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

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

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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, TiCl₄ and SnCl₄ gave different diastereomers.

Another InBr₃ catalyzed Prins reaction initiated polyene cyclization also has been developed, which allowed for the rapid synthesis of 3-oxaterpenoids. The first total synthesis of (±)-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.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>δ</td>
<td>chemical shift</td>
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<tr>
<td>°C</td>
<td>degree centigrade</td>
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<td>inverse centimeter</td>
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<td>diisobutylaluminium hydride</td>
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<td>TLC</td>
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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

---

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

\begin{center}
\textbf{Scheme 1.1} Mechanism of enzymatic polyene cyclization
\end{center}

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.\textsuperscript{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.

\section*{1.2 Biomimetic Polyene Cyclization Reactions}

\subsection*{1.2.1 Brønsted Acid Promoted Polyene Cyclization}

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

\begin{footnotesize}
\end{footnotesize}
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, Stork and Eschenmoser’s group has indicated the probability of biomimetic polyene cyclization under acid conditions (Scheme 1.2). They found the diene, even triene cyclized and provided the desired product in 69% yield.

![Scheme 1.2](image)

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:

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).

---

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.

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

---

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

Very recently, Corey group found that the reaction yield and enantioselectivity was dramatically improved by using \( o, o' \)-dichloro-BINOL as the ligand and SbCl\(_5\) as the Lewis acid (Scheme 1.6).\(^{11}\)

---


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. The methodology was also deeply studied by E. E. van Tamelen’s group. 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).

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). Interestingly, catalytic amount of Lewis acid is enough to furnish the reaction in good yield.

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). Interestingly, catalytic amount of Lewis acid is enough to furnish the reaction in good yield.

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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](image)

### 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. In 2007, Ishihara group made a breakthrough. 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.


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

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.

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In 1966, Johnson’s group first applied oxocarbenium in polyene cyclization.\(^\text{19}\) They found that acetal tethering polyene substrate cyclized smoothly upon treating with tin \textit{tetra}-chloride. Chiral alcohol protected acetal leaded to the desired product in moderated enantioselectivity (Scheme 1.11).

![Scheme 1.11](image)

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).\(^\text{20}\) The reaction simplifies mostly for polyene substrates, but it also introduces a bothersome side chain to the product.

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Scheme 1.12

Similar as oxocarbonium, 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).\textsuperscript{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 \textsuperscript{40} (Scheme 1.14).\textsuperscript{22}

Scheme 1.13

Scheme 1.14

1.2.5 Metal Induced Polyene Cyclization

Nonmetal Cation-\pi cyclizations constitutes an important strategy for the terpenoides 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.

Replacement of the proton by Hg$^{2+}$ constitutes a classical solution to polyene cyclization since the front stage of this area.\textsuperscript{23} Recently, this reaction was further extended to asymmetric version.\textsuperscript{24} In this reaction, the resulting C(sp$^3$)-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.

\begin{center}
\textbf{Scheme 1.15}
\end{center}

Palladium(II) catalyzed Cope rearrangement has been well studied by Overman et al.\textsuperscript{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).\textsuperscript{26}

\begin{center}
\textbf{Cope rearrangement}
\end{center}

\begin{itemize}
\item[(b)] Skeean, R. W.; Trammell, G. L.; White, J. D. Tetrahedron Lett. 1976, 17, 525.
\item[(c)] Corey, E. J.; Tias, M. A.; Das, J. J. Am. Chem. Soc. 1980, 102, 1742.
\item[(d)] Corey, E. J.; Reid, J. G.; Myers, A. G.; Hahl, R. W. J. Am. Chem. Soc. 1987, 109, 918.
\item[(j)] Snyder, S. A.; Trettler, D. S.; Schall, A. Tetrahedron 2010, 66, 4796.
\item[(k)] Overman, L. E.; Knoll, F. M. J. Am. Chem. Soc. 1980, 102, 865.
\end{itemize}
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

Chapter 1. Development of Biomimetic Polyene Cyclization

Very recently, Corey group developed another metal catalyzed cationic cascade cyclization.30 Given that InBr3 and InI3 are more soluble in solutions of 1-heptyne and CH2Cl2 mixture than in CH2Cl2 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 1.18

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

Chapter 1. Development of Biomimetic Polyene Cyclization

for this remarkable transformation. \(^{31}\)

![Scheme 1.20](image)

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 \(\beta\)-Keto ester under oxidation condition (Mn(OAc)\(_3\), Cu(OAc)\(_2\) etc). In 1985, Zoretic group reported a carbon radical initiated cascade annulation using \(\beta\)-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](image)

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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 1.22](image)

**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 1.23](image)

**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:


Chapter 1. Development of Biomimetic Polyene Cyclization

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](image)

**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.\(^\text{37}\) Hence, invent new strategies to construct multifarious skeletons is one of the challenges.

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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 going 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.\textsuperscript{38}

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

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 (±)-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. 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; Lucensimycin A has functional groups at 2- and 4- position (Figure 2.1).

![Figure 2.1](image-url)

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

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only with six or five member rings. For example, icetexanes have 6-7-6 core structure, while Cyathane diterpenoids have 7-6-5 fused rings. 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). 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.

\[
\text{Ph} - \text{O} - \text{O} - \text{O} - \text{Ph} + \text{SnCl}_4, \text{CH}_2\text{Cl}_2, -78^\circ \text{C} \rightarrow 89\% \text{ dr} = 66:18:16
\]

\text{Scheme 2.1}

Drawing lessons from the Mukaiyama-aldol-Prins cascade reaction that was developed in our group, 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

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 Wittg 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 Sn2 reaction (3). 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.

Having established a facile method for substrate synthesis, the reaction of 1,3-propanediol 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 SnCl₄ as the promoter at -78 ºC in CH₂Cl₂. TiCl₄ gave similar result (83% yield with 65:35 dr), but other Lewis acids (including BF₃.OEt₂, InBr₃ and AlClMe₂) 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 modle, the addition of silyl enol ether to cyclic acetals normally undergoes SN₁ mechanism and gives 10a as the major products in CH₂Cl₂. On the other hand, the 30:70 ratio of diastereomer resulting from this reaction in nonpolar solvent toluene suggests that the reaction follows SN₂ or via oxocarbenium ion pair mechanism for six membered cyclic acetals. The reaction did not work in other solvents (such as CH₃CN, THF and Et₂O). 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).

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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 diastereoselectivity (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

\[
\begin{array}{cccc}
\text{Entry} & \text{Substrate} & \text{LA} & \text{Solvent} & \text{Yield (\%)} & \text{Dr}^c \\
\hline
1 & \text{SnCl}_4 & \text{CH}_2\text{Cl}_2 & 11a & 90 & 64:36 \\
2 & \text{SnCl}_4 & \text{Toluene} & 11a & 83 & 68:32 \\
3 & \text{SnCl}_4 & \text{CH}_2\text{Cl}_2 & 12a & 76 & 82:18 \\
4 & \text{TiCl}_4 & \text{CH}_2\text{Cl}_2 & 12a & \text{messy} & \text{messy} \\
5 & \text{SnCl}_4 & \text{CH}_2\text{Cl}_2 & 13a & \text{--}^d & - \\
6 & \text{TiCl}_4 & \text{CH}_2\text{Cl}_2 & 13a & 72 & 91:9 \\
\end{array}
\]

\(a\) 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 \(^1\)H 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

\[
\begin{array}{cccc}
\text{Entry} & \text{Substrate} & \text{LA} & \text{Solvent} & \text{Yield (\%)} \\
\hline
1 & \text{SnCl}_4 & \text{CH}_2\text{Cl}_2 & 11a & 90 \\
2 & \text{SnCl}_4 & \text{Toluene} & 11a & 83 \\
3 & \text{SnCl}_4 & \text{CH}_2\text{Cl}_2 & 12a & 76 \\
4 & \text{TiCl}_4 & \text{CH}_2\text{Cl}_2 & 12a & \text{messy} \\
5 & \text{SnCl}_4 & \text{CH}_2\text{Cl}_2 & 13a & \text{--} \\
6 & \text{TiCl}_4 & \text{CH}_2\text{Cl}_2 & 13a & 72 \\
\end{array}
\]
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\[
\begin{align*}
\text{R} & = \text{OTIPS} \\
\text{R}^1 & = \text{H} \\
\text{R}^2 & = \text{RO} \\
\text{R}^3 & = \text{Br} \\
\text{R}^4 & = \text{TIPSO} \\
\text{R}^5 & = \text{OTIPS} \\
\text{R}^6 & = \text{OTIPS} \\
\text{R}^7 & = \text{H} \\
\text{R}^8 & = \text{OTIPS} \\
\text{R}^9 & = \text{OTIPS} \\
\text{R}^{10} & = \text{OTIPS} \\
\text{R}^{11} & = \text{OTIPS} \\
\text{R}^{12} & = \text{OTIPS} \\
\text{R}^{13} & = \text{OTIPS} \\
\end{align*}
\]

\[
\begin{align*}
& \text{TiCl}_4, \text{CH}_2\text{Cl}_2, \text{4Å MS} \\
& R = \text{CHOH}
\end{align*}
\]

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

\(^a\) 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 \(^1\)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$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
<th>Dr$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate" /></td>
<td><img src="image2" alt="Product" /></td>
<td>62</td>
<td>89:11</td>
</tr>
</tbody>
</table>
Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. Isolated yield. Dr value (7:7') determined by $^1$H 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).

![Diagram](image_url)

**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, 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).

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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/Et$_2$NH, 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.
### 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 TiCl₄, the desired product 29a’ was obtained in 38% yield with moderate disteroselectivity (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 disteroselectivity (77:23), and 3-oxaterpenoid was not observed. Other Lewis acid, such as SnCl₄ cased 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 CH₂Cl₂ and TiCl₄ were selected for further study.

Table 2.4 Preliminary studies of acetal with isobutene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>L.A.</th>
<th>Solvent</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Dr&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>TiCl₄</td>
<td>CH₂Cl₂</td>
<td>29a'</td>
<td>38</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>6a</td>
<td>TiCl₄</td>
<td>CH₂Cl₂</td>
<td>29a</td>
<td>85</td>
<td>77:23</td>
</tr>
<tr>
<td>3</td>
<td>6a</td>
<td>TiCl₄</td>
<td>Toluene</td>
<td>29a</td>
<td>76</td>
<td>58:42</td>
</tr>
<tr>
<td>4</td>
<td>6a</td>
<td>TiCl₄</td>
<td>NO&lt;sub&gt;₂&lt;/sub&gt;</td>
<td>29a</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>6a</td>
<td>SnCl₄</td>
<td>CH₂Cl₂</td>
<td>29a</td>
<td>17</td>
<td>-</td>
</tr>
</tbody>
</table>

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

\[
\begin{align*}
\text{Entry} & \quad \text{Substrate} & \quad \text{Product} & \quad \text{Yield} & \quad \text{Dr}^c \\
1 & \quad 6a & \quad 29a & \quad 85 & \quad 77:23 \\
2 & \quad 6b & \quad 29b & \quad 81 & \quad 89:11 \\
3 & \quad 6c & \quad 29c & \quad 77 & \quad 75:25 \\
4 & \quad 6d & \quad 29d & \quad 85 & \quad 75:25 \\
5 & \quad 6e & \quad 29e & \quad 53 & \quad 78:22
\end{align*}
\]
Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. Isolated yield. Dr value was determined by \(^1\)H 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

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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 SnCl4 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).
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). PhMe$_2$Si- 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$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>PG-</th>
<th>Yield (%)$^b$</th>
<th>Dr$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36a</td>
<td>TBDPS-</td>
<td>37e</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>36b</td>
<td>TIPS-</td>
<td>37eb</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>36c</td>
<td>PhMe$_2$Si-</td>
<td>37ec</td>
<td>21</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: 1 PCC, 2 KOH, THF/MeOH, TBAF.

$^b$ Yield (%)$^b$ = % of isolated product.

$^c$ Dr$^c$ = Diastereomeric ratio.
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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 diasteroselectivity. 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>LA</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="5a" /></td>
<td>TiCl4</td>
<td>37a</td>
<td>56</td>
<td>89:11</td>
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<tr>
<td></td>
<td></td>
<td>SnCl4</td>
<td>38a</td>
<td>54</td>
<td>80:20</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="5b" /></td>
<td>TiCl4</td>
<td>37b</td>
<td>51</td>
<td>90:10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SnCl4</td>
<td>38b</td>
<td>47</td>
<td>87:13</td>
</tr>
</tbody>
</table>

\( ^{a} \) 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 \(^{1}\)H NMR. \( ^{d} \) The reaction was too messy to analyze.
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 SnCl₄ 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 sily 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 quarternary 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 (TiCl₄ or SnCl₄). 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 (13C 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 SiMe4 (δ = 0.0) and relative to the signal of chloroform-d (δ = 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 (13C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe4 (δ 0.0) and relative to the signal of chloroform-d (δ = 77.23, triplet).

High-resolution mass spectral analysis (HRMS) was performed on Q-Tof Premier mass spectrometer (Waters Corporation).

\[
\begin{align*}
R\text{CH}_2\text{C} &= H + \text{R'}\text{CH}_2\text{C}\text{O} & \text{THF, 60 °C} & \rightarrow \text{R} & \text{CH}_2\text{C}\text{O} & \text{Me} \\
\text{PPh}_3 & & & & \\
\end{align*}
\]

To an oven-dried round bottom flask (100 mL) equipped with a magnetic stir bar, aldehyde (10 mmol) and wittig 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, CDCl3): 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,
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\[ \text{C}_{13}\text{H}_{17}\text{O}_2 \] requires \( m/z \) 205.1229, found \( m/z \) 205.1232.

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

Yield: 85%, yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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\(_3\)): \( \delta \) 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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.78 (s, 3H), 2.47 (q, \( J = 7.6 \) Hz, 2H), 2.73 (t, \( J = 7.6 \) Hz, 2H), 3.73 (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\(_3\)): \( \delta \) 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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.78 (s, 3H), 2.30 (s, 3H), 2.45 (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\(_3\)): \( \delta \) 12.38, 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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.55 (s, 3H), 1.95-2.04 (m, 2H), 2.69 (t, \( J = 7.6 \) Hz, 2H), 3.78 (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\(_3\)): \( \delta \) 12.39, 30.82, 33.80, 51.74, 55.27, 113.86, 128.09, 129.27, 133.28, 141.41, 157.96,
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168.64. HRMS (ESI⁺) exact mass calcd for C_{14}H_{19}O_{3} [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 C_{16}H_{22}O_{5}Na [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 C_{17}H_{24}O_{3}Na [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, 153.82, 168.50. HRMS (ESI⁺) exact mass calcd for C_{13}H_{16}ClO_{2} [M+H]⁺ requires m/z 239.0839, found m/z 239.0848.

(E)-Methyl 2-methyl-5-(1-tosyl-1H-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,
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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, J₁ = 1.5 Hz, J₂ = 15.7 Hz, 1H), 7.01 (td, J₁ = 6.9 Hz, J₂ = 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, J₁ = 2.2 Hz, J₂ = 15.7 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), 3.73 (s, 3H), 6.75 (t, J = 7.3 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 =
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7.6 Hz, 2H), 3.73 (s, 3H), 5.21 (t, J = 5.6 Hz, 1H), 6.74 (t, J = 7.2 Hz, 1H); 13C NMR (100 MHz, CDCl3): 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 C16H25O2 [M+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, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 C10H19O2 [M+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 CH2Cl2 and cooled to 0 °C. DIBAI-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 filtrated 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.

**\((E)-3\text{-Methyl-6-phenylhex-3-enenitrile}\)**

Yield: 87%, yellow oil. \(^1\)H 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 C\(_{13}\)H\(_{16}\)N [M+H]\(^+\) requires \(m/z\) 186.1283, found \(m/z\) 186.1287.

**\((E)-3\text{-Methyl-6-o-tolylhex-3-enenitrile}\)**

Yield: 88%, yellow oil. \(^1\)H 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 C\(_{14}\)H\(_{18}\)N [M+H]\(^+\) requires \(m/z\) 200.1439, found \(m/z\) 200.1435.

**\((E)-6-(2\text{-Methoxyphenyl})-3\text{-methylhex-3-enenitrile}\)**

Yield: 93%, yellow oil. \(^1\)H 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 C\(_{14}\)H\(_{18}\)NO [M+H]\(^+\) requires \(m/z\) 216.1388, found \(m/z\) 216.1383.

**\((E)-3\text{-Methyl-6-p-tolylhex-3-enenitrile}\)**

Yield: 79%, yellow oil. \(^1\)H 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 C\(_{14}\)H\(_{18}\)N [M+H]\(^+\) requires \(m/z\) 200.1439, found \(m/z\) 200.1430.

**\((E)-6-(4\text{-Methoxyphenyl})-3\text{-methylhex-3-enenitrile}\)**

Yield: 64%, yellow oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 1.67 (s, 3H), 2.35 (q, \(J = 7.5\)
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1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 C16H21NO3Na [M+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, CDCl3): 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, J1 = 1.2, J2 = 7.2 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.95 (dd, J1 = 2.1 Hz, J2 = 8.4 Hz, 1H), 7.00 (d, J = 2.1 Hz, 1H); 13C NMR (75 MHz, CDCl3): 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 C17H23NONa [M+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, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 C13H15ClN [M+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: 79%, yellow oil. 1H NMR (400 MHz, CDCl3): δ 1.64 (s, 3H), 2.33 (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); 13C NMR (125 MHz, CDCl3): 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 C14H18NO [M+H]^+ requires m/z 216.1388, found m/z 216.1379.
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Yield: 78%, yellow oil. \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 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 C\(_{22}\)H\(_{23}\)N\(_2\)O\(_2\)S [M+H]\(^{+}\) requires \(m/z\) 379.1480, found \(m/z\) 379.1469.

\((E)-6\)-Phenylhex-3-enenitrile

Yield: 75%. \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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, \(J_2 = 6.8\) 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\(_3\)): \(\delta\) 20.41, 33.94, 35.25, 117.75, 117.91, 126.03, 128.41, 135.28, 141.23. HRMS (ESI\(^{+}\)) exact mass calcd for C\(_{12}\)H\(_{13}\)NNa [M+Na]\(^{+}\) requires \(m/z\) 194.0946, found \(m/z\) 194.0946.

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

Yield: 73%, yellow oil. \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 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 C\(_{12}\)H\(_{13}\)NNa [M+Na]\(^{+}\) requires \(m/z\) 194.0946, found \(m/z\) 194.0952.

\((E)-3\)-Methyldec-3-en-7-ytenitrile

Yield: 75%, yellow oil. \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 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 C\(_{11}\)H\(_{15}\)NNa [M+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. \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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,
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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); 13C NMR (100 MHz, CDCl3): 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 C19H26NO [M+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, CDCl3): δ 1.12 (t, J = 7.1 Hz, 3H), 1.62 (s, 3H), 1.73 (s, 3H), 2.02-2.05 (m, 2H), 2.12-2.19 (m, 2H), 3.02 (s, 2H), 5.18 (t, J = 7.0 Hz, 1H), 5.54 (t, J = 7.1 Hz, 1H); 13C NMR (100 MHz, CDCl3): 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 C16H25N [M+H]+ requires m/z 230.1909, found m/z 230.1907.

(E)-3-Methylnon-3-enenitrile

Yield: 86%, yellow oil. 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 C10H17NNa [M+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 CH2Cl2 (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. NH4Cl (30 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 aqueus with EtOAc (2 x 30mL). The combined organic layers were washed with brine (50 mL), dried over Na2SO4, 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 ºC. 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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

- $1.18$ (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$_3$): $\delta$ 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 C$_{17}$H$_{26}$O$_2$Na [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

- $1.19$ (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$_3$): $\delta$ 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 C$_{18}$H$_{28}$O$_2$Na [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

- $1.19$ (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$_3$): $\delta$ 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 C$_{18}$H$_{29}$O$_3$ [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{18}$H$_{28}$O$_2$Na [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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, $J = 6.6$ Hz, 1H), 5.28 (t, $J = 6.8$ Hz, 1H), 6.41 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{20}$H$_{32}$O$_5$Na [M+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. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{21}$H$_{34}$O$_3$Na [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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, 1H), 7.08 (s, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{18}$H$_{28}$O$_2$ClNa [M+Cl]$^+$ requires $m/z$ 305.1648, found $m/z$ 305.1649.
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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\(_3\)): \( \delta \) 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 C\(_{17}\)H\(_{25}\)ClO\(_2\)Na \([M+Na]^{+}\) requires \( m/z \) 319.1441, found \( m/z \) 319.1444.

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

Yield: 69%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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), 4.56 (t, \( J = 5.7 \) 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\(_3\)): \( \delta \) 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, 124.55, 126.45, 126.74, 129.78, 131.16, 132.06, 135.32, 135.40, 144.66. HRMS (ESI\(^{+}\)) exact mass calcd for C\(_{26}\)H\(_{33}\)NO\(_4\)SNa \([M+Na]^{+}\) requires \( m/z \) 478.2028, found \( m/z \) 478.2027.

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

Yield: 73%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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\(_3\)): \( \delta \) 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 C\(_{16}\)H\(_{24}\)O\(_2\) \([M+H]^{+}\) requires \( m/z \) 249.1855, found \( m/z \) 249.1858.

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

Yield: 75%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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\(_3\)): \( \delta \) 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 C\(_{16}\)H\(_{25}\)O\(_2\) \([M+H]^{+}\) requires \( m/z \) 249.1855, found \( m/z \) 249.1849.
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**(E)-1,1-Diethoxy-3-methyldec-3-en-7-yne**  
Yield: 76%, yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{15}$H$_{26}$O$_2$Na [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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), 3.64 (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$_3$): $\delta$ 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 C$_{23}$H$_{36}$O$_3$Na [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.11 (t, $J = 7.0$ Hz, 3H), 1.19 (t, $J = 7.0$ Hz, 6H), 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), 4.57 (t, $J = 5.8$ Hz, 1H), 5.16-5.23 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{20}$H$_{35}$O$_2$ [M+H]$^+$ requires m/z 307.2637, found m/z 307.2638.

**(E)-1,1-Diethoxy-3-methylnon-3-ene**  
Yield: 66%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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 C$_{14}$H$_{29}$O$_2$ [M+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$_2$Cl$_2$ (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. $^1$H 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 C$_{17}$H$_{25}$O$_2$ [M+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. $^1$H 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 C$_{18}$H$_{27}$O$_2$ [M+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. $^1$H 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,
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\[ \text{2H} \], 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); \(^{13}\text{C NMR (100 MHz, CDCl}_3\): \( \delta \) 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 \( \text{C}_{18}\text{H}_{26}\text{O}_2\text{Na} \) [M+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. \(^1\text{H NMR (400 MHz, CDCl}_3\): \( \delta \) 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), 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); \(^{13}\text{C NMR (100 MHz, CDCl}_3\): \( \delta \) 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 \( \text{C}_{18}\text{H}_{26}\text{O}_3\text{Na} \) [M+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. \(^1\text{H NMR (400 MHz, CDCl}_3\): \( \delta \) 1.22 (d, \( J = 5.8 \) Hz, 3H), 1.29 (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); \(^{13}\text{C NMR (100 MHz, CDCl}_3\): \( \delta \) 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 \( \text{C}_{18}\text{H}_{26}\text{O}_2\text{Na} \) [M+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. \(^1\text{H NMR (400 MHz, CDCl}_3\): \( \delta \) 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\(_3\)): \(\delta\) 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 C\(_{20}\)H\(_{30}\)O\(_5\)Na [M+Na]\(^+\) requires \(m/z\) 373.1991, found \(m/z\) 373.2009.

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

Yield: 89\%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 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 C\(_{17}\)H\(_{24}\)ClO\(_2\) [M+H]\(^+\) requires \(m/z\) 295.1465, found \(m/z\) 295.1458.

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

Yield: 85\%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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), 3.0 (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\(_3\)): \(\delta\) 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 C\(_{26}\)H\(_{32}\)NO\(_4\)S [M+H]\(^+\) requires \(m/z\) 454.2052, found \(m/z\) 454.2047.

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

Yield: 95\%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 16.95, 17.24, 34.51, 35.82, 38.30, 78.17, 79.77, 102.95, 124.24, 125.73,
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128.26, 128.44, 133.25, 142.05. HRMS (ESI+) exact mass calcd for C_{16}H_{23}O_{2} [M+H]^+ requires m/z 247.1698, found m/z 247.1704.

**(4R,5R)-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 C_{16}H_{23}O_{2} [M+H]^+ requires m/z 247.1698, found m/z 247.1686.

**(4R,5R)-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, 17.02, 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 C_{15}H_{25}O_{2} [M+H]^+ requires m/z 237.1855, found m/z 237.1851.

**(4R,5R)-2-((2E,6E)-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 C_{23}H_{35}O_{3} [M+H]^+ requires m/z 359.2586, found m/z 359.2592.

**(4R,5R)-2-((2E,6E)-2,6-dimethyltrideca-2,6-dien-10-ynyl)-4,5-dimethyl-1,3-dioxolane (8m)**
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Yield: 88%, yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{20}$H$_{33}$O$_2$ [M+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$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_2$SO$_4$ 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)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.05-1.16 (m, 21H), 1.52 (s, 3H), 1.61 (s, 3H), 6.12 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 11.99, 14.69, 17.78, 19.27, 112.42, 133.99. HRMS (ESI$^+$) exact mass calcd for C$_{13}$H$_{29}$OSi [M+H]$^+$ requires m/z 229.1988, found m/z 229.1983.

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

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 12.02, 12.34, 13.40, 17.80, 19.61, 24.11, 123.71, 133.47. HRMS (ESI$^+$) exact mass calcd for C$_{15}$H$_{32}$OSiNa [M+Na]$^+$ requires m/z 279.2120, found m/z 279.2107.

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

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$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.05-1.16 (m, 21H), 1.52 (s, 3H), 1.61 (s, 3H), 6.12 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 11.99, 14.69, 17.78, 19.27, 112.42, 133.99. HRMS (ESI$^+$) exact mass calcd for C$_{12}$H$_{25}$BrOSiNa [M+H]$^+$ requires m/z 315.0756, found m/z 315.0771.

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

$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.06-1.23 (m, 21H), 1.81 (s, 3H), 4.02 (s, 1H), 4.05 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 12.59, 17.97, 22.76, 90.48, 156.38. HRMS (ESI$^+$) exact mass calcd for C$_{12}$H$_{27}$OSi [M+H]$^+$ requires m/z 215.1831, found m/z 215.1830.

Cyclopentenyloxytriisopropylsilane (9e)

$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 12.48, 17.89, 21.48, 28.69, 33.57, 102.18, 155.54. HRMS (ESI$^+$) exact mass calcd for C$_{14}$H$_{29}$OSi [M+H]$^+$ requires m/z 241.1988, found m/z 241.1979.

Cyclohexenyloxytriisopropylsilane (9f)

$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 12.64, 18.01, 22.37, 23.26, 23.87, 29.93, 103.63, 150.63. HRMS (ESI$^+$) exact mass calcd for C$_{15}$H$_{31}$OSi [M+H]$^+$ requires m/z 255.2144, found m/z 255.2133.

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

$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{20}$H$_{33}$OSi [M+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$_2$Cl$_2$ (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$_2$Cl$_2$, 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$_2$SO$_4$, 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%. $^1$H 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, 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 calced for C$_{29}$H$_{50}$O$_3$SiNa [M+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%. $^1$H 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 calced for
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C$_{29}$H$_{50}$O$_3$SiNa [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. $^1$H NMR (400 MHz, CDCl$_3$):

$\delta$ 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$_3$): $\delta$ 14.13, 18.53, 18.55, 19.58, 20.12, 25.59, 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$_3$Si [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. $^1$H NMR (400 MHz, CDCl$_3$):

$\delta$ 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$_3$): $\delta$ 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$_3$SiNa [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-octahydrophenanthen-3-yl)oxy)pentan-2-ol (12a)

Yield: 76%, dr: 82/18. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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,
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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 C$_{31}$H$_{54}$O$_3$SiNa [M+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. $^1$H 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 C$_{30}$H$_{52}$O$_3$SiNa [M+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. $^1$H 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), 1.23 (d, $J = 6.1$ Hz, 3H), 1.32 (s, 3H), 1.36-1.42 (m, 1H), 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 C$_{32}$H$_{57}$O$_3$Si [M+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. $^1$H 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, J1 = 2.8 Hz, J2 = 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); 13C NMR (100 MHz, CDCl3): 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 calcld for C29H50BrO3Si [M+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, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 calcld for C32H54O3SiNa [M+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, CDCl3): 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, J1 = 4.5 Hz, J2 = 12.4 Hz, 1H), 7.06-7.18 (m, 3H), 7.31 (d, J = 7.2 Hz, 1H); 13C NMR (100 MHz, CDCl3): 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 calcld for C31H52O3SiNa [M+Na]+ requires m/z 537.3740, found m/z 523.3599.

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

Yield: 62%, colorless Oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$
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$_3$): $\delta$
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 C$_{31}$H$_{54}$O$_3$SiNa [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$
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$_3$): $\delta$
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 C$_{31}$H$_{54}$O$_4$SiNa [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$
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\(_3\)): \(\delta 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 C\(_{31}\)H\(_{55}\)O\(_3\)Si [M+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,a,9,10,10a-octahydrophenanthren-3-yloxy)butan-2-ol (16e)

Yield: 76%, colorless Oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 0.92\) (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\(_3\)): \(\delta 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 C\(_{33}H_{58}O_6SiNa [M+Na]^{+}\) 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,a,9,10,10a-octahydrophenanthren-3-yloxy)butan-2-ol (16g)

Yield: 50%, colorless Oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 0.92\) (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\(_3\)): \(\delta 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 C\(_{30}H_{52}ClO_3Si [M+H]^{+}\) requires \(m/z\) 523.3374, found \(m/z\) 523.3388.
(2R,3R)-3-((2R,4R,4aS,11bR)-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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 14.17, 15.76, 18.75, 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 C$_{39}$H$_{60}$NO$_5$SSi [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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, $J_2 = 14.0$ 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$_3$): $\delta$ 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 C$_{29}$H$_{50}$O$_3$SiNa [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 12.29, 13.16, 13.64, 14.21, 15.76,
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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 C_{29}H_{51}O_{3}Si [M+H]⁺ requires m/z 475.3607, found m/z 475.3596.

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

Yield: 74%, colorless Oil, Dr: 1/1. \( ^1H \) NMR (400 MHz, CDCl₃):
\[ \delta 0.94 (s, 6H), 1.05-1.17 (m, 7H), 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);

\( ^{13}C \) NMR (100 MHz, CDCl₃): \[ \delta 13.41, 13.74, 13.86, 14.02, 14.62, 14.70, 17.69, 18.44, 18.48, 20.03, 20.08, 20.12, 21.04, 22.15, 22.21, 23.91, 24.87, 25.53, 29.01, 32.36, 33.14, 34.58, 35.26, 41.21, 41.75, 42.27, 44.28, 47.47, 51.65, 71.13, 74.73, 75.23, 77.63, 81.05, 82.60, 128.38, 128.60, 143.58, 145.63. \] HRMS (ESI⁺) exact mass calcd for C_{28}H_{53}ClO_{3}SiK [M+K]⁺ requires m/z 539.3090, found m/z 539.3096.

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

Yield: 58%, dr: 82/18, colorless Oil. \( ^1H \) NMR (400 MHz, CDCl₃):
\[ \delta 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, 0.82Hz) for the major, 6.67 (d, \( J = 8.0 \) Hz, 0.18Hz) for the minor, 6.89 (d, \( J = 8.0 \) Hz, 0.82Hz), 6.93 (d, \( J = 8.0 \) Hz, 0.18Hz), 7.12 (t, \( J = 7.6 \) Hz, 1H); \( ^{13}C \) NMR (100 MHz, CDCl₃): \[ \delta 14.48, 16.60, 17.25, 18.49, 18.57, 18.76, 18.86, 23.19, 23.68, 24.67, 25.33, 26.23, 36.64, 38.07, 38.14, 38.75, 39.00, 40.77, 45.30, 49.81, 54.65, 55.23, 71.24, 71.66, 78.30, 79.48, 106.41, 116.46, 124.15, 126.13, 151.70, 157.04. \] HRMS (ESI⁺) exact mass calcd for C_{38}H_{64}O_{4}SiNa [M+Na]⁺ requires m/z 635.4472, found m/z 635.4472.

(2R,3R)-3-((6R,8S,9S,1R,13S,14S)-17-(1-Chloropropylidene)-8,13-dimethyl-10-(triisopropylsilyloxy)hexadecahydro-1H-cyclopenta[a]phenanthren-6-yloxy)butan-2-ol (18)
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ol (22)
Yield: 61%, dr: 78/22, colorless Oil. $^1$H 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, 19.93, 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 C$_{35}$H$_{64}$ClO$_3$Si $[^{M+H}]^+$ 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. $^1$H 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), 1.20 (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 C$_{35}$H$_{57}$OCl$_3$Si $[^{M+Na}]^+$ 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$_2$Cl$_2$ and cooled to -78 °C. O$_3$ was inlet into the reaction mixture until the color turned to blue. Me$_2$S (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. \( ^1 \text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta 0.89-1.05 \) (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); \( ^{13} \text{C} \) NMR (100 MHz, CDCl\(_3\)): \( \delta 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 C\(_{32}\)H\(_{52}\)O\(_4\)SiNa [M+Na]\(^+\) requires \text{m/z} 551.3533, found \text{m/z} 551.3529.

To a round bottom flask equipped with a magnetic stir, the alcohol (1.0 equiv.) was dissolved in CH\(_2\)Cl\(_2\) (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\(_2\)O 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\(_2\)SO\(_4\). 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)

\( ^1 \text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta 0.89 \) (s, 3H), 1.19 (s, 3H), 1.30 (s, 3H), 1.66-1.80 (m, 4H), 1.99 (dd, \( J_1 = 2.8 \) Hz, \( J_2 = 11.6 \) Hz, 1H), 2.18-2.22 (m, 1H), 2.34 (dd, \( J_1 = 2.0 \) Hz, \( J_2 = 11.6 \) Hz, 1H), 2.89-2.98 (m, 2H), 3.76 (d, \( J = 8.4 \) Hz, 1H), 3.83 (t, \( J = 2.4 \) Hz, 1H), 7.09-7.15 (m, 3H), 7.24 (d, \( J = 6.4 \) Hz, 1H); \( ^{13} \text{C} \) NMR (100 MHz, CDCl\(_3\)): \( \delta 18.99, 19.41, 24.23, 26.64, 28.61, 38.34, 39.46, 40.33, 43.11, 73.56, 77.46, 123.92, 125.53, 125.59, 129.50, 134.82, 148.39. HRMS (ESI\(^+\)) exact mass calcd
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for C$_{17}$H$_{24}$O$_2$Na [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); 13C 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$_2$Cl$_2$ and then m-CPBA (1.2 equiv) was added. The reaction mixture was stirred for 2h at room temperature. The reaction mixture was diluted with CH$_2$Cl$_2$ and washed with Sat. Na$_2$CO$_3$. The organic layer was dried over Na$_2$SO$_4$ 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 ºC. 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,9,10a-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$_3$): $\delta$ 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.

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

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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-((1$R$,3$R$,4a$R$,10a$S$)-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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.84 (s, 3H), 1.07-1.11 (m, 2H), 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$_3$): $\delta$ 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.
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 reduced 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, J₁ = 1.2 Hz, J₂ = 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, J₁ = 1.6 Hz, J₂ = 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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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); \(^1\)^C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 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 \( \text{C}_{16}\text{H}_{23}\text{O}_3 \) [M+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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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); \(^1\)^C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 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 \( \text{C}_{16}\text{H}_{22}\text{O}_2\text{Na} \) [M+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. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 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); \(^1\)^C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 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. \(^1\)HRMS (ESI\(^+\)) exact mass calcd for \( \text{C}_{19}\text{H}_{28}\text{O}_3\text{Na} \) [M+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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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,
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1H), 7.18 (dd, J1 = 8.0, J2 = 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); 13C NMR (100 MHz, CDCl3): 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 C24H28NO4S [M+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, CDCl3): 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), 5.20 (dt, J1 = 1.2 Hz, J2 = 7.0 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H); 13C NMR (100 MHz, CDCl3): δ 16.76, 29.84, 35.19, 44.07, 64.79, 103.87, 126.74, 128.28, 129.85, 131.24, 131.4, 140.6. HRMS (ESI+) exact mass calcd for C15H20ClO2 [M+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, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 C14H19O2 [M+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, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 C13H20O2Na [M+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 CH2Cl2 (2 mL) and added via syringe. After
cooling the solution to -78 °C, 20 mL isobutene (S. T. P.) was added. TiCl$_4$ (0.24 mL of a 1.0M solution in CH$_2$Cl$_2$, 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). The reaction mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na$_2$SO$_4$, 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')

![](image)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{20}$H$_{31}$O$_2$ [M+H]$^+$ requires $m/z$ 303.2324, found $m/z$ 303.2309.

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

![](image)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 19.25, 22.22, 23.36, 24.62, 27.84, 31.24, 34.73, 35.75, 38.16, 43.91, 45.18, 45.75, 61.87, 71.06, 123.67, 125.73, 125.75, 129.20, 134.80, 147.03. HRMS (ESI$^+$) exact mass calcd for C$_{20}$H$_{31}$O$_2$ [M+H]$^+$ requires $m/z$ 303.2324, found $m/z$ 303.2328.

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

Yield: 85%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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,
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3H), 7.31-7.33 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{19}$H$_{28}$O$_2$Na [M+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)

\[
\text{HOC}_2\text{H}_4\text{O} \quad \text{Cl}
\]

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 18.54, 19.61, 19.94, 25.69, 26.07, 27.28, 32.51, 34.47, 38.65, 41.36, 43.55, 68.86, 75.89, 122.00, 125.28, 127.07, 133.51, 136.73, 148.62. HRMS (ESI$^+$) exact mass calcd for C$_{20}$H$_{30}$O$_2$Na [M+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%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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 = 6.2 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$_3$): $\delta$ 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$^+$)
2-(1,1,4a,6-Tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-3-yl)oxy)ethane (29d)

Yield: 85%. $^1$H 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$_3$ [M+H]$^+$ requires m/z 319.2273, found m/z 319.2270.

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

Yield: 53%, colorless oil. $^1$H 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-yl)oxy)ethanol (29f)

Yield: 68%. $^1$H 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,
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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, J₁ = 7.2 Hz, J₂ = 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-1H-inden-5-yl)oxy)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.
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3-(2-Iodoethoxy)-7-isopropyl-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 calcld 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, J1 = 2.9 Hz, J2 = 7.6 Hz, J3 = 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.
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128.43, 134.38, 138.78, 142.72, 154.85. HRMS (ESI+) exact mass calcd for C_{28}H_{38}O_{2}Na [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-octahydrophenanthren-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 H_{2}, then filtered through celite and the filtration was concentrated in vacuo to give the title compound. Yield: 98%. 1H NMR (400 MHz, CDCl_{3}): 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), 6.87 (s, 1H), 6.88 (s, 1H). 13C NMR (100 MHz, CDCl_{3}): 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 C_{21}H_{33}O_{2} [M+H]^{+} requires m/z 317.2481, found m/z 317.2482.

TsOH, CH_{2}Cl_{2}R

OEt

OEt

+ R

R'

O

O

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 CH_{2}Cl_{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. (E)-2-(2-Methyl-5-phenylpent-2-enyl)-1,3-dioxane (5a)

Yield: 93%, colorless oil. 1H NMR (400 MHz, CDCl_{3}): 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, CDCl_{3}): 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 C_{16}H_{23}O_{2} [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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

- 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, $J = 6.5$ Hz, 2H), 4.11 (dd, $J_1 = 4.8$ Hz, $J_2 = 11.8$ Hz, 1H), 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$_3$): $\delta$ 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 C$_{17}$H$_{25}$O$_2$ [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

- 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$_3$): $\delta$ 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 C$_{17}$H$_{24}$O$_3$Na [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

- 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$_3$): $\delta$ 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 C$_{17}$H$_{24}$O$_2$Na [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

- 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,
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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$_3$): $\delta$ 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 C$_{17}$H$_{25}$O$_3$ [M+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. $^1$H 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 C$_{16}$H$_{21}$ClO$_2$Na [M+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. $^1$H 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 C$_{20}$H$_{30}$O$_3$Na [M+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. $^1$H 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 C$_{13}$H$_{25}$O$_2$ [M+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 CH₂Cl₂ (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 hours before diluting with CH₂Cl₂ (25 mL). The organic solution was washed with H₂O (2 × 30 mL) 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.

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

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\text{1H NMR (400 MHz, CDCl₃): } \delta 1.08 \text{ (s, 9H), } 1.69 \text{ (s, 3H), } 4.08 \text{ (s, 2H), } 4.86 \text{ (s, 1H), } 5.14 \text{ (s, 1H), } 7.26-7.45 \text{ (m, 6H), } 7.68-7.71 \text{ (m, 4H); } \text{13C NMR (100 MHz, CDCl₃): } \delta 19.04, 19.31, 26.82, 67.26, 109.12, 127.66, 129.61, 133.73, 135.53, 144.24. \text{ HRMS (ESI⁺) exact mass calcd for C}_{20}H_{26}OSiNa [M+Na⁺] requires } m/z 333.1651, \text{ found } m/z 333.1642.
\]

2-Methylallyl benzoate (36f)

\[
\text{Yield: 97%, colorless oil. 1H NMR (400 MHz, CDCl₃): } \delta 1.84 \text{ (s, 3H), } 4.75 \text{ (s, 2H), } 4.99 \text{ (s, 1H), } 5.08 \text{ (s, 1H), } 7.43-7.47 \text{ (m, 2H), } 7.54-7.59 \text{ (m, 1H), } 8.07-8.09 \text{ (m, 2H); } \text{13C NMR (100 MHz, CDCl₃): } \delta 19.60, 68.13, 112.95, 128.39, 129.64, 130.21, 132.99, 140.01, 166.26. \text{ HRMS (ESI⁺) exact mass calcd for C}_{11}H_{13}O_{2} [M+H⁺] requires } m/z 177.0916, \text{ found } m/z 177.0908.
\]

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

\[
\text{Yield: 95%, colorless oil. 1H NMR (400 MHz, CDCl₃): } \delta 1.05-1.19 \text{ (m, 21H), } 1.73 \text{ (s, 3H), } 4.14 \text{ (s, 2H), } 4.84 \text{ (s, 1H), } 5.07 \text{ (s, 1H); } \text{13C NMR (100 MHz, CDCl₃): } \delta 12.04, 18.01, 18.94, 66.86, 108.76, 144.65. \text{ HRMS (ESI⁺) exact mass calcd for C}_{13}H_{28}OSiNa [M+Na⁺] requires } m/z 251.1807, \text{ found } m/z 251.1809.
\]

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

\[
\text{Yield: 95%, colorless oil. 1H NMR (400 MHz, CDCl₃): } \delta 0.39 \text{ (s, 6H), } 1.69 \text{ (s, 3H), } 4.02 \text{ (s, 2H), } 4.82 \text{ (s, 1H), } 4.99 \text{ (s, 1H), } 7.34-7.40 \text{ (m, 3H), } 7.57-7.59 \text{ (m, 2H); } \text{13C NMR (100 MHz, CDCl₃): } \delta -1.74, -0.88, 19.06, 66.78, 109.83, 127.86, 129.63, 133.51, 137.76, 144.19. \text{ HRMS (ESI⁺) exact mass calcd for C}_{12}H_{18}OSiK [M+K⁺] requires } m/z 245.0764, \text{ found } m/z 245.0767.
\]

((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 30 min, 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 h, the reaction mixture was poured into H₂O and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with H₂O (2 × 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, J₁
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= 10.8 Hz, \( J_2 = 13.8 \) Hz, (1H), 1.84-1.90 (m, 3H), 2.06-2.14 (m, 1H), 2.52 (dd, \( J_1 = 6.7 \) 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\(_3\))): \( \delta \) 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 C\(_{36}\)H\(_{49}\)O\(_3\)Si [M+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[\( a \)]naphtalen-10-yloxy)propan-1-ol (38a)

Yield: 54%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 0.80 (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\(_3\))): \( \delta \) 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 C\(_{36}\)H\(_{49}\)O\(_3\)Si [M+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[\( a \)]naphtalen-10-yloxy)propan-1-ol (37b)

Yield: 51%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 0.64 (d, \( J = 7.2 \) Hz, (3H), 1.10 (s, (9H), 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\(_3\))): \( \delta \) 20.01, 20.09, 22.29, 25.94, 26.00, 27.75, 28.54, 32.21,
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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 C_{37}H_{51}O_3Si [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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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, 134.65, 134.78, 136.26, 136.35, 147.48. HRMS (ESI+) exact mass calcd for C$_{37}$H$_{51}$O$_3$Si [M+H]$^+$ requires m/z 571.3603, 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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{37}$H$_{51}$O$_4$Si [M+H]$^+$ requires m/z 587.3557, found m/z 587.3547.

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

Yield: 58%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{37}$H$_{51}$O$_3$Si [M+H]$^+$ requires m/z 571.3607, found m/z 571.3594.

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

Yield: 49%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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 (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$_3$): $\delta$ 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 C$_{37}$H$_{51}$O$_3$Si [M+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-ylxy)propan-1-ol (37d)

Yield: 58%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{37}$H$_{51}$O$_3$Si [M+H]$^+$ requires m/z 571.3607, found m/z 571.3594.
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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 C$_{37}$H$_{51}$O$_4$Si [M+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. $^1$H 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 C$_{33}$H$_{53}$O$_4$Si [M+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)

$^1$H 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 C$_{29}$H$_{43}$O$_4$Si [M+H]$^+$ requires m/z 483.2931, found m/z 483.2939.

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 (38e)

Yield: 63%, yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): δ 0.78 (s, 3H), 0.98 (d, $J = 6.2$ Hz, 3H), 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 C$_{33}$H$_{53}$O$_4$Si [M+H]$^+$ requires m/z 541.3713, found m/z 541.3705.
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); 13C NMR (100 MHz, CDCl3): \( \delta \) 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, 135.25, 136.35, 148.65, 157.69. HRMS (ESI+) exact mass calced for C37H51O4Si [M+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-5H-cyclohepta[a]naphthalen-10-yloxy)propan-1-ol (37f)

Yield: 55%, colorless oil. \(^1\)H NMR (400 MHz, CDCl3): \( \delta \) 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); 13C NMR (100 MHz, CDCl3): \( \delta \) 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, 136.65, 136.89, 146.47, 154.97. HRMS (ESI+) exact mass calced for C40H57O4Si [M+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-5H-cyclohepta[a]naphthalen-10-yloxy)propan-1-ol (38f)

Yield: 63%, yellow oil. \(^1\)H NMR (400 MHz, CDCl3): \( \delta \) 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),
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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$_3$): \( \delta \) 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 C$_{40}$H$_{57}$O$_4$Si [M+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. \(^1\)H NMR (400 MHz, CDCl$_3$): \( \delta \) 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$_3$): \( \delta \) 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 C$_{33}$H$_{50}$O$_3$SiNa [M+Na]$^+$ requires \( m/z \) 545.3427, found \( m/z \) 545.3444.

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

\(^1\)H NMR (400 MHz, CDCl$_3$): \( \delta \) 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, \( J = 7.4 \text{ Hz}, 1\text{H} \)), 7.44 (d, \( J = 8.0 \text{ Hz}, 1\text{H} \)); \(^{13}\text{C NMR (100 MHz, CDCl}_3\)): \( \delta \) 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 \( \text{C}_{17}\text{H}_{25}\text{O}_2 [\text{M+H}]^+ \) requires \( m/z \) 261.1855, found \( m/z \) 261.1847.

\( 2\)-\text{Methoxy-8,11a-dimethyl-6,6a,7,8,9,10,11,11a-octahydro-5H-cyclohepta[a]napht halene-7,10-diol (42) \)

\(^1\text{H NMR (400 MHz, CDCl}_3\)): \( \delta \) 1.08 (d, \( J = 7.0 \text{ Hz}, 3\text{H} \)), 1.33 (s, 3\text{H} ), 1.42-1.60 (m, 3\text{H} ), 1.64-1.70 (m, 1\text{H} ), 1.72-1.80 (m, 2\text{H} ), 2.13-2.18 (m, 1\text{H} ), 2.25 (d, \( J = 14.1 \text{ Hz}, 1\text{H} \)), 2.63 (dd, \( J_1 = 2.7 \text{ Hz}, J_2 = 13.4 \text{ Hz}, 1\text{H} \)), 2.73-2.77 (m, 2\text{H} ), 3.51-3.55 (m, 1\text{H} ), 3.78 (s, 3\text{H} ), 3.98 (ddt, \( J_1 = 3.1 \text{ Hz}, J_2 = 4.3 \text{ Hz}, J_3 = 11.1 \text{ Hz}, 1\text{H} \)), 6.68 (dd, \( J_1 = 2.6 \text{ Hz}, J_2 = 8.4 \text{ Hz}, 1\text{H} \)), 6.91 (d, \( J = 2.5 \text{ Hz}, 1\text{H} \)), 6.97 (d, \( J = 8.4 \text{ Hz}, 1\text{H} \)); \(^{13}\text{C NMR (100 MHz, CDCl}_3\)): \( \delta \) 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 \( \text{C}_{18}\text{H}_{27}\text{O}_3 [\text{M+H}]^+ \) 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 (±)-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.

![Salvinorin A](image1)

![B](image2)

![Oxandrin](image3)

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](image)

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 (±)-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


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 InBr₃ (30
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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
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</tbody>
</table>
Chapter 3. Prins Polyene Cyclization for the Synthesis of Oxaterpenoid Skeleton and Its Application in Total Synthesis of (+)-Moluccanic Acid Methyl Ester

1. \[ \text{H} \text{O} \text{2a} \text{O} \text{H} \text{4a} \text{88} \]

2. \[ \text{H} \text{O} \text{2b} \text{O} \text{H} \text{4b} \text{79} \]

3. \[ \text{H} \text{O} \text{2c} \text{O} \text{H} \text{4c} \text{71} \]

4. \[ \text{H} \text{O} \text{2d} \text{O} \text{H} \text{4d} \text{87} \]

5. \[ \text{H} \text{O} \text{2e} \text{O} \text{H} \text{4e} \text{90} \]

6. \[ \text{H} \text{O} \text{2f} \text{O} \text{H} \text{Ph} \text{4f} \text{94} \]
Chapter 3. Prins Polyene Cyclization for the Synthesis of Oxaterpenoid Skeleton and Its Application in Total Synthesis of (+)-Moluccanic Acid Methyl Ester

7. \( \text{H}_2\text{O} \quad 2g \quad \begin{array}{c} \text{O} \\ \text{H} \end{array} \quad 4g \quad 81 \\

8. \( \text{O} \quad 2h \quad \begin{array}{c} \text{O} \\ \text{H} \end{array} \quad 4h \quad 88 \\

9. \( \text{H}_2\text{O} \quad 2i \quad \begin{array}{c} \text{O} \\ \text{H} \end{array} \quad 4i \quad 79 \\

10. \( \text{BnO} \quad 2j \quad \begin{array}{c} \text{O} \\ \text{H} \end{array} \quad 4j \quad 66 \\

11. \( \text{Ph} \quad 2k \quad \begin{array}{c} \text{O} \\ \text{H} \end{array} \quad 4k \quad 84^c \\

12. \( \text{O} \quad 2l \quad \begin{array}{c} \text{O} \\ \text{H} \end{array} \quad 4l \quad 73 \\

13. \( \text{Cl} \quad \text{O} \quad \text{OMe} \quad 2m \quad \begin{array}{c} \text{O} \\ \text{H} \end{array} \quad 4m \quad 69
Chapter 3. Prins Polyene Cyclization for the Synthesis of Oxaterpenoid Skeleton and Its Application in Total Synthesis of (±)-Moluccanic Acid Methyl Ester

![Chemical structures and text image]

When enantiomerically pure aldehyde 2o was used for this reaction, a single diastereomer 4o was obtained with good yield (74%) and the absolute stereochemistry has been assigned accordingly based on single crystal X-ray analysis (Figure 3.2).

![Diagram of reagents and products]

**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 InBr$_3$-Catalyzed Prins-Polyene Cyclization$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Substrate 1" /></td>
<td><img src="image2.png" alt="Product 1b" /></td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Substrate 2" /></td>
<td><img src="image4.png" alt="Product 1c" /></td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Substrate 3" /></td>
<td><img src="image6.png" alt="Product 1d" /></td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Substrate 4" /></td>
<td><img src="image8.png" alt="Product 1e" /></td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Substrate 5" /></td>
<td><img src="image10.png" alt="Product 1f" /></td>
<td>63</td>
</tr>
</tbody>
</table>
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 tetracyclic 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.

\[ \text{Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate.}\]
\[ \text{Isolated yield.}\]
\[ \text{The stereochemistry of alkene was 3/1, which determined by } ^1\text{H NMR.}\]
Table 3.3 InBr₃-Catalyzed Prins-Polyene Cyclization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate" /></td>
<td><img src="image2" alt="Product" /></td>
<td>10j 81</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate" /></td>
<td><img src="image4" alt="Product" /></td>
<td>10k 87</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate" /></td>
<td><img src="image6" alt="Product" /></td>
<td>10l 82</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate" /></td>
<td><img src="image8" alt="Product" /></td>
<td>10m 66</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Substrate" /></td>
<td><img src="image10" alt="Product" /></td>
<td>10n 59</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. <sup>b</sup> 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 SN2 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 TiCl4 in CH2Cl2 at room temperature did not yield any product (Scheme 3.4).

---

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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](image)

**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 Wittig 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. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 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 calced for C$_{11}$H$_{14}$O$_3$ [M+Na]$^+$ requires $m/z$ 217.0841, found $m/z$ 217.0843.

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

Yield: 85%, yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 12.48, 24.19, 29.41, 49.86, 51.72, 109.71, 114.79, 118.79, 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 calced for C$_{22}$H$_{23}$NO$_2$ [M+H]$^+$ requires $m/z$ 334.1807, found $m/z$ 334.1805.

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

Yield: 99%, yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 12.43,
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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 C\(_{18}\)H\(_{25}\)O\(_2\) [M+H]\(^+\) requires m/z 273.1855, found m/z 273.1844.

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

Yield: 83%, yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C\(_{21}\)H\(_{30}\)O\(_5\) [M+Na]\(^+\) requires m/z 385.1991, found m/z 385.2006.

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

Yield: 98%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C\(_{23}\)H\(_{32}\)O\(_2\) [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 CH\(_2\)Cl\(_2\) and cooled to 0 °C. DIBAI-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\(_4\)Cl, 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\(_2\)SO\(_4\) 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 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.

\((E)-6-(\text{Furan-2-yl})-3\text{-methylhex-3-enenitrile}\)

Yield: 67%, yellow oil. \(^{1}\)H NMR (400 MHz, CDCl₃): \(\delta\) 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); \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta\) 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.

\((E)-6-(1\text{-Benzyl-1H-indol-3-yl})-3\text{-methylhex-3-enenitrile}\)

Yield: 77%, yellow oil. \(^{1}\)H NMR (400 MHz, CDCl₃): \(\delta\) 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); \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta\) 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.

\((3E,7E)-3,7\text{-Dimethyl-10-phenyldeca-3,7-dienenitrile}\)

Yield: 87%, yellow oil. \(^{1}\)H NMR (500 MHz, CDCl₃): \(\delta\) 1.55 (s, 3H), 1.71 (s, 3H), 2.00-2.03 (m,
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(3E,7E)-3,7-Dimethyl-10-(3,4,5-trimethoxyphenyl)deca-3,7-dienenitrile

Yield: 60%, yellow oil. ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₁H₂₉NO₃ [M+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, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₇H₃₀N₂ [M+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, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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⁺)
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exact mass calcd for C_{23}H_{31}N [M+H]^+ requires m/z 322.2535, found m/z 322.2542.

\[
\begin{align*}
&\text{R}\text{CN} \\
&\text{DIBAL-H, CH}_2\text{Cl}_2 \text{ -78 °C} \\
&\text{NaBH}_4, \text{THF/MeOH} \rightarrow \text{R}\text{OH}
\end{align*}
\]

To an oven-dried round bottom flask (50 mL) equipped with a magnetic stir bar, the cyanide (1.0 mmol) was dissolved in dry CH₂Cl₂ (10 mL) and cooled to -78 °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 °C for 1h and then EtOH (0.1 mL) was added, the reaction mixture was diluted with EtOAc (10 mL) and poured into Sat. NH₄Cl (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 Na₂SO₄, and concentrated in vacuo. The crude product was dissolved in 10 mL MeOH/THF (1/4) and cooled to 0 °C. NaBH₄ (1.0 equiv.) was added and the mixture was stirred for 1 h at 0 °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 MgSO₄ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using EtOAc in hexane to provide the title compound.

\((E)-3\text{-Methyl-6-phenylhex-3-en-1-ol (1a)}\)

Yield: 84%, colorless oil. \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\)
- 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, CDCl₃): \(\delta\)
- 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 C₁₃H₁₈ONa [M+Na]^+ requires m/z 213.1255, found m/z 213.1260.

\((E)-6-(2\text{-Methoxyphenyl}-3\text{-methylhex-3-en-1-ol (1b)}\)

Yield: 80%, colorless oil. \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\)
- 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, CDCl₃): \(\delta\)
- 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 C\textsubscript{14}H\textsubscript{20}O\textsubscript{2}Na [M+Na]\textsuperscript{+} 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. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 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); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 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 C\textsubscript{14}H\textsubscript{20}O\textsubscript{2}Na [M+Na]\textsuperscript{+} requires m/z 243.1364, found m/z 243.1364.

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

Yield: 88%, yellow oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 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, \(J = 6.2\) Hz, 2H), 3.82 (s, 3H), 3.85 (s, 6H), 5.27 (t, \(J = 6.5\) Hz, 1H), 6.40 (s, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 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 C\textsubscript{16}H\textsubscript{24}O\textsubscript{4}Na [M+Na]\textsuperscript{+} 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. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 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); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 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 C\textsubscript{13}H\textsubscript{17}ClONa [M+Na]\textsuperscript{+} 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. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 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); \textsuperscript{13}C NMR (100
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MHz, CDCl$_3$): $\delta$ 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 C$_{11}$H$_{16}$O$_2$Na [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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{22}$H$_{25}$NONa [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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{11}$H$_{18}$ONa [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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): 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 C$_{15}$H$_{22}$ONa [M+H]$^+$ 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%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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,
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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); 1^3C 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 C_{18}H_{26}ONa [M+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); 1^3C 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 C_{19}H_{28}O_{2}Na [M+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); 1^3C 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 C_{21}H_{32}O_{4} [M+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); 1^3C NMR (100 MHz, CDCl_3): δ 15.71,
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15.93, 24.45, 26.48, 28.39, 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 C_{27}H_{33}NO [M+H]^+ requires m/z 388.2640, found m/z 388.2642.

(3E,7E,11E)-3,7,11-Trimethyl-14-phenyltetradeca-3,7,11-trien-1-ol (1n)
Yield: 83%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): 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); $^{13}$C NMR (100 MHz, CDCl$_3$): 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 C$_{23}$H$_{34}$O [M+Na]$^+$ requires m/z 349.2507, found m/z 349.2510.

Experimental Data for InBr$_3$ 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 CH$_2$Cl$_2$ (2 mL) and added via syringe. The solution was allowed to stir at room temperature for 48 h and then quenched with sat. NaHCO$_3$ (5mL), and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na$_2$SO$_4$, 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.

10b-Methyl-4-phenyl-2,4,4a,5,6,10b-hexahydro-1H-benzo[g]isochromene (4a)
Yield: 88%, white solid, mp: 83.9-84.8 °C. $^1$H NMR (400 MHz, CDCl$_3$): 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, $J = 114$
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 C$_{20}$H$_{22}$ONa [M+Na]$^+$ requires m/z 301.1568, found m/z 301.1564.

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

Yield: 79%, yellow solid, mp: 75.4–76.2 °C. $^1$H 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, $J_2 = 12.0$ 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 C$_{18}$H$_{21}$O$_2$ [M+H]$^+$ requires m/z 269.1542, found m/z 269.1533.

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

Yield: 71%, yellow solid, mp: 84.0–85.2 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ 1.32 (s, 3H), 1.37 (td, $J_1 = 3.3$ 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
10b-Methyl-4-((E)-styryl)-2,4,4a,5,6,10b-hexahydro-1H-benzo[f]isochromene (4d)

Yield: 87%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 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, 128.29, 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-1H-benzo[f]isochromene (4e)

Yield: 90%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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, \(J = 9.2\) Hz, 1H), 3.92 (dt, \(J_1 = 2.3\) Hz, \(J_2 = 12.3\) Hz, 1H), 4.00 (dddd, \(J_1 = 1.6\) 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\(_3\)): \(\delta\) 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-1H-benzo[f]isochromene (4f)

Yield: 94%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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 (dd, \(J_1 = 6.2\) 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
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(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$_3$): $\delta$ 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 C$_{22}$H$_{26}$ONa [M+Na]$^+$ requires $m/z$ 329.1881, found $m/z$ 329.1869.

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

Yield: 81%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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), 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$_3$): $\delta$ 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 C$_{18}$H$_{26}$ONa [M+Na]$^+$ requires $m/z$ 281.1881, found $m/z$ 281.1871.

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

Yield: 88%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{20}$H$_{28}$ONa [M+Na]$^+$ requires $m/z$ 307.2038, found $m/z$ 307.2029.

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

Yield: 79%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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,

\[ J_2 = 11.8 \text{ Hz}, 1H \], 7.05 (d, \( J = 7.0 \text{ Hz}, 1H \), 7.10 (t, \( J = 7.1 \text{ Hz}, 1H \), 7.16 (t, \( J = 7.0 \text{ Hz}, 1H \), 7.21 (d, \( J = 7.5 \text{ Hz}, 1H \); \^{13}C NMR (100 MHz, CDCl\(_3\): \( \delta \) 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 C\(_{18}\)H\(_{26}\)ONa [M+Na]\(^+\) requires \( m/z \) 281.1881, found \( m/z \) 281.1875.

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

Yield: 66%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\): \( \delta \) 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, \( J = 13.1 \text{ Hz}, 1H \), 2.86-2.90 (m, 2H), 3.55 (dd, \( J_1 = 4.8 \text{ Hz}, J_2 = 10.1 \text{ Hz}, 1H \), 3.60-3.64 (m, 1H), 3.68 (dd, \( J_1 = 2.3 \text{ Hz}, J_2 = 10.1 \text{ Hz}, 1H \), 3.91 (dt, \( J_1 = 2.4 \text{ Hz}, J_2 = 12.4 \text{ Hz}, 1H \), 4.06 (ddd, \( J_1 = 1.6 \text{ Hz}, J_2 = 5.1 \text{ Hz}, J_3 = 11.8 \text{ Hz}, 1H \), 4.53 (d, \( J = 12.3 \text{ Hz}, 1H \), 4.65 (d, \( J = 12.3 \text{ Hz}, 1H \), 7.07 (d, \( J = 6.9 \text{ Hz}, 1H \), 7.10 (dt, \( J_1 = 1.7 \text{ Hz}, J_2 = 7.0 \text{ Hz}, 1H \), 7.16 (t, \( J = 7.0 \text{ Hz}, 1H \), 7.19 (d, \( J = 7.4 \text{ Hz}, 1H \), 7.26-7.35 (m, 5H); \^{13}C NMR (100 MHz, CDCl\(_3\): \( \delta \) 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 C\(_{22}\)H\(_{26}\)O\(_2\)Na [M+Na]\(^+\) requires \( m/z \) 345.1831, found \( m/z \) 345.1842.

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

Yield: 84%, colorless oil, dr: 50:50. \(^1\)H NMR (400 MHz, CDCl\(_3\): \( \delta \) 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, \( J_1 = 6.3 \text{ Hz}, J_2 = 17.4 \text{ Hz}, 1H \), 2.96 (dd, \( J_1 = 5.4 \text{ Hz}, J_2 = 8.9 \text{ Hz}, 2H \), 3.00-3.07 (m, 2H), 3.57 (ddd, \( J_1 = 2.5 \text{ Hz}, J_2 = 5.8 \text{ Hz}, J_3 = 9.9 \text{ Hz}, 2H \), 3.68 (dt, \( J_1 = 2.3 \text{ Hz}, J_2 = 12.5 \text{ Hz}, 1H \), 3.84 (t, \( J = 12.3 \text{ Hz}, 1H \), 3.93 (ddd, \( J_1 = 1.5 \text{ Hz}, J_2 = 5.0 \text{ Hz}, J_3 = 11.8 \text{ Hz}, 1H \), 4.05 (ddd, \( J_1 = 1.6 \text{ Hz}, J_2 = 5.0 \text{ Hz}, J_3 = 11.7 \text{ Hz}, 1H \), 6.95 (d, \( J = 7.2 \text{ Hz}, 1H \), 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\(_3\): \( \delta \) 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
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C$_{22}$H$_{26}$O $[\text{M+H}]^+$ requires m/z 307.2062, found m/z 307.2060.

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

Yield: 69%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{15}$H$_{19}$ClONa $[\text{M+Na}]^+$ requires m/z 273.1022, found m/z 273.1016.

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

Yield: 58%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.24 (s, 3H), 1.56-1.62 (m, 1H), 1.70 (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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{15}$H$_{19}$BrONa $[\text{M+Na}]^+$ requires m/z 317.0517, found m/z 317.0526.

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

Yield: 73%, white solid, mp: 73.2-74.5 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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,
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1H; 13C NMR (100 MHz, CDCl3): 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 C16H22O [M+Na]+ requires m/z 253.1568, found m/z 253.1567.

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

Yield: 74%, white solid, mp: 149.5-151.0 °C. 1H NMR (400 MHz, CDCl3): 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, J1 = 5.2 Hz, J2 = 8.7 Hz, 2H), 3.42 (d, J = 9.8 Hz, 1H), 3.76 (t, J = 11.3 Hz, 1H), 3.98 (dd, J1 = 3.9 Hz, J2 = 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); 13C NMR (100 MHz, CDCl3): 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 C35H49O2 [M+H]+ requires m/z 501.3733, found m/z 501.3719.

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

Yield: 94%, white solid, mp: 96.5-97.8 °C. 1H NMR (400 MHz, CDCl3): δ 1.22-1.26 (m, 1H), 1.34 (s, 3H), 1.46 (ddt, J1 = 7.8 Hz, J2 = 10.6 Hz, J3 = 13.3 Hz, 1H), 1.88 (ddd, J1 = 3.0 Hz, J2 = 10.3 Hz, J3 = 13.3 Hz, 1H), 2.03 (dt, J1 = 5.2 Hz, J2 = 12.8 Hz, 1H), 2.13 (d, J = 13.1 Hz, 1H), 2.45-2.54 (m, 1H), 2.68 (dd, J1 = 7.5 Hz, J2 = 18.5 Hz, 1H), 3.77 (s, 3H), 4.02 (dt, J1 = 2.5 Hz, J2 = 12.2 Hz, 1H), 4.11 (ddd, J1 = 1.6 Hz, J2 = 5.1 Hz, J3 = 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); 13C NMR (100 MHz, CDCl3): 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 C21H25O2 [M+H]+ requires m/z 309.1855, found m/z 309.1859.
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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, CDCl3): δ 1.14-1.21 (m, 1H), 1.34 (s, 3H), 1.49 (ddt, J1 = 8.1 Hz, J2 = 10.2 Hz, J3 = 13.2 Hz, 1H), 1.87 (dddd, J1 = 3.3 Hz, J2 = 10.3 Hz, J3 = 13.3 Hz, 1H), 2.04-2.09 (m, 2H), 2.64-2.70 (m, 1H), 2.73 (dd, J1 = 7.1 Hz, J2 = 16.4 Hz, 1H), 3.80 (s, 3H), 4.03 (dt, J1 = 3.2 Hz, J2 = 11.9 Hz, 1H), 4.12 (dd, J1 = 1.9 Hz, J2 = 4.8 Hz, J3 = 11.9 Hz, 1H), 4.36 (d, J = 10.3 Hz, 1H), 6.69 (dd, J1 = 2.6 Hz, J2 = 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); 13C NMR (100 MHz, CDCl3): 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 C21H25O2 [M+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, CDCl3): δ 1.05-1.10 (m, 1H), 1.38 (t, J = 5.8 Hz, 1H), 1.46 (s, 3H), 1.88 (ddd, J1 = 2.1 Hz, J2 = 10.4 Hz, J3 = 12.6 Hz, 1H), 1.98 (td, J1 = 9.2 Hz, J2 = 13.4 Hz, 1H), 2.58-2.72 (m, 2H), 2.83 (d, J = 13.4 Hz, 1H), 3.80 (s, 3H), 3.84 (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); 13C NMR (100 MHz, CDCl3): 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, 141.51, 151.50, 153.29. HRMS (ESI+) exact mass calcd for C23H29O4 [M+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, CDCl3): δ 1.16-1.23 (m, 1H), 1.32 (s, 3H), 1.49 (ddt, J1 = 8.0 Hz, J2 = 10.1 Hz, J3 = 13.3 Hz, 1H), 1.84 (dddd, J1 = 3.3 Hz, J2 = 10.3 Hz, J3 = 13.3 Hz, 1H), 1.99-2.11 (m, 2H), 2.67 (dd, J1 = 9.2 Hz, J2 = 14.0 Hz, 1H), 2.75 (dd, J1 = 2.1 Hz, J2 = 10.4 Hz, J3 = 12.6 Hz, 1H), 4.02 (dt, J1 = 3.0 Hz, J2 = 12.0 Hz, 1H), 4.13 (dd, J1 = 1.9 Hz, J2 = 4.9 Hz, J3 = 12.0 Hz, 1H),
4.35 (d, J = 10.3 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 7.07 (dd, J₁ = 2.2 Hz, J₂ = 8.2 Hz, 1H), 7.20 (d, J = 2.2 Hz, 1H), 7.25-7.35 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₀H₂₁OClNa [M+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 ºC. ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₈H₂₀O₂Na [M+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, CDCl₃): 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, J₁ = 6.7 Hz, J₂ = 11.5 Hz, J₃ = 16.0 Hz, 1H), 2.73 (dd, J₁ = 5.6 Hz, J₂ = 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₉H₃₀NO [M+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, CDCl₃): 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, J₁ = 3.2 Hz, J₂ = 10.3 Hz, J₃ = 13.3 Hz, 1H), 2.21 (dd, J₁ = 1.9 Hz, J₂ = 12.9 Hz, 1H), 2.69-2.77 (m, 2H), 3.84 (dt, J₁ = 1.9 Hz, J₂ = 5.9 Hz, J₃ = 7.8 Hz, 1H), 4.40 (d, J = 10.2 Hz, 1H),
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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); 13C NMR (100 MHz, CDCl3): 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 C22H26ONa [M+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, CDCl3): 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, J1 = 3.3 Hz, J2 = 12.1 Hz, 1H), 4.05 (ddd, J1 = 1.8 Hz, J2 = 5.0 Hz, J3 = 12.2 Hz, 1H), 4.41 (d, J = 10.3 Hz, 1H), 7.27-7.35 (m, 5H); 13C NMR (100 MHz, CDCl3): 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 C18H23BrO2Na [M+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-1H-naphtho[2,1-f]isochromene (10j)

Yield: 81%, white solid, mp: 184.5-186.2 °C. 1H NMR (300 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 C25H31O [M+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-1H-naphtho[2,1-f]isochromene (10k)

Yield: 87%, white solid, mp: 198.3-200.5 °C. 1H NMR (400 MHz, CDCl3): δ 0.93 (d, J = 7.8Hz, 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, J1 = 3.0 Hz, J2 = 9.7 Hz, 1H), 2.57-2.69 (m, 1H), 2.92 (dd, J1 = 6.5 Hz, J2 = 18.2 Hz, 1H), 123
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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$_3$): $\delta$ 13.32, 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 C$_{26}$H$_{33}$O$_2$ [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{28}$H$_{36}$O$_4$ [M+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,7,8,12b,13,13b-dodecahydroisochromeno[6,5-a]carbazole (10m)

Yield: 66%, yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{34}$H$_{37}$NO [M+H]$^+$ requires $m/z$ 476.2953, found $m/z$ 476.2948.

6a,12b,14b-Trimethyl-4-phenyl-2,4,4a,5,6,6a,7,8,12b,13,14,14a,14b-tetradecah
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**Hydro-1H-phenanthro[2,1-f]isochromene (10n)**

Yield: 59%, white solid, mp: 134.0-136.1 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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, $J_3$ = 13.6 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{30}$H$_{38}$O$^{[M+Na]^+}$ 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-1H-benzo[f]isochromene (13)**

Yield: 74%, yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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 (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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{17}$H$_{25}$O$_2$$^{[M+H]^+}$ requires m/z 261.1855, found m/z 261.1864.

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

Yield: 51%, yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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), 3.87-3.90 (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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{17}$H$_{23}$O$_3$$^{[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-1H-benzo[f]isochromene**
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ochromene (17)

Yield: 64%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{16}$H$_{21}$ClO$_2$ [M+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)ethane (19)

Prepared by the following procedure: To a round bottom flask equipped with a magnetic stirrer, sodium hydride (0.16 g, 60% dispersion in mineral oil, 4.0 mmol) was dissolved in N,N-dimethylformamide (5 mL). After cooling to 0 °C, compound 19 (0.28 g, 1.0 mmol) was added slowly, the mixture was stirred for 10 h at 130 °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$_2$SO$_4$, and concentrated in vacuo. The crude product was dissolved in 10 mL acetone and followed 1 mL 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$_2$SO$_4$, 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%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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 (dd, $J_1 = 6.1$ 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$_3$): $\delta$ 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-tetrahydronapht halene (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 dropwise 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, J₁ = 5.1 Hz, J₂ = 9.6 Hz, J₃ = 12.0 Hz, 1H), 3.28 (ddd, J₁ = 4.9 Hz, J₂ = 9.6 Hz, J₃ = 12.6 Hz, 1H), 3.79 (s, 3H), 4.72 (s, 1H), 4.99 (s, 1H), 6.69 (dd, J₁ = 2.7 Hz, J₂ = 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)pro panenitrile (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%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{18}$H$_{23}$NO [$M+Na]^+$ 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$_2$O (10 mL, MeOH/H$_2$O: 4/1). Then KOH (224 mg, 4 mmol) was added and the mixture was stirred overnight at 60 $^\circ$C. The reaction mixture was poured into water and adjusted the pH value to 2 with 1M HCl, extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layer was washed with brine (2 x 30 mL), dried over Na$_2$SO$_4$, 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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{19}$H$_{26}$O$_3$ [$M+H]^+$ 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 CH$_2$Cl$_2$. Then BCl$_3$ (0.19 mL, 1.0 M in CH$_2$Cl$_2$, 0.19 mmol) was added to the mixture slowly at 0 °C. After 2 h, the reaction mixture was poured into sat. NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layer was washed with brine (2 x 30 mL), dried over Na$_2$SO$_4$, 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: 71%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{18}$H$_{24}$O$_3$ [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

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, englerin A, hedyosumin C and (+)-anthecularin (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. Englerin A, a guaiane sesquiterpene, selectively inhibits the growth of renal cancer cells. 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.

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

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

\[
\text{R}_1^1 \text{O} + \text{TMS} \text{SnX}_3^+ \rightarrow \text{R}_2^2 \text{O} \quad \text{43~91% yield}
\]

\[
\text{R}_1^1 \text{O} + \text{TMSO} \text{OMe}^+ \text{TiCl}_4 \rightarrow \text{R}_2^2 \text{O} \quad \text{49~82% yield}
\]

---

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

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 diasteroselectivity. 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). 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

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

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).  

Treating ACP ketone with Lewis acid provided 8-oxabicyclo[3.2.1]octane in high yield.

![Scheme 4.4](image)

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). 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](image)

---

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

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-yrones) 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).

![Scheme 4.6](image)

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

![Scheme 4.7](image)

---

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. After that, remarkable progress has been achieved in this area and the method has been successfully applied in many natural products synthesis. However, the reaction precursors, diazodione, are difficult to synthesize and handle. It inhibits the further application of this reaction.

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).

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. The aldehyde 3 can be protected with a series of alcohols to provide the raw material 4.

Our idea was sooner evaluated through employing 1,4-cyclic acetal-olefin 4a and silyl enol ether 5a with 1.2 equivalent of TiCl4 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

---

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](image)

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

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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 stabilized 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 \( \alpha \)-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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>6a</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>6b</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>6c</td>
<td>90</td>
</tr>
</tbody>
</table>
Chapter 4. Stereoselective Syntheses of 8-Oxatropane via Cationic Cascade Cyclization: Different Initiators, Opposite Diastereoselectivity

4  \[
\text{\begin{align*}
\text{4d} & \quad \text{6d} & \quad 88 \\
\text{4e} & \quad \text{6e} & \quad 92 \\
\text{4f} & \quad \text{6f} & \quad 84 \\
\text{4g} & \quad \text{6g} & \quad 89 \\
\text{4h} & \quad \text{6h} & \quad 84 \\
\text{4i} & \quad \text{6i} & \quad 85 \\
\text{4j} & \quad \text{6j} & \quad 71 \\
\text{4k} & \quad \text{6k} & \quad 66 \\
\text{4l} & \quad \text{6l} & \quad 52 \\
\text{4m} & \quad \text{6m} & \quad 56 \\
\text{4n} & \quad \text{6n} & \quad 74 \\
\text{4o} & \quad \text{6o} & \quad 46 
\end{align*}}
\]
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

---

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>4p</td>
<td>6p</td>
</tr>
<tr>
<td>17</td>
<td>4q</td>
<td>6q</td>
</tr>
<tr>
<td>18</td>
<td>4r</td>
<td>6r</td>
</tr>
<tr>
<td>19</td>
<td>4s</td>
<td>6s</td>
</tr>
<tr>
<td>20</td>
<td>4t</td>
<td>6t</td>
</tr>
<tr>
<td>21</td>
<td>4u</td>
<td>6u</td>
</tr>
</tbody>
</table>

---

\[a\] Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. \[b\] Single diastereomer (determined by \(^1\)H NMR). \[c\] Isolated yield. \[d\] No desired product.
Entry | Substrate | Product | Yield (%)\(^c\) | Dr\(^c\)
--- | --- | --- | --- | ---
1 | [\(\text{OTIPS}\)] \(\text{5b}\) | [\(\text{8b}\)] | 85 | 90:10
2 | [\(\text{OTIPS}\)] \(\text{5e}\) | [\(\text{8e}\)] | 87 | 96:4
3 | [\(\text{OTIPS}\)] \(\text{5d}\) | [\(\text{8d}\)] | 91 | 93:7
4 | [\(\text{Ph} \text{OTIPS}\)] \(\text{5e}\) | [\(\text{8e}\)] | 96 | 59:41
5 | [\(\text{OTIPS}\)] \(\text{5f}\) | [\(\text{8f}\)] | - | -
6 | [\(\text{Cl} \text{OTIPS}\)] \(\text{5g}\) | [\(\text{8g}\)] | - | -
7 | [\(\text{OTIPS}\)] \(\text{5h}\) | [\(\text{8h}\)] | - | -

\(a\) Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. \(^b\) Isolated yield \(^c\) Determined by \(^1\)H 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 \((2R,3R)-2,3\)-butanediol gave higher enantioselectivity in the final product than \((2R,4R)-2,4\)-petanediol 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(9a')</td>
<td>(6a)</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>(9a'')</td>
<td>(6a)</td>
<td>66</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>(9a)</td>
<td>(6a)</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>(9b)</td>
<td>(6e)</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>(9c)</td>
<td>(6i)</td>
<td>80</td>
<td>98</td>
</tr>
</tbody>
</table>
Chapter 4. Stereoselective Syntheses of 8-Oxatropine via Cationic Cascade Cyclization: Different Initiators, Opposite Diastereoselectivity

Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. Single diastereomer (determined by 1H NMR analysis). Isolated yield. Ee value was determined by chiral HPLC. No desired product. 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](image)

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 pathway, 7-6-6-6 fused cyclization product (12l) was generated in 38% yield.

**Table 4.4 Aldehyde induced cationic cascade cyclization**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Dr&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="3a" /></td>
<td><img src="image" alt="12a" /></td>
<td>51</td>
<td>97:3</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="3b" /></td>
<td><img src="image" alt="12b" /></td>
<td>53</td>
<td>93:7</td>
</tr>
</tbody>
</table>
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).

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Structure 3</th>
<th>Isolated Yield (%)</th>
<th>Dr Value</th>
</tr>
</thead>
<tbody>
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<td>Reaction 3</td>
<td><img src="image" alt="Structure 3c" /></td>
<td><img src="image" alt="Structure 12c" /></td>
<td>58</td>
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* 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.
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 comparision, 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 OTiCln 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 (2R,3R)-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 NH₄Cl solution (50 mL). The reaction mixture was extracted with Et₂O (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous MgSO₄ 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 NaHCO₃ solution (100 mL) and brine (100 mL). The organic layer was dried over NaSO₄ 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 Et₂O (3 × 20 mL). The combined organic layer was washed with brine (40 mL), dried over NaSO₄ 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)

\[ ^{1}H \text{ NMR (400 MHz, CDCl}_{3}\text{): } \delta 1.55 \text{(s, 3H), 2.27-2.32 (m, 4H), 2.49 (t, } J = 7.4 \text{ Hz, 2H), 2.63 (t, } J = 7.7 \text{ Hz, 2H), 5.21} \text{(t, } J = 7.0 \text{ Hz, 1H), 7.16-7.19 (m, 3H), 7.25-7.29 (m, 2H), 9.73 \text{(s, 1H); } ^{13}C \text{ NMR (100 MHz, CDCl}_{3}\text{): } \delta 16.05, 29.88, \]
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 C\(_{14}H_{19}O\) [M+H]\(^+\) requires m/z 203.1436, found m/z 203.1434.

\((E)-4\)-Methylhept-4-enal (3b)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 13.70, 21.91, 21.92, 31.70, 42.19, 127.51, 132.25, 202.77. HRMS (ESI\(^+\)) exact mass calcd for C\(_8H_{15}O\) [M+H]\(^+\) requires m/z 127.1123, found m/z 127.1126.

\((E)-4\)-Methyloct-4-enal (3c)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 13.76, 16.07, 22.82, 29.96, 31.90, 42.19, 125.73, 132.93, 202.78. HRMS (ESI\(^+\)) exact mass calcd for C\(_9H_{17}O\) [M+H]\(^+\) requires m/z 141.1279, found m/z 141.1278.

\((E)-4\)-Methyltridec-4-enal (3d)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C\(_{14}H_{27}O\) [M+H]\(^+\) requires m/z 211.2062, found m/z 211.2065.

\((E)-4\)-Methyl-6-phenylhex-4-enal (3e)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C\(_{13}H_{16}OK\) [M+K]\(^+\) requires m/z 227.0838, found m/z 227.0842.

\((E)-8\)-(Benzyloxy)-4-methyloct-4-enal (3f)
Chapter 4. Stereoselective Syntheses of 8-Oxatropane via Cationic Cascade Cyclization: Different Initiators, Opposite Diastereoselectivity

\[ ^1H \text{NMR (400 MHz, CDCl}_3): \delta \ \text{1.61 (s, 3H), 1.66 (q, } J = 7.0 \text{ Hz, 2H), 2.08 (q, } J = 7.3 \text{ Hz, 2H), 2.31 (t, } J = 7.5 \text{ Hz, 2H), 2.50 (t, } J = 7.5 \text{ Hz, 2H), 3.45 (t, } J = 6.4 \text{ Hz, 2H), 4.49 (s, 2H), 5.15 (t, } J = 7.2 \text{ Hz, 1H), 7.26-7.34 (m, 5H), 9.74 (t, } J = 1.7 \text{ Hz, 1H);} \]

\[ ^13C \text{NMR (100 MHz, CDCl}_3): \delta \ 16.08, 24.48, 29.68, 31.84, 42.16, 69.73, 72.91, 125.02, 127.51, 127.65, 128.36, 133.55, 138.64, 202.64. \]

HRMS (ESI) exact mass calcd for C\text{16H22O2Na} [M+Na]^+ requires \text{m/z 269.1517, found m/z 269.1524.} \]

(E)-9-(Benzyloxy)-4-methylnon-4-enal (3g)

\[ ^1H \text{NMR (400 MHz, CDCl}_3): \delta \ 1.42 (q, } J = 7.6 \text{ Hz, 2H), 1.60 (s, 3H), 1.60-1.64 (m, 2H), 2.00 (q, } J = 7.3 \text{ Hz, 2H), 2.31 (t, } J = 7.5 \text{ Hz, 2H), 2.51 (t, } J = 7.5 \text{ Hz, 2H), 3.46 (t, } J = 6.5 \text{ Hz, 2H), 4.50 (s, 2H), 5.16 (t, } J = 7.5 \text{ Hz, 1H), 7.26-7.34 (m, 5H), 9.75 (t, } J = 1.8 \text{ Hz, 1H);} \]

\[ ^13C \text{NMR (100 MHz, CDCl}_3): \delta \ 16.06, 26.26, 27.68, 29.38, 31.86, 42.18, 70.34, 72.91, 125.54, 127.50, 127.64, 128.36, 133.13, 138.67, 202.70. \]

HRMS (ESI) exact mass calcd for C\text{17H24O2Na} [M+Na]^+ requires \text{m/z 283.1674, found m/z 283.1675.} \]

(E)-7-(4-Methoxyphenyl)-4-methylhept-4-enal (3h)

\[ ^1H \text{NMR (400 MHz, CDCl}_3): \delta \ 1.55 (s, 3H), 2.26-2.32 (m, 4H), 2.49 (t, } J = 7.1 \text{ Hz, 2H), 2.57 (t, } J = 7.7 \text{ Hz, 2H), 3.78 (s, 3H), 5.19 (t, } J = 7.0 \text{ Hz, 1H), 6.82 (d, } J = 8.4 \text{ Hz, 2H), 7.08 (d, } J = 8.4 \text{ Hz, 2H), 9.73 (s, 1H);} \]

\[ ^13C \text{NMR (100 MHz, CDCl}_3): \delta \ 16.06, 30.11, 31.83, 34.98, 42.12, 55.26, 113.66, 124.77, 129.34, 133.68, 134.19, 157.75, 202.69. \]

HRMS (ESI) exact mass calcd for C\text{15H20O2Na} [M+Na]^+ requires \text{m/z 255.1361, found m/z 255.1357.} \]

(E)-7-(4-Chlorophenyl)-4-methylhept-4-enal (3i)

\[ ^1H \text{NMR (400 MHz, CDCl}_3): \delta \ 1.54 (s, 3H), 2.29 (q, } J = 7.8 \text{ Hz, 4H), 2.49 (t, } J = 7.6 \text{ Hz, 2H), 2.60 (t, } J = 7.6 \text{ Hz, 2H), 5.17 (t, } J = 7.0 \text{ Hz, 1H), 7.09 (d, } J = 8.0 \text{ Hz, 2H), 7.23 (d, } J = 8.0 \text{ Hz, 2H), 9.74 (s, 1H);} \]

\[ ^13C \text{NMR (100 MHz, CDCl}_3): \delta \ 16.06, 29.69, 31.77, 35.20, 42.08, 124.24, 128.31, 129.83, 131.47, 134.14, 140.46, 202.50. \]

HRMS (ESI) exact mass calcd for C\text{14H17ClO} [M+H]^+ requires \text{m/z 237.1046, found m/z 237.1042.}
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(E)-4-Methyl-7-(1-tosyl-1H-indol-3-yl)hept-4-enal (3j)

\[1H\text{ NMR (400 MHz, CDCl}_3\): } \delta 1.54 (s, 3H), 2.28-2.39 (m, 4H), 2.32 (s, 3H), 2.49 (t, \text{J} = 7.4 \text{ Hz}, 2H), 2.67 (t, \text{J} = 7.4 \text{ Hz}, 2H), 5.20 (t, \text{J} = 7.0 \text{ Hz}, 1H), 7.19-7.30 (m, 5H), 7.47 (d, \text{J} = 7.6 \text{ Hz}, 1H), 7.74 (d, \text{J} = 8.4 \text{ Hz}, 2H), 7.98 (d, \text{J} = 8.3 \text{ Hz}, 1H), 9.75 (t, \text{J} = 1.8 \text{ Hz}, 1H); \]^13C NMR (100 MHz, CDCl3): \delta 16.14, 21.55, 24.88, 27.38, 31.71, 42.11, 113.74, 119.44, 122.68, 122.89, 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 C23H25NO3SNa [M+Na]^+ requires \text{m/z} 418.1453, found \text{m/z} 418.1454.

(4E,8E)-4,8-Dimethyldodeca-4,8-dienal (3k)

\[1H\text{ NMR (400 MHz, CDCl}_3\): } \delta 0.89 (t, \text{J} = 7.4 \text{ Hz}, 3H), 1.35 (q, \text{J} = 7.3 \text{ Hz}, 2H), 1.59 (s, 3H), 1.62 (s, 3H), 1.93-2.01 (m, 4H), 2.08 (t, \text{J} = 7.2 \text{ Hz}, 2H), 2.31 (t, \text{J} = 7.4 \text{ Hz}, 2H), 2.51 (t, \text{J} = 7.5 \text{ Hz}, 2H), 5.10-5.18 (m, 2H), 9.75 (t, \text{J} = 1.8 \text{ Hz}, 1H); \]^13C NMR (100 MHz, CDCl3): \delta 13.80, 15.93, 22.98, 26.49, 29.99, 31.85, 39.53, 124.84, 125.43, 132.83, 134.63, 202.75. HRMS (ESI^+) exact mass calcd for C14H25O [M+H]^+ requires \text{m/z} 209.1905, found \text{m/z} 209.1907.

(4E,8E)-4,8-Dimethyl-11-phenylundeca-4,8-dienal (3l)

\[1H\text{ NMR (400 MHz, CDCl}_3\): } \delta 1.55 (s, 3H), 1.61 (s, 3H), 1.96-1.99 (m, 2H), 2.04-2.10 (m, 2H), 2.30 (q, \text{J} = 7.4 \text{ Hz}, 2H), 2.49 (t, \text{J} = 7.6 \text{ Hz}, 2H), 2.63 (t, \text{J} = 8.1 \text{ Hz}, 2H), 5.13 (t, \text{J} = 6.8 \text{ Hz}, 1H), 5.17 (t, \text{J} = 6.8 \text{ Hz}, 1H), 7.16-7.20 (m, 3H), 7.25-7.29 (m, 2H), 9.74 (s, 1H); \]^13C NMR (100 MHz, CDCl3): \delta 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 C19H26ONa [M+Na]^+ requires \text{m/z} 293.1881, found \text{m/z} 293.1875.

(E)-4-Methylundec-4-en-8-ynal (3m)

\[1H\text{ NMR (400 MHz, CDCl}_3\): } \delta 1.11 (t, \text{J} = 7.3 \text{ Hz}, 3H), 1.64 (s, 3H), 2.13-2.19 (m, 6H), 2.34 (t, \text{J} = 7.5 \text{ Hz}, 2H), 2.53 (t, \text{J} = 7.4 \text{ Hz}, 2H), 5.22 (t, \text{J} = 6.8 \text{ Hz}, 1H), 9.77 (s, 1H); \]^13C NMR (100 MHz, CDCl3): \delta 12.40, 14.31, 16.21, 19.06, 27.70,
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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)

\[ \text{1}^H \text{ NMR (400 MHz, CDCl} \text{)}: \delta 1.75 \text{(s, 3H), 2.35 (t, } J = 7.4 \text{ Hz, 2H), 2.58 (dt, } J_1 = 1.3 \text{ Hz, } J_2 = 7.3 \text{ Hz, 2H), 4.69 (s, 1H), 4.77 (s, 1H), 9.78 (t, } J = 1.7 \text{ Hz, 1H); } \text{1}^3 \text{C NMR (100 MHz, CDCl}\text{)}: \delta 22.61, 29.82, 41.76, 110.68, 143.75, 202.23. \]

3-(Cyclohept-1-en-1-yl)propanal (3p)

\[ \text{1}^H \text{ NMR (400 MHz, CDCl} \text{)}: \delta 1.41-1.50 \text{(m, 4H), 1.70-1.76 (m, 2H), 2.04-2.11 (m, 4H), 2.32 (t, } J = 7.4 \text{ Hz 2H), 2.49 (dt, } J_1 = 1.9 \text{ Hz, } J_2 = 7.4 \text{ Hz, 2H), 5.57 (t, } J = 6.4 \text{ Hz, 1H), 9.75 (t, } J = 1.9 \text{ Hz, 1H); } \text{1}^3 \text{C NMR (100 MHz, CDCl}\text{)}: \delta 26.66, 27.14, 28.20, 32.43, 32.53, 32.83, 42.17, 127.01, 142.49, 202.90. \]

3-Cyclohexenylpropanal (3r)

\[ \text{1}^H \text{ NMR (400 MHz, CDCl} \text{)}: \delta 1.52-1.57 (m, 2H), 1.59-1.65 (m, 2H), 1.91-2.00 (m, 4H), 2.27 (t, } J = 7.4 \text{ Hz 2H), 2.52 (dt, } J_1 = 1.99 \text{ Hz, } J_2 = 7.4 \text{ Hz, 2H), 5.41-5.43 (m, 1H), 9.76 (t, } J = 1.7 \text{ Hz, 1H); } \text{1}^3 \text{C NMR (100 MHz, CDCl}\text{)}: \delta 22.35, 22.82, 25.15, 28.42, 30.18, 41.86, 121.89, 135.71, 202.87. \]

(E)-7-(Furan-2-yl)-4-methylhept-4-enal (3t)

\[ \text{1}^H \text{ NMR (400 MHz, CDCl} \text{)}: \delta 1.59 (s, 3H), 2.33 (q, } J = 8.1 \text{ Hz, 4H), 2.50 (t, } J = 7.4 \text{ Hz, 2H), 2.64 (t, } J = 7.5 \text{ Hz, 2H), 5.18 (t, } J = 7.0 \text{ Hz, 1H), 5.96 (d, } J = 2.9 \text{ Hz, 1H), 6.27 (t, } J = 1.9 \text{ Hz, 1H), 7.29 (s, 1H), 9.73 (s, 1H); } \text{1}^3 \text{C NMR (100 MHz, CDCl}\text{)}: \delta 16.01, 26.51, 28.00, 31.80, 42.09, 104.95, 110.10, 124.23, 134.17, 140.81, 155.77, 202.58. \]

(E)-4,6-Dimethylhept-4-enal (3u)

\[ \text{1}^H \text{ NMR (400 MHz, CDCl} \text{)}: \delta 0.92 (d, } J = 6.7 \text{ Hz, 6H), 1.62 (s, 3H), 2.29 (t, } J = 7.5 \text{ Hz, 2H), 2.44-2.49 (m, 1H), 2.51 (t, } J = 7.2 \text{ Hz, 2H), 4.98 (d, } J = 9.0 \text{ Hz, 1H), 9.75 (s, 1H); } \text{1}^3 \text{C NMR (100 MHz, CDCl}\text{)}: \delta 22.61, 29.82, 41.76, 110.68, 143.75, 202.23. \]

HRMS (ESI⁺) exact mass calcd for C₁₀H₁₇O [M+H]⁺ requires m/z 153.1279, found m/z 153.1277.

HRMS (ESI⁺) exact mass calcd for C₁₂H₁₇O₂ [M+H]⁺ requires m/z 193.1229, found m/z 193.1225.

HRMS (ESI⁺) exact mass calcd for C₁₀H₁₄ONa [M+Na]⁺ requires m/z 161.0942, found m/z 161.0945.
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MHz, CDCl$_3$: $\delta$ 16.04, 23.03, 27.09, 31.79, 42.15, 130.52, 133.56, 202.76. HRMS (ESI$^+$) exact mass calcd for C$_9$H$_{16}$ONa [M+Na]$^+$ requires $m/z$ 163.1099, found $m/z$ 163.1092.

**(E)-5-Cyclohexyl-4-methylpent-4-enal (3v)**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{12}$H$_{20}$ONa [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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{17}$H$_{25}$O$_2$ [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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 14.34, 15.78, 21.15, 25.87, 33.66, 33.78, 66.90,
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, J₁ = 4.9 Hz, J₂ = 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, J₁ = 4.9 Hz, J₂ = 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, J₁ = 4.9 Hz, J₂ = 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-(Benzyl)oxy)-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, J₁ = 4.8 Hz, J₂ = 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$_3$): $\delta$ 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 C$_{19}$H$_{28}$O$_3$Na [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{20}$H$_{31}$O$_3$ [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 15.98, 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 C$_{18}$H$_{27}$O$_3$ [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 15.98, 25.86, 29.62, 33.60, 33.78, 35.31,
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66.89, 102.00, 123.36, 128.28, 129.85, 131.36, 135.45, 140.68. HRMS (ESI\(^+\)) exact mass calcd for C\(_{17}\)H\(_{24}\)Cl\(_2\)O\(_2\) [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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C\(_{26}\)H\(_{32}\)NO\(_4\)S [M+H\(^+\)] requires m/z 454.2052, found m/z 454.2062.

2-((3\(^E\),7\(^E\))-3,7-Dimethylundeca-3,7-dien-1-yl)-1,3-dioxane (4k)

Yield: 91% as colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C\(_{17}\)H\(_{30}\)O\(_2\)Na [M+Na\(^+\)] requires m/z 289.2143, found m/z 289.2145.

2-((3\(^E\),7\(^E\))-3,7-Dimethyl-10-phenyldeca-3,7-dien-1-yl)-1,3-dioxane (4l)

Yield: 90% as colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C\(_{22}\)H\(_{33}\)O\(_2\) [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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{15}$H$_{25}$O$_2$ [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); 13C NMR (100 MHz, CDCl$_3$): $\delta$ 22.55, 25.85, 31.92, 33.25, 66.91, 101.96, 109.91, 145.20. HRMS (ESI$^+$) exact mass calcd for C$_9$H$_{17}$O$_2$ [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 25.84, 28.15, 34.31, 66.90, 101.73, 114.74, 138.03. HRMS (ESI$^+$) exact mass calcd for C$_8$H$_{14}$O$_2$Na [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): 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 C$_{13}$H$_{25}$O$_2$ [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{14}$H$_{19}$O$_2$ [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{12}$H$_{21}$O$_2$ [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{15}$H$_{23}$O$_2$ [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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), 5.08 (s, 1H), 7.30-7.32 (m, 2H), 7.40-7.42 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 25.86, 29.50, 33.92, 66.90, 101.76, 112.30, 126.11, 127.38, 128.30, 141.08, 147.82. HRMS (ESI$^+$) exact mass calcd for C$_{14}$H$_{19}$O$_2$ [M+H]$^+$ requires m/z 219.1385, found m/z 219.1394.
Hz, 1H), 4.97 (d, J = 9.0 Hz, 1H); 13C NMR (100 MHz, CDCl3): 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 C12H22O2Na [M+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, CDCl3): 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, J1 = 4.3 Hz, J2 = 11.6 Hz, 2H), 4.48 (t, J = 4.2 Hz, 1H); 13C NMR (100 MHz, CDCl3): 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 C15H26O2Na [M+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 triethyl amine (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. [α]20D = 16.1° (c = 4.60 in CHCl3). 1H NMR (400 MHz, CDCl3): 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, J1 = 2.4 Hz, J2 = 6.2 Hz, J3 = 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); 13C NMR (100 MHz, CDCl3): 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 C19H29O2 [M+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. \([\alpha]_{D}^{20} = 10.0^\circ\ (c = 1.03\ \text{in CHCl}_3)\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\)

- 1.62 (s, 3H), 1.97-2.02 (m, 2H), 2.26-2.37 (m, 2H), 2.66 (t, \(J = 7.8\ \text{Hz}, 2\text{H}\)), 4.73 (d, \(J = 7.8\ \text{Hz}, 1\text{H}\)), 4.76 (d, \(J = 7.6\ \text{Hz}, 1\text{H}\)), 5.30 (t, \(J = 7.0\ \text{Hz}, 1\text{H}\)), 5.50 (t, \(J = 4.5\ \text{Hz}, 1\text{H}\)), 7.18-7.35 (m, 15H);

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\)

- 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 C\(_{28}\)H\(_{30}\)O\(_2\)Na [M+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. \([\alpha]_{D}^{20} = 59.8^\circ\ (c = 0.95\ \text{in CHCl}_3)\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\)

- 1.22 (d, \(J = 5.6\ \text{Hz}, 3\text{H}\)), 1.29 (d, \(J = 5.6\ \text{Hz}, 3\text{H}\)), 1.55 (s, 3H), 1.69-1.74 (m, 2H), 2.06-2.10 (m, 2H), 2.30 (q, \(J = 7.6\ \text{Hz}, 2\text{H}\)), 2.61-2.65 (m, 2H), 3.58-3.64 (m, 2H), 5.02 (t, \(J = 4.7\ \text{Hz}, 1\text{H}\)), 5.22 (t, \(J = 7.0\ \text{Hz}, 1\text{H}\)), 7.15-7.19 (m, 3H), 7.25-7.28 (m, 2H);

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\)

- 16.03, 16.98, 17.31, 29.94, 33.16, 33.69, 36.06, 78.10, 79.74, 103.03, 123.66, 125.67, 128.21, 128.48, 135.11, 142.33. HRMS (ESI\(^+\)) exact mass calcd for C\(_{18}\)H\(_{27}\)O\(_2\) [M+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. \([\alpha]_{D}^{20} = -11.9^\circ\ (c = 1.54\ \text{in CHCl}_3)\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\)

- 1.22 (d, \(J = 5.8\ \text{Hz}, 3\text{H}\)), 1.28 (d, \(J = 5.8\ \text{Hz}, 3\text{H}\)), 1.53 (s, 3H), 1.68-1.73 (m, 2H), 2.14-2.18 (m, 2H), 3.35 (d, \(J = 7.3\ \text{Hz}, 2\text{H}\)), 3.57-3.61 (m, 2H), 5.04 (t, \(J = 4.7\ \text{Hz}, 1\text{H}\)), 5.39 (t, \(J = 7.3\ \text{Hz}, 1\text{H}\)), 7.16-7.18 (m, 3H), 7.25-7.28 (m, 2H);

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\)

- 16.26, 16.98, 17.30, 33.19, 33.71, 34.18, 78.12, 79.76, 103.00, 123.07, 125.30, 128.31, 128.34, 135.59, 141.67. HRMS (ESI\(^+\)) exact mass calcd for C\(_{17}\)H\(_{25}\)O\(_2\) [M+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. \([\alpha]_{D}^{20} = 29.0^\circ\ (c = 0.99\ \text{in CHCl}_3)\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\)

- 1.22 (d, \(J = 5.8\ \text{Hz}, 3\text{H}\)), 1.28 (d, \(J = 5.8\ \text{Hz}, 3\text{H}\)), 1.53 (s, 3H), 1.68-1.73 (m,
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(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. [α]D 20 = 8.3° (c = 1.81 in CHCl₃). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): δ 16.06, 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 C₁₉H₂₉O₃ [M+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. [α]D 20 = 8.4° (c = 1.14 in CHCl₃). ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₀H₃₁O₃ [M+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)
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Yield: 93%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{23}$H$_{35}$O$_2$ [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{16}$H$_{27}$O$_2$ [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{13}$H$_{23}$O$_2$ [M+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 CH₂Cl₂ (2 mL) and added via syringe. After cooling the solution to -78 °C, TiCl₄ (0.24 mL of a 1.0M solution in CH₂Cl₂, 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. NaHCO₃ (5 mL), and extracted with EtOAc (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/diethyl ether mixture) to provide the title compound.

**Triisopropyl(((1S,2R,3R,5R)-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, CDCl₃): 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, ⁻J₁ = 5.2 Hz, ⁻J₂ = 7.6 Hz, ⁻J₃ = 12.5 Hz, 1H), 2.11-2.14 (m, 1H), 2.22-2.28 (m, 1H), 2.45 (dt, ⁻J₁ = 5.1 Hz, ⁻J₂ = 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₇H₄₆O₂SiNa [M+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, λ = 220 nm); tᵣ = 7.37 min (major) and 11.62 min (minor). 97% ee. Yield: 88%. [α]D²⁰ = 27.9° (c = 1.52 in CHCl₃).

**2-Ethyl-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropylsilane (6b)**

Yield: 91% as colorless oil. ¹H NMR (400 MHz, CDCl₃): 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, ⁻J₁ = 5.2 Hz, ⁻J₂ = 7.6 Hz, ⁻J₃ = 12.5 Hz, 1H), 2.11-2.14 (m, 1H), 2.22-2.28 (m, 1H), 2.45 (dt, ⁻J₁ = 5.1 Hz, ⁻J₂ = 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₇H₄₆O₂SiNa [M+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, λ = 220 nm); tᵣ = 7.37 min (major) and 11.62 min (minor). 97% ee. Yield: 88%. [α]D²⁰ = 27.9° (c = 1.52 in CHCl₃).
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Yield: 85% as colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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\(_3\)): \(\delta\) 12.92, 15.47, 18.50, 23.92, 25.28, 26.70, 36.73, 37.87, 53.13, 79.31, 80.94, 84.43. HRMS (ESI\(^+\)) exact mass calcd for C\(_{21}\)H\(_{43}\)O\(_2\)Si [M+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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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 (ddd, \(J_1 = 4.9\) 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\(_3\)): \(\delta\) 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 C\(_{22}\)H\(_{45}\)O\(_2\)Si [M+H]\(^+\) requires \(m/z\) 369.3189, found \(m/z\) 369.3202.

Triisopropyl((1,4,4-trimethyl-2-octyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)silane (6d)

Yield: 88%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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 (ddd, \(J_1 = 3.4\) 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\(_3\)): \(\delta\) 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 C\(_{27}\)H\(_{55}\)O\(_2\)Si [M+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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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
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(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); \(^{13}\text{C}\) NMR (100 MHz, CDCl₃): \(\delta 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 C₂₆H₄₅O₂Si [M+H]⁺ requires \(m/z 417.3189\), found \(m/z 417.3204\).

The enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H, 0.1% \(i\text{-PrOH/hexanes, flow rate 1.0 mL/min,}\) \(\text{t}_r = 5.18\) min (major) and 5.68 min (minor). 94% ee. Yield: 91%. \([\alpha]_D^{20} = -16.2° (c = 2.60\) in CHCl₃).

((1S,2R,3R,5R)-2-(3-(Benzyloxy)propyl)-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropylsilane (6f)

Yield: 84% as colorless oil. \(^1\text{H}\) NMR (400 MHz, CDCl₃): \(\delta 0.92\) (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); \(^{13}\text{C}\) NMR (100 MHz, CDCl₃): \(\delta 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 C₂₉H₅₁O₃Si [M+H]⁺ requires \(m/z 475.3607\), found \(m/z 475.3595\).

The enantiomeric excess was determined by chiral HPLC (Chiralpak OD-H, 0.5% \(i\text{-PrOH/hexanes, flow rate 1.0 mL/min,}\) \(\text{t}_r = 9.13\) min (minor). 94% ee. Yield: 79%. \([\alpha]_D^{20} = 4.6° (c = 1.68\) in CHCl₃).

((2-(4-(Benzyloxy)butyl)-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropylsilane (6g)

Yield: 89% as colorless oil. \(^1\text{H}\) NMR (400 MHz, CDCl₃): \(\delta 0.92\) (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); \(^{13}\text{C}\) NMR (100 MHz, CDCl₃): \(\delta 12.94, 18.53, 23.91, 25.38, 26.23, 26.82, 27.89, 30.42, 32.84, 36.64, 37.89, 51.73,
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70.12, 72.88, 80.13, 80.91, 84.48, 127.47, 127.58, 128.34, 138.67. HRMS (ESI+) exact mass calcd for C_{30}H_{53}O_{3}Si [M+H]^+ requires m/z 489.3764, found m/z 489.3752.

Triisopropyl(((1S,2R,3R,5R)-2-(4-methoxyphenethyl)-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy) (6h)
Yield: 84% as colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): 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), 2.64-2.72 (m, 1H), 3.67 (d, \(J = 8.5\) Hz, 2H), 7.09 (d, \(J = 8.5\) Hz, 2H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): 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 C_{28}H_{49}O_{3}Si [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, \(\lambda = 220\) nm); \(t_r = 8.78\) min (minor) and 9.53 min (major). 95% ee. Yield: 74%. \([\alpha]_D^{20} = 29.6^\circ (c = 1.98\) in CHCl\(_3\)).

(((1S,2R,3R,5R)-2-(4-chlorophenethyl)-1,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)oxy)triisopropylsilane (6i)
Yield: 85% as colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): 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); \(^1\)C NMR (100 MHz, CDCl\(_3\)): 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 C_{27}H_{46}O_{2}SiCl [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, \(\lambda = 220\) nm); \(t_r = 17.82\) min (minor) and 19.13 min (major). 98% ee. Yield: 80%. \([\alpha]_D^{20} = 32.9^\circ (c = 2.93\) in CHCl\(_3\)).

1-Tosyl-3-(2-(1,4,4-trimethyl-3-((triisopropylsilyl)oxy)-8-oxabicyclo[3.2.1]octan-2-yl)ethy)-1H-indole (6j)
Yield: 71% as colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 0.94 (s, 3H), 1.02-1.12 (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), 3.76 (d, \(J = 8.2\) Hz, 1H), 7.10 (d, \(J = 8.2\) Hz, 2H), 7.24 (d, \(J = 8.3\) Hz, 2H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): 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 C_{27}H_{46}O_{2}SiCl [M+H]^+ requires m/z 465.2956, found m/z 465.2953.\]
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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$_3$): $\delta$ 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 C$_{36}$H$_{54}$NO$_4$SSi [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 12.95, 13.85, 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 C$_{27}$H$_{53}$O$_2$Si [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{32}$H$_{55}$O$_2$Si [M+H]$^+$ requires $m/z$ 499.3971, found $m/z$ 499.3975.
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(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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

$0.93$ (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$_3$): $\delta$ 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 C$_{25}$H$_{47}$O$_2$Si [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

$0.93$ (s, 3H), $1.02$ (s, 3H), $1.09$-$1.11$ (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), $1.98$ (dd, $J_1 = 1.5$ Hz, $J_2 = 4.5$ Hz, $J_3 = 14.3$ Hz, 1H), $2.22$ (dd, $J_1 = 4.7$ 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$_3$): $\delta$ 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 C$_{19}$H$_{39}$O$_2$Si [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

$0.96$ (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$_3$): $\delta$ 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 C$_{18}$H$_{37}$O$_2$Si [M+H]$^+$ requires $m/z$ 313.2563, found $m/z$ 313.2566.

((2,2-Dimethyldecahydro-1H-3,5a-epoxyheptalen-1-yl)oxy)triisopropylsilane (6p)

Yield: 56% as colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

$0.93$ (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$_3$): $\delta$ 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 C$_{18}$H$_{37}$O$_2$Si [M+H]$^+$ requires $m/z$ 313.2563, found $m/z$ 313.2566.
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Yield: 54% as colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{23}$H$_{45}$O$_2$Si [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{27}$H$_{46}$O$_3$SiK [M+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-yloxy)propan-1-ol (6r)

Yield: 57% as colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{25}$H$_{49}$O$_3$Si [M+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)triisopropylsilane (8b)
Yield: 85% as colorless oil. Dr: 10:90. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{29}$H$_{51}$O$_2$Si [M+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'-cyclopentan]-3-yl)oxy)silane (8c)
Yield: 87% as colorless oil. Dr: 4:96. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{29}$H$_{49}$O$_2$Si [M+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'-cyclohexan]-3-yl)oxy)silane (8d)
Yield: 91% as colorless oil. Dr: 7:93. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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 (ddd, $J_1 = 5.4$ 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$_3$): $\delta$ 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 C$_{30}$H$_{51}$O$_2$Si [M+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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^1\)^C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C\(_{32}\)H\(_{49}\)O\(_2\)Si [M+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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^1\)^C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C\(_{26}\)H\(_{51}\)O\(_3\)Si [M+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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^1\)^C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 14.07, 18.81, 23.51, 25.90, 26.97, 27.45, 29.35, 31.48, 36.33, 39.35,
Chapter 4. Stereoselective Syntheses of 8-Oxatropane via Cationic Cascade Cyclization: Different Initiators, Opposite Diastereoselectivity

46.51, 78.89, 82.74, 83.26, 125.78, 128.29, 128.31, 142.34. HRMS (ESI+) exact mass calcd for C_{27}H_{47}O_{2}Si [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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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), 1.30-1.55 (m, 1H), 1.57-1.67 (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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C\(_{21}\)H\(_{43}\)O\(_2\)Si [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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C\(_{22}\)H\(_{45}\)O\(_2\)Si [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-yl)oxy)silane (12d)

Yield: 50%, colorless oil. Dr: 9:91. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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 C\(_{27}\)H\(_{55}\)O\(_2\)Si [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-yl)oxy)triisopropylsilane (12e)
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Yield: 57% as colorless oil, Dr: 55: 45. $^1$H NMR (400 MHz, CDCl$_3$):
\[
\begin{align*}
\delta & \quad 0.85-0.99 \text{ (m, 27H)}, \\
& \quad 1.03-1.20 \text{ (m, 32H)}, \\
& \quad 1.25 \text{ (s, 3H)}, \\
& \quad 1.38 \text{ (s, 3H)}, \\
& \quad 1.58 \text{ (dt, } J_1 = 4.8 \text{ Hz, } J_2 = 12.0 \text{ Hz, 1H)}, \\
& \quad 1.82-1.91 \text{ (m, 4H)}, \\
& \quad 2.22-2.28 \text{ (m, 1.2H)}, \\
& \quad 3.59 \text{ (s, 1H)}, \\
& \quad 3.67 \text{ (d, } J = 7.9 \text{ Hz, 1H)}, \\
& \quad 3.73 \text{ (d, } J = 7.5 \text{ Hz, 1H)}, \\
& \quad 3.86 \text{ (d, } J = 2.6 \text{ Hz, 1H)}, \\
& \quad 7.17-7.28 \text{ (m, 11H)};
\end{align*}
\]
$^{13}$C NMR (100 MHz, CDCl$_3$):
\[
\begin{align*}
\delta & \quad 12.43, \\
& \quad 14.06, \\
& \quad 18.24, \\
& \quad 18.38, \\
& \quad 18.41, \\
& \quad 18.74, \\
& \quad 23.33, \\
& \quad 24.25, \\
& \quad 25.83, \\
& \quad 26.13, \\
& \quad 26.62, \\
& \quad 26.88, \\
& \quad 27.58, \\
& \quad 28.03, \\
& \quad 31.27, \\
& \quad 35.48, \\
& \quad 36.76, \\
& \quad 37.03, \\
& \quad 38.15, \\
& \quad 47.78, \\
& \quad 52.90, \\
& \quad 75.50, \\
& \quad 80.40, \\
& \quad 81.01, \\
& \quad 83.03, \\
& \quad 83.16, \\
& \quad 84.43, \\
& \quad 125.71, \\
& \quad 125.81, \\
& \quad 128.18, \\
& \quad 128.33, \\
& \quad 128.58, \\
& \quad 129.62, \\
& \quad 141.51, \\
& \quad 142.75.
\end{align*}
\]
HRMS (ESI$^+$) exact mass calcd for C$_{26}$H$_{45}$O$_2$Si [M+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. $^1$H NMR (400 MHz, CDCl$_3$):
\[
\begin{align*}
\delta & \quad 0.95 \text{ (s, 3H)}, \\
& \quad 1.05 \text{ (s, 3H)}, \\
& \quad 1.07-1.17 \text{ (m, 21H)}, \\
& \quad 1.26-1.28 \text{ (m, 1H)}, \\
& \quad 1.30 \text{ (s, 3H)}, \\
& \quad 1.43-1.51 \text{ (m, 1H)}, \\
& \quad 1.76-1.87 \text{ (m, 3H)}, \\
& \quad 2.25-2.34 \text{ (m, 2H)}, \\
& \quad 2.63 \text{ (d, } J = 7.9 \text{ Hz, 1H)}, \\
& \quad 3.68 \text{ (d, } J = 2.6 \text{ Hz, 1H)}, \\
& \quad 3.79 \text{ (s, 3H)}, \\
& \quad 6.82 \text{ (d, } J = 8.6 \text{ Hz, 2H)}, \\
& \quad 7.07 \text{ (d, } J = 8.6 \text{ Hz, 2H)};
\end{align*}
\]
$^{13}$C NMR (100 MHz, CDCl$_3$):
\[
\begin{align*}
\delta & \quad 14.07, \\
& \quad 18.82, \\
& \quad 23.51, \\
& \quad 25.89, \\
& \quad 26.69, \\
& \quad 27.45, \\
& \quad 29.51, \\
& \quad 31.48, \\
& \quad 35.39, \\
& \quad 39.34, \\
& \quad 46.43, \\
& \quad 55.26, \\
& \quad 78.87, \\
& \quad 82.75, \\
& \quad 83.26, \\
& \quad 113.71, \\
& \quad 129.17, \\
& \quad 134.46, \\
& \quad 157.70.
\end{align*}
\]
HRMS (ESI$^+$) exact mass calcd for C$_{28}$H$_{49}$O$_3$Si [M+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) $^1$H NMR (400 MHz, CDCl$_3$):
\[
\begin{align*}
\delta & \quad 0.94 \text{ (s, 3H)}, \\
& \quad 1.07 \text{ (s, 3H)}, \\
& \quad 1.11-1.15 \text{ (m, 22H)}, \\
& \quad 1.25-1.38 \text{ (m, 5H)}, \\
& \quad 1.49-1.58 \text{ (m, 1H)}, \\
& \quad 1.61-1.64 \text{ (m, 1H)}, \\
& \quad 1.75-1.87 \text{ (m, 4H)}, \\
& \quad 1.92-1.93 \text{ (m, 1H)}, \\
& \quad 2.27-2.32 \text{ (m, 1H)}, \\
& \quad 2.36-2.42 \text{ (m, 1H)}, \\
& \quad 3.67 \text{ (s, 1H)}, \\
& \quad 3.67 \text{ (d, } J = 10.8 \text{ Hz, 1H)};
\end{align*}
\]
$^{13}$C NMR (100 MHz, CDCl$_3$):
\[
\begin{align*}
\delta & \quad 13.97, \\
& \quad 18.77, \\
& \quad 21.98, \\
& \quad 23.07, \\
& \quad 26.11, \\
& \quad 27.69, \\
& \quad 27.88, \\
& \quad 28.04, \\
& \quad 28.66, \\
& \quad 31.48, \\
& \quad 39.21, \\
& \quad 39.61, \\
& \quad 47.88, \\
& \quad 80.69, \\
& \quad 83.74, \\
& \quad 85.02.
\end{align*}
\]
HRMS (ESI$^+$) exact mass calcd for C$_{23}$H$_{45}$O$_2$Si [M+H]$^+$ requires m/z 381.3189, found m/z 381.3194.
Chapter 4. Stereoselective Syntheses of 8-Oxatropane via Cationic Cascade Cyclization: Different Initiators, Opposite Diastereoselectivity

4b,8,8,11a-tetramethyl-7-(triisopropylsilyloxy)-5,6,6a,7,8,9,10,11,11a,11b,12,13-do-decahydro-4bH-cyclohepta[a]phenanthren-9-ol (12l)

Yield: 38%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 calecd for C$_{32}$H$_{54}$O$_2$Si [M+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$_4$Cl (5 mL) and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine (25 mL) and dried over Na$_2$SO$_4$, 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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 calecd for C$_{18}$H$_{27}$O$_2$ [M+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. $^1$H 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, $J = 4.1$ 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 C$_{19}$H$_{29}$O$_3$ [M+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-one (11).

Yield: 88% as white solid, mp: 112-114 °C. CCDC No. 873239. $^1$H 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 (dddt, $J_1 = 5.8$ Hz, $J_2 = 10.9$ Hz, $J_3 = 15.8$ Hz, 1H), 2.24 (dtt, $J_1 = 4.3$ 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 C$_{18}$H$_{26}$O$_2$Cl [M+H]$^+$ requires $m/z$ 309.1621, found $m/z$ 309.1611.
Chapter 5. Classical Reaction, Different Product: Intriguing Behavior of Silyl Enol Ether Addition 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. The classical aldol reactions afford many byproducts, such as self-condensation products, unsaturated carbonyl compounds, 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). The Mukaiyama-aldol reaction, addition of silyl enol ether to aldehydes/ketones, developed

---

by Professor T. Mukaiyama and K. Narasaka,\textsuperscript{79} was one of the most important improvements in this area. Silyl enol ethers are stable, isolable, and that can be pre-prepared and separated regioselectively. Furthermore, the current strategy mostly simplified the outcomes compared with traditional methods.

$$\begin{align*}
O & \quad R^1 \quad + \quad OM \quad R^3 \quad R^4 \\
\text{1 Catalyst} & \quad \text{2 work up} \\
OH & \quad OH \\
R^4 & \quad R^3 \quad \text{or} \quad R^1 \quad R^4
\end{align*}$$

$$M = \text{Li, Na, B, Al, Si etc.}$$

$$M = \text{Si, named Mukaiyama-aldol reaction}$$

**Scheme 5.2 Modern Aldol Reaction**

Mukaiyama’s research demonstrated that many types of electrophile, such as aldehyde 5, ketone 8, acetal 6 and thioacetal 7 etc. could be applied in the reaction condition (Scheme 5.3). Furthermore, the reaction proceeded well neglected the nucleophile derived from aldehyde/ketone 9, unsaturated aldehyde 12, ester 10 or thioester 11 (Scheme 5.4).\textsuperscript{80}


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. 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.

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](image)

5.3 Result and Discussion

5.3.1 Preliminary Study

Our purpose was evaluated using 16a and 14a promoted by TiCl4 in CH2Cl2 at -78 ºC (Scheme 5.6). 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%).

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82 For the review of acetal induced Mukaiyama-Aldol reactions, see: Mukaiyama, T.; Murakami, M. *Synthesis* 1987, 1043.
Chapter 5. Classical Reaction, Different Product: Intriguing Behavior of Silyl Enol Ether Addition to Acetal

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TiCl4</td>
<td>19a</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>SnCl4</td>
<td>19a</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>BF3.OEt2</td>
<td>-</td>
<td>-c</td>
</tr>
<tr>
<td>4</td>
<td>InBr3</td>
<td>-</td>
<td>-c</td>
</tr>
<tr>
<td>5</td>
<td>AlBr3</td>
<td>19a</td>
<td>66</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-OH</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Ph-OH</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Ph-OH</td>
<td>22</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Ph-OH</td>
<td>16a 19a</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>Ph-OH</td>
<td>24</td>
<td>19a</td>
</tr>
<tr>
<td>6</td>
<td>Ph-OH</td>
<td>25</td>
<td>19a</td>
</tr>
<tr>
<td>7</td>
<td>Ph-OH</td>
<td>26</td>
<td>29a</td>
</tr>
<tr>
<td>8</td>
<td>Ph-OH</td>
<td>27a 29a</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td>Ph-OH</td>
<td>28</td>
<td>29a</td>
</tr>
</tbody>
</table>

Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. 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 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = TMS</td>
<td>14c</td>
<td>19c</td>
</tr>
<tr>
<td>2</td>
<td>R = TES</td>
<td>14d</td>
<td>19d</td>
</tr>
<tr>
<td>3</td>
<td>R = TBS</td>
<td>14e</td>
<td>19e</td>
</tr>
<tr>
<td>4</td>
<td>R = TIPS</td>
<td>14b</td>
<td>19b</td>
</tr>
<tr>
<td>5</td>
<td>R = Me</td>
<td>14f</td>
<td>19f</td>
</tr>
</tbody>
</table>

*Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. All yields were isolated yield. 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 kentones give classical Mukaiyama-aldol products.

Table 5.4 Mukaiyama-aldol cascade reaction of 1,3-propanediol protected acetals with varied silyl enol ethers

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14a</td>
<td>19a</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>14g</td>
<td>19g</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>14h</td>
<td>19h</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>14b</td>
<td>19b</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>14i</td>
<td>19i</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>14j</td>
<td>19j</td>
<td></td>
</tr>
</tbody>
</table>
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 revealed 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16b</td>
<td>31b</td>
<td>68</td>
</tr>
</tbody>
</table>
Chapter 5. Classical Reaction, Different Product: Intriguing Behavior of Silyl Enol Ether Addition to Acetal

<table>
<thead>
<tr>
<th>No.</th>
<th>Structure 16</th>
<th>Structure 31</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><img src="image" alt="Structure 16c" /></td>
<td><img src="image" alt="Structure 31c" /></td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Structure 16d" /></td>
<td><img src="image" alt="Structure 31d" /></td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Structure 16e" /></td>
<td><img src="image" alt="Structure 31e" /></td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Structure 16f" /></td>
<td><img src="image" alt="Structure 31f" /></td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Structure 16g" /></td>
<td><img src="image" alt="Structure 31g" /></td>
<td>77</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Structure 16h" /></td>
<td><img src="image" alt="Structure 31h" /></td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Structure 16i" /></td>
<td><img src="image" alt="Structure 31i" /></td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Structure 16j" /></td>
<td><img src="image" alt="Structure 31j" /></td>
<td>49</td>
</tr>
</tbody>
</table>

*Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. 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
Chapter 5. Classical Reaction, Different Product: Intriguing Behavior of Silyl Enol Ether Addition to Acetal

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](image)

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.
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![Scheme 5.8 Proposed Mechanistic Rationalization](image)

Form 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 R⁴ 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, R⁴ 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](image)

**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. 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.

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Table 5.6 Asymmetric Mukaiyama-aldol/[1,5]-H shift cascade reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = TIPS</td>
<td>14b</td>
<td>91</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>R = TBS</td>
<td>14e</td>
<td>89</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>R = Me</td>
<td>14f</td>
<td>95</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>14a</td>
<td>94</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>14k</td>
<td>81</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>14l</td>
<td>69</td>
<td>95</td>
</tr>
</tbody>
</table>

Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. All yields were isolated yield. Ee values were determined by chiral HPLC analysis. 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, \(\alpha\)-branched acetals were found to be not suitable for this reaction at this stage (entries
Table 5.7 Asymmetric Mukaiyama-aldol/[1,5]-H shift reaction of various acetals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27a</td>
<td>34a</td>
<td>69</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>27b</td>
<td>34b</td>
<td>79</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>27c</td>
<td>34c</td>
<td>-d</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>27d</td>
<td>34d</td>
<td>-d</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>27e</td>
<td>34e</td>
<td>64</td>
<td>91</td>
</tr>
</tbody>
</table>
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6  
\[
\begin{align*}
\text{TIPSO} & \quad \text{OH} & \quad \text{OTIPS} & \quad \text{Cbz} \\
\text{27f} & \quad \text{34f} & \quad 73 & \quad 95 
\end{align*}
\]

7  
\[
\begin{align*}
\text{BzO} & \quad \text{OH} & \quad \text{OTIPS} & \quad \text{Cbz} \\
\text{27g} & \quad \text{34g} & \quad 59 & \quad 95 
\end{align*}
\]

8  
\[
\begin{align*}
\text{Cbz} & \quad \text{OH} & \quad \text{OTIPS} & \quad \text{Cbz} \\
\text{27h} & \quad \text{34h} & \quad 58 & \quad 94 
\end{align*}
\]

\[a\] 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).

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

---

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](image)

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-methylbenzenesulphonate \(^{41}\) 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](image)

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,

---

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 (AlLiH₄). 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 was 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, J₁ = 5.3 Hz, J₂ = 8.1 Hz, J₃ = 10.2 Hz, 2H), 2.09 (tq, J₁ = 4.2 Hz, J₂ = 12.8 Hz, 1H), 2.70-2.74 (m, 2H), 3.74 (dt, J₁ = 2.4 Hz, J₂ = 12.4 Hz, 2H), 4.11 (dd, J₁ = 5.0 Hz, J₂ = 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, J₁ = 5.3 Hz, J₂ = 8.1 Hz, J₃ = 10.2 Hz, 2H), 2.09 (tq, J₁ = 4.2 Hz, J₂ = 12.8 Hz, 1H), 2.70-2.74 (m, 2H), 3.74 (dt, J₁ = 2.4 Hz, J₂ = 12.4 Hz, 2H), 4.11 (dd, J₁ = 5.0 Hz, J₂ = 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, 36.66, 66.91, 101.49, 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.
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2-Phenethyl-1,3-dioxolane (22)
Yield: 87%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 30.17, 35.52, 64.97, 66.91, 103.86, 125.89, 128.40, 141.60.

(3,3-Diethoxypropyl)benzene (24)
Yield: 94%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 15.39, 31.02, 35.10, 61.03, 102.20, 125.81, 128.37, 128.41, 141.79. HRMS (ESI$^+$) exact mass calcd for C$_{13}$H$_{21}$O$_2$ [M+H]$^+$ requires m/z 209.1542, found m/z 209.1551.

(3,3-Bis(hexyloxy)propyl)benzene (25)
Yield: 97%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.89 (t, $J = 6.7$ Hz, 6H), 1.33-1.43 (m, 12H), 1.54-1.61 (m, 4 H), 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$_3$): $\delta$ 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 C$_{21}$H$_{36}$O$_2$Na [M+Na]$^+$ requires m/z 343.2613, found m/z 343.2621.

(3-Phenylpropane-1,1-diyl)bis(oxy)bis(methylene)dibenzene (26)
Yield: 61%. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 C$_{23}$H$_{24}$O$_2$Na [M+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
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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, $J = 5.7$ 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.

(4S,6S)-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 (dqd, $J_1 = 2.4$ 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, 3H), 2.03-2.16 (t, $J = 7.4$ Hz, 3H), 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.
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<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>NMR (400 MHz, CDCl₃)</th>
<th>δ</th>
<th>13C NMR (100 MHz, CDCl₃)</th>
<th>δ</th>
<th>HRMS (ESI⁺) exact mass calcd for</th>
<th>m/z</th>
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<tr>
<td>2-Octyl-1,3-dioxane (16d)</td>
<td>67%</td>
<td>1H NMR: δ 0.87 (t, J = 6.7 Hz, 3H), 1.27-1.43 (m, 13H), 1.56-1.61 (m, 2H), 2.08 (tq, J₁ = 5.2 Hz, J₂ = 12.6 Hz, 1H), 3.76 (t, J = 11.4 Hz, 2H), 4.10 (dd, J₁ = 4.8 Hz, J₂ = 11.2 Hz, 2H), 4.50 (t, J = 5.2 Hz, 1H); 13C NMR (100 MHz, CDCl₃): 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 C₁₂H₂₅O₂ [M⁺H]⁺ requires m/z 201.1855, found m/z 201.1864.</td>
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<tr>
<td>2-(Pentan-3-yl)-1,3-dioxane (16e)</td>
<td>60%</td>
<td>1H NMR: δ 0.89 (t, J = 7.2 Hz, 6H), 1.40-1.48 (m, 4H), 1.52-1.55 (m, 2H), 2.06 (tq, J₁ = 4.9 Hz, J₂ = 12.6 Hz, 1H), 3.74 (t, J = 12.2 Hz, 2H), 4.11 (dd, J₁ = 4.7 Hz, J₂ = 12.2 Hz, 2H), 4.44 (d, J = 3.6 Hz, 1H); 13C NMR (100 MHz, CDCl₃): δ 11.52, 20.96, 26.05, 45.68, 67.06, 104.01. HRMS (ESI⁺) exact mass calcd for C₉H₁₈O₂Na [M+Na]⁺ requires m/z 182.1204, found m/z 182.1199.</td>
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<tr>
<td>2-Cyclohexyl-1,3-dioxane (16f)</td>
<td>71%</td>
<td>1H NMR: 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, J₁ = 5.0 Hz, J₂ = 12.6 Hz, 1H), 3.74 (dt, J₁ = 2.4 Hz, J₂ = 12.4 Hz, 2H), 4.10 (dd, J₁ = 5.0 Hz, J₂ = 10.7 Hz, 2H), 4.24 (d, J = 5.4 Hz, 1H); 13C NMR (100 MHz, CDCl₃): δ 25.83, 26.07, 26.47, 27.42, 42.60, 66.99, 105.43. HRMS (ESI⁺) exact mass calcd for C₁₀H₁₉O₂ [M+H]⁺ requires m/z 171.1385, found m/z 171.1391.</td>
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| 2-(3-(Benzyloxy)propyl)-1,3-dioxane (16g)     | 76%       | 1H NMR: 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, J₁ = 2.2 Hz, J₂ = 12.0 Hz, 2H), 4.09 (dd, J₁ = 5.0 Hz, J₂ = 11.9 Hz, 2H), 4.50 (s, 2H), 4.53 (t, J = 4.7 Hz, 1H), 7.26-7.34 (m, 5H); 13C NMR (100 MHz, CDCl₃): δ 24.23, 25.84, 31.90, 66.89, 70.00, 72.72, 102.10, 127.45,
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127.59, 128.32, 138.67. HRMS (ESI^+) exact mass calcd for C\textsubscript{14}H\textsubscript{21}O\textsubscript{3} [M+H\textsuperscript{+}] requires m/z 237.1491, found m/z 237.1496.

(4-(1,3-Dioxan-2-yl)butoxy)triisopropylsilane (16h)

Yield: 89%. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 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); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 12.00, 18.03, 20.34, 25.87, 32.84, 35.00, 63.32, 66.90, 102.38. HRMS (ESI^+) exact mass calcd for C\textsubscript{17}H\textsubscript{37}O\textsubscript{3}Si [M+H\textsuperscript{+}] requires m/z 317.2512, found m/z 317.2514.

3-(1,3-Dioxan-2-yl)propyl benzoate (16i)

Yield: 83%. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 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, \(J_1 = 2.0\) 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, \(J = 7.4\) 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); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 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 C\textsubscript{15}H\textsubscript{21}O\textsubscript{4} [M+H\textsuperscript{+}] requires m/z 265.1440, found m/z 265.1443.

Benzyl 3-(1,3-dioxan-2-yl)propylcarbamate (16j)

Yield: 54%. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 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); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 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 C\textsubscript{15}H\textsubscript{22}NO\textsubscript{4} [M+H\textsuperscript{+}] requires m/z 280.1549, found m/z 180.1540.

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\begin{align*}
\text{OH} & \quad \text{OMe} \\
\text{OMe} & \quad \text{OMe}
\end{align*}
\]

((4,4-Dimethoxybutan-2-yl)oxy)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, J₁ = 4.5 Hz, J₂ = 7.4 Hz, J₃ = 14.1 Hz, 1H), 1.89 (ddd, J₁ = 4.2 Hz, J₂ = 8.3 Hz, J₃ = 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.

(4S,6S)-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 (100 MHz, 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.

(4S,6S)-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.

(4S,6S)-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), 1.70-1.75 (m, 1H), 1.77-1.80 (m, 1H), 1.87-1.90 (m, 1H), 3.78-3.81 (m, 1H), 4.22-4.25 (m, 1H), 4.70-4.73 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.24, 21.92, 29.16, 29.43, 31.79, 35.28, 36.76, 67.33, 67.78, 94.24. HRMS (ESI⁺) exact mass calcd for C₁₃H₂₅O₂ [M+H]+ requires m/z 233.1817, found m/z 233.1830.
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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) 13C NMR (100MHz, CDCl3): 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 C12H23O2 [M+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, CDCl3): 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), 3.85 (t, J = 4.8 Hz, 1H), 7.25-7.34 (m, 5H); 13C NMR (100 MHz, CDCl3): 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 C16H25O3 [M+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, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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 C18H39O3Si [M+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, CDCl3): 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). 13C NMR (100MHz, CDCl3): 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 C17H25O4 [M+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, CDCl3): 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
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(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 C$_{17}$H$_{26}$NO$_4$ [M+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$_2$Cl$_2$ (25 mL). The flask was cooled to 0 °C prior to the addition of R$_3$SiOTf (5.5 mmol) via syringe. The reaction solution was allowed to stir at room temperature for 1 hour before diluting with CH$_2$Cl$_2$ (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$_2$SO$_4$ 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)**

$^1$H 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 C$_{13}$H$_{27}$OSi [M+H]$^+$ requires $m/z$ 227.1831, found $m/z$ 227.1839.

**tert-Butyl(cyclohexylidenemethoxy)dimethylsilane (14b)**

$^1$H 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 C$_{13}$H$_{27}$OSi [M+H]$^+$ requires $m/z$ 227.1831, found $m/z$ 227.1833.

**(2-ethylhex-1-en-1-yl)oxy)triisopropylsilane (14i)**

Z/E: 1/1. $^1$H 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 $\text{C}_{17}\text{H}_{37}\text{OSi}\ [\text{M+H}]^+$ requires $m/z$ 285.2614, found $m/z$ 285.2618.

$$\text{((Dihydro-2H-pyran-4(3H)-ylidene) methoxy)triisopropyl silane (14k)}$$

1H NMR (400 MHz, CDCl3): $\delta$ 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); 13C NMR (100 MHz, CDCl3): $\delta$ 11.96, 17.76, 26.32, 30.50, 68.42, 69.65, 115.17, 133.03. HRMS (ESI+) exact mass calcd for $\text{C}_{15}\text{H}_{31}\text{O}_2\text{Si} \ [\text{M+H}]^+$ requires $m/z$ 271.2093, found $m/z$ 271.2089.

$$\text{Benzyl 4-(((triisopropylsilyl)oxy)methylene)piperidine-1-carboxylate (14l)}$$

1H NMR (400 MHz, CDCl3): $\delta$ 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); 13C NMR (100 MHz, CDCl3): $\delta$ 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 $\text{C}_{23}\text{H}_{38}\text{NO}_3\text{Si} \ [\text{M+H}]^+$ requires $m/z$ 404.2621, found $m/z$ 404.2623.

$$\text{(Methoxymethylene)cyclohexane (14f)}$$

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 H2O. The aqueous layer was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with brine (20 mL). The organic layer was dried over anhydrous Na2SO4 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, CDCl3): $\delta$ 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); 13C NMR (100 MHz, CDCl3): $\delta$ 25.41, 26.88, 27.02, 28.38, 30.53, 59.14, 118.32, 138.77. HRMS (ESI+) exact mass calcd for $\text{C}_{8}\text{H}_{15}\text{O} \ [\text{M+H}]^+$ 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, J₁ = 2.8 Hz, J₂ = 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, J₃-D = 22.0 Hz), 80.65.
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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, J₁ = 2.2 Hz, J₂ = 10.3 Hz, 1H), 3.59 (dd, J₁ = 9.5 Hz, J₂ = 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); tᵣ = 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, J₁ = 2.2 Hz, J₂ = 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 -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 C₂₂H₃₉DO₂Si [M+H]⁺ requires m/z 366.2939, found m/z 366.2944.

1-(1-((tert-Butyldimethylsilyloxy)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-((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),
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**1-(1-(Methoxymethyl)cyclohexyl)-3-phenylpropan-1-one (19f)**

Yield: 75%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.30-1.37 (m, 5H), 1.44-1.51 (m, 3H), 1.95-1.98 (m, 2H), 2.79-2.91 (m, 4H), 3.23 (s, 3H), 3.35 (s, 2H), 7.16-7.21 (m, 3H), 7.26-7.29 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 22.59, 25.97, 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 C\(_{17}\)H\(_{25}\)O\(_2\) requires \(m/z\) 261.1857, found \(m/z\) 261.1855.

**3,3-Dimethyl-1-phenyl-4-(triisopropylsilyloxy)butan-2-one (31b)**

Yield: 68%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.90 (t, \(J = 7.4\) Hz, 3H), 1.02-1.07 (m, 21H), 1.11 (s, 6H), 1.26-1.34 (m, 10H), 1.52-1.55 (m, 2H), 2.52 (t, \(J = 7.4\) Hz, 2H), 3.69 (s, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 11.90, 14.10, 17.98, 18.08, 21.64, 22.67, 23.48, 29.20, 29.34, 29.50, 31.86, 38.14, 49.64, 70.88, 214.96. HRMS (ESI\(^+\)) exact mass calcd for C\(_{21}\)H\(_{36}\)O\(_2\)Si requires \(m/z\) 349.2566, found \(m/z\) 349.2563.

**2,2-Dimethyl-1-(triisopropylsilyloxy)hexan-3-one (31c)**

Yield: 72%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.88 (t, \(J = 6.7\) Hz, 3H), 1.02-1.07 (m, 21H), 1.11 (s, 6H), 1.26-1.34 (m, 10H), 1.52-1.55 (m, 2H), 2.52 (t, \(J = 7.4\) Hz, 2H), 3.69 (s, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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, 70.88, 214.96. HRMS (ESI\(^+\)) exact mass calcd for C\(_{17}\)H\(_{36}\)O\(_2\)Si requires \(m/z\) 301.2574, found \(m/z\) 301.2563.

**2,2-Dimethyl-1-(triisopropylsilyloxy)undecan-3-one (31d)**

Yield: 71%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.88 (t, \(J = 6.7\) Hz, 3H), 1.02-1.07 (m, 21H), 1.11 (s, 6H), 1.26-1.34 (m, 10H), 1.52-1.55 (m, 2H), 2.52 (t, \(J = 7.4\) Hz, 2H), 3.69 (s, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 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, 70.88, 214.96. HRMS (ESI\(^+\)) exact mass calcd for C\(_{21}\)H\(_{36}\)O\(_2\)Si requires \(m/z\) 349.2566, found \(m/z\) 349.2563.
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70.90, 215.15. HRMS (ESI+) exact mass calcd for C_{22}H_{46}O_{2}Si [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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 11.94, 11.99, 21.68, 24.14, 49.04, 49.97, 69.94, 217.85. HRMS (ESI+) exact mass calcd for C$_{19}$H$_{40}$O$_2$Si [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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{20}$H$_{40}$O$_2$Si [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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{24}$H$_{42}$O$_3$Si [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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{27}$H$_{58}$O$_3$Si$_2$ [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. $^1$H 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 C$_{24}$H$_{40}$O$_4$Si [M+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. $^1$H 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 C$_{25}$H$_{43}$NO$_4$Si [M+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. $^1$H 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 8.16, 11.96, 13.97, 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 C$_{26}$H$_{47}$O$_2$Si [M+H]$^+$ requires m/z 419.3345, found m/z 419.3355.

3-Phenyl-1-(1-(((triisopropylsilyl)oxy)methyl)cyclopentyl)propan-1-one (19h)
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Yield: 77%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

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$_3$): $\delta$ 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 C$_{24}$H$_{41}$O$_2$Si [M+H]$^+$ requires $m/z$ 389.2876, found $m/z$ 389.2883.

(S)-3-Phenyl-1-(4-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-4-yl)propanyl-1-ol (29k)

Yield: 81%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

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$_3$): $\delta$ 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 C$_{24}$H$_{43}$O$_3$Si [M+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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$

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$_3$): $\delta$ 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 C$_{32}$H$_{50}$NO$_4$Si [M+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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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\(_3\)): \( \delta \) 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 C\(_{25}\)H\(_{44}\)O\(_2\)SiNa \([\text{M+Na}]^+\) 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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): 6 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\(_3\)): \( \delta \) -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 C\(_{22}\)H\(_{39}\)O\(_2\)Si \([\text{M+H}]^+\) 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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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),
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7.16-7.30 (m, 5H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta \) 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 C\(_{17}\)H\(_{27}\)O\(_2\) \([M+H]^+\) 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, \(\lambda = 220\) 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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta \) 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), 7.15-7.29 (m, 5H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta \) 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 C\(_{22}\)H\(_{44}\)O\(_2\)SiNa \([M+Na]^+\) 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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta \) 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\(_3\)): \(\delta \) 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 C\(_{32}\)H\(_{58}\)NO\(_4\)SiNa \([M+Na]^+\) 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, \(\lambda = 220\) 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)
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Yield: 64%, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\)

- 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\(_3\)): \(\delta\)


HRMS (ESI\(^+\)) exact mass calcd for C\(_{34}\)H\(_{54}\)NO\(_5\)Si [M+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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\)

- 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\(_3\)): \(\delta\)

- 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 C\(_{36}\)H\(_{67}\)NO\(_5\)SiNa [M+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. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\)

- 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,
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**CDC13**: $\delta$ 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 C$_{35}$H$_{54}$NO$_6$Si [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, $\lambda$ = 220 nm); $t_r$ = 28.75 min (minor) and 46.65 min (major). 95% ee.

(S)-Benzyl-4-((benzyloxy)carbonyl)amino)-1-hydroxybutyl)-4-(((triisopropylsilyl)oxy)methyl)piperidine-1-carboxylate (34h)

Yield: 58%, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{35}$H$_{55}$N$_2$O$_6$Si [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, $\lambda$ = 220 nm); $t_r$ = 12.90 min (major) and 13.77 min (minor). 94% ee.

Experimental Procedure and Data for the Synthesis of Sufentanil
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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 H₂O. The aqueous layer was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with brine (20 mL). The organic layer was dried over anhydrous Na₂SO₄ 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, CDCl₃): 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); 

¹³C NMR (100 MHz, CDCl₃): 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 C₁₅H₂₀NO₃ [M+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 C18H32NO4 [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. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 calced for C$_{18}$H$_{26}$NO$_4$ [M+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, NH$_2$OH.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$_2$Cl$_2$ (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$_3$COOH and stirred for 2 hours at room temperature. The reaction was quenched with H$_2$O (50 mL) and extracted with CH$_2$Cl$_2$ (30 mL × 3). The combined organic layers were washed successively with H$_2$O (50 mL × 2) and NaHCO$_3$ (50 mL × 2, saturated aqueous solution), dried over anhydrous Na$_2$SO$_4$ 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.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 calced for C$_{18}$H$_{27}$N$_2$O$_4$ [M+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, J1 = 0.9 Hz, J2 = 3.4 Hz, 1H), 6.90 (dd, J1 = 3.5 Hz, J2 = 5.1 Hz, 1H), 7.14 (dd, J1 = 1.1 Hz, J2 = 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.

\[ N-(4-(\text{Methoxymethyl})-1-(2-(\text{thiophen-2-yl})ethyl)piperidin-4-yl)propionamide \] (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, J1 = 0.8 Hz, J2 = 3.4 Hz, 1H), 6.92 (dd, J1 = 3.4 Hz, J2 = 5.1 Hz, 1H), 7.13 (dd, J1 = 1.1 Hz, J2 = 5.2 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 9.96, 27.20, 30.59, 31.03, 48.89, 54.19,
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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, J₁ = 3.5 Hz, J₂ = 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 C₁₉H₂₇N₂O₂S [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, 0.03 mmol) 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%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 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 C$_{22}$H$_{31}$N$_2$O$_2$S [M+H]$^+$ requires $m/z$ 387.2106, found $m/z$ 387.2101.