 2H), 3.77 (s, 1H), 3.80 (d, $J = 7.8$ Hz, 1H), 7.16-7.20 (m, 3H), 7.25-7.30 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.95, 18.56, 23.90, 25.36, 25.72, 26.98, 33.03, 33.10, 36.50, 36.94, 37.15, 50.47, 50.99, 80.40, 81.24, 81.70, 125.88, 128.31, 128.40, 142.53. HRMS (ESI^+) exact mass calcd for $\text{C}_{29}\text{H}_{49}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 457.3502, found m/z 457.3514.

Triisopropyl((5-methyl-4-phenethyl-8-oxaspiro[bicyclo[3.2.1]octane-2,1'-cyclohexane]-3-yl)oxy)silane (8d)

Yield: 91% as colorless oil. Dr: 7:93. ^1H NMR (400 MHz, CDCl_3): δ 1.03-1.15 (m, 21H), 1.23-1.34 (m, 4H), 1.39 (s, 3H), 1.41-1.64 (m, 7H), 1.79-1.88 (m, 2H), 1.93 (d, $J = 12.8$ Hz, 1H), 2.03-2.13 (m, 1H), 2.24-2.30 (m, 1H), 2.42-2.49 (m, 1H), 2.68 (dtd, $J_1 = 5.4$ Hz, $J_2 = 13.2$ Hz, $J_3 = 19.2$ Hz, 2H), 3.68 (s, 1H), 4.26 (d, $J = 7.8$ Hz, 1H), 7.16-7.20 (m, 3H), 7.26-7.30 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.13, 18.62, 18.65, 21.46, 21.60, 25.46, 25.59, 26.44, 31.68, 33.71, 35.50, 36.90, 37.96, 39.80, 51.63, 79.25, 81.29, 81.42, 125.89, 128.30, 128.40, 142.52. HRMS (ESI^+) exact mass calcd for $\text{C}_{30}\text{H}_{51}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 471.3658, found m/z 471.3656.

4-Benzyl-1-methyl-2-phenethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropylsilane (8e)

Yield: 96% as colorless oil. Dr: 41:59. ^1H NMR (400 MHz, CDCl_3): δ 1.00-1.17 (m, 21H), 1.32 (s, 1.8H) for major isomer, 1.40 (s, 1.2H) for minor isomer, 1.44-1.67 (m, 3H), 1.71-1.83 (m, 1H), 1.88-1.99 (m, 0.6H), 2.05-2.24 (m, 2H), 2.32-2.38 (m, 0.6H), 2.52-2.61 (m, 1H), 2.65-2.79 (m, 3.6H), 2.85 (dd, $J_1 = 10.9$ Hz, $J_2 = 13.0$ Hz, 0.4H), 3.87 (dd, $J_1 = 2.9$ Hz, $J_2 = 7.4$ Hz, 0.6H), 3.92 (s, 0.4H), 4.07 (d, $J = 3.5$ Hz, 0.6H), 4.11 (d, $J = 7.6$ Hz, 0.4H), 7.14-7.32 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.18, 12.89, 18.27, 18.57, 25.38, 25.58, 25.82, 30.04, 32.28, 33.43, 35.48, 36.14, 36.31, 36.46, 37.01, 38.43, 42.04, 49.27, 50.32, 51.20, 75.64, 75.80, 76.87, 80.94, 81.43, 125.93, 125.98, 126.02, 128.33, 128.38, 128.48, 128.94, 129.40, 140.19, 140.90, 142.25, 142.47. HRMS (ESI^+) exact mass calcd for $\text{C}_{32}\text{H}_{49}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 493.3502, found m/z 493.3508.

(2R,3R)-3-((7R,9R,9aS)-8,8-Dimethyl-9-(triisopropylsilyloxy)-2,3,5,6,7,8,9,9a-octahydro-1H-benzo[7]annulen-7-yloxy)butan-2-ol (10h)

Yield: 70% as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.86 (s, 3H), 1.04 (d, $J = 7.6$ Hz, 3H), 1.05 (s, 3H), 1.10-1.14 (m, 24H), 1.25-1.33 (m, 1H), 1.40-1.58 (m, 2H), 1.75-1.78 (m, 2H), 1.97 (m, 2H), 2.09-2.15 (m, 2H), 2.25 (t, $J = 11.8$ Hz, 1H), 2.51 (d, $J = 11.6$ Hz, 1H), 2.84 (s, 1H), 3.16-3.22 (m, 1H), 3.42-3.50 (m, 1H), 3.69-3.73 (m, 2H), 5.37 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.05, 15.87, 17.71, 18.33, 18.51, 23.78, 25.52, 29.59, 30.88, 31.25, 32.64, 44.21, 48.62, 71.19, 77.34, 77.70, 84.79, 122.34, 141.12. HRMS (ESI^+) exact mass calcd for $\text{C}_{26}\text{H}_{51}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 439.3607, found m/z 439.3615.

Triisopropyl((1,4,4-trimethyl-2-phenethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)silane (12a)

Yield: 51% as colorless oil. Dr: 3:97. ^1H NMR (400 MHz, CDCl_3): δ 0.96 (s, 3H), 1.05 (s, 3H), 1.07-1.17 (m, 21H), 1.27 (d, $J = 12.3$ Hz, 1H), 1.29 (s, 3H), 1.49-1.51 (m, 1H), 1.80-1.87 (m, 3H), 2.28-2.35 (m, 2H), 2.68-2.73 (m, 2H), 3.64 (d, $J = 8.0$ Hz, 1H), 3.69 (d, $J = 2.5$ Hz, 1H), 7.14-7.19 (m, 3H), 7.25-7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.07, 18.81, 23.51, 25.90, 26.97, 27.45, 29.35, 31.48, 36.33, 39.35,

46.51, 78.89, 82.74, 83.26, 125.78, 128.29, 128.31, 142.34. HRMS (ESI⁺) exact mass calcd for C₂₇H₄₇O₂Si [M+H]⁺ requires *m/z* 431.3345, found *m/z* 431.3347.

((2-Ethyl-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropylsilane

(12b)

Yield: 53% as colorless oil. Dr: 7:93. ¹H NMR (400 MHz, CDCl₃): δ 0.96 (s, 3H), 0.99 (t, *J* = 7.6 Hz, 3H), 1.06 (s, 3H), 1.12-1.16 (m, 21H), 1.21-1.26 (m, 2H), 1.30 (s, 3H), 1.40-1.55 (m, 1H), 1.63-1.66 (m, 1H), 1.76-1.87 (m, 1H), 2.21-2.45 (m, 2H), 3.63 (d, *J* = 8.0 Hz, 1H), 3.70 (d, *J* = 3.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.01, 15.07, 18.51, 18.78, 20.49, 23.50, 26.94, 27.50, 31.34, 39.29, 49.46, 78.63, 82.81, 83.23. HRMS (ESI⁺) exact mass calcd for C₂₁H₄₃O₂Si [M+H]⁺ requires *m/z* 355.3032, found *m/z* 355.3038.

Triisopropyl((1,4,4-trimethyl-2-propyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)silane

(12c)

Yield: 58% as colorless oil. Dr: 7:93. ¹H NMR (400 MHz, CDCl₃): δ 0.91 (t, *J* = 7.11 Hz, 3H), 0.95 (s, 3H), 1.06 (s, 3H), 1.10 (s, 3H), 1.13-1.26 (m, 21H), 1.28 (s, 3H), 1.33-1.51 (m, 2H), 1.69-1.73 (m, 1H), 1.78-1.88 (m, 1H), 2.20-2.44 (m, 2H), 3.63 (d, *J* = 7.1 Hz, 1H), 3.67 (d, *J* = 4.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.05, 14.46, 18.51, 18.75, 23.54, 25.84, 26.96, 27.50, 30.02, 31.37, 39.30, 47.12, 79.10, 82.78, 83.22. HRMS (ESI⁺) exact mass calcd for C₂₂H₄₅O₂Si [M+H]⁺ requires *m/z* 369.3189, found *m/z* 369.3192.

Triisopropyl(1,4,4-trimethyl-2-octyl-8-oxabicyclo[3.2.1]octan-3-yloxy)silane (12d)

Yield: 50%, colorless oil. Dr: 9: 91. ¹H NMR (400 MHz, CDCl₃): δ 0.89 (t, *J* = 7.2 Hz, 3H), 0.95 (s, 3H), 1.06-1.20 (m, 27H), 1.27-1.38 (m, 14H), 1.68-1.75 (m, 2H), 1.79-1.84 (m, 1H), 2.21-2.49 (m, 2H), 3.63 (d, *J* = 8.0 Hz, 1H), 3.67 (d, *J* = 4.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 14.07, 14.11, 18.51, 18.76, 18.83, 22.65, 23.53, 25.91, 26.96, 27.50, 29.30, 29.57, 30.19, 30.61, 31.37, 31.89, 39.30, 47.41, 79.09, 82.82, 83.22. HRMS (ESI⁺) exact mass calcd for C₂₇H₅₅O₂Si [M+H]⁺ requires *m/z* 439.3971, found *m/z* 439.3992.

(2-Benzyl-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yloxy)triisopropylsilane

(12e)

Yield: 57% as colorless oil, Dr: 55: 45. ^1H NMR (400 MHz, CDCl_3): δ 0.85-0.99 (m, 27H), 1.03-1.20 (m, 32H), 1.25 (s, 3H), 1.38 (s, 3.6H), 1.58 (dt, $J_1 = 4.8$ Hz, $J_2 = 12.0$ Hz, 1H), 1.82-1.91 (m, 4H), 2.22-2.28 (m, 1.2H), 2.34-2.53 (m, 5.2H), 2.64 (dd, $J_1 = 10.8$ Hz, $J_2 = 14.0$ Hz, 1H), 2.91 (d, $J = 13.6$ Hz, 1H), 3.08 (dd, $J_1 = 5.4$ Hz, $J_2 = 14.0$ Hz, 1.2H), 3.59 (s, 1H), 3.67 (d, $J = 7.9$ Hz, 1.2H), 3.73 (d, $J = 7.5$ Hz, 1.2H), 3.86 (d, $J = 2.6$ Hz, 1H), 7.17-7.28 (m, 11H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.43, 14.06, 18.24, 18.38, 18.41, 18.74, 23.33, 24.25, 25.83, 26.13, 26.62, 26.88, 27.58, 28.03, 31.27, 35.48, 36.76, 37.03, 38.15, 39.53, 47.78, 52.90, 75.50, 80.40, 81.01, 83.03, 83.16, 84.43, 125.71, 125.81, 128.18, 128.33, 128.58, 129.62, 141.51, 142.75. HRMS (ESI^+) exact mass calcd for $\text{C}_{26}\text{H}_{45}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 417.3189, found m/z 417.3204.

Triisopropyl((2-(4-methoxyphenethyl)-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)silane (12h).

Yield: 56% as colorless oil. Dr: 5: 95. ^1H NMR (400 MHz, CDCl_3): δ 0.95 (s, 3H), 1.05 (s, 3H), 1.07-1.17 (m, 21H), 1.26-1.28 (m, 1H), 1.30 (s, 3H), 1.43-1.51 (m, 1H), 1.76-1.87 (m, 3H), 2.25-2.34 (m, 2H), 2.62-2.66 (m, 2H), 3.63 (d, $J = 7.9$ Hz, 1H), 3.68 (d, $J = 2.6$ Hz, 1H), 3.79 (s, 3H), 6.82 (d, $J = 8.6$ Hz, 2H), 7.07 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.07, 18.82, 23.51, 25.89, 26.69, 27.45, 29.51, 31.48, 35.39, 39.34, 46.43, 55.26, 78.87, 82.75, 83.26, 113.71, 129.17, 134.46, 157.70. HRMS (ESI^+) exact mass calcd for $\text{C}_{28}\text{H}_{49}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 461.3451, found m/z 461.3448.

((2,2-Dimethyldecahydro-1H-3,5a-epoxyheptalen-1-yl)oxy)triisopropylsilane (12p)

Yield: 55% for two isomers, 26% yield for the title compound. (another isomer data see **3n**) ^1H NMR (400 MHz, CDCl_3): δ 0.94 (s, 3H), 1.07 (s, 3H), 1.11-1.15 (m, 22H), 1.25-1.38 (m, 5H), 1.49-1.58 (m, 1H), 1.61-1.64 (m, 1H), 1.75-1.87 (m, 4H), 1.92-1.93 (m, 1H), 2.27-2.32 (m, 1H), 2.36-2.42 (m, 1H), 3.67 (s, 1H), 3.67 (d, $J = 10.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.97, 18.77, 21.98, 23.07, 26.11, 27.69, 27.88, 28.04, 28.66, 31.48, 39.21, 39.61, 47.88, 80.69, 83.74, 85.02. HRMS (ESI^+) exact mass calcd for $\text{C}_{23}\text{H}_{45}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 381.3189, found m/z 381.3194.

4b,8,8,11a-tetramethyl-7-(triisopropylsilyloxy)-5,6,6a,7,8,9,10,11,11a,11b,12,13-decahydro-4bH-cyclohepta[a]phenanthren-9-ol (12l)

Yield: 38%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.95 (s, 3H), 0.96 (s, 3H), 0.99 (s, 3H), 1.12-1.31 (m, 28H), 1.37-1.59 (m, 6H), 1.67-1.75 (m, 1H), 1.61-1.64 (m, 1H), 1.80-1.91 (m, 4H), 2.35 (d, $J = 12.0$ Hz, 1H), 2.83 (ddd, $J_1 = 6.4$ Hz, $J_2 = 10.2$ Hz, $J_3 = 16.4$ Hz, 1H), 2.94 (dd, $J_1 = 5.6$ Hz, $J_2 = 16.8$ Hz, 1H), 3.43 (d, $J = 9.4$ Hz, 1H), 3.95 (d, $J = 6.8$ Hz, 1H), 7.02 (d, $J = 7.2$ Hz, 1H), 7.06 (t, $J = 7.6$ Hz, 1H), 7.12 (t, $J = 6.8$ Hz, 1H), 7.27 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.26, 17.06, 18.74, 18.87, 19.11, 19.60, 19.88, 22.30, 25.13, 28.80, 31.20, 37.77, 39.18, 39.22, 43.24, 43.55, 45.48, 54.61, 76.50, 79.69, 124.76, 125.25, 125.75, 128.83, 135.00, 149.66. HRMS (ESI^+) exact mass calcd for $\text{C}_{32}\text{H}_{54}\text{O}_2\text{Si}$ $[\text{M}+\text{K}]^+$ requires m/z 537.3530, found m/z 537.3555.

Procedure for removing TIPS group

To a solution of corresponding ether (0.1 mmol) in 5 mL THF was added TBAF (1.0 M in THF, 0.5 mL, 3.0 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with half saturated NH_4Cl (5 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine (25 mL) and dried over Na_2SO_4 , then concentrated *in vacuo* and purified by chromatography with hexane/EA as eluent gave desired alcohols in 88-94% yields

1,4,4-Trimethyl-2-phenethyl-8-oxabicyclo[3.2.1]octan-3-ol (7)

Yield: 94% as white solid, mp: 108-110 °C. CCDC NO. 873237. ^1H NMR (400 MHz, CDCl_3): δ 0.96 (s, 3H), 1.10 (s, 3H), 1.34 (s, 3H), 1.48-1.51 (m, 2H), 1.55-1.71 (m, 2H), 1.84 (ddt, $J_1 = 4.9$ Hz, $J_2 = 7.6$ Hz, $J_3 = 12.4$ Hz, 1H), 2.05 (ddd, $J_1 = 5.8$ Hz, $J_2 = 11.0$ Hz, $J_3 = 15.7$ Hz, 1H), 2.17-2.32 (m, 2H), 2.62-2.77 (m, 2H), 3.59 (s, 1H), 3.73 (d, $J = 7.7$ Hz, 1H), 7.17-7.19 (m, 3H), 7.26-7.31 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 22.73, 25.11, 26.09, 26.82, 33.25, 35.99, 37.26, 37.39, 50.71, 77.16, 80.80, 83.83, 125.88, 128.34, 128.44, 142.33. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{27}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 275.2011, found m/z 275.2003.

2-(4-Methoxyphenethyl)-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-ol (13)

Yield: 89% as white solid. CCDC No. 873238. ^1H NMR (400 MHz, CDCl_3): δ 0.98 (s, 3H), 1.05 (s, 3H), 1.26 (s, 3H), 1.29 (t, $J = 11.6$ Hz, 1H), 1.40 (d, $J = 3.6$ Hz, 1H), 1.58-1.66 (m, 1H), 1.71-1.89 (m, 3H), 2.21 (dtd, $J_1 = 4.1$ Hz, $J_2 = 9.8$ Hz, $J_3 = 21.4$ Hz, 2H), 2.45 (ddd, $J_1 = 6.5$ Hz, $J_2 = 9.7$ Hz, $J_3 = 13.6$ Hz, 1H), 2.72 (ddd, $J_1 = 5.1$ Hz, $J_2 = 10.5$ Hz, $J_3 = 13.6$ Hz, 1H), 3.51 (s, 1H), 3.71 (d, $J = 7.9$ Hz, 1H), 3.79 (s, 3H), 6.83 (d, $J = 8.5$ Hz, 2H), 7.12 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 22.08, 25.54, 26.57, 26.70, 28.89, 31.21, 32.06, 38.43, 45.18, 55.28, 73.45, 82.18, 82.71, 113.82, 129.17, 134.77, 157.76. HRMS (ESI^+) exact mass calcd for $\text{C}_{19}\text{H}_{29}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires m/z 305.2117, found m/z 305.2130.

(1S,2R,3R,5R)-2-(4-Chlorophenethyl)-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-ol (11).

Yield: 88% as white solid, mp: 112-114 °C. CCDC No. 873239. ^1H NMR (400 MHz, CDCl_3): δ 0.95 (s, 3H), 1.09 (s, 3H), 1.33 (s, 3H), 1.46-1.50 (m, 2H), 1.55-1.69 (m, 2H), 1.84 (ddt, $J_1 = 4.8$ Hz, $J_2 = 7.7$ Hz, $J_3 = 12.6$ Hz, 1H), 2.01 (ddd, $J_1 = 5.8$ Hz, $J_2 = 10.9$ Hz, $J_3 = 15.8$ Hz, 1H), 2.24 (dtd, $J_1 = 4.3$ Hz, $J_2 = 9.9$ Hz, $J_3 = 13.2$ Hz, 2H), 2.58-2.73 (m, 2H), 3.55 (s, 1H), 3.73 (d, $J = 7.7$ Hz, 1H), 7.11 (d, $J = 8.3$ Hz, 2H), 7.25 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 22.70, 25.11, 26.08, 26.81, 33.23, 35.31, 37.21, 37.39, 50.49, 77.17, 80.73, 83.82, 128.53, 129.67, 131.57, 140.73. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{26}\text{O}_2\text{Cl}$ $[\text{M}+\text{H}]^+$ requires m/z 309.1621, found m/z 309.1611.

Chapter 5. Classical Reaction, Intriguing Behavior: the

Addition of Silyl Enol Ether to Acetal

5.1 Introduction

Development of new carbon-carbon or carbon-heteroatom bond forming reaction is critical to the advancement of organic chemistry. Aldol reaction continues withdrawing much attention since aldol reaction is one of the most important C-C bond forming reactions as well as aldol products are useful building blocks for organic synthesis.⁷⁷ The classical aldol reactions afford many byproducts, such as self-condensation products **4**, unsaturated carbonyl compounds **2**, polymer and so on, for it proceeds under thermodynamic control (Scheme 5.1). How to generate aldol products in a practical and selective manner remained an urgent task for chemists.

Scheme 5.1 Classical Aldol reaction

In order to address these limitations, modern aldol reactions were developed, which uses preformed enolates as a nucleophile (Scheme 5.2).⁷⁸ The Mukaiyama-aldol reaction, addition of silyl enol ether to aldehydes/ketones, developed

⁷⁷ Nielsen, A. T.; Houlihan, W. J. In *Organic Reactions*, Adams, R.; Blatt, A. H.; Boekelheide, V., Cairns; T. L., Cram, D. J.; House H. O. Eds., John Wiley & Sons: New York, **1968**, Vol. 16.

⁷⁸ Mahrwald, R. *Modern Aldol Reactions*, Wiley-VCH-Verlag GmbH & Co.: Germany, **2004**; Vol. 1 and 2.

Scheme 5.3 Mukaiyama-aldol reaction with various electrophiles

Scheme 5.4 Mukaiyama-aldol reaction with various nucleophiles

Stimulated by the results disclosed in Prof. Mukaiyama group, many groups were drawn into this area and phenomena progresses have been achieved including the asymmetric version.⁸¹ However, most of the reported Mukaiyama-aldol reaction gave the classical aldol product: the lower oxidative state C-O bonds come from the acceptor (electrophile), while the higher oxidative state C-O bonds generate from the donor/nucleophile (Scheme 5.2). Consequently, how to manipulate the Mukaiyama-aldol reaction to produce new type of product are well received.

Based on our previous work on cationic cascade reactions, we presented here a novel Mukaiyama-aldol/[1,5] H-shift cascade reaction between acetal and relatively stabilized enol ethers (TIPS-, TBS- and Methyl-enol ether), which affords different products comparing with classical Mukaiyama-aldol reaction.

81 (a) Carreira, E. M. Mukaiyama aldol reaction. *Comprehensive Asymmetric Catalysis I-III* **1999**, 3, 997. (b) Machajewski, T. D., Wong, C.-H., Lerner, R. A. *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 1352. (c) Palomo, C., Oiarbide, M., Garcia, J. M. *Chem. Soc. Rev.* **2004**, 33, 65.

5.2 The Origin of This Project

In accord with our efforts towards the development of cationic cascade reaction to construct 8-oxabicyclo[3.2.1]octane **15**, we were curious about the results of replacing C-C double bond of substrate **13** with aromatic rings (**16a**). If the reaction went through the same way, it should be an interesting method to construct fused rings **17** involving a de-aromatization (Scheme 5.5).

Scheme 5.5 Our proposed cascade reaction

5.3 Result and Discussion

5.3.1 Preliminary Study

Our purpose was evaluated using **16a** and **14a** promoted by TiCl_4 in CH_2Cl_2 at $-78\text{ }^\circ\text{C}$ (Scheme 5.6).⁸² Unfortunately, we could not get our proposed product **17** at all. Instead, the reaction gave a peculiarly “aldol product” **19a**, which has reversed oxidative state of two C-O bonds compared with the classical aldol product **18**. At the same time, a triol product **20a** also obtained in similar yield (71%).

⁸² For the review of acetal induced Mukaiyama-Aldol reactions, see: Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043.

Scheme 5.6 Preliminary study of our design

With this typical result in hand, we first studied the effect of Lewis acids. As the result showed in Table 5.1, a series of Lewis acids were tested. SnCl₄ and AlBr₃ also gave the product **19a** but with lower yields. Other Lewis acids, such as BF₃·OEt₂ and InBr₃ could not promote this reaction.

Table 5.1 Lewis acids effects^a

Entry	Lewis acid	Product	Yield (%) ^b
1	TiCl ₄	19a	70
2	SnCl ₄	19a	43
3	BF ₃ ·OEt ₂	-	- ^c
4	InBr ₃	-	- ^c
5	AlBr ₃	19a	66

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b All yields were isolated yield. ^c No reactions.

With this knowledge in hand, we next explored a series of alcohols protected 3-phenylpropanal acetals, and the results were summarized in Table 5.2. As expected, 3-phenylpropanal **16** leading to the normal Mukaiyama-aldol product, but methanol a 1,2-glycol derived acetal (entry 2 and 3) also gave classical product. Ethanol (entry 5) and hexanol (entry 6) protected acetal gave the product **19a** as with 1,3-propanediol

originated acetal. Interestingly, another intriguing product, 1,3-diol **21a**, was obtained while using 2-propanol (entry 9), 2,4-pentandiol (entry 8) and benzyl alcohol (entry 7) protected 3-phenylpropanal. Although the mechanism of this reaction was not very clear at this stage, but the protecting group of acetal played a key role in this reaction could be concluded.

Table 5.2 Protecting group effects^a

Entry	Substrate	Product	Yield (%)
1		-	-
2		-	-
3		-	-
4		19a	70
5		19a	85
6		19a	78
7		29a	87
8		29a	94
9		29a	55

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b All yields were isolated yield.

With the knowledge of the reactivity of acetals derived from various alcohols in

hand, in the next set of reactions a list of enol ether substrates with different protecting groups were explored (Table 5.3). Unsurprisingly, classical Mukaiyama-aldol products **30** were obtained when TMS- and TES- enol ether were subjected in the same condition (entries 1-2). TBS- and TIPS- silyl enol ethers (**14e** and **14b**) reacted with acetal **16a** to give the desired products **19e** and **19b** in 77% and 82%, respectively. The alkyl (Methyl) enol ether (**14f**) proceeded as well as TIPS silyl enol ether (Entry 5). This result indicated that the stability of enol ethers might be another key point causes for the difference with the classical Mukaiyama-aldol reaction and the present reaction.

Table 5.3 Enol ether effects^a

Entry	Substrate		Product	Yield (%) ^b
1	R = TMS	14c	19c	- ^c
2	R = TES	14d	19d	- ^c
3	R = TBS	14e	19e	77
4	R = TIPS	14b	19b	82
5	R = Me	14f	19f	75

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b All yields were isolated yield. ^c Normal Mukaiyama-aldol product was obtained.

5.3.2 Cascade Mukaiyama-Aldol/[1,5]-H Shift Reaction of 1,3-Propanol Protected

Acetal with Enol Ethers

To further extend the synthetic utility of this method, we next examine the silyl enol ether component in this reaction. Considering the ease of preparing starting

materials and removing the protecting group, TIPS-silyl enol ethers were used for further studies. As results summarized in Table 5.4, both the symmetric silyl enol ethers (entry 1-4) and asymmetric substrate (entry 5) proceeded well to afford β -ketyl alcohols in high yield. On the other hand, the silyl enol ether tethering a heteroatom (such as O and N) provided 1,3-diols in good yields (entry 7 and 8). Bromo- tethering silyl enol ether cannot be tolerated at this stage (entry 5). Di-substituted silyl ethers were not suitable for this reaction. Silyl enol ethers derived from ketones give classical Mukaiyama-aldol products.

Table 5.4 Mukaiyama-aldol cascade reaction of 1,3-propanediol protected acetals with varied silyl enol ethers^a

Entry	Substrate	Product	Yield (%) ^b		
1			70	14a	19a
2			71	14g	19g
3			77	14h	19h
4			82	14b	19b
5			79	14i	19i
6			-	14j	19j

7		14k		29k	81
8		14l		29l	69

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b Isolated yield.

Having identified the scope of enol ethers, we reacted different 1,3-propanediol protected acetals with **14a** under the optimized condition to furnish this abnormal Mukaiyama-aldol reaction. As results reveled in Table 5.5, the desired product was obtained in high yield in the most of cases. Altering the tail length did not affect the reaction performance (entries 2-3). Steric demanding acetals still work well (entries 4-5). The reaction also tolerated in a variety of functional groups, benzyl ether (entry 6) and silyl ether (entry 7) tethering substrates react smoothly leading to β -ketyl alcohol in high yield. Ester group have no effect on the reaction (entry 8). Furthermore, Cbz-protected primary amine also can be tolerated in this reaction, although the reaction yield is a little bit lower (entry 9). However, acetals from corresponding aromatic aldehyde and α,β -unsaturated aldehydes are not suitable for this reaction.

Table 5.5 Substrates scope of Mukaiyama-aldol/[1,5] shift cascade reaction^a

Entry	Substrate		Product		Yield (%) ^b
1		16b		31b	68

2		16c		31c	72
3		16d		31d	71
4		16e		31e	63
5		16f		31f	68
6		16g		31g	77
7		16h		31h	73
8		16i		31i	76
9		16j		31j	49

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b Isolated yield.

5.3.3 Mechanism Study

Having clarified the reaction scope, we next focused on the reaction mechanism. Two deuterium-labeling reactions were carried out (Scheme 5.7). Firstly, treating deuterium-labeled acetal **26-d** with silyl enol ether **14a** under standard reaction conditions, afforded the corresponding deuterated product **29a-d** in 85% yield. This result clearly showed that the newly installed deuterium at OCHD of **29a-d** came from the benzylic OCD₂ of **26-d**. Secondly, the reaction of deuterium-labeled **16a-d** with

14a gave **19a** bearing no deuterium atom. On the other hand, compound **20a-d** was found to have a deuterium atom at one of the OCH₂ protons. This result indicated that the OCH₂ protons of **20a-d** originated from the 2-benzylethylidene hydrogen of acetal **16a-d**.

Scheme 5.7 Mechanistic experiments

On the basis of the above deuterium-labeling studies and products obtained in the previous tables, a plausible reaction mechanism is proposed as depicted in Scheme 5.8. First, the substrates undergo a conventional Mukaiyama-aldol reaction, generating oxocarbenium intermediate II, following by [1,5] hydride shift to afford a new oxocarbenium intermediate III. Then the second silyl enol ether reacts with III to form intermediate IV, which spontaneously undergoes a second [1,5] hydride shift to give an oxocarbenium species V. After aqueous workup, the desired β -ketyl alcohols VII are obtained. However, if the intermediate III is unable to undergo a second Mukaiyama-aldol reaction due to steric hindrance from substituents on acetals (Table 5.2, entries 7 to 9), it will be hydrolyzed to 1,3-diol compound VI upon workup.

Scheme 5.8 Proposed Mechanistic Rationalization

From the reaction mechanism, we understand that the reaction undergoes Mukaiyama-aldol/[1,5] hydride shift cascade reaction to give the unconventional product. It is worthy of noting that the stability of **II** is critical for the success of the [1, 5] hydride shift step. If the protecting groups R^4 was too labile to acidic condition (e.g. TMS, TES), the intermediate **II** is not stable and the reaction provides classical Mukaiyama-aldol products (Table 5.3, entries 1-2). In our cases, R^4 are TIPS-, TBS- and Me- groups which make intermediate **II** relatively stable toward acidic reaction condition and the following [1, 5] hydride shift proceeded smoothly. Secondly, the steric hindrance of the protecting group can control the reaction product, secondary alcohol protected acetal give 1,3-diols instead of β -ketyl alcohols because the second Mukaiyama-aldol reaction cannot proceed for the steric repulsion. On the other hand,

in the case of acetals derived from methanol, [1,5] hydride shift is impossible between the methyl group and the silylated oxocarbenium at intermediate II stage (Scheme 5.8). However, [1,5] hydride shift can proceed if another α -OCH bond exists (Scheme 5.9). This approach also exemplifies a “redox economical” way to refunctionalize carbonyl and ether. It also indicated that the [1,5]-hydride shift reaction under thermal dynamic control.

Scheme 5.9 Mukaiyama-aldol/[1,5]-H shift cascade reaction

5.3.4 Cascade Mukaiyama-Aldol/[1,5]-H Shift Reaction of 2,4-Pentanediol Protected Acetal with Enol Ethers

With the confident evidences for the mechanism of this Mukaiyama-aldol/[1,5] hydride shift cascade reaction, we would like to further explore the reaction possibilities. In view of the results showed in Table 5.2, secondary alcohol induced acetals gave mono-protected 1,3-diols. We hypothesized that the asymmetric version might be achieved using chiral acetals.⁸³ With this idea in mind, we selected **27a** as the reaction component, and a series of enol ethers were tested. The steric factor strongly affects the enantioselectivity of the product. The TIPS-governed enol ether resulted in the best enantioselectivity and it was selected for further studies. For the acyclic enol ethers, the reaction gave good yield while poor enantioselectivity was observed. Interestingly, enol ethers tethering a hetero atom (O and N) caused the desired product with excellent enantioselectivity. However, when **14h** was applied in this reaction, there was no desired product was obtained.

83 For reviews of chiral acetals, see: Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477.

Table 5.6 Asymmetric Mukaiyama-aldol/[1,5]-H shift cascade reaction^a

Entry	Substrate	Product	Yield (%) ^b	Ee (%) ^c
1				
2			91	85
3			89	69
4			95	44
5			94	37
6			88	- ^d
7			- ^c	-
8			81	95
9			69	95

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b All yields were isolated yield. ^c Ee values were determined by chiral HPLC analysis. ^d The ee value of **29g** cannot be determined at this stage.

Considering the usefulness of optically pure piperidine compound, **14l** was selected to address the acetal degree. The tail length makes no difference on the reaction yield and the enantioselectivities (entries 1-2). Many functional groups, such as ester, ether and carbonate, were tolerated in this reaction as well. However, α -branched acetals were found to be not suitable for this reaction at this stage (entries

3-4).

Table 5.7 Asymmetric Mukaiyama-aldol/[1,5]-H shift reaction of various acetals^a

Entry	Substrate	Product	Yield (%) ^b	Ee (%) ^c	
1	27a	34a	69	95	
2	27b	34b	79	97	
3	27c	34c	- ^d	-	
4	27d	34d	- ^d	-	
5	27e	34e	64	91	

6		27f		34f	73	95
7		27g		34g	59	95
8		27h		34h	58	94

^a Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. ^b All yields were isolated yield. ^c Ee values were determined by chiral HPLC analysis. ^d No desired product was obtained.

5.3.5 Applications: the Total Synthesis of Sufentanil

Having demonstrated a novel Mukaiyama-aldol/[1,5]-H shift cascade reaction, we would like to apply it in natural products or drug molecule synthesis. Sufentanil, a FDA approved drug for analgesic use, which has a sterically hindered 4,4'-disubstituted piperidine core.⁸⁴ We envisioned that the Sufentanil might be synthesized from compound **II**, while intermediate **II** could be prepared from **III** by Beckmann rearrangement. Furthermore, the Beckmann rearrangement precursor can be made following our developed Mukaiyama-aldol/[1,5]-H shift cascade reaction (Scheme 5.10).

84 (a) Van Daele, P. G.; De Bruyn, M. F.; Boey, J. M.; Sanczuk, S.; Agten, J. T.; Janssen, P. A.; *Arzneim.-Forsch. Drug Res.* **1976**, 26, 1521. (b) Niemegeers, C. J.; Schellekens, K. H.; Van Bever, W. F.; Janssen, P. A. *Arzneim.-Forsch. Drug Res.* **1976**, 26, 1551.

Scheme 5.10 Retro-synthetic analysis of Sufentanil

Starting from enol ether **14m**, under the standard reaction conditions, Mukaiyama-aldol/[1,5]-H shift product **36** was obtained in 81% yield. The alcohol **36** was converted to β -methoxy ketone in 80% yield through Swern oxidation. Treatment of **37** with hydroxylamine, followed by Beckmann rearrangement afforded the key substituted piperidine intermediate **39** in 74% yield over two steps by a one-pot process (Scheme 5.11).⁸⁵

Scheme 5.11 Synthesis of key intermediate **39** of Sufentanil

With the key intermediate **39** in hand, we came to the step to install the phenyl

85 (a) Beckmann, E. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 998. (b) Tatsumi, T. In *Beckmann Rearrangement*, Sheldon, R. A.; Bekkum, H.; Eds.; Weinheim: Wiley-VCH, New York **1970**. pp 73.

group by C-N bond coupling reaction. Unfortunately, attempts to introduce a phenyl group on the amide nitrogen **39** at this stage proved futile (scheme 5.12).

Scheme 5.12

Failed to install the phenyl group at this stage, an alternative synthetic route was proposed. The Cbz-group was removed using Pd/C as the catalyst under hydrogen atmosphere, then the amine reacted with 2-(thiophen-2-yl)ethyl 4-methylbenzenesulfonate **41** through S_N2 reaction to give **42** in 95% yield over two steps (Scheme 5.13). Disappointingly, our effort was in vain to do C-N bond coupling reaction as well, we attributed this to the steric hindrance of the substrate.

Scheme 5.13

The effort to do C-N bond coupling reaction by using amide as the coupling partner was unsuccessful, we decided to remove the propional group and introduce the phenyl group to the primary amine. In the acid conditions, the propional group can be removed cleanly. The arylation of the amine **43** by palladium catalyzed C-N bond coupling reaction was failed again, fortunately, this reaction was found to be successful when using Chan-Lam coupling reaction to give **44** in 46% yield.⁸⁶ Finally,

⁸⁶ Chan, D. M. T.; Monaco, K. L.; Wang, M. R.; Winters, M. P.; *Tetrahedron Lett.* **1998**, 39, 2933.

the installation of the propionyl group completed the total synthesis of Sufentanil with an overall yield of ca. 18% yield over 9 steps (Scheme 5.14). Our reaction conditions are mild without using very toxic reagent (such as NaCN) and highly flammable reagent (AlLiH_4). It provided a valuable alternative way to synthesize Sufentanil.

Scheme 5.14 Total synthesis of Sufentanil

5.4 Conclusion

We present here a novel Mukaiyama-aldol/[1,5] hydride shift cascade reaction by using TIPS-, TBS- or Me-enol ether instead of traditional TMS-silyl enol ether. The reaction was found to proceed via one or two times Mukaiyama-aldol/[1,5] hydride shift to provide 1,3-diols or β -ketyl alcohols receptively. In addition, the reaction mechanism has been clearly and compellingly illustrated. Finally, to demonstrate the applicability of this method, we designed and completed a novel and efficient synthetic route for the commercialized analgesic drug Sufentanil (18% yield over 9 steps). In a word, our findings enriched and also opened a new window for Mukaiyama-aldol reaction.

5.5 Experimental Section

General procedure and experimental data for acetals:

To a round bottom flask equipped with a magnetic stirring bar, aldehyde (5.0 mmol), alcohol (15.0 mmol), *p*-toluenesulfonic acid monohydrate (0.5 mmol) and toluene (25 mL) were added. To this solution, triethyl orthoformate (15.0 mmol) was added slowly via syringe. The solution was allowed to stir at room temperature for 10 hours before diluting with EtOAc (25 mL). The organic layer washed successively with NaHCO₃ (2 × 30 mL, sat. aqueous solution) and brine (2 × 30 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel using appropriate solvents (hexane/EtOAc mixture) to provide the title compounds.

2-Phenethyl-1,3-dioxane (16a)

Yield: 87%. ¹H NMR (400 MHz, CDCl₃): δ 1.33 (d, *J* = 13.4 Hz, 1H), 1.91 (ddd, *J*₁ = 5.3 Hz, *J*₂ = 8.1 Hz, *J*₃ = 10.2 Hz, 2H), 2.09 (tq, *J*₁ = 4.2 Hz, *J*₂ = 12.8 Hz, 1H), 2.70-2.74 (m, 2H), 3.74 (dt, *J*₁ = 2.4 Hz, *J*₂ = 12.4 Hz, 2H), 4.11 (dd, *J*₁ = 5.0 Hz, *J*₂ = 10.7 Hz, 2H), 4.51 (t, *J* = 5.2 Hz, 1H), 7.16-7.20 (m, 3H), 7.25-7.29 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 25.87, 30.13, 36.66, 66.91, 101.49, 125.83, 128.38, 128.48, 141.75. HRMS (ESI⁺) exact mass calcd for C₁₂H₁₇O₂ [M+H]⁺ requires *m/z* 193.1229, found *m/z* 193.1225.

2-Phenethyl-1,3-dioxane-1-*d* (16a-*d*)

Yield: 85%. ¹H NMR (400 MHz, CDCl₃): δ 1.33 (d, *J* = 13.4 Hz, 1H), 1.91 (ddd, *J*₁ = 5.3 Hz, *J*₂ = 8.1 Hz, *J*₃ = 10.2 Hz, 2H), 2.09 (tq, *J*₁ = 4.2 Hz, *J*₂ = 12.8 Hz, 1H), 2.70-2.74 (m, 2H), 3.74 (dt, *J*₁ = 2.4 Hz, *J*₂ = 12.4 Hz, 2H), 4.11 (dd, *J*₁ = 5.0 Hz, *J*₂ = 10.7 Hz, 2H), 7.16-7.20 (m, 3H), 7.25-7.29 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 25.87, 30.10, 36.53, 66.89, 101.05 (t, *J*_{C-D} = 24.0 Hz), 125.83, 128.38, 128.48, 141.75. HRMS (ESI⁺) exact mass calcd for C₁₂H₁₆DO₂ [M+H]⁺ requires *m/z* 194.1291, found *m/z* 194.1290.

(3,3-Dimethoxypropyl)benzene (21)

Yield: 78%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.90-1.95 (m, 2H), 2.65-2.69 (m, 2H), 3.33 (s, 6H), 4.37 (t, *J* = 5.7 Hz, 1H), 7.16-7.20 (m, 3H), 7.26-7.30 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 30.89, 34.11, 52.73, 103.76, 125.90, 128.42, 141.65.

2-Phenethyl-1,3-dioxolane (22)

Yield: 87%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.96-2.01 (m, 2H), 2.73-2.77 (m, 2H), 3.85-3.91 (m, 2H), 3.95-4.01 (m, 2H), 4.90 (t, $J = 4.7$ Hz, 1H), 7.16-7.22 (m, 3H), 7.26-7.30 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 30.17, 35.52, 64.97, 66.91, 103.86, 125.89, 128.40, 141.60.

(3,3-Diethoxypropyl)benzene (24)

Yield: 94%. ^1H NMR (400 MHz, CDCl_3): δ 1.21 (t, $J = 7.0$ Hz, 6H), 1.94 (td, $J_1 = 5.9$ Hz, $J_2 = 7.6$ Hz, 2H), 2.67-2.71 (m, 2H), 3.50 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.2$ Hz, 2H), 3.64 (qd, $J_1 = 7.1$ Hz, $J_2 = 9.2$ Hz, 2H), 4.49 (t, $J = 5.7$ Hz, 1H), 7.16-7.21 (m, 3H), 7.26-7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.39, 31.02, 35.10, 61.03, 102.20, 125.81, 128.37, 128.41, 141.79. HRMS (ESI^+) exact mass calcd for $\text{C}_{13}\text{H}_{21}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 209.1542, found m/z 209.1551.

(3,3-Bis(hexyloxy)propyl)benzene (25)

Yield: 97%. ^1H NMR (400 MHz, CDCl_3): δ 0.89 (t, $J = 6.7$ Hz, 6H), 1.33-1.43 (m, 12H), 1.54-1.61 (m, 4H), 1.91-1.97 (m, 2H), 2.68 (t, $J = 8.0$ Hz, 2H), 3.41 (td, $J_1 = 6.7$ Hz, $J_2 = 9.1$ Hz, 2H), 3.58 (td, $J_1 = 6.7$ Hz, $J_2 = 8.9$ Hz, 2H), 4.47 (t, $J = 5.7$ Hz, 1H), 7.16-7.20 (m, 3H), 7.26-7.30 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.07, 22.65, 25.98, 29.90, 31.07, 31.70, 35.04, 65.66, 102.37, 125.79, 128.35, 128.40, 141.86. HRMS (ESI^+) exact mass calcd for $\text{C}_{21}\text{H}_{36}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 343.2613, found m/z 343.2621.

(3-Phenylpropane-1,1-diyl)bis(oxy)bis(methylene)dibenzene (26)

Yield: 61%. ^1H NMR (400 MHz, CDCl_3): δ 2.06-2.11 (m, 2H), 2.72 (t, $J = 7.2$ Hz, 2H), 4.57 (t, $J = 11.6$ Hz, 2H), 4.67 (t, $J = 7.2$ Hz, 2H), 4.75 (t, $J = 6.8$ Hz, 1H), 7.14-7.19 (m, 3H), 7.25-7.35 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3): δ 31.03, 34.97, 67.32, 101.51, 125.89, 127.65, 127.86, 128.43, 128.46, 138.22, 141.57. HRMS (ESI^+) exact mass calcd for $\text{C}_{23}\text{H}_{24}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 355.1674, found m/z 355.1675.

(3-Phenylpropane-1,1-diyl)bis(oxy)bis(methylene)dibenzene-*d* (26-*d*)

Prepared by the following procedure: In a round bottom flask equipped with a magnetic stirring bar, (3,3-diethoxypropyl)benzene (0.42 g, 2.0 mmol) and *p*-toluenesulfonic acid monohydrate (0.2 mmol) were dissolved in

d-benzyl alcohol (1.09 g, 10.0 mmol). The reaction was allowed to stir for 10 hours at 50 °C before quenching with triethylamine (0.5 mL). The reaction mixture was purified by flash chromatography on silica gel using 5% diethyl ether in hexane to provide the title compound as colorless oil. Yield: 53%. ¹H NMR (400 MHz, CDCl₃): δ 2.08 (td, *J*₁ = 2.4 Hz, *J*₂ = 8.0 Hz, 2H), 2.70-2.74 (m, 2H), 4.74 (t, *J*₁ = 5.7 Hz, 1H), 7.13-7.19 (m, 3H), 7.22-7.37 (m, 12H); ¹³C NMR (100 MHz, CDCl₃): δ 31.06, 35.01, 66.63 (m), 101.39, 125.92, 127.70, 127.93, 128.44, 128.45, 128.49, 138.13, 141.59. HRMS (ESI⁺) exact mass calcd for C₂₃H₂₀D₄O₂Na [M+Na]⁺ requires *m/z* 359.1925, found *m/z* 359.1917.

(4*S*,6*S*)-4,6-dimethyl-2-phenethyl-1,3-dioxane (27a)

Yield: 95%. ¹H NMR (400 MHz, CDCl₃): δ 1.21 (d, *J* = 6.2 Hz, 3H), δ 1.33 (d, *J* = 7.0 Hz, 3H), 1.32-1.35 (m, 1H), 1.81-1.92 (m, 3H), 2.72 (dt, *J*₁ = 2.8 Hz, *J*₂ = 8.2 Hz, 2H), 3.92 (dq, *J*₁ = 2.4 Hz, *J*₂ = 6.2 Hz, *J*₃ = 12.1 Hz, 1H), 4.32 (p, *J* = 6.7 Hz, 1H), 4.82 (t, *J* = 5.2 Hz, 1H), 7.15-7.21 (m, 3H), 7.25-7.29 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 17.20, 21.85, 30.23, 36.59, 36.83, 67.47, 67.98, 93.38, 125.70, 128.25, 128.48, 141.83. HRMS (ESI⁺) exact mass calcd for C₁₄H₂₁O₂ [M+H]⁺ requires *m/z* 221.1542, found *m/z* 221.1548.

(3,3-Diisopropoxypropyl)benzene (28)

Yield: 43%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.14 (d, *J* = 6.0 Hz, 6H), 1.20 (d, *J* = 6.0 Hz, 6H), 1.89-1.94 (m, 2H), 2.69 (t, *J* = 7.6 Hz, 2H), 3.83-3.89 (m, 2H), 4.56 (t, *J* = 5.6 Hz, 1H), 7.16-7.21 (m, 3H), 7.26-7.29 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 22.62, 23.43, 31.06, 36.93, 67.73, 99.66, 125.72, 128.31, 128.38, 142.00. HRMS (ESI⁺) exact mass calcd for C₁₅H₂₄O₂Na [M+Na]⁺ requires *m/z* 259.1674, found *m/z* 259.1676.

2-Benzyl-1,3-dioxane (16b)

Yield: 75%. ¹H NMR (400 MHz, CDCl₃): δ 1.33 (d, *J* = 13.4 Hz, 1H), 2.03-2.16 (m, 1H), 2.90 (d, *J* = 4.4 Hz, 2H), 3.73 (t, *J* = 11.6 Hz, 2H), 4.10 (dd, *J*₁ = 4.7 Hz, *J*₂ = 11.2 Hz, 2H), 4.71 (t, *J* = 5.3 Hz, 1H), 7.20-7.31 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 25.74, 42.00, 67.02, 102.72, 126.46, 128.25, 129.65, 136.60. HRMS (ESI⁺) exact mass calcd for C₁₁H₁₅O₂ [M+H]⁺ requires *m/z* 179.1072, found *m/z* 179.1074.

2-Propyl-1,3-dioxane (16c)

Yield: 63%. ¹H NMR (400 MHz, CDCl₃): δ 0.92 (t, *J* = 7.4 Hz, 3H), 1.33 (d, *J* = 13.4

Hz, 1H), 1.38-1.46 (m, 2H), 1.55-1.62 (m, 2H), 2.08 (tq, $J_1 = 5.0$ Hz, $J_2 = 12.6$ Hz, 1H), 3.76 (dt, $J_1 = 2.4$ Hz, $J_2 = 12.4$ Hz, 2H), 4.10 (dd, $J_1 = 5.0$ Hz, $J_2 = 10.7$ Hz, 2H), 4.52 (t, $J = 5.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.98, 17.31, 25.88, 37.27, 66.90, 102.25. HRMS (ESI^+) exact mass calcd for $\text{C}_7\text{H}_{14}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 153.0891, found m/z 153.0885.

2-Octyl-1,3-dioxane (16d)

Yield: 67%. ^1H NMR (400 MHz, CDCl_3): δ 0.87 (t, $J = 6.7$ Hz, 3H), 1.27-1.43 (m, 13H), 1.56-1.61 (m, 2H), 2.08 (tq, $J_1 = 5.2$ Hz, $J_2 = 12.6$ Hz, 1H), 3.76 (t, $J = 11.4$ Hz, 2H), 4.10 (dd, $J_1 = 4.8$ Hz, $J_2 = 11.2$ Hz, 2H), 4.50 (t, $J = 5.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.11, 22.67, 23.98, 25.88, 29.22, 29.50, 29.51, 31.87, 35.27, 66.91, 102.48. HRMS (ESI^+) exact mass calcd for $\text{C}_{12}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 201.1855, found m/z 201.1864.

2-(Pentan-3-yl)-1,3-dioxane (16e)

Yield: 60%. ^1H NMR (400 MHz, CDCl_3): δ 0.89 (t, $J = 7.2$ Hz, 6H), 1.40-1.48 (m, 4H), 1.52-1.55 (m, 2H), 2.06 (tq, $J_1 = 4.9$ Hz, $J_2 = 12.6$ Hz, 1H), 3.74 (t, $J = 12.2$ Hz, 2H), 4.11 (dd, $J_1 = 4.7$ Hz, $J_2 = 12.2$ Hz, 2H), 4.44(d, $J = 3.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.52, 20.96, 26.05, 45.68, 67.06, 104.01. HRMS (ESI^+) exact mass calcd for $\text{C}_9\text{H}_{18}\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ requires m/z 182.1204, found m/z 182.1199.

2-Cyclohexyl-1,3-dioxane (16f)

Yield: 71%. ^1H NMR (400 MHz, CDCl_3): δ 1.02-1.09 (m, 2H), 1.12-1.20 (m, 3H), 1.32 (d, $J = 13.4$ Hz, 1H), 1.48-1.51(m, 1H), 1.62-1.65 (m, 1H), 1.71-1.80 (m, 4H), 2.06 (tq, $J_1 = 5.0$ Hz, $J_2 = 12.6$ Hz, 1H), 3.74 (dt, $J_1 = 2.4$ Hz, $J_2 = 12.4$ Hz, 2H), 4.10 (dd, $J_1 = 5.0$ Hz, $J_2 = 10.7$ Hz, 2H), 4.24(d, $J = 5.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 25.83, 26.07, 26.47, 27.42, 42.60, 66.99, 105.43. HRMS (ESI^+) exact mass calcd for $\text{C}_{10}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 171.1385, found m/z 171.1391.

2-(3-(Benzyloxy)propyl)-1,3-dioxane (16g)

Yield: 76%. ^1H NMR (400 MHz, CDCl_3): δ 1.32 (d, $J = 13.4$ Hz, 1H), 1.68-1.74(m, 4H), 2.02-2.11 (m, 1H), 3.48 (t, $J = 6.0$ Hz, 2H), 3.74 (dt, $J_1 = 2.2$ Hz, $J_2 = 12.0$ Hz, 2H), 4.09 (dd, $J_1 = 5.0$ Hz, $J_2 = 11.9$ Hz, 2H), 4.50 (s, 2H), 4.53(t, $J = 4.7$ Hz, 1H), 7.26-7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 24.23, 25.84, 31.90, 66.89, 70.00, 72.72, 102.10, 127.45,

127.59, 128.32, 138.67. HRMS (ESI⁺) exact mass calcd for C₁₄H₂₁O₃ [M+H]⁺ requires *m/z* 237.1491, found *m/z* 237.1496.

(4-(1,3-Dioxan-2-yl)butoxy)triisopropylsilane (16h)

Yield: 89%. ¹H NMR (400 MHz, CDCl₃): δ 1.02-1.09 (m, 21H), 1.33 (d, *J* = 13.4 Hz, 1H), 1.40-1.48 (m, 2H), 1.53-1.64 (m, 4H), 2.08 (tq, *J*₁ = 5.4 Hz, *J*₂ = 12.8 Hz, 1H), 3.67 (t, *J* = 6.6 Hz, 2H), 3.76 (dt, *J*₁ = 2.0 Hz, *J*₂ = 12.3 Hz, 2H), 4.10 (dd, *J*₁ = 4.9 Hz, *J*₂ = 11.1 Hz, 2H), 4.51 (t, *J* = 5.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.00, 18.03, 20.34, 25.87, 32.84, 35.00, 63.32, 66.90, 102.38. HRMS (ESI⁺) exact mass calcd for C₁₇H₃₇O₃Si [M+H]⁺ requires *m/z* 317.2512, found *m/z* 317.2514.

3-(1,3-Dioxan-2-yl)propyl benzoate (16i)

Yield: 83%. ¹H NMR (400 MHz, CDCl₃): δ 1.34 (d, *J* = 13.4 Hz, 1H), 1.52-1.61 (m, 2H), 1.65-1.70 (m, 2H), 1.76-1.83 (m, 2H), 2.08 (tq, *J*₁ = 5.0 Hz, *J*₂ = 12.8 Hz, 1H), 3.76 (dt, *J*₁ = 2.2 Hz, *J*₂ = 12.3 Hz, 2H), 4.10 (dd, *J*₁ = 4.5 Hz, *J*₂ = 11.4 Hz, 2H), 4.32 (t, *J* = 6.6 Hz, 2H), 4.55 (t, *J* = 5.0 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 8.04 (d, *J* = 7.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 20.64, 25.82, 28.64, 34.84, 64.95, 66.91, 102.06, 128.31, 129.57, 130.46, 132.81, 166.66. HRMS (ESI⁺) exact mass calcd for C₁₅H₂₁O₄ [M+H]⁺ requires *m/z* 265.1440, found *m/z* 265.1443.

Benzyl 3-(1,3-dioxan-2-yl)propylcarbamate (16j)

Yield: 54%. ¹H NMR (400 MHz, CDCl₃): δ 1.30 (d, *J* = 10.8 Hz, 1H), 1.62-1.63 (m, 4H), 2.05 (tq, *J*₁ = 4.8 Hz, *J*₂ = 12.8 Hz, 1H), 3.21 (d, *J* = 6.0 Hz, 2H), 3.73 (t, *J* = 10.4 Hz, 2H), 4.07 (dd, *J*₁ = 4.0 Hz, *J*₂ = 11.6 Hz, 2H), 4.53 (s, 1H), 4.98 (brs, 1H), 5.08 (s, 2H), 7.26-7.35 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 24.21, 25.73, 32.16, 40.76, 66.51, 66.86, 101.74, 128.03, 128.08, 128.49, 136.72, 156.40. HRMS (ESI⁺) exact mass calcd for C₁₅H₂₂NO₄ [M+H]⁺ requires *m/z* 280.1549, found *m/z* 280.1540.

((4,4-Dimethoxybutan-2-yloxy)methyl)benzene (32)

Prepared by the following procedure: To a round bottom flask equipped with a magnetic stir, sodium hydride (0.80 g, 60% dispersion in mineral oil, 20.0 mmol) was dissolved in N,N-dimethylformamide (50

mL). After cooling to 0 °C, 4,4-dimethoxybutan-2-ol (1.34 g, 10.0 mmol) was added slowly, the mixture was stirred for 10 min. Then benzyl bromide (2.05 g, 12.0 mmol) was added by syringe and the reaction mixture was stirred for 10 h at rt. After that, the reaction mixture was poured into ice water, extracted with diethyl ether (3 x 40 mL). The combined organic layer was washed with water (2 x 50 mL) and brine (50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 5% EtOAc in hexane to provide the title compound as colorless oil. Yield: 64%. ¹H NMR (400 MHz, CDCl₃): δ 1.22 (d, *J* = 6.0 Hz, 3H), 1.72 (ddd, *J*₁ = 4.5 Hz, *J*₂ = 7.4 Hz, *J*₃ = 14.1 Hz, 1H), 1.89 (ddd, *J*₁ = 4.2 Hz, *J*₂ = 8.3 Hz, *J*₃ = 14.1 Hz, 1H), 3.29 (s, 3H), 3.31 (s, 3H), 3.62-3.70 (m, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.56 (t, *J* = 3.2 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 7.25-7.33 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 19.87, 40.24, 52.71, 53.33, 70.53, 71.65, 102.28, 127.50, 127.75, 128.35, 138.84. HRMS (ESI⁺) exact mass calcd for C₁₃H₂₁O₃ [M+H]⁺ requires *m/z* 225.1491, found *m/z* 225.1493.

(4*S*,6*S*)-4,6-Dimethyl-2-octyl-1,3-dioxane (27b)

Yield: 95%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.83 (t, *J* = 8.0 Hz, 3H), 1.15-1.32 (m, 21H), 1.76-1.79 (m, 1H), 3.89-3.91 (m, 1H), 4.23-4.26 (m, 1H), 4.79 (t, *J* = 4.0 Hz, 1H); ¹³C NMR (100MHz, CDCl₃): δ 14.02, 17.13, 21.80, 22.58, 24.08, 29.16, 29.43, 31.79, 35.28, 36.76, 67.33, 67.78, 94.24. HRMS (ESI⁺) exact mass calcd for C₁₄H₂₉O₂ [M+H]⁺ requires *m/z* 229.2168, found *m/z* 229.2171.

(4*S*,6*S*)-4,6-Dimethyl-2-(pentan-3-yl)-1,3-dioxane (27c)

Yield: 89%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.86-0.90 (m, 6H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.34 (d, *J* = 7.0 Hz, 3H), 1.29-1.38 (m, 4H), 1.45-1.55 (m, 2H), 1.76-1.84 (m, 1H), 3.87-3.95 (m, 1H), 4.25-4.32 (m, 1H), 4.74 (d, *J* = 4.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 11.18, 11.44, 17.16, 20.62, 20.91, 21.96, 36.98, 45.30, 67.55, 67.80, 95.59. HRMS (ESI⁺) exact mass calcd for C₁₁H₂₃O₂ [M+H]⁺ requires *m/z* 187.1698, found *m/z* 187.1704.

(4*S*,6*S*)-2-Cyclohexyl-4,6-dimethyl-1,3-dioxane (27d)

Yield: 91%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.99-1.07 (m, 2H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.23-1.26 (m, 3H), 1.30-1.31 (m, 1H), 1.33 (d, *J* = 7.0 Hz, 3H), 1.41-1.49 (m, 1H), 1.57-1.65 (m, 1H),

1.70-1.74 (m, 2H), 1.77-1.83 (m, 3H), 3.87-3.95 (m, 1H), 4.25-4.31 (m, 1H), 4.53 (d, $J = 5.6$ Hz, 1H) ^{13}C NMR (100MHz, CDCl_3): δ 17.27, 21.90, 25.82, 26.51, 27.50, 27.68, 37.02, 42.44, 67.47, 67.80, 97.28. HRMS (ESI^+) exact mass calcd for $\text{C}_{12}\text{H}_{23}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 199.1698, found m/z 199.1695.

(4S,6S)-2-(3-(Benzyloxy)propyl)-4,6-dimethyl-1,3-dioxane (27e)

Yield: 93%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.19 (d, $J = 6.2$ Hz, 3H), 1.30-1.31 (m, 1H), 1.33 (d, $J = 7.0$ Hz, 3H), 1.60-1.73 (m, 5H), 3.48 (t, $J = 6.4$ Hz, 2H), 3.88-3.96 (m, 1H), 4.24-4.31 (m, 1H), 4.50 (s, 2H), 4.85 (t, $J = 4.8$ Hz, 1H), 7.25-7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 17.21, 21.87, 24.46, 31.93, 36.81, 67.45, 67.92, 70.09, 72.76, 94.03, 127.44, 127.60, 128.32, 138.68. HRMS (ESI^+) exact mass calcd for $\text{C}_{16}\text{H}_{25}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires m/z 265.1804, found m/z 265.1791.

(3-((4S,6S)-4,6-Dimethyl-1,3-dioxan-2-yl)propoxy)triisopropylsilane (27f)

Yield: 94%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.02-1.11 (m, 21H), 1.20 (d, $J = 6.2$ Hz, 3H), 1.31-1.33 (m, 1H), 1.35 (d, $J = 7.0$ Hz, 3H), 1.58-1.66 (m, 5H), 1.79-1.87 (m, 2H), 3.67-3.78 (m, 1H), 3.91-3.97 (m, 1H), 4.25-4.32 (m, 1H), 4.87 (t, $J = 4.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.99, 17.24, 18.05, 21.88, 27.66, 31.77, 36.83, 63.25, 67.45, 67.91, 94.27. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{39}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 331.2668, found m/z 331.2672.

4-((4S,6S)-4,6-Dimethyl-1,3-dioxan-2-yl)butyl benzoate (27g)

Yield: 89%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.20 (d, $J = 5.9$ Hz, 3H), 1.35 (d, $J = 6.7$ Hz, 4H), 1.53-1.59 (m, 3H), 1.62-1.67 (m, 2H), 1.76-1.85 (m, 3H), 3.90-3.98 (m, 1H), 4.27-4.31 (m, 1H), 4.32 (t, $J = 6.5$ Hz, 1H), 4.87 (t, $J = 5.0$ Hz, 1H), 7.41-7.45 (m, 2H), 7.53-7.57 (m, 1H), 8.03-8.06 (m, 2H). ^{13}C NMR (100MHz, CDCl_3): δ 17.22, 20.78, 21.86, 28.63, 34.93, 36.80, 65.01, 67.47, 67.94, 93.98, 128.30, 129.57, 130.49, 132.79, 166.66. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}]^+$ requires m/z 293.1753, found m/z 293.1743.

Benzyl (3-((4S,6S)-4,6-dimethyl-1,3-dioxan-2-yl)propyl)carbamate (27h)

Yield: 82%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.17-1.19 (d, $J = 6.4$ Hz, 3H), 1.28-1.29 (m, 1H), 1.33 (d, $J = 6.6$ Hz, 3H), 1.61 (s, 4H), 1.76-1.90 (m, 2H), 3.19-3.21

(m, 2H), 3.90-3.94 (m, 1H), 4.23-4.30 (m, 1H) 4.85 (s, 1H), 5.07-5.19 (m, 2H), 7.28-7.36 (m, 5H); ^{13}C NMR (100MHz, CDCl_3): δ 17.16, 21.82, 24.80, 32.36, 36.68, 40.82, 66.42, 67.46, 67.94, 93.74, 127.97, 128.03, 128.45, 136.76, 156.43. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_4$ $[\text{M}+\text{H}]^+$ requires m/z 308.1862, found m/z 308.1866.

General procedure and experimental data for preparing the enol ethers:

In a round bottom flask equipped with a magnetic stirring bar, aldehyde (5.0 mmol) and triethyl amine (9.0 mmol) were dissolved in CH_2Cl_2 (25 mL). The flask was cooled to 0 °C prior to the addition of R_3SiOTf (5.5 mmol) via syringe. The reaction solution was allowed to stir at room temperature for 1 hour before diluting with CH_2Cl_2 (25 mL). The organic solution was washed with NaHCO_3 (2×30 mL, saturated aqueous solution) and brine (2×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel using appropriate solvents (hexane/EtOAc mixture) to provide the title compounds.

(Cyclohexylidenemethoxy)triethylsilane (14d)

^1H NMR (400 MHz, CDCl_3): δ 0.65 (q, $J = 3.6$ Hz, 6H), 0.98 (t, $J = 4.8$ Hz, 9H), 1.45-1.56 (m, 6H), 1.92 (t, $J = 5.6$ Hz, 2H), 2.19 (t, $J = 5.6$ Hz, 2H), 6.04 (t, $J = 1.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 4.44, 6.60, 25.23, 26.98, 27.03, 28.43, 30.53, 121.78, 130.61. HRMS (ESI^+) exact mass calcd for $\text{C}_{13}\text{H}_{27}\text{OSi}$ $[\text{M}+\text{H}]^+$ requires m/z 227.1831, found m/z 227.1839.

tert-Butyl(cyclohexylidenemethoxy)dimethylsilane (14b)

^1H NMR (400 MHz, CDCl_3): δ 0.11 (s, 6H), 0.92 (s, 9H), 1.44-1.55 (m, 6H), 1.93 (t, $J = 4.2$ Hz, 2H), 2.18 (t, $J = 5.6$ Hz, 2H), 6.02 (t, $J = 0.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ -2.95, 18.35, 25.30, 25.70, 25.74, 26.96, 27.02, 28.42, 30.49, 121.57, 130.86. HRMS (ESI^+) exact mass calcd for $\text{C}_{13}\text{H}_{27}\text{OSi}$ $[\text{M}+\text{H}]^+$ requires m/z 227.1831, found m/z 227.1833.

((2-ethylhex-1-en-1-yl)oxy)triisopropylsilane (14i)

Z/E: 1/1. ^1H NMR (400 MHz, CDCl_3): δ 0.87-0.97 (m, 12H), 1.03-1.17 (m, 42H), 1.26-1.37 (m, 8H), 1.84-1.91 (m, 4H), 2.08-2.17 (m, 4H), 6.11 (s, 1H), 6.14 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.00, 12.28, 12.36, 13.43, 13.97, 14.07, 17.69, 17.80, 19.66, 22.40, 22.84, 24.48, 26.17, 29.88, 30.54, 30.72, 121.93, 122.16, 133.89, 133.99. HRMS (ESI^+)

exact mass calcd for $C_{17}H_{37}OSi$ $[M+H]^+$ requires m/z 285.2614, found m/z 285.2618.

((Dihydro-2H-pyran-4(3H)-ylidene)methoxy)triisopropylsilane (14k)

1H NMR (400 MHz, $CDCl_3$): δ 1.05-1.18 (m, 21H), 2.07 (t, J = 5.4 Hz, 2H), 2.36 (t, J = 5.5 Hz, 2H), 3.64 (t, J = 5.6 Hz, 4H), 6.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.96, 17.76, 26.32, 30.50, 68.42, 69.65, 115.17, 133.03. HRMS (ESI $^+$) exact mass calcd for $C_{15}H_{31}O_2Si$ $[M+H]^+$ requires m/z 271.2093, found m/z 271.2089.

Benzyl 4-(((triisopropylsilyl)oxy)methylene)piperidine-1-carboxylate (14l)

1H NMR (400 MHz, $CDCl_3$): δ 1.03-1.18 (m, 21H), 2.02 (brs, 2H), 2.32 (brs, 2H), 3.44-3.47 (m, 4H), 5.14 (s, 2H), 6.24 (s, 1H), 7.30-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.95, 17.70, 17.75, 44.65, 46.03, 66.98, 115.55, 127.81, 127.90, 128.47, 133.67, 136.99, 155.32. HRMS (ESI $^+$) exact mass calcd for $C_{23}H_{38}NO_3Si$ $[M+H]^+$ requires m/z 404.2621, found m/z 404.2623.

(Methoxymethylene)cyclohexane (14f)

In a round bottom flask equipped with a magnetic stir bar, (methoxymethyl)- triphenylphosphonium chloride (3.43 g, 10.0 mmol) was dissolved in anhydrous THF (40 mL) and cooled to 0 °C. A solution of *tert*-BuOK (10.5 mL, 1.0 M in THF) was added slowly. After stirring for 10 min, cyclohexanone (0.98 g, 10.0 mmol) was added. After stirring for 10 hours at room temperature, the reaction was quenched with H_2O . The aqueous layer was extracted with EtOAc (3 $\times$ 30 mL) and the combined organic layers were washed with brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The mixture was purified by flash chromatography on silica gel using 15% EtOAc in hexane to provide the title compound. Yield: 86%, colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ 1.48-1.52 (m, 6H), 1.93 (t, J = 5.6 Hz, 2H), 2.17 (t, J = 5.8 Hz, 2H), 3.51 (s, 3H), 5.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.41, 26.88, 27.02, 28.38, 30.53, 59.14, 118.32, 138.77. HRMS (ESI $^+$) exact mass calcd for $C_8H_{15}O$ $[M+H]^+$ requires m/z 127.1123, found m/z 127.1124.

Experimental procedure and data for Mukaiyama-aldol/[1,5]-H shift reaction:

General procedure for the Mukaiyama-aldol/[1,5] Hydride Shift Reaction: An oven-dried round bottom flask (10 mL) equipped with a magnetic stirring bar was charged with 4Å molecular sieves (300 mg) and sealed with a rubber septum. To this flask, a dry CH₂Cl₂ (2 mL) solution of acetal 1 (0.2 mmol) and silyl enol ether (0.5 mmol, 2.5 equiv) was added. After cooling the solution to -78 °C for 15 minutes, TiCl₄ solution (0.24 mL, 0.24 mmol, 1.2 equiv, 1.0 M solution in CH₂Cl₂) was added dropwise via syringe. The reaction solution was allowed to stir at -78 °C for 10 hours. The reaction was then quenched with NaHCO₃ (5mL, saturated aqueous solution) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel using appropriate solvents (hexane/ether or hexane/EtOAc mixture) to provide the corresponding title compounds.

2,2-Dimethyl-5-phenyl-1-(triisopropylsilyloxy)pentan-3-one (19a)

Yield: 70%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.01-1.08 (m, 21H), 1.10 (s, 6H), 2.86 (s, 4H), 3.68 (s, 2H), 7.16-7.18 (m, 3H), 7.24-7.28 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 11.91, 18.01, 21.58, 29.78, 40.34, 49.66, 71.02, 125.91, 128.40 (x 2), 141.78, 213.97. HRMS (ESI⁺) exact mass calcd for C₂₂H₃₈O₂Si [M+H]⁺ requires *m/z* 363.2719, found *m/z* 363.2727.

4,4-Dimethyl-5-(triisopropylsilyloxy)pentane-1,3-diol (20a)

Yield: 71%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.86 (s, 3H), 0.94 (s, 3H), 1.07-1.16(m, 21H), 1.62-1.73 (m, 2H), 3.17 (brs, 1H), 3.62 (q, *J* = 9.6 Hz, 2H), 3.75 (d, *J* = 10.1 Hz, 1H), 3.85-3.87 (m, 2H), 4.29 (d, *J* = 2.5 Hz, 1H), ¹³C NMR (100 MHz, CDCl₃): δ 11.72, 17.95, 18.96, 22.42, 33.10, 38.53, 62.65, 74.30, 80.78. HRMS (ESI⁺) exact mass calcd for C₁₆H₃₆O₃Si [M+H]⁺ requires *m/z* 305.2512, found *m/z* 305.2525.

20a-d ¹H NMR (400 MHz, CDCl₃): δ 0.86 (s, 3H), 0.93 (s, 3H), 1.05-1.16 (m, 21H), 1.61-1.75 (m, 2H), 3.21 (brs, 1H), **3.58 (s, 0.95 H for major isomer), 3.63 (s, 0.05 H for minor isomer)**, 3.76 (dd, *J*₁ = 2.8 Hz, *J*₂ = 10.4 Hz, 1H), 3.82-3.87 (m, 2H), 3.89-4.29 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 11.72, 17.94, 18.95, 22.38, 33.10, 38.21, 38.30, 62.59, 73.86 (t, *J*_{C-D} = 22.0 Hz), 80.65.

HRMS (ESI⁺) exact mass calcd for C₁₆H₃₅DO₃Si [M+H]⁺ requires *m/z* 306.2575, found *m/z* 306.2581.

2,2-Dimethyl-5-phenyl-1-(triisopropylsilyloxy)pentan-3-ol (29a)

Yield: 94%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.84 (s, 3H), 0.90 (s, 3H), 1.07-1.13 (m, 21H), 1.63-1.75 (m, 2H), 2.58-2.65 (m, 1H), 2.96-3.03 (m, 1H), 3.45 (dt, *J*₁ = 2.2 Hz, *J*₂ = 10.3 Hz, 1H), 3.59 (dd, *J*₁ = 9.5 Hz, *J*₂ = 27.6 Hz, 2H), 3.81 (d, *J* = 3.6 Hz, 1H), 7.17-7.30 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 11.76, 17.99, 19.09, 22.61, 33.02, 34.15, 38.54, 74.13, 78.79, 125.61, 128.29, 128.58, 142.97. HRMS (ESI⁺) exact mass calcd for C₂₂H₄₀O₂Si [M+H]⁺ requires *m/z* 365.2876, found *m/z* 365.2885. The enantiomeric excess was determined by chiral HPLC (Chiracel AD-H, 0.1% *i*-PrOH/hexanes, flow rate 1.0 mL/min, λ = 220 nm); *t*_r = 8.78 min (major) and 9.59 min (minor). 37% ee.

29a-d (62 mg, dr: 68:32, Yield: 85%) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.84 (s, 3H), 0.90 (s, 3H), 1.07-1.14 (m, 21H), 1.65-1.75 (m, 2H), 2.58-2.65 (m, 1H), 2.96-3.03 (m, 1H), 3.45 (dt, *J*₁ = 2.2 Hz, *J*₂ = 10.3 Hz, 1H), **3.53 (s, 0.68 H for major isomer), 3.60 (s, 0.32 H for minor isomer)**, 3.81 (d, *J* = 3.6 Hz, 1H), 7.15-7.29 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 11.76, 17.98, 19.09, 22.61, 33.02, 34.15, 38.54, 73.74 (t, *J*_{C-D} = 20.8 Hz), 78.79, 125.61, 128.29, 128.58, 142.97. HRMS (ESI⁺) exact mass calcd for C₂₂H₃₉DO₂Si [M+H]⁺ requires *m/z* 366.2939, found *m/z* 366.2944.

1-(1-(((*tert*-Butyldimethylsilyl)oxy)methyl)cyclohexyl)-3-phenylpropan-1-one (19e)

Yield: 77%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.01 (s, 6H), 0.86 (s, 9H), 1.29-1.31 (m, 5H), 1.49-1.61 (m, 3H), 1.96-1.98 (m, 2H), 2.85-2.87 (m, 4H), 3.56 (s, 2H), 7.18-7.20 (m, 3H), 7.25-7.29 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ -5.62, 18.19, 22.75, 25.82, 26.07, 29.82, 30.29, 40.66, 53.41, 69.74, 125.86, 128.39, 128.42, 141.97, 213.74. HRMS (ESI⁺) exact mass calcd for C₂₂H₃₆O₂Si [M+H]⁺ requires *m/z* 361.2563, found *m/z* 361.2556.

3-Phenyl-1-(1-((triisopropylsilyloxy)methyl)cyclohexyl)propan-1-one (19b)

Yield: 82%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.02-1.08 (m, 21H), 1.30-1.36 (m, 4H), 1.48-1.51 (m, 4H), 2.01-2.04 (m, 2H), 2.87 (s, 4H), 3.67 (s, 2H),

HRMS (ESI^+) exact mass calcd for $\text{C}_{25}\text{H}_{42}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 403.3032, found m/z 403.3026.

1-(1-(Methoxymethyl)cyclohexyl)-3-phenylpropan-1-one (19f)

29.80, 30.52, 39.89, 52.50, 59.29, 78.74, 125.88, 128.37, 128.46, 141.88, 213.27.

HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{25}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 261.1855, found m/z 261.1857.

3,3-Dimethyl-1-phenyl-4-(triisopropylsilyloxy)butan-2-one (31b)

^{13}C NMR (100 MHz, CDCl_3): 11.94, 18.04, 21.77, 44.98, 50.14, 70.88, 126.56, 128.32, 129.75, 134.86, 211.94. HRMS (ESI^+) exact mass calcd for $\text{C}_{21}\text{H}_{36}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 349.2563, found m/z 349.2566.

2,2-Dimethyl-1-(triisopropylsilyloxy)hexan-3-one (31c)

^{13}C NMR (100 MHz, CDCl_3): δ 11.90, 11.98, 13.80, 16.86, 17.97, 21.61, 40.05, 49.59, 70.88, 214.96. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{36}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 301.2563, found m/z 301.2574.

2,2-Dimethyl-1-(triisopropylsilyloxy)undecan-3-one (31d)

2H), 2.52 (t, $J = 7.4$ Hz, 2H), 3.69 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.91, 14.10, 17.98, 18.08, 21.64, 22.67, 23.48, 29.20, 29.34, 29.50, 31.86, 38.14, 49.64,

70.90, 215.15. HRMS (ESI⁺) exact mass calcd for C₂₂H₄₆O₂Si [M+H]⁺ requires *m/z* 371.3345, found *m/z* 371.3360.

4-Ethyl-2,2-dimethyl-1-(triisopropylsilyloxy)hexan-3-one (31e)

Yield: 63%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.84 (t, *J* = 7.4 Hz, 6H), 1.05-1.08 (m, 21H), 1.14 (s, 6H), 1.40 (dt, *J*₁ = 7.1 Hz, *J*₂ = 13.9 Hz, 2H), 1.63 (dt, *J*₁ = 7.1 Hz, *J*₂ = 13.9 Hz, 2H), 2.75 (p, *J* = 6.4 Hz, 1H), 3.71 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 11.94, 11.99, 21.68, 24.14, 49.04, 49.97, 69.94, 217.85. HRMS (ESI⁺) exact mass calcd for C₁₉H₄₀O₂Si [M+H]⁺ requires *m/z* 329.2876, found *m/z* 329.2886.

1-Cyclohexyl-2,2-dimethyl-3-(triisopropylsilyloxy)propan-1-one (31f)

Yield: 68%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.83-1.11 (m, 21H), 1.13 (s, 6H), 1.24-1.42 (m, 5H), 1.66-1.77 (m, 5H), 2.82-2.88 (m, 1H), 3.72 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 11.91, 17.98, 21.42, 25.77, 25.81, 29.62, 45.60, 50.17, 70.45, 218.09. HRMS (ESI⁺) exact mass calcd for C₂₀H₄₀O₂Si [M+H]⁺ requires *m/z* 341.2876, found *m/z* 341.2879.

6-(Benzyloxy)-2,2-dimethyl-1-(triisopropylsilyloxy)hexan-3-one (31g)

Yield: 77%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.02-1.06 (m, 21H), 1.11 (s, 6H), 1.84-1.90 (m, 2H), 2.65 (t, *J* = 7.1 Hz, 2H), 3.47 (t, *J* = 6.2 Hz, 2H), 3.69 (s, 2H), 4.48 (s, 2H), 7.27-7.36 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 11.90, 17.99, 21.64, 23.67, 34.80, 49.69, 69.62, 70.85, 72.79, 127.50, 127.62, 128.34, 138.57, 214.66. HRMS (ESI⁺) exact mass calcd for C₂₄H₄₂O₃Si [M+H]⁺ requires *m/z* 407.2981, found *m/z* 407.2966.

2,2-Dimethyl-1,7-di(triisopropylsilyloxy)heptan-3-one (31h)

Yield: 73%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.03-1.06 (m, 42H), 1.12 (s, 6H), 1.51-1.62 (m, 4H), 2.56 (t, *J* = 7.1 Hz, 2H), 3.66-3.69 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 11.91, 11.99, 17.98, 18.03, 20.00, 21.64, 32.63, 38.01, 49.61, 63.35, 70.91, 214.90. HRMS (ESI⁺) exact mass calcd for C₂₇H₅₈O₃Si₂ [M+H]⁺ requires *m/z* 487.4003, found *m/z* 487.3992.

5,5-Dimethyl-4-oxo-6-(triisopropylsilyloxy)hexyl benzoate (31i)

Yield: 76%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.01-1.09 (m, 21H), 1.13 (s, 6H), 1.71-1.78 (m, 4H), 2.62 (t, J = 6.7 Hz, 2H), 3.69 (s, 2H), 4.32 (t, J = 6.0 Hz, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 8.04 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.89, 17.71, 17.98, 20.06, 21.65, 28.34, 37.67, 49.64, 64.81, 71.00, 128.31, 129.56, 130.41, 132.83, 166.63, 214.52. HRMS (ESI^+) exact mass calcd for $\text{C}_{24}\text{H}_{40}\text{O}_4\text{Si}$ $[\text{M}+\text{Na}]^+$ requires m/z 457.2750, found m/z 457.2762.

Benzyl 5,5-dimethyl-4-oxo-6-(triisopropylsilyloxy)hexylcarbamate (31j)

Yield: 49%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.02-1.04 (m, 21H), 1.11 (s, 6H), 1.76 (p, J = 6.9 Hz, 2H), 2.59 (t, J = 6.9 Hz, 2H), 3.19 (dd, J_1 = 6.6 Hz, J_2 = 13.1 Hz, 2H), 3.68 (s, 2H), 4.87 (brs, 1H), 5.08 (s, 2H), 7.29-7.35 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.88, 17.97, 21.65, 23.67, 35.40, 40.73, 49.70, 66.58, 70.95, 128.07, 128.11, 128.50, 136.64, 156.43, 214.58. HRMS (ESI^+) exact mass calcd for $\text{C}_{25}\text{H}_{43}\text{NO}_4\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 450.3040, found m/z 450.3052.

4-Ethyl-1-phenyl-4-((triisopropylsilyloxy)methyl)hexan-3-one (19g)

Yield: 71%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.71 (t, J = 7.5 Hz, 6H), 1.03-1.06 (m, 21H), 1.50-1.60 (m, 2H), 1.65-1.74 (m, 2H), 2.76-2.80 (m, 2H), 2.84-2.88 (m, 2H), 3.75 (s, 2H), 7.16-7.19 (m, 3H), 7.25-7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 8.15, 11.96, 18.02, 23.77, 29.61, 40.44, 56.82, 63.95, 125.92, 128.40, 128.46, 141.77, 214.03. HRMS (ESI^+) exact mass calcd for $\text{C}_{24}\text{H}_{42}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 391.3032, found m/z 391.3042.

4-Ethyl-1-phenyl-4-(((triisopropylsilyloxy)methyl)octan-3-one (19i)

Yield: 79%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.71 (t, J = 7.8 Hz, 3H), 0.85 (t, J = 7.5 Hz, 3H), 0.99-1.10 (m, 21H), 1.20-1.32 (m, 4H), 1.42-1.73 (m, 4H), 2.75-2.79 (m, 2H), 2.84-2.88 (m, 2H), 3.75 (s, 2H), 7.16-7.19 (m, 3H), 7.25-7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 8.16, 11.95, 13.97, 18.01, 23.35, 24.12, 25.94, 29.60, 31.21, 40.38, 56.52, 64.25, 125.93, 128.40, 128.48, 141.77, 214.09. HRMS (ESI^+) exact mass calcd for $\text{C}_{26}\text{H}_{47}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 419.3345, found m/z 419.3355.

3-Phenyl-1-(1-(((triisopropylsilyloxy)methyl)cyclopentyl)propan-1-one (19h)

Yield: 77%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.01-1.09 (m, 21H), 1.51-1.57 (m, 6H), 1.89-1.92 (m, 2H), 2.88 (s, 4H), 3.75 (s, 2H), 7.16-7.19 (m, 3H), 7.25-7.28 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.94, 18.02, 25.29, 30.02, 31.64, 40.96, 61.80, 69.08, 124.88, 125.89, 128.39, 141.83, 213.00. HRMS (ESI^+) exact mass calcd for $\text{C}_{24}\text{H}_{41}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 389.2876, found m/z 389.2883.

(S)-3-Phenyl-1-(4-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-4-yl)propan-1-ol (29k)

Yield: 81%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.06-1.12 (m, 21H), 1.25 (td, $J_1 = 3.3$ Hz, $J_2 = 12.4$ Hz, 1H), 1.34 (ddd, $J_1 = 4.5$ Hz, $J_2 = 9.2$ Hz, $J_3 = 13.7$ Hz, 1H), 1.68-1.80 (m, 3H), 1.91 (ddd, $J_1 = 4.3$ Hz, $J_2 = 9.2$ Hz, $J_3 = 13.7$ Hz, 1H), 2.66 (ddd, $J_1 = 7.4$ Hz, $J_2 = 9.3$ Hz, $J_3 = 13.6$ Hz, 1H), 3.02-3.10 (m, 1H), 3.42-3.49 (m, 3H), 3.57-3.65 (m, 2H), 3.79 (td, $J_1 = 4.8$ Hz, $J_2 = 11.8$ Hz, 1H), 3.87 (q, $J = 10.2$ Hz, 2H), 7.18-7.22 (m, 3H), 7.26-7.30 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.73, 17.97, 17.99, 30.31, 30.68, 33.00, 33.87, 38.19, 63.41, 63.76, 67.52, 77.75, 125.73, 128.37, 128.55, 142.65. HRMS (ESI^+) exact mass calcd for $\text{C}_{24}\text{H}_{43}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 407.2981, found m/z 407.2971. The enantiomeric excess was determined by chiral HPLC (Chiracel AD-H, 1% *i*-PrOH/hexanes, flow rate 1.0 mL/min, $\lambda = 220$ nm); $t_r = 13.36$ min (minor) and 14.08 min (major). 95% ee.

(S)-Benzyl-4-(1-hydroxy-3-phenylpropyl)-4-(((triisopropylsilyl)oxy)methyl)piperidine-1-carboxylate (29l)

Yield: 69%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.07-1.14 (m, 21H), 1.27-1.30 (m, 2H), 1.65-1.70 (m, 1H), 1.74-1.78 (m, 2H), 1.87-1.94 (m, 1H), 2.65 (td, $J_1 = 8.2$ Hz, $J_2 = 13.7$ Hz, 1H), 3.04 (ddd, $J_1 = 5.3$ Hz, $J_2 = 9.0$ Hz, $J_3 = 13.9$ Hz, 1H), 3.19-3.23 (m, 1H), 3.37-3.49 (m, 4H), 3.67 (brs, 1H), 3.69 (d, $J = 10.0$ Hz, 1H), 3.89 (d, $J = 10.0$ Hz, 1H), 5.11 (s, 2H), 7.16-7.21 (m, 3H), 7.25-7.35 (m, 7H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.73, 17.99, 18.00, 29.05, 32.95, 33.92, 39.04, 39.47, 39.66, 67.04, 67.97, 76.34, 125.78, 127.90, 127.98, 128.40, 128.49, 128.54, 136.83, 142.51, 155.32. HRMS (ESI^+) exact mass calcd for $\text{C}_{32}\text{H}_{50}\text{NO}_4\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 540.3509, found m/z 540.3511. The enantiomeric

excess was determined by chiral HPLC (Chiracel AD-H, 5% *i*-PrOH/hexanes, flow rate 1.0 mL/min, $\lambda = 220$ nm); $t_r = 20.16$ min (minor) and 29.53 min (major). 95% ee.

(S)-3-Phenyl-1-(1-(((triisopropylsilyl)oxy)methyl)cyclohexyl)propan-1-ol (29b)

Yield: 91%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.05-1.16 (m, 21H), 1.22-1.45 (m, 7H), 1.53-1.58 (m, 1H), 1.67-1.83 (m, 4H), 2.64 (ddd, $J_1 = 6.8$ Hz, $J_2 = 9.9$ Hz, $J_3 = 13.6$ Hz, 1H), 3.02-3.09 (m, 1H), 3.48 (t, $J = 9.3$ Hz, 1H), 3.60 (d, $J = 8.5$ Hz, 1H), 3.67 (d, $J = 9.9$ Hz, 1H), 3.85 (d, $J = 9.9$ Hz, 1H), 7.16-7.30 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.76, 17.99, 18.02, 21.32, 21.59, 26.32, 30.11, 33.24, 33.97, 40.10, 69.16, 77.53, 125.55, 128.28, 128.58, 143.11. HRMS (ESI $^+$) exact mass calcd for $\text{C}_{25}\text{H}_{44}\text{O}_2\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 427.3008, found m/z 427.3007. The enantiomeric excess was determined by chiral HPLC (Chiracel OD-H, 0.5% *i*-PrOH/hexanes, flow rate 1.0 mL/min, $\lambda = 220$ nm); $t_r = 4.53$ min (major) and 5.24 min (minor). 84% ee.

(S)-1-(1-(((tert-Butyldimethylsilyl)oxy)methyl)cyclohexyl)-3-phenylpropan-1-ol (29e)

Yield: 89%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.08 (s, 6H), 0.91 (s, 9H), 1.11-1.15 (m, 1H), 1.23-1.56 (m, 8H), 1.61-1.68 (m, 2H), 1.80-1.84 (m, 1H), 2.63 (ddd, $J_1 = 6.8$ Hz, $J_2 = 9.9$ Hz, $J_3 = 13.6$ Hz, 1H), 3.02-3.09 (m, 1H), 3.44 (t, $J = 9.3$ Hz, 1H), 3.49 (d, $J = 8.4$ Hz, 1H), 3.55 (d, $J = 9.9$ Hz, 1H), 3.73 (d, $J = 9.9$ Hz, 1H), 7.16-7.30 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ -5.68, 18.08, 21.25, 21.54, 25.83, 26.30, 29.97, 30.61, 33.28, 33.96, 39.86, 68.30, 77.81, 125.58, 128.29, 128.57, 143.09. HRMS (ESI $^+$) exact mass calcd for $\text{C}_{22}\text{H}_{39}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 363.2719, found m/z 363.2723. The enantiomeric excess was determined by chiral HPLC (Chiracel AD-H, 0.1% *i*-PrOH/hexanes, flow rate 1.0 mL/min, $\lambda = 220$ nm); $t_r = 8.13$ min (minor) and 9.84 min (major). 60% ee.

(S)-1-(1-(Methoxymethyl)cyclohexyl)-3-phenylpropan-1-ol (29f)

Yield: 95%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.11-1.13 (m, 1H), 1.26-1.64 (m, 9H), 1.82-1.86 (m, 1H), 2.63 (ddd, $J_1 = 6.7$ Hz, $J_2 = 10.0$ Hz, $J_3 = 13.7$ Hz, 1H), 3.03 (ddd, $J_1 = 6.8$ Hz, $J_2 = 10.0$ Hz, $J_3 = 13.7$ Hz, 1H), 3.16 (d, $J = 8.7$ Hz, 1H), 3.31 (s, 3H), 3.35 (d, $J = 9.3$ Hz, 1H), 3.41 (t, $J = 9.7$ Hz, 1H), 3.46 (d, $J = 9.3$ Hz, 1H),

7.16-7.30 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 21.25, 21.58, 26.27, 30.38, 33.34, 33.92, 40.08, 59.42, 77.82, 77.88, 125.64, 128.31, 128.58, 142.98. HRMS (ESI^+) exact mass calcd for $\text{C}_{17}\text{H}_{27}\text{O}_2$ $[\text{M}+\text{H}]^+$ requires m/z 263.2011, found m/z 263.2002. The enantiomeric excess was determined by chiral HPLC (Chiracel OD-H, 0.5% *i*-PrOH/hexanes, flow rate 1.0 mL/min, λ = 220 nm); t_r = 8.57 min (major) and 9.43 min (minor). 44% ee.

(S)-4-Ethyl-1-phenyl-4-(((triisopropylsilyl)oxy)methyl)hexan-3-ol (29g)

Yield: 88%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.71 (t, J = 7.6 Hz, 3H), 0.81 (t, J = 7.5 Hz, 3H), 1.03-1.27 (m, 23H), 1.63 (q, J = 7.5 Hz, 2H), 1.66-1.78 (m, 3H), 2.63 (ddd, J_1 = 7.1 Hz, J_2 = 9.6 Hz, J_3 = 13.5 Hz, 1H), 3.6 (ddd, J_1 = 5.4 Hz, J_2 = 9.6 Hz, J_3 = 13.7 Hz, 1H), 3.48 (d, J = 9.2 Hz, 1H), 3.61 (d, J = 9.9 Hz, 1H), 3.68 (brs, 1H), 3.73 (d, J = 9.9 Hz, 1H), 7.15-7.29 (m, 5H); ^{13}C NMR (100MHz, CDCl_3): δ 7.44, 7.47, 11.79, 18.00, 22.83, 23.06, 33.25, 34.33, 42.53, 68.91, 76.44, 125.57, 128.28, 128.60, 143.10. HRMS (ESI^+) exact mass calcd for $\text{C}_{22}\text{H}_{44}\text{O}_2\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 391.3008, found m/z 391.3018.

(S)-Benzyl-4-(1-hydroxynonyl)-4-(((triisopropylsilyl)oxy)methyl)piperidine-1-carboxylate (34b)

Yield: 79%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 0.88 (t, J = 7.0 Hz, 3H), 1.06-1.15 (m, 21H), 1.27-1.48 (m, 16H), 1.65-1.70 (m, 2H), 1.87-1.93 (m, 1H), 3.19 (d, J = 8.5 Hz, 1H), 3.35-3.40 (m, 1H), 3.46 (t, J = 8.4 Hz, 1H), 3.57 (td, J_1 = 5.6 Hz, J_2 = 13.7 Hz, 1H), 3.68 (d, J = 10.0 Hz, 2H), 3.90 (d, J = 10.0 Hz, 1H), 5.13 (s, 2H), 7.29-7.36 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.75, 14.13, 17.98, 17.99, 22.69, 26.82, 29.04, 29.32, 29.59, 29.79, 31.68, 31.92, 39.13, 39.61, 39.73, 67.04, 67.80, 77.24, 127.90, 127.97, 128.49, 136.88, 155.40. HRMS (ESI^+) exact mass calcd for $\text{C}_{32}\text{H}_{58}\text{NO}_4\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 548.4135, found m/z 548.4136. The enantiomeric excess was determined by chiral HPLC (Chiracel OD-H, 2% *i*-PrOH/hexanes, flow rate 1.0 mL/min, λ = 220 nm); t_r = 9.43 min (minor) and 10.75 min (major). 97% ee.

(S)-Benzyl-4-(4-(benzyloxy)-1-hydroxybutyl)-4-(((triisopropylsilyl)oxy)methyl)piperidine-1-carboxylate (34e)

Yield: 64%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.05-1.14 (m, 21H), 1.21-1.39 (m, 4H), 1.64-1.70 (m, 2H), 1.85-2.01 (m, 2H), 3.21-3.28 (m, 1H), 3.34-3.40 (m, 2H), 3.45-3.58 (m, 4H), 3.65 (brs, 1H), 3.69 (d, $J = 10.0$ Hz, 1H), 3.89 (d, $J = 10.0$ Hz, 1H), 4.50 (s, 2H), 5.13 (s, 2H), 7.25-7.37 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.75, 17.99, 26.96, 28.45, 28.99, 39.20, 39.60, 67.04, 67.59, 70.28, 72.86, 127.54, 127.67, 127.91, 127.99, 128.36, 128.50, 136.89, 138.56, 155.39. HRMS (ESI^+) exact mass calcd for $\text{C}_{34}\text{H}_{54}\text{NO}_5\text{Si}$ $[\text{M}+\text{H}]^+$ requires m/z 584.3771, found m/z 584.3763. The enantiomeric excess was determined by chiral HPLC (Chiracel IA, 1% *i*-PrOH/hexanes, flow rate 1.0 mL/min, $\lambda = 220$ nm); $t_r = 29.63$ min (minor) and 35.47 min (major). 91% ee.

(S)-Benzyl-4-(1-hydroxy-4-(((triisopropylsilyl)oxy)butyl)-4-(((triisopropylsilyl)oxy)methyl)piperidine-1-carboxylate (34f)

Yield: 73%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.03-1.14 (m, 42H), 1.32-1.48 (m, 2H), 1.59-1.76 (m, 3H), 1.86-1.93 (m, 2H), 3.23-3.30 (m, 2H), 3.34-3.39 (m, 2H), 3.48-3.61 (m, 2H), 3.68-3.80 (m, 4H), 3.90 (d, $J = 10.0$ Hz, 1H), 5.13 (s, 2H), 7.29-7.36 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 11.76, 11.98, 17.99, 18.04, 28.26, 29.03, 30.33, 39.24, 39.64, 39.74, 63.42, 67.00, 67.48, 127.87, 127.95, 128.48, 136.89, 155.40. HRMS (ESI^+) exact mass calcd for $\text{C}_{36}\text{H}_{67}\text{NO}_5\text{SiNa}$ $[\text{M}+\text{Na}]^+$ requires m/z 644.4686, found m/z 644.4681. The enantiomeric excess was determined by chiral HPLC (Chiracel AD-H, 1% *i*-PrOH/hexanes, flow rate 1.0 mL/min, $\lambda = 220$ nm); $t_r = 15.03$ min (minor) and 18.84 min (major). 97% ee.

(S)-Benzyl-4-(5-(benzoyloxy)-1-hydroxypentyl)-4-(((triisopropylsilyl)oxy)methyl)piperidine-1-carboxylate (34g)

Yield: 59%, colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.06-1.15 (m, 21H), 1.29-1.35 (m, 2H), 1.50-1.59 (m, 3H), 1.66-1.72 (m, 1H), 1.78-1.92 (m, 4H), 3.21-3.28 (m, 1H), 3.32 (d, $J = 8.7$ Hz, 1H), 3.35-3.40 (m, 1H), 3.46-3.51 (m, 1H), 3.54-3.60 (m, 1H), 3.71 (brs, 1H), 3.70 (d, $J = 10.0$ Hz, 1H), 3.90 (d, $J = 10.0$ Hz, 1H), 4.29-4.39 (m, 2H), 5.13 (s, 2H), 7.26-7.36 (m, 5H), 7.43 (t, $J = 7.6$ Hz, 2H), 7.55 (t, $J = 7.4$ Hz, 1H), 8.04 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz,

CDCl₃): δ 11.72, 17.98, 23.37, 28.86, 29.03, 31.32, 39.09, 39.57, 39.68, 64.95, 67.06, 67.79, 127.91, 127.99, 128.32, 128.49, 129.56, 130.47, 132.82, 136.83, 155.60, 166.67. HRMS (ESI⁺) exact mass calcd for C₃₅H₅₄NO₆Si [M+H]⁺ requires m/z 612.3720, found m/z 612.3724. The enantiomeric excess was determined by chiral HPLC (Chiracel OD-H, 5% *i*-PrOH/hexanes, flow rate 1.0 mL/min, λ = 220 nm); t_r = 28.75 min (minor) and 46.65 min (major). 95% ee.

(S)-Benzyl-4-(4-(((benzyloxy)carbonyl)amino)-1-hydroxybutyl)-4-(((triisopropylsilyl)oxy)methyl)piperidine-1-carboxylate (34h)

Yield: 58%, colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.05-1.14 (m, 21H), 1.29-1.32 (m, 3H), 1.53-1.70 (m, 3H), 1.83-1.89 (m, 2H), 3.18-3.25 (m, 3H), 3.31-3.37 (m, 1H), 3.47 (brs, 2H), 3.53-3.59 (m, 1H), 3.70 (d, J = 10.0 Hz, 2H), 3.88 (d, J = 10.0, 1H), 4.97 (brs, 1H), 5.08 (s, 2H), 5.12 (s, 2H), 7.26-7.36 (m, 10H); ¹³C NMR (100 MHz, CDCl₃): δ 11.72, 17.97, 27.40, 28.77, 28.94, 39.10, 39.55, 39.66, 41.10, 66.56, 67.09, 67.68, 77.21, 127.93, 128.01, 128.06, 128.11, 128.51, 136.72, 136.82, 155.37, 156.50. HRMS (ESI⁺) exact mass calcd for C₃₅H₅₅N₂O₆Si [M+H]⁺ requires m/z 627.3829, found m/z 627.3828. The enantiomeric excess was determined by chiral HPLC (Chiracel AD-H, 3% *i*-PrOH/hexanes, flow rate 1.0 mL/min, λ = 220 nm); t_r = 12.90 min (major) and 13.77 min (minor). 94% ee.

Experimental Procedure and Data for the Synthesis of Sufentanil

Benzyl 4-(methoxymethylene)piperidine-1-carboxylate (14m)

Prepared by the following procedure: In a round bottom flask equipped with a magnetic stir bar, (methoxymethyl)-triphenylphosphonium chloride (3.43 g, 10.0 mmol) was dissolved in anhydrous THF (40 mL) and cooled to 0°C . A solution of *tert*-BuOK (10.5 mL, 1.0 M in THF) was added slowly, then benzyl 4-oxopiperidine-1-carboxylate (2.33 g, 10.0 mmol) was added. After stirring for 10 hours at room temperature, the reaction was quenched with H_2O . The aqueous layer was extracted with EtOAc ($3 \times 30 \text{ mL}$) and the combined organic layers were washed with brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The mixture was purified by flash chromatography on silica gel using 15% EtOAc in hexane to provide the title compound (2.43 g, Yield: 93%). ^1H NMR (400 MHz, CDCl_3): δ 2.03 (brs, 2H), 2.27 (brs, 2H), 3.44-3.47 (m, 4H), 3.56 (s, 3H), 5.14 (s, 2H), 5.86 (s, 1H), 7.30-7.36 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 44.65, 45.94, 59.46, 67.03, 113.15, 127.86, 127.95, 128.48, 136.93, 140.85, 155.28. HRMS (ESI^+) exact mass calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_3$ $[\text{M}+\text{H}]^+$ requires m/z 262.3242, found m/z 262.3244.

((Propane-1,1-diylbis(oxy))bis(methylene))dibenzene (35)

Prepared by the following procedure: In a round bottom flask equipped with a magnetic stirring bar, 1,1-diethoxypropane (1.32 g, 10.0 mmol) and *p*-toluenesulfonic acid monohydrate (0.5 mmol) were dissolved in

benzyl alcohol (4.32 g, 40.0 mmol). After stirring for 10 hours at 50 °C, the reaction was quenched with triethylamine (0.5 mL). The reaction mixture was purified by flash chromatography on silica gel using 5% diethyl ether in hexane to provide the title compound (1.89 g, Yield: 74%) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.96 (t, *J* = 7.6 Hz, 3H), 1.75-1.82 (m, 2H), 4.57 (d, *J* = 11.6 Hz, 2H), 4.66 (d, *J* = 11.6 Hz, 2H), 4.67 (t, *J* = 5.2 Hz, 1H), 7.23-7.34 (m, 10H); ¹³C NMR (100 MHz, CDCl₃): δ 9.14, 26.39, 67.15, 103.40, 127.60, 127.81, 128.45, 138.39. HRMS (ESI⁺) exact mass calcd for C₁₇H₂₀O₂Na [M+Na]⁺ requires *m/z* 279.1361, found *m/z* 279.1372.

Benzyl 4-(1-hydroxypropyl)-4-(methoxymethyl)piperidine-1-carboxylate (36)

Prepared by the general procedure for Mukaiyama-aldol/[1,5] hydride shift cascade reaction. Yield: 81% as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.05 (t, *J* = 7.2 Hz, 3H), 1.25-1.32 (m, 1H), 1.35-1.38 (m, 2H), 1.54-1.57 (m, 2H), 1.71-1.78 (m, 2H), 2.85 (brs, 1H), 3.14-3.29 (m, 2H), 3.32 (s, 3H), 3.39 (d, *J* = 9.4 Hz, 1H), 3.49 (d, *J* = 9.4 Hz, 1H), 3.64 (td, *J*₁ = 5.3 Hz, *J*₂ = 13.6 Hz, 1H), 3.66 (brs, 1H), 5.12 (s, 2H), 7.27-7.36 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 11.55, 24.48, 29.39, 38.99, 39.62, 39.67, 59.41, 66.99, 76.21, 79.38, 127.85, 127.95, 128.48, 136.87, 155.39. HRMS (ESI⁺) exact mass calcd for C₁₈H₂₈NO₄ [M+H]⁺ requires *m/z* 322.2018, found *m/z* 322.2021.

Benzyl 4-(methoxymethyl)-4-propionylpiperidine-1-carboxylate (37)

Prepared by the following procedure: In a round bottom flask equipped with a magnetic stirring bar, (COCl)₂ (0.31 g, 1.2 equiv) was dissolved in CH₂Cl₂. The flask was cooled to -78 °C and anhydrous DMSO (0.20 g, 1.3 equiv) was added slowly. The reaction mixture was stirred for additional 15 min before a solution of compound **36** (0.64 g, 2.0 mmol, 1.0 equiv, 0.4 M in CH₂Cl₂) was added slowly via syringe and the reaction mixture was stirred for 30 minutes at -78 °C. Then, triethyl amine (1.11 mL, 4.0 equiv) was added. The reaction mixture was warmed up and stirred for 1 hour at room temperature. The reaction mixture was poured into H₂O and the aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography on silicone gel (20% EtOAc/Hexane) to give the title product (0.51 g, Yield: 80%) as

colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 1.04 (t, $J = 7.2$ Hz, 3H), 1.50 (brs, 2H), 2.07 (td, $J_1 = 3.2$ Hz, $J_2 = 7.9$ Hz, 2H), 2.51 (q, $J = 7.2$ Hz, 2H), 3.16 (brs, 2H), 3.26 (s, 3H), 3.39 (s, 2H), 3.73 (brs, 2H), 5.11 (s, 2H), 7.26-7.35 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 7.83, 31.22, 40.89, 50.88, 59.38, 67.07, 78.28, 127.86, 127.99, 128.49, 136.80, 155.27, 213.22. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_4$ $[\text{M}+\text{H}]^+$ requires m/z 320.1862, found m/z 320.1867.

Benzyl 4-(methoxymethyl)-4-propionamidopiperidine-1-carboxylate (39)

Prepared by the following procedure: In a round bottom flask equipped with a magnetic stirring bar, compound **37** (0.48 g, 1.5 mmol) was dissolved in MeOH (30 mL). To this solution, $\text{NH}_2\text{OH}\cdot\text{HCl}$ (0.21 g, 3.0 mmol, 2.0 equiv) and pyridine (0.24 mL, 3.0 mmol, 2.0 equiv) were added. The reaction mixture was

refluxed for 12 hours before concentrating *in vacuo* to provide the crude oxime **38**.

The crude oxime **38** was dissolved in CH_2Cl_2 (30 mL). To this solution, tosyl chloride (0.34 g, 1.8 mmol, 1.2 equiv) and DMAP (0.24 g, 1.95 mmol, 1.3 equiv) were added. The reaction was stirred for 2 hours at room temperature and concentrated *in vacuo* to give the crude tosylated oxime product.

The crude tosylated oxime product was dissolved in 10 mL CH_3COOH and stirred for 2 hours at room temperature. The reaction was quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (30 mL $\times$ 3). The combined organic layers were washed successively with H_2O (50 mL $\times$ 2) and NaHCO_3 (50 mL $\times$ 2, saturated aqueous solution), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (67% EtOAc/hexane) to provide the title compound (0.37 g, Yield: 74%) as colorless oil.

^1H NMR (400 MHz, CDCl_3): δ 1.13 (t, $J = 7.6$ Hz, 3H), 1.56 (brs, 2H), 2.20 (q, $J = 7.6$ Hz, 2H), 3.13 (t, $J = 11.2$ Hz, 2H), 3.32 (s, 3H), 3.52 (s, 2H), 3.86 (brs, 2H), 5.12 (s, 2H), 5.39 (brs, 1H), 7.28-7.36 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 9.98, 30.55, 31.15, 39.46, 54.70, 59.25, 67.08, 75.67, 127.85, 128.00, 128.49, 136.72, 155.25, 174.39. HRMS (ESI^+) exact mass calcd for $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ requires m/z 335.1971, found m/z 335.1967.

2-(Thiophen-2-yl)ethyl 4-methylbenzenesulfonate (41)

Prepared by the following procedure: In a round bottom flask equipped with a magnetic stirring bar, 2-(thiophen-2-yl)ethanol

(0.64 g, 5.0 mmol) and TsCl (1.15 g, 6.0 mmol) were dissolved in CH₂Cl₂ (20 mL). DMAP (0.80 g, 6.5 mmol) was added to the reaction solution and the mixture was stirred for 2 hours at room temperature. Solvent was removed *in vacuo*. The crude product was purified by column chromatography on silicon gel (10% EtOAc/Hexane) to give the title product (1.21 g, Yield: 86%) as light yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 2.44 (s, 3H), 3.17 (t, *J* = 6.7 Hz, 2H), 4.21 (t, *J* = 6.9 Hz, 2H), 6.80 (dd, *J*₁ = 0.9 Hz, *J*₂ = 3.4 Hz, 1H), 6.90 (dd, *J*₁ = 3.5 Hz, *J*₂ = 5.1 Hz, 1H), 7.14 (dd, *J*₁ = 1.1 Hz, *J*₂ = 5.1 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 21.66, 29.56, 70.08, 124.38, 126.09, 127.00, 127.91, 129.85, 132.92, 138.03, 144.81. HRMS (ESI⁺) exact mass calcd for C₁₃H₁₅O₃S₂ [M+H]⁺ requires *m/z* 283.0463, found *m/z* 283.0465.

***N*-(4-(Methoxymethyl)-1-(2-(thiophen-2-yl)ethyl)piperidin-4-yl)propionamide**

(42)

Prepared by the following procedure: In a round bottom flask equipped with a magnetic stirring bar, compound **39** (0.33 g, 1.0 mmol) was dissolved in MeOH (20 mL). To this reaction flask, Pd/C (10%, 100 mg) was added and the reaction mixture was stirred for 12 hours under hydrogen. The Pd/C was filtered off and the organic layer was concentrated *in vacuo* to provide *N*-(4-(methoxymethyl)piperidin-4-yl)-propionamide.

N-(4-(methoxymethyl)piperidin-4-yl)propionamide (1.0 mmol) was dissolved in CH₃CN (50 mL). To this solution, compound **41** (0.34 g, 1.2 mmol) and K₂CO₃ (0.28 g, 2.0 mmol) were added and the reaction mixture was then refluxed for 12 hours. The reaction mixture was poured into H₂O (40 mL) and the aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL × 2), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silicone gel (2% CH₂Cl₂/MeOH) to give the title product (0.30 g, Yield: 95%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 1.14 (t, *J* = 7.6 Hz, 3H), 1.77-1.84 (m, 2H), 2.23 (q, *J* = 7.6 Hz, 2H), 2.27 (d, *J* = 14.4 Hz, 2H), 2.45 (t, *J* = 11.2 Hz, 2H), 2.75-2.79 (m, 2H), 2.86 (d, *J* = 12.0 Hz, 2H), 3.07-3.13 (m, 2H), 3.33 (s, 3H), 3.57 (s, 2H), 5.38 (brs, 1H), 6.84 (dd, *J*₁ = 0.8 Hz, *J*₂ = 3.4 Hz, 1H), 6.92 (dd, *J*₁ = 3.4 Hz, *J*₂ = 5.1 Hz, 1H), 7.13 (dd, *J*₁ = 1.1 Hz, *J*₂ = 5.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 9.96, 27.20, 30.59, 31.03, 48.89, 54.19,

59.26, 59.58, 75.92, 123.74, 124.93, 126.74, 141.72, 174.20. HRMS (ESI⁺) exact mass calcd for C₁₆H₂₇N₂O₂S [M+H]⁺ requires *m/z* 311.1793, found *m/z* 311.1790.

4-(Methoxymethyl)-N-phenyl-1-(2-(thiophen-2-yl)ethyl)piperidin-4-amine (44)

Prepared by the following procedure: In a round bottom flask equipped with a magnetic stirring bar, compound **42** (0.280 g, 0.9 mmol) was dissolved in 3M HCl (25 mL). The solution was allowed to reflux for 24 hours. Adjusted the pH of reaction mixture to 10 with NaOH (3 M) and the aqueous layer was extracted with CH₂Cl₂ (30 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give 4-(methoxymethyl)-1-(2-(thiophen-2-yl)ethyl)piperidin-4-amine **43**. The crude product was used for the next step without further purification.

In a round bottom flask equipped with a magnetic stirring bar, **43** (25.4 mg, 0.1 mmol) were dissolved in CH₂Cl₂ (2 mL). Then, Cu(OAc)₂ (18.2 mg, 0.1 mmol), phenylboronic acid (24.4 mg, 0.2 mmol) and pyridine (23.7 mg, 0.3 mmol) were added. The solution was allowed to stir at room temperature for 24 hours under O₂. The reaction mixture was filtered through a short pad of silica gel. The filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (2% CH₂Cl₂/MeOH) to provide the title compound (15 mg, Yield: 46% over two steps) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.73-1.80 (m, 2H), 1.97 (d, *J* = 14.0 Hz, 2H), 2.56 (t, *J* = 10.5 Hz, 2H), 2.67-2.71 (m, 4H), 3.04 (t, *J* = 8.0 Hz, 2H), 3.30 (s, 3H), 3.34 (s, 2H), 6.81-6.85 (m, 4H), 6.92 (dd, *J*₁ = 3.5 Hz, *J*₂ = 5.1 Hz, 1H), 7.12 (d, *J* = 5.1 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 27.83, 32.79, 49.03, 55.10, 59.14, 60.11, 119.80, 123.49, 124.62, 126.60, 126.64, 128.88, 143.02, 146.08. HRMS (ESI⁺) exact mass calcd for C₁₉H₂₇N₂OS [M+H]⁺ requires *m/z* 331.1844, found *m/z* 331.1839.

Sufentanil (45)

Prepared by the following procedure: In a round bottom flask equipped with a magnetic stirring bar, compound **44** (10 mg, 0.03mmol) were dissolved in CH₂Cl₂ (2 mL). The flask was cooled to 0 °C followed by the addition of propionyl chloride (0.06 mmol) and triethyl amine (9.1 mg, 0.09 mmol) via syringe. The solution was allowed to stir at room temperature for 2 hours. Solvent was

removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc: 2/1) to provide the title compounds (10.3 mg, Yield: 88%). ¹H NMR (400 MHz, CDCl₃): δ 0.94 (t, *J* = 7.4 Hz, 3H), 1.69-1.75 (m, 2H), 1.83 (q, *J* = 7.4 Hz, 2H), 2.19-2.27 (m, 4H), 2.58-2.62 (m, 2H), 2.67-2.70 (m, 2H), 2.95-2.98 (m, 2H), 3.43 (s, 3H), 4.07 (s, 2H), 6.78 (dd, *J*₁ = 0.8 Hz, *J*₂ = 3.3 Hz, 1H), 6.90 (dd, *J*₁ = 3.4 Hz, *J*₂ = 5.1 Hz, 1H), 7.11 (dd, *J*₁ = 1.1 Hz, *J*₂ = 5.2 Hz, 1H), 7.26-7.37 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 9.50, 27.73, 30.71, 33.06, 50.15, 59.19, 60.01, 61.50, 70.52, 123.44, 124.60, 126.65, 127.82, 128.61, 131.34, 141.23, 142.63, 174.67. HRMS (ESI⁺) exact mass calcd for C₂₂H₃₁N₂O₂S [M+H]⁺ requires *m/z* 387.2106, found *m/z* 387.2101.