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Syntheses of the four stereoisomers of *Phytophthora* mating hormone α2 and a concise synthesis of mating hormone α1

Arata Yajima [a,*], Kou Toda [a], Shylaja D. Molli [b], Makoto Ojika [b], Tomoo Nukada [a]

[a] *Department of Fermentation Science, Faculty of Applied Biological Science, Tokyo University of Agriculture (NODAI), Sakuragaoka 1-1-1, Setagaya-ku, Tokyo 156-8502, Japan*
[b] *Graduate School of Bioagricultural Sciences, Nagoya University, Nagoya 464-8601, Japan*

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ABSTRACT

Four stereoisomers of *Phytophthora* mating hormone α2 were synthesized using both enantiomers of citronellol as starting materials. The absolute configuration of the natural product was determined to be 7*S*,11*R*,15*R* by oospore-inducing assays of the synthetic isomers. A concise synthetic procedure of α1 was also established using a common synthetic intermediate of α2.

1. Introduction

The fungus-like genus *Phytophthora* comprises approximately 80 pathogenic species that are responsible for the devastation of hundreds of crops worldwide, including potato and tomato crops.[1] *Phytophthora*, which means 'plant destroyer,' are some of the most destructive pathogens in the world. In the mid-1840s, a massive potato disease, late blight, destroyed the potato crops in Europe and in the United States. This disease was caused by a member of the genus, *Phytophthora infestans*. The late blight epidemic completely destroyed Ireland's staple potato crops, which led to the Great Irish Famine of 1845 and 1846.[2] *Phytophthora ramorum* has recently been identified as an aggressive pathogen that induces extensive mortality among the oak trees in California,[3] known as sudden oak death. In the 20th century, these diseases were effectively managed with fungicides. Unfortunately, certain virulent and fungicide-resistant strains have recently undergone extensive migration, causing a worldwide resurgence of late blight in potatoes.[2]

An important biological event in the lifecycle of *Phytophthora* is sexual reproduction, which is conducted by two mating types, A1 and A2, in heterothallic species.[1,2] Each individual is bisexual and capable of producing both male (antheridia) and female (oogonia) organs. Hormone α1 is secreted by the A1 mating type and induces the formation of sexual spores (oospores) in the A2 mating type, whereas hormone α2 is secreted by A2 and induces oospores in the A1 mating type. The oospores from *Phytophthora* have a doubly thick-walled structure that allows them to survive for months or years under harsh conditions, such as drying or freezing. Managing phytopathogens with common fungicides is difficult. Furthermore, sexual reproduction is thought to be the cause of the rapid spread of fungicide-resistant species. Chemical studies of hormones α1 and α2 date back to 1929 when Ashby proposed that sexual reproduction in *Phytophthora* was regulated by hormone-like compounds.[4] Data that were later reported by Galloway[5a] and Kouyears[5b] supported the hypothesis of chemical stimulation for oospore formation. In 1978, Ko reported evidence for the hormonal regulation of sexual reproduction, and the hormone-like compounds were named hormones α1 and α2. Conflicting reports argue that the compounds are more appropriately termed pheromones.[6] Although extensive studies, including Ko's partial characterization[7] of α1 and α2, have been conducted with the aim of isolating α1 and α2, their structures remained undetermined due to their scarcity.[8] More than 70 years after the first proposal of the existence of these hormone-like compounds, Ojika and co-workers succeeded in isolating α1 from 1830 L of the A1 mating type culture broth of *Phytophthora nicotianae*.[9] The structure of α1 was determined as **1** by spectral analyses (Fig. 1). The absolute configurations of C-3 and C-15 were elucidated based on NMR studies of the corresponding bis-MTPA ester of α1.[10] We synthesized the stereoisomeric mixture and the four possible stereoisomers of α1. We determined the absolute configuration of the natural product by direct comparison of the biological activities of the synthetic samples with natural α1.[11,12]

* Corresponding author. Tel./fax: +81 3 5477 2264; e-mail address: ayaji@nodai.ac.jp (A. Yajima).

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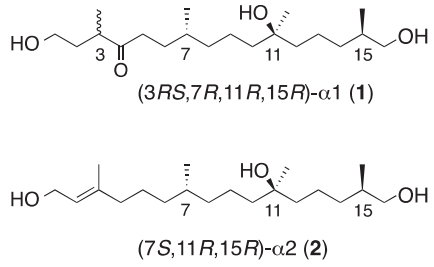


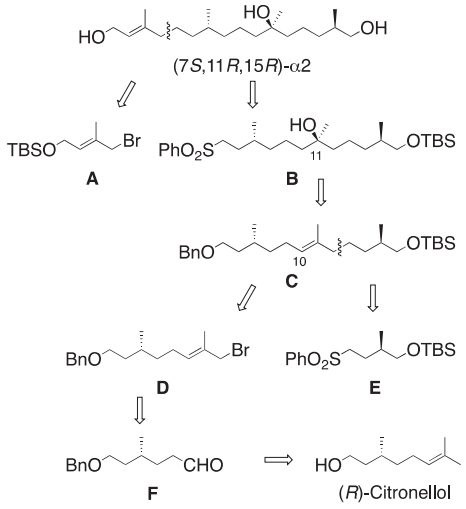
Fig. 1. Structures of *Phytophthora* mating hormones α1 and α2.

The importance of this compound has attracted the attention of many synthetic organic chemists.[13] The non-stereoselective[14a] and stereoselective syntheses of natural[14b] and unnatural[14c] isomers of α1 have since been reported. Very recently, the final component of the mating hormone of *Phytophthora* was isolated and characterized by Ojika and co-workers.[15] The structure of α2, which is very similar to that of α1, was determined as **2** after extensive MS and NMR studies and total synthesis (Fig. 1). Herein, we report details regarding the total syntheses and biological activities of the four stereoisomers of *Phytophthora* mating hormone α2. We also report a concise synthesis of a biologically active form of α1 using a common synthetic intermediate of α2.

2. Results and discussion

Our retrosynthetic analysis is summarized in Scheme 1. Because the structure of α2 is similar to that of α1, we employed a similar synthetic approach for α1.[12] The carbon skeleton of α2 was constructed by a coupling between the corresponding dianion of sulfone **B** with known bromide **A**.[16] The hydroxyl group at C-11 was introduced using a Sharpless asymmetric dihydroxylation (AD)[17] of **C**, followed by deoxygenation of the unnecessary resulting secondary hydroxyl group at C-10. The bond between C-12 and C-13 of **C** was generated by the coupling of bromide **D** and known sulfone **E**.[18] Fragment **D** was prepared from the aldehyde **F**,[19] which can be derived from citronellol. Although α2 possesses three stereogenic centers at C-7, C-11, and C-15 that lead to eight possible stereoisomers of α2, we speculated that the absolute configuration of C-15 could be determined by analogy to α1.[12] The determined stereogenic center, C-15, could be derived from a known compound with distinct absolute configuration. The remaining stereogenic center, C-11, could be derived using the appropriate AD-mix-α or β. Thus, to identify the absolute stereostructure of α2, the four possible stereoisomers with a fixed configuration of 15*R* were synthesized. If the isomers showed weak activity, the other four isomers with the 15*S* configuration could be synthesized.

The stereoselective total synthesis of α2 is shown in Scheme 2. The optically active (97% ee) citronellol was converted into known aldehyde **4**.[19] Wittig condensation of **4** with (carbethoxyethylidene) triphenylphosphorane (98%), followed by reduction of the resulting ester moiety, afforded alcohol **5** (90%). Alcohol **5** was converted to the allylic bromide and then coupled to the bromide with the known sulfone **6**.[18] Further desulfonation with sodium amalgam afforded **7a**. The stereoselective dihydroxylation[17] of **7a** with AD-mix-α produced diol **8a**. For the synthesis of α1, the reaction proceeded in a 95:5 diastereomeric ratio (dr), as determined by HPLC analysis.[12] The diastereomeric ratio of **8a** could not be determined by chiral HPLC analysis. The biological properties of the final products, however, supported the high stereoselectivity of the AD reactions as the synthesis of α1 (vide infra). Monomesylation of the secondary hydroxyl group and demesylation with K_2CO_3 yielded epoxide **9a**. The regioselective reductive opening of the epoxy ring with Super-Hydride® ($LiEt_3BH$) yielded tertiary alcohol **10a** in a 91%

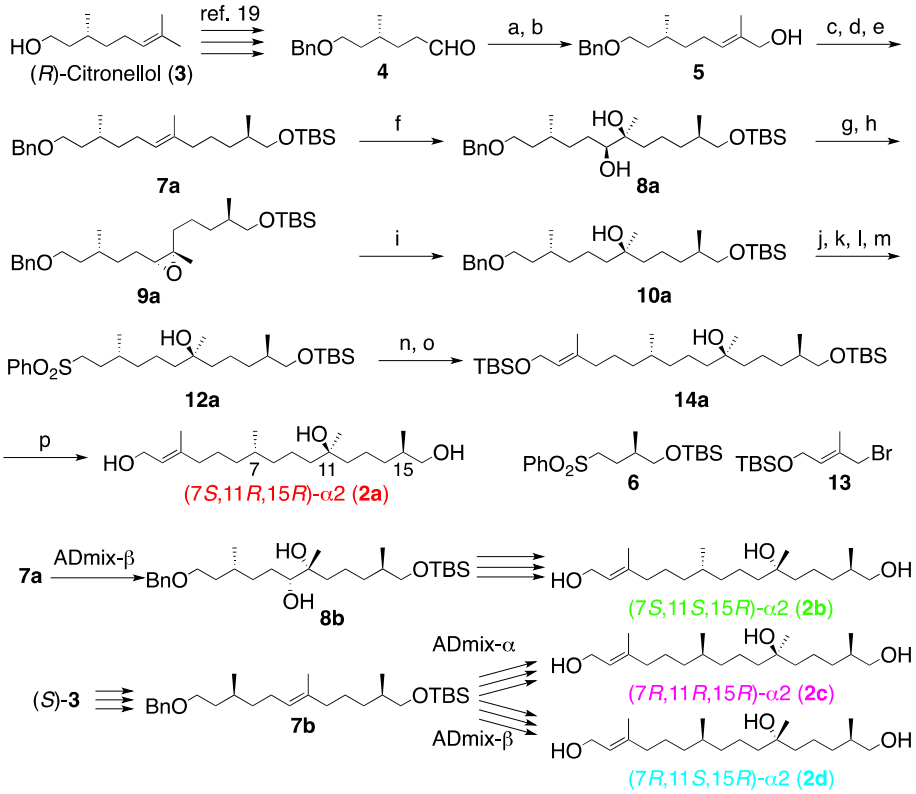


Scheme 1. Retrosynthetic analysis of α2.

yield. Removal of the benzyl group in **10a** under Birch conditions (98%), followed by tosylation and successful iodination of the resulting alcohol, yielded the corresponding iodide (64% in two steps). The iodide was converted into corresponding sulfone **12a** with sodium sulfinate (92%). Further alkylation of the corresponding dianion of **12a** with known bromide **13**[16] at low temperature (88%), followed by desulfonation, afforded **14a** with the full carbon skeleton of α2. The ^1H NMR analysis of the obtained **14a** showed additional olefin proton signals, indicating contamination by side reaction products such as β-elimination of the sulfonyl group. Fortunately, the undesired side products were easily removed by column chromatography with silver nitrate-impregnated silica gel. The yield of pure **14a** was 64%. Removal of the two TBS groups in **14a** with TBAF afforded (7*S*,11*R*,15*R*)-**2a** in an overall yield of 5.8% from known aldehyde **4**. Because both the enantiomers of citronellol and the reagents for asymmetric dihydroxylation were readily available, the possible four stereoisomers of α2 were synthesized using the above methodology to yield (7*S*,11*S*,15*R*)-**2b**, (7*R*,11*R*,15*R*)-**2c**, and (7*R*,11*S*,15*R*)-**2d**.

NMR studies of the four synthetic stereoisomers of α2 (**2a**–**d**) were conducted for verification of the asymmetric carbon configurations. However, no significant differences between the ^1H and ^{13}C NMR spectra of the four synthetic stereoisomers and those of the natural product were observed. Thus, determining the relative and absolute configuration of natural α2 by NMR analyses is impossible. The same observation applied to α1.[11,12]

Next, the biological activities of the four stereoisomers of α2 were measured using previously described methods.[15] Fig. 2 shows the dose-dependent increase in the oospore formation activities of the natural and synthetic stereoisomers of α2 (**2a**–**d**) against the A1 mating type of *P. nicotianae*. Only the (7*S*,11*R*,15*R*)-isomer (**2a**) showed significant hormonal activity at dosages of 3 ng/disc, which was comparable to that of the natural product. The other three isomers were essentially inactive. The very weak activity observed in the (7*S*,11*S*,15*R*)-isomer (**2b**) would reflect contamination by the active (7*S*,11*R*,15*R*)-isomer from the asymmetric dihydroxylation step. According to the findings of the unique bioactivity of the (7*S*,11*R*,15*R*)-isomer (**2a**), the absolute configuration of natural α2 was determined to be 7*S*,11*R*,15*R*, which is consistent with α1. Surprisingly, α2 was found to be biosynthesized from phytol (**15**) in the A2 mating type and then converted to α1 by the A1 mating type to initiate sexual reproduction when both the mating types shared the same habitat (Scheme 3).[15] The absolute configurations of all the stereogenic centers of α2 are consistent with α1.



Scheme 2. Asymmetric synthesis of α2. Reagents, conditions and yields: (a) $Ph_3P{=}C(Me)CO_2Et$, benzene, reflux, 98%; (b) DIBAL, CH_2Cl_2, hexane, −78 °C, 90%; (c) *n*-BuLi, MsCl, THF, −78 °C, then LiBr, 86%; (d) **6**, *n*-BuLi, THF, HMPA, −78 °C, 82%; (e) Na/Hg, Na_2HPO_4, THF, MeOH, −15 °C, 72%; (f) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C, 77%; (g) Ms_2O, Et_3N, CH_2Cl_2, 0 °C; (h) K_2CO_3, MeOH, 65% in two steps; (i) $LiEt_3BH$, THF, 0 °C, 91%; (j) Li, NH_3, THF, −78 °C, 98%; (k) TsCl, pyridine, 0 °C; (l) NaI, acetone, reflux, 64% in two steps; (m) $PhSO_2Na$, DMF, 92%; (n) *n*-BuLi, **13**, THF, HMPA, −78 °C, 88%; (o) Na/Hg, Na_2HPO_4, THF, MeOH, −15 °C, 64%; (p) TBAF, THF, 0 °C, 87%.

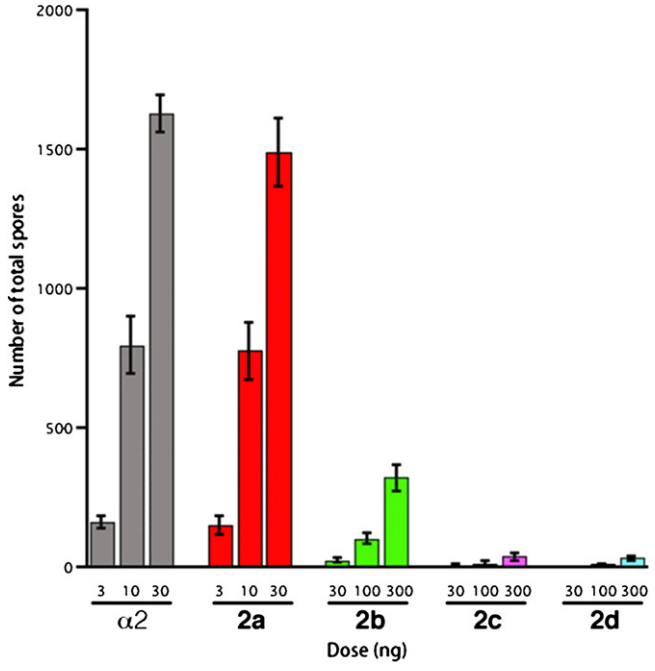
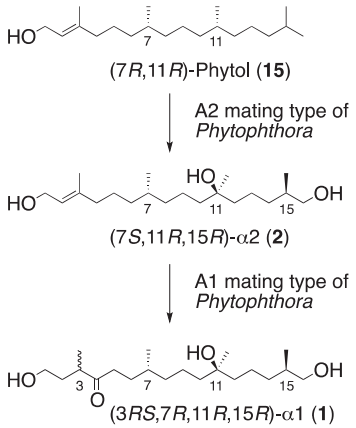


Fig. 2. The dose-dependent increase of oospore formation in the A1 mating type of *P. nicotianae*, as induced by synthetic samples (ng/disc) in comparison with natural α2 at doses of 3–300 ng/disc. Values represent the mean of four replicates.

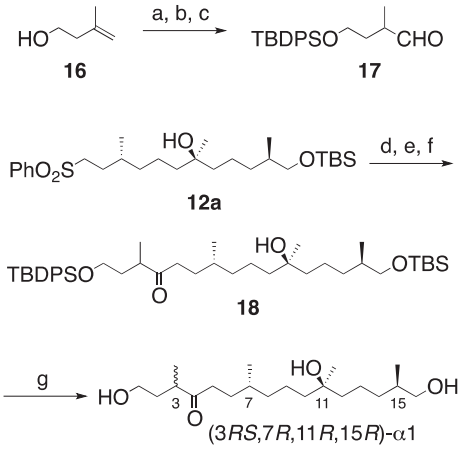


Scheme 3. Biosynthetic pathway for α1 and α2.

The first stereoselective synthesis of α1 was not satisfactory based on the product yield. Namely, the yield of the coupling of the C1–C5 fragment and the C6–C12 fragment was only 43%.[12] Therefore, we examined the application of the synthetic intermediate of α2, sulfone **12a**, for the total synthesis of α1 (Scheme 4). The coupling of sulfone **12a** with aldehyde **17**, which was prepared from **16**, followed by oxidation and desulfonation, afforded the protected α1 (**18**). Removal of the two silyl protecting groups of **18** yielded (3*RS*,7*R*,11*R*,15*R*)-α1. Although the product was a diastereomeric mixture at C3, we have reported that the stereochemically pure (3*R*,7*R*,11*R*,15*R*)-α1 exhibited almost the same biological activity with the natural product, which is a diastereomeric mixture at C3 (*R*/*S*=ca. 3:2).[12] This result indicates that the synthetic (3*RS*)-**1** will be as active as the natural product.

3. Conclusion

In summary, we achieved the first total synthesis of *Phytophthora* mating hormone α2. The biological activities of the four



Scheme 4. Synthesis of α1. Reagents, conditions and yields: (a) TBDPSCl, imidazole, DMF, 98%; (b) 9-BBN, THF then H_2O_2 NaOH aq, 95%; (c) PCC, MS4 A, CH_2Cl_2, 87%; (d) *n*-BuLi, THF −78 °C, then **17**; (e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 81% in two steps; (f) Al/Hg, THF, 62% (81% based on recovered starting material); (g) TBAF, THF, quant.

synthetic stereoisomers were evaluated using an oospore-inducing assay, and only the (7*S*,11*R*,15*R*)-isomer of α2 was found to be as significantly active as the natural product. Based on the bioactivity, the absolute configuration of the natural α2 was determined to be 7*S*,11*R*,15*R*. We also developed an alternative synthetic method for α1 using a common synthetic intermediate for α2 synthesis. Notably, both α1 and α2 have been found to induce sexual reproduction in most of the heterothallic species.[9,15] These results demonstrate the interspecific universality of the *Phytophthora* mating hormones. With a pair of the mating hormones, establishing the molecular mechanism of the hormones using synthetic α1 or α2 as chemical probes is possible and would contribute to the development of agricultural pest management methods for controlling *Phytophthora* sexual reproduction. The complete stereostructures of the *Phytophthora* mating hormones have finally been established since Ashby proposed the existence of hormone-like compounds over 80 years ago.

4. Experimental

4.1. General

Optical rotations were measured on a Jasco P-2100. IR spectra were measured on a Jasco IR-4100 spectrometer. ^{1}H NMR spectra were recorded on Jeol ECS400 (400 MHz) spectrometer using the residual solvent peak at δ=7.26 (for $CDCl_3$) or 3.30 (for CD_3OD) as an internal standard. ^{13}C NMR spectra were recorded on Jeol ECS400 (100 MHz) spectrometer using $CDCl_3$ at δ=77.0 or CD_3OD at δ=49.0 as an internal standard. Elemental compositions were analyzed on a J-Science MICROCORDER JM10. High resolution ESI-TOF-MS data were recorded on Mariner Biospectrometry Workstation (Applied Biosystems), Bioapex II (Brucker), Jeol JMS-T100 and Jeol JMS-HX110 spectrometers. Column chromatography was performed with silica gel Wakogel-C200. Flush column chromatography was performed with Kanto Silica Gel 60 (spherical).

4.1.1. (2E,6R)-Ethyl 2,6-dimethyl-8-benzyloxy-2-octenoate. To a solution of (*R*)-**4** (4.00 g, 16.8 mmol) in benzene (45 ml) was added[1-(ethoxycarbonyl)ethylidene]triphenylphosphorane (9.13 g, 25.2 mmol), and the resulting mixture was refluxed for 4 h. After cooling to room temperature, the solution was concentrated. The residue was purified by silica gel column chromatography with AcOEt/hexane (1:60) to give the *title compound* (5.34 g, 98%) as a colorless oil. [Found: C, 74.85; H, 9.01. $C_{19}H_{28}O_3$ requires C, 74.96; H, 9.27%]; $[\alpha]_D^{24}$ +4.5 (*c* 1.2, $CHCl_3$); ν_{max} (liquid film) 2928, 2923, 2866, 1709, 1649, 1454, 1366, 1273, 1191, 1139, 1099, 1028, 736, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.90 (d, *J*=6.3 Hz, 3H), 1.27–1.33 (m, 4H), 1.45 (m, 2H) 1.65 (m, 2H), 1.82 (d, *J*=1.0, 3H), 2.17 (m, 2H), 3.50 (m, 2H), 4.18 (m, 2H), 4.51 (d, *J*=12.2 Hz, 1H), 6.73 (m, 1H), 7.24–7.36 (m, 5H); δ_C (100 MHz, $CDCl_3$) 12.3, 14.3, 19.4, 26.2, 29.7, 35.7, 36.6, 60.3, 68.4, 72.9, 127.5, 127.58, 127.61, 128.3, 138.6, 142.3, 168.2.

*4.1.2. (2E,6R)-2,6-Dimethyl-8-benzyloxy-2-octen-1-ol (**5**).* To a stirred and cooled (−78 °C) solution of the above compound (5.34 g, 17.4 mmol) in CH_2Cl_2 (40 ml) was added dropwise DIBAL (1.05 M solution in hexane, 38.9 ml, 40.1 mmol) under Ar atmosphere. After stirring for 30 min, MeOH and satd potassium sodium tartrate solution were added carefully to the mixture. The mixture was warmed to room temperature and stirred for 1 h. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography with AcOEt/hexane (1:20) to give **5** (4.16 g, 90%) as a colorless oil. $[\alpha]_D^{24}$ +2.7 (*c* 1.1, $CHCl_3$). [Found: C, 77.91; H, 9.91. $C_{17}H_{26}O_2$ requires C, 77.82; H, 9.99%]; ν_{max} (liquid film) 3395, 2923, 2864, 1739, 1455, 1367, 1240, 1205, 1098, 1013, 846, 737, 698, 612 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.90 (d, *J*=6.3 Hz, 3H), 1.27–1.33 (m, 2H), 1.45 (m, 2H) 1.65 (m, 2H), 1.82 (d, *J*=1.0, 3H), 2.17 (m, 2H), 3.50 (m, 2H), 4.18 (m, 2H), 4.48 (d, *J*=12.2 Hz, 1H), 4.51 (d, *J*=12.2 Hz, 1H), 6.73 (m, 1H), 7.24–7.36 (m, 5H); δ_C (100 MHz, $CDCl_3$) 13.6, 14.2, 19.5, 25.0, 29.5, 36.6, 36.8, 68.6, 69.0, 72.9, 126.5, 127.5, 127.6, 128.3, 134.5, 138.6.

4.1.3. (2R,6E,10R)-12-Benzyloxy-1-tert-butyldimethylsilyloxy-2,6,10-trimethyl-6-dodecen-4-yl phenyl sulfone. To a stirred and cooled (−78 °C) solution of **5** (1.59 g, 6.09 mmol) in THF (10 ml) was added *n*-BuLi (1.65 M solution in hexane, 5.54 ml, 9.14 mmol) under Ar atmosphere. After stirring for 20 min, methanesulfonyl chloride (1.05 g, 9.14 mmol) was added to the mixture. After stirring for 1 h, a solution of LiBr (794 mg, 9.14 mmol) in THF (6 ml) was added to the mixture. The mixture was stirred for 1 h at the same temperature and 1 h at room temperature, and then poured into satd $NaHCO_3$ solution. The aqueous layer was extracted with hexane, and the combined organic layers were washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography with AcOEt/hexane (1:150) to give 1.70 g of the corresponding allylic bromide as a colorless oil. This was immediately used for the next reaction. To a stirred and cooled (−78 °C) solution of **6** (1.29 g, 3.77 mmol) in THF (10 ml) and HMPA (1 ml) was added dropwise *n*-BuLi (1.65 M solution in hexane, 2.74 ml, 4.52 mmol). After stirring for 30 min, a solution of 1.35 g of the allylic bromide (4.15 mmol) in THF (15 ml) was added. The mixture was stirred for 40 min, and then quenched with water. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with satd $Na_2S_2O_3$ solution, satd $NaHCO_3$ solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography with AcOEt/hexane (1:30) to give the *title compound* (1.82 g, 70% for two steps) as a colorless oil. $[\alpha]_D^{24}$ −7.2 (*c* 1.1, $CHCl_3$); [Found: C, 69.32; H, 9.32. $C_{34}H_{54}O_4SSi$ requires C, 69.57; H, 9.27%]; ν_{max} (liquid film) 2955, 2927, 2856, 1447, 1387, 1362, 1304, 1252, 1145, 1086, 1027, 837, 777, 754, 734, 694, 606 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.00–0.02 (m, 6H), 0.74–0.87 (m, 15H), 1.11 (m, 1H), 1.29 (m, 2H), 1.40 (m, 1H), 1.49–1.69 (m, 5H), 1.75–2.06 (m, 5H), 2.59, 2.62 (2×br s, 1H), 3.17–3.52 (m, 5H), 4.46 (d, *J*=12.2 Hz, 1H), 4.49 (d, *J*=12.2 Hz, 1H), 5.11 (m, 1H), 7.24–7.35 (m, 5H), 7.54 (m, 2H), 7.63 (m, 1H), 7.88 (m, 2H); δ_C (100 MHz, $CDCl_3$) −5.46, −5.42, 15.4, 16.4, 16.6, 18.3, 19.5, 25.47, 25.52, 25.91, 25.94, 29.6, 32.0, 33.3, 36.59, 36.62, 36.8, 40.1, 40.4, 60.2, 67.3, 68.3,

68.6, 72.9, 127.5, 127.6, 128.3, 128.94, 128.96, 129.03, 129.1, 129.3, 129.4, 129.8, 133.44, 133.45, 137.8, 137.9, 138.60, 138.62.

*4.1.4. (2R,6E,10R)-tert-Butyldimethylsilyl 12-benzyloxy-2,6,10-trimethyl-6-dodecenyl ether (**7a**).* To a stirred and cooled (−15 °C) solution of the above compound (1.90 g, 3.24 mmol) in MeOH (7 ml) and THF (14 ml) were added Na_2HPO_4 (1.37 g, 9.72 mmol) and 5% Na/Hg (3.0 g). The mixture was stirred for 1 h at the same temperature and for 30 min at room temperature, and then filtered through a Celite pad. The filtrate was poured into water, and aqueous layer was extracted with AcOEt. The combined organic layer was washed with satd NH_4Cl solution, satd $NaHCO_3$ solution, water and brine. The organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography with AcOEt/hexane (1:90) to give **7a** (1.05 g, 72%) as a colorless oil. $[\alpha]_D^{25}$ −0.8 (*c* 1.2, $CHCl_3$); [Found: C, 75.42; H, 11.22. $C_{28}H_{50}O_2Si$ requires C, 75.27; H, 11.28%]; ν_{max} (liquid film) 2954, 2928, 2856, 1461, 1362, 1254, 1097, 826, 775, 733, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.03 (s, 6H), 0.83 (d, *J*=6.7 Hz, 3H), 0.84 (d, *J*=6.7 Hz, 3H), 0.84 (s, 9H), 0.93–1.09 (m, 1H), 1.25 (m, 1H), 1.26–1.47 (m, 5H), 1.49–1.75 (m, 7H), 1.88–2.01 (m, 3H), 3.34 (dd, *J*=6.7, 9.5 Hz, 1H), 3.43 (dd, *J*=5.9, 9.5 Hz, 1H), 3.50 (m, 2H), 4.48 (d, *J*=12.2 Hz, 1H), 4.51 (d, *J*=12.2 Hz, 1H), 5.09 (dt, *J*=1.1, 7.1 Hz, 1H), 7.25–7.36 (m, 5H); δ_C (100 MHz, $CDCl_3$) −5.3, 15.8, 16.8, 18.4, 19.6, 25.4, 26.0, 29.6, 32.8, 35.7, 36.7, 37.2, 40.0, 68.4, 68.8, 72.9, 124.5, 127.5, 127.6, 128.3, 138.7.

*4.1.5. (2R,6S,7S,10R)-12-Benzyloxy-1-tert-butyldimethylsilyloxy-2,6,10-trimethyldodecane-6,7-diol (**8a**).* To a stirred and cooled (0 °C) solution of **7a** (651 mg, 1.45 mmol) in *t*-BuOH (9 ml) and water (9 ml) were added AD-mix-α® (4.08 g) and metanesulfonamide (415 mg, 3.36 mmol). After stirring for 24 h, $Na_2S_2O_3$ pentahydrate was added to the mixture, which was allowed to warm to room temperature over 1 h. The mixture was extracted with AcOEt, and the combined organic layer was washed with brine. The organic layer was dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography with AcOEt/hexane (1:10) to give **8a** as a colorless oil (545 mg, 77%). $[\alpha]_D^{25}$ −12.2 (*c* 0.97, $CHCl_3$); [Found: C, 69.92; H, 10.62. $C_{28}H_{52}O_4Si$ requires C, 69.95; H, 10.90%]; ν_{max} (liquid film) 3435, 2952, 2929, 2856, 1461, 1362, 1254, 1096, 836, 776, 734, 776, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.03 (s, 6H), 0.86 (d, *J*=6.7 Hz, 3H), 0.88 (s, 9H), 0.90 (d, *J*=6.3 Hz, 3H), 1.02–1.73 (m, 14H), 1.09 (s, 3H), 1.75 (br s, 2H), 3.37 (m, 2H), 3.43 (dd, *J*=5.9, 9.5 Hz, 1H), 3.51 (m, 2H), 4.49 (d, *J*=12.2 Hz, 1H), 4.51 (d, *J*=12.2 Hz, 1H), 7.25–7.36 (m, 5H); δ_C (100 MHz, $CDCl_3$) −5.3, 16.7, 18.4, 19.8, 20.6, 21.0, 26.0, 28.9, 30.1, 33.7, 34.3, 35.7, 36.5, 39.3, 68.4, 68.6, 72.9, 74.9, 77.7, 127.5, 127.7, 128.3, 138.6.

*4.1.6. (2R,6S,7R,10R)-12-Benzyloxy-1-tert-butyldimethylsilyloxy-6,7-epoxy-2,6,10-trimethyldodecane (**9a**).* To a stirred and cooled (0 °C) solution of **8a** (545 mg, 1.13 mmol) in CH_2Cl_2 (5 ml) were added Et_3N (631 μl, 4.54 mmol) and methanesulfonic anhydride (296 mg, 1.70 mmol). After stirring for 3.5 h, the mixture was poured into water. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with satd $NaHCO_3$ solution, water and brine. The organic layer was dried over Na_2SO_4, and concentrated to give a crude mesylate. This was dissolved in MeOH (5 ml), and K_2CO_3 (235 mg, 1.70 mmol) was added to the resulting solution at room temperature. After stirring for 40 min, the mixture was poured into water. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography with AcOEt/hexane (1:75) to give **9a** (345 mg, 65%) as a colorless oil. $[\alpha]_D^{24}$ +5.1 (*c* 1.1, $CHCl_3$); [Found: C, 72.43; H, 10.81. $C_{28}H_{50}O_3Si$ requires C, 72.67; H, 10.89%]; ν_{max} (liquid film) 2955, 2928, 2856, 1462, 1377, 1361, 1252, 1097, 836, 776, 734, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.03 (s, 6H), 0.83 (d, *J*=6.7 Hz, 3H), 0.84 (d, *J*=6.7 Hz, 3H), 0.84 (s, 9H), 1.08 (m, 1H), 1.27 (s, 3H), 1.32–1.73 (m, 13H), 2.67 (t, *J*=5.9 Hz, 1H), 3.36 (dd, *J*=6.3, 9.9 Hz, 1H), 3.44 (dd, *J*=5.9, 9.9 Hz, 1H) 3.51 (m, 2H), 4.48 (d, *J*=12.2 Hz, 1H), 4.51 (d, *J*=12.6 Hz, 1H), 7.25–7.63 (m, 5H); δ_C (100 MHz, $CDCl_3$) −5.3, 16.7, 18.3, 19.5, 22.3, 22.9, 25.9, 26.0, 29.8, 33.1, 33.5, 33.8, 35.7, 36.5, 61.0, 65.0, 68.2, 68.5, 72.9, 127.5, 127.6, 128.3, 138.6.

*4.1.7. (2R,6R,10R)-12-Benzyloxy-1-tert-butyldimethylsilyloxy-2,6,10-trimethyldodecan-6-ol (**10a**).* To a stirred and cooled (0 °C) solution of **9a** (315 mg, 680 μmol) in THF (3 ml) was added Super-hydride® (1.0 M solution in THF, 2.72 ml, 2.72 mmol) under Ar atmosphere. The mixture was warmed to room temperature and stirred for 5.5 h. The reaction was quenched with water (1 ml), and then 5% NaOH solution (2 ml) and 30% H_2O_2 solution (2 ml) were successively added to the mixture. After stirring for 1.5 h, the mixture was diluted with water. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography with AcOEt/hexane (1:20) to give **10a** (291 mg, 91%) as a colorless oil. $[\alpha]_D^{24}$ −0.1 (*c* 1.0, $CHCl_3$); [Found: C, 72.27; H, 11.01. $C_{28}H_{52}O_3Si$ requires C, 72.35; H, 11.28%]; ν_{max} (liquid film) 3459, 2953, 2932, 2903, 2856, 1470, 1462, 1362, 1254, 1097, 836, 776, 735, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.03 (s, 6H), 0.83 (d, *J*=6.7 Hz, 3H), 0.84 (d, *J*=6.7 Hz, 3H), 0.84 (s, 9H), 1.02–1.16 (m, 2H), 1.15 (s, 3H), 1.25–1.46 (m, 12H), 1.56–1.71 (m, 3H), 3.36 (dd, *J*=6.3, 9.9 Hz, 1H), 3.44 (dd, *J*=5.9, 9.9 Hz, 1H) 3.51 (m, 2H), 4.48 (d, *J*=11.8 Hz, 1H), 4.51 (d, *J*=11.2 Hz, 1H), 7.25–7.63 (m, 5H); δ_C (100 MHz, $CDCl_3$) -5.3, 16.7, 18.3, 19.6, 21.2, 21.3, 25.9, 27.0, 29.8, 33.7, 35.7, 36.8, 37.7, 42.1, 42.2, 68.3, 68.7, 72.8, 72.9, 127.5, 127.6, 128.3, 138.7.

4.1.8. (3R,7R,11R)-12-tert-Butyldimethylsilyloxy-3,7,11-trimethyldodecane-1,7-diol. Lithium (43.5 mg, 6.27 mmol) was added to liquid NH_3 (3 ml) at −78 °C. After stirring for 30 min below −40 °C, a solution of **10a** (291 mg, 620 μmol) in THF (3 ml) was added dropwise. After stirring for 1 h, the reaction was quenched with NH_4Cl. Then NH_3 was removed by gentle warming, and the residue was diluted with water. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography with AcOEt/hexane (1:5) to give the *title compound* (231 mg, 98%) as a colorless oil. $[\alpha]_D^{23}$ −0.5 (*c* 1.0, $CHCl_3$); [Found: C, 67.12; H, 12.30. $C_{21}H_{46}O_3Si$ requires C, 67.32; H, 12.37%]; ν_{max} (liquid film) 3349, 2952, 2933, 2902, 2857, 1470, 1462, 1375, 1254, 1096, 1062, 836, 775 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.03 (s, 6H), 0.86 (d, *J*=6.7 Hz, 3H), 0.88 (s, 9H), 0.90 (d, *J*=6.3 Hz, 3H), 1.06 (m, 2H), 1.24–1.44 (m, 13H), 1.26 (s, 3H), 1.61 (m, 3H), 3.36 (dd, *J*=6.3, 9.5 Hz, 1H), 3.43 (dd, *J*=5.9, 9.5 Hz, 1H), 3.67 (m, 2H); δ_C (100 MHz, $CDCl_3$) −5.4, 16.7, 18.3, 19.6, 21.2, 21.3, 25.9, 27.0, 29.4, 33.7, 35.7, 37.6, 39.9, 42.0, 42.2, 61.1, 68.4, 72.8.

*4.1.9. (2R,6R,10R)-1-tert-Butyldimethylsilyloxy-12-phenylsulfonyl-2,6,10-trimethyldodecan-6-ol (**12a**).* To a stirred and cooled (0 °C) solution of the above compound (217 mg, 580 μmol) in pyridine (2.5 ml) was added *p*-toluenesulfonyl chloride (132 mg, 690 μmol). After stirring for 4 h, the reaction was quenched with water. The aqueous layer was extracted with ether, and the combined organic layer was washed with satd $CuSO_4$ solution, water, and brine. The organic layer was dried over Na_2SO_4, and concentrated to give crude tosylate. This was dissolved in acetone (2.5 ml), and then NaI (130 mg, 870 μmol) was added to the resulting solution at room temperature. After stirring for 3.5 h under reflux condition, the

reaction mixture was poured into water. The aqueous layer was extracted with ether, and the combined organic layer was washed with satd $NaHCO_3$ solution, water and brine. The organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography with AcOEt/hexane (1:50) to give the corresponding iodide (180 mg). This was dissolved in DMF (2 ml), and to the resulting solution was added benzensulfinic acid sodium salt dihydrate (297 mg, 1.48 mmol). After stirring for 6 h, the mixture was poured into water. The aqueous layer was extracted with ether, and combined organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography with AcOEt/hexane (1:10) to give **12a** (171 mg, 59% for three steps) as a colorless oil. $[\alpha]_D^{24}$ −3.7 (*c* 1.0, $CHCl_3$); [Found: C, 64.72; H, 9.90. $C_{27}H_{50}O_4SSi$ requires C, 65.01; H, 10.10%]; ν_{max} (liquid film) 3541, 2953, 2934, 2902, 2857, 1470, 1463, 1447, 1306, 1252, 1148, 1087, 837, 776, 742, 689 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.02 (s, 6H), 0.84 (d, *J*=6.3 Hz, 3H), 0.86 (d, *J*=6.3 Hz, 3H), 0.88 (s, 9H), 0.96–1.73 (m, 17H), 1.12 (s, 3H), 3.07 (m, 2H), 3.36 (dd, *J*=6.5, 9.5 Hz, 1H), 3.42 (dd, *J*=5.9, 9.5 Hz, 1H), 7.56 (m, 2H), 7.65 (m, 1H), 7.90 (d, *J*=1.1, 8.3 Hz, 2H); δ_C (100 MHz, $CDCl_3$) −5.3, 16.7, 18.3, 19.1, 21.0, 21.3, 25.9, 26.9, 29.2, 31.9, 33.7, 35.7, 36.9, 41.9, 42.3, 54.4, 68.3, 72.6, 128.0, 129.2, 133.6, 139.2.

4.1.10. (2R,6R,10R,14E)-1,16-Bis-(tert-butyldimethylsilyloxy)-12-phenylsulfonyl-2,6,10,14-tetramethyl-14-hexadecen-6-ol. To a stirred and cooled (−78 °C) solution of **12a** (155 mg, 310 μmol) in THF (1.5 ml) and HMPA (0.15 ml) was added *n*-BuLi (1.65 M solution in hexane, 430 μl, 710 μmol) under Ar atmosphere. After stirring for 30 min, a solution of **13** (112 mg, 400 μmol) in THF (1 ml) was added. After stirring for 2.5 h, the mixture was warmed to 0 °C and poured into water. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with satd $NaHCO_3$ solution, water and brine. The organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography with AcOEt/hexane (1:15) to give the *title compound* (191 mg, 88%) as a colorless oil. $[\alpha]_D^{25}$ −6.3 (*c* 1.0, $CHCl_3$); [Found: C, 65.69; H, 10.22. $C_{38}H_{72}O_5SSi$ requires C, 65.46; H, 10.41%]; ν_{max} (liquid film) 3532, 2931, 2856, 1470, 1462, 1385, 1360, 1304, 1254, 1146, 1086, 1006, 836, 813, 776, 733, 691, 666, 605 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.03 (m, 12H), 0.75–0.89 (m, 24H), 0.95–2.11 (m, 24H), 2.61 (m, 1H), 3.14 (m, 1H), 3.34–3.39 (m, 1H), 3.41–3.46 (m, 1H), 4.10 (m, 2H), 5.31 (m, 1H), 7.56 (m, 2H), 7.64 (m, 1H), 7.87 (m, 2H); δ_C (100 MHz, $CDCl_3$) −5.4, −5.2, 15.3, 15.8, 15.9, 16.7, 18.3, 18.4, 19.25 19.30, 21.0, 21.3, 25.9, 26.0, 26.9, 30.3, 30.5, 33.8, 35.5, 35.8, 36.0, 37.3, 37.5, 39.8, 40.2, 42.0, 42.1, 42.3, 59.9, 60.0, 60.2, 60.3, 65.8, 68.4, 72.7, 129.0, 129.1, 129.4, 131.2, 131.5, 133.55, 133.58, 137.9.

*4.1.11. (2R,6R,10S,14E)-1,16-Bis-(tert-butyldimethylsilyloxy)-2,6,10,14-tetramethyl-14-hexadecen-6-ol (**14a**).* To a stirred and cooled (−15 °C) solution of the above compound (168 mg, 240 μmol) in THF (1.2 ml) and MeOH (0.6 ml) were added Na_2HPO_4 (102 mg, 720 μmol) and 5% Na/Hg (350 mg). After stirring for 2.5 h, the mixture was filtered through a Celite pad and poured into water. The aqueous layer was extracted with AcOEt, and the combined organic layers were washed with satd $NaHCO_3$ solution, water, and brine. The organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography with AcOEt/hexane (1:30) to give the product (108 mg). This was further purified with $AgNO_3$-impregnated silica gel column chromatography with AcOEt/hexane (1:50) to give **14a** (87 mg, 64%) as a colorless oil. $[\alpha]_D^{27}$ −2.1 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3388, 2931, 2857, 1462, 1377, 1361, 1253, 1095, 1063, 938, 916, 835, 775, 666 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.03 (s, 6H), 0.06 (s, 6H), 0.85 (d, *J*=6.3 Hz, 3H), 0.87 (d, *J*=6.3 Hz, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 1.04–1.12 (m, 3H), 1.15 (s, 3H), 1.20–1.48 (m, 15H), 1.54–1.63 (m, 1H), 1.60 (s, 3H), 1.96 (m, 2H), 3.36 (dd, *J*=6.3, 9.7 Hz, 1H), 3.43 (dd, *J*=5.9, 9.7 Hz, 1H), 4.18 (d, *J*=6.4 Hz, 2H), 5.28 (br t, *J*=6.3 Hz, 1H); δ_C (100 MHz, $CDCl_3$) −5.4, −5.0, 16.3, 16.7, 18.35, 18.44, 19.6, 21.3, 21.4, 25.1, 25.96, 26.04, 27.0, 32.7, 33.8, 35.7, 36.7, 37.6, 39.8, 42.22, 42.24, 60.3, 68.4, 72.8, 124.2, 137.3; HRMS (ESI): MNa^+, found 579.4597. $C_{32}H_{68}O_3Si_2Na$ requires 579.4599.

*4.1.12. (7S,11R,15R)-α2 (**2a**).* To a stirred and cooled (0 °C) solution of **14a** (84 mg, 0.15 mmol) in THF (0.9 ml) was added TBAF (1.0 M solution in THF, 0.60 ml, 0.60 mmol). After stirring for 7 h, the reaction mixture was poured into water. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with brine. The organic layer was dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography with AcOEt/hexane (1:1) to give (7*S*,11*R*,15*R*)-α2 (**2a**) (43 mg, 87%) as a colorless oil. $[\alpha]_D^{24}$ −6.0 (*c* 1.0, $CHCl_3$), lit.[15]; $[\alpha]_D$ −5 ($CHCl_3$); ν_{max} (liquid film) 3346 (br), 2935, 2868, 1742, 1725, 1669, 1462, 1375, 1242, 1042, 1012, 755 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.84 (d, *J*=6.3 Hz, 3H), 0.90 (d, *J*=6.7 Hz, 3H), 1.01–1.13 (m, 3H), 1.14 (s, 3H), 1.21–1.45 (m, 14H), 1.58–1.62 (m, 1H), 1.64 (s, 3H), 1.80 (br s, 3H), 1.96 (t, *J*=7.5 Hz, 2H), 3.40 (dd, *J*=6.3, 10.5 Hz, 1H), 3.46 (dd, *J*=5.9, 10.5 Hz, 1H), 4.11 (d, *J*=6.7 Hz, 2H), 5.37 (tq, *J*=6.7, 1.1 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 16.1, 16.6, 19.7, 21.15, 21.23, 24.9, 26.9, 32.4, 33.7, 35.6, 36.2, 37.4, 39.6, 41.9, 42.1, 59.2, 68.1, 72.8, 123.3, 139.7; HRMS (ESI): MNa^+, found 351.2879. $C_{20}H_{40}O_3Na$ requires 351.2870. The ^1H and ^{13}C NMR spectra were identical with those of the natural α2. Diastereomers, (7*R*,11*R*,15*R*)-, (7*S*,11*S*,15*R*)-, and (7*R*,11*S*,15*R*)-α2, were successively synthesized in a similar fashion.

*4.1.13. Properties of (7R,11R,15R)-α2 (**2b**).* $[\alpha]_D^{24}$ −5.2 (*c* 0.5, $CHCl_3$); HRMS (ESI): MNa^+, found 351.2842. $C_{20}H_{40}O_3Na$ requires 351.2870. The ^1H and ^{13}C NMR spectra, and IR spectrum were indistinguishable with those of (7*S*,11*R*,15*R*)-α2.

*4.1.14. Properties of (7S,11S,15R)-α2 (**2c**).* $[\alpha]_D^{23}$ −5.0 (*c* 1.0, $CHCl_3$); HRMS (ESI): MNa^+, found 351.2851. $C_{20}H_{40}O_3Na$ requires 351.2870. The ^1H and ^{13}C NMR spectra, and IR spectrum were indistinguishable with those of (7*S*,11*R*,15*R*)-α2.

*4.1.15. Properties of (7R,11S,15R)-α2 (**2d**).* $[\alpha]_D^{25}$ −4.3 (*c* 1.0, $CHCl_3$); HRMS (ESI): MNa^+, found 351.2842. $C_{20}H_{40}O_3Na$ requires 351.2870. The ^1H and ^{13}C NMR spectra, and IR spectrum were indistinguishable with those of (7*S*,11*R*,15*R*)-α2.

4.1.16. 4-tert-Butyldiphenylsilyloxy-2-methyl-1-butene. To a stirred solution of **16** (200 mg, 2.33 mmol) in DMF (2 ml) were added imidazole (317 mg, 4.66 mmol) and *tert*-butyldiphenylchlorosilane (650 μl, 4.66 mmol). After stirring for 6 h, the mixture was poured into water. The aqueous layer was extracted with hexane, and the combined organic layer was washed with water and brine, and dried over $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography with hexane to give the *title compound* (742 mg, 98%) as a colorless oil. [Found: C, 77.53; H, 8.07. $C_{21}H_{28}OSi$ requires C, 77.72; H, 8.70%]; ν_{max} (liquid film) 3071, 2930, 1651, 1472, 1428, 1111 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.04 (s, 9H), 1.68 (s, 3H), 2.28 (t, *J*=6.9 Hz, 2H), 3.76 (t, *J*=6.9 Hz, 2H), 4.68 (s, 1H), 4.74 (s, 1H), 7.36–7.44 (m, 6H), 7.66–7.73 (m, 4H); δ_C (100 MHz, $CDCl_3$) 19.2, 22.7, 26.8, 40.9, 62.8, 111.7, 127.6, 129.5, 134.0, 135.6, 143.0.

4.1.17. 4-tert-Butyldiphenylsilyloxy-2-methylbutan-1-ol. To a stirred and cooled (0 °C) solution of the above compound (1.00 g, 3.09 mmol) in THF (8 ml) was added 9-BBN (0.5 M, in THF, 18.5 ml, 9.26 mmol) under Ar atmosphere. After stirring for 6 h at room temperature, the mixture was cooled to 0 °C, and 6 N NaOH (8.18 ml) and 30% H_2O_2 (9.57 ml) were added to the mixture. After stirring for 4 h at room temperature, the mixture was extracted

with ether. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography with AcOEt/hexane (1:20) to give the *title compound* (1.01 g, 95%) as a colorless oil. [Found: C, 73.34; H, 8.66. $C_{21}H_{30}O_2Si$ requires C, 73.63; H, 8.83%]; ν_{max} (liquid film) 3371 (br), 3071, 2928, 2858, 1472, 1428, 1390, 1112, 703 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.90 (d, *J*=6.9 Hz, 3H), 1.05 (s, 9H), 1.50 (m, 1H), 1.62 (m, 1H), 1.85 (s×t, *J*=6.9 Hz, 1H), 3.48 (dd, *J*=6.9, 11.0 Hz, 1H), 3.50 (m, 2H), 3.67–3.79 (m, 2H), 7.37–7.46 (m, 6H), 7.66–7.69 (m, 4H); δ_C (100 MHz, $CDCl_3$) 17.1, 19.1, 26.8, 33.9, 36.8, 62.5, 68.3, 127.7, 129.7, 133.5, 133.6.

*4.1.18. 4-tert-Butyldiphenylsilyloxy-2-methylbutanal (**17**).* To a stirred solution of the above compound (1.03 g, 3.01 mmol) in CH_2Cl_2 (10 ml) were added powdered MS4 Å (1.0 g) and PCC (1.30 g, 6.02 mmol) at room temperature. After stirring for 3 h, the mixture was diluted with ether. The mixture was filtered through a silica gel pad, and the silica gel pad was rinsed with ether. After concentration in vacuo, the residue was purified by column chromatography with AcOEt/hexane (1:20) to give **17** (873 mg, 87%) as a colorless oil. [Found: C, 74.07; H, 8.18. $C_{21}H_{28}O_2Si$ requires C, 74.07; H, 8.29%]; ν_{max} (liquid film) 3071, 2930, 1708, 1472, 1428, 1112, 1048 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.04 (s, 9H), 1.08 (d, *J*=6.9 Hz, 3H), 1.62 (m, 1H), 2.01 (m, 1H), 2.58 (m, 1H), 3.66–3.77 (m, 2H), 7.36–7.45 (m, 6H), 7.63–7.67 (m, 4H), 9.68 (d, *J*=1.4 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 13.1, 19.1, 26.8, 33.4, 43.5, 61.1, 127.7, 129.7, 133.5, 135.5, 204.9.

4.1.19. (3RS,5RS,7R,11R,15R)-16-tert-Butyldimethylsilyloxy-1-tert-butyldiphenylsilyloxy-11-hydroxy-5-phenylsulfonyl-3,7,11,15-tetramethyl-4-hexadecanone. To a stirred and cooled (−78 °C) solution of **12a** (400 mg, 803 μmol) in THF (4 ml) was added *n*-BuLi (1.63 M solution in hexane, 1.08 ml, 1.77 mmol) under Ar atmosphere. After stirring for 30 min, a solution of **17** (328 mg, 964 μmol) in THF (3 ml) was added. The mixture was gradually warmed to −20 °C for 1.5 h and poured into water. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with water and brine. The organic layer was dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography with AcOEt/hexane (1:8) to give the coupled product as a stereoisomeric mixture (658 mg). This was dissolved in CH_2Cl_2 (10 ml), and to a stirred and cooled (0 °C) solution were added $NaHCO_3$ (500 mg) and Dess–Martin periodinane (511 mg, 1.20 mmol). After stirring for 30 min at the same temperature and for 30 min at room temperature, the mixture was poured into water. The aqueous layer was extracted with ether, and the combined organic layer was washed with satd $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography with AcOEt/hexane (1:5) to give the titled product as a stereoisomeric mixture (541 mg, 81% for two steps). $[\alpha]_D^{24}$ +6.3 (*c* 0.92, $CHCl_3$); ν_{max} (liquid film) 3565, 3072, 2934, 2855, 1716, 1471, 1321, 1255, 1112, 1007, 836, 776, 704 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.03–0.04 (m, 6H), 0.82–0.89 (m, 21H), 1.00–2.15 (m, 28H), 3.18 (m, 1H), 3.37 (m, 1H), 3.42 (m, 1H), 3.70 (m, 2H), 4.40 (m, 1H), 7.32–7.78 (m, 15H); HRMS (ESI): MNa^+, found 859.47800. $C_{48}H_{76}O_6SSi_2Na$ requires 859.47988.

*4.1.20. (3RS,7R,11R,15R)-16-tert-Butyldimethylsilyloxy-1-tert-butyldiphenylsilyloxy-11-hydroxy-3,7,11,15-tetramethyl-4-hexadecanone (**18**).* To a stirred solution of the above compound (187 mg, 224 μmol) in THF (2 ml) was added portionwise Al/Hg (prepared from 400 mg of Al foil with 2% $HgCl_2$ solution). After stirring for 2 h at 70 °C, the mixture was cooled and filtered through a Celite pad, and the filtrate was concentrated. The residue was purified by flash chromatography with AcOEt/hexane (1:15) to give **18** as a colorless oil (97 mg, 62%). Further elution with AcOEt/hexane (1:5) gave 52 mg of the starting material. $[\alpha]_D^{24}$ −0.02 (*c* 0.85, $CHCl_3$); ν_{max} (liquid film) 3502, 3070, 2932, 2861, 1712, 1462, 1389, 1255, 1112, 837, 775, 703 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.03 (s, 6H), 0.86 (d, *J*=6.3 Hz, 3H), 0.87 (d, *J*=6.3 Hz, 3H), 0.89 (s, 9H), 1.05 (d, *J*=6.3 Hz, 3H), 1.06 (s, 9H), 1.15 (s, 3H), 1.20–1.48 (m, 14H), 1.54–1.63 (m, 4H), 1.96 (m, 1H), 2.44 (m, 2H), 2.81 (m, 1H), 3.37 (dd, *J*=6.3, 9.9 Hz, 1H), 3.42 (dd, *J*=5.9, 9.9 Hz, 1H), 3.65 (t, *J*=6.2 Hz, 2H), 7.36–7.44 (m, 6H), 7.63–7.66 (m, 4H); δ_C (100 MHz, $CDCl_3$) −5.4, 16.33, 16.35 16.7, 18.3, 19.2, 19.32, 19.33 21.21, 21.23, 21.27, 25.9, 26.8, 26.9, 30.7, 32.5, 33.7, 35.4, 35.5, 35.7, 37.39, 37.43, 39.0, 39.1, 42.2, 42.54, 42.57, 61.6, 68.3, 72.7, 127.6, 129.6, 133.67, 133.72, 135.5, 214.79, 214.81; HRMS (ESI): MNa^+, found 719.48850. $C_{42}H_{72}O_4Si_2Na$ requires 719.48668.

*4.1.21. (3RS,7S,11R,15R)-α1 (**1**).* To a stirred solution of **18** (30 mg, 43 μmol) in THF (0.5 ml) was added TBAF (1.0 M solution in THF, 0.17 ml, 0.17 mmol). After stirring for 3 h, the reaction mixture was poured into water. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with brine. The organic layer was dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography with AcOEt/hexane (3:1) to give (3*RS*,7*S*,11*R*,15*R*)-α1 (15 mg, quant.) as a colorless oil. $[\alpha]_D^{24}$ +5.4 (*c* 0.3, MeOH); ν_{max} (liquid film) 3375, 2936, 2870, 1704, 1462, 1406, 1377, 1152, 1052, 918, 736 cm^{-1}; δ_H (400 MHz, CD_3OD) 0.89 (d, *J*=6.4 Hz, 3H), 0.91 (d, *J*=6.8 Hz, 3H), 1.07 (d, *J*=6.8 Hz, 3H), 1.10–1.65 (m, 15H), 1.12 (s, 3H), 1.89 (s×t, *J*=6.8 Hz, 1H), 2.53 (m, 2H), 2.76 (s×t, *J*=6.8 Hz, 1H), 3.33 (m, 1H), 3.41 (dd, *J*=6.6, 10.7 Hz, 1H), 3.52 (t, *J*=6.6 Hz, 2H); δ_C (100 MHz, CD_3OD) 16.9, 17.1, 19.88, 19.90, 22.3, 22.4, 26.9, 31.7, 33.6, 35.0, 36.71, 36.75, 36.9, 38.6, 40.0, 43.0, 44.0, 60.6, 68.4, 73.4, 217.48, 217.50; HRMS (ESI): MNa^+, found 367.2827. $C_{20}H_{40}O_4Na$ requires 367.2824. The ^1H and ^{13}C NMR spectra were in good accord with those of the natural α1.[9]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.066.

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