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Concise total syntheses of heliannuols B and D

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ABSTRACT

Concise and efficient enantioselective total syntheses of heliannuols B and D have been accomplished using chirality transfer through a Lewis acid-promoted Claisen rearrangement for the construction of the C7 tertiary stereogenic center and a relay ring-closing metathesis for assembling the dihydrobenzo[*b*]oxepine backbone of the natural products as the key steps.

1. Introduction

The helianane sesquiterpenoids heliannuols B (**1**) and D (**2**) were isolated from the moderately polar active fractions of the aqueous leaf extract of *Helianthus annuus* L. var. SH-222 and VYP.[1] Their structures were elucidated by extensive spectroscopic studies, X-ray crystallographic analysis (for **2**), and chemical correlations. The absolute configurations were established by our first enantioselective total synthesis of heliannuol D (**2**).[2] These sesquiterpenoids significantly inhibit the growth of both dicotyledon (*Lactuca sativa* and *Lepidium sativum*) and monocotyledon species (*Hordeum vulgare* and *Triticum aestivum*). Consequently they are excellent candidates for natural herbicide models with certain specificity against dicotyledon species.[3] Because of their intriguing structural features, biological profiles, and limited availability, these natural products represent attractive targets for total synthesis. To date, several successful total syntheses have been reported in racemic and optically active forms.[4,5] In this report, we describe the concise enantioselective total syntheses of heliannuols B (**1**) and D (**2**) via chirality transfer through a Lewis acid-mediated Claisen rearrangement for the construction of the benzylic tertiary stereogenic center at C7 and relay ring-closing metathesis (RRCM) for assembling the dihydrobenzo[*b*]oxepine skeleton, the core structure of the natural products, as the key steps (Fig. 1).

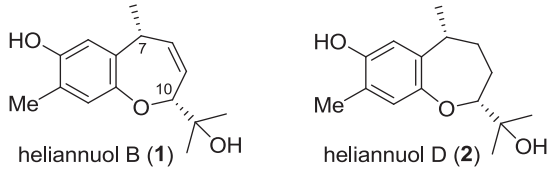
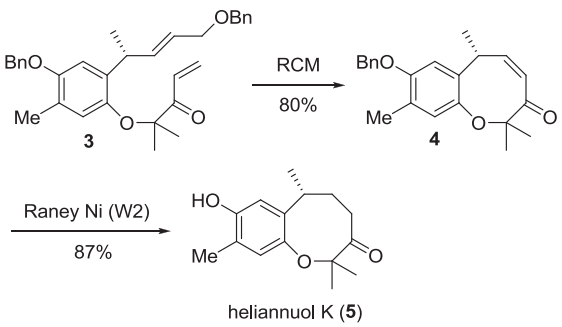


Fig. 1. Structures of heliannuols B and D.

During the course of our synthetic studies on the related helianane sesquiterpenoid heliannuol K (**5**), we developed a useful technique for constructing the dihydrobenzo[*b*]oxocinone **4**, which was efficiently converted to **5**, employing the ring-closing metathesis (RCM) of the functionalized diene **3** (Scheme 1).[6] It was thought that this strategy could also be applied to the assembly of the dihydrobenzo[*b*]oxepine backbone of heliannuol B (**1**).



Scheme 1. Synthesis of heliannuol K via RCM.

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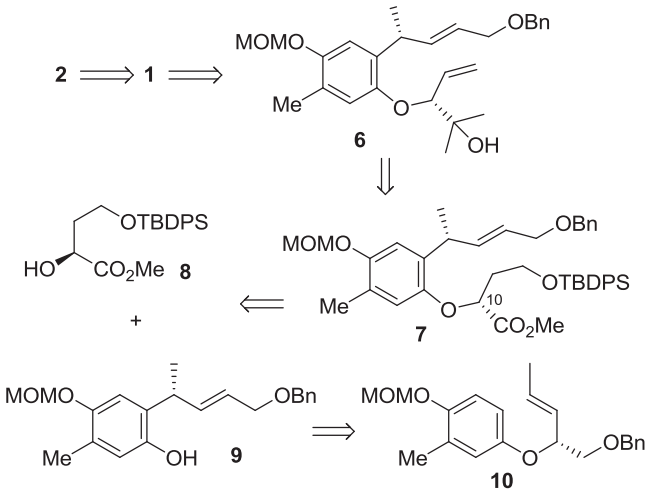
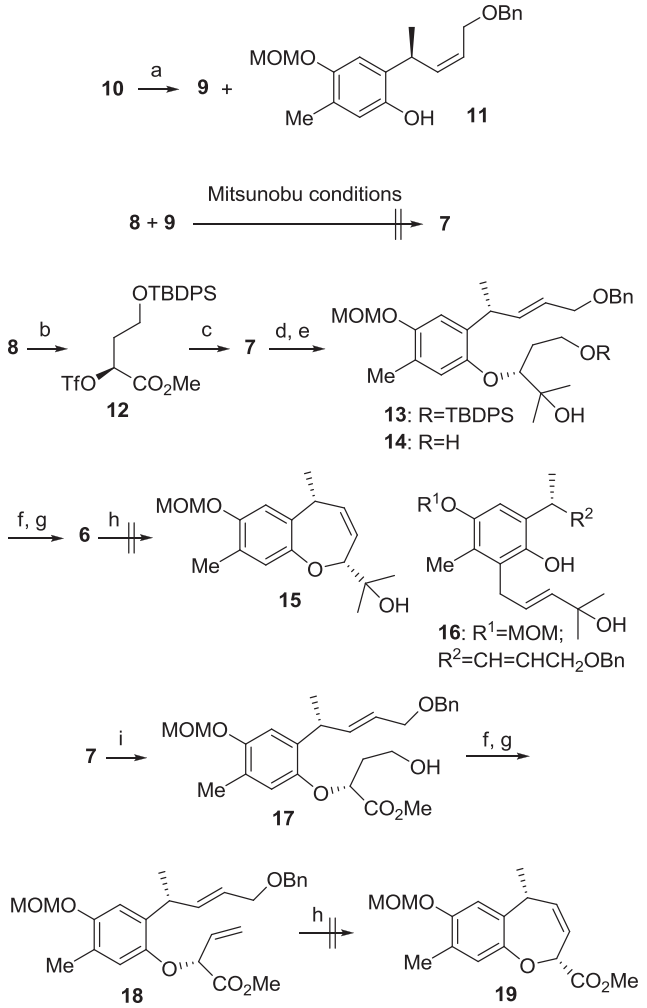
2. Results and discussion

Our retrosynthetic analysis is shown in Scheme 2. We envisioned a sequential RCM[7] of the suitably functionalized dienyl alcohol **6**, possessing the correct absolute configurations of the two stereogenic centers at C7 and C10, and deprotection to give heliannuol B (**1**), which could be converted to heliannuol D (**2**) by hydrogenation.[4a] The diene **6** would be derived from **7** by desilylation followed by dehydration of the resulting primary alcohol. Compound **7**, in turn, would be prepared by coupling of (*S*)-methyl 4-(*tert*-butyldiphenylsilyloxy)-2-hydroxybutanoate (**8**)[8] with the phenol **9**,[5d,6] which can be prepared by the substrate controlled chirality transfer through the Lewis acid-promoted Claisen rearrangement of **10**, with inversion of configuration at the future C10 (Scheme 2).



Scheme 2. Retrosynthetic analysis.

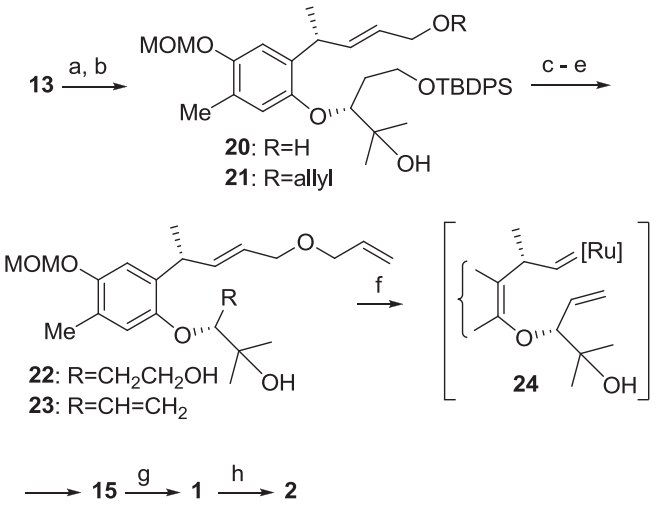
Treatment of **10** with trimethylaluminum in hexane at room temperature for 0.5 h provided a chromatographically separable mixture of **9** and **11** in 88% (>99% ee) and 10% yield, respectively.[5d,6] For the synthesis of **7**, we initially examined the Mitsunobu reaction of the phenol **9** with the optically pure alcohol **8**, using various Mitsunobu conditions;[9] however, the reaction did not work and only the unreacted starting materials were recovered. Therefore, we turned our attention to an S_N2 type coupling of the triflate **12**, derived from **8**, and **9**. Treatment of **12** with **9** in the presence of K_2CO_3 in acetonitrile at room temperature provided **7** quantitatively.[10] Grignard reaction of **7** with methylmagnesium bromide followed by desilylation of the resulting tertiary carbinol **13** produced the diol **14**. Selective dehydration of the primary alcohol using the Nishizawa–Grieco protocol[11] provided the requisite diene **6** for the key RCM. Treatment of **6** in refluxing CH_2Cl_2 with 5 mol % of Grubbs' second-generation catalyst[12] did not give the expected cyclized product **15** and the unreacted **6** was recovered in 94% yield.[13] When the reaction was conducted in toluene at 80 °C, **6** was also recovered in 92% yield. Under refluxing toluene for two days, only the phenol **16**, generated via the Claisen rearrangement, was produced in 26% yield. Since this result can be attributed to the steric bulkiness around the allyl ether moiety, we therefore chose the ester **17** as the substrate for the RCM leading to **19** because it was likely to be less sterically congested than the tertiary carbinol functionality in **6**. Sequential desilylation and dehydration provided **18**, which was exposed to the RCM conditions under refluxing CH_2Cl_2 or toluene; however, only the unreacted **18** was produced in 72% and 94% yield, respectively (Scheme 3).



Scheme 3. Attempted RCM of **6** and **13**. Reagents and Conditions: (a) Me_3Al, hexane, room temperature, 0.5 h, 88% for **9**, 10% for **11**; (b) Tf_2O, 2,6-lutitine, CH_2Cl_2, −20 °C, 20 min, quant.; (c) **9**, K_2CO_3, MeCN, room temperature, 4 h, quant.; (d) MeMgBr, THF, 0 °C, 0.5 h, 89%; (e) TBAF, THF, room temperature, 0.5 h, 87%; (f) *o*-$NO_2C_6H_4SeCN$, $^nBu_3P$, THF, room temperature, 0.5 h; (g) H_2O_2 (aqueous), THF, 60 °C, 15 min, 50% (two steps for **6**), 47% (two steps for **18**); (h) Grubbs' second-generation cat. (5 mol %), CH_2Cl_2 or toluene reflux; (i) HF·pyridine, THF, pyridine, room temperature, 1.5 h, 78%.

As seen in the previous paper, the ineffectiveness of standard RCM protocols led us to use a RRCM, which worked well with a substrate possessing a higher level of steric congestion around the olefinic bonds.[14] Consequently, we decided to use this methodology for assembling the functionalized dihydrobenzo[*b*]oxepine, the backbone of the heliannuols B and D. Selective debenzylation of **13** with LiDBB[15] followed by allylation of the resulting alcohol **20** provided the allyl ether **21** in 90% yield for the two steps. This was subjected to sequential desilylation and dehydration to give **23** in 62% overall yield. Treatment of a solution of **23** in CH_2Cl_2 with Grubbs' second-generation catalyst (5 mol %) at room temperature for 3 h delivered the requisite **15** quantitatively via the ruthenium alkylidene species **24**. Thus, the problem was overcome by the use of RRCM to affect the crucial cyclization. Exposure of **15** to 6 M aqueous hydrochloric acid in THF gave (−)-heliannuol B (**1**) quantitatively. The only discrepancy concerned the specific rotation: we observed in repeated measurements under higher concentrations a value of $[\alpha]_D^{25}$ −77.5 (*c* 1.10, $CHCl_3$) for synthetic heliannuol B (**1**), whereas significantly lower values of $[\alpha]_D^{25}$ −15.0 (*c* 0.10, $CHCl_3$),[1] and $[\alpha]_D^{25}$ −22 (*c* 0.7, $CHCl_3$)[4a] were reported for the natural and synthetic **1**, respectively. This noticeable discrepancy remains unresolved at the present time. Compound **1** was then hydrogenated over palladium on carbon to

provide (+)-heliannuol D (**2**), {$[\alpha]_D^{25}$ +18.2 (*c* 0.75, $CHCl_3$); lit.[1] $[\alpha]_D^{25}$ +16 (*c* 0.10, $CHCl_3$); lit.[5b] $[\alpha]_D^{28}$ +18.0 (*c* 1.01, $CHCl_3$)}, in 94% yield. The spectral properties of **1** and **2** were identical with those for the natural heliannuols B and D (Scheme 4).



Scheme 4. RRCM approach for the syntheses of **1** and **2**. Reagents and conditions: (a) LiDBB, THF, −78 °C, 3 min, 91%; (b) NaH, allyl bromide, THF, room temperature, 6 h, 99%; (c) TBAF, THF, room temperature, 3 min, quant.; (d) *o*-$NO_2C_6H_4SeCN$, $^nBu_3P$, THF, 0 °C, 5 min; (e) H_2O_2 (aqueous), THF, 60 °C, 20 min, 62% (two steps); (f) Grubbs' second-generation cat. (5 mol %), CH_2Cl_2, room temperature, 3 h, quant.; (g) 6 M HCl (aqueous), THF, 0 °C, 0.5 h, quant.; (h) H_2, 10% Pd–C, AcOEt, room temperature, 2.5 h, 94%.

3. Conclusion

We have completed concise enantioselective total syntheses of heliannuols B (**1**) and D (**2**) using the RRCM of **23** for assembling the dihydrobenzo[*b*]oxepine backbone of the natural products as the key step. The syntheses were efficiently achieved in a longest linear sequence of eight steps in 50% yield and nine steps in 47% yield, respectively, from the phenol **9**, which was prepared by the use of chirality transfer through a Lewis acid-promoted Claisen rearrangement for the construction of the tertiary stereogenic center at C7 (natural product numbering).[16] The synthetic route developed here could be applied to the synthesis of not only other helianane sesquiterpenoids but also new families of man-made compounds for biological screening.

4. Experimental

4.1. General experimental methods

All nonaqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise indicated. Materials were obtained from commercial suppliers and used without further purification expect when otherwise noted. Solvents were dried and distilled according to standard protocols. The phrase 'residue upon workup' refers to the residue obtained when the organic layer was separated and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. NMR spectra were recorded on a 400 MHz or 500 MHz instrument. ^1H NMR were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm). ^{13}C NMR were measured in $CDCl_3$ solution and referenced to $CDCl_3$ (77.0 ppm). Chemical shifts are reported in parts per million (from TMS). When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broadened. IR spectra were measured on FT/IR spectrometer. Type of mass analyzer was time of flight mass spectrometry (TOF-mass). Column chromatography was performed on silica gel using the indicated solvent. Thin layer chromatography was performed on precoated plates, and compounds were visualized with UV light and *p*-anisaldehyde stains. All melting points were reported as uncorrected.

*4.1.1. (2R,3E)-2-[5-(Benzyloxy)pent-3-en-2-yl]-4-(methoxymethoxy)-5-methylphenol and (2S,3Z)-2-[5-(benzyloxy)pent-3-en-2-yl]-4-(methoxymethoxy)-5-methylphenol (**9** and **11**).* To a stirred solution of aryl allyl ether **10**[5d,6] (500 mg, 1.46 mmol) in hexane (10.0 mL) was added Me_3Al (1.08 M in hexane, 4.00 mL, 4.38 mmol) at 0 °C. After being stirred for 0.5 h at room temperature, the reaction mixture was diluted with Et_2O. The resultant mixture was quenched with water, and then filtered through a pad of Celite. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (9:1 v/v) as eluent to afford phenol **9** (441 mg, 88%, >99% ee) as a colorless oil and the *Z*-isomer **11** (48.5 mg, 10%) as a colorless oil; **9**: $[\alpha]_D^{25}$ −3.83 (*c* 1.20, $CHCl_3$); IR (neat) 3375, 2960, 2928, 1513, 1453, 1398, 1148, 1004, 740, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.36 (5H, m), 6.82 (1H, s), 6.61 (1H, s), 5.94 (1H, dd, *J*=6.0 and 15.6 Hz), 5.71 (1H, ddt, *J*=1.2, 6.0, and 15.6 Hz), 5.09 (2H, s), 4.60 (1H, s, OH, D_2O exchangeable), 4.50 (2H, s), 4.02 (2H, d, *J*=6.0 Hz), 3.66 (1H, quint., *J*=7.2 Hz), 3.49 (3H, s), 2.18 (3H, s), 2.18 (3H, s), 1.38 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 149.5 (C), 148.1 (C), 138.2 (C), 138.0 (CH), 138.0 (CH), 128.8 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 126.8 (C), 126.8 (C), 125.7 (CH), 114.9 (CH), 118.3 (CH), 95.8 (CH_2), 71.9 (CH_2), 70.6 (CH_2), 56.0 (CH_3), 36.1 (CH), 19.3 (CH_3), 15.8 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{27}O_4$ $[M+H]^+$ 343.1909, found 343.1902. Enantiomeric excess was determined by HPLC analysis [Chiralcel AD column, 10% isopropanol/hexane, 1.0 mL/min, λ=254 nm, retention times 22.1 min (*R*) and 25.3 min (*S*)]; **11**: $[\alpha]_D^{25}$ +154.1 (*c* 2.59, $CHCl_3$); IR (neat) 3365, 2960, 2927, 1513, 1454, 1398, 1190, 1149, 1007, 738, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.37 (5H, m), 6.87 (1H, s), 6.64 (1H, s), 6.42 (1H, s, OH, D_2O exchangeable), 5.60 (1H, dt, *J*=6.4 and 10.8 Hz), 5.55 (1H, dd, *J*=8.4 and 10.8 Hz), 5.10 (2H, s), 4.62 (1H, d, *J*=12.0 Hz), 4.58 (1H, d, *J*=12.0 Hz), 4.23 (1H, dd, *J*=4.4 and 11.2 Hz), 4.03 (1H, dq, *J*=2.8 and 6.8 Hz), 3.93 (1H, dd, *J*=6.0 and 11.2 Hz), 3.50 (3H, s), 2.18 (3H, s), 1.32 (3H, d, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 149.5 (C), 148.8 (C), 140.0 (CH), 140.0 (CH), 137.3 (C), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.9 (CH), 127.0 (C), 127.0 (C), 122.9 (CH), 118.9 (CH), 113.5 (CH), 95.9 (CH_3), 72.8 (CH_3), 65.1 (CH_3), 56.0 (CH_2), 31.5 (CH), 19.8 (CH_2), 15.8 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{27}O_4$ $[M+H]^+$ 343.1909, found 343. 1895.

*4.1.2. (2S)-Methyl 2-(trifluoromethylsulfonyloxy)-4-(tert-butyldiphenylsilyloxy)butanoate (**12**).* To a stirred solution of alcohol **8**[8] (100 mg, 0.268 mmol) in CH_2Cl_2 (0.500 mL) were added 2,6-lutidine (40.0 μL, 0.295 mmol) and Tf_2O (50.0 μL, 0.298 mmol) at −20 °C. After being stirred for 20 min at the same temperature, the reaction mixture was quenched with silica gel (35.0 mg) and stirred at room temperature for 10 min, then filtered off the silica gel and concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (4:1 v/v) as eluent to afford triflate **12** (135 mg, quant.) as a colorless oil; $[\alpha]_D^{30}$ −20.0 (*c* 1.15, $CHCl_3$); IR (neat) 2932, 1769, 1419, 1212, 1145, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.66–7.64 (4H, m), 7.46–7.37 (6H, m), 5.48 (1H, dd, *J*=2.8 and 7.6 Hz), 3.82 (3H, s), 3,77 (2H, t, *J*=6.0 Hz), 2.26–2.13 (2H, m), 1.05 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 167.8 (C), 135.5 (CH), 135.5 (CH), 135.5 (CH), 135.5 (CH), 132.9 (C), 132.8 (C), 129.9 (CH), 129.9 (CH), 127.8 (CH), 127.8 (CH), 127.8 (CH), 127.8 (CH), 118.4 (C, q, J_{CF}=318 Hz), 80.2 (CH), 58.0 (CH_2), 53.2 (CH_3), 34.8 (CH_2), 26.6 (CH_3), 26.6 (CH_3), 26.6 (CH_3), 19.1 (C); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{28}O_6SiSF_3$ $[M+H]^+$ 505.1328, found 505.1324.

*4.1.3. (2R)-Methyl 2-{2-[(2R,3E)-5-(benzyloxy)pent-3-en-2-yl]-4-(methoxymethoxy)-5-methylphenoxy}-4-(tert-butyldiphenylsilyloxy)butanoate (**7**).* To a stirred solution of phenol **9** (100 mg, 0.292 mmol) and K_2CO_3 (60.5 mg, 0.438 mmol) in MeCN (2.00 mL) was added

a solution of triflate **12** (221 mg, 0.438 mmol) in MeCN (1.00 mL) at room temperature. After being stirred for 4 h, the reaction mixture was filtered off, and then the filtrate was concentrated. The residue was dissolved in AcOEt. The combined extracts were washed with water, saturated aqueous $NaHCO_3$ and brine, and the residue upon workup was chromatographed on silica gel with hexane/AcOEt (3:2 v/v) as eluent to afford ether **7** (204 mg, quant.) as a colorless oil; $[\alpha]_D^{31}$ +33.0 (*c* 0.42, $CHCl_3$); IR (neat) 3425, 2930, 2857, 1758, 1505, 1195, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.65 (2H, d, *J*=7.2 Hz), 7.58 (2H, d, *J*=7.2 Hz), 7.43–7.25 (11H, m), 6.84 (1H, s), 6.58 (1H, s), 5.91 (1H, dd, *J*=5.6 and 15.6 Hz), 5.61 (1H, dt, *J*=5.6 and 15.6 Hz), 5.10 (1H, d, *J*=10.4 Hz), 5.08 (1H, d, *J*=10.4 Hz), 4.96 (1H, dd, *J*=4.0 and 8.4 Hz), 4.48 (2H, s), 3.98 (2H, d, *J*=6.0 Hz), 3.80–3.96 (3H, m), 3.69 (3H, s), 3.47 (3H, s), 2.24–2.09 (2H, m), 2.16 (3H, s), 1.23 (3H, d, *J*=7.2 Hz), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 172.5 (C), 150.1 (C), 149.7 (C), 138.6 (C), 138.5 (CH), 135.6 (CH), 135.6 (CH), 135.5 (CH), 135.5 (CH), 133.5 (C), 133.5 (C), 132.9 (C), 129.7 (CH), 129.6 (CH), 128.3 (CH), 127.8 (CH), 127.8 (CH), 127.7 (CH), 127.7 (CH), 127.7 (CH), 127.7 (CH), 127.5 (CH), 126.1 (C), 124.9 (CH), 124.9 (CH), 115.0 (CH), 114.9 (CH), 95.7 (CH_2), 73.7 (CH), 71.7 (CH_2), 71.0 (CH_2), 59.5 (CH_2), 56.0 (CH_3), 52.1 (CH_3), 36.0 (CH_2), 34.5 (CH), 26.9 (CH_3), 26.9 (CH_3), 26.9 (CH_3), 19.8 (CH_3), 19.2 (C), 16.2 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{42}H_{53}O_7Si$ $[M+H]^+$ 697.3561, found 697.3558.

*4.1.4. (3R)-3-[2-(2R,3E)-5-Benzyloxypent-3-en-2-yl-4-methoxymethoxy-5-methylphenoxy]-5-(tert-butyldiphenylsilyloxy)-2-methylpentan-2-ol (**13**).* To a stirred solution of ester **7** (542 mg, 0.777 mmol) in THF (3.10 mL) was added MeMgBr (1.11 M in THF, 2.80 mL, 3.11 mmol) at −78 °C. After being stirred for 0.5 h at 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel hexane/AcOEt (4:1 v/v) as eluent to afford alcohol **13** (454 mg, 84%) as a colorless oil; $[\alpha]_D^{25}$ +7.60 (*c* 1.04, $CHCl_3$); IR (neat) 3476, 2960, 2930, 1499, 1190, 1150, 1111, 1075, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.63 (2H, dd, *J*=1.2 and 8.0 Hz), 7.48 (2H, dd, *J*=1.2 and 8.0 Hz), 6.94 (1H, s), 7.27–7.44 (11H, m), 6.87 (1H, s), 5.85 (1H, dd, *J*=6.4 and 15.6 Hz), 5.57 (1H, dt, *J*=6.0 and 15.6 Hz), 5.12 (1H, d, *J*=10.4 Hz), 5.09 (1H, d, *J*=10.4 Hz), 4.55 (1H, dd, *J*=3.2 and 8.4 Hz), 4.48 (2H, s), 3.96 (2H, d, *J*=6.4 Hz), 3.88 (1H, m), 3.69 (2H, dd, *J*=3.6 and 7.6 Hz), 3.49 (3H, s), 2.55 (1H, br s, OH, D_2O exchangeable), 1.55 (3H, s), 1.94–1.86 (1H, m), 1.78–1.71 (1H, m), 1.27 (3H, s), 1.27 (3H, d, *J*=6.4 Hz), 1.26 (3H, s), 1.03 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 151.1 (C), 149.4 (C), 138.8 (CH), 138.3 (C), 135.4 (CH), 135.4 (CH), 135.3 (CH), 135.3 (CH), 133.3 (C), 133.3 (C), 131.5 (C), 129.6 (CH), 129.5 (CH), 128.2 (CH), 127.7 (CH), 127.7 (CH), 127.6 (CH), 127.6 (CH), 127.6 (CH), 127.6 (CH), 127.4 (CH), 126.2 (C), 124.9 (CH), 124.9 (CH), 115.4 (CH), 114.5 (CH), 95.6 (CH_2), 81.1 (CH), 72.9 (C), 71.9 (CH_2), 70.7 (CH_2), 60.2 (CH_2), 55.9 (CH_3), 34.7 (CH), 34.0 (CH_2), 26.7 (CH_3), 26.7 (CH_3), 26.7 (CH_3), 26.0 (CH_3), 25.0 (CH_3), 19.8 (CH_3), 19.0 (C), 16.1 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{43}H_{57}O_6Si$ $[M+H]^+$ 697.3924, found 697.3931.

*4.1.5. (3R)-3-{2-[(2R,3E)-5-(Benzyloxy)pent-3-en-2-yl]-4-(methoxymethoxy)-5-methylphenoxy}-4-methylpentane-1,4-diol (**14**).* To a stirred solution of alcohol **13** (15.0 mg, 21.5 μmol) in THF (0.500 mL) was added TBAF (1.00 M in THF, 20.0 μL, 23.7 μmol) at room temperature. After being stirred for 0.5 h, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel hexane/AcOEt (7:3 v/v) as eluent to afford alcohol **14** (8.6 mg, 87%) as a colorless oil; $[\alpha]_D^{32}$ +6.06 (*c* 0.78, $CHCl_3$); IR (neat) 3380, 2930, 1500, 1393, 1190, 1150, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.37–7.25 (5H, m), 6.87 (1H, s), 6.77 (1H, s), 5.88 (1H, dd, *J*=15.6 and 6.4 Hz), 5.60 (1H, dtd, *J*=15.6, 6.4, and 1.2 Hz), 5.10 (2H, s), 4.51 (1H, d, *J*=12.0 Hz), 4.48 (1H, d, *J*=12.0 Hz), 4.33 (1H, dd, *J*=6.4 and 4.8 Hz), 3.98 (2H, d, *J*=6.0 Hz), 3.86 (1H, quint., *J*=6.8 Hz), 3.77 (1H, dt, *J*=10.8 and 5.6 Hz), 3.66–3.59 (1H, m), 3.48 (3H, s), 2.52 (1H, br s, OH, D_2O exchangeable), 2.40 (1H, br s, OH, D_2O exchangeable), 2.20 (3H, s), 2.02–1.87 (2H, m), 1.33 (3H, d, *J*=6.8 Hz), 1.30 (3H, s), 1.27 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 150.2 (C), 149.4 (C), 138.8 (CH), 138.2 (C), 131.8 (C), 128.3 (CH), 128.3 (CH), 127.8 (CH), 127.8 (CH), 127.5 (CH), 126.2 (C), 124.9 (CH), 114.9 (CH), 114.8 (CH), 95.6 (CH_2), 81.2 (CH), 73.0 (C), 72.0 (CH_2), 70.7 (CH_2), 59.0 (CH_2), 56.0 (CH_3), 35.2 (CH), 32.8 (CH_2), 26.2 (CH_3), 25.7 (CH_3), 19.9 (CH_3), 16.3 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{27}H_{38}O_6Na$ $[M+Na]^+$ 481.2566, found 481.2592.

*4.1.6. (3R)-3-{2-[(2R,3E)-5-(Benzyloxy)pent-3-en-2-yl]-4-(methoxymethoxy)-5-methylphenoxy}-2-methylpent-4-en-2-ol (**6**).* To a stirred solution of diol **14** (14.0 mg, 30.5 μmol) in THF (2.00 mL) was added *o*-nitrophenylselenocyanide (20.8 mg, 91.5 μmol) and $^nBu_3P$ (18.9 μL, 91.5 μmol) at room temperature. After being stirred for 0.5 h, the reaction mixture was concentrated. The residue was filtered through silica gel column chromatography (hexane/EtOAc, 4:1 v/v) to give the corresponding selenide (21.2 mg), as a yellow oil, which was used to the next reaction without further purification. To a stirred solution of selenide in THF (2.00 mL) was added 30% aqueous H_2O_2 (0.300 mL) at room temperature. After being stirred for 15 min at 60 °C, the reaction mixture was treated with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with hexane/AcOEt (3:2 v/v) as eluent to afford diene **6** (6.70 mg, 50% for two steps) as a yellow oil; $[\alpha]_D^{33}$ −4.77 (*c* 0.57, $CHCl_3$); IR (neat) 3500, 2972, 1501, 1393, 1191, 1150, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.36–7.21 (5H, m), 6.86 (1H, s), 6.63 (1H, s), 5.90 (1H, ddd, *J*=14.4, 6.4, and 1.2 Hz), 5.82 (1H, ddd, *J*=17.6, 10.8, and 6.8 Hz), 5.59 (1H, dtd, *J*=15.2, 6.4, and 1.6 Hz), 5.32 (1H, dt, *J*=9.6 and 1.2 Hz), 5.28 (1H, dt, *J*=17.6 and 1.2 Hz), 5.09 (2H, s), 4.49 (2H, s), 4.37 (1H, d, *J*=6.8 Hz), 4.03–3.96 (2H, m), 3.92 (1H, quint., *J*=7.2 Hz), 3.47 (3H, s), 2.48 (1H, br s, OH, D_2O exchangeable), 2.19 (3H, s), 1.34 (3H, d, *J*=7.2 Hz), 1.29 (3H, s), 1.27 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 149.6 (C), 149.4 (C), 138.8 (CH), 138.3 (C), 134.2 (CH), 132.0 (C), 128.3 (CH), 128.3 (CH), 127.7 (CH), 127.7 (CH), 127.5 (CH), 125.9 (CH), 125.1 (C), 119.7 (CH), 116.2 (CH), 114.4 (CH), 95.6 (CH_2), 86.2 (CH), 72.4 (C), 71.9 (CH_2), 70.7 (CH_2), 56.0 (CH_3), 34.8 (CH_2), 25.6 (CH_3), 24.6 (CH_3), 19.9 (CH_3), 16.2 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{27}H_{36}O_5Na$ $[M+Na]^+$ 463.2460, found 463.2490.

*4.1.7. 6-[(2R,3E)-5-(Benzyloxy)pent-3-en-2-yl]-2-[(2E)-4-hydroxy-4-methylpent-2-enyl]-4-(methoxymethoxy)-3-methylphenol (**16**).* To a stirred solution of diene **6** (3.90 mg, 8.85 μmol) in degassed toluene (10.0 mL) was added Grubbs' second-generation catalyst (1.30 mg, 0.443 μmol) at room temperature. After being stirred for 53 h at 110 °C, the resultant mixture was concentrated and the residue was chromatographed on silica gel with hexane/AcOEt (4:1 v/v) as eluent to afford the phenol (**16**) (1.00 mg, 26%) as a yellow oil; $[\alpha]_D^{29}$ −9.00 (*c* 0.02, $CHCl_3$); IR (neat) 3446, 2922, 2357, 1152, 972, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.34–7.23 (5H, m), 6.78 (1H, s), 5.93 (1H, dd, *J*=5.6 and 15.6 Hz), 5.75–5.68 (3H, m), 5.63 (1H, d, *J*=15.6 Hz), 5.10 (2H, s), 4.81 (1H, s), 4.50 (2H, s), 4.01 (2H, d, *J*=5.6 Hz), 3.68 (1H, m), 3.49 (3H, s), 3.40 (2H, d, *J*=5.6 Hz), 2.17 (3H, s), 1.39 (3H, d, *J*=7.2 Hz), 1.27 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) 149.6 (C), 147.0 (C), 139.0 (CH), 138.3 (C), 137.6 (CH), 131.2 (C), 128.4 (CH), 128.4 (CH), 128.3 (C), 127.8 (CH), 127.8 (CH), 127.6 (CH), 126.3 (CH), 125.7 (C), 124.1 (CH), 113.1 (CH), 96.0 (CH_2), 72.1 (CH_2), 70.7 (C), 70.5 (CH_2), 56.1 (CH_3), 36.8 (CH), 29.8 (CH_3), 29.8 (CH_3), 26.5 (CH_2), 19.2 (CH_3) 11.9 (CH_3),; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{36}O_5Na$ $[M+Na]^+$ 463.2460, found 463.2474.

*4.1.8. (3R)-Methyl 2-{2-[(2R,3E)-5-(benzyloxy)pent-3-en-2-yl]-4-(methoxymethoxy)-5-methylphenoxy}-4-hydroxybutanoate (**17**).* To

a stirred solution of ester **7** (20.0 mg, 28.7 μmol) in THF/pyridine (0.500 mL, 3/1 v/v) was added a drop of HF·pyridine at 0 °C. After being stirred at room temperature for 1.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel hexane/AcOEt (7:3 v/v) as eluent to afford alcohol **17** (10.2 mg, 78%) as a colorless oil; $[\alpha]_D^{32}$ +37.0 (*c* 0.47, $CHCl_3$); IR (neat) 3468, 2957, 1753, 1502, 1192, 1150, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.34–7.25 (5H, m), 6.85 (1H, s), 6.52 (1H, s), 5.95 (1H, ddt, *J*=15.6, 5.6, and 1.2 Hz), 5.65 (1H, dtd, *J*=15.6, 6.4, and 1.6 Hz), 5.10 (1H, d, *J*=6.8 Hz), 5.07 (1H, d, *J*=6.8 Hz), 4.83 (1H, t, *J*=6.0 Hz), 4.50 (2H, s), 4.02 (1H, dd, *J*=6.4 and 0.8 Hz), 3.92 (1H, quint., *J*=6.8 Hz), 3.85 (1H, q, *J*=5.2 Hz), 3.72 (3H, s), 3.46 (3H, s), 2.18 (3H, s), 2.22–2.17 (2H, m), 1.88 (1H, br s, OH, D_2O exchangeable), 1.34 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 172.5 (C), 150.1 (C), 149.5 (C), 138.4 (C), 138.3 (CH), 132.6 (C), 128.3 (CH), 128.3 (CH), 127.8 (CH), 127.8 (CH), 127.5 (CH), 126.3 (CH), 126.1 (C), 125.0 (CH), 115.2 (CH), 114.8 (CH), 95.6 (CH_2), 74.4 (CH), 71.9 (CH_2), 71.0 (CH_2), 56.0 (CH_3), 55.2 (CH_3), 35.5 (CH), 35.3 (CH_3), 19.7 (CH_3), 16.2 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{34}O_7Na$ $[M+Na]^+$ 481.2202, found 481.2214.

*4.1.9. (3R)-Methyl 2-{2-[(2R,3E)-5-(benzyloxy)pent-3-en-2-yl]-4-(methoxymethoxy)-5-methylphenoxy}but-3-enoate (**18**).* To a stirred solution of alcohol **17** (10.2 mg, 22.2 μmol) in THF (1.00 mL) was added *o*-nitrophenylselenocyanide (15.1 mg, 66.7 μmol) and $^nBu_3P$ (13.8 μL, 66.7 μmol) at room temperature. After being stirred for 0.5 h, the reaction mixture was concentrated. The residue was filtered through silica gel column chromatography (hexane/EtOAc, 4:1 v/v) to give the corresponding selenide (21.0 mg), as a yellow oil, which was used to the next reaction without further purification. To a stirred solution of selenide in THF (2.00 mL) was added 30% aqueous H_2O_2 (0.300 mL) at room temperature. After being stirred for 15 min at 60 °C, the reaction mixture was treated with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with hexane/AcOEt (4:1 v/v) as eluent to afford diene **18** (4.60 mg, 47% for two steps) as a yellow oil; $[\alpha]_D^{32}$ +22.28 (*c* 0.78, $CHCl_3$); IR (neat) 2955, 1761, 1503, 1394, 1193, 1151, 1015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.35–7.24 (5H, m), 6.91 (1H, s), 6.55 (1H, s), 6.06 (1H, ddd, *J*=5.6, 10.4, and 16.0 Hz), 5.96 (1H, ddt, *J*=6.0, 15.6, and 1.2 Hz), 5.68 (1H, ddt, *J*=1.6, 15.6, and 6.0 Hz), 5.60 (1H, dq, *J*=17.2 and 1.2 Hz), 5.40 (1H, dq, *J*=10.8 and 1.2 Hz), 5.11 (1H, d, *J*=6.4 Hz), 5.07 (1H, d, *J*=6.4 Hz), 5.06 (1H, dt, *J*=5.6 and 1.6 Hz), 4.04–4.01 (3H, m), 4.50 (2H, s), 3.75 (3H, s), 3.47 (3H, s), 2.19 (3H, s), 1.35 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 170.3 (C), 150.3 (C), 149.1 (C), 138.4 (CH), 138.4 (C), 133.3 (C), 132.2 (CH), 128.2 (CH), 128.2 (CH), 127.7 (CH), 127.7 (CH), 127.4 (CH), 126.0 (C), 125.0 (CH), 118.9 (CH_2), 115.9 (CH), 114.7 (CH), 95.4 (CH_2), 78.7 (CH), 71.6 (CH_3), 70.9 (CH_2), 56.0 (CH_3), 52.4 (CH_3), 34.7 (CH), 19.8 (CH_3), 16.2 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{32}O_6Na$ $[M+Na]^+$ 463.2097, found 463.2103.

*4.1.10. (4R,2E)-4-{2-[(3R)-1-(tert-Butyldiphenylsilyloxy)-4-hydroxy-4-methylpentan-3-yloxy]-5-(methoxymethoxy)-4-methylphenyl}pent-2-en-1-ol (**20**).* To a stirred solution of benzyl ether **13** (50.0 mg, 71.7 μmol) in THF (5.00 mL) was added solution of lithium di-*tert*-buthylbiphenilide (LiDBB) (1.45 M in THF, 0.500 mL, 0.717 mmol) at −78 °C. After being stirred for 3 min at −78 °C, the reaction mixture was treated with saturated aqueous NH_4Cl and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel hexane/AcOEt (2:1 v/v) as eluent to afford allyl alcohol **20** (39.6 mg, 91%) as a colorless oil; $[\alpha]_D^{25}$ −8.22 (*c* 1.06, $CHCl_3$); IR (neat) 3408, 2961, 1500, 1391, 1190, 1150, 1111, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.63 (2H, dd, *J*=1.2 and 6.4 Hz), 7.50 (2H, dd, *J*=1.2 and 6.4 Hz), 7.44–7.29 (6H, m), 6.97 (1H, s), 6.89 (1H, s), 5.82 (1H, dd, *J*=6.4 and 15.6 Hz), 5.60 (1H, dt, *J*=6.0 and 15.6 Hz), 5.12 (2H, t, *J*=1.2 Hz), 4.55 (1H, dd, *J*=3.2 and 8.4 Hz), 4.06 (2H, br m), 3.87 (1H, m), 3.71 (2H, m), 3.51 (3H, s), 2.13 (3H, s), 1.78–1.70 (1H, m), 2.63 (1H, br s, OH, D_2O exchangeable), 1.92–1.84 (1H, m), 1.79–1.70 (1H, m), 1.28 (3H, d, *J*=7.2 Hz), 1.26 (6H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 151.2 (C), 149.4 (C), 137.7 (CH), 135.5 (CH), 135.5 (CH), 135.4 (CH), 135.4 (CH), 133.4 (C), 133.3 (C), 131.3 (C), 129.7 (CH), 129.5 (CH), 128.1 (CH), 127.7 (CH), 127.7 (CH), 127.6 (CH), 127.6 (CH), 126.4 (C), 115.3 (CH), 114.5 (CH), 95.6 (CH_2), 81.1 (CH), 73.2 (C), 63.5 (CH_2), 60.2 (CH_2), 56.0 (CH_3), 34.7 (CH), 34.1 (CH_2), 26.8 (CH_3), 26.8 (CH_3), 26.8 (CH_3), 26.1 (CH_3), 24.8 (CH_3), 19.8 (CH_3), 19.1 (C), 16.1 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{36}H_{51}O_6Si$ $[M+H]^+$ 607.3455, found 607.3450.

*4.1.11. (3R)-3-{2-[(2R,3E)-5-(Allyloxy)pent-3-en-2-yl-4-(methoxymethoxy)-5-methylphenoxy]-5-tert-butyldiphenylsilyloxy}-2-methylpentan-2-ol (**21**).* To a stirred solution of allyl alcohol **20** (349 mg, 0.575 mmol) in THF (2.50 mL) was added NaH (69.0 mg, 1.73 mmol) at 0 °C. After being stirred for 0.5 h, the resultant mixture was added allyl bromide (0.150 mL, 1.73 mmol) at 0 °C. The mixture was allowed to warm to room temperature, and then stirring was continued for 6 h at the same temperature. The resultant mixture was treated with H_2O and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with hexane/AcOEt (4:1 v/v) as eluent to afford diene **21** (360 mg, 99%) as a colorless oil; $[\alpha]_D^{25}$ +3.21 (*c* 1.00, $CHCl_3$); IR (neat) 3463, 2960, 1500, 1190, 1111, 1011, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.62 (2H, d, *J*=6.4 Hz), 7.47 (2H, d, *J*=6.4 Hz), 7.44–7.28 (6H, m), 6.94 (1H, s), 6.87 (1H, s), 5.94–5.81 (2H, m), 5.54 (1H, dt, *J*=6.0 and 15.6 Hz), 5.25 (1H, dd, *J*=1.6 and 17.2 Hz), 5.16 (1H, dd, *J*=1.6 and 10.8 Hz), 5.12 (1H, d, *J*=10.8 Hz), 5.10 (1H, d, *J*=10.8 Hz), 4.55 (1H, dd, *J*=3.2 and 8.4 Hz), 3.94 (2H, d, *J*=8.8 Hz), 3.92 (2H, d, *J*=8.8 Hz), 3.87 (1H, m), 3.69 (2H, d, *J*=3.6 and 7.6 Hz), 3.50 (3H, s), 2.55 (1H, br s, OH, D_2O exchangeable), 2.13 (3H, s), 1.95–1.86 (1H, m), 1.79–1.72 (1H, m), 1.28–1.25 (9H, m), 1.02 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 151.1 (C), 149.4 (C), 138.8 (CH), 135.5 (CH), 135.5 (CH), 135.4 (CH), 135.4 (CH), 134.8 (CH), 133.4 (C), 133.4 (C), 131.6 (C), 129.7 (CH), 129.5 (CH), 127.7 (CH), 127.7 (CH), 127.6 (CH), 127.6 (CH), 126.3 (C), 124.9 (CH), 116.9 (CH_2), 115.4 (CH), 114.6 (CH), 95.7 (CH_2), 81.2 (CH), 73.0 (C), 70.9 (CH_2), 70.7 (CH_2), 60.3 (CH_2), 56.0 (CH_3), 34.7 (CH), 34.0 (CH_2), 26.8 (CH_3), 26.8 (CH_3), 26.8 (CH_3), 26.1 (CH_3), 25.0 (CH_3), 19.8 (CH_3), 19.1 (C), 16.2 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{39}H_{55}O_6Si$ $[M+H]^+$ 647.3768, found 647.3771.

*4.1.12. (3R)-3-{2-[(2R,3E)-5-(Allyloxy)pent-3-en-2-yl]-4-(methoxymethoxy)-5-methylphenoxy}4-methyl-pentane-1,4-diol (**22**).* To a stirred solution of TBDPS ether **21** (33.5 mg, 53.1 μmol) in THF (3.00 mL) was added TBAF (1.00 M in THF, 60.0 μL, 58.4 μmol) at room temperature. After being stirred for 3 min at room temperature, the reaction mixture was treated with water and extracted with CH_2Cl_2. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with hexane/AcOEt (3:2 v/v) as eluent to afford diol **22** (25.9 mg, quant.) as a colorless oil; $[\alpha]_D^{31}$ +5.72 (*c* 0.48, $CHCl_3$); IR (neat) 3398, 2966, 1500, 1190, 1150, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 6.86 (1H, s), 6.77 (1H, s), 5.95–5.84 (2H, m), 5.57 (1H, dt, *J*=6.4 and 15.6 Hz), 5.26 (1H, d, *J*=17.2 Hz), 5.17 (1H, d, *J*=10.4 Hz), 5.10 (2H, s), 4.33 (1H, t, *J*=5.6 Hz), 3.96–3.93 (4H, m), 3.85 (1H, dq, *J*=6.8 and 7.2 Hz), 3.80–3.75 (1H, m), 3.63–3.57 (1H, m), 3.49 (3H, s), 2.50 (2H, br s, OH, D_2O exchangeable), 2.21 (3H, s), 2.04–1.87 (2H, m), 1.33 (3H, d, *J*=7.2 Hz), 1.31 (3H, s), 1.29 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 150.2 (C), 149.4 (C), 138.7 (CH), 134.7 (CH), 131.8 (C), 126.2 (C), 124.9 (CH), 117.0 (CH_2), 115.0 (CH), 114.8 (CH), 95.6 (CH_2), 81.2 (CH), 72.9 (C), 71.0 (CH_2), 70.7 (CH_2), 59.1 (CH_2), 56.0 (CH_3), 35.2 (CH), 32.9 (CH_2),

26.2 (CH_3), 25.8 (CH_3), 19.9 (CH_3), 16.3 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{37}O_6$ $[M+H]^+$ 409.2590, found 409.2580.

*4.1.13. (3R)-3-{2-[(2R,3E)-5-(Allyloxy)pent-3-en-2-yl]-4-(methoxymethoxy)-5-methylphenoxy}-2-methyl-pent-4-en-2-ol (**23**).* To a stirred solution of diol **22** (20.0 mg, 49.0 μmol) in THF (2.00 mL) was added *o*-nitrophenylselenocyanide (22.2 mg, 97.9 μmol) and $^nBu_3P$ (20.2 μL, 97.9 μmol) at 0 °C. After being stirred for 5 min at 0 °C, the reaction mixture was concentrated to give the corresponding selenide (28.7 mg), as a yellow oil, which was used to the next reaction without further purification. To a stirred solution of selenide in THF (2.00 mL) was added 30% aqueous H_2O_2 (80.0 μL) at room temperature. After being stirred for 20 min at 60 °C, the reaction mixture was treated with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with hexane/AcOEt (4:1 v/v) as eluent to afford triene **23** (11.8 mg, 62% for two steps) as a yellow oil; $[\alpha]_D^{25}$ −8.35 (*c* 1.11, $CHCl_3$); IR (neat) 3467, 2973, 1501, 1392, 1191, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 6.86 (1H, s), 6.63 (1H, s), 5.95–5.78 (3H, m), 5.56 (1H, dt, *J*=6.0 and 15.6 Hz), 5.33–5.23 (3H, m), 5.16 (1H, dd, *J*=1.2 and 10.4 Hz), 5.10 (2H, s), 4.37 (1H, d, *J*=7.2 Hz), 3.96–3.87 (5H, m), 3.48 (3H, s), 2.48 (1H, br s, OH, D_2O exchangeable), 2.19 (3H, s), 1.34 (3H, d, *J*=6.8 Hz), 1.30 (3H, s), 1.27 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 149.7 (C), 149.5 (C), 138.7 (CH), 134.9 (CH), 134.3 (CH), 132.1 (C), 126.0 (C), 125.1 (CH), 119.7 (CH_2), 116.9 (CH_2), 116.2 (CH), 114.5 (CH), 95.7 (CH_2), 86.3 (CH), 72.5 (C), 71.0 (CH_2), 70.7 (CH_2), 56.0 (CH_3), 34.8 (CH), 25.7 (CH_3), 24.6 (CH_3), 19.9 (CH_3), 16.2 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{35}O_5$ $[M+H]^+$ 391.2484, found 391.2478.

*4.1.14. 2-{(2R,5R)-7-(Methoxymethoxy)-5,8-dimethyl-2,5-dihydrobenzo[b]oxepin}-2-ylpropan-2-ol (**15**).* To a stirred solution of triene **23** (11.8 mg, 30.2 μmol) in degassed CH_2Cl_2 (10.0 mL) was added Grubbs' second-generation catalyst (1.30 mg, 1.51 μmol) at room temperature. After being stirred for 3 h at room temperature, the reaction mixture was concentrated and the residue was chromatographed on silica gel with hexane/AcOEt (3:2 v/v) as eluent to afford *O*-MOM heliannuol B (**15**) (9.40 mg, quant.) as a yellow oil; $[\alpha]_D^{31}$ −51.1 (*c* 0.35, $CHCl_3$); IR (neat) 3446, 2972, 1502, 1150, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 6.84 (1H, s), 6.78 (1H, s), 5.99 (1H, ddd, *J*=2.4, 7.6, and 12.0 Hz), 5.48 (1H, d, *J*=12.0 Hz), 5.15 (1H, d, *J*=11.2 Hz), 5.13 (1H, d, *J*=11.2 Hz), 4.07 (1H, br s, OH, D_2O exchangeable), 3.49 (3H, s), 3.20 (1H, m), 2.76 (1H, br s, OH, D_2O exchangeable), 2.19 (3H, s), 1.44 (3H, d, *J*=7.2 Hz), 1.32 (3H, s), 1.30 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 151.8 (C), 151.0 (C), 137.9 (C), 134.0 (CH), 126.7 (C), 125.5 (CH), 123.9 (CH), 114.4 (CH), 95.1 (CH_2), 87.2 (CH), 72.3 (CH_3), 56.0 (CH), 40.0 (CH), 25.3 (CH_3), 24.7 (CH_3), 23.2 (CH_3), 15.8 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{24}O_4Na$ $[M+Na]^+$ 315.1572, found 315.1561.

*4.1.15. (−)-Heliannuol B (**1**).* To a stirred solution of *O*-MOM heliannuol B (**15**) (5.00 mg, 1.71 μmol) in THF (0.400 mL) was added 6 M aqueous HCl (1.60 mL) at 0 °C. After being stirred for 0.5 h at 0 °C, the reaction mixture was extracted with Et_2O. The combined extracts were washed with water and brine, and the residue upon workup was chromatographed on silica gel with hexane/AcOEt (7:3 v/v) as eluent to afford heliannuol B (**1**) (4.24 mg, quant.) as a yellow oil; $[\alpha]_D^{25}$ −75.5 (*c* 1.10, $CHCl_3$); IR (neat) 3364, 2975, 1508, 1417, 1192, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 6.81 (1H, s), 6.51 (1H, s), 5.97 (1H, ddd, *J*=1.2, 8.0, and 12.0 Hz), 5.49 (1H, dd, *J*=1.2 and 12.0 Hz), 4.81 (1H, br s, OH, D_2O exchangeable), 4.06 (1H, br s), 3.15 (1H, dq, *J*=7.5 and 7.5 Hz), 2.82 (1H, br s, OH, D_2O exchangeable), 2.19 (3H, s), 1.43 (3H, d, *J*=7.2 Hz), 1.32 (3H, s), 1.30 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 150.2 (C), 150.0 (C), 138.3 (C), 133.9 (CH), 125.6 (CH), 124.0 (CH), 122.7 (C), 114.8 (CH), 87.3 (CH), 72.5 (C), 39.7 (CH), 25.3 (CH_3), 24.7 (CH_3), 23.2 (CH_3), 15.4 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}O_3$ $[M+H]^+$ 249.1491, found 249.1506.

*4.1.16. (+)-Heliannuol D (**2**).* A suspension of heliannuol B (**1**) (4.00 mg, 1.61 μmol) and Pd–C (0.400 mg, 10% w/w) in AcOEt (2.00 mL) was stirred under 1 atm of hydrogen gas. After being stirred for 2.5 h at room temperature, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (3:2 v/v) as eluent to afford alcohol **16** (3.80 mg, 94%) as a colorless oil; mp 157–158 °C (lit.[5f,h] 161–162 °C); $[\alpha]_D^{25}$ +18.2 (*c* 0.75, $CHCl_3$); IR (neat) 3365, 2931, 1508, 1417, 1192, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 6.73 (1H, s), 6.54 (1H, s), 4.55 (1H, br s, OH, D_2O exchangeable), 3.30 (1H, d, *J*=10.8 Hz), 2.90 (1H, br s), 2.70 (1H, br s, OH, D_2O exchangeable), 2.16 (3H, s), 2.09–1.99 (1H, m), 1.92–1.88 (1H, m), 1.79–1.70 (2H, m), 1.28 (3H, d, *J*=7.2 Hz), 1.28 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) 151.7 (C), 149.6 (C), 138.1 (C), 123.5 (CH), 122.1 (C), 115.8 (CH), 90.5 (CH), 72.7 (C), 38.5 (CH), 31.8 (CH_2), 26.1 (CH_2), 25.5 (CH_3), 24.4 (CH_3), 18.6 (CH_3), 15.3 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1647, found: 251.1643.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.11.070. These data include MOL files and InChiKeys of the most important compounds described in this article.

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