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Stereoselective Synthesis of Tetrahydropyran *D*-Ring of Methyl Sartortuoate

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A stereoselective synthesis of functionalized tetrahydropyran *D*-ring of methyl sartortuoate (**1**) was achieved starting from geraniol in a high yield. Sharpless asymmetric kinetic resolution, asymmetric dihydroxylation as well as asymmetric epoxidation were applied as key steps to establish all the four stereocenters of the *D*-ring.

Keywords methyl sartortuoate, stereoselective synthesis, Sharpless asymmetric kinetic resolution, Sharpless asymmetric dihydroxylation, Sharpless asymmetric epoxidation

Introduction

Methyl sartortuoate (**1**) and methyl isosartortuoate (**2**), two representative members of the structurally novel class of biscembranoids, were isolated from the marine *Sarcophyton tortuosum tixierduriant* by Su *et al*.[1,2] (Figure 1). The relative configurations of **1** and **2** were elucidated by extensive NMR studies and their absolute stereochemistry was supported by X-ray analysis.[1] A preliminary bioassay proved that both of them displayed inhibitory effects against mouse S180 and cytotoxic activities towards KB cells.[1] It was hypothesized that **1** and **2** were formed by a biosynthetic Diels-Alder reaction of two cembrenanes as the precursors. This hypothesis could be supported by the isolation of methyl sarcoate (**4**), a dienophile unit of methyl sarcophytoate (**3**), although none of such precursors of **1** and **2** has been isolated to date.[2] Recently, Nakata *et al*.[3] reported an elegant total synthesis of methyl sarcophytoate by an intermolecular Diels-Alder reaction, as well as the asymmetric syntheses of both the diene unit and the dienophile unit of **3**. For a long term concern, we[4] initiated the total synthesis of **1** and **2** in order to investigate the potential bioactivity and the intriguing structural features as well as the interesting biogenetic possibility of them. Previously, we reported the asymmetric synthesis of the dienophile unit of **1** and **2** and the diene init of **1**. Herein, we wish to describe an efficient synthesis of the diene unit of **1**, which is necessary for the completion of the total synthesis of **1**.

Results and discussion

Although we have reported the synthesis of **6** from geraniol,[4d] its total yield was pretty low, which hampered our synthetic game. As shown in Scheme 1, we envisaged that **1** could be formed from D-A reaction from dienophile unit and diene unit **5**, which, in turn, was synthesized from the key intermediate tetrahydropyran *D*-ring **6**. Based on the retrosynthesis, a Sharpless asymmetric kinetic resolution of racemic allylic alcohol **8** available from geraniol furnished optically active epoxide **9** in over 40% yield in 94% *ee* (HPLC),[5] which was subsequently protected with TESCl to give ether **10**. Then the conversion of epoxide of **10** to vicinal diol that we previously described using modified Marshall's method with a sulfone-stablized allylic anion provided

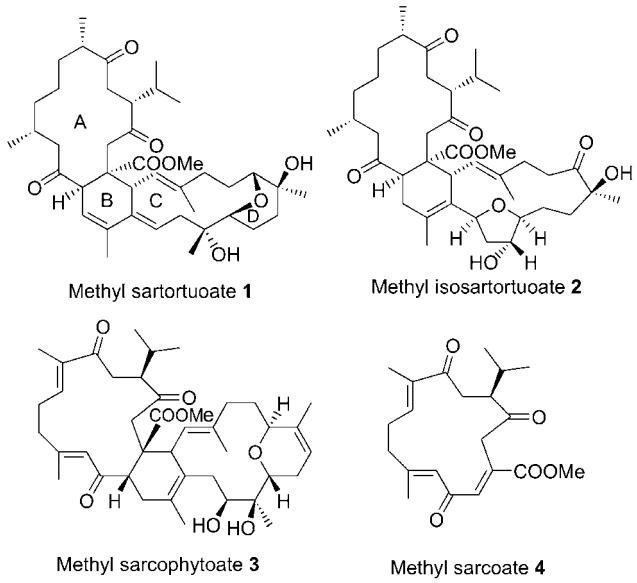

Figure 1 The structures of selected biscembranoids **1**—**3** and methyl sarcoate **4**.

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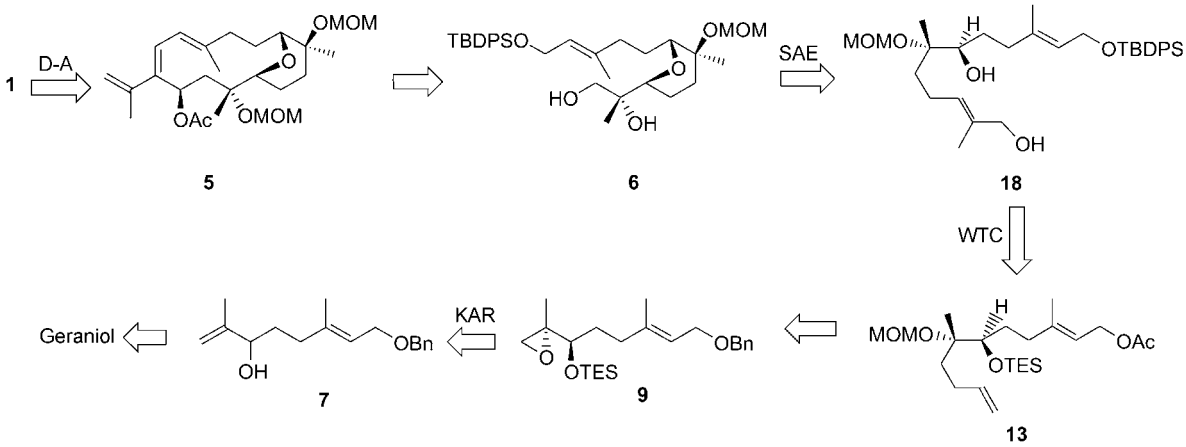
Scheme 1



the desired tertiary alcohol in a decent yield. However, the subsequent allylic oxidation with SeO_2 only gave allylic alohol in a very poor yield with numerous side products. Thus, many nuclephilic reagents such as $LiCH_2CN$,[6] $NaCH(COOEt)_2$,[7] allylic metallic reagent[8] were screened and tested to open epoxide **9**, but it was found that the former two methods failed to give the desired products. Satisfyingly, success was realized when we treated **10** with allylic magnesium chloride in anhydrous THF at 40 ℃ for 4 h leading to tertiary alcohol **11** in an almost quantitative yield with no trace of chloride addition side product. It was noteworthy that Cu(I) catalyst was unnecessary for this step. Subsequent protection of the tertiary hydroxyl group with MOMCl of **11** afforded ether **12**. To extend the left chain, regioselective dihydroxylation at the terminal double bond in the presence of a trisubstituted double bond was performed in advance. On the basis of the electron-withdrawing effect of the allylic substituent, a preference for dihydroxylation at the remote double bond under Sharpless asymmetric dihydroxylation condition was anticipated when the allylic alchohol was protected with acetyl group. Accordingly, removal of the benzyl group with lithium naphthalenide gave allylic alcohol **13**, which was subsequently derived to acetate **14**. Indeed, the dihydroxylation of acetate **14** under the standard condition (*i.e.* *t*-BuOH/H_2O, $V:V=1:1$, 0 ℃, 24 h)[5] in the presence of $(DHQD)_2PYR$ suppressed oxidation of the tri-substituted double bond giving the 1,2-diol (**15**) as a major product. This volume ratio was further increased to over 10 ∶ 1 when $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$ was used, while a 3 ∶ 1 mixture was achieved by direct dihydroxylation of **13** in the absence of chiral ligand. Treatment of diol with $NaIO_4$ in THF/H_2O gave rise to aldehyde, and subsequent coupling with $Ph_3P=C(CH_3)COOEt$ in toluene afforded conjugated ester (**18**) (*trans* ∶ *cis* > 95 ∶ 5). Saponification of acetyl group, silylation of primary hydroxyl group with TBDPSCl, and reduction with DIBAL-H provided allylic alcohol (**17**), which was then selectively desilylated with PPTs/MeOH at 0 ℃ affording diol (**18**). Finally, Sharpless asymmetric epoxidation of **18** smoothly produced the desired tetrahydropyran *D*-ring (**7**) whose relative configuration was determined by a 2D-NOESY technique (Scheme 2).[5,9]

Conclusion

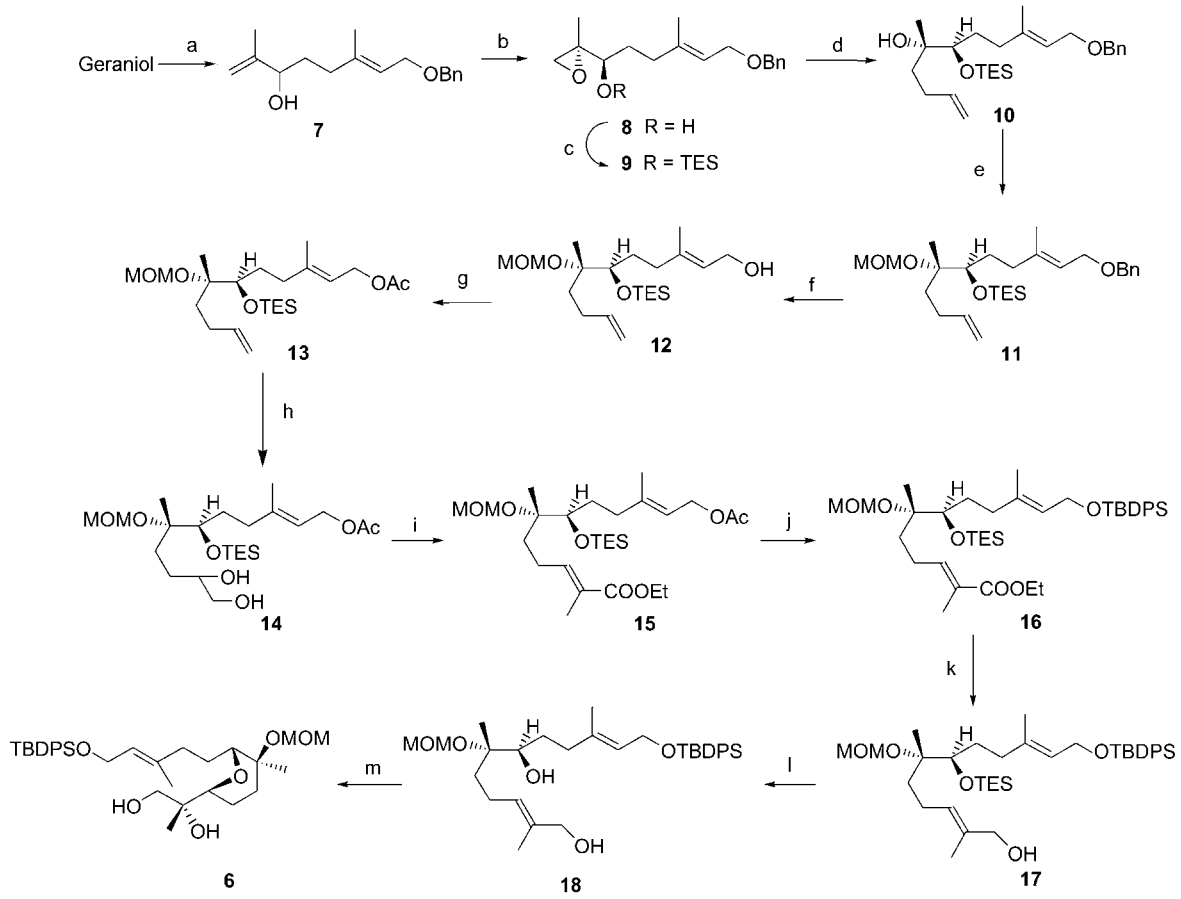
In summary, an efficient asymmetric synthesis of 14-membered diene unit, required for the total synthesis of methyl sartortuoate, has been accomplished from geraniol. The total yield was increased to over 12%, while that of our previous synthetic route was only 4.0%. The synthesis is highlighted by using Sharpless asymmetric kinetic resolution, dihydroxylation and epoxidation to establish all the four stereocenters of the diene unit in a relatively high yield, which paved a way to the completion of the total synthesis of methyl sartortuoate. Further application of **6** to the total synthesis of methyl sartortuoate by a Diels-Alder reaction is in progress and will be reported in due course.

Experimental

General methods Unless stated otherwise, all reactions were carried out in dried glassware under a dry argon atmosphere. All solvents were purified and dried prior to use. Flash chromatography was performed on silica gel H (400 mesh). Optical rotations were measured on a precision automated polarimeter. Infrared spectra were recorded on an FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are reported as δ values relative to internal chloroform (δ 7.26 for ^1H and 77.0 for ^{13}C NMR). Elemental analyses, ESI-MS and ESI-HRMS were carried out at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

(*R*,*E*)-6-(Benzyloxy)-4-methyl-1-[(*S*)-2-methyloxiran-2-yl]hex-4-en-1-ol (8) To a solution of **7** (13.0 g, 50 mmol) in CH_2Cl_2 (250 mL) were added molecular sieves (4 Å, 2 g) under argon. The solution was cooled to −25 ℃ and to this solution was added *D*-(−) DIPT (1.4 mL, 0.55 mmol) and $(i\text{-PrO})_4Ti$ (1.5 mL, 0.52 mmol). After stirring at −25 ℃ for 30 min, a solution of

Scheme 2



(a) Ref. 4e; (b) *D*-(—) DIPT, (*i*-PrO)$_4$Ti, TBHP, 4 Å MS, −20 ℃, 40%; (c) TESCl, NEt$_3$, DMAP, CH_2Cl_2, r.t., 98%; (d) allylic magnesium chloride, THF, 40 ℃, 4 h, 98%; (e) MOMCl, DIPEA, KI, DMAP, CH_2Cl_2, reflux, 6 h, 98%; (f) Li-naphthalenide, THF, 0 ℃, 80%; (g) Ac_2O, NEt$_3$, DMAP, CH_2Cl_2, r.t., 95%; (h) $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, *t*-BuOH-H_2O, 0 ℃, 24 h; (i) $NaIO_4$, THF-H_2O, r.t., then $Ph_3P{=}C(CH_3)COOEt$, toluene, > 95:5 (*trans*:*cis*), 69% (for 3 steps); (j) K_2CO_3, EtOH, r.t.; then TBDPSCl, NEt$_3$, DMAP, CH_2Cl_2, r.t., 96%; (k) DIBAL-H, THF, −78 ℃, 97%; (l) PPTS, MeOH, 0 ℃, 24 h, 92%; (m) *D*-(−)DIPT, (*i*-PrO)$_4$Ti, TBHP, 4 Å, MS, −20 ℃, 2 h, 84%.

freshly prepared TBHP in CH_2Cl_2 (5.5 mL, 37 mmol) was added. The reaction mixture was stirred at −25 ℃ for 6 h and quenched with a solution of $FeSO_4$/tartaric acid. After stirring the mixture for 30 min at 0 ℃, the organic layer was separated and the aqueous layer was extracted with ether (100 mL×3). The combined organic layers were treated with 100 mL of 30% NaOH/brine at 0 ℃ for 30 min. The organic layer was separated and the aqueous layer was extracted with ether (50 mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **8** (5.7 g, 40%, 94% *ee*) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.34 (s, 3H), 1.67 (s, 3H), 1.45—1.80 (m, 2H), 2.11—2.30 (m, 3H), 2.61 (d, J=4.8 Hz, 1H), 2.90 (d, J=4.8 Hz, 1H), 3.64 (d, 1H), 4.03 (d, J=6.9 Hz, 2H), 4.51 (s, 2H), 5.44 (t, J=6.6 Hz, 1H), 7.31—7.47 (m, 5H).

(*R*,*E*)-1-Benzyl-3-methyl-6-[(*S*)-2-methyloxiran-2-yl]-6-(triethylsilyloxy)hex-2-en-1-ol (9) To a solution of **8** (20 g, 47 mmol) and DMAP (480 mg, 4.0 mmol) in CH_2Cl_2 (200 mL) were added NEt$_3$ (10 mL, 73 mmol) and TESCl (8.6 mL, 52 mmol) at 0 ℃. The resulting mixture was stirred for 2 h at room temperature and quenched with saturated NH_4Cl and the organic layer was separated. The aqueous phase was extracted with Et_2O (100 mL×3). The combined organic layers were washed with 1 mol•L^{-1} HCl (aq.) (50 mL×2), saturated $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography to afford **9** (27.7 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ +1.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.58 (q, J=7.8 Hz, 6 H), 0.95 (t, J=7.8 Hz, 9H), 1.29 (s, 3H), 1.74 (s, 3H), 1.61—1.80 (m, 2H), 2.01—2.20 (m, 2H), 2.58 (d, J=4.8 Hz, 1H), 2.68 (d, J=4.8 Hz, 1H), 3.24—3.28 (m, 1H), 4.03 (d, J=6.6 Hz, 2H), 4.51 (s, 2H), 5.43 (t, J=6.6 Hz, 1H), 7.26—7.36 (m, 5H); IR (film) ν: 2995, 2877, 1455, 1116, 1076, 740 cm^{-1}; EI-MS (70 eV) *m*/*z* (%): 391 (M+H$^+$, 2), 359 (5). Anal. calcd for $C_{23}H_{38}O_3Si$: C 71.02, H 10.00; found C 70.72, H 9.81.

(5*S*,6*R*,*E*)-11-(Benzyloxy)-6-(triethylsilyloxy)-5,9-dimethylundeca-1,9-dien-5-ol (10) To a solution of **9** (27.0 g, 69.0 mmol) in anhydrous THF (200 mL) was added 100 mL of Grinard reagent (2.0 mol•L^{-1}, 200 mmol) at 0 ℃. The resulting mixture was warmed to 40 ℃. After being stirred for additional 2 h, the reaction mixture was diluted with 200 mL of ethyl ether and quenched with 200 mL of 1 mol•L^{-1} NH_4Cl (aq.). The organic layer was separated and the aqueous phase was extracted with Et_2O (200 mL×3). The combined organic layers were washed with 1 mol•L^{-1} HCl (50 mL ×2), saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography to afford **10** (29.3 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ +2.0 (*c* 1.0, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.58 (q, *J*=7.5 Hz, 6H), 0.98 (t, *J*=7.5 Hz, 9H), 1.12 (s, 3H), 1.65 (s, 3H), 1.40—1.70 (m, 4H), 1.95—2.30 (m, 4H), 3.46—3.50 (m, 1H), 4.02 (d, *J*=6.9 Hz, 2H), 4.51 (s, 2H), 4.93—5.08 (m, 2H), 5.41 (d, *J*=6.9 Hz, 1H), 5.79—5.92 (m, 1H), 7.26—7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 5.41, 6.99, 16.58, 23.56, 27.77, 31.08, 35.51, 36.85, 66.51, 72.10, 74.48, 79.87, 114.15, 120.73, 127.45, 127.75, 128.28, 138.41, 139.19, 140.40; IR (film) *v*: 3476, 2956, 2914, 2877, 1641, 1455, 1097, 1006, 738 cm^{-1}; ESI-MS *m*/*z*: 450.3 ($M+NH_4^+$), 455.3 ($M+Na^+$). Anal. calcd for $C_{26}H_{44}O_3Si$: C 72.17, H 10.25; found C 72.03, H 10.12.

(6*R*,7*S*,*E*)-1-Benzyl-6-(triethylsilyloxy)-7-(methoxymethoxy)-3,7-dimethylundeca-2,10-dien-1-ol (11) To a solution of **10** (55.5 g, 130 mmol) in anhydrous CH_2Cl_2 (250 mL) was added DIPEA (85 mL, 490 mmol), DMAP (420 mg, 3.5 mmol) and KI (800 mg, 5.0 mmol). The reaction mixture was cooled to 0 ℃, to which MOMCl (22 mL, 300 mmol) was added dropwise. After being stirred for 20 min at this temperature, the reaction mixture was refluxed for 8 h and cooled to r.t. The resulting mixture was quenched with saturated NH_4Cl and the organic layer was separated. The aqueous phase was extracted with Et_2O (300 mL×3). The combined organic layers were washed with 1 mol•L^{-1} HCl (aq.) (100 mL×2), saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography to yield ether **11** (60.0 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ +2.2 (*c* 1.0, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.61 (q, *J*=7.8 Hz, 6H), 0.96 (t, *J*=7.8 Hz, 9H), 1.18 (s, 3H), 1.66 (s, 3H), 1.40—1.90 (m, 4H), 1.95—2.30 (m, 4H), 3.36 (s, 3H), 3.52—3.56 (m, 1H), 4.03 (d, *J*=6.6 Hz, 2H), 4.51 (s, 2H), 4.64 (d, *J*=6.9 Hz, 1H, B of AB), 4.79 (d, *J*=6.9 Hz, 1H, A of AB), 4.92—5.05 (m, 2H), 5.42 (d, *J*=6.6 Hz, 1H), 5.80—5.89 (m, 1H), 7.26—7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 5.54, 7.06, 16.53, 19.09, 27.55, 31.02, 35.58, 37.32, 55.49, 66.51, 71.98, 77.15, 80.46, 91.18, 114.05, 120.56, 127.44, 127.72, 128.25, 138.43, 138.86, 140.76; IR (film) *v*: 3066, 2955, 2878, 1455, 1145, 1113, 1033, 919, 737 cm^{-1}; ESI-MS *m*/*z*: 494.3 ($M+NH_4^+$), 499.3 ($M+Na^+$). Anal. calcd for $C_{28}H_{48}O_4Si$: C 70.54, H 10.15; found C 70.72, H 10.30.

(6*R*,7*S*,*E*)-6-(Triethylsilyloxy)-7-(methoxymethoxy)-3,7-dimethylundeca-2,10-dien-1-ol (12) To a solution of **11** (24.8 g, 52 mmol) in anhydrous THF (200 mL) was added freshly prepared lithium naphthalenide in THF at −25 ℃. After the reaction mixture became blue for 30 min, it was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous phase was extracted with Et_2O (200 mL×3). The combined organic layers were washed with 1 mol•L^{-1} HCl (aq.), saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography to give alcohol **12** (15.8 g, 80%) as a colorless oil. $[\alpha]_D^{20}$ +26.2 (*c* 0.50, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.63 (q, *J*=8.1 Hz, 6H), 0.98 (t, *J*=8.1 Hz, 9H), 1.18 (s, 3H), 1.77 (s, 3H), 1.40—1.95 (m, 4H), 1.95—2.30 (m, 4H), 3.37 (s, 3H), 3.53—3.56 (m, 1H), 4.16 (d, *J*=6.6 Hz, 2H), 4.65 (d, *J*=7.2 Hz, 1H, B of AB), 4.79 (d, *J*=7.2 Hz, 1H, A of AB), 4.93—5.06 (m, 2H), 5.43 (t, *J*=6.6 Hz, 1H), 5.77—5.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 5.53, 7.03, 16.25, 18.99, 27.52, 31.06, 35.49, 37.25, 55.45, 59.07, 77.09, 80.51, 91.13, 114.06, 123.28, 138.81, 139.60; IR (film) *v*: 3352, 2956, 2879, 1642, 1458, 1113, 1033, 1010, 740 cm^{-1}; ESI-MS *m*/*z*: 404.2 ($M+NH_4^+$), 409.2 ($M+Na^+$). Anal. calcd for $C_{21}H_{42}O_4Si$: C 65.24, H 10.93; found C 65.33, H 10.90.

(6*R*,7*S*,*E*)-6-(Triethylsilyloxy)-7-(methoxymethoxy)-3,7-dimethylundeca-2,10-dienyl acetate (13) To a solution of **12** (38.8 g, 100 mmol) in CH_2Cl_2 (200 mL) were added DMAP (480 mg, 4.0 mmol), NEt_3 (25 mL, 180 mmol) and Ac_2O (10.5 mL, 110 mmol) at 0 ℃. The resulting mixture was stirred for 2 h at room temperature, quenched with saturated NH_4Cl and the organic layer was separated. The aqueous phase was extracted with Et_2O (200 mL×3). The combined organic layers were washed with 1 mol•L^{-1} HCl (aq.), saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography to provide acetate **13** (40.9 g, 95%) as a colorless oil. $[\alpha]_D^{20}$ +2.1 (*c* 1.0, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.63 (q, *J*=7.8 Hz, 6H), 0.97 (t, *J*=7.8 Hz, 9H), 1.18 (s, 3H), 1.76 (s, 3H), 1.38—1.86 (m, 4H), 2.06 (s, 3H), 1.95—2.35 (m, 4H), 3.27 (s, 3H), 3.52—3.56 (m, 1H), 4.59 (d, *J*=7.2 Hz, 2H), 4.65 (d, *J*=7.2 Hz, 1H, B of AB), 4.79 (d, *J*=7.2 Hz, 1H, A of AB), 4.93—5.05 (m, 2H), 5.36 (t, *J*=7.2 Hz, 1H), 5.76—5.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 5.48, 6.98, 16.39, 18.98, 20.90, 27.49, 30.88, 35.47, 37.15, 55.42, 61.21, 77.00, 80.40, 91.14, 114.01, 118.02, 138.79, 142.54, 170.91; IR (film) *v*: 2956, 2879, 1743, 1234, 1031, 918, 736 cm^{-1}; ESI-MS *m*/*z*: 446.2 ($M+NH_4^+$), 451.2 ($M+Na^+$). Anal. calcd for $C_{23}H_{44}O_5Si$: C 64.44, H 10.35; found C 64.31, H 10.25.

(2*E*,6*S*,7*R*,10*E*)-Ethyl 12-acetoxy-6-(methoxymethoxy)-2,6,10-trimethyl-7-(triethylsilyloxy)dodeca-2,10-dienoate (15) To a solution of **13** (15.7 g, 36.7 mmol) in *tert*-butyl alcohol were added H_2O (180 mL), $K_3Fe(CN)_6$ (36.7 g, 110 mmol), KC_2O_3 (16.1 g, 110

mmol) and $(DHQ)_2$ PHAL (140 mg, 0.19 mmmol). The reaction mixture was cooled at 0 ℃ for 10 min, then $K_2OsO_2(OH)_4$ (30 mg, 0.08 mmol) was added. After being vigorously stirred for 24 h at this termperature, the reaction mixture was quenched with 20 g of Na_2SO_3 and extracted with EtOAc (150 mL×4). The combined organic layers were washed with 1 mol•L^{-1} HCl (aq.), saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo* to crude diol. The residue was then dissolved in THF (100 mL) and water (100 mL) and treated with $NaIO_4$ (9.1 g, 43 mmol) at room temperature for 2 h. The reaction mixture was filtered, the biscuit was washed with ethyl ether (30 mL×3) and the organic layer was separated. The aqueous phase was extracted with Et_2O (200 mL×3). The combined organic layers were washed with 1 mol•L^{-1} HCl (aq.), saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo* to give crude aldehyde, which was treated with $Ph_3P{=}C(CH_3)COOEt$ (10.0 g, 27.6 mmol) in toluene (60 mL) at room temperature. The reaction mixture was stirred overnight and concentrated *in vacuo*. The resulting residue was purified by flash chromatography to provide ester **15** (9.8 g, 69 %) as a colorless oil. $[\alpha]_D^{20}$ +3.4 (*c* 1.0, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.63 (q, *J*=8.1 Hz, 6H), 0.98 (t, *J*=8.1 Hz, 9H), 1.20 (s, 3H), 3.54—3.57 (m, 1H), 1.33 (t, *J*=7.5 Hz, 3H), 1.72 (s, 3H), 1.85 (s, 3H), 1.40—1.90 (m, 4H), 2.06 (s, 3H), 1.93—2.40 (m, 4H), 3.38 (s, 3H), 4.20 (q, *J*=7.5 Hz, 2H), 4.59 (d, *J*=7.2 Hz, 2H), 4.65 (d, *J*=7.2 Hz, 1H, B of AB), 4.80 (d, *J*=7.2 Hz, 1H, A of AB), 5.37 (t, *J*=7.2 Hz, 1H), 6.74 (t, *J*=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 5.47, 6.99, 12.21, 14.16, 16.42, 19.08, 20.91, 22.71, 30.93, 34.90, 37.12, 55.46, 60.26, 61.19, 77.12, 80.35, 91.09, 118.08, 127.57, 142.11, 142.43, 168.06, 170.94; IR (film) *v*: 2957, 2879, 1741, 1711, 1459, 1367, 1279, 1233, 1100, 1032, 741 cm^{-1}; ESI-MS *m*/*z*: 532.4 ($M+NH_4^+$), 537.3 ($M+Na^+$). Anal. calcd for $C_{27}H_{50}O_7Si$: C 63.00, H 9.79; found C 63.18, H 9.86.

(2*E*,6*S*,7*R*,10*E*)-Ethyl 7-(triethylsilyloxy)-12-(*tert*-butyldiphenylsilyloxy)-6-(methoxymethoxy)-2,6,10-trimethyldodeca-2,10-dienoate (16) To a solution of **15** (10.4 g, 20.2 mmol) in ethanol (30 mL) was added K_2CO_3 (6.0 g, 43.3 mmol) at room temperature. After being stirred overnight, the reaction mixture was filtered and concentrated. The resulting residue was dissolved in CH_2Cl_2 (100 mL). To this solution were added NEt_3 (10 mL, 73 mmol), DMAP (240 mg, 2 mmol) and TBDPSCl (6.2 mL, 23.5 mmol) at 0 ℃. The reaction mixture was warmed to r.t. and stirred overnight. After quenching the mixture with saturated NH_4Cl, the organic layer was separated. The aqueous phase was extracted with Et_2O (200 mL×3). The combined organic layers were washed with 1 mol•L^{-1} HCl (aq.) (100 mL×2), saturated $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography to afford ether **16** (13.8 g, 96 %) as a colorless oil. $[\alpha]_D^{20}$ +1.8 (*c* 1.0, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.63 (q, *J*=7.8 Hz, 6H), 0.97 (t, *J*=7.8 Hz, 9H), 1.05 (s, 9H), 1.19 (s, 3H), 1.30 (t, *J*=7.2 Hz, 3H), 1.44 (s, 3H), 1.40—1.85 (m, 4H), 1.84 (s, 3H), 1.90—2.30 (m, 4H), 3.37 (s, 3H), 3.53—3.57 (m, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 4.21 (d, *J*=6.0 Hz, 2H), 4.65 (d, *J*=7.5 Hz, 1H, B of AB), 4.79 (d, *J*=7.5 Hz, 1H, A of AB), 5.39 (t, *J*=6.0 Hz, 1H), 6.74 (t, *J*=7.2 Hz, 1H), 7.34—7.47 (m, 6H), 7.68—7.71 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 5.58, 7.08, 12.29, 14.23, 16.35, 19.08, 19.16, 22.79, 26.75, 31.11, 34.97, 37.11, 55.51, 60.30, 61.04, 77.17, 80.45, 91.13, 123.92, 127.50, 127.61, 129.43, 133.92, 135.51, 137.23, 142.24, 168.09; IR (film) *v*: 2958, 2878, 1712, 1473, 1429, 1280, 1113, 1038, 740 cm^{-1}; ESI-MS *m*/*z*: 728.4 ($M+NH_4^+$), 733.4 ($M+Na^+$). Anal. calcd for $C_{41}H_{66}O_6Si_2$: C 69.56, H 9.26; found C 69.25, H 9.35.

(2*E*,6*S*,7*R*,10*E*)-7-(Triethylsilyloxy)-12-(*tert*-butyldiphenylsilyloxy)-6-(methoxymethoxy)-2,6,10-trimethyldodeca-2,10-dien-1-ol (17) To a solution of **16** (13.8 g, 19.4 mmol) in anhydrous THF (200 mL) at −78 ℃ was slowly added 50 mL of DIBAL-H (1 mol•L^{-1}, 50 mmol) over 20 min. The reaction mixture was stirred for 20 min and quenched with 5 mL of water. The reaction mixture was diluted with 1.2 L of ethyl ether and 50 g of $MgSO_4$. After being stirred for 2 h, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to yield alcohol (**17**) (12.6 g, 97%) as a colorless oil. $[\alpha]_D^{20}$ +3.4 (*c* 1.0, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.64 (s, 6H), 0.97 (s, 9H), 1.05 (s, 9H), 1.19 (s, 3H), 1.44 (s, 3H), 1.70 (s, 3H), 1.40—1.80 (m, 4H), 1.90—2.20 (m, 4H), 3.37 (s, 3H), 3.53—3.56 (m, 1H), 4.01 (d, *J*=1.8 Hz, 2H), 4.21 (d, *J*=6.3 Hz, 2H), 4.68 (d, *J*=7.2 Hz, 1H, B of AB), 4.78 (d, *J*=7.2 Hz, 1H, A of AB), 5.40—5.44 (m, 2H), 7.34—7.45 (m, 6 H), 7.68—7.71 (m, 4H); IR (film) *v*: 3422, 3072, 2957, 1461, 921, 823 cm^{-1}; ESI-MS *m*/*z*: 686.5 ($M+NH_4^+$), 691.5 ($M+Na^+$). Anal. calcd for $C_{39}H_{64}O_5Si_2$: C 70.01, H 9.64; found C 70.05, H 10.03.

(2*E*,6*S*,7*R*,10*E*)-12-(*tert*-Butyldiphenylsilyloxy)-6-(methoxymethoxy)-2,6,10-trimethyldodeca-2,10-diene-1,7-diol (18) To a solution of **17** (4.2 g, 20.2 mmol) in methanol (20 mL) was added PPTS (200 mg, 0.8 mmol) at 0 ℃. After being stirred overnight, the reaction mixture was concentrated and dissolved in 100 mL of EtOAc. The solution was washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography to afford diol **18** (3.2 g, 92 %) as a colorless oil. $[\alpha]_D^{20}$ +11.4 (*c* 0.50, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.06 (s, 9H), 1.20 (s, 3H), 1.48 (s, 3H), 1.40—1.59 (m, 2H), 1.62 (s, 3H), 1.72—1.87 (m, 2H), 1.97—2.32 (m, 4H), 3.40 (s, 3H), 3.40—3.50 (m, 1 H), 4.01 (s, 2H), 4.24 (d, *J*=6.3 Hz, 2H), 4.66 (d, *J*=7.2 Hz, 1H, B of AB), 4.79 (d, *J*=7.2 Hz, 1H, A of AB), 5.40—5.44 (m, 2H), 7.34—7.45 (m, 6H), 7.68—7.71 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 16.49, 19.09, 20.44, 21.02, 23.00, 25.10, 26.79, 30.14, 34.98, 55.54, 61.01, 67.60, 73.11, 73.93, 74.98, 78.48, 90.70, 124.20, 127.51,

129.45, 133.88, 135.52, 136.58; IR (film) *v*: 3422, 2858, 1429, 1112, 1031, 740 cm^{-1}; EI-MS (70 eV) *m*/*z* (%): 553 (M−1, 0.66), 515 (M−39, 0.67). Anal. calcd for $C_{33}H_{50}O_6Si$: C 71.44, H 9.08; found C 71.58, H 9.14.

(2*R*,3*S*,6*S*)-2-[(*E*)-5-*tert*-Butyldiphenylsilyloxy-3-methylpent-3-enyl]-6-[(*S*)-1,2-dihydroxylpropan-2-yl]-3-(methoxymethoxy)-3-methyl-tetrahydro-2*H*-pyran (6) To a solution of **18** (9.03 g, 16.3 mmol) in CH_2Cl_2 (200 mL) were added molecular sieves (4 Å, 1.5 g) under argon. The solution was cooled to −25 ℃ and to this solution were added *D*-(−) DIPT (4.6 g, 20 mmol) and (*i*-PrO)$_4$Ti (5.0 g, 17.8 mmol). After stirring at −25 ℃ for 30 min, a solution of freshly prepared TBHP in CH_2Cl_2 (6.45 mL, 5.0 mol•L^{-1}, 32 mmol) was added. The reaction mixture was stirred at −20 ℃ for 4 h and warmed to −10 ℃ and kept for an additional 2 h. The reaction mixture was quenched with a solution of $FeSO_4$/tartaric acid. After being stirred for 1 h at 0 ℃, the organic layer was separated and the aqueous layer was extracted with Et_2O (100 mL×3). The combined organic layers were treated with 50 mL of 30% NaOH/brine at 0 ℃ for 30 min. The organic layer was separated and the aqueous layer was extracted with ether (100 mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **6** (7.8 g, 84%) as a colorless oil. $[\alpha]_D^{20}$ +25 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.05 (s, 9H), 1.16 (s, 6H), 1.36—1.44 (m, 1H), 1.47 (s, 3H), 1.52—2.03 (m, 6H), 2.10—2.22 (m, 1H), 3.30 (d, *J*=11.2 Hz, 1H), 3.40 (s, 3H), 3.48—3.53 (m, 1H), 3.76—3.79 (m, 1H), 3.85 (d, *J*=11.2 Hz, 1H), 4.23 (d, *J*=6.3 Hz, 2H), 4.77 (s, 2H), 5.40 (t, *J*=6.3 Hz, 1H), 7.35—7.45 (m, 6H), 7.68—7.71 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 16.49, 19.09, 20.44, 21.02, 23.00, 25.10, 26.79, 30.14, 34.98, 55.54, 61.01, 67.60, 73.11, 73.93, 74.98, 78.48, 90.70, 124.20, 127.51, 129.45, 133.88, 135.52, 136.58; IR (film) *v*: 3450, 3072, 2957, 2858, 1670, 1472, 823 cm^{-1}; HRMS (ESI) calcd for $(C_{33}H_{50}O_6Si+Na)^+$ 593.3269, found 593.3279.

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