Development of Biomimetic Polyene Cyclization Directed towards Total Synthesis of Polycyclic Terpenoids

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Nagoya, 2007

Contents

Chapter 1

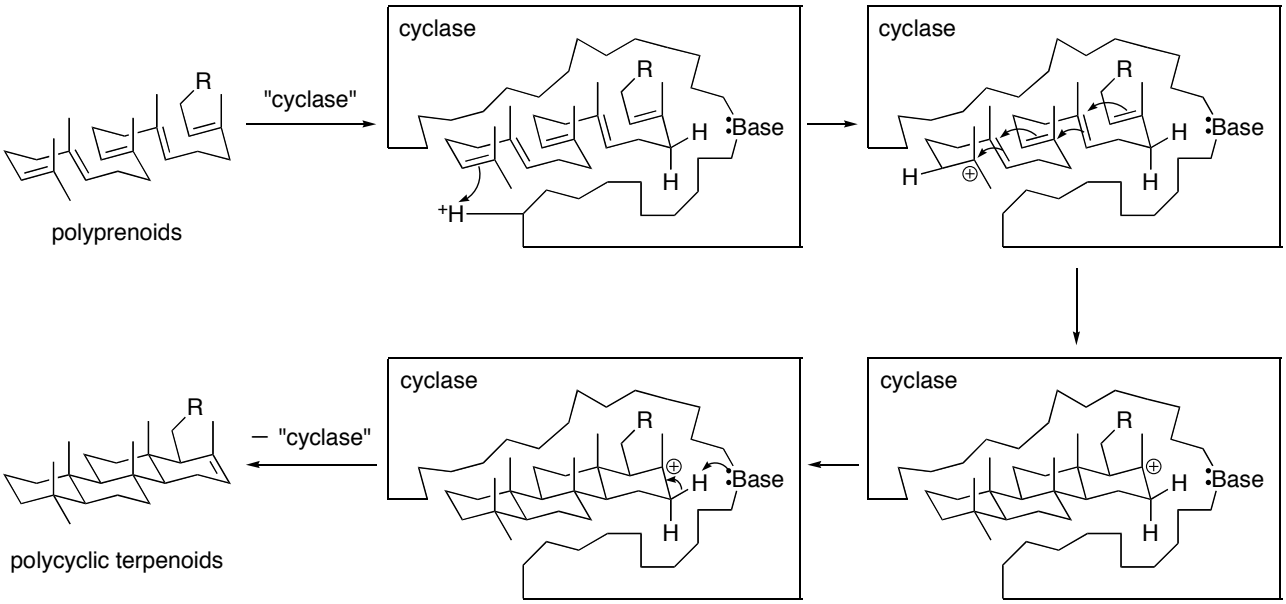
Introduction and General Summary

Natural products are essential to our life, and their total synthesis is a very significant source.[1] Cascade reactions are some of the most powerful tools for the total synthesis of complex natural products, since complicated structures can be constructed directly in one-pot sequences. The benefits of cascade reactions include atom economy, as well as savings in, labor, resource management, and waste generation.[2]

Terpenoids are second-metabolic products that are a structurally diverse and widely distributed family of natural products that includes well over 30,000 defined compounds found in essentially all forms of life. All of these compounds play a wide range of important roles in the mediation of cell-wall and glycoprotein biosynthesis, electron transport and redox chemistry, photooxidative protection and photosynthetic light harvesting, lipid membrane structure, modification of proteins involved in signal transduction, interspecies defense as antibiotics, etc. Many terpenoids are of economic importance, and include essential oils, medicines, carotenoid pigments and natural rubber.[3]

The fundamental carbon skeletons of polycyclic terpenoids have diverse stereocenters including quaternary carbon centers. According to the Stork–Eschenmoser hypothesis, they are mainly biosynthesized stereospecifically in only one cyclization reaction, which is considered to the enzyme-controlled asymmetric cationic polyene cyclization of acyclic linear polyene substrates such as

geranyl pyrophosphate, farnesyl pyrophosphate, geranylgeranyl pyrophosphate, squalene, etc.[3,4] Therefore, biomimetic polyene cyclization is thought to be one of the most powerful and efficient reactions in synthetic chemistry (Scheme 1).



Scheme 1. A hypothetical cyclase-induced cyclization of polyprenoids

To control cationic polycyclization, it is necessary to consider a reaction design based on the following steps: (1) generation of a carbocation, (2) control of the conformation of the substrate, (3) stabilization of intermediates, and (4) quenching of the final carbocation.[5] Based on this scheme, the origin of the stereoselectivity of polycyclization lies in the generation of the carbocation, which is the most important step in the four ones. In nature, carbocations generated on substrates, which are folded in cavities with their stereochemistry controlled by cyclases, are stabilized during successive cyclization.[4,5] There known to be three main approaches to generate carbocations: leaving group elimination, olefin protonation and epoxide opening. The protonation of olefins is one of the simplest routes for the generation of

carbocations and asymmetric induction can be achieved by enantioselective protonation of the isoprenyl group of polyprenoids.[5c,6] However, without an enzyme ($Enz^{-}H^{+}$), it is difficult to recognize the stereoface of a simple olefin that does not bear a directing group. Additionally, it is difficult to site-selectively generate a terminal carbocation on polyprenoids by protonation. There is usually competition between terminal and internal isoprenyl groups. The most important feature required for an artificial enzyme is asymmetric induction in protonation of the terminal isoprenyl group of polyprenoids.

Since the 1950s, several studies on the synthesis of polycycles via nonenzymatic polyene cyclization have been reported.[7] However, these reactions generally have a low yield and low stereoselectivity due to the difficulty of completely controlling cationic cyclization. Despite extensive studies on acid-catalyzed diastereoselective polyene cyclizations, such as achiral acid-catalyzed diastereoselective polyene cyclizations using chiral auxiliaries[7a] and antibody-catalyzed diastereoselective polyene cyclizations,[8] the corresponding enantioselective processes have not yet been reported. Recently, our group demonstrated that Lewis acid-assisted chiral Brønsted acids (chiral LBAs, Figure 1) prepared in situ from chiral alcohols and tin(IV) chloride were highly effective as artificial cyclases for the enantioselective biomimetic cyclization of polyprenoids (Scheme 2).[9] First, the A-ring is constructed via cyclization initiated by enantioselective protonation of the terminal isoprenyl group using chiral LBA, and the B- and C-rings are then constructed via diastereoselective cyclization using achiral LBA. This is the first example of proton-induced enantioselective polyene cyclization in synthetic chemistry.

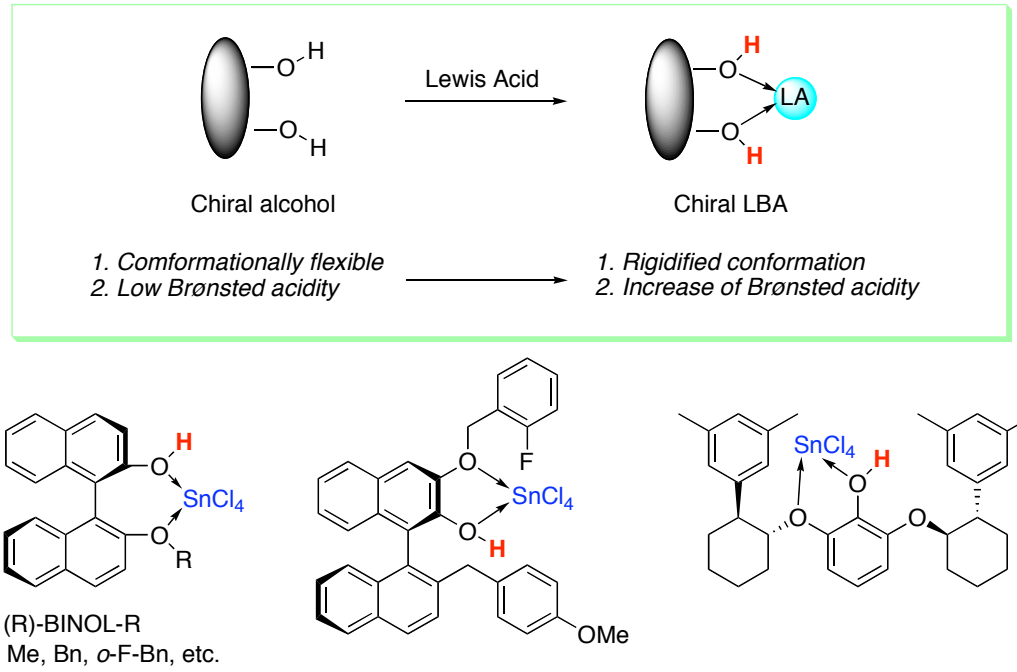
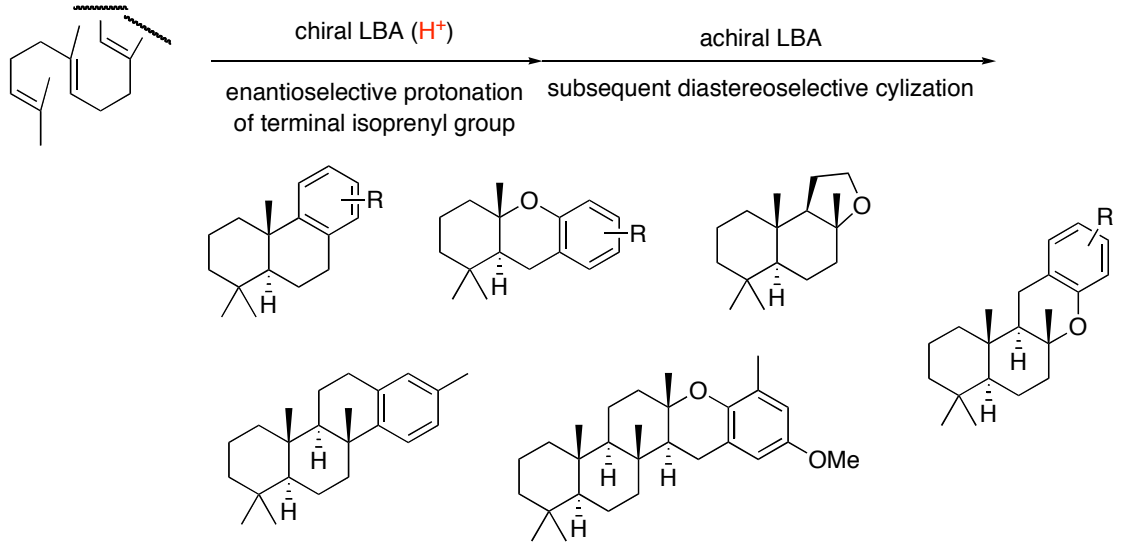


Figure 1. Chiral LBAs as "designer acids"

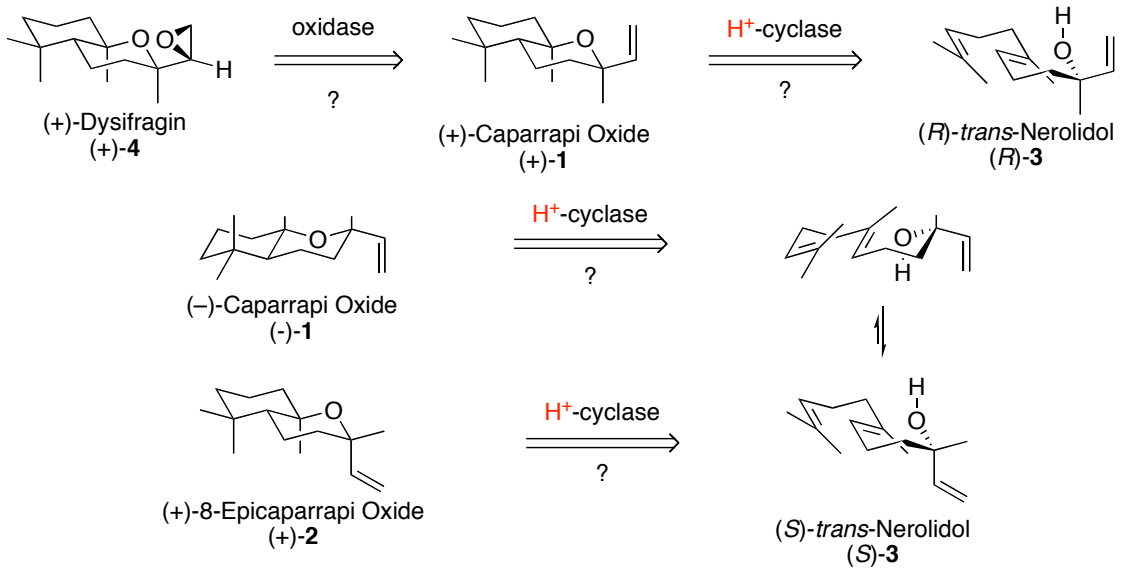
Chiral LBAs as “designer acids” are generated in situ from optically pure binaphthol derivatives (BINOLs) and tin(IV) chloride in dichloromethane or toluene at room temperature, and are stable as a coordination complex in solution even at room temperature.[9,10] The coordination of a Lewis acid to Brønsted acid (BINOLs) would restrict the direction of the proton and increase its acidity (Figure 1). Furthermore, the bulkiness of a chiral counter anion, which acts as an “artificial cavity”, would not only provide an asymmetric environment, but would also recognize the terminal olefin of polyprenoids. Therefore, chiral LBAs can recognize the enantioface of an olefin and can initiate polyene cyclization site-selectively. The stereochemical implications of polyene cyclizations initiated by protonation at the terminal C–C double bond can be explained by the Stork–Eschenmoser hypothesis, which postulates synchronous internal *anti*-additions via chair-like conformations of nascent cyclohexane rings.[7b]



Scheme 2. Biomimetic polyene cyclization and application to total synthesis of polycycles

Chapter 2 describes the successful application of chiral LBA-induced polyene cyclization of a chiral substrate toward the total synthesis of acid-sensitive bicyclic sesquiterpenes.

Natural bicyclic sesquiterpene ethers such as (–)- and (+)-caparrapi oxides (**1**)[11, 12] and 8-epicaparrapi oxide (**2**)[13] can be formally obtained by the biomimetic proton-induced cyclization of (*S*)-(+)- or (*R*)-(–)-nerolidol (**3**) (Scheme 3). (–)-**1** has been isolated from the neutral fraction of the essential oil of *Ocotea caparrapi Nates* (Dugand).[11] On the other hand, (+)-**1** and (+)-dysifragin (**4**) have been isolated from the sponge *Dysidea fragilis Montagu* (family Dysideidae).[12] However, the absolute and relative stereochemistries of (+)-**4** have not been determined. 8-Epicaparrapi oxide **2** has been isolated as a minor constituent of the defensive secretion of the termite *Amitermes evuncifer*.[13]



Scheme 3. Formal biosynthetic routes for sesquiterpene ethers

According to Zefirov and co-workers, the cyclization of (±)-**3** induced by 5 equivalents of HSO_3F gives (±)-**2** diastereoselectively (via substrate control) with low yield.[14] However, there have been no successful examples of the diastereoselective cyclization of (±)-**3** to (±)-**1**. Kametani and co-workers obtained a 1:1 diastereomeric mixture of (±)-**1** and (±)-**2** through the cyclization of ß-hydroxy phenylselenide derived from 10,11-epoxynerolidol induced by 5.7 equivalents of CF_3CO_2H.[15]

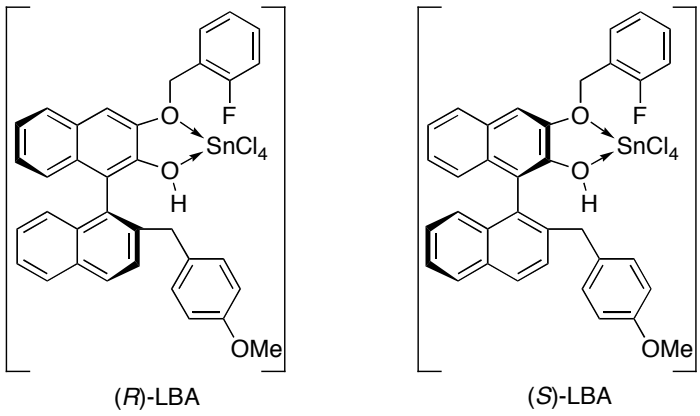
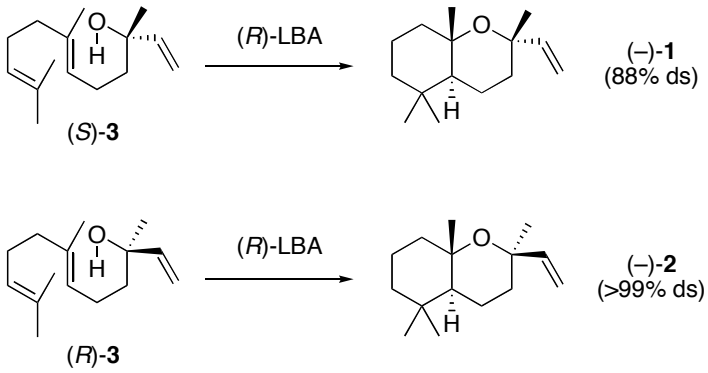


Figure 2. Artificial cyclases that are available in both enantiomeric forms

To concisely synthesize (+)-**1** and (–)-**1** through the polyene cyclization of (*R*)-**3** and (*S*)-**3**, respectively, asymmetric control with artificial cyclases should be able to overcome substrate control, and both enantiomers of the artificial cyclases should be readily available (Figure 2).

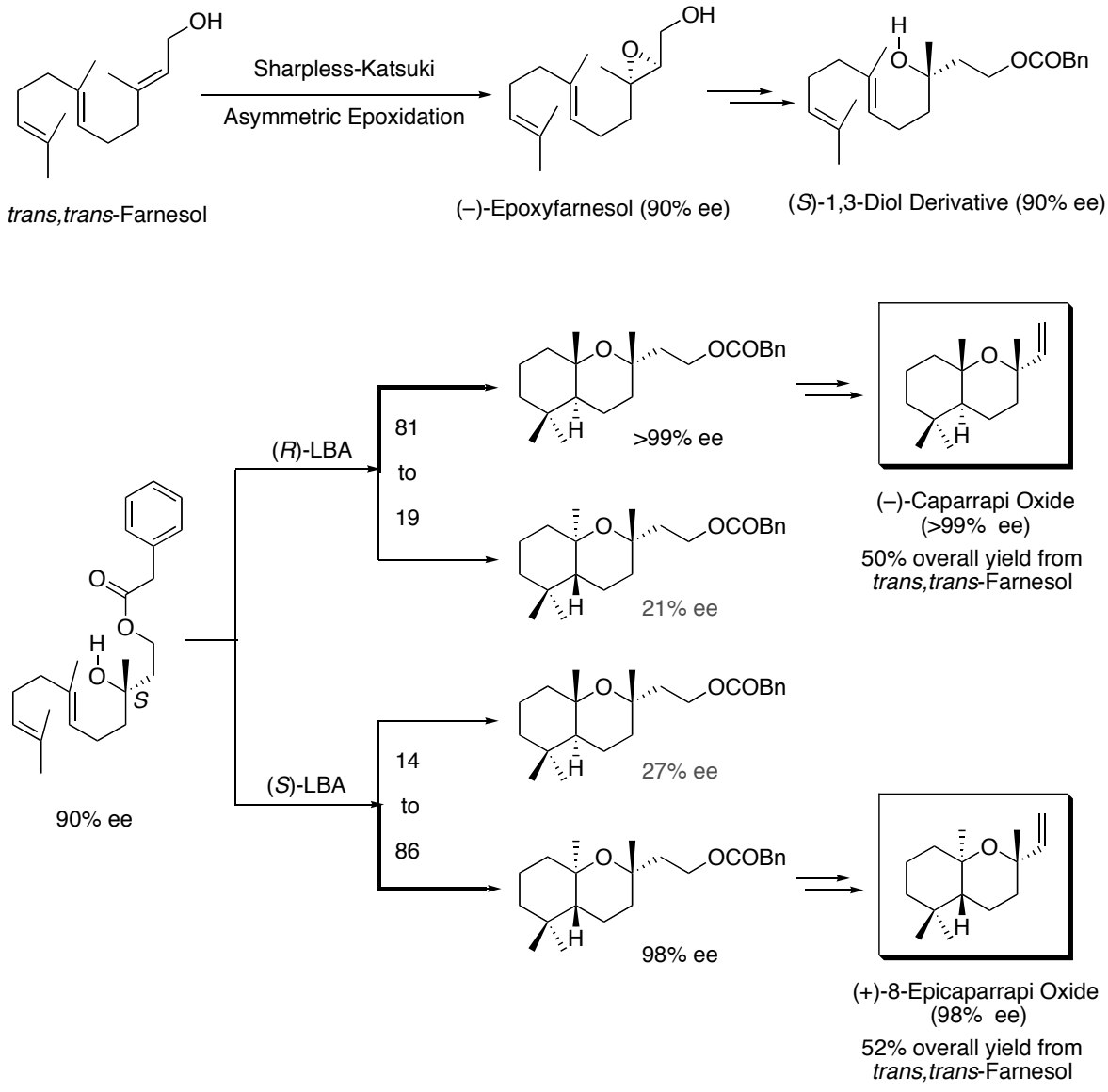
We were interested in substrate control versus reagent control in the polyene cyclization of chiral substrates. Thus, we decided to apply the of chiral LBA-induced polyene cyclization of chiral substrates such nerolidol, and the total synthesis of sesquiterpenes, caparrapi oxides and 8-epicaparrapi oxides.



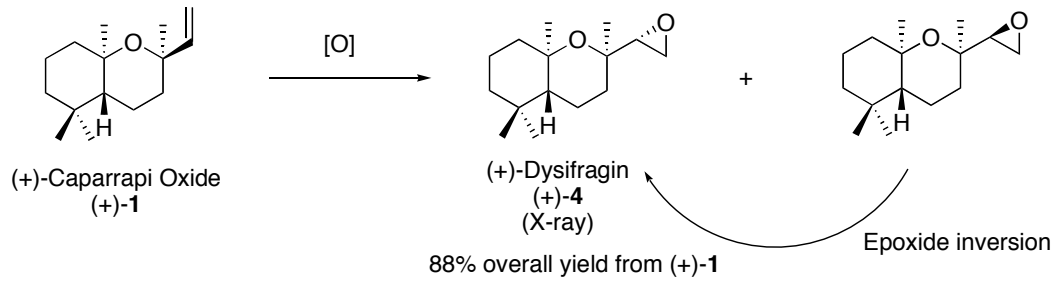
Scheme 4. Reagent control overcame to substrate control

(–)-**1** can be directly synthesized from (*S*)-nerolidol (**3**) and (*R*)-LBA with 88% ds by reagent control which overcomes substrate control, while (–)-**2** is obtained from (*R*)-**3** and (*R*)-LBA with >99% ds by double asymmetric induction (Scheme 4). However, the chemical yield was low, reasoned to **1**, **2**, and **3** bearing acid-sensitive allylic *tert*-alcohol or ether moiety that suggested some decomposition occurred in the acidic reaction medium. Thus, we decided to change the terminal ally alcohol moiety to acid-stable and synthetically transformable ester group. This chapter describes the concise asymmetric total synthesis of acid-sensitive (–)- and (+)-caparrapi oxides (**1**) and (+)-8-epicaparrapi oxide (**2**) from farnesol (**10**) using Sharpless–Katsuki

epoxidation[16] and chiral LBA-induced polyene cyclization[9] as key steps and diastereoselective transformation from (+)-**1** to (+)-**4** (Schemes 5 and 6). Additionally, the absolute stereochemical structure of (+)-**4** was established by ^{13}C NMR spectroscopy and X-ray diffraction.



Scheme 5. Total synthesis of Caparrapi Oxide and 8-Epicaparrapi Oxide



Scheme 6. Total synthesis of (+)-Dysifragin

Chapter 3 describes the development of a new biomimetic cyclization system toward the synthesis of A-ring functionalized polycycles.

Biomimetic polyene cyclization is an important key step in the concise total synthesis of polycyclic natural products.[7] A variety of A-ring functionalized polycyclic terpenoids are found in nature.[3] As noted in Chapter 2, we recently reported that the Lewis acid-assisted chiral Brønsted acid (LBA)-induced biomimetic polyene cyclization of geraniol, farnesol and geranylgeraniol derivatives gave the desired polycyclic terpenoids with high diastereo- and enantioselectivities.[9] However, A-ring functionalization for these polycyclic products is synthetically difficult. Thus, we were interested in the polyene cyclization of functionalized polyprenoids.

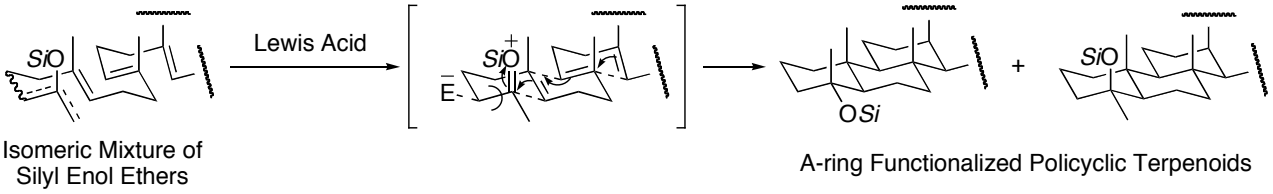
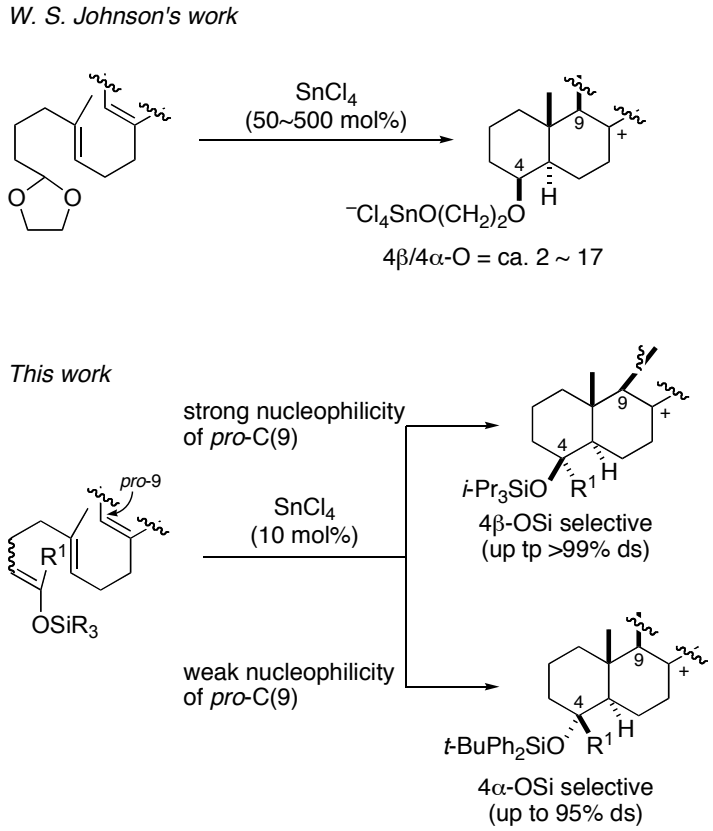


Figure 3. A new biomimetic polyene cyclization system

The Lewis acid-promoted diastereoselective cyclization of polyenic aldehyde acetals to 4ß(axial)-alkoxypolycycles has been established by Johnson et al. (Scheme 7).[7a] However, excess $SnCl_4$ is often required as a Lewis acid and no methods are

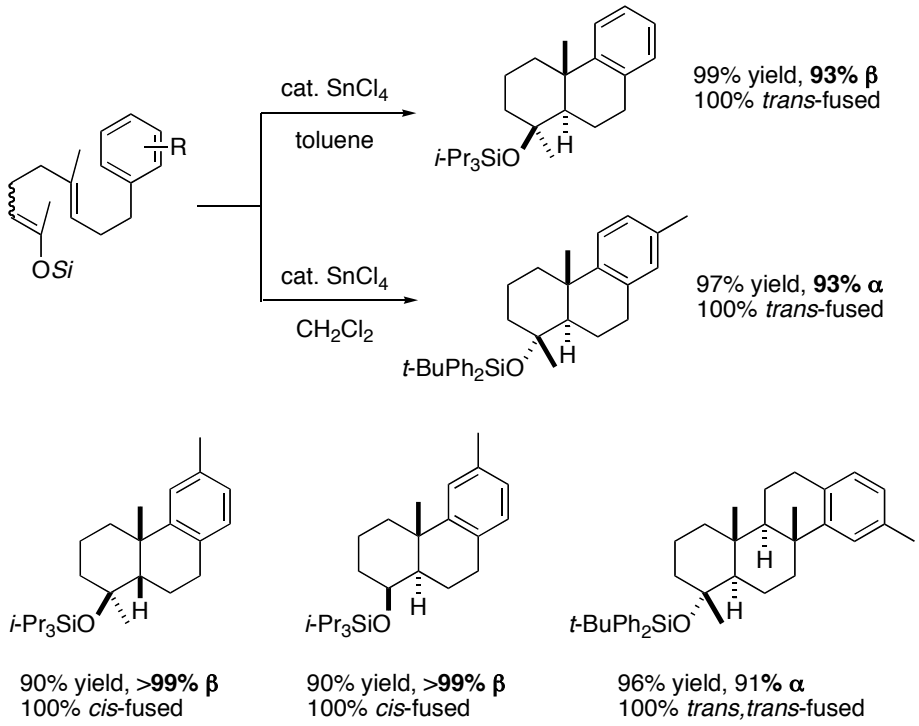
available for the synthesis of 4α(equatorial)-alkoxypolycycles. Although it was difficult to directly generate silyloxocarbenium ion intermediates from aldehydes and ketones with silyl Lewis acids, we succeeded in their catalytic generation with $SnCl_4$ from silyl enol ethers instead of carbonyl compounds (Figure 3). This chapter describes the $SnCl_4$ (10 mol%)-catalyzed polycyclization of homo(polyprenyl)arene analogues bearing terminal siloxyvinyl groups, which were much more reactive than other initiators such as acetals, aldehydes, and ketones.[17]



Scheme 7. Johnson's approach and our approach for the diastereoselective synthesis of 4-hydroxy polycyclic terpenoids

For example, cyclization of the triisopropylsilyloxy analogue of homogeranylbenzene induced by $SnCl_4$ gave *trans*-fused β-siloxy tricyclic product

with 93% ds. On the other hand, the cyclization of its *tert*-butyldiphenylsilyloxy analogue induced by $SnCl_4$ gave *trans*-fused α-siloxy tricyclic product with 93% ds (Scheme 8). These diastereoselectivities were independent of the (*E*)/(*Z*)-stereochemistry and *endo*/*exo*-regiochemistry of the terminal trialkylsilyloxyvinyl group of the starting materials.

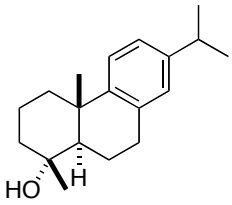


Scheme 8. Polycyclization of trialkylsilyloxy analogues of homo(polyprenyl)arenes

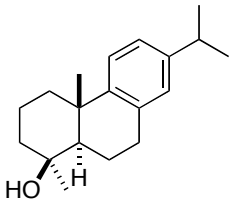
The α (equatorial)/ β (axial) selectivity of the 4-siloxy group at polycycles could be controlled by the nucleophilicity of *pro*-C(9) and the steric effect of a silyl group. A strong nucleophilicity of *pro*-C(9), a (6*E*)-geometry and a bulky silyl group effectively favored the 4α-preference (up to 95% ds), while a weak nucleophilicity of *pro*-C(9), a (6*Z*)-geometry and less steric hindrance of a silyl group favored the 4β-preference (up to >99% ds) (Schemes 7 and 8). Similarly, the cyclization of

homonerylarene, homogeranylarene derived from aldehyde, and homofarnesylarene analogues gave *cis*-fused β–isomer, *trans*-fused β–isomer, and *trans*,*trans*-fused α –isomer with >99% ds, 100% ds, and 91% ds, respectively (Scheme 8). Thus, we succeeded in the stereoselective synthesis of α- and β-trialkylsiloxy-substituted diastereomers. In Chapter 3, we also discuss the reaction mechanism as well as the substrate scope and some limitations.

With this new polyene cyclization approach, two natural diterpenoids, 18-norabieta-8,11,13-trien-4-ol,[18] which has antibacterial activity, and its 4-epimer,[18] were diastereoselectively synthesized from the corresponding silyl (6*E*)-dienol ethers, with >99% 4α and >99% 4β, respectively (Scheme 9).



18-*nor*-abieta-8,11,13-trien-4-ol
89% yield (2 steps), **>99% α**



19-*nor*-abieta-8,11,13-trien-4-ol
95% yield (4 steps), **>99% β**

Scheme 9. Application to natural product synthesis

In summary, a biomimetic polyene cyclization based on the concept of LBA has been applied to the total synthesis of naturally occurring acid-sensitive sesquiterpene ethers. Furthermore, a new polyene cyclization toward A-ring functionalized polycycles has been developed and applied to the total synthesis of some diterpenoids. The details are presented in the following chapters.

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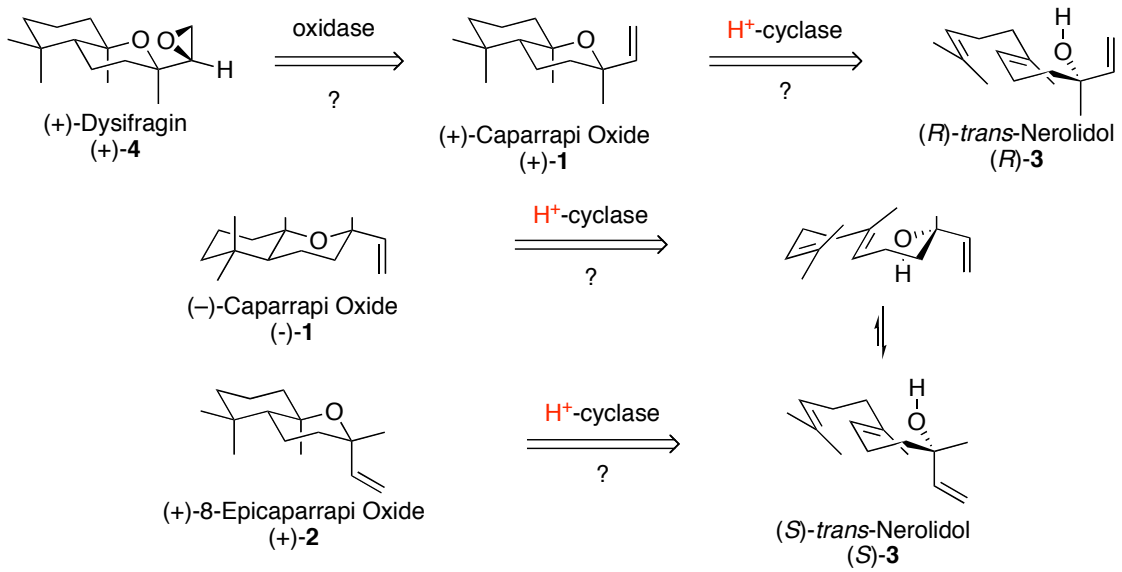
Chapter 2

Biomimetic Synthesis of Acid-Sensitive (–)- and (+)-Caparrapi Oxides, (–)- and (+)-8-Epicaparrapi Oxides, and (+)-Dysifragin induced by Artificial Cyclases

Abstract: Asymmetric total synthesis of acid-sensitive (–)- and (+)-caparrapi oxides and (+)-8-epicaparrapi oxide from farnesol are achieved using Sharpless–Katsuki epoxidation and Lewis acid-assisted chiral Brønsted acid (chiral LBA)-induced polyene cyclization as key steps. The relative configuration of (+)-dysifragin is determined by a single-crystal X-ray diffraction and its total synthesis is accomplished by the diastereoselective epoxidation of (+)-caparrapi oxide. Furthermore, (–)-caparrapi oxide can be directly synthesized from (*S*)-nerolidol and (*R*)-LBA with 88% ds by reagent control which overcame substrate control, while (–)-caparrapi oxide is obtained from (*R*)- nerolidol and (*R*)-LBA with >99% ds by the double asymmetric induction.

Introduction

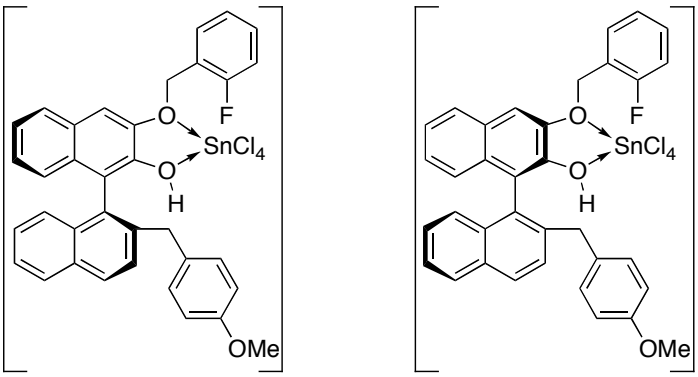
Natural bicyclic sesquiterpene ethers such as (5*S*,8*S*,10*S*)-(–)- and (5*R*,8*R*,10*R*)-(+)-caparrapi oxides (**1**)[1,2] and 8-epicaparrapi oxide (**2**)[3] can be formally derived by biomimetic proton-induced cyclization of (*S*)-(+)- or (*R*)-(–)-nerolidol (**3**) (Scheme 1). (–)-**1** has been isolated from the neutral fraction of the essential oil of *Ocotea caparrapi Nates* (Dugand).[1] On the other hand, (+)-**1** and (+)-dysifragin (**4**) have been isolated from the sponge *Dysidea fragilis Montagu* (family Dysideidae).[2] However, the absolute and relative stereochemistry of (+)-**4** has not been determined. 8-Epicaparrapi oxide **2** has been isolated as a minor constituent of the defense secretion of the termite *Amitermes evuncifer*.[3] Unfortunately, it has not yet been confirmed whether the absolute configuration of natural product **2** by analogy to (3*R*,5*R*,8*S*,10*R*)-(+)-3b-bromo-8-epicaparrapi oxide[4] is (5*R*,8*S*,10*R*)-(+).



Scheme 1. Formal biosynthetic routes for bicyclic and tricyclic sesqueterpene ethers **1**,**2**, and **4**.

According to Zefirov and co-workers, the cyclization of (±)-**3** induced by 5 equivalents of HSO_3F gives (±)-**2** diastereoselectively (via substrate control).[5]

However, there have been no successful examples of the diastereoselective cyclization of (±)-**3** to (±)-**1**. Kametani and co-workers obtained a 1:1 diastereomeric mixture of (±)-**1** and (±)-**2** through the cyclization of b-hydroxy phenylselenide derived from 10,11-epoxynerolidol induced by 5.7 equivalents of CF_3CO_2H.[6] To concisely synthesize (+)-**1** and (–)-**1** through the polyene cyclization of (*R*)-**3** and (*S*)-**3**, respectively, asymmetric control with artificial cyclases should be able to overcome substrate control, and both enantiomers of artificial cyclases should be readily available.



(*R*)-**5**•$SnCl_4$ (*S*)-**5**•$SnCl_4$

Figure 1. Artificial cyclases that are available in both enantiomeric forms.

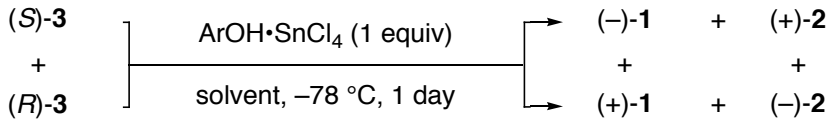
Recently, we demonstrated that Lewis acid-assisted chiral Brønsted acids (chiral LBAs) prepared in situ from chiral alcohols and tin(IV) chloride were highly effective as artificial cyclases for the enantioselective biomimetic cyclization of polyprenoids.[7] For example, tri-, tetra- and pentacyclic terpenpoids bearing a chroman skeleton give products with up to 91% ee by enantioselective cyclization of the corresponding 2-(polyprenyl)phenol derivatives induced by chiral catechol derivative **5**·$SnCl_4$ (Figure 1).[7f] We describe here a concise total synthesis of acid-sensitive bicyclic sesquiterpenes (–)-**1**, (+)-**1** and (+)-**2** based on a biomimetic pathway induced by the chiral LBAs (*R*)-**5**·$SnCl_4$ and (*S*)-**5**·$SnCl_4$ and the

diastereoselective transformation from (+)-**1** to (+)-**4**.[8] The absolute stereochemical structure of (+)-**4** was established by ^{13}C NMR spectroscopic method and X-ray diffraction.

Result and Discussion

First, the diastereoselective cyclization of (±)-**3**, which was obtained commercially, was examined with 1 equivalent of the achiral LBA, 2-methoxyphenol (**6**)·SnCl4, in dichloromethane at –78 °C (entry 1, Table 1). Cyclization of (±)-**3** bearing an acid-sensitive allylic hydroxy group gave a complex reaction mixture, and the desired *trans*-fused 2-oxabicyclo[4.4.0]decanes were obtained in less than 10% yield as a 37:63 mixture of (±)-**1** and (±)-**2**, which were stable under the reaction conditions. This diastereomeric ratio is due to substrate control: transition-state assembly TS-**B** is more favorable than transition-state assembly TS-**A** due to the steric difference between 3-vinyl group and 3-methyl group of (±)-**3** (Figure 2). When (*R*)-**5** was used as a Brønsted acid instead of **6**, a 9:91 mixture of (–)-**1** (91% ee) and (–)-**2** (78% ee) was obtained in 32% yield (entry 3). This result indicates that (+)-**2** and (–)-**2** were obtained from (*S*)-**3** and (*R*)-**3** with 55% and >99% diastereoselectivity, respectively. In the former case, low diastereoselectivity was observed due to the mismatch in asymmetric induction between substrate control and reagent control. In the latter case, high diastereoselectivity was observed due to the double asymmetric induction of substrate control and reagent control. The use of toluene in place of CH_2Cl_2 lowered the chemical yield of **1** and **2**, but raised their enantioselectivities to 97% ee and 90% ee. Notably, (–)-**1** was obtained from (*S*)-**3** with 88% diastereoselectivity due to reagent control, which overcame substrate control. The activated proton in (*R*)-**5**·$SnCl_4$ preferentially attacked the *si*-face of the terminal isoprenyl group because the OH/π interaction between (*R*)-**5**·$SnCl_4$ and **3** in the initial protonation step should be stronger in less polar solvents like toluene.[7f]

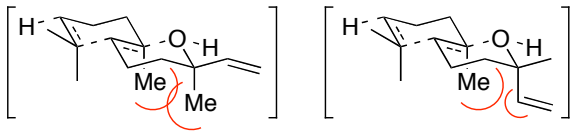
Table 1. Double asymmetric induction in the cyclization of (±)-**3** with (*R*)-**5**·$SnCl_4$



Entry	ArOH	Solvent	Yield [%][a] **1**+**2**	Ratio[b] (+)-**1** : (–)-**1** : (+)-**2** : (–)-**2**	Ratio **1** : **2**	Ee [%] (rotn.) **1**, **2**	From (*S*)-**3** (–)-**1** : (+)-**2**	From (*R*)-**3** (+)-**1** : (–)-**2**
1	**6**[c]	CH_2Cl_2	<10	18.5 : 18.5 : 31.5 : 31.5	37 : 63	–	37 : 63	37 : 63
2	**6**[c]	Toluene	0	–	–	–	–	–
3	(*R*)-**5**	CH_2Cl_2	32	0.4 : 8.2 : 9.9 : 81.5	9 : 91	91 (–), 78 (–)	45 : 55	<1 : >99
4	(*R*)-**5**	Toluene	13	0.4 : 27.5 : 3.7 : 68.4	28 : 32	97 (–), 90 (–)	88 : 12	<1 : >99

[a] Isolated yield. [b] The ratio was determined by GC analysis (PEG and b-DM columns).

[c] 2-Methoxyphenol (**6**).



TS-**A** *(favored)* TS-**B** *(disfavored)*

Figure 2. TS-**A** and TS-**B** in the proton-induced cyclization of (±)-**3**.

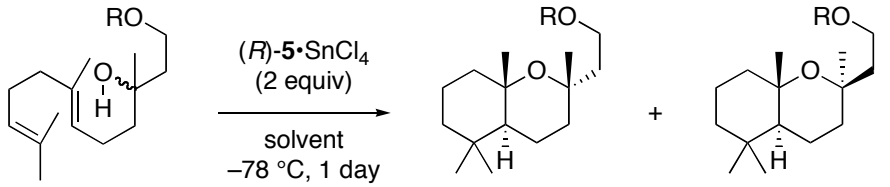
To improve the chemical yield of **1** or **2** (±)-(*E*)-3,7,11-trimethyl-6,10-dodecadiene-1,3-diol derivatives **7a–f**, which were less acid-sensitive than (±)-**3**, were examined as substrates for cyclization with (*R*)-**5**·$SnCl_4$ (Table 2).

Although the cyclizations of 1,3-diol **7a** and 1-*tert*-butyldiphenylsilyl ether **7b** were carried out in the presence of 2 equivalents of (*R*)-**5**·$SnCl_4$ in toluene at –78 °C for 1 day, no desired bicyclic ethers were obtained, probably due to the tight bidentate-chelation between the substrates and $SnCl_4$ (entries 1 and 2). This

undesirable chelation disturbs not only the generation of (*R*)-**5**·$SnCl_4$ but also the internal nucleophilic attack of the 3-hydroxy group in the final step of the cyclization of **7** (Figure 3). In the course of screening various protecting groups for the 1-hydroxy group of **7a**, we found that 1-acylates such as 1-benzoate **7e** and 1-phenylacetate **7f** were effective for the cyclization of **7** and gave *trans*-fused 2-oxabicyclo[4.4.0]decanes **8** and **9** (entries 5–9). Interestingly, aliphatic esters such as isovalerate **7c** were inert under the same reaction conditions (entry 3), and 3-phenylpropionate **7d** was less reactive than **7e** and **7f** (entry 4). These experimental data suggest the existence of some attractive interaction between Sn(IV) and a phenyl group of **7e** and **7f** (Figure 3). The cyclization of (±)-**7f** with (*R*)-**5**·$SnCl_4$ gave a 62:38 mixture of (–)-**7f** (87% ee) and (–)-**8f** (82% ee) in 29% yield (entry 6). Judging from the enantioselectivity and chemical yield of **8** and **9**, (±)-**7f** gave slightly better results than (±)-**7e** (entry 5 versus entry 6). Next, the solvent effect was investigated in the cyclization of (±)-**7f** with (*R*)-**5**·$SnCl_4$ (entries 6–8): the enantioselectivity was higher in the order CH_2Cl_2 << toluene < chloropropane, while the chemical yield of **8** and **9** increased in the order toluene < chloropropane << CH_2Cl_2. Thus, chloropropane was superior to toluene with respect to both enantioselectivity and reactivity. Finally, when a 1:1 mixed solvent of chloropropane and CH_2Cl_2 was used, a 44:56 mixture of (–)-**8f** (82% ee) and (–)-**9f** (82% ee) was obtained in 65% yield (entry 9). These experimental results indicate that the substrate control of **7** is relatively lower than that of **3** because of little difference in the thermodynamic stabilities of **8** and **9** (Table 1 versus Table 2).

Fortunately, **8f** and **9f** were easily separable by column chromatography on silica gel. In contrast, it was difficult to separate **1** and **2** without any chemical modification.[6]

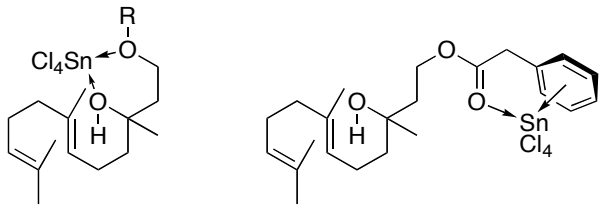
Table 2. Double asymmetric induction in the cyclization of (±)-**7** with (*R*)-**5**·$SnCl_4$



(±)-**7a–f** (–)-**8a–f** (–)-**9a–f**

Entry	R, **7**	Solvent	Yield (%)[a] **8** + **9**	Ratio[b] (+)-**8** : (–)-**8** : (+)-**9** : (–)-**9**	Ratio **8** : **9**	Ee (%) (–)-**8**, (–)-**9**
1	H, **7a**	Toluene	0	–	–	–
2	Si*t*-$BuPh_2$, **7b**	toluene	0	–	–	–
3	CO*i*-Bu, **7c**	toluene	0	–	–	–
4	$CO(CH_2)_2Ph$, **7d**	toluene	16	3.7 : 49.3 : 4.5 : 42.5	53 : 47	86, 81
5	COPh, **7e**	toluene	21	5.8 : 49.2 : 4.0 : 41.0	55 : 45	79, 82
6	COBn, **7f**	toluene	29	4.0 : 58.0 : 3.4 : 34.6	62 : 38	87, 82
7	COBn, **7f**	CH_2Cl_2	78	8.5 : 38.5 : 8.7 : 44.3	47 : 53	64, 67
8	COBn, **7f**	PrCl	41	3.1 : 48.9 : 2.6 : 45.4	52 : 48	88, 89
9	COBn, **7f**	CH_2Cl_2–PrCl[c]	65	4.0 : 40.0 : 5.0 : 51.0	44 : 56	82, 82

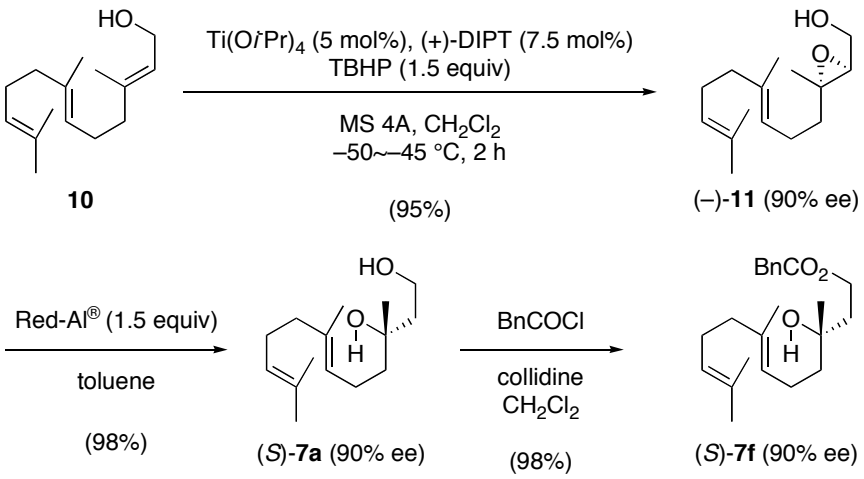
[a] Isolated yield. [b] The ratio was determined by GC (PEG column) and HPLC analyses (AD-H columns). [c] A 1:1 (v:v) mixed solvent.



Undesirable chelation *Desirable chelation*

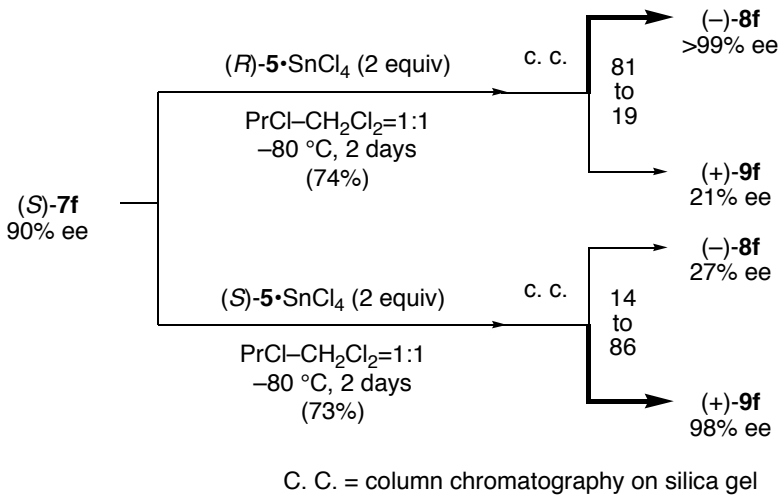
Figure 3. Predictable chelation structures of **7** with $SnCl_4$.

Compound (*S*)-**7f** had to be prepared to synthesize (–)-**8f**, which is a synthetic precursor of (–)-caparrapi oxide **1**.[8] (*S*)-**7f** was prepared with 90% ee in 91% overall yield from farnesol (**10**) in three steps (Scheme 2): a) Sharpless–Katsuki epoxidation of **10** to (2*S*,3*S*)-(–)-epoxyfarnesol (**11**) with 90% ee,[9] b) regioselective reduction of (–)-**11** to (*S*)-**7a** (>99% regioselectivity) with Red–Al® (65% sodium bis(2-methoxyethoxy)aluminum hydride in toluene),[10] and c) regioselective acylation of (*S*)-**7a** with phenylacetyl chloride to (*S*)-**7f** (>99% regioselectivity).[11]



Scheme 2. Preparation of (*S*)-**7f**

The asymmetric cyclization of (*S*)-**7f** induced by 2 equivalents of (*R*)-**5**·$SnCl_4$ gave an 81:19 mixture of (–)-**8f** (>99% ee) and (+)-**9f** (21% ee) in 74% yield. On the other hand, the asymmetric cyclization of (*S*)-**7f** induced by 2 equivalents of (*S*)-**5**·$SnCl_4$ gave a 14:86 mixture of (–)-**8f** (27% ee) and (+)-**9f** (98% ee) in 73% yield. These experimental results indicate that the substrate control of **7f** was much lower than the reagent control by **5**·$SnCl_4$. Optically pure (–)-**8f** and (+)-**9f** were easily separated by column chromatography on silica gel (Scheme 3).

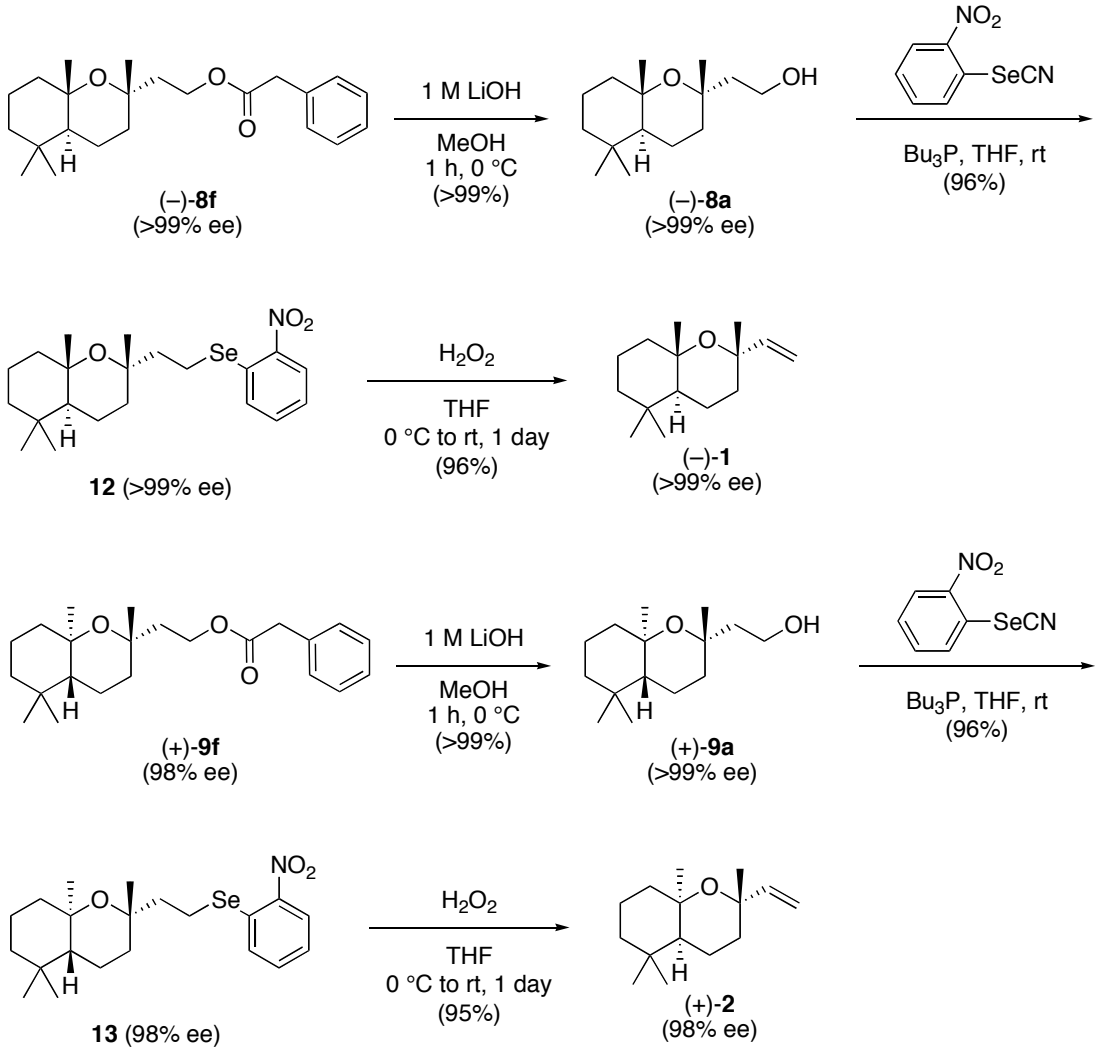


Scheme 3. Diastereoselective Preparation of (-)-**8f** and (+)-**9f** from (*S*)-**7f**

Optically pure (–)-caparrapi oxide **1** was obtained in 92% overall yield from (–)-**8f** in three steps (Scheme 4): hydrolysis of (–)-**8f** to (–)-**8a** under basic conditions and subsequent Grieco elimination to (–)-**1** through alkyl *o*-nitrophenyl selenide **12**.[12] In the same manner, (+)-8-epicaparrapi oxide **2** (98% ee) was obtained in 91% overall yield from (+)-**9d**: a) hydrolysis of (+)-**9f** to (+)-**9a** (>99%), b) *o*-nitrophenylselenylation of **9a** (96%), and c) oxidative elimination of **13** to (+)-**3** (95%).

(+)-Caparrapi oxide **1** and its epoxide, (+)-dysifragin **4**, have been isolated from the sponge *Dysidea fragilis* Montagu.[2] However, the absolute and relative stereochemistry of (+)-**4** is not determined. To elucidate the structure of (+)-**4**, it was necessary to synthesize diastereomeric epoxides of (+)-**1** in enantiomerically pure form. Diastereoselective epoxidation of (+)-**1**, which was synthesized from (+)-**11** as above, was examined with various oxidants. The representative results sre shown in Table 3. In most cases, unfortunately, the diastereomer of (+)-**4**, (+)-**14**, was obatined as a major product. However, two diastereomers were easily separated by flash column chromatography on silica gel. Peroxytrifluoroacetic acid prepared from urea

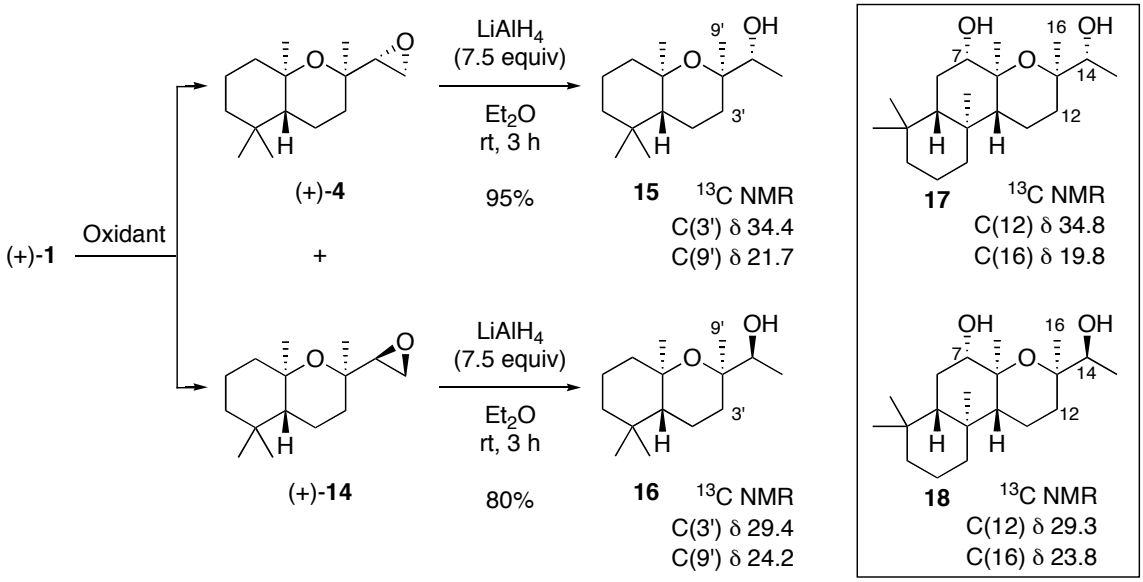
hydrogen peroxide and trifluoroacetic anhydride in situ gave the best result: (+)-**4** was obtained with 50% ds (entry 1).



(–)-**8f** (>99% ee)
(–)-**8a** (>99% ee)
12 (>99% ee)
(–)-**1** (>99% ee)
(+)-**9f** (98% ee)
(+)-**9a** (>99% ee)
13 (98% ee)
(+)-**2** (98% ee)

Scheme 4. Synthetic transformation to (-)-**1** and (+)-**2** using Grieco's method[12]

Table 3. Diastereoselective epoxidation of (+)-**1**



Entry	Oxidant (equiv)	Additives (equiv)	Solvent	Temp (°C), Time (h)	Yield (%)[a] (+)-**4** + (+)-**14**	Ratio[b] (+)-**4** : (+)-**14**
1[a]	H_2O_2•$(H_2N)_2CO$ (10) $(CF_3CO)_2O$ (2.5)	K_2HPO_4 (8.8)	CH_2Cl_2	23, 3	97	50 : 50
2	*m*CPBA (1.5)	–	CH_2Cl_2	23, 24	96	45 : 55
3[b]	Oxone (5) Acetone (10)	Na_2CO_3 (5)	EtOAc–water	23, 16	70	37 : 63
4[c]	H_2O_2 (4)	$MeReO_3$ (0.015) 3-Cyanopyridine (0.3)	Pyridine	23, 72	95	35 : 65

[a] Ref. 14. [b] Ref. 15. [c] Ref. 16.

^{1}H NMR, ^{13}C NMR, and IR spectra and absolute values of the specific rotation for synthetic product (+)-**4** and for natural dysifragin[2] were nearly identical. Based on the Rodriguez' ^{13}C NMR method for the determination of C(14) configuration of 8,13-epoxylabdane-7,14-diols, **17** and **18**,[13] the relative stereochemistries of (+)-**4** and (+)-**14** were presumed by ^{13}C NMR spectral analysis of

15 and **16**, which were transformed from (+)-**4** and (+)-**14**, respectively, by the regioselective reductive cleavage using lithium aluminum hydride (Table 3): the C(3') and C(9') chemical shifts of **15** were analogous to the C(12) and C(16) chemial shifts of **17**, while the C(3') and C(9') chemical shifts of **16** were analogous to the C(12) and C(16) chemial shifts of **18**.

Fortunately, the relative stereochemical structure of (+)-**4** was determined by its X-ray diffraction (Figure 4), and it was ascertained that the Rodriguez' ^{13}C NMR method[13] was also useful for determination of analogous chemical structures like dysifragin.

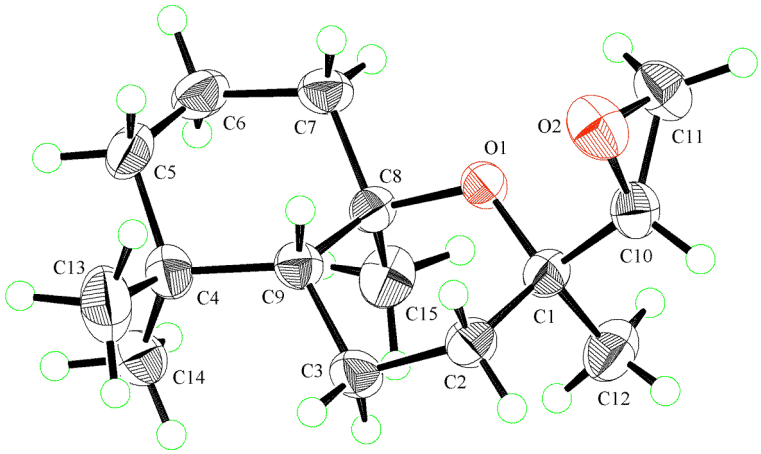
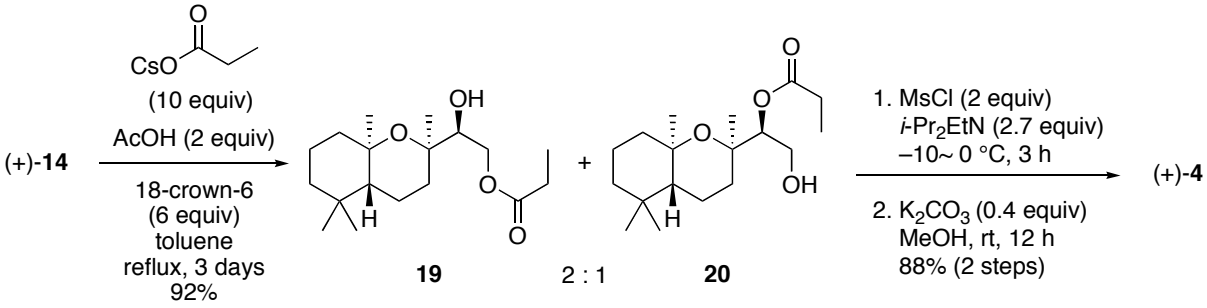


Figure 4. X-ray diffraction of (+)-**4**

Unnatural diastereomer (+)-**14** could be transformed to (+)-**4** with three steps in 81% yield according to the Prieto's method[17] (Scheme 5): the treatment of **14** with cesium propionates as the epoxide-cleaving agent gave a 2:1 molar mixture of regioisomeric propionates, **19** and **20**, that was mesylated and methanolyzed to produce the inverted epoxide (+)-**4**. Thus, (+)-**4** was obtained in 88% over all yield from (+)-**1**.



Scheme 5. Inversion from (+)-**14** to (+)-**4**[17]

Conclusions

In summary, we have demonstrated that the chiral LBA **5**·$SnCl_4$ is an artificial cyclase that is useful for both achiral and chiral substrates: (–)-caparrapi oxide **1** and (+)-8-epicaparrapi oxide **2** could be diastereoselectively synthesized from (*S*)-**7f** by the reagent control of (*R*)-**5**·$SnCl_4$ and (*S*)-**5**·$SnCl_4$, respectively, regardless of the chirality of (*S*)-**7f**. Furthermore, in the cyclization of (±)-**3** induced by (*R*)-**5**·$SnCl_4$, (–)-**1** was diastereoselectively obtained from (*S*)-**3** by reagent control which overcame substrate control, while (–)-**2** was highly diastereoselectively obtained from (*R*)-**3** by the double asymmetric induction of substrate control and reagent control. (+)-Dysifragin **4** was synthesized from (+)-**1** in high yield and its structure was fully determined by X-ray diffraction (Figure 4).

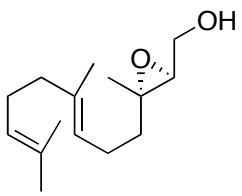
Experimental Section

General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 (300 MHz) or Varian INOVA-500 (500 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a Varian Gemini-2000 (75 MHz) or Varian INOVA-500 (125 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). High-performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm x 25 cm) or Daicel CHIRALPAK AD-H (4.6 mm x 25 cm). Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. GC analysis was performed with Shimadzu 17A instruments using PEG (0.25 mm x 25 m). All experiments were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University. In experiments that required dry solvent, ether and tetrahydorofuran (THF) were purchased from Aldrich or Wako as the “anhydrous” and stored over 4A molecular sieves. Hexane, toluene, 1-chloropropane, and dichloromethane were freshly distilled from calcium hydride. Tin(IV) chloride was distilled under nitrogen. Other simple chemicals were analytical-grade and obtained commercially

Preparation of Chiral Catechol Derivatives (Chiral BA of (*S*)-5 and (*R*)-5):[7f] Chiral catechols (*S*)- and (*R*)-**5** were prepared from (*R*)-BINOL and (*S*)-BINOL, respectively.

Diastereoselective Cyclization of *trans*-Nerolidol Induced by Chiral LBA 5·$SnCl_4$ (Table 1): To a solution of chiral catechol (*R*)-**5** (154 mg, 0.30 mmol) or 2-methoxyphenol (**6**, 33 mL , 0.30 mmol) in toluene or CH_2Cl_2 (6 mL) was added a 1 *M* solution of tin(IV) chloride in hexane (for toluene as reaction solvent) or CH_2Cl_2 (for CH_2Cl_2 as reaction solvent) (300 mL, 0.30 mmol) under N_2 at room temperature, and the mixture was stirred for 5 min. After the solution was cooled to –78 °C, *trans*-nerolidol (85 mL, 0.30 mmol) was added dropwise. The reaction mixture was stirred for 1 day, quenched with saturated aqueous $NaHCO_3$, and extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane–ether = 50:1~30:1) to give bicyclic compounds contained a small amount of unknown products. **1** and **2** could not be separated by column chromatography on silica gel.[6] See Table 1 on the paper for yield of bicyclic compounds.

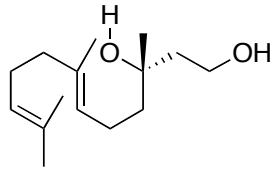
Total Synthesis of (5*S*,8*S*,10*S*)-(–)-Caparrapi Oxide (1) and (5*R*,8*S*,10*R*)-(+)-Epicaparrapi Oxide (2) from Farnesol (10).



(2*S*,3*S*)-(–)-Epoxyfarnesol (11):[9b,d] A mixture of powdered, activated 4A molecular sieves (20 mg) and CH_2Cl_2 (1 mL) was cooled to –20 °C. L-(+)-Diisopropyl tartrate (L-(+)-DIPT, 18 mg, 0.075 mmol, Aldrich) and Ti(O*i*-Pr)$_4$

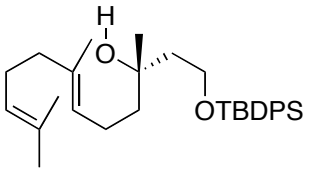
(14 mg, 15 mL, 0.05 mmol, distilled) were added sequentially. After the mixture was cooled to –50 °C, TBHP (400 mL, 1.50 mmol, 3.74 *M* in toluene) was added and the resulting mixture was stirred for 30 min, whereupon freshly distilled *trans, trans*-farnesol (222 mg, 1.00 mmol) was added. Stirring was maintained for 2 h at –50 ~ –45 ° C. Diluted with 10% aqueous tartaric acid solution (5 mL) and stirred at same temperature for further 30 min, and the reaction mixture was allowed to warm to room temperature and the stirring was continued for 1 h. Extracted with CH_2Cl_2 (3 × 10 mL) and washed with water, dried over anhydrous Na_2SO_4 and concentrated. To a residual oil in ether (10 mL) was added aqueous 1 *M* NaOH (3 mL) and the mixture was stirred at 0 °C for 30 min. Extracted with ether (3 × 10 mL), washed with NH_4Cl and brine, dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 4:1) to give **11** (226 mg, 0.95 mmol, 95% yield with 90% ee. TLC (hexane–EtOAc, 2:1) R_f = 0.40; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (s, 3H), 1.45–1.75 (m, 2H), 1.61 (s, 6H), 1.68 (s, 3H), 1.95–2.14 (m, 7H), 2.99 (dd, *J* = 4.5, 6.6 Hz, 1H), 3.69 (ddd, *J* = 4.8, 6.6, 11.7 Hz, 1H), 3.81 (ddd, *J*=4.5, 7.5, 11.7 Hz, 1H), 5.05–5.13 (m, 2H). Determination of the ee value of 11 via mosher ester: A mixture of 4-(dimethylamino)pyridine (DMAP, 5 mg, 0.04 mmol) and Et_3N (27 mL) in CH_2Cl_2 (140 mL) was treated with 10 (9.8 mg, 0.04 mmol). Immediately, (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl, 8mL) was added. After 30 min, quenched with water, dried, and concentrated. The residue was through pipette column on silica gel to give MTPA ester of epoxyfarnesol (90% ee). TLC (hexane-EtOAc, 4:1) R_f= 0.46; ^{1}H NMR analysis focused on the M or AB part of the ABM pattern, ^{1}H NMR (C_6D_6, 300 MHz) δ 0.97 (s, 3H), 1.22-1.45 (m, 2H), 1.50 (s, 3H), 1.56 (s, 3H), 1.68 (s, 3H), 1.90-2.20 (m, 8H), 2.74 (dd, *J* = 4.5, 7.2 Hz, 1H, M part of ABM pattern, major diastereomer, while appearing of minor diastereomer at δ 2.84), 3.43 (s, 3H), 4. 04 (dd, *J*= 7.2, 12.0 Hz, 1H,

A part of ABM pattern, major diastereomer, while appearing of minor diastereomer at δ 3.87), 4.18 (dd, *J*= 4.5, 12.0 Hz, 1H, B part of ABM pattern, major diastereomer, while appearing of minor diastereomer at δ 3.91), 5.08 (t, *J* = 7.2 Hz, 1H), 5.21 (t, *J* = 7.2 Hz, 1H), 7.00-7.13 (m, 3H), 7.71 (d, *J* = 7.8 Hz, 2H).

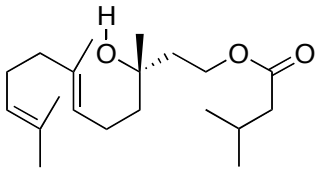


(*S*)-3,7,11-Trimethyl-6,10-dodecadiene-1,3-diol (7a):[10] A 100-mL flask was charged with **(–)-11** (1.458 g, 6.12 mmol) and dry toluene(17 mL). The mixture was stirred under N_2 at 0°C during the addition of Red-Al® (Kanto, 65% sodium bis(2-methoxyethoxy)aluminum hydride in toluene, 1.95 mL, 6.50mmol). The reaction was allowed to warm to room temperature, over 3 h, at which time TLC analysis of an acidified sample disclosed the formation of single polar product. The reaction was cooled to 0 °C and quenched by addition of 2-propanol (2 mL). Acidification with 5% aqueous HCl was followed by phase separation and washing the organic layer with water and brine and drying over anhydrous $MgSO_4$. The residue was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 2:1) to give 7a (1.440 g, 5.99 mmol, 98% yield) as colorless oil. TLC (hexane–EtOAc, 1:1) R_f=0.16; IR (film) 3550–3150, 2973, 2929, 2858, 1436, 1379, 1110, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (s, 3H), 1.54–1.71 (m, 3H), 1.60 (s, 3H), 1.63 (s, 3H), 1.68 (s, 3H), 1.81 (ddd, *J* = 4.8, 7.5, 15.0 Hz, 1H), 1.97–2.14 (m, 6H), 2.34 (brs, 1H), 2.78 (brs, 1H), 3.86–3.95 (m, 2H), 5.08 (t, *J* = 7.0 Hz, 1H), 5.15 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6, 17.3, 22.3, 25.3, 26.1, 26.3, 39.4, 41.3, 42.0, 58.8, 72.9, 123.9, 124.0, 130.7, 134.6; $[a]^{22.3}_D$ = 0.80 (*c* 2.0, $CHCl_3$) for 90% ee; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{28}O_2Na$ (M + Na) 263.1987, found 263.1980.

Selective Silylation or Acylation of 1-Hydroxy Group of 7a.[11]

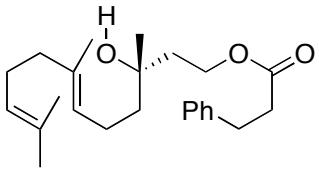


(±)-1-*t*-Butyldimethylsiloxy-3,7,11-trimethyl-6,10-dodecadi ene-3-ol (7b): To a solution of **7a** (1.010g, 4.20 mmol) and imidazole (572 mg, 8.4 mmol) in *N*,*N*-dimethylformamide (DMF, 8 mL) was added slowly *t*-butylchlorodiphenylsilane (1.196 mL, 4.60 mmol) in DMF (2 mL) at room temperature. After stirring 3 h at rt, quenched with water, extracted with hexane, washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 10:1) to give **7b** (2.01 g, 4.20 mmol, 100% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.44; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 9H), 1.24 (s, 3H), 1.50–1.85 (m, 4H), 1.60 (s, 6H), 1.68 (s, 3H), 1.94–2.12 (m, 6H), 3.71 (s, OH), 3.92 (t, *J* = 7.2 Hz, 2H), 5.08–5.16 (m, 2H), 7.37–7.44 (m, 6H), 7.68–7.71 (m, 4H).



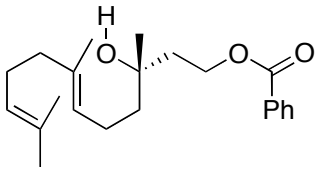
(±)-1-Isovaleryloxy-3,7,11-trimethyl-6,10-dodecadiene-3-ol (7c): To a solution of **7a** (159 mg, 0.66 mmol), 2,4,6-collidine (114 mL, 0.86 mmol) in CH_2Cl_2 (1.3 mL) at –78 °C under N_2 was added isovaleryl chloride (105 mL, 0.86 mmol) dropwise and stirred for 5 h at –78 °C. Then 1 *M* HCl was poured into this mixture, extracted with hexane (twice), washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 10:1) to give **7c** (204 mg, 0.63 mmol, 95% yield) as

colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.30; IR (film) 3600–3250 (br, OH), 2968, 2930, 2872, 1726 (C=O), 1523, 1436, 1385, 1296, 1120, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (d, *J* = 6.3 Hz, 3H), 1.06 (s, 3H), 1.34–1.39 (m, 2H), 1.44 (s, 3H), 1.46 (s, 3H), 1.52 (s, 3H), 1.67 (dt, *J* = 1.5, 6.9 Hz, 2H), 1.80–2.03 (m, 9H), 4.08 (t, *J* = 6.9 Hz, 2H), 4.90–5.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.9, 17.6, 22.3 (2C), 22.5, 25.6 (2C), 26.5, 26.8, 39.6, 39.7, 42.1, 43.4, 60.9, 71.7, 123.9, 124.1, 131.3, 135.4, 173.1; HRMS (FAB) *m*/*z* calcd for $C_{20}H_{36}O_3Na$ (M + Na) 347.2562, found 347.2572.

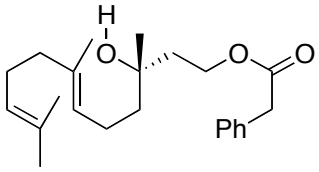


(±)-1-(3-Phenylpropionyloxy)-3,7,11-trimethyl-6,10-dodecadiene-3-ol (7d): To a solution of **7a** (180 mg, 0.75 mmol), 2,4,6-collidine (130 mL, 0.98 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C under N_2 was added hydrocinnamoyl chloride (146 mL, 0.98 mmol) dropwise and stirred for 5 h at –78 °C. Then 1 *M* HCl was poured into this mixture, extracted with hexane (twice), washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 8:1) to give **7d** (265 mg, 0.71 mmol, 95% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.28; IR (film) 3600–3250 (br, OH), 2972, 2928, 2863, 1728 (C=O), 1454, 1383, 1046, 929 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (s, 3H), 1.46–1.52 (m, 2H), 1.59 (s, 3H), 1.61 (s, 3H), 1.67 (s, 3H), 1.78 (dt, *J* = 2.1, 7.2 Hz, 2H), 1.96–2.07 (m, 7H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.93 (t, *J* = 7.8 Hz, 2H), 4.23 (t, *J* = 6.9 Hz, 2H), 5.06–5.14 (m, 2H), 7.16–7.20 (m, 3H), 7.24–7.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.9, 17.5, 22.4, 25.6 (2C), 26.5, 26.7, 30.8, 35.8, 39.5, 42.0, 61.2, 71.6, 123.9, 124.1, 126.1, 128.1 (2C), 128.3 (2C), 131.2, 135.3, 140.2, 172.8; HRMS (FAB) *m*/*z* calcd for $C_{24}H_{36}O_3Na$ (M + Na) 395.2562, found

395.2576.



(±)-1-Benzoxy-3,7,11-trimethyl-6,10-dodecadiene-3-ol (7e): To a solution of **7a** (240 mg, 1.0 mmol), pyridine (105 mL, 1.3 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 was added benzoyl chloride (151 mL, 1.3 mmol) drop wise and stirred for 10 h at –78 °C. Then 1 *M* HCl was poured into this mixture, extracted with hexane (twice), washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 10:1) to give **7e** (327 mg, 0.95 mmol, 95% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.23; IR (film) 3600–3250 (br, OH), 2972, 2928, 2858, 1714 (C=O), 1452, 1279, 1114 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (s, 3H), 1.50–1.70 (m, 2H), 1.60 (s, 3H), 1.62 (s, 3H), 1.68 (s, 3H), 1.79 (s, 1H), 1.96–2.15 (m, 8H), 4.50 (t, *J* = 7.0 Hz, 2H), 5.08 (t, *J* = 7.0 Hz, 1H), 5.14 (t, *J* = 7.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.0, 17.7, 22.5, 25.7, 26.6, 27.0, 39.6, 39.8, 42.2, 61.7, 71.9, 123.9, 124.1, 128.3 (2C), 129.5 (2C), 130.2, 131.5, 132.9, 135.6, 166.6; HRMS (FAB) *m*/*z* calcd for $C_{22}H_{32}O_3Na$ (M + Na) 367.2249, found 367.2245.

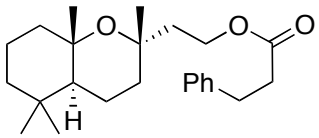


(*S*)-1-Phenylacetoxy-3,7,11-trimethyl-6,10-dodecadiene-3-ol (7f): To a solution of **7a** (841 mg, 3.50 mmol), 2,4,6-collidine (604 mL, 4.55 mmol) in CH_2Cl_2 (7 mL) at –78 °C under N_2 was added phenyl acetyl chloride (602 mL, 4.55 mmol) dropwise and stirred for 5 h at -78 °C. Then 1 *M* HCl was poured into this mixture,

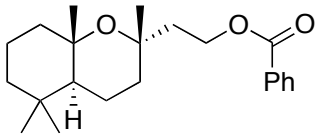
extracted with hexane (twice), washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane-ethyl acetate = 10:1) to give **7f** (1.23 mg, 3.43 mmol, 98% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.22; HPLC (two linear OD-H columns, hexane–*i*-PrOH = 40:1, flow rate=0.5 mL/min) t_R=20.2 min for (*S*)-7f, 21.2 min for (*R*)-7f; IR (film) 3650–3150 (br, OH), 2968, 2925, 2855, 1734 (C=O), 1454, 1257, 1142, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (s, 3H), 1.45–1.53 (m, 2H), 1.60 (s, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 1.81 (t, *J* = 6.9 Hz, 2H), 1.95–2.08 (m, 7H), 3.62 (s, 2H), 4.26 (t, *J* = 6.9 Hz, 2H), 5.05–5.14 (m, 2H), 7.28–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.9, 17.5, 22.4, 25.6, 26.5, 26.6, 39.5 (2C), 41.3, 41.9, 61.6, 71.5, 123.9, 124.1, 127.0, 128.4 (2C), 129.1 (2C), 131.2, 133.7, 135.3, 171.4; $[a]^{22.3}_D$ = –1.70 (*c* 2.0, $CHCl_3$) for 90% ee; HRMS (FAB) *m*/*z* calcd for $C_{23}H_{34}O_3Na$ (M + Na) 381.2406, found 381.2409.

General Procedure for the Diastereoselective Cyclization of 7 Induced by Chiral LBA 5·$SnCl_4$ (Table 2): To a solution of chiral catechol (*R*)-5 (103 mg, 0.20 mmol) in toluene or CH_2Cl_2 or *n*-PrCl (2 mL) was added a 1 *M* solution of tin(IV) chloride in hexane (for toluene as reaction solvent) or CH_2Cl_2 (for CH_2Cl_2 or *n*-PrCl as reaction solvent) (200 mL, 0.20 mmol) at room temperature, and the mixture was stirred for 5 min. After the solution was cooled to –78 °C, 1.0 *M* solution of 7 in toluene (for toluene as reaction solvent) or CH_2Cl_2 (for CH_2Cl_2 or *n*-PrCl as reaction solvent) (100 mL, 0.10 mmol) was added dropwise. The reaction mixture was stirred for 1 day, quenched with saturated aqueous $NaHCO_3$, and extracted with ether. The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane–ether = 10:1 → 5:1 → 2:1) to give bicyclic compounds, chiral catechol and

monocyclic compounds. Further column chromatography (see below for conditions of each compound) of bicyclics gave **8** and **9**. Yields, ratio and enantioselectivity of bicyclics are described in Table 2.

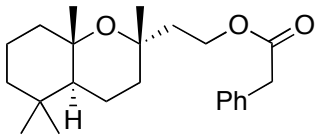


(2'*S*,4'a*S*,8'a*S*)-(–)-2-(2',5',5',8'a-Tetramethyloctahydrochromen-2'-yl)ethyl 3-Phenylpropionate (8d): TLC (hexane–EtOAc, 4:1) R_f = 0.68; column chromatography, hexane–Et_2O = 20:1; HPLC (two linear AD-H columns, hexane–*i*-PrOH = 250:1, flow rate = 0.5 mL/min) t_R=45.1 min for **(+)-8d**, 47.2 min for **(–)-8d**; GC (PEG, column temp. 210 °C, 120 kPa) t_R = 54.3 min; IR (film) 2992, 2938, 2868, 1725 (C=O), 1455, 1377, 1134, 1101, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75 (s, 3H), 0.88 (s, 3H), 1.13–1.82 (m, 10H), 1.24 (s, 3H), 1.25 (s, 3H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.94 (t, *J* = 7.8 Hz, 2H), 4.18 (ddd, *J* = 6.3, 8.4, 11.1 Hz, 1H), 4.25 (ddd, *J* = 6.3, 8.7, 11.1 Hz, 1H), 7.19–7.21 (m, 3H), 7.28–7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.2, 20.0, 20.8, 23.5, 28.1, 30.9, 32.2, 33.4, 36.0, 36.9, 41.4, 41.5, 43.5, 54.1, 61.5, 72.1, 74.9, 126.2, 128.3 (2C), 128.4 (2C), 140.6, 173.1; HRMS (FAB) *m*/*z* calcd for $C_{24}H_{36}O_3Na$ (M + Na) 395.2562, found 395.2576.

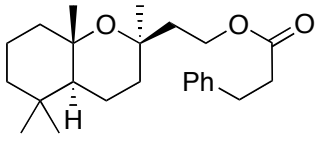


(2'*S*,4'a*S*,8'a*S*)-(–)-2-(2',5',5',8'a-Tetramethyloctahydrochromen-2'-yl)ethyl Benzoate (8e): TLC (hexane–EtOAc, 12:1) R_f = 0.40; column chromatography, hexane–Et_2O = 25:1 ~ 20:1; HPLC (AD-H column, hexane–*i*-PrOH = 200:1, flow rate = 1.0 mL/min) t_R=7.9 min for **(+)-8e**, 8.7 min for **(–)-8e**; GC (PEG, column temp.

210 °C, 120 kPa) t_R = 31.6 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.77 (s, 3H), 0.89 (s, 3H), 1.16–1.71 (m, 11H), 1.28 (s, 3H), 1.31 (s, 3H), 1.83 (ddd, *J* = 6.0, 8.4, 13.8 Hz, 1H), 1.94 (ddd, *J* = 6.0, 8.1, 13.2 Hz, 1H), 4.44 (ddd, *J* = 2.4, 6.0, 11.1 Hz, 1H), 4.50 (ddd, *J* = 1.8, 8.1, 11.1 Hz, 1H), 7.43 (t, *J* = 1.5, 7.5 Hz, 2H), 7.55 (dd, *J* = 1.5, 7.5 Hz, 1H), 8.03 (dd, *J* = 1.5, 7.5 Hz, 2H).

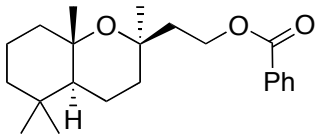


(2'*S*,4'a*S*,8'a*S*)-(–)-2-(2',5',5',8'a-Tetramethyloctahydrochromen-2'-yl)ethyl Phenylacetate (8f): TLC (hexane–EtOAc–CH_2Cl_2, 4:1:1) R_f = 0.62; column chromatography, hexane–Et_2O = 15:1; HPLC (two linear AD-H columns, hexane–*i*-PrOH = 250:1, flow rate = 0.5 mL/min) t_R=39.7 min for **(+)-8f**, 41.2 min for **(–)-8f**; GC (PEG, column temp. 210 °C, 120 kPa) t_R = 39.0 min; IR (film) 2975, 2936, 1726, 1523, 1426, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (s, 3H), 0.87 (s, 3H), 1.07–1.60 (m, 11H), 1.22 (s, 3H), 1.24 (s, 3H), 1.66 (ddd, *J* = 6.3, 8.4, 13.8 Hz, 1H), 1.78 (ddd, *J* = 6.3, 8.4, 13.8 Hz, 1H), 3.60 (s, 2H), 4.20 (ddd, *J* = 6.3, 8.4, 11.1 Hz, 1H), 4.26 (ddd, *J* = 6.3, 8.7, 11.1 Hz, 1H), 7.23–7.24 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 20.7 (2C), 23.4, 28.0, 32.0 (2C), 36.7 (2C), 41.4 (2C), 43.3, 54.0, 61.8, 72.0, 74.6, 126.9, 128.4 (2C), 129.7 (2C), 134.1, 171.7; $[a]^{22.8}_D$ = –8.21 (*c* 1.0, $CHCl_3$) for >99% ee; HRMS (FAB) *m*/*z* calcd for $C_{23}H_{34}O_3Na$ (M + Na) 381.2406, found 381.2409.

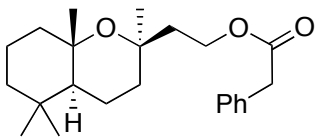


(2'*S*,4'a*R*,8'a*R*)-(+)-2-(2',5',5',8'a-Tetramethyloctahydrochromen-2'-yl)ethyl 3-Phenylpropionate (9d): TLC (hexane–EtOAc, 4:1) R_f = 0.66; column chromatography, hexane–Et_2O = 15:1; HPLC (AD-H column, hexane–*i*-PrOH = 250:1,

flow rate = 1.0 mL/min) t_R = 9.8 min for **(–)-9d**, 14.0 min for **(+)-9d**; GC (PEG, column temp. 210 °C, 120 kPa) t_R = 56.8 min; IR (film) 2982, 2938, 2870, 1726 (C=O), 1456, 1375, 1180, 1100, 974 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (s, 3H), 0.89 (s, 3H), 1.14 (s, 3H), 1.17–1.80 (m, 19H), 1.25 (s, 3H), 2.05 ((quintet, *J* = 7.5 Hz, 1H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.95 (t, *J* = 7.8 Hz, 2H), 4.15–4.27 (m, 2H), 7.19–7.21 (m, 3H), 7.28–7.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.2, 20.2, 20.8, 23.1, 30.5, 31.0, 32.2, 33.5, 36.0, 38.1, 39.4, 41.4, 42.0, 53.5, 61.9, 72.3, 75.3, 126.2, 128.3 (2C), 128.5 (2C), 140.5, 173.0; HRMS (FAB) *m*/*z* calcd for $C_{24}H_{36}O_3SeNa$ (M + Na) 395.2562, found 395.2576.

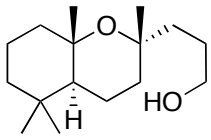


(2'*S*,4'a*R*,8'a*R*)-(+)-2-(2',5',5',8'a-Tetramethyloctahydrochromen-2'-yl)ethyl Benzoate (9e): TLC (hexane–Et_2O–CH_2Cl_2, 12:1) R_f = 0.32; column chromatography, hexane–Et_2O = 20:1 ~ 15:1; HPLC (AD-H column, hexane–*i*-PrOH = 200:1, flow rate = 1.0 mL/min) t_R = 8.1 min for **(–)-9e**, 9.5 min for **(+)-9e**; GC (PEG, column temp. 210 °C, 210 kPa) t_R = 34.4 min; ^1H NMR ($CDCl_3$, 300 MHz) d 0.78 (s, 3H), 0.90 (s, 3H), 1.12–1.70 (m, 10H), 1.23 (s, 3H), 1.32 (s, 3H), 1.84–1.95 (m, 2H), 2.17–2.30 (m, 1H), 4.40–4.51 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 8.04 (dd, *J* = 1.5, 7.5 Hz, 2H).

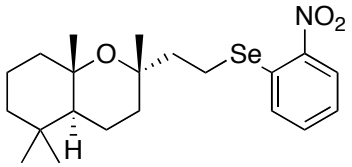


(2'*S*,4'a*R*,8'a*R*)-(+)-2-(2',5',5',8'a-Tetramethyloctahydrochromen-2'-yl)ethyl Phenylacetate (9f): TLC (hexane–Et_2O–CH_2Cl_2, 4:1:1) R_f = 0.60; column chromatography, hexane–Et_2O = 15:1 ~ 10:1; HPLC (AD-H column, hexane–*i*-PrOH =

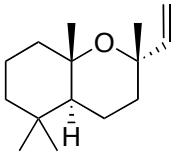
250:1, flow rate = 1.0 mL/min) t_R = 9.4 min for **(–)-9f**, 12.8 min for **(+)-9f**; GC (PEG, column temp. 210 °C, 120 kPa) t_R = 40.1 min; IR (film) 2976, 2936, 1727, 1523, 1426, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.76 (s, 3H), 0.88 (s, 3H), 1.11 (s, 3H), 1.12–1.82 (m, 12H), 1.24 (s, 3H), 2.05 (dd, *J* = 5.7, 8.1 Hz, 1H), 2.09 (dd, *J* = 6.0, 7.5 Hz, 1H), 3.60 (s, 2H), 4.15 (ddd, *J* = 6.6, 8.1, 11.1 Hz, 1H), 4.25 (ddd, J = 6.0, 8.4, 11.1 Hz, 1H), 7.24–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 20.1, 20.8, 23.1, 30.5, 32.2, 33.4, 37.9, 39.3, 41.4, 41.5, 42.0, 53.3, 62.3, 72.2, 75.2, 127.0, 128.5 (2C), 129.3 (2C), 134.1, 171.6; $[a]^{23.4}_D$ = 23.4 (*c* 1.0, $CHCl_3$) for 98% ee; HRMS (FAB) *m*/*z* calcd for $C_{23}H_{34}O_3Na$ (M + Na) 381.2406, found 381.2409.



(2'*S*,4'a*S*,8'a*S*)-(–)-2-(2',5',5',8'a-Tetramethyloctahydrochromen-2'-yl)ethanol (8a): To a solution of **8f** (100 mg, 0.58 mmol) in methanol (2 mL) at 0 °C was added 1 *M* aqueous LiOH (870 mL, 0.87 mmol). After stirring for an additional 1 h poured into brine and extracted with ether (twice). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated. The crude product was through pipette column on silica gel to give **8a** (139 mg, 0.58 mmol, 100% yield) as colorless oil. TLC (hexane–EtOAc, 2.5:1) R_f = 0.37; IR (film) 3550–3250 (br, OH), 2975, 2941, 2872, 1711, 1523, 1427, 1046, 929 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (s, 3H), 0.90 (s, 3H), 1.21–1.75 (m, 13H), 1.29 (s, 3H), 1.32 (s, 3H), 3.72–3.88 (m, 2H), 4.04 (t, *J* = 5.0 Hz, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 20.0, 20.8, 23.3, 27.6, 32.1, 33.4, 37.3, 41.3, 41.7, 45.8, 54.2, 59.7, 76.0, 76.1; $[a]^{23.4}_D$ = –6.41 (*c* 1.0, $CHCl_3$) for >99% ee; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{28}O_2Na$ (M + Na) 263.1987, found 263.1980.

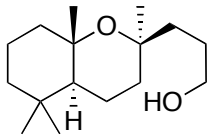


(2'*S*,4'a*S*,8'a*S*)-(–)-*o*-Nitrophenyl-2-(2',5',5',8'a-tetramethyloctahydrochromen-2'-yl)ethylselenide (12):[12] To a stirring solution of **8a** (166 mg, 0.69 mmol) and *o*-nitrophenyl selenocyanate (384 mg, 1.73 mmol) in dry THF (3 mL) under N_2 at room temperature was added tri-*n*-butylphosphine (427 mL, 1.73 mmol). After stirring for 3 h, quenched with ethanol and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane–ether = 15:1) to give **12** (282 mg, 0.66 mmol, 96% yield) as yellow oil. TLC (hexane–EtOAc, 4:1) R_f = 0.54; HPLC (OD-H column, hexane–*i*-PrOH = 80:1, flow rate = 1.0 mL/min) t_R = 6.7 min for (+)-12, 8.0 min for (–)-13; IR (film) 2976, 2932, 1515, 1426, 1335, 1046, 929 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (s, 3H), 0.90 (s, 3H), 1.16–1.73 (m, 11H), 1.28 (s, 3H), 1.30 (s, 3H), 1.78 (ddd, *J* = 5.7, 10.8, 13.4 Hz, 1H), 1.87 (ddd, *J* = 5.7, 11.1, 13.4 Hz, 1H), 2.97 (dt, *J* = 5.8, 12.4 Hz, 1H), 3.06 (dt, *J* = 5.8, 12.4 Hz, 1H), 7.30 (ddd, *J* = 1.2, 7.2, 8.2 Hz, 1H), 7.52 (ddd, *J* = 1.2, 7.2, 8.2 Hz, 1H), 7.74 (dd, *J* = 1.2, 8.2 Hz, 1H), 8.30 (dd, *J* = 1.2, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.3, 20.1, 20.5, 20.8, 23.5, 27.4, 32.3, 33.5, 36.8, 41.5, 41.7, 44.5, 54.3, 73.2, 75.0, 125.0, 126.4, 129.2, 133.5, 134.4; $[a]^{23.7}_D$ = –8.97 (*c* 1.0, $CHCl_3$) for >99% ee; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{31}O_3SeNa$ (M + Na) 448.1367, found 443.1383.



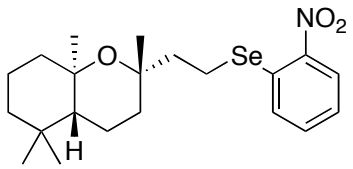
(5*S*,8*S*,10*S*)-(–)-Caparrapi Oxide (1):[1,2,18] To a solution of **12** (276 mg, 0.65 mmol) in THF (15 mL) was slowly added 30% aqueous hydrogen peroxide (592 mL) at

0 °C. Stirring was maintained for 1 day at room temperature. Water was added, extracted with ether (twice), washed with water, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane–ether = 10:1) to give **1** (139 mg, 0.625 mmol, 96% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.45; GC (PEG, column temp. 60 °C, 60 kPa) t_R=109.8 min; GC (b-DM column, column temp. 70 °C, 70 kPa) t_R = 104.9 min for **(+)-1**, t_R = 108.6 min for **(–)-1**; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (s, 3H), 0.86 (s, 3H), 1.15–1.84 (m, 11H), 1.29 (s, 3H), 1.30 (s, 3H), 4.92 (dd, *J* = 1.5, 10.7 Hz, 1H), 5.15 (dd, *J* =1.5, 17.4 Hz, 1H), 5.89 (dd, *J* = 10.7, 17.4 Hz, 1H); $[a]^{22.7}_D$ = –18.5 (*c* 0.065, $CHCl_3$) for >99% ee.

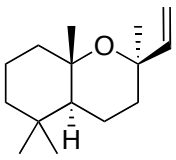


(2'*S*,4'a*R*,8'a*R*)-(+)-2-(2',5',5',8'a-Tetramethyloctahydrochromen-2'-yl)ethanol (9a): To a solution of **9f** (22 mg, 0.061 mmol) in methanol (1 mL) at 0 °C was added 1 *M* aqueous LiOH (92 mL, 0.092 mmol). After stirring for an additional 1 h poured into brine and extracted with ether (twice). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated. The crude product was through pipette column on silica gel to give **9a** (14.6 mg, 0.061 mmol, 100% yield) as colorless oil. TLC (hexane–EtOAc, 2.5:1) R_f = 0.20; IR (film) 3550–3250 (br, OH), 2976, 2941, 2872, 1523, 1427, 1046, 926 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.67 (s, 3H), 0.74 (s, 3H), 1.00–1.60 (m, 11H), 1.11 (s, 3H), 1.17 (s, 3H), 1.76–1.90 (m, 2H), 3.23 (brs, OH), 3.60 (quintet, *J* = 5.1 Hz, 1H), 3.79 (ddd, *J* = 4.8, 9.0, 11.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6, 20.0, 20.5, 24.0, 28.8, 31.9, 33.7, 35.1, 41.5, 42.3, 44.0, 50.0, 60.0, 74.6, 75.5; $[a]^{23.1}_D$ = 28.8 (*c* 1.0, $CHCl_3$) for 98% ee; HRMS (FAB) *m*/*z* calcd for

$C_{15}H_{28}O_2Na$ (M + Na) 263.1987, found 263.1978.



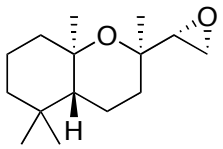
(2'*S*,4'a*R*,8'a*R*)-(+)-*o*-Nitrophenyl-2-(2',5',5',8'a-tetramethyloctahydrochromen-2'-yl)ethyl-selenide (13):[12] To a stirring solution of **9a** (19.2 mg, 0.080 mmol) and *o*-nitrophenyl selenocyanate (44.4 mg, 0.200 mmol) in dry THF (1 mL) under N_2 at room temperature was added tri-*n*-butylphosphine (49 mL, 0.200 mmol). After stirring for 3 h, quenched with ethanol and concentrated. The crude product was purified by column chromatography on silica gel (eluent: hexane–ether = 10:1) to give **13** (32.4 mg, 0.076 mmol, 95% yield) as yellow oil. TLC (hexane–EtOAc, 4:1) R_f = 0.48; IR (film) 2977, 2932, 1520, 1425, 1335, 1046, 929 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (s, 3H), 0.90 (s, 3H), 1.18–1.90 (m, 12H), 1.24 (s, 3H), 1.28 (s, 3H), 2.19 (ddd, *J* = 4.2, 12.0, 14.1 Hz, 1H), 2.96 (dt, *J* = 5.1, 10.6 Hz, 1H), 3.06 (dt, *J* = 3.9, 106 Hz, 1H), 7.31 (ddd, *J* = 1.5, 6.9, 9.5 Hz, 1H), 7.52 (ddd, *J* = 1.5, 6.9, 9.5 Hz, 1H), 7.59 (dd, *J* = 1.5, 8.4 Hz, 1H), 8.31 (dd, *J* = 1.5, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 20.2, 20.8, 21.3, 22.9, 30.0, 32.2, 33.5, 37.9, 38.9, 41.4, 42.1, 53.3, 73.4, 75.4, 125.2, 126.4, 129.2, 133.6, 134.4; $[a]^{23.7}_D$ = 28.7 (*c* 1.0, $CHCl_3$) for 98% ee; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{31}O_3SeNa$ (M + Na) 448.1367, found 448.1367.



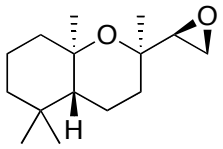
(5*R*,8*S*,10*R*)-(+)-Epicaparrapi Oxide (2):[4a, 18] To a solution of **13** (21.3 mg, 0.050 mmol) in THF (1 mL) was slowly added 30% aqueous hydrogen peroxide (46

mL) at 0 °C. Stirring was maintained for 1 day at room temperature. Water was added, extracted with ether (twice), washed with water, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane–ether = 10-1) to give **2** (10.6 mg, 0.048 mmol, 96% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.45; GC (PEG, column temp. 60 °C, 60 kPa) t_R=114.4 min; GC (b-DM column, column temp. 80 °C, 100 kPa) t_R = 61.1 min for **(+)-2**, t_R = 66.6 min for **(–)-2**; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73 (s, 3H), 0.89 (s, 3H), 1.18–1.67 (m, 10H), 1.14 (s, 3H), 1.22 (s, 3H), 2.18–2.28 (m, 1H), 4.91 (dd, *J* = 1.0, 11.1 Hz, 1H), 4.97 (dd, *J* =1.0, 18.0 Hz, 1H), 6.02 (dd, *J* = 11.1, 18.0 Hz, 1H); $[a]^{23.0}_D$ = 43.0 (*c* 1.1, EtOH) and $[a]^{22.5}_D$ = 47.7 (c 1.0, $CHCl_3$) for 98% ee.

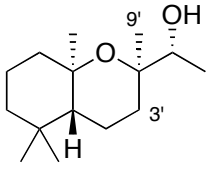
Diastereoselective Epoxidation of (+)-1 with Peroxytrifluoroacetic Acid (Entry 1, Table 3). To a stirred mixture of urea hydrogen peroxide (144 mg, 1.5 mmol), potassium hydrogen phosphate (230 mg, 1.32 mmol) and **(+)-1** (33 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) was added trifluroacetic anhydride (54 mL, 0.38 mmol) dropwise at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for additional 3 hours. A saturated solution of sodium hydrogen carbonate (1 mL) was added to neutralize the acids present and an aqueous layer was then extracted with CH_2Cl_2 (twice). The combined organic layers were washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane–diethyl ether = 15:1 to 10:1) to give (+)-dysifragin (**4**, 17.5 mg, 0.073 mmol, 49% yield) as amorphous solid and its (+)-epimer (**14**, 17.3 mg, 0.073 mmol, 49% yield) as amorphous solid, respectively.



(+)-Dysifragin (3):[2] TLC (hexane–EtOAc, 4:1) R_f = 0.55; IR (film) 2998, 2938, 2868, 1459, 1377, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.78 (s, 3H), 0.89 (s, 3H), 1.19–1.71 (m, 11H), 1.22 (s, 3H), 1.28 (s, 3H), 2.65 (dd, *J* = 4.0, 5.5 Hz, 1H), 2.76 (dd, *J* = 3.0, 5.5 Hz, 1H), 2.82 (dt, *J* = 3.0, 4.0 Hz, 1H); For ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 4; $[a]^{21.3}_D$ = 12.5 (*c* 1.3, $CHCl_3$) for 98% ee; HRMS (FAB) *m*/*z* calcd for $C_{23}H_{34}O_3Na$ (M + Na) 261.1830, found 261.1833.

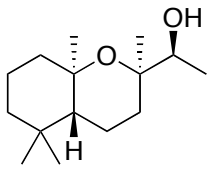


(+)-Epidysifragin (14): TLC (hexane–EtOAc, 4:1) R_f = 0.49; IR (film) 2997, 2934, 2863, 1457, 1378, 1222, 1209, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.77 (s, 3H), 0.90 (s, 3H), 1.20–1.70 (m, 11H), 1.23 (s, 3H), 1.29 (s, 3H), 2.66 (dd, *J* = 4.0, 5.0 Hz, 1H), 2.71 (dd, *J* = 3.0, 5.0 Hz, 1H), 2.87 (dt, *J* = 3.0, 4.0 Hz, 1H); For ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 4; $[a]^{21.5}_D$ = 15.0 (*c* 0.08, $CHCl_3$) for 98% ee; HRMS (FAB) *m*/*z* calcd for $C_{23}H_{34}O_3Na$ (M + Na) 261.1830, found 261.1827.



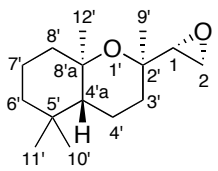
(1*R*,2'*R*,4'a*R*,8'a*R*)-1-(2',5',5',8'a-Tetramethyloctahydrochromen-2'-yl)ethanol (15):[13] To a solution of **(+)-4** (10 mg, 0.04 mmol) in Et_2O (2 mL) was added $LiAlH_4$ (11 mg, 0.3 mmol) at 0 °C, and allowed to warm to room temperature. After

being stirred for 3 h at the same temperature, excess $LiAlH_4$ was decomposed with EtOAc, then with H_2O at 0 °C. Anhydrous Na_2SO_4 was added and stirred for 30 min at room temperature. The resulting mixture was filtered, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (eluent: hexane–diethyl ether = 5:1) to give **15** (9 mg, 0.038 mmol, 95% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.45; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.76 (s, 3H), 0.89 (s, 3H), 1.06 (d, J = 6.6 Hz, 1H), 1.15 (s, 3H), 1.20–1.66 (m, 11H), 1.27 (s, 3H), 2.76 (d, J = 5.1 Hz, OH), 3.26–3.41 (m, 1H); For ^{13}C NMR ($CDCl_3$, 75 MHz), see Table 1.

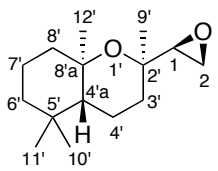


(1*S*,2'*R*,4'a*R*,8'a*R*)-1-(2',5',5',8'a-Tetramethyloctahydrochromen-2'-yl)ethanol (16):[13] To a solution of **(+)-14** (12 mg, 0.05 mmol) in Et_2O (2 mL) was added $LiAlH_4$ (11 mg, 0.3 mmol) at 0 °C, and allowed to warm to room temperature. After being stirred for 3 h at the same temperature, excess $LiAlH_4$ was decomposed with EtOAc, then with H_2O at 0 °C. Anhydrous Na_2SO_4 was added and stirred for 30 min at room temperature. The resulting mixture was filtered, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (eluent: hexane–diethyl ether = 5:1) to give **16** (9.6 mg, 0.04 mmol, 80% yield) as colorless oil. TLC (hexane–EtOAc, 4:1) R_f = 0.36; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.77 (s, 3H), 0.90 (s, 3H), 1.04 (d, J = 6.3 Hz, 1H), 1.10–1.82 (m, 11H), 1.20 (s, 3H), 1.32 (s, 3H), 3.05 (s, OH), 3.48 (ddd, J = 2.0, 6.9, 13.6 Hz, 1H); For ^{13}C NMR ($CDCl_3$, 75 MHz), see Table 1.

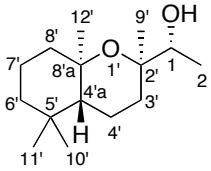
Table 4. ^{13}C Chemical Shifts (d) of (+)-**4**, (+)-**14**, **15**, and **16**



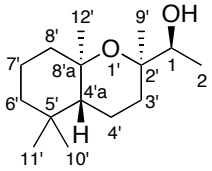
(+)-**4**



(+)-**14**



15



16

C(n)	(+)-**4**	(+)-**14**	Δδ((+)–**4**,(+)-**14**)	**15**	**16**	Δδ((+)–**15**,(+)-**16**)
C(1)	59.8	59.9	–0.1	**75.7**	**73.2**	**+2.5**
C(2)	43.9	43.8	+0.1	16.3	15.3	+1.0
C(2')	70.7	71.2	–0.5	75.2	76.4	–1.2
C(3')	33.7	33.6	+0.1	**34.4**	**29.4**	**+5.0**
C(4')	20.0	20.0	±0	20.0	20.0	±0
C(4'a)	53.0	53.7	–0.7	54.1	54.5	–0.4
C(5')	33.5	33.6	–0.1	33.4	33.4	±0
C(6')	41.4	41.5	–0.1	41.5	41.4	+0.1
C(7')	15.9	15.7	+0.2	16.0	15.7	+0.3
C(8')	41.4	41.5	–0.1	41.7	41.7	±0
C(8'a)	75.0	75.3	–0.3	75.1	75.8	–0.7
C(9')	23.7	23.5	+0.2	23.4	23.2	+0.2
C(10')	32.0	32.1	–0.1	32.1	32.1	±0
C(11')	20.8	20.8	±0	20.8	20.8	±0
C(12')	24.6	24.2	+0.4	**21.7**	**24.2**	**–2.5**

X-ray Crystallographic Analysis of (+)-4: (+)-**4** was crystallized without any solvents at –25 °C (Figure 4). Crystal data: $C_{15}H_{26}O_2$, M = 238.36, crystal dimensions 0.30x.20x0.07 mm^3, orthorhombic, space group $P2_12_12_1$ (#19), a = 6.9005 (19), b = 11.488 (3), c = 17.729 (5) Å, V = 1405.4 (7) Å^3, Z = 4, D_c = 1.127 g/cm^3, T =

223 K. X-ray crystallographic analysis was performed with a Bruker SMART APEX CCD diffractometer (graphite monochromator, MoKα radiation, λ = 0.71073 Å), and the structure was solved by direct methods and expanded using Fourier techniques (Sir97 and SHELXL[19]). 3651 reflections were independent and unique, and 2018 with $I > 2s(I)$ ($2\theta_{max}$ = 29.09°) were used for the solution of the structure. The non-hydrogen stoms were refined anisotropically. R = 0.0544 and Rw = 0.1110.

Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC 265385 for (+)-**4**. Copy of the data can be obtained free of charge via http//www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail deposit@ccdc.cam.ac.uk).

Epoxide Inversion from (+)-14 to (+)-4:[17] Cesium propionate (168 mg, 0.6 mmol) and 18-crown-6 (95 mg, 0.36 mmol) were added to the flask and removed moistures under high-vacuum pressure (0.04 mmHg) while stirring overnight. Dry toluene (4 mL) and freshly distilled AcOH (7 mL, 0.12 mmol) were added to the flask and the mixture was vigorously stirred. When the solids dispersed, (+)-**14** (14 mg, 0.06 mmol) was added, and the resulting mixture was heated to reflux for 3 days. Poured in to aqueous $NaHCO_3$ and extracted with EtOAc (3 times). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was through pipette column on silica gel to give a mixture of regioisomeric propionates, **19** and **20** (2:1 on TLC, 17 mg, 0.055 mmol, 92% yield), and used next step without further purification. Distilled MsCl (10 mL, 0.11 mmol) was added to a stirred solution of **19**, **20**, *N*,*N*-diisopropylethylamine (26 mL, 0.15 mmol) and DMAP (15 mg, 0.12 mmol) in

CH_2Cl_2 was added dropwise at –10 °C. The reaction mixture was stirred for additional 3 h at –10 ~ 0 °C, quenched with NH_4Cl (aq.), and the aqueous layer was extracted with Et_2O (twice). The combined organic layer was washed with water, dried over anhydrous $MgSO_4$, concentrated, and used next step without further purification. To a mixture of regioisomeric mesylates were added MeOH (2.5 mL) and K_2CO_3 (4 mg, 0.022 mmol), and stirred for 12 h at room temperature. After the reaction completed, the resultant mixture was passed through a short-column chromatography on silica gel, and concentrated under reduced pressure. The residue was purified on flash column chromatography on silica gel (eluent: hexane–diethyl ether = 10:1) to give (+)-**4** (11.5 mg, 0.048 mmol, 88% yield in two steps) as amorphous solid.

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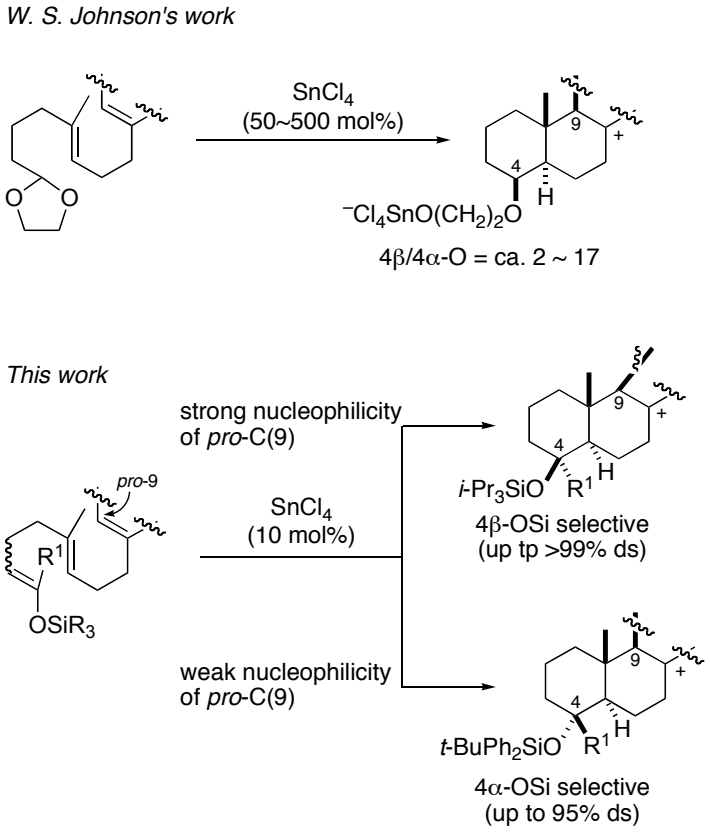
Chapter 3

Catalytic Diastereoselective Polycyclization of Homo(polyprenyl)arene Analogues Bearing Terminal Siloxyvinyl Groups

Abstract: We report here the highly diastereoselective polycyclization of homo(polyprenyl)arene analogues bearing terminal siloxyvinyl groups catalyzed by tin(IV) chloride (10 mol%). The cyclization of *tert*-butyldiphenylsilyl polyenol ethers gave 4α(equatorial)-siloxypolycycles as major isomers in high yield. On the other hand, the cyclization of triisopropylsilyl polyenol ethers gave 4β(axial)-siloxypolycycles as major isomers in high yield. A strong nucleophilicity of *pro*-C(9), a (6*E*)-geometry and a bulky silyl group effectively favored the 4α-preference (up to 95% ds), while a weak nucleophilicity of *pro*-C(9), a (6*Z*)-geometry and less steric hindrance of a silyl group favored the 4b-preference (up to >99% ds). Therefore, 4α-selective cyclization would concertedly proceed through an antiperiplanar transition state, while 4β-selective cyclization would proceed stepwise through a synclinal transition state. With this approach, two natural diterpenoids, 18-norabieta-8,11,13-trien-4-ol and its 4-epimer, were distereoselectively synthesized from the corresponding silyl (6*E*)-dienol ethers.

Introduction

Biomimetic polyene cyclization is an important key step in the concise total synthesis of polycyclic natural products.[1,2] In particular, the Lewis acid-promoted diastereoselective cyclization of polyenic aldehyde acetals to 4β(axial)-alkoxypolycycles[3] has been established by Johnson et al. (Scheme 1)[1] However, excess $SnCl_4$ is often required as Lewis acid and there are no methods available for the synthesis of 4α(equatorial)-alkoxypolycycles. We report here the $SnCl_4$ (10 mol%)-catalyzed polycyclization of homo(polyprenyl)arene analogues bearing terminal siloxyvinyl groups, which were much more reactive than other initiators such as acetals, aldehydes, and ketones (Scheme 1).[4]

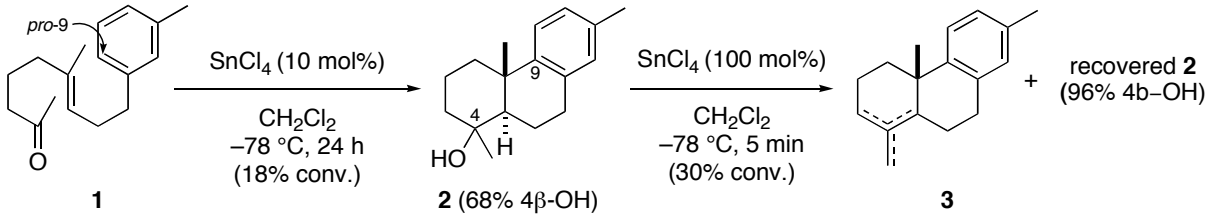


Scheme 1. Johnson's approach and the present approach for the diastereoselective synthesis of 4-hydroxy polycyclic terpenoids

The α(equatorial)/β(axial) selectivity of 4-siloxy group[3] at polycycles could be controlled by the nucleophilicity of *pro*-C(9)[3] and the steric effect of a silyl group.

Results and Discussion

Initially, we investigated the reactivity and diastreoselectivity of the cyclization of (*E*)-enone **1** in the presence of 10 mol% of $SnCl_4$ in CH_2Cl_2 at –78 °C (Scheme 2). The conversion to *trans*-tricycles **2** (4β-OH: 68% ds) was 18% even after 24 h because of their relatively strong basicity.[5] Interestingly, **2a** (4α-OH) was converted to dehydrated alkene **3** under more acidic conditions, but **2b** (4β-OH) was stable under the same conditions.

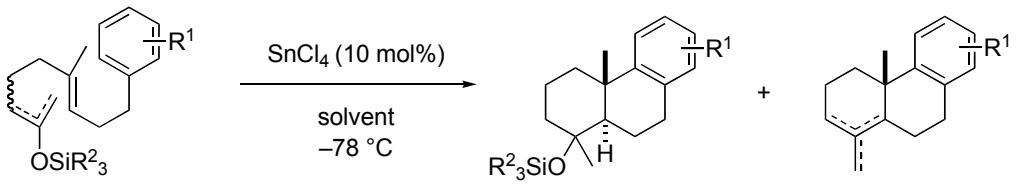


Scheme 2. Cyclization of (*E*)-Enone **1** to *trans*-Tricyclic Alcohols **2**

Next, (2*E*,6*E*)-, (2*Z*,6*E*)-, and (1,6*E*)-isomeric mixtures of silyl (6*E*)-dienol ethers **4** derived from (*E*)-6-enones were examined in the presence of 10 mol% of $SnCl_4$ (Table 1).[6] Fortunately, the 4α/4β-selective cyclization of **4** to 4-siloxytricycles **5** proceeded smoothly independent of the isomeric ratio of **4** (entries 3–6). These results suggested that the cyclization of **4** proceeded via siloxycarbenium ion intermediates. Although similar 4α/4β-selectivities were observed in CH_2Cl_2 and toluene (entries 3–6), not only cyclization but also the subsequent over-reaction from **5a** to alkene **6** proceeded more rapidly in CH_2Cl_2. 4β-Siloxy isomer **5b** was produced as a major isomer from less bulky triisopropylsilyl (TIPS) dienol ethers **4**, while 4α-siloxy isomer **5a** was produced as a major isomer from more bulky

tert-butyldimethylsilyl(TBDPS) dienol ethers **4**. The substituents of the phenyl group of **4** also influenced the 4α/4β-selectivity: weaker nucleophilicity at the *ortho*-position (*pro*-C(9)[3]) of **4** increased 4β-selectivity, while stronger nucleophilicity increased 4α-selectivity. Thus, **5ab** was produced from **4a** in 90% yield with >99% ds (entry 1). On the other hand, **5fa** was produced from **4f** in 90% yield with 93% ds (entry 9). The α-selectivity of **4f** was opposite that of the corresponding ketone **1** (see Scheme 2).

Table 1. Cyclization of Silyl (6*E*)-Dienol Ethers **4** to *trans*-Tricycles **5**



4 **5** **6**

entry	**4** [R^1, SiR^2_3][a]	solvent, time (h)	**5**, yield (%)[b]	(**5α**:**6**):**5β**
1[c]	**4a** [*p*-F, TIPS]	toluene, 24	**5a**, 90	(<1:<1):>99
2	**4b** [H, TIPS]	toluene, 2	**5b**, 99	(7:<1):93
3	**4c** [*p*-Me, TIPS][d]	CH_2Cl_2, 3	**5c**, 90	(1:10):89
4	**4c** [*p*-Me, TIPS][d]	toluene, 2	**5c**, 95	(11:5):84
5	**4c** [*p*-Me, TIPS][e]	CH_2Cl_2, 2.5	**5c**, 91	(9:8):83
6	**4c** [*p*-Me, TIPS][e]	toluene, 1.5	**5c**, 93	(13:2):85
7	**4d** [*m*-Me, TIPS]	toluene, 3	**5d**, 95	(36:4):60
8	**4e** [*p*-Me, TBDPS]	CH_2Cl_2, 3	**5e**, 93	(63:6):31
9	**4f** [*m*-Me, TBDPS]	CH_2Cl_2, 3	**5f**, 90	(85:9):6

[a] A (2*E*)-2-, (2*Z*)-2-, and 1-enyl mixture of **4**. [b] Isolated yield. See also ref. 7. No detectable amount of *cis*-isomer **11** was obtained. [c] $SnCl_4$ (1 equiv) was used. [d] Isomeric ratio of (2*E*)-2-, (2*Z*)-2-, 1-enes **4c** = 14:71:15. [e] Isomeric ratio of (2*E*)-2-, (2*Z*)-2-, 1-enes **4c** = 2:29:69.

The relative stereochemistries of **5cα** and **5cβ** were determined based on the X-ray diffraction analysis of **5cβ**. Other relative stereochemistries of **5α** and **5β** were determined as analogues of **5cα** and **5cβ** in comparison with their ^{1}H and ^{13}C NMR spectra.

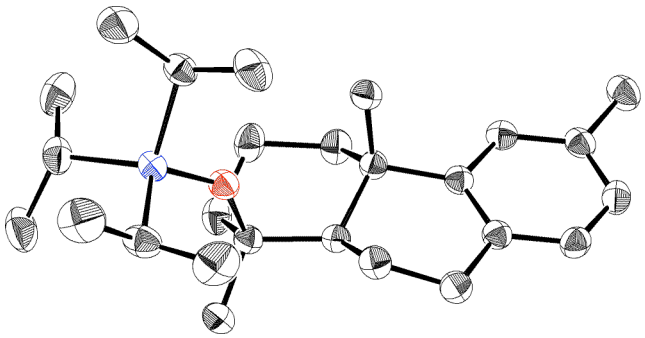
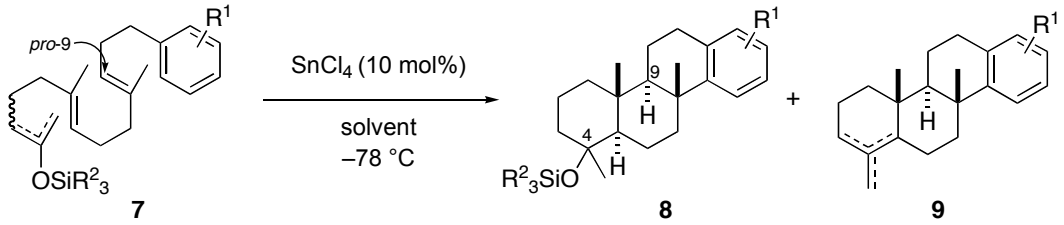


Figure 1. Molecular structure of **5cβ**. Carbon, silicon and oxygen atoms are shown in black, blue and red colors, respectively. All hydrogen atoms are omitted for clarity.

Next, (2*E*,6*E*)-, (2*Z*,6*E*)-, and (1,6*E*)-isomeric mixtures of silyl (6*E*,10*E*)-trienol ethers **7** derived from (*E*,*E*)-6,10-dienones were examined in the presence of 10 mol% of $SnCl_4$ (Table 2). Surprisingly, 4α-selective cyclization of **7** to 4-siloxytetracycles **8** proceeded catalytically independent of the nucleophilicity of the terminal aryl groups (entries 1 and 2). The cyclization of *tert*-butyldimethylsilyl trienol ether **7c** gave **8α** with 91% ds in 96% yield (entry 3). The α-preference for **8** could be understood by the relatively strong nucleophilicity of *pro*-C(9)[3] of **7**.[8]

The relative stereochemistries of **8aα** and **8aβ** were determined based on the X-ray diffraction analyses of desilylated **8aα** and desilylated **8aβ** (Figures 2 and 3). Other relative stereochemistries of **8α** and **8β** were determined as analogues of **8aα** and **8aβ** in comparison with their ^{1}H and ^{13}C NMR spectra.

Table 2. Cyclization of Silyl (6*E*,10*E*)-Trienol Ethers **7** to **8**



7 **8** **9**

entry	**7** [R^1, SiR^2_3][a]	Solvent, time (h)	**8**+**9**, yield (%)[b]	(**8α**:**9**):**8β**
1	**7a** [*p*-Me, TIPS]	toluene, 4	**8a**+**9a**, 92	(58:5):37
2	**7b** [*m*-Me, TIPS]	toluene, 3	**8b**+**9b**, 91	(57:6):37
3	**7c** [*m*-Me, TBDPS]	CH_2Cl_2, 2	**8c**, 96	(91:<1):9

[a] A (2*E*)-2-, (2*Z*)-2-, and 1-enyl mixture of **7**. [b] **8** and **9** were inseparable. See also ref. 7. No detectable amounts of *cis*-isomers **8** were obtained.

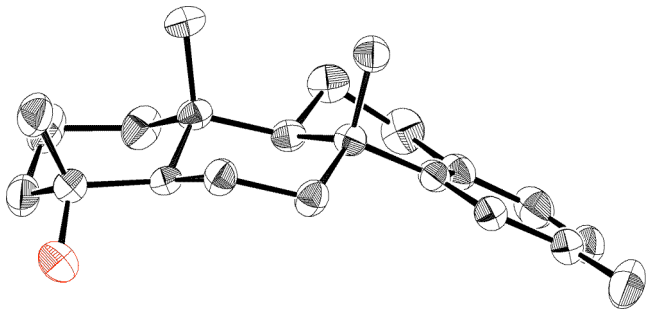


Figure 2. Molecular structure of desilylated **8aα**. Carbon and oxygen atoms are shown in black and red colors, respectively. All hydrogen atoms are omitted for clarity.

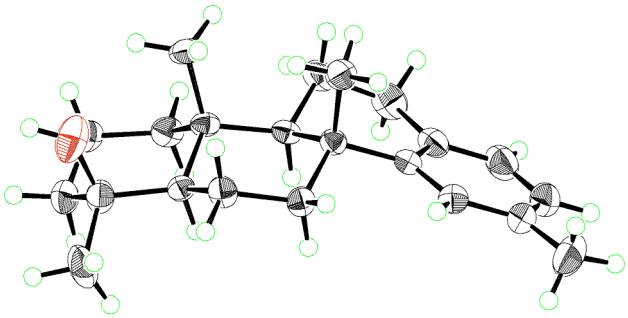
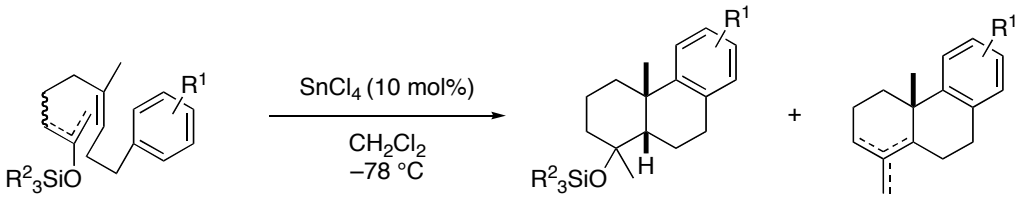


Figure 3. Molecular structure of desilylated **8aβ**. Carbon, hydrogen and oxygen atoms are shown in black, green and red colors, respectively.

For comparison with silyl (6*E*)-dienol ethers **4**, cyclization of its (6*Z*)-isomers **10** was also performed under the same conditions (Table 3). Surprisingly, *cis*-tricycles **11** were produced in high yield without any detectable **5**. Overall, the reactivity of **10** was much lower than that of **4** because the B-ring formation of **11** should occur through the thermodynamically unfavorable boat-like transition state. Interestingly, 4β-selectivity of **11** was increased in comparison with that of **5**. For example, the cyclization of **10a** gave **11aβ** in 90% yield with >99% ds (entry 1), while the cyclization of **4c** gave **5cβ** in 90% yield with 89% ds (entry 3, Table 1).

Table 3. Cyclization of Silyl (6*Z*)-Dienol Ethers **10** to *cis*-Tricycles **11**



10 **11** **12**

entry	**10** [R^1, SiR^2_3][a]	time (h)	**11**, yield (%)[b]	(**11α**:**12**):**11β**
1	**10a** [*p*-Me, TIPS]	24	**11a**, 90	(<1:<1):>99
2	**10b** [*m*-Me, TIPS]	1	**11b**, 94	(6:7):87
3	**10c** [*m*-Me, TBDPS]	1	**11c**, 98	(62:<1):38

[a] A (2*E*)-2-, (2*Z*)-2-, and 1-enyl mixture of **10**. [b] Isolated yield. See also ref. 7. No detectable amount of *cis*-isomer **11** was obtained.

The relative stereochemistries of **11aα** and **11aβ** were determined based on the X-ray diffraction analysis of desilylated **11aβ** (Figure 4). Other relative stereochemistries of **11α** and **11β** were determined as analogues of **11aα** and **11aβ** in comparison with their ^{1}H and ^{13}C NMR spectra.

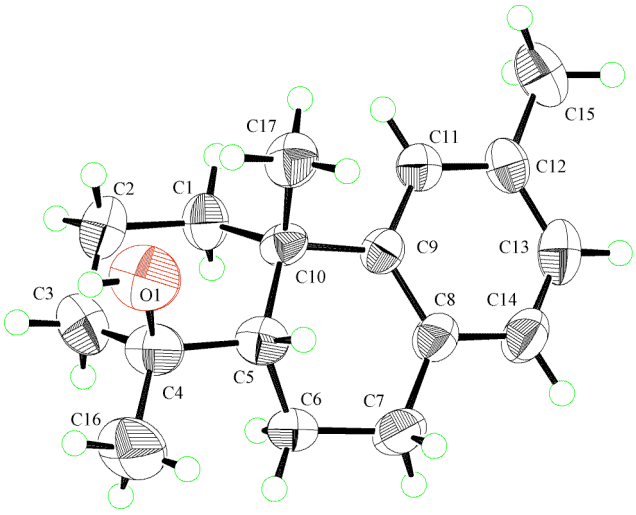
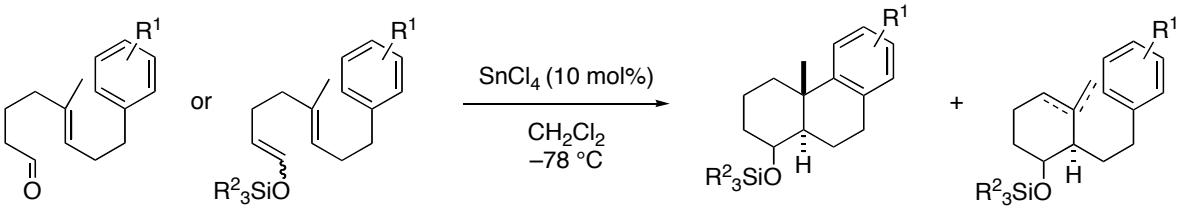


Figure 4. Molecular structure of desilylated **11aβ**. Carbon, hydrogen and oxygen atoms are shown in black, green and red colors, respectively.

The cyclization of (*E*)-5-enals **13** and their silyl (5*E*)-dienol ethers **14** was also examined under the same conditions (Table 4). In the cyclization of **13**, A-ring formation occurred quantitatively with very low 4a/4b-selectivities,[9] but monocycles **17** were produced in ca. 10% yield together with bicycles **15** (entries 1 and 2). In contrast, in the cyclization of (1*Z*)-**14**, **16b** was produced in 97% yield with ≥99% ds regardless of the nucleophilicity of the aryl group of **14** (entries 3 and 4). Although (1*E*)-**14b** was much less reactive than (1*Z*)-**14b**, (1*E*)-**14b** also give **16bβ** as a major isomer (entry 5). This result suggested that the *E*/*Z*-isomerization of silyl enol ethers derived from aldehydes was relatively slow and cyclization to **16α** was essentially disfavored. The relative stereochemistries of **15α** and **15β** were determined as analogues of **15α** (R^1 = H) and **15β** (R^1 = H) in comparison with their ^{1}H and ^{13}C NMR spectra.[10]

Table 4. Cyclization of (*E*)-Enals **13** and their Silyl Dienol Ethers **14**.



13 **14** **15** (R^2_3Si = H) or **16** **17** (R^2_3Si = H) or **18**

entry	**13** or **14** [R^1, SiR^2_3]	time (h)	**15** or **16**, yield (%)[a]	4α:4β[b]
1[c]	**13a** [*p*-Me]	0.5	**15a**, 87	40:60
2[c]	**13b** [*m*-Me]	0.5	**15b**, 89	55:45
3	**14a** [*p*-Me, TIPS][d]	1	**16a**, 97	1:99
4	**14b** [*m*-Me, TIPS][d]	3	**16b**, 97	<1:>99
5[c,e]	**14b** [*m*-Me, TIPS][f]	12	**16b**, ca. 80	ca. 25:75

[a] Isolated yield. See also ref. 7. No detectable amount of *cis*-isomer was obtained. [b] For **15** or **16**. [c] Yields of **17** or **18** were 11% (entry 1), 10% (entry 2), and ca 20% (entry 5). [d] 1*E*/1*Z* ratio of **14** = <1:>99. [e] $SnCl_4$ (20 mol%) was used. [f] 1*E*/1*Z* ratio of **14** = 76:24.

The proposed mechanism is shown in Figure 5. The regioselective stannylation of polyenic silyl enol ethers with $SnCl_4$ or protonation with $SnCl_4•(H_2O)_n$ would induce the subsequent polycyclization.[11] The 4α-Selective cyclization would proceed concertedly or stepwise through antiperiplanar (chair–chair-like) transition state (TS) **19**. On the other hand, the 4β-selective cyclization would proceed stepwise through synclinal TS-**20** or **21** stabilized by Coulomb attractive interaction (minimalization of charge separation) between O and *pro*-C(10).[3,12] A strong nucleophilicity of *pro*-C(9),[3] a (6*E*)-geometry and a bulky silyl group would effectively favor TS-**19**, while a weak nucleophilicity of *pro*-C(9),[3] a (6*Z*)-geometry and less steric hindrance of a silyl group would favor TS-**20** or **21**.

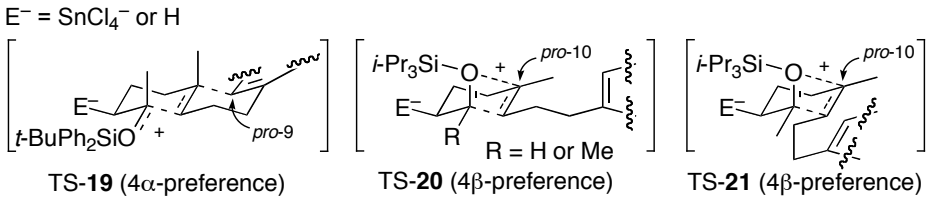
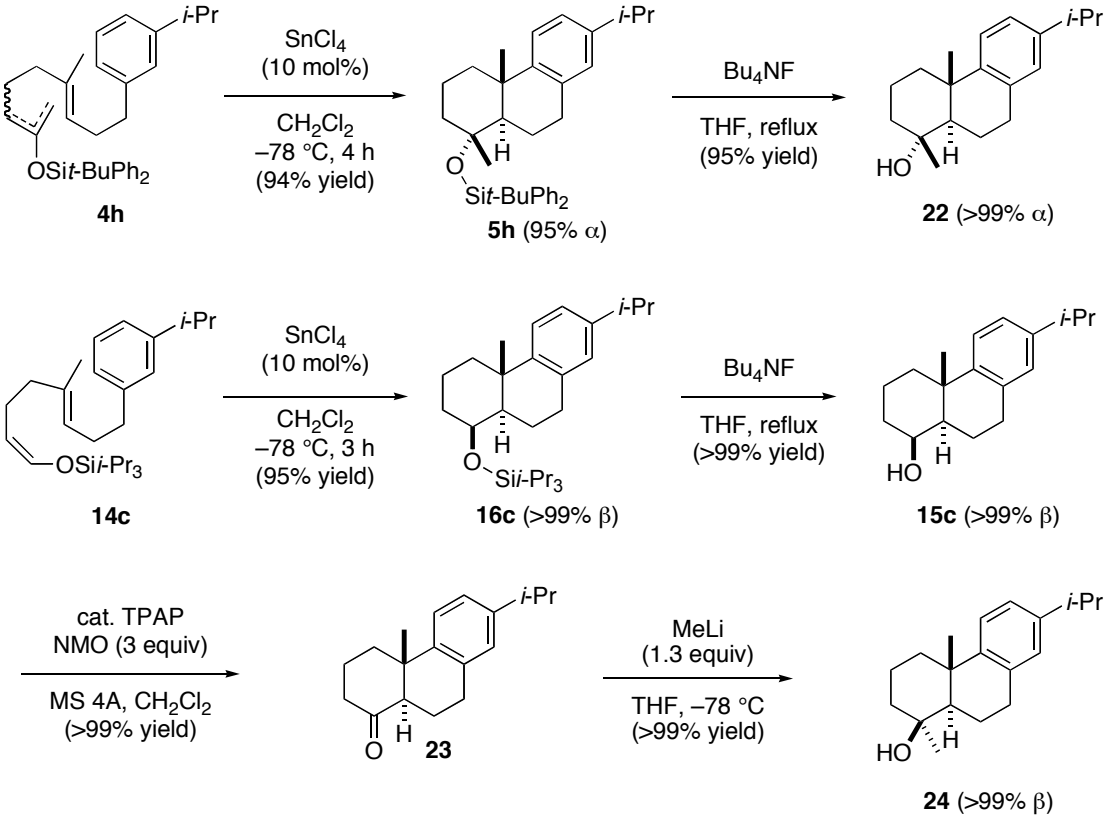


Figure 5. Proposed transition-state assemblies **19**-**21**.

Based on the above experimental results, two natural diterpenoids, 18-norabieta-8,11,13-trien-4-ol (**22**),[13] which has antibacterial activity, and its epimer **24**[13] were synthesized from **4h** and **14c** with >99% 4α and >99% 4β, respectively (Scheme 3).[7] The anti-herpes active diterpenoid **15c**,[14] a synthetic intermediate of **24**, was also synthesized with >99% ds.

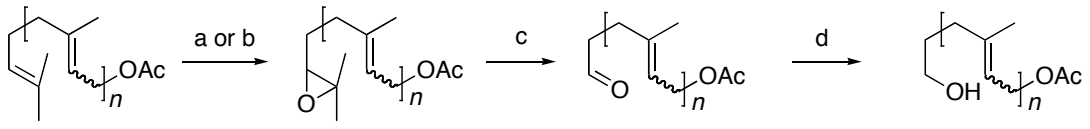


Scheme 3. Total Syntheses of Epimers **22** and **24**

Preparation of Silyl Polyenol Ethers

Silyl polyenol ethers **4**, **7**, **10**, and **14** were prepared from geranyl acetate (**25a**), neryl acetate (**25b**) and farnesyl acetate (**25c**) with 10 steps (Scheme 4). Regioselective epoxidation of **25a** and **25b** with *m*CPBA gave (*E*)- and (*Z*)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-enyl acetates (**26a** and **26b**) in quantitative yield, respectively. Regioselective epoxidation of **25c** to (2*E*,6*E*)-9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dienyl acetate (**26c**) was accomplished according to Corey's method using NBS.[15] The oxidative cleavage of epoxides **26** with HIO_4 and the subsequent selective reduction of aldehydes **27** with $NaBH_4$ gave alcohols **28** in high yield. The protection of alcohols **28** with TBDPSCl and the subsequent hydrolysis of acetates **29** with K_2CO_3 in methanol gave TBDPS ethers **30** in quantitative yield. Butsugan coupling reaction[16] of allylic diethyl phosphonate **31**, which were prepared from alcohols **30** and diethyl chlorophosphate, with arylmethylmagnesium halides and the subsequent desilylation with TBAF gave alcohols **32** in high yield. The carbon-chain homologation from alcohols **32** to nitriles **33** was accomplished through the substitution reaction of the mesylate of **32** with KCN in high yield. The addition of nitriles **33** with MeLi and DIBAL-H gave ketones **34** and **1** and aldehydes **13** in high yield, respectively. The treatment of ketones **34** and **1** and aldehydes **13** with triisopropylsilyl triflate or *tert*-butyldiphenylsilyl triflate in the presence of triethylamine gave silyl polyenol ethers **4**, **7**, **10** and **14** in high yield.

Scheme 4. Preparation of Silyl Polyenol Ethers[a]

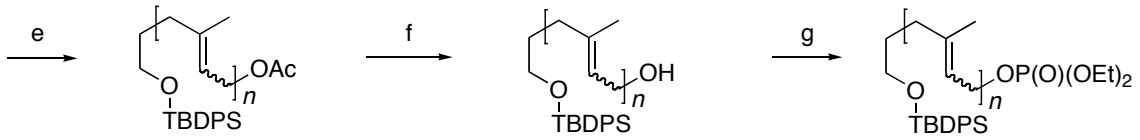


25a (*n*=1, *2E*)
25b (*n*=1, *2Z*)
25c (*n*=2, *2E*)

26a (*n*=1, *2E*)
26b (*n*=1, *2Z*)
26c (*n*=2, *2E*)

27a (*n*=1, *2E*)
27b (*n*=1, *2Z*): 96% from **25b**
27c (*n*=2, *2E*)

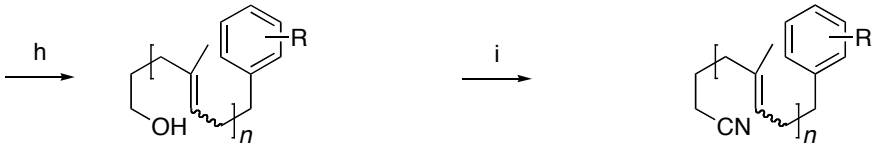
28a (*n*=1, *2E*)
28b (*n*=1, *2Z*): 96% from **27c**
28c (*n*=2, *2E*): 96% from **25c**



29a (*n*=1, *2E*)
29b (*n*=1, *2Z*): 98% from **28b**
29c (*n*=2, *2E*)

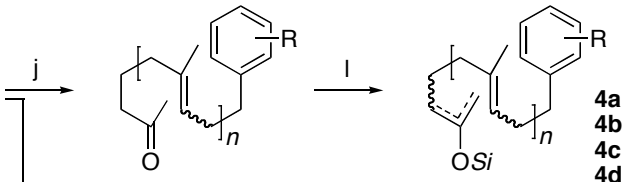
30a (*n*=1, *2E*): 80% from **25a**
30b (*n*=1, *2Z*): 98% from **29b**
30c (*n*=2, *2E*): 95% from **28c**

31a (*n*=1, *2E*): 90% from **30a**
31b (*n*=1, *2Z*): 98% from **30b**
31c (*n*=2, *2E*): 91% from **30c**



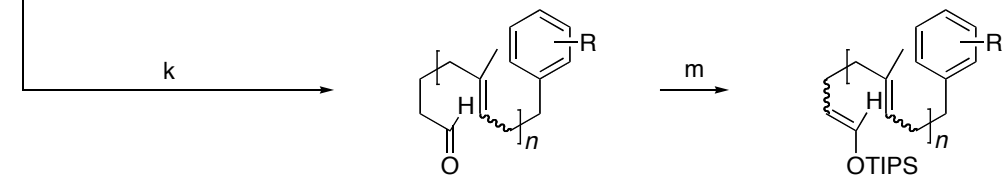
32aa (*n*=1, *4E,* R=*p*-F): >99% from **31a**
32ab (*n*=1, *4E,* R=H): 97% from **31a**
32ac (*n*=1, *4E,* R=*p*-Me): 95% from **31a**
32ad (*n*=1, *4E,* R=*m*-Me): 94% from **31a**
32ae (*n*=1, *4E,* R=*m*-*i*Pr): 95% from **31a**
32ba (*n*=1, *4Z,* R=*p*-Me): 94% from **31b**
32bb (*n*=1, *4Z,* R=*m*-Me): 94% from **31b**
32ca (*n*=2, *8E,* R=*p*-Me): 99% from **31c**
32cb (*n*=2, *8E,* R=*m*-Me): 97% from **31c**

33aa (*n*=1, *5E,* R=*p*-F)
33ab (*n*=1, *5E,* R=H)
33ac (*n*=1, *5E,* R=*p*-Me): 95% from **32ac**
33ad (*n*=1, *5E,* R=*m*-Me): 96% from **32ad**
33ae (*n*=1, *4E,* R=*m*-*i*Pr): 95% from **32ae**
33ba (*n*=1, *5Z,* R=*p*-Me): 98% from **32ba**
33bb (*n*=1, *5Z,* R=*m*-Me): 98% from **3bb**
33ca (*n*=2, *9E,* R=*p*-Me): 97% from **32ca**
33cb (*n*=2, *9E,* R=*m*-Me): 93% from **32cb**



34aa (*n*=1, *6E,* R=*p*-F): 96% from **32aa**
34ab (*n*=1, *6E,* R=H): 96% from **32ab**
34ac (*n*=1, *6E,* R=*p*-Me): 94% from **33ac**
1 (*n*=1, *6E,* R=*m*-Me): 97% from **33ad**
34ae (*n*=1, *4E,* R=*m*-*i*-Pr): 96% from **33ae**
34ba (*n*=1, *6Z,* R=*p*-Me): 94% from **33ba**
34bb (*n*=1, *6Z,* R=*m*-Me): 95% from **33bb**
34ca (*n*=2, *10E,* R=*p*-Me): 95% from **33ca**
34cb (*n*=2, *10E,* R=*m*-Me): 96% from **33cb**

4a (*n*=1, *6E,* R=*p*-F, *Si*=TIPS): >99% from **34aa**
4b (*n*=1, *6E,* R=H, *Si*=TIPS): >99% from **34ab**
4c (*n*=1, *6E,* R=*p*-Me, *Si*=TIPS): >99% from **34ac**
4d (*n*=1, *6E,* R=*m*-Me, *Si*=TIPS): >99% from **1**
4e (*n*=1, *6E,* R=*p*-Me, *Si*=TBDPS): 84% from **34ac**
4f (*n*=1, *6E,* R=*m*-Me, *Si*=TBDPS): 65% from **1**
4h (*n*=1, *4E,* R=*m*-*i*-Pr, *Si*=TBDPS) 93% from **34ae**
7a (*n*=1, *6Z,* R=*p*-Me, *Si*=TIPS): 98% from **34ba**
7b (*n*=1, *6Z,* R=*m*-Me, *Si*=TIPS): >99% from **34bb**
7c (*n*=1, *6Z,* R=*m*-Me, *Si*=TBDPS): 92% from **34bb**
10a (*n*=2, *10E,* R=*p*-Me, *Si*=TIPS): >99% from **34ca**
10b (*n*=2, *10E,* R=*m*-Me, *Si*=TIPS): >99% from **34cb**
10c (*n*=2, *10E,* R=*m*-Me, *Si*=TBDPS): 81% from **34cb**



13a (R=*p*-Me): 94% from **33ac**
13b (R=*m*-Me): 96% from **33ad**
13c (R=*m*-*i*-Pr): 93% from **33ae**

14a (R=*p*-Me): >95% yield from **13a**
14b (R=*m*-Me): >95% yield from **13b**
14c (R=*m*-*i*-Pr): >95% yield from **13c**

[a] Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, –20 °C to rt, 2 h; (b) *i*. NBS, THF–H_2O,

–5 °C to 0 °C, 3 h; *ii*. K_2CO_3, MeOH, rt, 2 h; *iii*. Ac_2O, pyridine, rt, 1 d; (c) $HIO_4 \bullet 2H_2O$, THF–Et_2O, 0 °C, 30 min.; (d) $NaBH_4$, EtOH, 0 °C, 1 h; (e) TBDPSCl, Imidazole, DMF, rt, on; (f) K_2CO_3, MeOH, 0 °C to rt, 1 h; (g) $(EtO)_2POCl$, Et_3N, hexane, 0 °C to rt, 1 d; (h) *i*. ArMgX, THF, 0 °C to rt, on; *ii*. TBAF, THF, rt, on; (i) *i*. MsCl, Et_3N, CH_2Cl_2, 0 °C for 1 h, rt for 30 min.; *ii*. KCN, 18-crown-6, CH3CN, reflux, 3–6 h; (j) MeLi, Et_2O, –78 °C to 0 °C, 1h; (k) DIBAL-H, hexane–toluene, –78 °C, 1 h; (l) *Si*OTf, Et_3N, CH_2Cl_2, 0 °C to rt, 3–12 h; (m) TIPSOTf, Et_3N–CH_2Cl_2, –78 °C to 0 °C, 2 h.

Conclusion

Although it was difficult to directly generate silyloxocarbenium ion intermediates from aldehydes and ketones with silyl Lewis acids,[6] we succeeded in their catalytic generation with $SnCl_4$ from silyl enol ethers instead of carbonyl compounds. The main advantage in the catalytic use of $SnCl_4$ is to avoid or to minimize secondary reactions of the polycyclic products, ie. elimination of the siloxy groups (See Scheme 2). The present results demonstrate the synthetic advantages of using polyprenoid analogues bearing a terminal siloxyvinyl group as substrates of polyene cyclization with respect to both the reactivity and 4α/4β-diastereocontrol.[5]

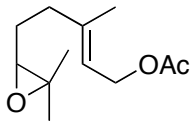
Experimental Section

General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 (300 MHz) or Varian INOVA-500 (500 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a Varian Gemini-2000 (75 MHz) or Varian INOVA-500 (125 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). High-performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm x 25 cm). Low-resolution mass analysis (LRMS) and GC analysis were performed with a Shimadzu GC/MS instrument [GC-17A/QP-5050A; column: TC-1 (0.25 mm x 30 m)] by direct insertion for chemical ionization (CI) with isobutane. The temperature program employed was 70 °C for 5 min with an increase to 250 °C at 10 °C/min. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385) or aluminum oxide 150 basic (type T) (Merck). High-resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University. In experiments that required dry solvent, ether and tetrahydorofuran (THF) were purchased from Aldrich or Wako as the “anhydrous” and stored over 4A molecular sieves. Hexane, toluene and dichloromethane were freshly distilled from calcium hydride. Tin(IV) chloride was distilled under nitrogen. Other simple chemicals were analytical-grade and obtained

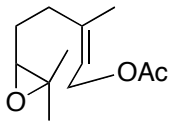
commercially.

Synthesis of Starting Materials.

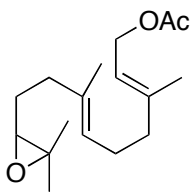
General Procedure for the Regioselective Epoxidation of 25a and 25b (Step a, Scheme 3). To a stirring solution of **25** (50.0 mmol) in CH_2Cl_2 (100 mL) at –20 °C was added a solution of *m*CPBA (77%, Aldrich; 11.2 g, 55.0 mmol) in 100 mL CH_2Cl_2 over 1h. After stirring for 2 h at –20 °C to room temperature, the reaction was quenched with 3 *M* NaOH (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3x20 mL) and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give **26** in quantitative yield. The crude product was used for next step without further purification.



(*E*)-5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-enyl Acetate (26a):[17] TLC, R_f = 0.42 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 3H), 1.31 (s, 3H), 1.60–1.73 (m, 2H), 1.73 (s, 3H), 2.06 (s, 3H), 2.06–2.26 (m, 2H), 2.71 (t, *J* = 6.3 Hz, 1H), 4.59 (d, *J* = 7.2 Hz, 2H), 5.39 (t, *J* = 6.6 Hz, 1H).



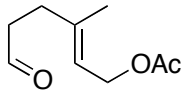
(*Z*)-5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-enyl Acetate (26b):[17b,18] TLC, R_f = 0.43 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 3H), 1.31 (s, 3H), 1.58–1.69 (m, 2H), 1.79 (s, 3H), 2.05 (s, 3H), 2.26 (t, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 6.3 Hz, 1H), 4.58 (d, *J* = 7.2 Hz, 2H), 5.41 (t, *J* = 7.2 Hz, 1H).



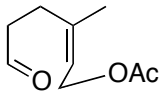
(2*E*,6*E*)-9-(3,3-Dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dienyl Acetate

(26c) (Step b, Scheme 3):[15] To a solution of **25c** (9.14 mL, 30.0 mmol) in THF (700 mL) was added water (530 mL) at 0 °C until the solution became cloudy. NBS (recrystallized, 5.82 g, 32.7 mmol) was then added in small portions over 1 h and the reaction was allowed to stir for another hour at 0°C. The THF was evaporated *in vacuo* at ~5 °C (2 h) and the suspension was extracted with hexane–Et_2O (4:1; 4x150 mL). The organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a yellow oil as crude product. The oil was purified by flash chromatography (SiO_2, hexane–EtOAc = 9:1–4:1) to give pure bromohydrine (8.30 g, 23.0 mmol) as colorless oil in 77% yield. To a solution of bromohydrine in anhydrous MeOH was added K_2CO_3 (7.94 g, 57.4 mmol). The reaction was stirred for 2 h at room temperature. The solvent was removed *in vacuo* and the residue was taken up in Et_2O (100 mL) to form white suspension. The suspension was filtered through a plug of tightly packed celite which was washed with Et_2O (3 times). The combined ether fractions were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give epoxy alcohol as colorless oil. Epoxy alcohol was taken upon in pyridine (15 mL) and was treated with Ac_2O (8.70 mL, 92.0 mmol) at room temperature for 2 hours. The mixture was poured into ice-water (100 mL) and the product was extracted with Et_2O (2x100 mL). The organic layers were washed with citric acid (20%, 2x10 mL), water (30 mL), saturated $NaHCO_3$ (2x30 mL) and brine (2x30 mL). The organics were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give **26c** as a colorless oil. TLC, R_f = 0.41 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (s, 3H), 1.30 (s, 3H), 1.58–1.66 (m, 2H), 1.62 (s, 3H), 1.71 (s, 3H), 2.04–2.21 (m, 6H), 2.04 (s, 3H), 2.69 (dt, *J* = 2.7, 6.3 Hz, 1H), 4.59 (t, *J* = 6.9 Hz, 2H), 5.16 (dt, *J* = 1.2, 5.4 Hz, 1H), 5.34 (tq, *J* = 1.2, 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6, 16.1, 18.4, 20.6, 24.5, 25.8, 27.1, 36.0, 39.1, 57.8, 60.9, 63.6, 118.2, 123.9, 134.2, 141.5, 170.5.

General Procedure for the Oxidative Cleavage of Epoxides 26 to Aldehydes 27 (Step c, Scheme 3): A solution of **26** (50.0 mmol) in Et_2O (50 mL) was added to a solution of $HIO_4 \cdot 2H_2O$ (13.7 g, 60.0 mmol) in THF (250 mL) at 0 °C. The mixture was stirred for 30 min. and then diluted with saturated $NaHCO_3$. After stirring for 15 min, the resulting solution was filtered through celite, and the filter cake was washed with Et_2O. The combined filtrates were extracted with Et_2O. The extracts were washed with water, saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.



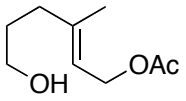
(*E*)-3-Methyl-6-oxohex-2-enyl acetate (27a, Scheme 4):[17a,19] The product was obtained as pale yellow oil and used for next step without further purification. TLC, R_f = 0.31 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.73 (s, 3H), 2.06 (s, 3H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.56–2.62 (m, 2H), 4.58 (d, *J* = 7.2 Hz, 2H), 5.33–5.29 (m, 1H), 9.78 (dd, *J* = 1.8, 3.0 Hz, 1H).



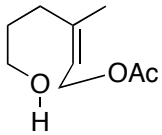
(*Z*)-3-Methyl-6-oxohex-2-enyl Acetate (27b, Scheme 4):[18] 96% yield for 2 steps. SiO_2 column chromatography (hexane–EtOAc = 10:1); colorless oil; TLC, R_f = 0.32 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.76 (s, 3H), 2.06 (s, 3H), 2.43 (t, *J* = 7.5 Hz, 2H), 2.54-2.59 (m, 2H), 4.58 (d, *J* = 7.2 Hz, 2H), 5.41 (m, *J* = 7.2 Hz, 1H), 9.79 (t, *J* = 1.2 Hz, 1H).

General Procedure for the Reduction of Aldehydes 27 to Alcohols 28 (Step d, Scheme 3): To a stirred solution of **27** (50.0 mmol) in EtOH (150 mL) was added $NaBH_4$ (2.08 g, 55.0 mmol) slowly at 0 °C and the mixture stirred for 1 h at 0 °C.

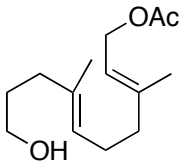
Then 1 *M* HCl was added and the aqueous phase was extracted with EtOAc (3 times). The combined organic layers were washed with saturated $NaHCO_3$, brine and water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.



(*E*)-6-Hydroxy-3-methylhex-2-enyl Acetate (28a):[20] The product was obtained as a pale yellow oil and used for next step without further purification. TLC, R_f = 0.10 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.69–1.76 (m, 2H), 1.72 (s, 3H), 2.06 (s, 3H), 2.06–2.16 (m, *2*H), 3.65 (t, *J* = 6.6 Hz, 2H), 4.58 (d, *J* = 7.2 Hz, 2H), 5.35–5.41 (m, 1H).



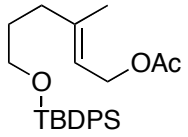
(*Z*)-6-Hydroxy-3-methylhex-2-enyl Acetate (28b):[21] 96% yield. SiO_2 column chromatography (hexane–EtOAc = 1:1); colorless oil; TLC, R_f = 0.11 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.67 (quintet, *J* = 6.6 Hz, 2H), 1.75 (s, 3H), 1.95 (brs, OH), 2.04 (s, 3H), 2.20 (t, *J* = 7.5 Hz, 2H), 3.60 (brs, *J* = 2H), 4.58 (d, *J* = 7.2 Hz, 2H), 5.36 (t, *J* = 7.2 Hz, 1H).



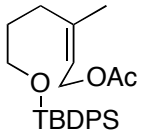
(2*E*,6*E*)-10-Hydroxy-3,7-dimethyldeca-2,6-dienyl Acetate (28c):[22] 96% yield for 4 steps. SiO_2 column chromatography (hexane–EtOAc = 1:1); pale yellow oil; TLC, R_f = 0.11 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.61 (s, 3H), 1.61–1.70 (m, 2H), 1.71 (s, 3H), 2.02–2.14 (m, 6H), 2.06 (s, 1H), 2.59 (s, OH), 3.59 (t, *J* = 6.6 Hz, 2H), 4.58 (t, *J* = 7.2 Hz, 2H), 5.13 (dt, *J* = 1.2, 7.2 Hz, 1H), 5.34 (tq, *J* =

1.2, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.7, 16.2, 20.8, 25.8, 30.5, 35.6, 39.2, 61.2, 62.1, 118.1, 123.7, 134.9, 141.9, 171.1.

General Procedure for the Silylation of Alcohols 28 to Silyl Ethers 29 (Step e, Scheme 3): To a solution of **28** (22.1 mmol), imidazole (3.20 g, 24.3 mmol), in DMF (22 mL) was added TBDPSCl (6.30 mL, 24.3 mmol) at 0 °C. After the mixture was stirred for over night, the reaction was quenched with water. The aqueous phase was extracted with Et_2O (3 times), washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.



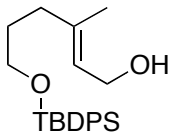
(*E*)-6-(*tert*-Butyldiphenylsilyloxy)-3-methylhex-2-enyl Acetate (29a):[23] The product was obtained as a pale yellow oil and used for next step without further purification. TLC, R_f = 0.50 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 9H), 1,63–1,73 (m, 2H), 1.67 (s, 3H), 2.05 (s, 3H), 2.13 (t, *J* = 7.5 Hz, 2H), 3.65 (t, *J* = 6.3 Hz, 2H), 4.56 (d, *J* = 7.2 Hz, 2H), 5.33 (tq, *J* = 1.2, 7.2 Hz, 1H), 7.35–7.45 (m, 6H), 7.65–7.73 (m, 4H).



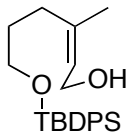
(*Z*)-6-(*tert*-Butyldiphenylsilyloxy)-3-methylhex-2-enyl Acetate (29b): 98% yield; SiO_2 column chromatography (hexane–EtOAc = 20:1); colorless oil; TLC, R_f = 0.64 (hexane–EtOAc = 4:1); IR (film) 3012, 2933, 2896, 2859, 1731 (C=O), 1428, 1381, 1241, 1111, 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 9H), 1.57–1.67 (m, 2H), 1.73 (s, 3H), 2.03 (s, 3H), 2.18 (t, *J* = 7.5 Hz, 2H), 3.65 (t, *J* = 6.3 Hz, 2H), 4.56 (t,

J = 7.2 Hz, 2H), 5.35 (t, J = 7.2 Hz, 1H), 7.35–7.45 (m, 6H), 7.65–7.69 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.9, 20.6, 23.1, 26.6 (3C), 28.0, 30.7, 60.6, 63.0, 119.2, 127.4 (4C), 129.3 (2C), 133.5 (2C). 135.2 (4C), 141.8, 170.3 (C=O); HRMS (FAB) m/z calcd for $C_{25}H_{34}O_3SiNa$ (M+Na) 433.2175, found 433.2175.

General Procedure for the Alcoholysis of Acetates 29 to Alcohols 30 (Step f, Scheme 3): To a solution of **29** (22.0 mmol) in anhydrous MeOH (22 mL) was added K_2CO_3 (1.52 g, 11.0 mmol). The reaction was stirred for 1 h at room temperature. The K_2CO_3 was filtered off and the MeOH was evaporated. The residue was extracted with EtOAc (2 times), washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude alcohols were purified by column chromatography on silica gel with hexane–EtOAc = 2:1 as eluent to afford pure **30**.

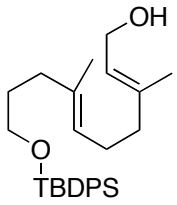


(*E*)-6-(*tert*-Butyldiphenylsilyloxy)-3-methylhex-2-en-1-ol (30a):[23] 80% yield for 5 steps. Pale yellow oil; TLC, R_f = 0.22 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 9H), 1.64–1.75 (m, 2H), 1.65 (s, 3H), 2.08 (t, J = 8.1 Hz, 2H), 3.65 (t, J = 6.3 Hz, 2H), 4.12 (t, J = 6.0 Hz, 2H), 5.38 (tq, J = 1.2, 7.2 Hz, 1H), 7.35–7.45 (m, 6H), 7.65–7.73 (m, 4H).



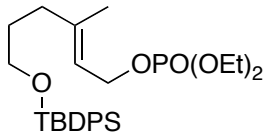
(*Z*)-6-(*tert*-Butyldiphenylsilyloxy)-3-methylhex-2-en-1-ol (30b): 98% yield. Colorless oil; TLC, R_f = 0.26 (hexane–EtOAc = 4:1); IR (film) 3610, 3550–3200 (br), 3010, 2932, 2860, 1472, 1428, 1389, 1240, 1107 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ

1.06 (s, 9H), 1.46 (t, J = 5.4 Hz, 1H), 1.59 (quintet, J = 6.0 Hz, 3H), 1.70 (s, 3H), 2.19 (t, J = 7.8 Hz, 2H), 3.65 (t, J = 6.0 Hz, 2H), 4.11 (t, J = 6.0 Hz, 2H), 5.46 (t, J = 6.0 Hz, 1H), 7.35–7.47 (m, 6H), 7.64–7.69 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 23.2, 26.8 (3C), 27.8, 30.7, 58.6, 63.1, 124.7, 127.5 (4C), 129.5 (2C), 133.6 (2C), 135.4 (4C), 139.2; HRMS (FAB) m/z calcd for $C_{23}H_{32}O_2SiNa$ (M+Na) 391.2069, found 391,2057.

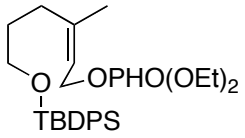


(2*E*,6*E*)-10-(*tert*-Butyldiphenylsilyloxy)-3,7-dimethyldeca-2,6-dien-1-ol (30c): 95% yield for 2 steps. Pale yellow oil; TLC, R_f = 0.22 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 9H), 1.46 (brs, OH), 1.56 (s, 3H), 1.60–1.70 (m, 2H), 1.66 (s, 3H), 1.98-2.12 (m, 6H), 3.64 (t, J = 6.6 Hz, 2H), 4.12 (d, J = 6.9 Hz, 2H), 5.09 (dt, J = 0.9, 7.2 Hz, 1H), 5.39 (dt, J = 1.2, 7.2 Hz, 1H), 7.34–7.44 (m, 6H), 7.66–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.9, 16.2, 19.1, 26.2, 26.8 (3C), 30.8, 35.7, 39.4, 59.2, 63.4, 123.3, 123.8, 127.5 (4C), 129.4 (2C), 134.0 (2C), 134.9, 135.5 (4C), 139.5.

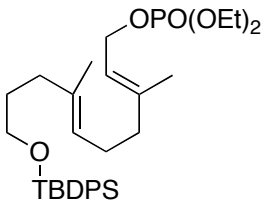
General Procedure for the Condensation of Alcohols 30 to Phosphonates 31 (Step g, Scheme 3): To a solution of **30** (22.0 mmol) and Et_3N (4.60 mL, 33.0 mmol) in hexane (30 mL) was added $(EtO)_2POCl$ (4.80 mL, 33.0 mmol) dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 24 h. The reaction was quenched with saturated NH_4Cl, extracted with EtOAc (3 times), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude phosphonates were purified by column chromatography on silica gel to afford pure **31**.



(*E*)-6-(*tert*-Butyldiphenylsilyloxy)-3-methylhex-2-enyl Diethyl Phosphate (31a): 90% yield. Column chromatography (hexane–EtOAc = 3:1 to 1:1); pale yellow oil; TLC, R_f = 0.29 (hexane–EtOAc = 2:1); IR (film) 3550–3250 (br), 3000, 2932, 2859, 1472, 1428, 1391, 1259, 1111, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 6H), 1.64–1.74 (m, 2H), 1.69 (s, 3H), 2.14 (t, *J* = 7.8 Hz, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 4H), 4.55 (t, *J* = 7.5 Hz, 2H), 5.41 (t, *J* = 7.5 Hz, 1H), 7.34–7.44 (m, 6H), 7.65–7.69 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.0, 16.3, 19.0, 26.7, 30.3, 35.6, 63.1, 63.4, 63.5, 63.8, 63.9, 118.8, 127.5 (4C), 129.4 (2C), 133.7 (2C), 135.4 (4C), 142.3; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{42}O_5PSi$ (M+H) 505.2539, found 505.2544.



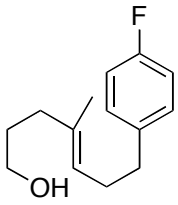
(*Z*)-6-(*tert*-Butyldiphenylsilyloxy)-3-methylhex-2-enyl Diethyl Phosphate (31b): 98% yield. Column chromatography (hexane–EtOAc = 2:1); colorless oil; TLC, R_f = 0.29 (hexane–EtOAc = 2:1); IR (film) 3500–3250 (br), 3000, 2959, 2860, 1472, 1428, 1391, 1259, 1111, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 9H), 1.31 (t, *J* = 7.5 Hz, 6H), 1.57–1.66 (m, 2H), 1.73 (s, 3H), 2.18 (t, *J* = 7.8 Hz, 2H), 3.64 (t, *J* = 6.0 Hz, 2H), 4.08 (q, *J* = 7.5 Hz, 4H), 4.54 (t, *J* = 7.5 Hz, 2H), 5.40 (t, *J* = 6.9 Hz, 1H), 7.30–7.50 (m, 6H), 7.64–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.0, 19.0, 23.3, 26.7 (3C), 28.2, 30.9, 63.2, 63.4 (2C), 63.5, 63.6, 119.8 (d, *J* = 26 Hz), 127.5 (4C), 129.5 (2C), 133.7 (2C), 135.4 (4C), 142.4; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{42}O_5PSi$ (M+H) 505.2539, found 505.2548.



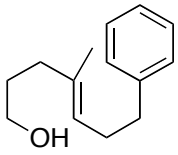
(2*E*,6*E*)-10-(*tert*-Butyldiphenylsilyloxy)-3,7-dimethyldeca-2,6-dienyl Diethyl Phosphate (31c): 91% yield. Column chromatography (hexane–EtOAc = 2:1); colorless oil; TLC, R_f = 0.25 (hexane–EtOAc = 2:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 9H), 1.33 (t, *J* = 7.2 Hz, 6H), 1.56 (s, 3H), 1.56–1.70 (m, 2H), 1.70 (s, 3H), 1.99–2.12 (m, 6H), 3.63 (t, *J* = 6.6 Hz, 2H), 4.11 (quintet, *J* = 7.2 Hz, 4H), 4.56 (t, *J* = 7.2 Hz, 2H), 5.08 (dt, *J* = 1.2, 7.2 Hz, 1H), 5.39 (dt, *J* = 1.5, 7.2 Hz, 1H), 7.35–7.46 (m, 6H), 7.65–7.69 (m, 4H).

General Procedure for Butsugan Coupling of Phosphonates 31 with Arylmethyl Grignard Reagents (Step h, Scheme 3):[16] Mg (144 mg, 6.0 mmol) was activated with stirring 2 days under N_2 atmosphere and THF (5 mL) was added. The resulting mixture was cooled to 0 °C and arylmethyl chloride (4.50 mmol) was added dropwise with stirring over period 30 min. at 0 °C. After stirring for 3 h used for next step. The solution of **31** (3.0 mmol) in THF (6 mL) was cooled to 0 °C under N_2 atmosphere and Grignard reagent was added to this solution via cannula slowly. The mixture was warmed to room temperature and stirred for 12 h. After the reaction was completed (TLC), quenched with saturated NH_4Cl, the aqueous phase was extracted with Et_2O (twice), the combined organic layers was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was dissolved in THF (30 mL) and to this solution was added TBAF (1.0 *M* in THF, TCI, 6.0 mL, 6.0 mmol). After the resulting mixture was stirred for 6 h, the reaction was quenched with water and the aqueous layer was extracted with EtOAc (3 times). The combined organic layers

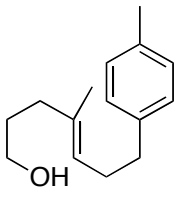
were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to afford pure **32**.



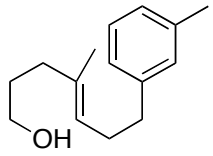
(*E*)-7-(4-Fluorophenyl)-4-methylhept-4-en-1-ol (32aa): >99% yield. Column chromatography (hexane–EtOAc = 3:1); pale yellow oil; TLC, R_f = 0.13 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (brs, OH), 1.54 (s, 3H), 1.60–1.69 (m, 2H), 2.05 (t, *J* = 7.5 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 3.60 (dd, *J* = 6.0, 9.9 Hz, 2H), 5.19 (tq, *J* =1.5, 7.2 Hz, 1H), 6.91–6.99 (m, 2H), 7.09–7.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6, 29.8, 30.6, 35.0, 35.7, 62.2, 114.6, 114.8, 123.4, 129.5, 129.6, 135.4, 137.6, 161.0 (d, $J_{C\text{-}F}$ = 242 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –118.5 (dd, $J_{C\text{-}F}$ = 9.0, 15.0 Hz).



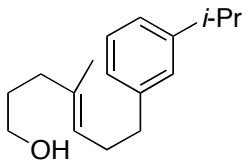
(*E*)-4-Methyl-7-phenylhept-4-en-1-ol (32ab)[24] 97% yield. Column chromatography (hexane–EtOAc = 5:1); colorless oil; TLC, R_f = 0.15 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1,25 (t, *J* = 5.1 Hz, OH), 1.56 (s, 3H), 1.66 (q, *J* = 6.6 Hz, 2H), 2.05 (t, *J* = 7.2 Hz, 2H), 2.33 (q, *J* = 7.5 Hz, 2H), 2.64 (t, *J* = 7.8 Hz, 2H), 3.60 (dd, *J* = 6.3, 11.7 Hz, 2H), 5.22 (dt, *J* = 1.5, 7.2 Hz, 1H), 7.18–7.20 (m, 3H), 7.26–7.30 (m, 2H).



(*E*)-4-Methyl-7-*p*-tolylhept-4-en-1-ol (32ac): 95% yield. Column chromatography (hexane–EtOAc = 3:1); colorless oil; TLC, R_f = 0.19 (hexane–EtOAc = 4:1); IR (film) 3619, 3550–3200 (br), 3010, 2939, 1514, 1449, 1385, 1054, 1008, 814 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (brs, OH), 1.57 (s, 3H), 1.65 (quintet, *J* = 6.9 Hz, 2H), 2.05 (t, *J* = 7.5 Hz, 2H), 2.24–2.35 (m, 2H), 2.32 (s, 3H), 2.60 (t, *J* = 7.8 Hz, 2H), 3.60 (t, *J* = 6.6 Hz, 2H), 5.22 (tq, *J* = 1.2, 7.2 Hz, 1H), 7.08 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6, 20.7, 29.8, 35.4, 35.6, 62.0, 123.8, 128.0 (2C), 128.7 (2C), 134.9, 138.9; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{23}O$ (M+H) 219.1749, found 219.1739.

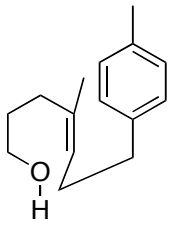


(*E*)-4-Methyl-7-*m*-tolylhept-4-en-1-ol (32ad): 94% yield. Column chromatography (hexane–EtOAc = 4:1); pale yellow oil; TLC, R_f = 0.24 (hexane–EtOAc = 4:1); IR (film) 3627, 3500–3300 (br), 3011, 2940, 2850, 2360, 1456, 1054, 1010 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 3H), 1.62 (quintet, *J* = 7.2 Hz, 2H), 2.02 (t, *J* = 7.5 Hz, 2H), 2.24–2.31 (m, 2H), 2.30 (s, 3H), 2.48 (brs, OH), 2.58 (t, *J* = 7.8 Hz, 2H), 3.54 (t, *J* = 6.6 Hz, 2H), 5.20 (brt, *J* = 7.2 Hz, 1H), 6.95–6.98 (m, 3H), 7.14 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.7, 21.2, 29.8, 30.6, 35.7, 35.8, 62.3, 123.9, 125.3, 126.3, 128.0, 129.1, 135.1, 137.5, 142.0; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{23}O$ (M+H) 219.1749, found 219.1759.

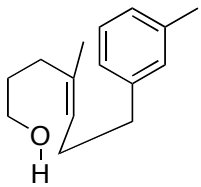


(*E*)-7-(3-Isopropylphenyl)-4-methylhept-4-en-1-ol (32ae): 95% yield. Column chromatography (hexane–EtOAc = 5:1); colorless oil; TLC, R_f = 0.25 (hexane–EtOAc = 4:1); IR (film) 3623, 3600–3250 (br), 3009, 2962, 2938, 2871, 1604,

1.445, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (d, *J* = 6.9 Hz, 6H), 1.30 (t, *J* = 5.4 Hz, OH), 1.57 (s, 3H), 1.65 (quintet, *J* = 7.5 Hz, 2H), 2.06 (t, *J* = 7.5 Hz, 2H), 2.31 (q, *J* = 7.5 Hz, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.80–2.94 (m, 1H), 3.60 (dd, *J* = 6.0, 9.0 Hz, 2H), 5.23 (t, *J* = 7.2 Hz, 1H), 6.99–7.06 (m, 3H), 7.21 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.7, 23.9 (2C), 29.8, 30.6, 33.9, 35.7, 35.9, 62.1, 123.5, 123.9, 125.7, 125.4, 128.0, 135.0, 142.0, 148.5; HRMS (FAB) *m*/*z* calcd for $C_{17}H_{26}ONa$ (M+Na) 269.1881, found 269.1873.

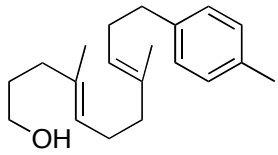


(*Z*)-4-Methyl-7-*p*-tolylhept-4-en-1-ol (32ba): 94% yield. Column chromatography (hexane–EtOAc = 5:1); colorless oil; TLC, R_f = 0.21 (hexane–EtOAc = 4:1); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, *J* = 5.4 Hz, OH), 1.54–1.63 (m, 2H), 1.70 (s, 3H), 2.07 (t, *J* = 7.5 Hz, 2H), 2.26–2.35 (m, 2H), 2.32 (s, 3H), 2.60 (t, *J* = 7.5 Hz, 2H), 3.58 (q, *J* = 6.3 Hz, 2H), 5.21 (t, *J* = 7.2 Hz, 1H), 7.09 (s, 4H).

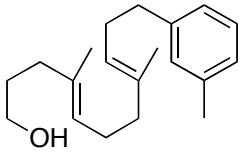


(*Z*)-4-Methyl-7-*m*-tolylhept-4-en-1-ol (32bb): 94% yield. Column chromatography (hexane–EtOAc = 5:1); colorless oil; TLC, R_f = 0.33 (hexane–EtOAc = 4:1); IR (film) 3628, 3650–3250 (br), 3012, 2932, 2860, 1607, 1456, 1378, 1041, 1009 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, *J* = 5.4 Hz, OH), 1.58 (dt, *J* = 6.6, 13.2 Hz, 2H), 1.70 (s, 3H), 2.07 (t, *J* = 7.8 Hz, 2H), 2.26–2.33 (m, 2H), 2.33 (s, 3H), 2.60 (t, *J* = 7.8 Hz, 2H), 3.58 (dd, *J* = 3.3, 11.7 Hz, 2H), 5.22 (t, *J* = 6.9 Hz, 1H), 6.97–7.00 (m, 3H), 7.15–7.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 23.2, 27.9,

29.8, 30.6, 36.1, 62.5, 124.8, 125.3, 126.3, 128.0, 129.1, 135.2, 137.6, 142.1; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{23}O$ (M+H) 219.1749, found 219.1740.

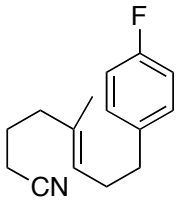


(4*E*,8*E*)-4,8-Dimethyl-11-*p*-tolylundeca-4,8-dien-1-ol (32ca): 99% yield. Column chromatography (hexane–EtOAc = 5:1); colorless oil; TLC, R_f = 0.28 (hexane–EtOAc = 4:1); IR (film) 3619, 3650–3200 (br), 3010, 2925, 2858, 1514, 1449, 1384, 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.56 (s, 3H), 1.60 (s, 3H), 1.60–1.69 (m, 2H), 1.72 (brs, OH), 1.96–2.11 (m, 6H), 2.24–2.34 (m, 2H), 2.31 (s, 3H), 2.60 (dd, *J* = 6.7, 9.0 Hz, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 5.12–5.21 (m, *J* = 1.2, 6.6 Hz, 2H), 7.08 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8, 15.9, 20.9, 26.4, 30.0, 30.6, 35.6, 35.9, 39.5, 62.6, 123.8, 124.6, 128.2 (2C), 128.8 (2C), 134.5, 135.0, 135.4, 139.2; HRMS (FAB) *m*/*z* calcd for $C_{20}H_{30}ONa$ (M+Na) 309.2194, found 309.2197.



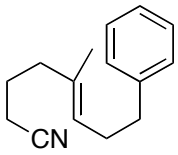
(4*E*,8*E*)-4,8-Dimethyl-11-*m*-tolylundeca-4,8-dien-1-ol (32cb): 97% yield. Column chromatography (hexane–EtOAc = 10:1); colorless oil; TLC, R_f = 0.26 (hexane–EtOAc = 4:1); IR (film) 3620, 3650–3200 (br), 3010, 2926, 2858, 1607, 1449, 1384, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (brs, OH), 1.57 (s, 3H), 1.62 (s, 3H), 1.62–1.72 (m, 2H), 1.97–2.12 (m, 6H), 2.26–2.34 (m, 2H), 2.34 (s, 3H), 2.60 (t, *J* = 7.5 Hz, 2H), 3.63 (t, *J* = 6.6 Hz, 2H), 5.13–5.22 (m, 2H), 6.99–7.02 (m, 3H), 7.18 (dt, *J* = 1.5, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8, 15.9, 21.4, 26.5, 30.0, 30.6, 35.9, 36.0, 39.6, 62.6, 123.8, 124.6, 125.4, 126.3, 128.1, 129.2, 134.6, 135.5, 137.6, 142.3; HRMS (EI) *m*/*z* calcd for $C_{20}H_{30}O$ (M) 286.2297, found 286.2301.

General Procedure for the Carbon Chain Homologation from Alcohols 32 to Nitriles 33 (Step I, Scheme 3): To a solution of **32** (5.86 mmol) in CH_2Cl_2 was added Et_3N (2.45 mL, 17.6 mmol) and MsCl (680 μL, 8.79 mmol) dropwise at 0 °C. After the resulting mixture was stirred for 1 h at 0 °C, the mixture was allowed to warm to room temperature and stirred for 30 min. Then the solvent was evaporated *in vacuo*. The residue was taken in the EtOAc–water (1:1) and the aqueous layer was extracted with EtOAc (3 times). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude mesylate was dissolved in CH_3CN (30 mL) and was added 18-crown-6 (4.65 g, 17.6 mmol) and KCN (1.14 g, 17.6 mmol). The resulting mixture was heated to reflux and stirred for 6 h. After the reaction was quenched with water, the aqueous layer was extracted with Et_2O (twice), the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

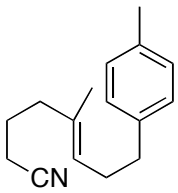


(*E*)-8-(4-Fluorophenyl)-5-methyloct-5-enenitrile (33aa): The product was obtained as a pale yellow oil and used for next step without further purification. TLC, R_f = 0.44 (hexane–EtOAc = 4:1); IR (film) 3022, 2927, 2859, 2249, 1603, 1509, 1456, 1223, 1157, 830; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 3H), 1.72 (quintet, J = 7.2 Hz, 2H), 2.11 (t, J = 7.2 Hz, 2H), 2.20 (t, J = 7.2 Hz, 2H), 2.30 (q, J = 7.2 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 5.21 (tq, J =1.2, 7.2 Hz, 1H), 6.92–7.00 (m, 2H), 7.09–7.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.1, 15.7, 22.9, 29.6, 34.6, 37.8, 114.4, 114.7, 119.8, 125.2, 129.5, 129.6, 133.1, 137.4, 160.4 (d, $J_{C\text{-}F}$ = 242); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –118.3 (dd, J_{CF} = 9.0, 18 Hz); HRMS (FAB) *m/z* calcd for $C_{15}H_{19}NF$ (M+H) 232.1502,

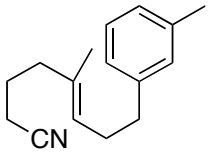
found 232.1490.



(*E*)-5-Methyl-8-phenyloct-5-enenitrile (33ab): The product was obtained as a pale yellow oil and used for next step without further purification. TLC, R_f = 0.41 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.51 (s, 3H), 1.72 (quintet, J = 7.2 Hz, 2H), 2.11 (t, J = 7.2 Hz, 2H), 2.17 (t, J = 7.2 Hz, 2H), 2.33 (t, J = 7.2 Hz, 2H), 2.67 (t, J = 7.5 Hz, 2H), 5.22 (tq, J = 1.2, 7.2 Hz, 1H), 7.17–7.21 (m, 3H), 7.26–7.28 (m, 2H).

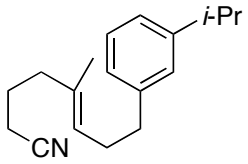


(*E*)-5-Methyl-8-*p*-tolyloct-5-enenitrile (33ac): 95% yield. SiO_2 column chromatography (hexane–EtOAc = 10:1); colorless oil; TLC, R_f = 0.46 (hexane–EtOAc = 4:1); IR (film) 3019, 2925, 2858, 2249, 1515, 1455, 1424, 1384, 1110, 812 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52 (s, 3H), 1.72 (quintet, J = 7.2 Hz, 2H), 2.10 (t, J = 7.2 Hz, 2H), 2.16 (t, J = 7.2 Hz, 2H), 2.27–2.34 (m, 2H), 2.32 (s, 3H), 2.62 (t, J = 7.5 Hz, 2H), 5.22 (tq, J = 1.2, 7.2 Hz, 1H), 7.05–7.11 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.0, 15.4, 20.5, 22.8, 29.4, 34.9, 37.6, 119.3, 125.5, 127.9 (2C), 128.5 (2C), 132.5, 134.6, 138.4; HRMS (FAB) m/z calcd for $C_{16}H_{22}N$ (M+H) 228.1752, found 228.1755.

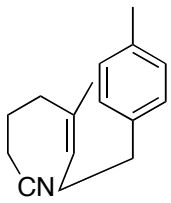


(*E*)-5-Methyl-8-*m*-tolyloct-5-enenitrile (33ad): 96% yield. SiO_2 column chromatography (hexane–EtOAc = 10:1); colorless oil; TLC, R_f = 0.56 (hexane–EtOAc

= 4:1); IR (film) 3020, 3012, 2925, 2858, 2249, 1608, 1456, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 3H), 1.62 (quintet, *J* = 7.2 Hz, 2H), 2.05 (t, *J* = 7.2 Hz, 2H), 2.25–2.32 (m, 4H), 2.30 (s, 3H), 2.59 (t, *J* = 7.2 Hz, 2H), 5.19 (tq, *J* = 1.2, 7.2 Hz, 1H), 6.93–6.96 (m, 3H), 7.13 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.1, 15.5, 21.0, 22.8, 29.5, 35.4, 37.7, 119.4, 125.1, 125.6, 126.1, 127.8, 128.9, 132.6, 137.3, 141.5; HRMS (FAB) *m/z* calcd for $C_{16}H_{22}N$ (M+H) 228.1752, found 228.1761.

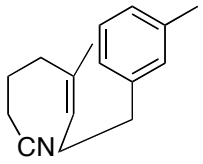


(*E*)-8-(3-Isopropylphenyl)-5-methyloct-5-enenitrile (33ae): 95% yield. SiO_2 column chromatography (hexane–EtOAc = 20:1); colorless oil; TLC, R_f = 0.43 (hexane–EtOAc = 4:1); IR (film) 2962, 2926, 2870, 2249, 1604, 1487, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1 1.24 (d, *J* = 6.9 Hz, 6H), 1.52 (s, 3H), 1.72 (quintet, *J* = 7.5 Hz, 2H), 2.08–2.19 (m, 4H), 2.32 (q, *J* = 7.5 Hz, 2H), 2.64 (t, *J* = 7.8 Hz, 2H), 2.80–2.94 (m, 1H), 5.23 (dt, *J* = 1.2, 6.9 Hz, 1H), 6.99–7.07 (m, 3H), 7.21 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.2, 15.7, 23.0, 23.8 (2C), 29.5, 33.8, 35.6, 37.8, 119.5, 123.5, 125.7, 125.8, 126.3, 127.9, 132.7, 141.6, 148.5; HRMS (FAB) *m/z* calcd for $C_{18}H_{25}NNa$ (M+Na) 278.1885, found 278.1884.

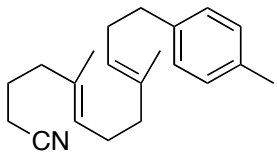


(*Z*)-5-Methyl-8-*p*-tolyloct-5-enenitrile (33ba): 98% yield. SiO_2 column chromatography (hexane–EtOAc = 20:1); colorless oil; TLC, R_f = 0.44 (hexane–EtOAc = 4:1); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55–1.66 (m, 2H), 1.66 (s, 3H), 2.09 (t, *J* = 7.5 Hz, 2H), 2.16 (t, *J* = 7.5 Hz, 2H), 2.25–2.32 (m, 2H), 2.32 (s, 3H), 2.60 (t, *J* = 7.5 Hz, 2H), 5.27 (t, *J* = 7.2 Hz, 1H), 7.04–7.11 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8,

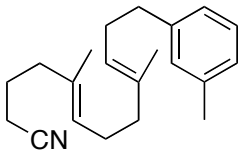
20.6, 22.5, 23.1, 29.6, 29.9, 35.3, 119.3, 126.1, 128.0 (2C), 128.5 (2C), 132.7, 134.7, 138.4.



(*Z*)-5-Methyl-8-*m*-tolyloct-5-enenitrile (33bb): 98% yield. SiO_2 column chromatography (hexane–EtOAc = 20:1); colorless oil; TLC, R_f = 0.54 (hexane–EtOAc = 4:1); IR (film) 3013, 2957, 2934, 2860, 1715, 1604, 1452, 1363, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.56–1.67 (m, 2H), 1.66 (d, *J* = 1.2 Hz, 3H), 2.10 (t, *J* = 7.5 Hz, 2H), 2.26–2.33 (m, 2H), 2.33 (s, 3H), 2.60 (t, *J* = 7.5 Hz, 2H), 5.28 (t, *J* = 7.5 Hz, 1H), 6.97–7.01 (m, 3H), 7.17–7.20 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.9, 21.0, 22.6, 23.1, 29.6, 29.9, 35.7, 119.4, 125.2, 126.2, 127.8, 129.0, 132.8, 137.3, 141.5; HRMS (FAB) *m*/*z* calcd for $C_{16}H_{22}N$ (M+H) 228.1752 found 228.1759.

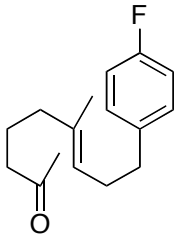


(5*E*,9*E*)-5,9-Dimethyl-12-*p*-tolyldodeca-5,9-dienenitrile (33ca): 97% yield. SiO_2 column chromatography (hexane–EtOAc = 10:1); colorless oil; TLC, R_f = 0.55 (hexane–EtOAc = 4:1); IR (film) 3009, 2924, 2857, 2249, 1515, 1455, 1385, 1107, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.56 (s, 3H), 1.57 (s, 3H), 1.71 (quintet, *J* = 7.2 Hz, 2H), 1.95–2.02 (m, 2H), 2.05–2.11 (m, 4H), 2.22 (t, *J* = 7.2 Hz, 2H), 2.26–2.30 (m, 2H), 2.30 (s, 3H), 2.59 (dd, *J* = 6.7, 9.0 Hz, 2H), 5.13–5.20 (m, 2H), 6.98–7.07 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.4, 15.8, 16.0, 20.8, 23.2, 26.3, 29.9, 35.5, 38.0, 39.3, 119.7, 123.8, 126.4, 128.1 (2C), 128.7 (2C), 132.1, 134.8, 135.1, 139.1; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{30}N$ (M+H) 296.2378, found 296.2386.



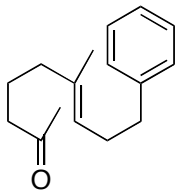
(5*E*,9*E*)-5,9-Dimethyl-12-*m*-tolyldodeca-5,9-dienenitrile (33cb): 93% yield. SiO_2 column chromatography (hexane–EtOAc = 10:1); colorless oil; TLC, R_f = 0.63 (hexane–EtOAc = 4:1); IR (film) 3011, 2925, 2857, 2249, 1607, 1456, 1385, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.56 (s, 3H), 1.58 (s, 3H), 1.72 (quintet, *J* = 7.2 Hz, 2H), 2.02 (q, *J* = 7.2 Hz, 2H), 2.08 (q, *J* = 7.2 Hz, 4H), 2.22–2.32 (m, 4H), 2.32 (s, 3H), 2.59 (t, *J* = 6.6 Hz, 2H), 5.17 (dt, *J* = 6.9 Hz, 2H), 6.98–7.00 (m, 3H), 7.18 (q, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.5, 15.8, 16.0, 21.3, 23.2, 26.4, 30.0, 35.9, 38.1, 39.4, 119.7, 123.9, 125.3, 126.3, 126.4, 128.0, 129.2, 132.2, 135.2, 137.6, 142.2; HRMS (FAB) *m/z* calcd for $C_{21}H_{30}N$ (M+1) 296.2378, found 296.2378.

General Procedure for the Transformation from Nitriles 33 to Ketones 34 (Step j, Scheme 4): To a solution of **33** (5.54 mmol) in dry Et_2O was added MeLi (1.0 M in Et_2O, Kanto, 16.6 mL, 16.6 mmol) dropwise at –78 °C and then the resulting mixture was allowed to warm to 0 °C. The resulting mixture was stirred for 1 h and then saturated NH_4Cl (50 mL) was added while stirring for another 10 min. at 0 °C. The layers were separated and the organic layer was washed with saturated $NaHCO_3$, the aqueous layer was extracted with Et_2O (twice) the combined organic layers was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*.

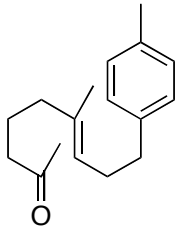


(*E*)-9-(4-Fluorophenyl)-6-methylnon-6-en-2-one (34aa): 96% yield for 2

steps. SiO_2 column chromatography (hexane–EtOAc = 20:1); colorless oil; TLC, R_f = 0.45 (hexane–EtOAc = 4:1); IR (film) 3011, 2937, 2859, 1710 (C=O), 1603, 1509, 1362, 1223, 1157, 830; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52 (s, 3H), 1.65 (quintet, J = 7.5 Hz, 2H), 1.96 (t, J = 7.2 Hz, 2H), 2.12 (s, 3H), 2.27 (t, J = 7.5 Hz, 2H), 2.33 (t, J = 7.5 Hz, 2H), 2.61 (t, J = 7.8 Hz, 2H), 5.13 (dt, J = 0.9, 7.2 Hz, 1H), 6.91–6.99 (m, 2H), 7.09–7.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.4, 21.5, 29.6 (2C), 35.0, 38.6, 42.6, 114.5, 114.8, 123.9, 129.5, 129.6, 135.0, 137.6, 160.9 (d, J_{CF} = 242), 208.7; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –118.5 (dd, J_{CF} = 9.0, 15 Hz); HRMS (FAB) m/z calcd for $C_{16}H_{22}OF$ (M+H) 249.1655, found 249.1655.

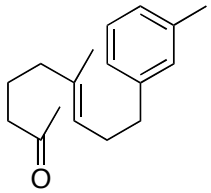


(*E*)-6-Methyl-9-phenylnon-6-en-2-one (34ab): 96% yield for 2 steps. SiO_2 column chromatography (hexane–EtOAc = 20:1); colorless oil; TLC, R_f = 0.45 (hexane–EtOAc = 4:1); IR (film) 3013, 2937, 2858, 1710 (C=O), 1603, 1496, 1453, 1362, 1159, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (s, 3H), 1.65 (quintet, J = 7.5 Hz, 2H), 1.96 (t, J = 7.5 Hz, 2H), 2.11 (s, 3H), 2.31 (q, J = 7.5 Hz, 2H), 2.33 (t, J = 7.5 Hz, 2H), 2.64 (t, J = 7.8 Hz, 2H), 5.16 (dt, J = 1.2, 7.2 Hz, 1H), 7.15–7.20 (m, 3H). 7.25–7,30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.3, 21.3, 29.5 (2C), 35.7, 38.5, 42.4, 124.1, 125.4, 127.9 (2C), 128.1 (2C), 134.6, 141.8, 208.4; HRMS (FAB) m/z calcd for $C_{16}H_{23}O$ (M+H) 231.1749, found 231.1755.

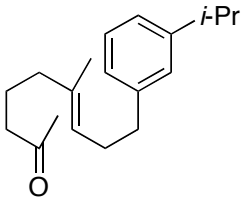


(*E*)-6-Methyl-9-*p*-tolylnon-6-en-2-one (34ac): 94% yield. SiO_2 column

chromatography (hexane–EtOAc = 20:1); colorless oil; TLC, R_f = 0.51 (hexane–EtOAc = 4:1); IR (film) 3011, 2925, 2864, 1710 (C=O), 1515, 1455, 1362, 1159, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 3H), 1.65 (quintet, J = 7.5 Hz, 2H), 1.96 (t, J = 7.5 Hz, 2H), 2.11 (S, 3H), 2.25–2.36 (m, 4H), 2.31 (s, 3H), 2.60 (t, J = 7.8 Hz, 2H), 5.16 (tq, J = 1.2, 7.2 Hz, 1H), 7.08 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.3, 17.5, 20.7, 21.3, 29.5, 29.6, 35.3, 38.5, 42.4, 124.3, 128.0 (2C), 128.6 (2C), 134.4, 134.6, 138.7, 208.5; HRMS (EI) *m*/*z* calcd for $C_{17}H_{24}O$ (M+H) 244.1827, found 244.1837.

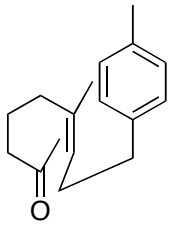


(*E*)-6-Methyl-9-*m*-tolylnon-6-en-2-one (1): 97% yield. SiO_2 column chromatography (hexane–EtOAc = 20:1); colorless oil; TLC, R_f = 0.48 (hexane–EtOAc = 4:1); IR (film) 3019, 2929, 2868, 1709 (C=O), 1457, 1362, 1158 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 3H), 1.60 (quintet, J = 7.2 Hz, 2H), 1.91 (t, J = 7.2 Hz, 2H), 1.98 (s, 3H), 2.20–2.30 (m, 4H), 2.27 (s, 3H), 2.56 (t, J = 7.8 Hz, 2H), 5.13 (t, J = 7.2 Hz, 1H), 6.91–6.94 (m, 3H), 7.09 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.0, 20.8, 21.1, 29.1, 29.3, 35.4, 38.3, 42.0, 123.9, 124.9, 125.9, 127.5, 128.7, 134.2, 136.9, 141.4, 207.6; HRMS (EI) *m*/*z* calcd for $C_{17}H_{24}O$ (M+H) 245.1905, found 244.1819.

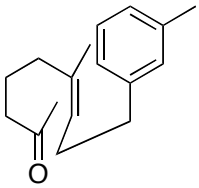


(*E*)-9-(3-Isopropylphenyl)-6-methylnon-6-en-2-one (34ae): 96% yield. SiO_2 column chromatography (hexane–EtOAc = 20:1); colorless oil; TLC, R_f = 0.46 (hexane–EtOAc = 4:1); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (d, J = 6.9 Hz, 6H), 1.54 (s,

3H), 1.66 (quintet, J = 7.5 Hz, 2H), 1.97 (t, J = 7.2 Hz, 2H), 2.11 (s, 3H), 2.27–2.37 (m, 4H), 2.63 (t, J = 7.8 Hz, 2H), 2.80–2.94 (m, 1H), 5.17 (tq, J = 1.2, 6.3 Hz, 1H), 6.99–7.06 (m, 3H), 7.18–7.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.5, 21.6, 23.9 (2C), 29.7, 29.8, 33.9, 35.9, 38.7, 42.7, 123.6, 124.4, 125.7, 126.4, 128.0, 134.6, 142.0, 148.6, 208.8 (C=O).

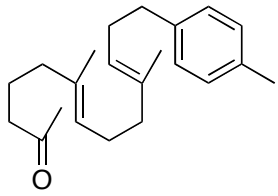


(*Z*)-6-Methyl-9-*p*-tolylnon-6-en-2-one (34ba): 97% yield. SiO_2 column chromatography (hexane–EtOAc = 10:1); colorless oil; TLC, R_f = 0.45 (hexane–EtOAc = 4:1); IR (film) 3010, 2929, 2857, 2359, 1710 (C=O), 1515, 1456, 1362, 1162, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55–1.67 (m, 2H), 1.66 (d, J = 1.2 Hz, 3H), 1.99 (t, J = 7.8 Hz, 2H), 2.11 (s, 3H), 2.22–2.36 (m, 2H), 2.31 (s, 3H), 2.59 (t, J = 7.2 Hz, 2H), 5.21 (t, J = 7.2 Hz, 1H), 7.08 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 21.5, 22.9, 29.6, 29.8, 30.6, 35.6, 42.8, 125.0, 128.1 (2C), 128.7 (2C), 134.6, 134.8, 138.8, 208.5 (C=O); HRMS (FAB) m/z calcd for $C_{17}H_{25}O$ (M+H) 245.1905, found 245.1898.

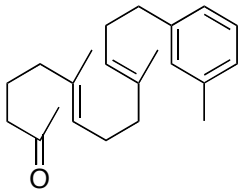


(*Z*)-6-Methyl-9-*m*-tolylnon-6-en-2-one (34bb): 95% yield. SiO_2 column chromatography (hexane–EtOAc = 20:1); colorless oil; TLC, R_f = 0.54 (hexane–EtOAc = 4:1); IR (film) 3019, 2931, 2858, 1710 (C=O), 1456, 1362, 1213, 1161, 1044, 928 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56–1.67 (m, 2H), 1.67 (s, 3H), 1.99 (t, J = 7.6 Hz, 2H), 2.12 (s, 3H), 2.23–2.37 (m, 2H), 2.33 (s, 3H), 2.59 (t, J = 7.8 Hz, 2H), 5.21 (t, J = 7.2 Hz, 1H), 6.98–7.00 (m, 3H), 7.17–7.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ

21.0, 21.4, 22.8, 29.4, 29.6, 30.5, 35.9, 42.6, 124.9, 125.1, 126.1, 127.8, 128.9, 134.5, 137.2, 141.7, 208.0; HRMS (FAB) *m*/*z* calcd for $C_{17}H_{25}O$ (M+H) 245.1905, found 245.1904.



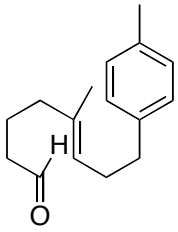
(6*E*,10*E*)-6,10-Dimethyl-13-*p*-tolyltrideca-6,10-dien-2-one (34ca): 95% yield. SiO_2 column chromatography (hexane–EtOAc = 10:1); colorless oil; TLC R_f = 0.51 (hexane–EtOAc = 4:1); IR (film) 3010, 2925, 2857, 1710 (C=O), 1515, 1456, 1362, 1227, 1158 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.56 (s, 3H), 1.57 (s, 3H), 1.67 (quintet, *J* = 7.5 Hz, 2H), 1.93–2.00 (m, 4H), 2.04–2.11 (m, 2H), 2.11 (s, 3H), 2.24-2.31 (m, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.31 (s, 3H), 2.59 (dd, *J* = 7.9, 9.9 Hz, 2H), 5.10 (dt, *J* = 1.2, 6.9 Hz, 1H), 5.18 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.08 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6, 15.9, 20.9, 21.7, 26.4, 29.9, 30.0, 35.6, 38.8, 39.6, 42.8, 123.7, 125.0, 128.2 (2C), 128.8 (2C), 134.0, 134.9, 135.4, 139.2, 209.1; HRMS (FAB) *m*/*z* calcd for $C_{22}H_{32}ONa$ (M+Na) 335.2351, found 335.2348.



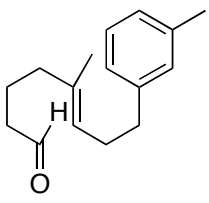
(6*E*,10*E*)-6,10-Dimethyl-13-*p*-tolyltrideca-6,10-dien-2-one (34cb): 96% yield. SiO_2 column chromatography (hexane–EtOAc = 10:1); colorless oil; TLC, R_f = 0.48 (hexane–EtOAc = 4:1); IR (film) 3010, 2925, 2857, 1710 (C=O), 1607, 1450, 1362, 1158 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.57 (s, 3H), 1.58 (s, 3H), 1.67 (quintet, *J* = 7.2 Hz, 2H), 1.94–2.09 (m, 6H), 2.13 (s, 3H), 2.25–2.33 (m, 4H), 2.33 (s, 3H), 2.59 (dd, *J* = 7.5, 9.9 Hz, 2H), 5.10 (dt, *J* = 1.2, 6.9 Hz, 1H), 5.19 (dt, *J* = 1.2, 7.2 Hz, 1H), 6.99–7.01 (m, 3H), 7.17 (dt, *J* = 1.5, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz)

δ 15.5, 15.8, 21.3, 21.6, 26.4, 29.8, 29.9, 35.9, 38.7, 39.5, 42.7, 123.6, 124.9, 125.3, 126.3, 128.0, 129.1, 133.9, 135.4, 137.5, 142.1, 208.9; HRMS (FAB) *m*/*z* calcd for $C_{22}H_{33}O$ (M+H) 313.2531, found 313.2526.

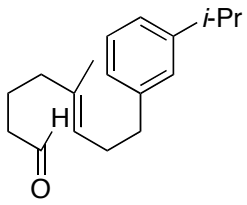
General Procedure for the Transformation from Nitriles 33 to Aldehydes 13 (Step k, Scheme 3): To a solution of **33** (782 mg, 3.44 mmol) in toluene–hexane (1:2 *v*/*v*, 45 mL) was added DIBAL-H (1.0 *M* in toluene, Kanto, 30 mL, 30.0 mmol) at –78 °C slowly with stirring and the resulting mixture was stirred for 1 h at –78 °C. Acetone (5 mL), EtOAc (5 mL), buffer (*p*H 7, 3 mL) was added and stirred for 20 min (–78 °C to 0 °C). Then Na_2SO_4 was added and stirred for additional 30 min at room temperature. The resulting mixture was filtered through celite and Na_2SO_4 and solvents were removed under *vacuo* to give crude products **13**.



(*E*)-5-Methyl-8-*p*-tolyloct-5-enal (13a): 94% yield. SiO_2 column chromatography (hexane–EtOAc = 10:1); colorless oil; TLC, R_f = 0.48 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 3H), 1.71 (qn, *J* = 7.2 Hz, 2H), 2.00 (t, *J* = 7.2 Hz, 2H), 2.25-2.35 (m, 4H), 2.32 (s, 3H), 2.60 (t, *J* = 7.8 Hz, 2H), 5.17 (tq, *J* = 1.2, 6.9 Hz, 1H), 7.08 (s, 4H), 9.74 (t, *J* = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.3, 19.8, 20.7, 29.7, 35.2, 38.5, 42.7, 124.7, 128.0 (2C), 128.6 (2C), 134.1, 134.7, 138.7, 202.0.



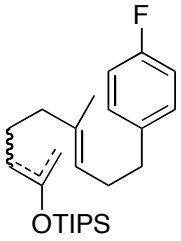
(*E*)-5-Methyl-8-*m*-tolyloct-5-enal (13b): 96% yield. SiO_2 column chromatography (hexane–EtOAc = 10:1); colorless oil; TLC, R_f = 0.48 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 3H), 1.71 (quintet, *J* = 7.2 Hz, 2H), 2.00 (t, *J* = 7.2 Hz, 2H), 2.26–2.36 (m, 4H), 2.33 (s, 3H), 2.61 (dd, *J* = 7.2, 8.1 Hz, 2H), 5.18 (ddq, *J* = 1.2, 2.4, 7.2 Hz, 1H), 6.97–7.00 (m, 3H), 7.17 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.4, 19.8, 21.1, 29.6, 35.6, 38.5, 42.7, 124.7, 125.2, 126.2, 127.9, 129.0, 134.2, 137.3, 141.8, 202.1.



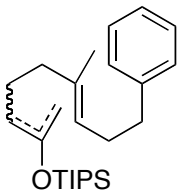
(*E*)-8-(3-Isopropylphenyl)-5-methyloct-5-enal (13c): 93% yield. SiO_2 column chromatography (hexane–EtOAc = 20:1); colorless oil; TLC, R_f = 0.50 (hexane–EtOAc = 4:1); IR (film) 2962, 2931, 2727, 1721 (C=O), 1604, 1459 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (d, *J* = 6.5 Hz, 6H), 1.54 (s, 3H), 1.71 (quintet, *J* = 7.2 Hz, 2H), 2.00 (t, *J* = 7.5 Hz, 2H), 2.28–2.36 (m, 4H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.80–2.94 (m, 1H), 5.18 (dt, *J* = 1.2, 7.2 Hz, 1H), 6.99–7.06 (m, 3H), 7.18–7.23 (m, 1H), 9.73 (t, *J* = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6, 20.0, 24.0 (2C), 29.8, 34.0, 35.9, 38.7, 43.0, 123.7, 124.9, 125.8, 126.5, 128.1, 134.3, 142.0, 148.7, 202.6 (C=O); HRMS (FAB) *m*/*z* calcd for $C_{18}H_{27}O$ (M+H) 259.2062, found 259.2058.

General Procedure for the Synthesis of Triisopropylsilyl Enol Ethers 4, 7, and 10 from Ketones 34 (Step l, Scheme 4): To a solution of **34** (1.80 mmol) and Et_3N (627 μL, 4.50 mmol) in dry CH_2Cl_2 (3.6 mL) was added TIPSOTf (473 μL, 1.82 mmol) dropwise at 0 °C, and the resulting mixture was stirred for 3 h at 0 °C. After the reaction was quenched with saturated $NaHCO_3$ and extracted with Et_2O (twice), the

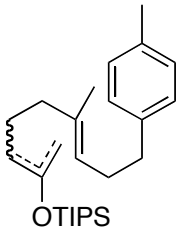
combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on aluminum oxide 150 basic (type T, deactivated with water) eluted with hexane to give **4**, **7**, or **10**. The product regio- and stereo-isomeric ratio[25] was determined by ^{1}H NMR analysis.



A Mixture (4a) of (2*E*,6*E*)- and (2*Z*,6*E*)-9-(4-Fluorophenyl)-6-methylnona-2,6-dien-2-yloxy)triisopropylsilane and (*E*)-(9-(4-Fluorophenyl)-6-methylnona-1,6-dien-2-yloxy)triisopropylsilane: >99% yield, (2*E*)-2-:(2*Z*)-2-:1-enyl-**4a** = 1:30:69. Colorless oil; TLC, R_f = 0.72 (hexane–EtOAc = 4:1), 0.20 (hexane); IR (film) 2946, 2867, 1671, 1620, 1509, 1464, 1381, 1157, 1016, 883 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, note: all peaks could not be determined exactly) δ 1.06–1.23 (m, 21H), 1.51–1.63 (m, 2H), 151 (s, 3H), 1.76 (s, 3H, (2*E*)-2-enyl isomer), 1.82 (s, 3H, (2*Z*)-2-enyl isomer), 1.93–2.02 (m, 4H), 2.09-2.16 (m, 2H, (2*E*)-2- and (2*Z*)-2-enyl isomers), 2.28 (q, *J* = 7.5 Hz, 2H), 2.32 (s, 3H), 2.60 (t, *J* = 7.5 Hz, 2H), 3,97 (s, 1H, 1-enyl isomer), 4.01 (s, 1H, 1-enyl isomer), 4.30 (t, *J* = 6.6 Hz, 1H, *Z*-isomer), 4.61 (t, *J* = 6.6 Hz, 1H, (2*E*)-2-enyl isomer), 5.15 (dt, *J* = 1.2, 7.1 Hz, 1H), 6.90–6.99 (m, 2H), 7.10–7.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, note: all peaks could not be determined exactly) δ 12.6 (3C, TIPS), 13.2, 15.7, 15.9, 18.0 (6C, TIPS), 22.9, 24.1, 25.2, 30.0, 35.3, 36.2, 39.1, 39.7, 88.8, 107.5, 114.7, 115.0, 123.1, 123.4, 129.7, 129.8, 135.9, 136.2, 137.8, 146.7, 159.6, 162.8; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –118.7 (m); HRMS (FAB) *m*/*z* calcd for $C_{25}H_{42}OFSi$ (M+H) 405.2989, found 405.2987.

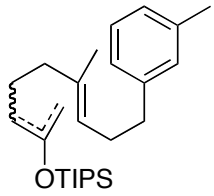


A Mixture of Triisopropyl((2*E*,6*E*)- and (2*Z*,6*E*)-6-methyl-9-phenylnona-2,6-dien-2-yloxy)silanes and (*E*)-Triisopropyl(6-methyl-9-phenylnona-1,6-dien-2-yloxy)silane (4b): >99% yield, (2*E*)-2-:(2*Z*)-2-:1-enyl-**4b** = 1:30:69. Colorless oil; TLC, R_f = 0.70 (hexane–EtOAc = 4:1), 0.09 (hexane); IR (film) 2946, 2867, 1670, 1622, 1464, 1382, 1268, 1157, 1015, 883 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, note: all peaks could not be determined exactly.) δ 1.00–1.26 (m, 21H), 1.53–1.64 (m, 2H), 153 (s, 3H), 1.76 (s, 3H, (2*E*)-2-enyl isomer), 1.82 (s, 3H, (2*Z*)-2-enyl isomer), 1.96–2.02 (m, 4H), 2.10–2.17 (m, 2H, (2*E*)-2- and (2*Z*)-2-enyl isomers), 2.29 (q, *J* = 7.2 Hz, 2H), 2.63 (t, *J* = 8.4 Hz, 2H), 3,97 (s, 1H, 1-enyl isomer), 4.01 (s, 1H, 1-enyl isomer), 4.31 (t, *J* = 6.0 Hz, 1H, (2*Z*)-2-enyl isomer), 4.61 (t, *J* = 6.0 Hz, 1H, (2*E*)-2-enyl isomer), 5.18 (t, *J* = 6.9 Hz, 1H), 7.15–7.20 (m, 3H), 7.25–7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz, note: all peaks could not be determined exactly.) δ 21.7 (6C, TIPS, (2*E*)-2- and (2*Z*)-2-enyl isomers), 13.2, 15.7, 15.9, 18.1 (6C, TIPS, 1-enyl isomer), 22.9, 24.1, 25.2, 30.0, 31.7, 36.2, 39.1, 39.7, 88.8, 107.5, 123.4, 123.8, 125.6, 128.2, 128.4, 135.6, 142.3, 146.6, 159.6; HRMS (FAB) *m/z* calcd for $C_{25}H_{43}OSi$ (M+H) 387.3083, found 387.3076.



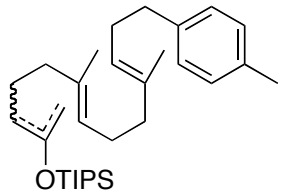
A Mixture (4c) of Triisopropyl((2*E*,6*E*)- and (2*Z*,6*E*)-6-methyl-9-*p*-tolylnona-2,6-dien-2-yloxy)silanes and (*E*)-Triisopropyl(6-methyl-9-*p*-tolylnona-1,6-dien-2-yloxy)silane: >99% yield, (2*E*)-2-:(2*Z*)-2-:1-enyl-**4c** = 2:29:69. If a

(2*E*)-2-:(2*Z*)-2-:1-enyl ratio of 4c was changed to 14:71:15 by partial hydrolysis (ca. 50% conversion) passing through silica column chromatography eluting with hexane. Colorless oil. TLC, R_f = 0.80 (hexane–EtOAc = 4:1), 0.22 (hexane); IR (film) 3007, 2946, 2867, 1671, 1514, 1464, 1381, 1250, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, note: all peaks could not be determined exactly.) δ 1.04–1.26 (m, 21H), 1.55–1.64 (m, 3H), 1.55 (s, 3H), 1.77 (s, 3H, (2*E*)-2-enyl isomer), 1.82 (s, 3H, (2*Z*)-2-enyl isomer), 1.94-2.03 (m, 4H for 1-enyl isomer and 2H for (2*E*)- and (2*Z*)-2-enyl isomers), 2.09–2.18 (m, 2H, (2*E*)- and (2*Z*)-2-enyl isomers), 2.22–2.32 (m, 2H), 2.32 (s, 3H), 2.59 (t, *J* = 7.8 Hz, 2H), 3,98 (s, 1H, 1-enyl isomer), 4.01 (s, 1H, 1-enyl isomer), 4.31 (dt, *J* = 1.2, 6.9 Hz, 1H, (2*Z*)-2-enyl isomer), 4.62 (t, *J* = 7.8 Hz, 1H, (2*E*)-2-enyl isomer), 5.19 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.08 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz, note: all peaks could not be determined exactly.) δ 12.6 (3C, TIPS), 13.2, 13.4, 15.8, 15.9, 17.7, 18.1 (6C, TIPS), 18.6, 21.0, 22.9, 24.0, 25.2, 25.7, 30.1, 30.2, 35.7, 36.2, 39.1, 39.7, 40.3, 88.8, 106.5, 107.6, 123.6, 123.9, 124.0, 128.3 (2C), 128.9, 130.6, 134.9, 135.0, 135.4, 135.5, 135.8, 139.3 (2C), 146.6, 147.9, 159.6; HRMS (FAB) *m/z* calcd for $C_{26}H_{45}OSi$ (M+H) 401.3240, found 401.3225.

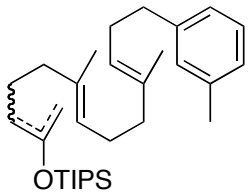


A Mixture (4d) of Triisopropyl((2*E*,6*E*)- and *(2Z*,6*E*)-6-methyl-9-*m*-tolylnona-2,6-dien-2-yloxy)silanes and (*E*)-Triisopropyl(6-methyl-9-*m*-tolylnona -1,6-dien-2-yloxy)silane: >99% yield, (2*E*)-2-:(2*Z*)-2-:1-enyl-**4d** = 2:30:68. Colorless oil; TLC, R_f = 0.80 (hexane–EtOAc = 4:1), R_f = 0.22 (hexane); ^1H NMR ($CDCl_3$, 300 MHz, note: all peaks could not be determined exactly) δ 1.06–1.24 (m, 21H), 1.56–1.64 (m, 1H), 1.56 (s, 3H), 1.77 (s, 3H, (2*E*)-2-enyl isomer), 1.82 (s, 3H, (2*Z*)-2-enyl isomer), 1.92–2.04 (m, 4H for 1-enyl isomer and 2H for (2*E*)-2- and

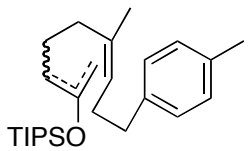
(2*Z*)-2-enyl isomers), 2.08-2.18 (m, 2H, (2*E*)-2- and (2*Z*)-2-enyl isomers), 2.24-2.33 (m, 2H), 2.33 (s, 3H), 2.59 (t, *J* = 7.8 Hz, 2H), 3,98 (s, 1H, 1-enyl isomer), 4.01 (s, 1H, 1-enyl isomer), 4.32 (t, *J* = 6.9 Hz, 1H, (2*Z*)-2-enyl isomer), 4.63 (t, *J* = 7.2 Hz, 1H, (2*E*)-2-enyl isomer), 5.19 (dt, *J* = 0.9, 7.2 Hz, 1H), 6.98–7.01 (s, 3H), 7.17 (t, *J* = 7.5 Hz, 1H).



A Mixture (7a) of ((2*E*,6*E*,10*E*)- and (2*Z*,6*E*,10*E*)-6,10-Dimethyl-13-*p*-tolyltrideca-2,6,10-trien-2-yloxy)triisopropylsilanes and ((6*E*,10*E*)-6,10-Dimethyl-13-*p*-tolyl trideca-1,6,10-trien-2-yloxy)triisopropylsilane: >99% yield, (2*E*)-2-:(2*Z*)-2-:1-enyl -**7a** = 2:28:70. Colorless oil; TLC, R_f = 0.77 (hexane–EtOAc = 4:1); IR (film) 2945, 2867, 1669, 1621, 1464, 1382, 1268, 1157, 1016, 883 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, note: all peaks could not be determined exactly.) δ 1.04–1.22 (m, 21H), 1.56–1.64 (m, 2H), 1.57 (s, 3H), 1.60 (s, 3H), 1.76 (s, 3H, (2*E*)-2-enyl isomer), 1.81 (s, 3H, (2*Z*)-2-enyl isomer), 1.96–2.18 m, 8H), 2.24–2.32 (m, 2H), 2.32 (s, 3H), 2.59 (dd, *J* = 6.9, 8.7 Hz, 2H), 3.98 (s, 1H, 1-enyl isomer), 4.01 (s, 1H, 1-enyl isomer), 4.32 (t, *J* = 6.6 Hz, 1H, (2*Z*)-2-enyl isomer), 4.62 (t, *J* = 7.8 Hz, 1H, (2*E*)-*2*-enyl isomer), 5.10 (t, *J* = 6.6 Hz, 1H), 5.19 (t, *J* = 7.2 Hz, 1H), 7.09 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz, note: all peaks could not be determined exactly.) δ 12.6 (3C, TIPS), 13.2, 15.9 (2C), 16.0, 18.0 (6C, TIPS), 21.0, 22.9, 24.1, 25.2, 26.6,(2C), 30.1, 35.7, 36.1, 39.1, 39.7, 88.8, 107.5, 123.7(2C), 124.1, 124.5, 128.3, 128.9, 134.7, 134.9, 135.1, 135.5, 135.6, 139.3, 146.6, 159.7; HRMS (FAB) *m/z* calcd for $C_{31}H_{53}OSi$ (M+H) 469.3866, found 469.3869.

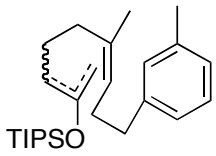


A Mixture (7b) of ((2*E*,6*E*,10*E*)- and (2*Z*,6*E*,10*E*)-6,10-Dimethyl-13-*m*-tolyltrideca-2,6,10-trien-2-yloxy)triisopropylsilanes and ((6*E*,10*E*)-6,10-Dimethyl-13-*m*-tolyltrideca-1,6,10-trien-2-yloxy)triisopropylsilane: >99% yield, (2*E*)-2-:(2*Z*)-2-:1-enyl-**7b** = 2:28:70. Colorless oil; TLC, R_f = 0.77 (hexane–EtOAc = 4:1); IR (film) 2945, 2867, 1669, 1609, 1464, 1382, 1268, 1157, 1015, 883cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, note: all peaks could not be determined exactly.) δ 1.06–1.20 (m, 21H), 1.55–1.62 (m, 2H), 1.56 (s, 3H), 1.59 (s, 3H), 1.76 (s, 3H, (2*E*)-2-enyl isomer), 1.81 (s, 3H, (2*Z*)-2-enyl isomer), 1.96–2.16 m, 8H), 2.24–2.31 (m, 2H), 2.31 (s, 3H), 2.59 (t, *J* = 7.8 Hz, 2H), 3,98 (s, 1H, 1-enyl isomer), 4.01 (s, 1H, 1-enyl isomer), 4.32 (t, *J* = 6.6 Hz, 1H, (2*Z*)-2-enyl isomer), 4.61 (t, *J* = 6.6 Hz, 1H, (2*E*)-2-enyl isomer), 5.10–5.21 (m, 2H), 6.96–7.00 (m, 3H), 7.12–7.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, note: all peaks could not be determined exactly.) δ 12.6 (3C, TIPS), 13.2, 15.8, 15.9, 18.0 (6C, TIPS), 21.4, 22.9, 24.1, 25.2, 26.6, 26.7, 30.1, 36.1 (2C), 39.1, 39.7, 88.8, 107.6, 123.7 (2C), 124.1, 124.5, 125.4, 126.4, 128.1, 129.2, 134.7, 135.1, 135.6, 137.6, 142.3, 146.6, 159.6; HRMS (FAB) *m*/*z* calcd for $C_{31}H_{53}OSi$ (M+H) 469.3866, found 469.3879.



A Mixture (10a) of Triisopropyl((2*Z*,6*Z*)- and (2*E*,6*Z*)-6-methyl-9-*p*-tolyl nona-2,6-dien-2-yloxy)silanes and (*Z*)-Triisopropyl(6-methyl-9-*p*-tolylnona-1,6-dien-2-yloxy)silane: 98% yield. (2*E*)-1-:(2*Z*)-2-:1-enyl **10a** = 1:30:69. Colorless oil; TLC, R_f = 0.78 (hexane–EtOAc = 4:1); IR (film) 2946, 2867, 1624, 1515, 1464,

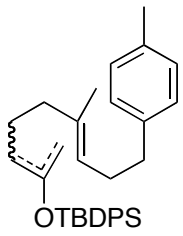
1380, 1314, 1265, 1018, 883 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, note: all peaks could not be determined exactly.) δ 1.01–1.22 (m, 21H), 1.50–1.60 (m, 2H), 1.67 (s, 3H), 1.76 (s, 3H, (2*E*)-2-enyl isomer), 1.81 (s, 3H, (2*Z*)-2-enyl isomer), 2.01 (t, *J* = 7.5 Hz, 4H), 2.10 (t, *J* = 7.2 Hz, 2H, (2Z)-2- and (2*E*)-2-enyl isomers), 2.22–2.32 (m, 2H), 2.32 (s, 3H), 2.58 (t, *J* = 7.2 Hz, 2H), 3,98 (s, 1H, 1-enyl isomer), 4.01 (s, 1H, 1-enyl isomer), 4.30 (t, *J* = 6.6 Hz, 1H, (2*Z*)-2-enyl isomer), 4.61 (t, *J* = 6.6 Hz, 1H, (2*E*)-2-enyl isomer), 5.18 (t, *J* = 6.9 Hz, 1H), 7.08 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz, note: all peaks could not be determined exactly.) δ 12.6 (3C, TIPS), 13.2, 18.0 (6C, TIPS), 21.0, 22.0, 23.3, 23.8, 25.3, 30.0 (2C), 31.3, 32.9, 36.0, 36.6, 88.9, 107.5, 124.4, 124.6, 128.2 (2C), 128.9 (2C), 135.0, 135.7, 135.9, 139.2, 139.3, 146.7, 159.5; HRMS (FAB) *m/z* calcd for $C_{26}H_{45}OSi$ (M+H) 401.3240, found, 401.3251.



A Mixture (10b) of Triisopropyl((2*Z*,6*Z*)- and (2*E*,6*Z*)-6-methyl-9-*m*-tolyl nona-2,6-dien-2-yloxy)silanes and (*Z*)-Triisopropyl(6-methyl-9-*p*-tolylnona-1,6-dien-2-yloxy)silane: >99% yield, (2*E*)-2-:(2*Z*)-2-:1-enyl **10b** = 2:26:72. Colorless oil; TLC, R_f = 0.74 (hexane–EtOAc = 4:1); IR (film) 2946, 2867, 1656, 1609, 1464, 1380, 1314, 1265, 1016, 883 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, note: all peaks could not be determined exactly.) δ 1.03–1.22 (m, 21H), 1.51–1.61 (m, 2H), 1.68 (s, 3H), 1.76 (s, 3H, (2*E*)-2-enyl isomer), 1.81 (s, 3H, (2*Z*)-2-enyl isomer), 2.02 (t, *J* = 7.5 Hz, 4H), 2.08–2.13 (m, 2H, (2*E*)-2-enyl *and* (2*Z*)-2-enyl isomers), 2.25–2.33 (m, 2H), 2.33 (s, 3H), 2.58 (t, *J* = 7.5 Hz, 2H), 3,98 (s, 1H, 1-enyl isomer), 4.01 (s, 1H, 1-enyl isomer), 4.31 (t, *J* = 6.6 Hz, 1H, (2*Z*)-2-enyl isomer), 4.61 (t, *J* = 6.6 Hz, 1H, (2*E*)-2-enyl isomer), 5.19 (t, *J* = 7.2 Hz, 1H), 6.98-7.00 (m, 3H), 7.16 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, note: all peaks could not be determined exactly.) δ

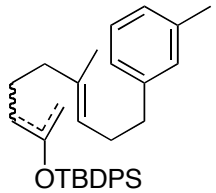
12.6 (3C, TIPS), 13.2, 18.0 (6C, TIPS), 21.4, 23.0, 23.3 (2 C), 23.8, 25.3, 29.9, 31.3, 31.3, 31.9, 36.3, 36.4, 36.6, 88.9, 107.5, 124.4, 124.6, 125.4, 126.4, 126.4, 128.1, 129.2, 135.7, 135.9, 137.6, 142.3, 146.7, 159.5; HRMS (FAB) *m/z* calcd for $C_{26}H_{45}OSi$ (M+H) 401.3240, found 401.3236.

General Procedure for the Synthesis of *tert*-Butyldiphenylsilyl Enol Ethers 4, 7, and 10 from Ketones 34 (Step l, Scheme 4): To a AgOTf (257mg, 1.0 mmol) in CH_2Cl_2 (2.0 mL) in a round bottom flask covered with aluminum foil was added TBDPSCl (260 μL, 1.0 mmol) and the resulting suspension was stirred for 2 days at room temperature under N_2 atmosphere. The mixture was then added via cannula to a solution of 34 (0.50 mmol) in dry CH_2Cl_2 (1 mL) was added Et_3N (209 μL, 1.50 mmol) at 0 °C. The resulting mixture was warmed to room temperature while being stirred for 12 h. After the reaction was quenched with saturated $NaHCO_3$ and the aqueous layer was extracted with Et_2O (twice), the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to give 4e, 7, or 10 as a colorless oil. The regio- and stereo-isomeric ratio[25] of products was determined by ^1H NMR analysis.



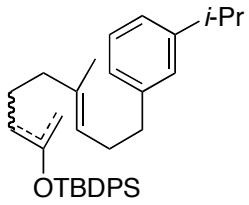
A Mixture (4e) of *tert*-Butyl((2*Z*,6*E*)- and (2*E*,6*E*)-6-methyl-9-*p*-tolyl nona-2,6-dien-2-yloxy)diphenylsilane and (*E*)-*tert*-Butyl(6-methyl-9-*p*-tolylnona-1,6-dien-2-yloxy)diphenylsilane: 84% yield, (2*E*)-2-enyl:(2*Z*)-2-enyl:1-enyl **4e** = 3:37:60. Column chromatography (hexane–EtOAc = 50:1); colorless oil; TLC, R_f = 0.70 (hexane–EtOAc = 4:1); ^1H NMR ($CDCl_3$, 300 MHz, note: all peaks could not be

determined exactly.) δ 1.04 (s, 9H, (2*E*)-2-enyl isomer), 1.07 (s, 9H, (2*Z*)-2-enyl isomer), 1.43 (s, 3H, (2*Z*)-2-enyl isomer), 1.50 (s, 3H, (2*E*)-2-enyl isomer), 1.56 (s, 3H), 1.69 (q, *J* = 7.5 Hz, 2H), 1.95–2.11 (m, 3H), 2.20–2.33 (m, 3H), 2.30 (s, 3H), 2.60 (t, *J* = 7.8 Hz, 2H), 3,71 (s, 1H, 1-enyl isomer), 3.91 (s, 1H, 1-enyl isomer), 4.34 (t, *J* = 6.6 Hz, 1H, (2*Z*)-2-enyl isomer), 4.50 (t, *J* = 7.5 Hz, 1H, (2*E*)-2-enyl isomer), 5.16–5.22 (m, 1H), 7.08 (s, 4H), 7.34-7.44 (m, 6H), 7.70–7.76 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz, note: all peaks could not be determined exactly.) δ 15.8, 15.9, 19.3, 19.4, 21.0, 22.8, 24.0, 25.1, 26.5, 26.7, 30.1, 35.7, 36.1, 39.0, 39.6, 91.4, 107.7, 123.6, 124.0, 127.6, 128.3, 128.9, 129.7, 132.9, 134.3, 135.3, 135.3, 135.5, 135.8, 139.3, 147.0, 158.8.

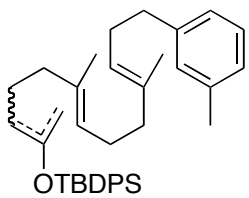


A Mixture (4f) of *tert*-Butyl((2*Z*,6*E*)- and (2*E*,6*E*)-6-methyl-9-*m*-tolyl nona-2,6-dien-2-yloxy)diphenylsilanes and (*E*)-*tert*-Butyl(6-methyl-9-*m*-tolylnona-1,6-dien-2-yloxy)diphenylsilane: 65% yield, (2*E*)-2-enyl:(2*Z*)-2-enyl:1-enyl **4f** = 4:34:62. Column chromatography (hexane–EtOAc = 50:1 to 20:1); colorless oil; TLC, R_f = 0.70 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz, note: all peaks could not be determined exactly.) δ 1.04 (s, 9H, 1-enyl isomer), 1.06 (s, 9H, (2*Z*)-2-enyl isomer), 1.43 (s, 3H, (2*Z*)-2-enyl isomer), 1.50 (s, 3H, (2*E*)-2-enyl isomer), 1.62–1.78 (m, 2H), 1.94–2.12 (m, 3H), 2.14–2.32 (m, 3H), 2.32 (s, 3H), 2.60 (t, *J* = 7.5 Hz, 2H), 3,71 (s, 1H, 1-enyl isomer), 3.90 (s, 1H, 1-enyl isomer), 4.34 (t, *J* = 7.2 Hz, 1H, (2*Z*)-2-enyl isomer), 4.51 (t, *J* = 8.7 Hz, 1H, (2*E)*-2-enyl isomer), 5.19 (t, *J* = 7.2 Hz, 1H), 6.97–7.00 (m, 3H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.32–7.45 (m, 6H), 7.69–7.76 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz, note: all peaks could not be determined exactly.) δ 15.8, 15.9, 19.3, 19.4, 21.4, 22.8, 24.0, 25.1, 26.5, 26.7, 30.0, 36.0, 36.1(2C), 39.0, 39.6, 91.4,

107.7, 123.6, 124.0, 125.4, 126.4(2C), 127.6, 128.1, 129.3, 129.7, 132.9, 134.3, 135.3, 135.5 (2C), 135.8, 137.7, 142.3, 142.4, 147.0, 158.7.

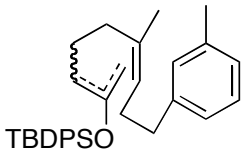


A Mixture (4h) of *tert*-Butyl((2*Z*,6*E*)-9-(3-isopropylphenyl)-6-methylnona-2,6-dien-2-yloxy)diphenylsilane and (*E*)-*tert*-Butyl(9-(3-isopropylphenyl)-6-methyl nona-1,6-dien-2-yloxy)diphenylsilane: 93% yield, (2*E*)-2-enyl:(2*Z*)-2-enyl:1-enyl **4h** = <1:31:69. Column chromatography (hexane–EtOAc = 50:1); colorless oil; TLC, R_f = 0.34 (hexane–EtOAc = 25:1); IR (film) 2961, 1932, 2859, 2360, 1630, 1429, 1112 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, note: all peaks could not be determined exactly.) δ 1.03 (s, 9H, 1-enyl isomer), 1.06 (s, 9H, (2*Z*)-2-enyl isomer), 1.24 (d, *J* = 6.9 Hz, 6H), 1.50 (s, 3H, (2*E*)-2-enyl isomer), 1.54 (s, 3H), 1.62–1.72 (m, 2H, 1-enyl isomer), 1.94–2.35 (m, 6H), 2.62 (t, *J* = 7.8 Hz, 2H), 2.80–2.94 (m, 1H), 3,70 (s, 1H, 1-enyl isomer), 3.90 (s, 1H, 1-enyl isomer), 4.34 (t, *J* = 7.2 Hz, 1H, (2*Z*)-2-enyl isomer), 5.20 (t, *J* = 6.6 Hz, 1H), 7.00–7.05 (m, 3H), 7.18–7.23 (m, 1H), 7.35–7.46 (m, 6H), 7.71–7.75 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz, note: all peaks could not be determined exactly.) δ 15.8, 15.9, 19.3, 19.4, 22.8, 24.1, 25.1, 26.5, 26.7, 30.0, 34.1, 36.1, 36.2, 36.3, 39.0, 39.6, 91.5, 107.7, 123.7 (2C), 124.0, 125.9, 126.6, 127.5, 127.6, 125.2, 129.7, 133.0, 134.3, 135.3, 135.4, 135.5, 135.8, 142.3, 142.4, 147.0, 148.7, 158.6; HRMS (FAB) *m/z* calcd for $C_{35}H_{47}OSi$ (M+H) 511.3396, found 511.3380.



A Mixture (7c) of *tert*-Butyl((2*E*,6*E*,10*E*)- and (2*Z*,6*E*,10*E*)-6,10-dimethyl-

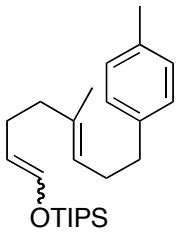
13-*m*-tolyltrideca-2,6,10-trien-2-yloxy)diphenylsilanes *and* *tert*-Butyl ((6*E*,10*E*)-6,10-dimethyl-13-*m*-tolyltrideca-1,6,10-trien-2-yloxy)diphenylsilane: 81% yield, (2*E*)-2-:(2*Z*)-2-:1-enyl **7c** = 3:26:11. Column chromatography (hexane–EtOAc = 50:1); colorless oil; TLC, R_f = 0.76 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz, note: all peaks could not be determined exactly.) δ 1.04 (s, 9H, 1-enyl isomer), 1.06 (s, 9H, (2*Z*)-enyl isomer), 1.47 (s, 3H, (2*Z*)-enyl isomer), 1.50 (s, 3H, (2*E*)-enyl isomer), 1.57 (s, 3H), 1.60 (s, 3H), 1.64–1.75 (m, 2H), 1.94–2.12 (m, 8H), 2.21–2.31 (m, 2H), 2.31 (S, 3H), 2.59 (t, *J* = 7.8 Hz, 2H), 3,72 (s, 1H, 1-enyl isomer), 3.92 (s, 1H, 1-enyl isomer), 4.35 (t, *J* = 6.9 Hz, 1H, (2*Z*)-enyl isomer), 4.51 (t, *J* = 6.6 Hz, 1H, (2*E*)-enyl isomer), 5.13 (t, *J* = 6.6 Hz, 1H), 5.20 (t, *J* = 6.9 Hz, 1H), 6.97–6.99 (m, 3H), 7.15 (t, *J* = 752 Hz, 1H), 7.34–7.43 (m, 6H), 7.69–7.76 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz, note: all peaks could not be determined exactly.) δ 15.8, 15.9, 16.0 (2C), 19.3, 19.4, 21.4, 22.8, 24.1, 25.1, 26.5, 26.6, 30.0, 36.0, 39.0, 39.7 (2C), 39.8, 65.8, 91.5, 107.8, 123.7 82C), 124.1, 124.5, 125.4, 126.4, 127.6, 128.1, 129.2, 129.7, 132.9, 134.3, 134.7, 135.1, 135.3, 135.4, 135.5, 135.6, 137.6, 142.3, 146.9, 158.6.



A Mixture (10c) of *tert*-Butyl((2*Z*,6Z)- and (2*E*,6*Z*)-6-methyl-9-*m*-tolyl nona-2,6-dien-2-yloxy)diphenylsilanes and (*Z*)-*tert*-Butyl(6-methyl-9-*m*-tolylnona-1,6-dien-2-yloxy)diphenylsilane: 92% yield. (2*E*)-2-:(2*Z*)-2-:1-enyl **10c** = 3:23:74. Column chromatography (hexane–EtOAc = 50:1); colorless oil; TLC, R_f = 0.76 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz, note: all peaks could not be determined exactly.) δ 1.04 (s, 9H, 1-enyl isomer), 1.06 (s, 9H, (2*Z*)-2-enyl isomer), 1.50 (s, 3H, (2*Z*)-2-enyl isomer), 1.54 (s, 3H, (2*E*)-2-enyl isomer), 1.65-1.75 (m, 2H), 1.70 (s, 3H), 2.08 (q, *J* = 7.5 Hz, 4H), 2.20-2.33 (m, 2H), 2.29 (s, 3H), 2.56 (t, *J* = 8.7

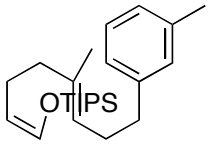
Hz, 2H), 3,74 (s, 1H, 1-enyl isomer), 3.92 (s, 1H, 1-enyl isomer), 4.35 (t, *J* = 6.6 Hz, 1H, (2*Z*)-2-enyl isomer), 4.51 (t, *J* = 6.6 Hz, 1H, (2*E*)-2-enyl isomer), 5.21 (t, *J* = 6.6 Hz, 1H), 6.96–6.98 (m, 3H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.31–7.40 (m, 6H), 7.70–7.76 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz, note: all peaks could not be determined exactly.) δ 19.3, 19.4, 21.4, 22.9, 23.3, 23.4, 23.8, 25.2, 26.5, 26.7, 29.9, 31.3, 31.8, 36.3, 36.4, 91.5, 107.7, 124.5, 124.8, 125.5, 126.4 (2C), 127.6, 127.7, 128.1, 129.2, 129.7, 132.9, 134.2, 135.3, 135.4, 135.5, 135.8, 137.6, 142.2, 142.3, 147.8, 158.5.

General Procedure for the Synthesis of Triisopropylsilyl Enol Ethers 14 from Aldehydes 13 (Step m, Scheme 4): To a solution of 13 (1.17 mmol) in dry CH_2Cl_2–Et_3N (1:1 *v*/*v*, 4 mL) was added TIPSOTf (338 μL, 1.30 mmol) dropwise at –78 °C. The mixture was stirred for 2 h while the temperature was allowed to warm to 0 °C. After the reaction was quenched with saturated $NaHCO_3$, the aqueous layer was extracted with Et_2O (twice). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The (1*E*)/(1*Z*)-isomeric ratio[25] of crude products 14 was determined to be <5:>95 by ^{1}H NMR analysis. The residue was purified by flash chromatography (SiO_2, hexane → hexane:EtOAc = 100:1) to give (1*Z*)-14 (>99% 1*Z*) as a colorless oil. (1*E*)-14 was partially obtained by flash chromatography.

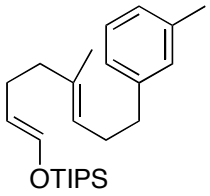


Triisopropyl((1*Z*,5*E*)-5-methyl-8-*p*-tolylocta-1,5-dienyloxy)silane (14a): >95% yield. >99% 1*Z*. TLC, R_f = 0.71 (hexane–EtOAc = 4:1), 0.33 (hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03–1.19 (m, 21H), 1.56 (s, 3H), 2.00 (t, *J* = 7.5 Hz, 1H),

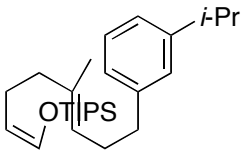
2.16–2.32 (m, 4H), 2.32 (s, 3H), 2.59 (dd, *J* = 6.9, 8.7 Hz, 2H), 4.36 (td, *J* = 5.7, 7.0 Hz, 1H), 5.19 (tm, *J* = 7.2 Hz, 1H), 6.26 (dt, *J* = 1.5, 5.7 Hz, 1H), 7.08 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.0 (3C, TIPS), 15.8, 17.7 (6C, TIPS), 21.0, 22.3, 30.1, 35.7, 39.6, 109.5, 123.7, 128.3, 128.9, 135.0, 135.7, 138.9, 139.4.



Triisopropyl((1*Z*,5*E*)-5-methyl-8-*m*-tolylocta-1,5-dienyloxy)silane (14b): >95% yield. >99% 1*Z*. Column chromatography (hexane); colorless oil; TLC, R_f = 0.74 (hexane–EtOAc = 4:1), R_f = 0.17 (hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03–1.19 (m, 21H), 1.57 (s, 3H), 2.04 (t, *J* = 7.6 Hz, 2H), 2.17–2.33 (m, 4H), 2.33 (s, 3H), 2.59 (t, *J* = 7.8 Hz, 2H), 4.37 (td, *J* = 5.7, 6.4 Hz, 1H), 5.20 (tm, *J* = 6.9 Hz, 1H), 6.26 (dt, *J* = 1.2, 5.7 Hz, 1H), 6.98–7.00 (m, 3H), 7.16 (t, *J* = 7.5 Hz, 1H).



Triisopropyl((1*E*,5*E*)-5-methyl-8-*m*-tolylocta-1,5-dienyloxy)silane (14b): **14b** ((1*E*):(1*Z*) = 76:24) was partially obtained by flash chromatography (SiO_2, hexane:EtOAc = 100:1). Colorless oil; TLC, R_f = 0.74 (hexane–EtOAc = 4:1), 0.17 (hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03–1.20 (m, 21H), 1.55 (s, 3H), 1.90–2.10 (brs, 4H), 2.23–2.33 (m, 2H), 2.33 (s, 3H), 2.59 (t, *J* = 8.1 Hz, 2H), 4.94–5.02 (m, 1H), 5.19 (t, *J* = 6.9 Hz, 1H), 6.31 (d, *J* = 12.0 Hz, 1H), 6.98–7.00 (m, 3H), 7.17 (t, *J* = 7.6 Hz, 1H).

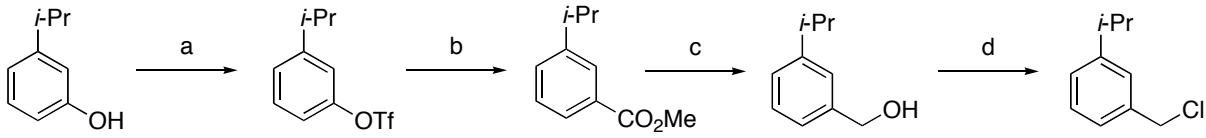


Triisopropyl((1*Z*,5*E*)-8-(3-isopropylphenyl)-5-methylocta-1,5-dienyloxy)silane (14c): >95% yield. >99% 1*Z*. Column chromatography (hexane); colorless oil; TLC, R_f = 0.70 (hexane–EtOAc = 4:1), 0.22 (hexane); IR (film) 2961, 2946, 2868, 1652, 1464, 1118. 883 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.03–1.19 (m, 21H), 1.24 (d, *J* = 6.9 Hz, 6H), 1.56 (s, 3H), 2.01 (t, *J* = 7.5 Hz, 2H), 2.17–2.33 (m, 4H), 2.62 (t, *J* = 7.8 Hz, 2H), 2.80–2.94 (m, 1H), 4.36 (dd, *J* = 6.9, 12.9 Hz, 1H), 5.21 (dt, *J* = 0.9, 6.9 Hz, 1H), 6.25 (brd, *J* = 5.7 Hz, 1H), 7.00–7.05 (s, 3H), 7.17–7.23 (m, *1*H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.9 (3C, TIPS), 15.8, 17.7 (6C, TIPS), 22.2, 24.0 (2C), 30.1, 34.1, 36.2, 39.6, 109.4, 123.6, 123.7, 125.9, 126.6, 128.1, 135.7, 138.9, 142.4, 148.7; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{46}OSiNa$ (M+Na) 437.3216, found 437.3205.

Preparation of 1-(Chloromethyl)-3-isopropylbenzene (39)

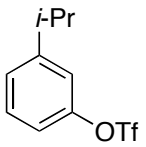
1-(Chloromethyl)-3-isopropylbenzene (**39**), which was a starting material of Butsugan coupling to synthesize **4h** and **14c**, was prepared as shown in Scheme 5.

Scheme 5. Preparation of **39**[a]



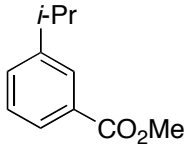
35 **36** **37** **38** **39**

[a] *Reagents and conditions:* a) Tf_2O, pyridine, $ClCH_2CH_2Cl$, 0 °C to rt, 1 h; b) $Pd(OAc)_2$, dppp, *i*-Pr_2NEt, MeOH, CO, DMSO, 80 °C, 12 h; c) $LiAlH_4$, THF, 0 °C, 1 h; d) SO_2Cl, pyridine, benzene, reflux, 5 h.

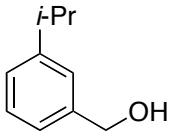


3-Isopropylphenyl Trifluoromethanesulfonate (36) (Step a, Scheme 4): To a solution of **35** (4.11 mL, 30.0 mmol) in dichloroethane (30 mL) was added

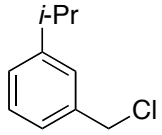
pyridine (4.81 mL, 60.0 mmol) and Tf_2O (10.1 mL, 60.0 mmol) at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was poured into brine, washed with H_2O (twice), and extracted with Et_2O (twice). Solvents were removed in *vacuo* and the crude oil was distilled (50–55 °C, 1 torr) to give **36** (7.73 g, 28.8 mmol) as a colorless oil in 96% yield. TLC, R_f = 0.65 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (d, J = 6.9 Hz, 6H), 2.89-3.02 (m, 1H), 7.07–7.12 (m, 2H), 7.24–7.27 (m, 1H), 7.36 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.6 (2C), 33.9, 118.5, 118.8 (q, J_{CF} = 319 Hz), 119.3, 126.5, 130.0, 149.7, 151.9; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –73.7 (s, 3F).



Methyl 3-Isopropylbenzoate (37) (Step b, Scheme 5): **36** (6.71g, 25.0 mmol), $Pd(OAc)_2$ (853 mg, 3.80 mmol), dppp (1.57 g, 3.80 mmol), *i*-Pr_2NEt (9.6 mL, 55.0 mmol) and MeOH (25 mL, 625 mmol) in DMSO (100 mL) was sealed and quickly cycled three times between open-air (in draft) and CO atmosphere. The CO pressure in the flask was increased to ca. 1.5 atm and partially immersed in an 80 °C oil bath. After 12 h, the mixture was cooled to room temperature and poured into brine, extracted with Et_2O (twice), washed with brine (twice) and water (3 times). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was passed a short pad of silica gel to give **37**, which was used for next step without further purification. TLC, R_f = 0.62 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (d, J = 6.9 Hz, 6H), 2.89–3.04 (m, 1H), 3.92 (s, 3H), 7.36 (t, J = 7.5 Hz, 1H), 7.43 (dt, J = 1.5, 7.5 Hz, 1H), 8.76 (dt, J = 1.5, 6.0 Hz, 1H), 7.91 (t, J = 1.5 Hz, 1H).



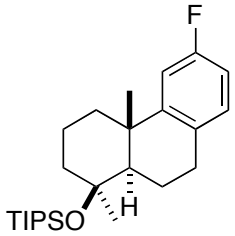
(3-Isopropylphenyl)methanol (38) (Step c, Scheme 4): To a solution of **37** (1.10 g, 6.15 mmol) in THF (20 mL) was added $LiAlH_4$ (350 mg, 9.23 mmol) slowly at 0 °C. After stirring for 1 h at 0 °C, excess of $LiAlH_4$ was decomposed with EtOAc and H_2O. After that Na_2SO_4 was added and stirred for 1–2 h at room temperature. The resulting mixture was through celite and the solvent evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with hexane–EtOAc = 5:1 to give **38** (896 mg, 5.97 mmol, 97% for 2 steps) as a colorless oil. TLC, R_f = 0.62 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (d, J = 6.9 Hz, 6H), 1.85–1.94 (m, OH), 2.84–2.98 (m, 1H), 4.65 (d, J = 5.7 Hz, 2H), 7.15–7.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.8 (2C), 33.9, 64.7, 124.3, 124.9, 125.3, 128.2, 140.7, 148.8.



1-(Chloromethyl)-3-isopropylbenzene (39) (Step d, Scheme 4): To a solution of **38** (793 mg, 5.28 mmol) in benzene (6 mL) was added pyridine (one drop) and $SOCl_2$ (616 μL, 8.45 mmol) dropwise at rt and the resulting mixture was heated to reflux at 80 °C. After stirring for 5 h, the solution was cooled and concentrated under vacuum. The residue was extracted with Et_2O, and washed with water and brine. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* and the residue was purified by short column chromatography on silica gel eluting with hexane to give **39** (821 mg, 4.87 mmol, 92%) as a colorless oil. TLC, R_f = 0.48 (hexane–EtOAc = 25:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (d, J = 7.2 Hz, 6H),

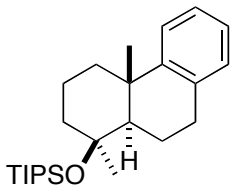
2.85–2.99 (m, 1H), 4.59 (s, 2H), 7.17–7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.8 (2C), 33.9, 42.3, 125.9, 126.3, 126.6, 128.6, 137.3, 149.2.

General Procedure for the $SnCl_4$-Promoted Cyclization (Tables 1–4 and Scheme 2): To a flame-dried schlenk charged with toluene or CH_2Cl_2 (2 mL) was added a 0.1 M solution of $SnCl_4$ in hexane or CH_2Cl_2 (100 μL, 10 μmol), and the mixture was cooled to –78 °C. To this solution was added a 1.0 M solution of starting material (**1**, **4**, **7**, **10**, **13**, **14**) in toluene or CH_2Cl_2 (100 μL, 0.1 mmol) dropwise over 1 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was analyzed directly or purified by column chromatography on silica gel to give cyclic compounds.

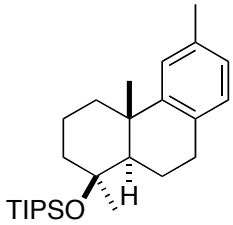


(1*S,4a*S**,10a*R**)-6-Fluoro-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydro-phenanthren-1-yloxy)triisopropylsilane (5aβ) (Entry 1, Table 1):** Column chromatography (hexane); amorphous solid; TLC, R_f = 0.76 (hexane–EtOAc = 4:1), 0.50 (hexane); IR (film) 2945, 2868, 1496, 1465, 1051, 883 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.09–1.13 (m, 21H), 1.19–1.45 (m, 3H), 1.29 (s, 3H), 1.33 (s, 3H), 1.53–1.59 (m, 1H), 1.86–1.89 (m, 1H), 1.90–2.07 (m, 3H), 2.18-2.21 (m, 1H), 2.78–2.85 (m, 1H), 2.95 (dd, *J* = 7.0, 17.0 Hz, 1H), 6.76 (dt, *J* = 2.5, 8.5 Hz, 1H), 6.93 (dd, *J* = 2.5, 11.0 Hz, 1H), 6.98 (dd, *J* = 6.0, 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (3C), 18.4 (3C), 18.5, 18.6 (3C), 18.8, 24.7, 28.8, 30.3, 37.7, 38.5, 41.3, 50.5, 74.9, 110.6, 112.0, 130.0, 130.5, 151.9, 161.2 (d, $J_{C\text{-}F}$ = 240 Hz); ^{19}F NMR ($CDCl_3$, 282

MHz) δ –118.5 (dd, J = 9.0, 18.0 Hz); HRMS (EI) m/z calcd for $C_{22}H_{34}FOSi$ (M–*i*-Pr) 361.2363, found 361.2355. No detectable amounts of **5aα** and **6a** were obtained.

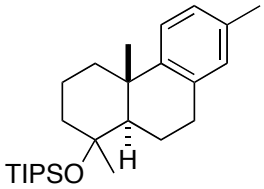


((1*S,4a*S**,10a*R**)-1,4a-Dimethyl-1,2,3,4,4a,9,10,10a-octahydro-phenanthren-1-yloxy)triisopropylsilane (5bβ) (Entry 2, Table 1):** Column chromatography (hexane); amorphous solid; TLC, R_f = 0.76 (hexane–EtOAc = 4:1), 0.33 (hexane); IR (film) 2945, 2868, 1464, 1051, 993, 883 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.04–1.16 (m, 21H), 1.26–1.40 (m, 2H), 1.31 (s, 3H), 1.33 (s, 3H), 1.44 (dt, J = 3.5, 13.0 Hz, 1H), 1.53–1.59 (m, 1H), 1.88 (dd, J = 1.5, 14.0 Hz, 1H), 1.95–2.08 (m, 3H), 2.30 (dm, J = 12.5 Hz, 1H), 2.84–2.91 (m, 1H), 2.98 (ddd, J = 2.5, 7.0, 17.6 Hz, 1H), 7.04–7.08 (s, 2H), 7.11 (dt, J = 12.0, 17.0 Hz, 1H), 7.25–7.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (3C), 18.4 (3C), 18.56 (3C), 18.62, 18.9, 24.8, 29.6, 30.3, 37.5, 38.6, 41.4, 50.8, 75.0, 124.1, 125.1, 125.5, 128.9, 135.2, 149.8; HRMS (EI) m/z calcd for $C_{22}H_{35}OSi$ (M–*i*-Pr) 343.2457, found 343.2445. The **5bα**/**5bβ** ratio was determined by GC/MS analysis of crude products: GC/MS t_R = 23.1 min for **5bα**, 23.9 min for **5bβ**. No detectable amount of **6b** was obtained.



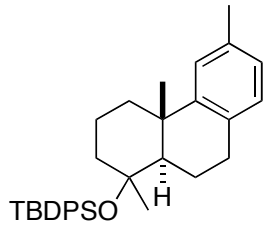
Triisopropyl((1*S,4a*S**,10a*R**)-1,4a,6-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yloxy)silane (5cβ) (Entries 3–6, Table 1):** Column chromatography (hexane); white solid; TLC, R_f = 0.76 (hexane–EtOAc = 4:1), 0.56 (hexane); IR (film) 3006, 2943, 2868, 1499, 1464, 1374, 1052, 993, 883 cm^{-1}; ^1H NMR

($CDCl_3$, 500 MHz) δ 1.00–1.16 (m, 21H), 1.25–1.33 (m, 1H), 1.30 (s, 3H), 1.32 (s, 3H), 1.35 (dt, *J* = 4.0, 13.5 Hz, 1H), 1.43 (dt, *J* = 3.5, 13.0 Hz, 1H), 1.53–1.58 (m, 1H), 1.87 (ddd, *J* = 3.0, 4.5, 13.5 Hz, 1H), 1.93–2.06 (m, 3H), 2.28–2.31 (m, 1H), 2.29 (s, 3H), 2.79–2.86 (m, 1H), 2.94 (ddd, *J* = 1.0, 10.0, 16.0 Hz, 1H), 6.89 (dd, *J* = 1.0, 7.5 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 7.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (3C), 18.5 (3C), 18.6 (3C), 18.7, 19.0, 21.3, 24.8, 29.2, 30.4, 37.5, 38.6, 41.4, 50.9, 75.1, 124.6, 126.0, 128.8, 132.0, 134.7, 149.7; HRMS (EI) *m*/*z* calcd for $C_{26}H_{44}OSi$ (M) 400.3161, found 400.3145. The **5c**/**6c** ratio was determined by ^{1}H NMR analysis of crude products: **6c** was characterized by ^{1}H NMR chemical shifts [δ 4.59 (s, 1H), 4.84 (s, 1H), 5.43 (brs, 1H), other resonances could not be discerned.] and GC/MS analysis (*m*/*z* 226 [M+1]). The **5cα**/**5cβ** ratio was determined by chiral HPLC analysis of crude products: HPLC (four linear OD-H columns, hexane–*i*-PrOH = 2000/1, flow rate = 0.3 mL/min) t_R = 52.2 min for **5cα** (inseparable enantiomers), 54.8 and 67.7 min for **5bβ** enantiomers.

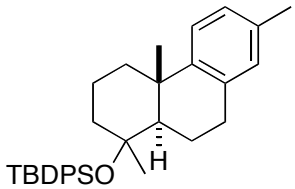


Triisopropyl((4a*S,10a*R**)-1,4a,7-trimethyl-1,2,3,4,4a,9,10,10a-octa-hydro phenanthren-1-yloxy)silane (5d) (Entry 7, Table 1):** Column chromatography (hexane); colorless oil; TLC, R_f = 0.80 (hexane–EtOAc = 4:1), 0.44 for α and 0.42 for β (hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00–2.34 (m, 9H), 1.04–1.12 (m, 21H), 1.15 (s, 3H for α), 1.26 (s, 3H for α), 1.30 (s, 3H for β), 1.32 (s, 3H for β), 2.27 (s, 3H), 2.77–3.00 (m, 2H), 6.88–7.22 (m, 3H). The 5d/6d ratio was determined by ^{1}H NMR analysis of crude products: **6d** was characterized by ^{1}H NMR chemical shifts [δ 4.59 (s, 1H), 4.85 (s, 1H), 5.43 (brs, 1H), other resonances could not be discerned.] and GC/MS analysis (*m*/*z* 226 [M+1]). The **5dα**/**5dβ** ratio was determined by chiral

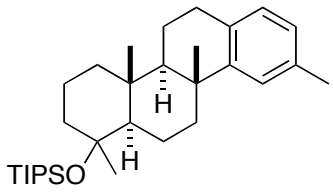
HPLC analysis of crude products: HPLC (two linear OD-H columns, hexane–*i*-PrOH = 2000/1, flow rate = 0.5 mL/min) t_R = 14.8 and 16.0 min for **5dα** enantiomers, 17.1 min for **5dβ** (inseparable enantiomers).



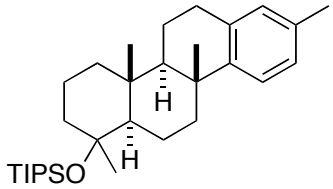
***tert*-Butyldiphenyl((4a*S**,10a*R**)-1,4a,6-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yloxy)silane (5e) (Entry 8, Table 1):** Column chromatography (hexane–EtOAc = 50:1); amorphous solid; TLC, R_f = 0.77 (hexane–EtOAc = 4:1), 0.19 (hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81–2.55 (m, 11H), 1.02 (s, 9H for α), 1.05 (s, 9H for β), 1.08 (s, 3H for β), 1.10 (s, 3H for α), 1.16 (s, 3H for α), 1.50 (s, 3H for β), 2.30 (s, 3H), 2.80–3.05 (m, 2H), 6.90–7.09 (m, 3H), 7.30–7.44 (m, 6H), 7.66–7.75 (m, 4H for α), 7.79–7.88 (m, 4H for β). The **5eα**/**5eβ**/**6e**(=**6c**) ratio was determined by ^{1}H NMR analysis of crude products.



***tert*-Butyldiphenyl((4a*S**,10a*R**)-1,4a,7-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yloxy)silane (5f) (Entry 9, Table 1):** Column chromatography (hexane–EtOAc = 50:1); amorphous solid; TLC, R_f = 0.73 (hexane–EtOAc = 4:1), 0.16 (hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00–2.49 (m, 9H), 1.02 (s, 9H for α), 1.05 (s, 9H for β), 1.07 (s, 3H for β), 1.09 (s, 3H for α), 1.16 (s, 3H for α), 1.49 (s, 3H for β), 2.28 (s, 3H for β), 2.29 (s, 3H for α), 2.80–3.12 (m, 2H), 6.89–6.97 (m, 2H), 7.12–7.19 (m, 1H), 7.31–7.44 (m, 6H), 7.66–7.76 (m, 4H for α), 7.79–7.88 (m, 4H for β). The **5fα**/**5fβ**/**6f**(=**6d**) ratio was determined by ^{1}H NMR analysis of crude products.

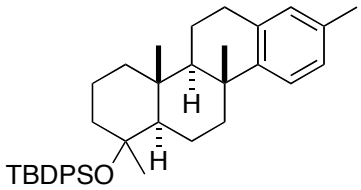


Triisopropyl((4a*R,4b*R**,10b*R**,12a*R**)-1,4a,9,10b-tetramethyl-1,2,3,4,4a, 4b,5,6,10b,11,12,12a-dodecahydrochrysen-1-yloxy)silane (8a) (entry 1, Table 2):** Column chromatography (hexane); colorless oil (as an inseparable mixture of 8a and 9a); TLC, R_f = 0.81 (hexane–EtOAc = 4:1), 0.37 (hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80–3.00 (m, 16H), 0.88 (s, 3H for α), 1.02–1.12 (m, 21H), 1.07 (s, 3H for β), 1.18 (s, 3H for α), 1.20 (s, 3H for α), 1.24 (s, 3H for β), 1.27 (s, 3H for β), 2.30 (s, 3H), 6.89–7.11 (m, 3H). The **8a**/**9a** ratio was determined by ^{1}H NMR analysis of crude products: **9a** was characterized by ^{1}H NMR chemical shifts [δ 4.53 (s, 1H), 4.73 (s, 1H), 5.30 (1brs, 1H), other resonances could not be discerned.]. The **8aα**/**8aβ** ratio was determined by the separation of the corresponding alcohols after desilylation with TBAF.

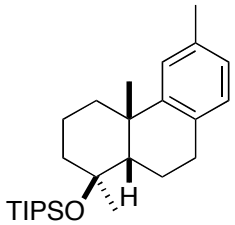


Triisopropyl((4a*R,4b*R**,10b*R**,12a*R**)-1,4a,8,10b-tetramethyl-1,2,3,4,4a, 4b,5,6,10b,11,12,12a-dodecahydrochrysen-1-yloxy)silane (8b) (Entry 2, Table 2):** Column chromatography (hexane); colorless oil (as an inseparable mixture of 8b and 9b); TLC, R_f = 0.85 (hexane–EtOAc = 4:1), R_f = 0.50 (hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82–2.44 (m, 14H), 0.88 (s, 3H for α), 1.01–1.11 (m, 21H), 1.07 (s, 3H for β), 1.18 (s, 3H for α), 1.19 (s, 3H for α), 1.23 (s, 3H for β), 1.26 (s, 3H for β), 2.27 (s, 3H), 2.74–2.93 (m, 2H), 6.86–7.19 (m, 3H). The 8b/9b ratio was determined by ^{1}H NMR analysis of crude products: **9b** was characterized by ^{1}H NMR chemical shifts [δ 4.53 (s, 1H), 4.74 (s, 1H), 5.31 (1brs, 1H), other resonances could not be discerned.]. The

8bα/8bβ ratio was determined by chiral HPLC analysis of crude products: HPLC (two linear OD-H columns, hexane–*i*-PrOH = 2000:1, flow rate = 0.3 mL/min) t_R = 26.2 and 30.5 min for **8bα** enantiomers, 28.5 and 38.2 min for **8bβ** enantiomers.

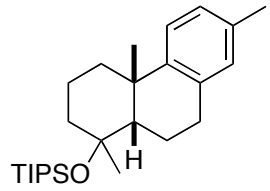


***tert*-Butyldiphenyl((4a*R**,4b*R**,10b*R**,12a*R**)-1,4a,8,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-1-yloxy)silane (8c) (Entry 3, Table 2):** Column chromatography (hexane–EtOAc = 50:1); amorphous solid; TLC, R_f = 0.65 (hexane–EtOAc = 4:1), 0.18 (hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.77–2.50 (m, 14H), 0.84 (s, 3H for α), 0.90 (s, 3H for β), 1.01 (s, 9H for α), 1.03 (s, 3H for β), 1.06 (s, 9H for β), 1.12 (s, 3H for α), 1.22 (s, 3H for α), 1.45 (s, 3H for β), 2.30 (s, 3H), 2.75–2.99 (m, 2H), 6.89 (s, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.30–7.44 (m, 6H), 7.30–7.44 (m, 6H), 7.64–7.74 (m, 4H for α), 7.80–7.86 (m, 4H for β). The **8cα/8cβ** ratio was determined by ^{1}H NMR analysis of crude products. No detectable amount of **9c** was obtained.

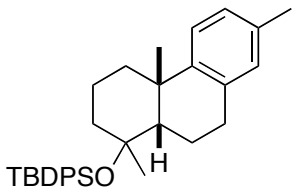


Triisopropyl((1*S,4a*S**,10a*S**)-1,4a,6-trimethyl-1,2,3,4,4a,9,10,10a-octa-hydrophenanthren-1-yloxy)silane (11aβ) (Entry 1, Table 3):** Column chromatography (hexane); colorless oil; TLC, R_f = 0.77 (hexane–EtOAc = 4:1), 0.35 (hexane); IR (film) 2944, 2866, 2360, 1502, 1464, 1378, 1130, 1054, 1013, 883 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (s, 3H), 1.08 (m, 21H), 1.33 (s, 3H), 1.33–1.41 (m, 1H), 1.46–1.51 (m, 1H), 1.62 (t, *J* = 6.0 Hz, 2H), 1.66–1.75 (m, 1H), 1.80 (t, *J* = 5.5 Hz,

1H), 2.00–2.13 (m, 2H), 2.16–2.24 (m, 1H), 2.32 (s, 3H), 2.76–2.90 (m, 2H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 7.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8 (3C), 18.5 (3C), 18.6 (3C), 18.8, 20.2, 21.4, 26.3, 27.1, 32.4, 37.1, 38.5, 41.9, 52.4, 76.5, 125.2, 125.9 (2C), 128.6, 133.8, 134.7; HRMS (EI) *m*/*z* calcd for $C_{26}H_{44}OSi$ (M) 400.3161, found 400.3165. No detectable amounts of **11aα** and **12a** were obtained.

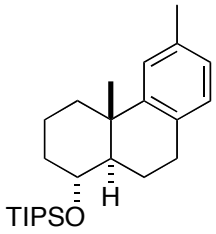


Triisopropyl((4a*S,10a*S**)-1,4a,7-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yloxy)silane (11b) (Entry 2, Table 3):** Column chromatography (hexane); colorless oil; TLC, R_f = 0.72 (hexane–EtOAc = 4:1), 0.49 (hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 3H for β), 0.96 (s, 3H for α), 0.98 (s, 3H for □), 1.06 (brs, 21H), 1.25–2.17 (m, 9H), 1.32 (s, 3H for β), 2.27 (s, 3H), 2.72–2.92 (m, 2H), 6.82 (s, 1H for α), 6.85 (s, 1H for β), 6.90–6.93 (m, 1H for α), 6.93 (d, *J* = 8.1 Hz, 1H for β), 7.13 (d, *J* = 8.1 Hz, 1H for β), 7.17 (d, *J* = 8.1 Hz, 1H for α). The **11b**/**12b** ratio was determined by ^{1}H NMR analysis of crude products. **12b** was characterized by ^{1}H NMR chemical shifts [δ 4.74 (s, 2H), 5.42 (brs, 1H), other resonances could not be discerned.] and GC/MS analysis (*m*/*z* 226 [M+1]). The **11bα**/**11bβ** ratio was determined by GC/MS analysis of crude products: GC/MS t_R = 23.4 min for **5bβ**, 23.5 min for **5bα**.

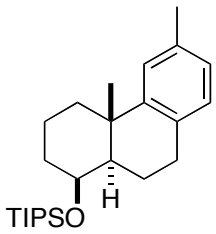


***tert*-Butyldiphenyl((4a*S**,10a*S**)-1,4a,7-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yloxy)silane (11c) (Entry 3, Table 3):** Column

chromatography (hexane–EtOAc = 50:1); colorless oil; TLC, R_f = 0.74 (hexane–EtOAc = 4:1), 0.14 (hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.67 (s, 3H for β), 0.80 (s, 9H for α), 1.02 (s, 9H for β), 1.02–2.34 (m, 8H for α and 9H for β), 1.24 (s, 3H for α), 1.27 (s, 3H for β), 1.28 (s, 3H for α), 2.25 (s, 3H for β), 2.27 (s, 3H for α), 2.42–2.53 (m, 1H for α), 2.70–2.91 (m, 1H for α and 2H for β), 3.10–3.22 (m, 1H for α), 6.83–7.07 (m, 3H), 7.21–7.43 (m, 6H), 7.68–7.77 (m, 4H). The **11cα**/**11cβ** ratio was determined by ^{1}H NMR analysis of crude products. No detectable amount of **12c** was obtained.

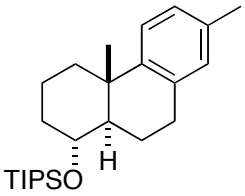


((1*R,4a*S**,10a*R**)-4a,6-Dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yloxy)triisopropylsilane (16aα) (Entry 3, Table 4):** Column chromatography (hexane–EtOAc = 20:1); colorless oil; TLC, R_f = 0.66 (hexane–EtOAc = 4:1), 0.13 (hexane); IR (film) 2943, 2867, 1464, 1380, 1114, 1091, 1067, 882 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00–1.77 (m, 6H), 1.03–1.09 (m, 24H), 1.32 (s, 3H), 2.03–2.35 (m, 3H), 2.29 (s, 3H), 2.74–2.87 (m, 2H), 3.76 (td, *J* = 4.2, 9.9 Hz, 1H), 6.90 (d, *J* = 7.8Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 7.06 (s, 1H); HRMS (EI) *m*/*z* calcd for $C_{25}H_{42}OSi$ (M) 386.3005, found 386.2991. The 16aα/16aβ ratio was determined by ^{1}H NMR analysis of crude products.

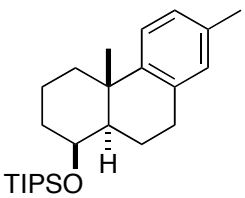


((1*S,4a*S**,10a*R**)-4a,6-Dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yloxy)triisopropylsilane (16aβ) (Entry 3, Table 4):** Column chromatography

(hexane); white solid; TLC, R_f = 0.76 (hexane–EtOAc = 4:1), R_f = 0.56 (hexane); IR (film) 2943, 2867, 1464, 1132, 1084, 1033, 932, 883 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90–1.14 (m, 21H), 1.32 (s, 3H), 1.38–1.51 (m, 3H), 1.55–1.64 (m, 2H), 1.86 (dd, *J* = 2.0, 13.5 Hz, 1H), 2.03 (tq, *J* = 3.5, 13.5 Hz, 1H), 2.16 (ddt, *J* = 8.0, 10.8, 13.0 Hz, 1H), 2.25–2.33 (m, 1H), 2.29 (s, 3H), 2.82–2.92 (m, 2H), 4.16 (dd, *J* = 2.0, 5.0 Hz, 1H), 6.89 (dd, *J* = 1.5, 7.5 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 7.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.8 (3C), 17.7, 18.3 (6C), 21.3, 23.9, 25.7, 29.3, 34.5, 37.0, 38.2, 46.0, 73.0, 124.8, 126.1, 129.0, 132.0, 134.8, 149.2; HRMS (EI) *m/z* calcd for $C_{25}H_{42}OSi$ (M) 386.3005, found 386.2991. The **16aα/16aβ** ratio was determined by ^1H NMR analysis of crude products.

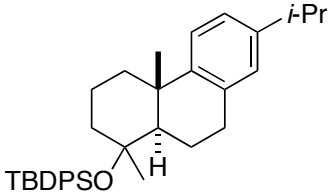


((1*R,4a*S**,10a*R**)-4a,7-Dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yloxy)triisopropylsilane (16bα) (Entries 4 and 5, Table 4):** A small amount of 5-Me-regioisomer was contained; column chromatography (hexane–EtOAc = 20:1); colorless oil; TLC, R_f = 0.80 (hexane–EtOAc = 4:1), 0.12 (hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.97–1.78 (m, 6H), 0.97–1.09 (m, 24H), 1.21 (s, 3H for 5-Me-regioisomer), 2.03–2.50 (m, 3H), 2.28 (s, 3H for 7-Me-regioisomer), 2.50 (s, 3H for 5-Me-regioisomer), 2.80–2.87 (m, 2H), 3.76 (td, *J* = 4.5, 9.6 Hz, 1H), 6.89 (s, 1H), 6.94 (dm, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H). The **16bα/16bβ** ratio was determined by ^1H NMR analysis of crude products.



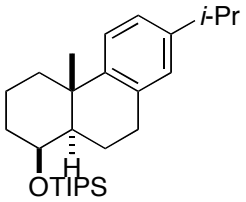
((1*S,4a*S**,10a*R**)-4a,7-Dimethyl-1,2,3,4,4a,9,10,10a-octahydro-phenanthr**

en-1-yloxy)triisopropylsilane (16bβ) (Entries 4 and 5, Table 4): Column chromatography (hexane); colorless oil; TLC, R_f = 0.42 (hexane); IR (film) 3006, 2941, 2867, 1496, 1464, 1383, 1084, 1033, 931, 884 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.10 (m, 21H), 1.31 (s, 3H), 1.31–1.66 (m, 5H), 1.87 (brd, *J* = 13.2 Hz, 1H), 2.02 (tq, *J* = 3.6, 13.5 Hz, 1H), 2.12–2.30 (m, 1H), 2.27 (s, 3H), 2.84-2.92 (m, 2H), 4.16 (d, *J* = 2.4 Hz, 1H), 6.87 (s, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.8 (3C), 17.8, 18.3 (6C), 20.8, 23.8, 25.8, 29.6, 34.5, 36.7, 38.3, 46.1, 72.9, 124.2, 126.4, 129.7, 134.6, 135.1, 146.5; HRMS (EI) *m*/*z* calcd for $C_{25}H_{42}OSi$ (M) 386.3005, found 386.2980. The **16bα/16bβ** ratio was determined by ^1H NMR analysis of crude products.



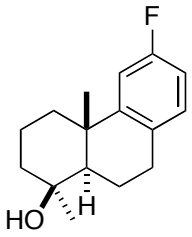
***tert*-Butyl((1*R**,4a*S**,10a*R**)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yloxy)diphenylsilane (5h) (Scheme 2):** Column chromatography (hexane–EtOAc = 50:1 → 20:1); amorphous solid; TLC (hexane–EtOAc = 25:1) R_f = 0.35; IR (film) 3004, 2961, 2859, 1471, 1427, 1383, 1107, 1049, 909, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 9H), 1.05 (s, 3H), 1.16 (s, 3H), 1.24 (d, *J* = 7.0 Hz, 6H), 1.33–1.56 (m, 5H), 1.67–1.76 (m, 1H), 1.96 (dd, *J* = 2.0, 12.5 Hz, 1H), 2.10–2.16 (m, 1H), 2.40–2.44 (m, 1H), 2.80-3.00 (m, 3H), 6.92 (brs, 1H for β), 6.94 (d, *J* = 1.5 Hz, 1H for α), 7.00 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H for α), 7.19 (d, *J* = 8.5 Hz, 1H for β), 7.30–7.43 (m, 6H), 7.66–7.74 (m, 4H for α), 7.80-7.86 (m, 4H for β); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.4, 19.5, 20.6, 24.0 (3C), 24.6, 27.2, 30.6, 33.4, 37.8, 38.2, 42.1, 52.9, 77.6, 123.9, 124.6, 127.0 (2C), 127.3 (2C), 129.2 (2C), 129.3, 135.1, 136.1 (2C), 136.3 (4C), 145.6, 146.9; HRMS (EI) *m*/*z* calcd for $C_{31}H_{37}OSi$ (M–*t*-Bu) 453.2614, found 453.2952. The **5hα/5hβ** ratio was

determined by ^{1}H NMR analysis of crude products.

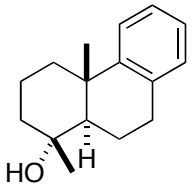


Triisopropyl((1*S,4a*S**,10a*R**)-7-isopropyl-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yloxy)silane (16cβ) (Scheme 2):** Column chromatography (hexane); colorless oil; TLC, R_f = 0.41 (hexane); IR (film) 2930, 2867, 1457, 1085, 1033, 883 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.10 (m, 21H), 1.22 (d, *J* = 7.0 Hz, 6H), 1.32 (s, 3H), 1.38–1.65 (m, 5H), 1.86 (dm, *J* = 13.5 Hz, 1H), 2.03 (tq, *J* = 3.5, 13.5 Hz, 1H), 2.13–2.22 (m, 1H), 2.17 (s, 3H), 2.27 (brd, *J* = 13.0 Hz, 1H), 2.78–2.86 (m, 1H), 2.88–2.92 (m, 2H), 4.17 (dm, *J* = 2.5 Hz, 1H), 6.89 (d, *J* = 1.0 Hz, 1H), 6.98 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.8 (3C), 17.8, 18.3 (6C), 23.9, 24.0, 25.8, 29.8, 30.9, 33.5, 34.5, 36.8, 38.2, 46.1, 73.0, 123.7, 124.1, 127.0, 134.9, 145.4, 146.8; HRMS (EI) *m*/*z* calcd for $C_{27}H_{46}OSi$ (M) 414.3318, found 414.3312. No detectable amounts of **16cβ** and **18c** were obtained.

General Procedure for the Desilylation of 4-Siloxy Polycycles: To a round-bottomed flask charged with 4-siloxy polycycles (**5**, **8**, **11**, **16**) was added tetrabutylammonium fluoride (a 1.0 M THF solution, TCI (Tokyo Chemical Industry Co., Ltd., Japan), 2-10 equiv), and the mixture was refluxed for 2–12 h. The reaction was quenched with water, and the aqueous layer was extracted with EtOAc (3 times). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to give the corresponding alcohol almost in quantitative yield.

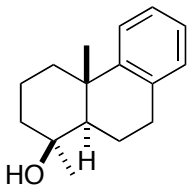


(1*S,4a*S**,10a*R**)-6-Fluoro-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydro-phenanthren-1-ol (5aβ-OH) (Table 1):** Column chromatography (hexane–EtOAc = 5:1); colorless oil; TLC, R_f = 0.29 (hexane–EtOAc = 4:1); IR (film) 3608, 2936, 1587, 1496, 1375, 941, 868 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, OH), 1.26 (s, 3H), 1.30 (s, 3H), 1.36–1.45 (m, 3H), 1.60–1.66 (m, 1H), 1.74 (d, *J* = 14.0 Hz, 1H), 1.87 (ddt, *J* = 7.5, 10.5, 13.0 Hz, 1H), 1.95 (ttd, *J* = 3.5, 7.0, 14.0 Hz, 1H), 2.00–2.05 (m, 1H), 2.23 (d, *J* = 12.5 Hz, 1H), 2.82–2.89 (m, 1H), 2.96 (dd, *J* = 7.5, 17.0 Hz, 1H), 6.78 (dt, *J* = 2.5, 8.5 Hz, 1H), 6.94 (dd, *J* = 2.5, 11.0 Hz, 1H), 6.99 (dd, *J* = 6.0, 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.8, 18.3, 24.2, 28.5, 0.8, 37.7, 38.1, 40.7, 48.3, 72.1, 110.6, 112.2, 130.1, 130.4, 151.4, 161.1 (d, $J_{C\text{-}F}$ = 240 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –118.2 (dd, *J* = 6.6, 18.2 Hz); HRMS (EI) *m/z* calcd for $C_{17}H_{21}FO$ (M) 248.1576, found 248.1552.

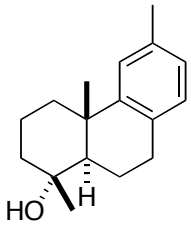


(1*R,4a*S**,10a*R**)-1,4a-Dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-ol (5bα-OH) (Table 1):** Column chromatography (hexane–EtOAc = 5:1); colorless oil; TLC (hexane–EtOAc = 4:1) R_f = 0.22; IR (film) 3595, 3010, 2930, 2863, 2360, 2320, 1457, 1381 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, OH), 1.17 (s, 3H), 1.24 (s, 3H), 1.37–1.48 (m, 2H), 1.60–1.80 (m, 4H), 1.84-1.90 (m, 1H), 2.12 (dd, *J* = 7.5, 12.5 Hz, 1H), 2.25–2.28 (m, 1H), 2.90 (ddd, *J* = 7.0, 12.5, 17.0 Hz, 1H), 2.96 (dd, *J* = 6.5, 17.0 Hz, 1H), 7.05 (t, *J* = 6.5 Hz, 1H), 7.09 (dt, *J* = 1.0, 7.0 Hz, 1H), 7.13 (t, *J*

= 7.5 Hz, 1H), 7.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.9, 20.5, 23.0, 24.5, 30.3, 37.9, 38.5, 42.7, 52.3, 72.4, 124.7, 125.4, 125.7, 129.2, 135.1, 148.9; HRMS (EI) *m*/*z* calcd for $C_{16}H_{22}O$ (M) 230.1671, found 230.1682.

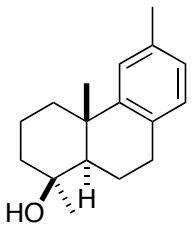


(1*S,4a*S**,10a*R**)-1,4a-Dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-ol (5bβ-OH) (Table 1):** Column chromatography (hexane–EtOAc = 10:1); colorless oil; TLC, R_f = 0.38 (hexane–EtOAc = 4:1); IR (film) 3608, 3009, 2936, 1488, 1457, 1375, 1077, 1019 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (s, OH), 1.26 (s, 3H), 1.31 (s, 3H), 1.41-1.48 (m, 3H), 1.60–1.66 (m, 1H), 1.75 (dm, *J* = 13.5 Hz, 1H), 1.89 (ddt, *J* = 7.5, 10.5, 13.0 Hz, 1H), 1.97 (ttd, *J* = 3.5, 7.0, 14.0 Hz, 1H), 2.00–2.06 (m, 1H), 2.23 (dd, *J* = 1.5, 13.0 Hz), 2.93 (ddd, *J* = 8.0, 10.5, 17.5 Hz, 1H), 3.00 (ddd, *J* = 2.0, 8.0, 17.5 Hz, 1H), 7.06 (brt, *J* = 6.5 Hz, 1H), 7.08 (dt, *J* = 1.0, 7.0 Hz, 1H), 7.13 (brt, *J* = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.8, 18.4, 24.4, 29.3, 30.8, 37.4, 38.1, 40.7, 48.5, 72.2, 124.1, 125.3, 125.7, 129.0, 135.0, 149.3; HRMS (EI) *m*/*z* calcd for $C_{16}H_{22}O$ (M) 230.1671, found 230.1682.

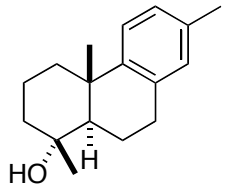


(1*R,4a*S**,10a*R**)-1,4a,6-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-ol (5cα-OH) (Table 1):** Column chromatography (hexane–EtOAc = 2:1); colorless oil; TLC, R_f = 0.25 (hexane–EtOAc = 4:1), 0.50 (hexane–EtOAc = 30:1); IR (film) 3596, 3379, 3007, 2929, 2856, 1499, 1457, 1164, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, OH), 1.16 (s, 3H), 1.23 (s, 3H), 1.38–1.80 (m, 6H), 1.84–1.90 (dm,

J = 12.3 Hz, 1H), 2.02–2.13 (m, 1H), 2.23–2.30 (m, 1H), 2.30 (s, 3H), 2.78–2.30 (m, 2H), 6.90–6.97 (m, 2H), 7.06 (s, 1H); HRMS (EI) *m*/*z* calcd for $C_{17}H_{24}O$ (M) 244.1827, found 244.1833.

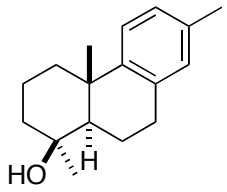


(1*S,4a*S**,10a*R**)-1,4a,6-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-ol (5cβ-OH) (Table 1):** Column chromatography (hexane–EtOAc = 5:1); white solid; TLC, R_f = 0.38 (hexane–EtOAc = 4:1); IR (film) 3607, 3600–3250 (br), 3042, 3007, 2940, 1500, 1456, 1375, 937 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, OH), 1.26 (s, 3H), 1.31 (s, 3H), 1.40–1.47 (m, 3H), 1.60–1.64 (m, 1H), 1.75 (dm, *J* = 14.0 Hz, 1H), 1.86 (ddt, *J* = 7.5, 10.5, 13.0 Hz, 1H), 1.97 (dtt, *J* = 3.5, 7.0, 13.5 Hz, 1H), 1.98–2.05 (m, 1H), 2.30 (s, 3H), 2.30–2.34 (m, 1H), 2.83–2.90 (m, 1H), 2.94–2.98 (m, 1H), 6.91 (dd, *J* = 1.0, 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.9, 18.4, 21.3, 24.4, 28.9, 30.8, 37.4, 38.1, 40.7, 48.7, 72.3, 124.6, 126.2, 128.9, 131.8, 134.9, 149.1; HRMS (EI) *m*/*z* calcd for $C_{17}H_{24}O$ (M) 244.1827, found 244.1837.

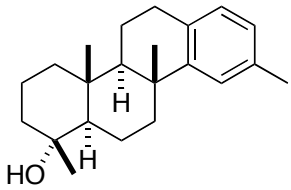


(1*R,4a*S**,10a*R**)-1,4a,7-Trimethyl-1,2,3,4,4a,9,10,10a-octahydro-phenanthren-1-ol (5dα-OH) (Table 1):** Column chromatography (hexane–EtOAc = 5:1); white solid; TLC, R_f = 0.32 (hexane–EtOAc = 10:1); IR (film) 3596, 3007, 2930, 2856, 1496, 1457, 1380, 891, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, OH), 1.15 (s, 3H), 1.24 (s, 3H), 1.36–1.45 (m, 2H), 1.59 (dd, *J* = 2.0, 13.0 Hz, 1H), 1.63–1.80 (m,

3H), 1.87 (dm, *J* = 12.5 Hz, 1H), 2.10 (ddt, *J* = 2.0, 7.0, 12.5 Hz, 1H), 2.23–2.27 (m, 1H), 2.27 (s, 3H), 2.82–2.95 (m, *2*H), 6.88 (s, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.9, 20.6, 20.8, 20.8, 22.9, 24.5, 30.2, 38.1, 38.2, 42.7, 52.5, 72.4, 124.6, 126.6, 129.7, 134.8, 134.9, 146.1; HRMS (EI) *m*/*z* calcd for $C_{17}H_{24}O$ (M) 244.1827, found 244.1837.

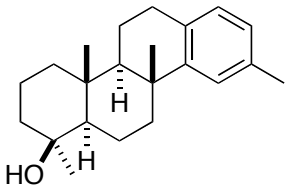


(1*S,4a*S**,10a*R**)-1,4a,7-Trimethyl-1,2,3,4,4a,9,10,10a-octahydro-phenanthren-1-ol (5dβ-OH) (Table 1):** Column chromatography (hexane–EtOAc = 10:1); white solid; TLC, R_f = 0.49 (hexane–EtOAc = 4:1); IR (film) 3608, 3007, 2934, 2859, 1459, 1456, 1375, 934, 879, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (s, OH), 1.26 (s, 3H), 1.30 (s, 3H), 1.38–1.47 (m, 3H), 1.62 (ttd, *J* = 3.5, 7.0, 14.0 Hz, 1H), 1.74 (dm, *J* = 13.5 Hz, 1H), 1.87 (ddt, *J* = 7.5, 10.5, 13.0 Hz, 1H), 1.96 (ttd, *J* = 3.5, 7.0, 14.0 Hz, 1H), 1.99–2.05 (m, 1H), 2.28 (s, 3H), 2.28-2.33 (m, 1H), 2.87 (ddd, *J* = 8.0, 10.5, 18.0 Hz, 1H), 2.96 (ddd, *J* = 2.0, 7.5, 18.0 Hz, 1H), 6.89 (s, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.9, 18.4, 20.8, 24.4, 29.2, 30.8, 37.1, 38.2, 40.8, 48.8, 72.2, 124.0, 126.5, 129.5, 134.7, 134.8, 146.5; HRMS (EI) *m*/*z* calcd for $C_{17}H_{24}O$ (M) 244.1827, found 244.1837.

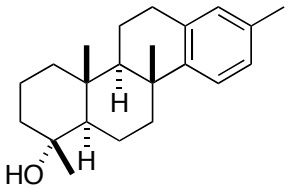


(1*R,4a*R**,4b*R**,10b*R**,12a*R**)-1,4a,9,10b-Tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-1-ol (8aα-OH) (Table 2):** Column chromatography (hexane–EtOAc = 5:1); white solid; TLC R_f = 0.31 (hexane–EtOAc = 4:1); IR (film) 3593, 3550–3300 (br), 2930, 2855, 1500, 1458, 1387, 1096, 1062 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86–0.93 (m, 1H), 0.89 (s, 3H), 1.10–2.05 (12H), 1.17 (s, 3H), 1.20 (s, 3H), 2.29 (s, 3H), 2.43 (dd, *J* = 3.0, 9.5 Hz, 1H), 2.79 (ddd, *J* = 7.5, 11.5, 17.0 Hz, 1H), 2.89 (dd, *J* = 6.0, 17.0 Hz, 1H), 6909 (dd, *J* = 1.5, 7.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 7.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.7, 18.0, 18.3, 19.8, 21.3, 22.7, 26.1, 30.4, 38.1, 38.4, 39.0, 39.9, 42.9, 55.0, 57.7, 72.3, 125.1, 126.1, 128.7, 131.8, 135.0, 149.9; HRMS (EI) *m/z* calcd for $C_{22}H_{32}O$ (M) 312.2453, found 312.2441.

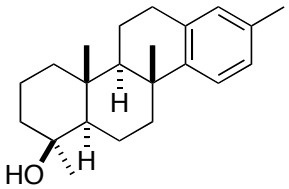


(1*S,4a*R**,4b*R**,10b*R**,12a*R**)-1,4a,9,10b-Tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-1-ol (8aβ-OH) (Table 2):** Column chromatography (hexane–EtOAc = 10:1); amorphous solid; TLC (hexane–EtOAc = 4:1) R_f = 0.50; IR (film) 3609, 3006, 2927, 2854, 1716, 1500, 1457, 1379, 1262 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86-0.93 (m, 1H), 0.99 (dd, *J* = 2.5, 12.5 Hz, 1H), 1.08 (s, 3H), 1.20 (s, 3H), 1.23 (s, 3H), 1.26 (dd, *J* = 2.5, 12.5 Hz, 1H), 1.34-1.90 (m, 10H), 2.29 (s, 3H), 2.44 (dt, *J* = 3.5, 13.0 Hz, 1H), 2.78 (ddd, *J* = 7.5, 11.5, 16.5 Hz, 1H), 2.90 (ddm, *J* = 6.5, 16.5 Hz, 1H), 6.89 (dd, *J* = 1.0, 7.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 7.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.7, 17.8, 17.9, 18.3, 21.3, 26.1, 30.2, 30.6, 37.5, 37.9, 39.2, 40.2, 40.9, 54.4, 54.5, 72.2, 124.9, 126.1, 128.7, 131.9, 134.9, 150.2; HRMS (EI) *m/z* calcd for $C_{22}H_{32}O$ (M) 312.2453, found 312.2441.

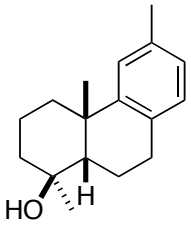


(1*R,4a*R**,4b*R**,10b*R**,12a*R**)-1,4a,8,10b-Tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-1-ol (8bα-OH) (Table 2):** Column

chromatography (hexane–EtOAc = 5:1); amorphous solid; TLC, R_f = 0.36 (hexane–EtOAc = 4:1); IR (film) 3598, 3600–3250 (br), 3006, 2931, 2855, 1459, 1387, 1096, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.84–2.43 (m, 14H), 0.90 (s, 3H), 1.17 (s, 3H), 1.19 (s, 3H), 2.27 (s, 3H), 2.77–2.92 (m, 2H), 6.86 (s, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.7, 18.0, 18.3, 19.8, 20.8, 22.7, 26.1, 30.7, 37.8, 38.3, 39.0, 40.0, 42.9, 55.1, 57.7, 72.3, 124.6, 126.6, 129.4, 134.6, 134.8, 147.2; HRMS (EI) *m/z* calcd for $C_{22}H_{32}O$ (M) 312.2453, found 312.2441.

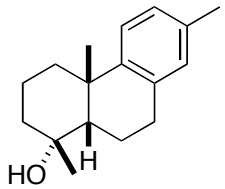


(1*S,4a*R**,4b*R**,10b*R**,12a*R**)-1,4a,8,10b-Tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-1-ol (8bβ-OH) (Table 2):** Column chromatography (hexane–EtOAc = 10:1); amorphous solid; TLC, R_f = 0.56 (hexane–EtOAc = 4:1); IR (film) 3608, 3006, 2927, 1457, 1379, 1262, 1092, 1024, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.83–0.94 (m, 1H), 0.99 (dd, *J* = 2.5, 12.5 Hz, 1H), 1.07 (s, 3H), 1.20 (s, 3H), 1.22 (s, 3H), 1.26 (dd, *J* = 2.0, 12.0 Hz, 1H), 1.36–1.89 (m, 10H), 2.27 (s, 3H), 2.43 (dt, *J* = 3.0, 12.5 Hz, 1H), 2.79 (ddd, *J* = 7.5, 11.5, 17.5 Hz, 1H), 2.90 (dd, *J* = 7.0, 17.5 Hz, 1H), 6.85 (s, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.7, 17.8 (2C), 18.3, 20.8, 26.2, 30.6 (2C), 37.5, 37.7, 39.2, 40.2, 40.9, 54.5 (2C), 72.2, 124.4, 126.6, 129.4, 134.6, 134.9, 147.5; HRMS (EI) *m/z* calcd for $C_{22}H_{32}O$ (M) 312.2453, found 312.2463.

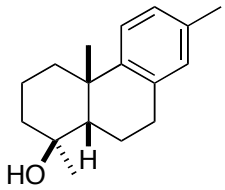


(1*S,4a*S**,10a*S**)-1,4a,6-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanth**

ren-1-ol (11aβ-OH) (Table 3): Column chromatography (hexane–EtOAc = 5:1); white solid; TLC, R_f = 0.23 (hexane–EtOAc = 4:1); IR (film) 3598, 3007, 2930, 2868, 1505, 1457, 1376, 1084, 813 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 3H), 1.37–2.00 (m, 9H), 1.50 (s, 3H), 2.30 (s, 3H), 2.73–2.85 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.4, 21.2, 21.4, 29.1, 29.3 (2C), 30.5, 37.0, 38.5, 52.2, 73.8, 126.0, 126.4, 128.4, 133.0, 135.0, 145.9; HRMS (EI) *m*/*z* calcd for $C_{17}H_{24}O$ (M) 244.1827, found 244.1837.

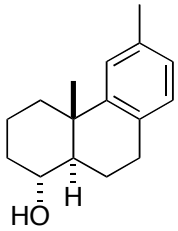


(1*R,4a*S**,10a*S**)-1,4a,7-Trimethyl-1,2,3,4,4a,9,10,10a-octahydro-phenant hren-1-ol (11bα-OH) (Table 3):** Column chromatography (hexane–EtOAc = 10:1); colorless oil; TLC, R_f = 0.52 (hexane–EtOAc = 4:1); IR (film) 3568, 3006, 2927, 2858, 1719, 1456, 1379, 1261, 1102, 818 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17 (s, 3H), 1.23 (s, 3H), 1.37–1.68 (m, 6H), 2.14–2.31 (m, 2H), 2.27 (s, 3H), 2.44 (dd, *J* = 3.0, 14.5 Hz, 1H), 2.77 (ddd, *J* = 3.0, 8.5, 17.5 Hz, 1H), 3.11–3.19 (m, 1H), 6.90 (s, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.1, 18.3, 20.9, 26.3, 28.8, 35.2, 36.7, 37.4, 41.7, 48.6, 73.0, 124.3, 126.8, 130.1, 135.3, 138.1, 138.4; HRMS (EI) *m*/*z* calcd for $C_{17}H_{24}O$ (M) 244.1827, found 244.1819.

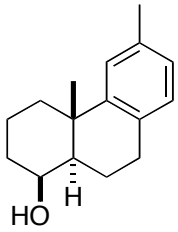


(1*S,4a*S**,10a*S**)-1,4a,7-Trimethyl-1,2,3,4,4a,9,10,10a-octahydro-phenant hren-1-ol (11bβ-OH) (Table 3):** Column chromatography (hexane–EtOAc = 5:1); colorless oil; TLC, R_f = 0.31 (hexane–EtOAc = 4:1); IR (film) 3596, 3550–3250 (br), 3007, 2932, 2868, 1499, 1457, 1377, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s,

3H), 1.37–1.68 (m, 6H), 1.49 (s, 3H), 1.72–2.00 (m, 4H), 2.27 (s, 3H), 2.73–2.86 (m, 2H), 6.85 (s, 1H), 6.96 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3, 20.8, 21.2, 29.3, 29.5, 29.7, 30.5, 37.1, 38.3, 52.2, 73.8, 125.8, 126.7, 129.1, 134.5, 135.9, 143.2; HRMS (EI) m/z calcd for $C_{17}H_{24}O$ (M) 244.1827, found 244.1837.

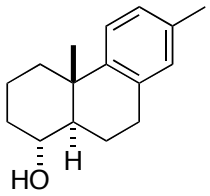


(1*R,4a*S**,10a*R**)-4a,6-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-ol (15aα) (Entry 1, Table 4):** Column chromatography (hexane–EtOAc = 5:1); colorless oil; TLC, R_f = 0.21 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.09 (s, 1H), 1.21–1.31 (m, 1H), 1.37–1.44 (m, 3H), 1.59 (ddt, J = 7.0, 11.5, 13.0 Hz, 1H), 1.70 (tq, J = 4.0, 14.0 Hz, 1H), 1.76–1.81 (m, 1H), 2.07–2.14 (m,1H), 2.18–2.26 (m, 2H), 2.30 (s, 3H), 2.80–2.91 (m, 2H), 3.60 (dt, J = 4.5, 11.0 Hz, 1H), 6.92 (dd, J = 1.5, 7.5 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 7.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.6, 20.6, 21.3, 23.2, 28.9, 36.1, 37.1, 38.2, 49.7, 70.4, 125.2, 126.4, 129.2, 132.2, 134.9, 147.2.

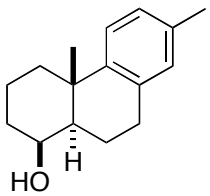


(1*S,4a*S**,10a*R**)-4a,6-Dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-ol (15aβ) (Entry 1, Table 4):** Column chromatography (hexane–EtOAc = 10:1); amorphous solid; TLC, R_f = 0.30 (hexane–EtOAc = 4:1); IR (film) 3619, 3008, 2933, 2870, 1499, 1455, 1075, 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.32 (s, 3H), 1.43

(dt, J = 3.0, 13.0 Hz, 1H), 1.53–1.67 (m, 4H), 1.88 (dm, J = 14.0 Hz, 1H), 2.00 (tq, J = 3.5, 13.5 Hz, 1H), 2.07–2.17 (m, 1H), 2.30 (s, 3H), 2.30–2.34 (m, 1H), 2.9–-2.94 (m, 2H), 4.03 (s, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 7.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.3, 21.3, 22.9, 25.4, 29.1, 33.6, 36.8, 37.8, 44.9, 72.3, 124.7, 126.3, 129.1, 131.8, 135.0, 148.7; HRMS (EI) m/z calcd for $C_{16}H_{22}O$ (M) 230.1671 found 230.1682.

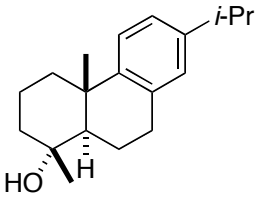


(1*R,4a*S**,10a*R**)-4a,7-Dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-ol (15bα) (Entry 2, Table 4):** Containing a small amount of 5-Me-regioisomer; column chromatography (hexane–EtOAc = 5:1); colorless oil; TLC, R_f = 0.21 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83–1.77 (m, 6H), 1.08 (s, 3H for 7-Me-regioisomer), 1.26 (s, 3H for 5-Me-regioisomer), 2.07–2.33 (m, 3H), 2.28 (s, 3H for 7-Me-regioisomer), 2.51 (s, 3H for 5-Me-regioisomer), 2.71–2.96 (m, 2H), 3.66 (td, J = 4.2, 10.5 Hz, 1H), 6.90 (s, 1H), 6.96 (dm, J = 7.5 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H).

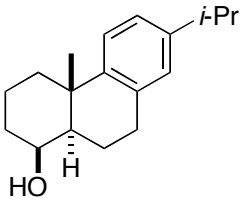


(1*S,4a*S**,10a*R**)-4a,7-Dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-ol (15bβ) (Entry 2, Table 4):** Column chromatography (hexane–EtOAc = 10:1); amorphous solid; TLC, R_f = 0.29 (hexane–EtOAc = 4:1); IR (film) 3619, 3007, 2930, 2870, 1496, 1455, 1159, 1074, 1000, 821 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.31 (s, 3H), 1.41 (dt, J = 3.0, 13.0 Hz, 1H), 1.54–1.67 (m, 4H), 1.88 (brd, J = 14.5 Hz, 1H), 2.00 (dq, J = 3.5, 13.5 Hz, 1H), 2.07–2.17 (m, 1H), 2.27 (s, 3H), 2.27–2.32 (m, 1H),

2.92–2.94 (m, 2H), 4.03 (s, 1H), 6.88 (s, 1H), 6.96 (d, J = 7.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.3, 20.8, 22.9, 25.5, 29.4, 33.7, 36.5, 37.9, 45.0, 72.2, 124.1, 126.6, 129.7, 134.8 (2C), 146.1; HRMS (EI) m/z calcd for $C_{16}H_{22}O$ (M) 230.1671 found, 230.1679.



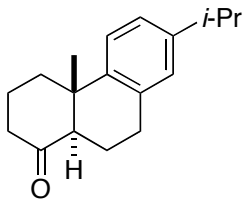
(1*R,4a*S**,10a*R**)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydro phenanthren-1-ol (22) (Scheme 2):**[26] Column chromatography (hexane–EtOAc = 5:1); amorphous solid; TLC, R_f = 0.20 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.16 (s, 3H), 1.24 (d, J = 7.0 Hz, 6H), 1.24 (s, 3H), 1.36–1.48 (m, 2H), 1.60–1.79 (m, 4H), 1.87 (dm, J = 13.0 Hz, 1H), 2.11 (dd, J =7.0, 12.5 Hz, 1H), 2.26 (dm, J = 13.0 Hz, 1H), 2.78–2.2.92 (m, 3H), 6.91 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.0, 20.6, 22.9, 23.9, 24.0, 24.5, 30.4, 33.4, 38.0, 38.2, 42.7, 52.5, 72.5, 123.9, 124.6, 127.0, 134.8, 145.7, 146.4.



(1*S,4a*S**,10a*R**)-7-Isopropyl-4a-methyl-1,2,3,4,4a,9,10,10a-octahydro-ph enanthren-1-ol (15cβ) (Scheme 2):**[27] Column chromatography (hexane–EtOAc = 5:1); amorphous solid; TLC, R_f = 0.31 (hexane–EtOAc = 4:1); IR (film) 3619, 3004, 2932, 2871, 1497, 1456, 1074, 998, 887, 827 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (d, J = 7.0 Hz, 6H), 1.32 (s, 3H), 1.40-1.46 (m, 1H), 1.52–1.56 (m, 4H), 1.88 (dd, J = 3.5, 13.5 Hz, 1H), 2.00 (tq, J = 3.5, 13.5 Hz, 1H), 2.07–2.16 (m, 1H), 2.27–2.32 (m, 1H), 2.79–2.86 (m, 1H), 2.93–2.96 (m, 2H), 4.03 (d, J = 2.5 Hz, 1H), 6.91 (s, 1H), 7.00

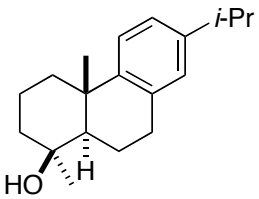
(dd, J = 1.5, 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.3, 22.9, 24.0 (2C), 25.5, 29.6, 33.4, 33.6, 36.5, 37.8, 44.9, 72.2, 123.8, 124.0, 127.0, 134.7, 145.6, 146.3; HRMS (EI) m/z calcd for $C_{18}H_{26}O$ (M) 258.1984, found 258.1974.

Total Synthesis of 24 from 15c: To a stirred suspension of **15c** (50 mg, 0.19 mmol) and activated molecular sieves 4A (190 mg) in CH_2Cl_2 (8 mL) was added 4-methylmorpholine *N*-oxide (NMO, 67 mg, 0.57 mmol) and tetra-*n*-propylammonium perruthenate(VII) (TPAP, 3.5 mg, 0.01 mmol) successively at 0 °C and stirred for 3 h at room temperature.[28] The resulting mixture was filtered through a short pad of silica gel and the resulting residue was washed with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluent: hexane–EtOAc = 10:1) to gave **23** (49 mg, 0.19 mmol, >99% yield) as white solid. To a solution of **23** (256 mg, 1.0 mmol) in THF (10 mL) was added MeLi (1.0 M in Et_2O, Kanto, 1.3 mL, 1.3 mmol) at –78 °C. After 30 minutes the reaction was quenched with aqueous NH_4Cl and extracted with Et_2O (twice). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was passed through a short pad of silica gel to give pure **24** (271 mg, 0.99 mmol, >99% yield) as an amorphous solid.



(4a*S,10a*R**)-7-Isopropyl-4a-methyl-2,3,4,4a,10,10a-hexahydro-phenanthren-1(9*H*)-one (23):**[29] Column chromatography (hexane–EtOAc = 10:1); white solid; TLC, R_f = 0.50 (hexane–EtOAc = 4:1); IR (film) 3006, 2961, 2872, 1709 (C=O), 1497, 1378, 1315, 1069, 827 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (s, 3H), 1.23 (d, J =

7.0 Hz, 6H), 1.81 (ddt, *J* = 6.5, 12.3, 14.0 Hz, 1H), 1.89 (dt, *J* = 5.0, 13.5 Hz, 1H), 1.98–2.16 (m, 3H), 2.34–2.43 (m, 3H), 2.66 (dd, *J* = 2.5, 12.5 Hz, 1H), 2.77–2.91 (m, 3H), 6.94 (s, 1H), 7.03 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.8, 22.9, 23.9, 24.2, 29.1, 33.8, 37.3, 41.2, 42.5, 55.7, 124.4, 125.2, 127.6, 134.9, 143.3, 146.6, 212.7 (C=O); HRMS (EI) *m*/*z* calcd for $C_{18}H_{24}O$ (M) 256.1827, found 256.1826.



(1*S,4a*S**,10a*R**)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydro phenanthren-1-ol (24):**[26] Column chromatography (hexane–EtOAc = 10:1); amorphous solid; TLC, R_f = 0.39 (hexane–EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24 (d, *J* = 7.0 Hz, 6H), 1.25 (s, 3H), 1.30 (s, 3H), 1.39-1.48 (m, 3H), 1.59–1.64 (m, 1H), 1.73 (dm, *J* = 13.5 Hz, 1H), 1.87 (ddt, *J* = 7.5, 10.5, 13.0 Hz, 1H), 1.96 (tq, *J* = 3.5, 14.0 Hz, 1H), 1.99–2.05 (m, 1H), 2.31 (d, *J* = 13.0 Hz, 1H), 2.78–3.00 (m, 3H), 6.90 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.9, 18.4, 24.0 (2C), 24.4, 29.4, 30.8, 33.4, 37.1, 38.2, 40.8, 48.7, 72.2, 123.8, 123.9, 126.8, 134.7, 145.6, 146.7.

X-Ray Diffraction Analysis of 5cβ and Desilylated 8aα, 8aβ and 11aβ

X-ray crystallographic analysis was performed with a Bruker SMART APEX diffractometer (graphite monochromator, MoKa radiation, λ = 0.71073 Å) and the structure was solved by direct methods and expanded using Fourier techniques (Sir97 and SHELXL[30]).

Recrystallization of **5cβ** was carried out in the solution of MeOH–hexane at room temperature (Table 5). Mp: 114–116 °C. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC 293029 for **5cβ**. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Table 5. Crystallographic Data and Structure Refinement for **5cβ**

Compound	**5cβ**
empirical formula	$C_{26}H_{44}OSi$
formula weight	400.70
T	223(2) K
λ	0.71073 Å
crystal system	triclinic
space group	*P*1
A	7.654(3) Å
B	8.087(3) Å
C	21.574(8) Å
α	89.127(7)°

β	85.581(7)°
γ	66.067(6)°
V	1216.7(8) Å^3
Z	2
D_{calcd}	1.094 g/cm^3
absorption coefficient	0.110 mm^{-1}
F(000)	444
crystal size	0.20 x 0.15 x 0.15 mm^3
theta range for data collection	1.89 to 29.22°
reflections collected	8913
independent reflections	6145
R_{int}	0.0305
refinement based on	F^2
no. of data	6145
no. of parameters	429
no. of restraints	0
GOF	0.997
R(F) for $I > 2s(I)$	0.0541
wR2(F^2) for all data	0.1513
$\Delta\rho_{min}$	–0.358 eÅ^{-3}
$\Delta\rho_{max}$	0.536 eÅ^{-3}

Recrystallization of desilylated **8aα** was carried out in wet acetone at room temperature (Table 6). Mp: 116–118 °C. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC 296031 for desilylated **8aα**. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Table 6. Crystallographic Data and Structure Refinement for Desilylated **8aα**

Compound	Desilylated **8aα**
empirical formula	$C_{44}H_{64}O_2$
formula weight	624.95
T	223(2) K
λ	0.71073 Å
crystal system	Triclinic
space group	$P1$
A	7.147(7) Å
b	12.736(12) Å
C	19.488(18) Å
α	90.337(19)°
β	90.130(19)°
γ	98.734(19)°
V	1753(3) Å^3
Z	2
D_{calcd}	1.184 g/cm^3
absorption coefficient	0.070 mm^{-1}

$F(000)$	688
crystal size	0.20 x 0.15 x 0.15 mm^3
theta range for data collection	1.04 to 29.35°
reflections collected	13039
independent reflections	8985
R_{int}	0.0256
refinement based on	F^2
no. of data	8985
no. of parameters	431
no. of restraints	0
GOF	0.964
R(F) for $I > 2s(I)$	0.0531
wR2(F^2) for all data	0.1577
$\Delta\rho_{min}$	–0.224 $eÅ^{-3}$
$\Delta\rho_{max}$	0.308 $eÅ^{-3}$

Desilylated **8aβ** was recrystallized in wet acetone at room temperature (Table 7). Mp: 103–105 °C. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC 296030 for desilylated **8aβ**. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Table 7. Crystallographic Data and Structure Refinement for Desilylated **8aβ**

Compound	Desilylated **8ab**
empirical formula	$C_{88}H_{140}O_{10}$
formula weight	1358.00
T	223(2) K
λ	0.71073 Å
crystal system	Monoclinic
space group	*P*21/c
A	21.254(6) Å
B	7.386(2) Å
C	25.122(7) Å
α	90°
β	109.476(6)°
γ	90°
V	3718.2(19) $Å^3$
Z	2
D_{calcd}	1.213 g/cm^3

absorption coefficient	0.077 mm^{-1}
$F(000)$	1496
crystal size	0.20 x 0.15 x 0.12 mm^3
theta range for data collection	1.68 to 29.23°
reflections collected	26715
independent reflections	9794
R_{int}	0.0503
refinement based on	F^2
no. of data	9794
no. of parameters	458
no. of restraints	0
GOF	1.020
R(F) for $I > 2s(I)$	0.0837
wR2(F^2) for all data	0.2853
$\Delta\rho_{min}$	–0.707 $eÅ^{-3}$
$\Delta\rho_{max}$	0.747 $eÅ^{-3}$

Recrystallization of desilylated **11aβ** was carried out in chloroform at room temperature (Table 8). Mp: 90-93 °C. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC 296032 for desilylated **11aβ**. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Table 8. Crystallographic Data and Structure Refinement for Desilylated **11aβ**

Compound	desilylated **11ab**
empirical formula	$C_{17}H_{24}O$
formula weight	244.36
T	223(2) K
λ	0.71073 Å
crystal system	monoclinic
space group	*P*21/c
A	14.862(4) Å
B	7.073(2) Å
C	13.688(4) Å
α	90°
β	104.242(7)°
γ	90°
V	1394.6(7) $Å^3$
Z	4
D_{calcd}	1.164 g/cm^3
absorption coefficient	0.070 mm^{-1}

$F(000)$	536
crystal size	0.40 x 0.20 x 0.20 mm^3
theta range for data collection	2.83 to 29.16°
reflections collected	9990
independent reflections	3699
R_{int}	0.0387
refinement based on	F^2
no. of data	3699
no. of parameters	170
no. of restraints	0
GOF	1.076
R(F) for $I > 2s(I)$	0.0849
wR2(F^2) for all data	0.2970
$\Delta\rho_{min}$	–0.245 $eÅ^{-3}$
$\Delta\rho_{max}$	0.639 $eÅ^{-3}$

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Publication List

1. Biomimetic Synthesis of Acid-Sensitive (–)-Caparrapi Oxide and (+)-8-Epicaparrapi Oxide Induced by Artificial Cyclases
   Muhammet Uyanik, Hideaki Ishibashi, Kazuaki Ishihara, Hisashi Yamamoto
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Acknowledgement

The author would like to express his grateful acknowledgment to his supervisors, Professor Kazuaki Ishihara and Professor Hisashi Yamamoto (Univ. of Chicago, USA) whose encouragement and helpful suggestions; encouragement, pertinent and tolerant advice; practical guidance; and helpful discussions have been indispensable to the completion of the present thesis.

He is indebted to Drs. Akira Sakakura and Manabu Hatano for practical and hours of fruitful discussions. It is pleasant to express his appreciation to the former and present colleagues, especially Dr. Hideaki Ishibashi and Miss Keiko Kumazawa.

He is very grateful to the scholarship of Japanese Government for foreigner students, during 2004-2007. He is also grateful to the scholarship of Iwakuni Foundation, during 2000-2004.

He would like to express special thanks to Professor Takashi Yamane, Professor Asanuma Hiroyuki, and Associate Professor Toshio Nishikawa for serving on his discussion committee.

The author wishes to thank his parents and friends, especially Emre and Hikmet who made this work possible through for their support and sacrifice. At the last, he would like to take opportunity to especially thank Tomoko for everything.