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Asymmetric syntheses of heliannuols B and D

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Abstract—The synthesis of heliannuol D along with the first synthesis of heliannuol B has been achieved using Mitsunobu reaction and ring-closing metathesis as the key steps.

1. Introduction

Heliannuols (A–L), a new class of sesquiterpenes possessing interesting allelopathic activity were isolated from *Helianthus annuus* by Macías and co-workers.[1] These compounds feature novel structure of benzo-fused six-, seven-, and eight-membered cyclic ethers. The confluence of structural distinction and notable biological activity has made these sesquiterpenes attractive targets for chemical synthesis.[2] Heliannuols B (**1**) and D (**2**) contain the same basic skeleton (Fig. 1). The absolute configuration of **2** as (7*R*,10*R*) has been determined by two total syntheses of Shishido.[2c,f] To the best of our knowledge, none preparations of **1** have been reported. Herein we report the synthesis of heliannuol D along with the first synthesis of heliannuol B with a common strategy.

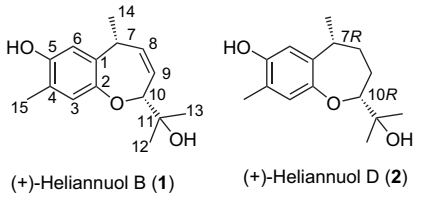
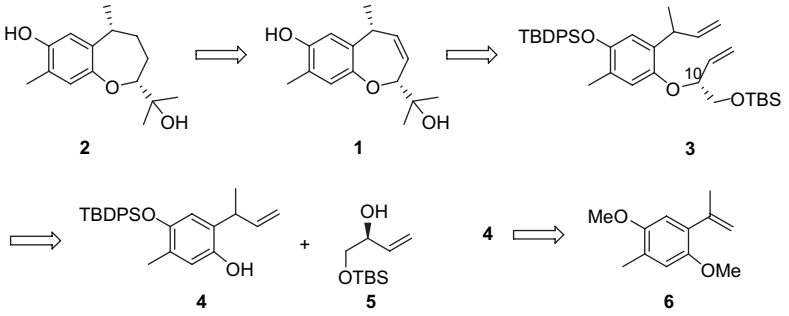


Figure 1.

Our retrosynthetic analysis of **1** and **2** is depicted in Scheme 1. Heliannuol D (**2**) could be derived from **1** via a catalytic hydrogenation reaction. Through a ring-closing metathesis reaction, the construction of the benzo-fused seven-membered framework of **1** was envisioned available from **3**, which could be accomplished by Mitsunobu reaction of phenol **4** and alcohol **5**. The stereocenter at C-10 could be established at this stage. The compound **4**, in turn, would be prepared from styrene **6**.



Scheme 1. Retrosynthetic analysis of **1** and **2**.

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2. Results and discussion

The syntheses commenced from olefin **6**.[3] As shown in Scheme 2, hydroboration of **6** gave the racemic alcohol **7**, which was then oxidized to aldehyde **8** with Dess–Martin periodinane[4] followed by a Wittig reaction to afford olefin **9**. After an oxidation with CAN, compound **9** was converted to quinone **10**.[5] Reduction of the quinone with $Na_2S_2O_4$ gave hydroquinone **11**. Selective protection of the sterically less congested hydroxyl moiety (C-5) of **11** as the *tert*-butyldiphenylsilyl ether led to phenol **4**.

With phenol **4** in hand, we turned to construct the framework of the final products (Scheme 3). The (*S*)-allylic alcohol **5** was obtained from mannitol through literature procedures.[6] Mitsunobu reaction[7] between **4** and (*S*)-**5** furnished diene **3** with inversion of the C-10 configuration. Treatment of **3** with the second-generation Grubbs catalyst **12**[8] produced the separable benzoxepenes (7*R*,10*R*)-**13** and (7*S*,10*R*)-**14**, via ring-closing metathesis reaction.

To achieve heliannuol B (**2**) from **13**, several functional group transformations were required (Scheme 4). Selective cleavage of the TBS ether of **13** under acidic conditions, followed by oxidation with IBX[9] of the resulting primary alcohol **15**, gave the corresponding aldehyde **16**. This crude aldehyde was not purified and was directly attacked by MeMgI to obtain secondary alcohol **17**. A second oxidation/MeMgI attack operation of **18**, the tertiary alcohol **19** was gained. Finally, deprotection of the TBDPS of **19** with TBAF in THF gave the desired (−)-heliannuol B (**2**). Furthermore, catalytic hydrogenation of **2** was conducted with Pd/C (5%) in EtOAc to afford (+)-heliannuol D (**1**).

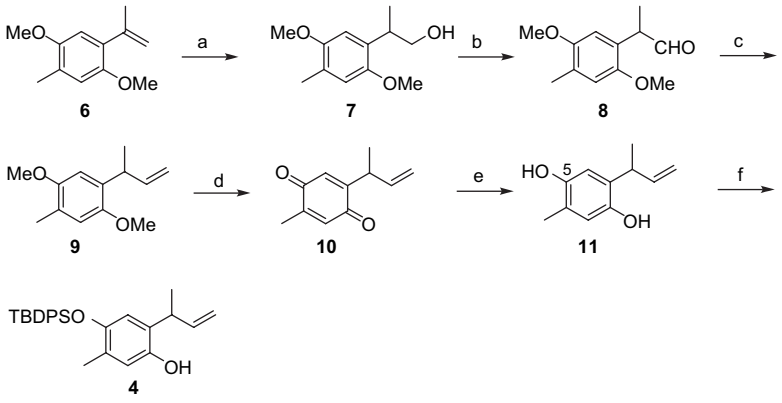
3. Conclusion

In summary, asymmetric syntheses of the sesquiterpenes heliannuols B and D have been accomplished with a common strategy, in which heliannuol B was synthesized for the first time. The stereocenter at C-10 was introduced from allylic alcohol (*S*)-**5** via Mitsunobu reaction. Two diastereoisomers (7*R*,*10R*)-**12** and (7*S*,*10R*)-**13** were separated after a ring-closing metathesis reaction.

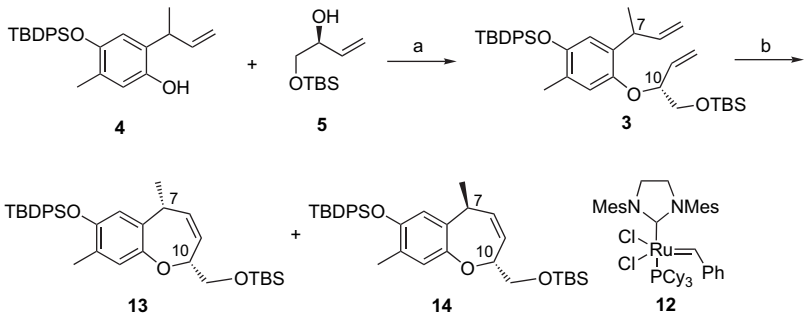
4. Experimental

4.1. General

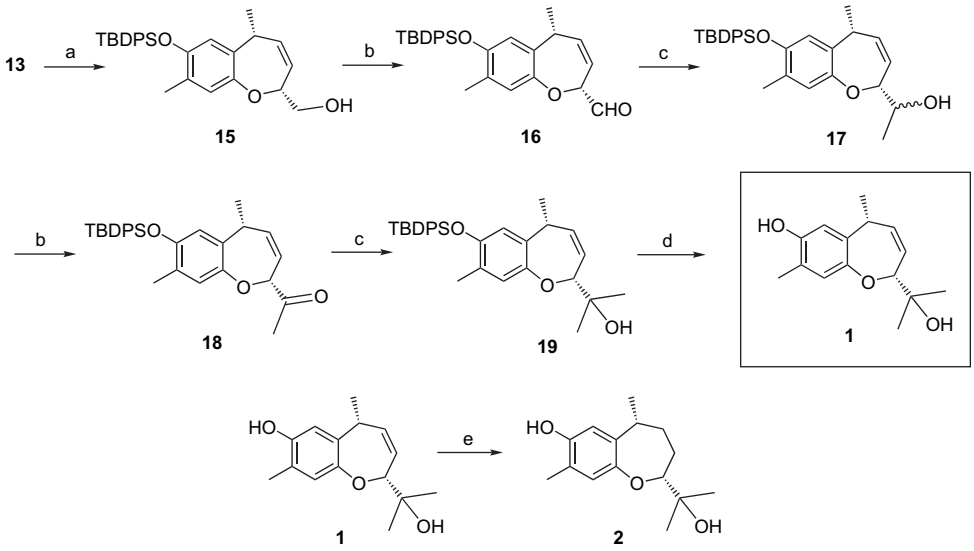
Oxygen- and moisture-sensitive reactions were carried out an under argon atmosphere. Solvents were purified and dried by standard methods prior to use. All commercially available reagents were used without further purification unless otherwise noted. Column chromatography was performed on silica gel (200–300 mesh). Melting points were measured on a Kofler apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer model 341 polarimeter. Infrared spectra were recorded on a Nicolet NEXUS 670 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded



Scheme 2. Reagents and conditions: (a) $BH_3\cdot$THF, THF, 0 °C, then NaOH, H_2O_2, rt, 87%; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 93%; (c) $Ph_3P^+CH_2I^-$, *n*-BuLi, THF, 0 °C–rt, 87%; (d) CAN, 1:1 CH_3CN/H_2O, rt, 98%; (e) $Na_2S_2O_4$, Et_2O, H_2O, rt, 97%; and (f) TBDPSCl, imidazole, DMAP (cat), 0 °C, 73%.



Scheme 3. Reagents and conditions: (a) DIAD, PPh_3, THF, rt, 71% and (b) second-generation Grubbs catalyst **12**, CH_2Cl_2, rt, 47% for **13** and 45% for **14**.



Scheme 4. Reagents and conditions: (a) TsOH, 10:1 THF/H_2O, rt, 91%; (b) IBX, 9:1 THF/DMSO, rt; (c) MeMgI, Et_2O, rt, 84% for **17** and 81% for **19** over 2 steps; (d) TBAF, THF, rt, 96%; and (e) Pd/C, H_2, EtOAc, rt, 98%.

on Varian Mercury-300 (300 MHz) spectrometers. Chemical shifts are reported as δ values relative to internal chloroform (δ 7.26 for ^{1}H and 77.0 for ^{13}C).

4.1.1. 2-(2,5-Dimethoxy-4-methylphenyl)propan-1-ol (7). To a solution of $BH_3\cdot$THF in THF (1.0 M, 22.0 mL, 22.0 mmol) at 0 °C was added a solution of olefin **6** (3.84 g, 20.0 mmol) in 60 mL THF. After 1 h, 8 mL of 30% H_2O_2 and 16 mL of 10% NaOH were added. The resulting mixture was warmed to rt and stirred for an additional 2 h. The reaction mixture was then diluted with EtOAc and the layers were separated. The aqueous phase was extracted with EtOAc (3×50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 6:1) to give alcohol **7** (3.652 g, 87%) as white crystals. Mp 74–75 °C; IR (KBr) 3375, 1506, 1208, 1046 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, J=7.2 Hz, 3H), 2.21 (s, 3H), 3.36–3.45 (m, 1H), 3.70 (dd, J=7.5, 1.2 Hz), 3.79 (s, 3H), 3.80 (s, 3H), 6.70 (s, 1H), 6.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 16.4, 35.4, 56.1, 56.2, 67.9, 110.2, 114.3, 125.2, 129.6, 151.0, 151.9; HRMS (*m*/*z*) calcd for $C_{12}H_{18}O_3Na$, 233.1154 [M+Na]$^+$; found, 233.1158.

4.1.2. 2-(2,5-Dimethoxy-4-methylphenyl)propanal (8). To a stirred solution of alcohol **7** (3.61 g, 17.2 mmol) in dry CH_2Cl_2 (100 mL) was added Dess–Martin periodinane (10.20 g, 24.07 mmol) in one portion. The mixture was stirred for 1 h at rt and quenched with a 1:1 mixture of saturated $Na_2S_2O_3$ (40 mL) and saturated $NaHCO_3$ (40 mL). The resulting mixture was diluted with CH_2Cl_2 (50 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 15:1) to give aldehyde **8** (3.318 mg, 93%) as colorless oil. IR (KBr) 2935, 1733, 1411, 1258, 861 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, J=7.2 Hz, 3H), 2.23 (s, 3H), 3.78 (s, 3H), 3.78 (s, 3H), 3.81–3.88 (m, 1H), 6.58 (s, 1H), 6.75 (s, 1H), 9.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 16.2, 47.2, 56.0, 111.5, 114.1, 124.4, 126.6, 150.7, 151.9, 202.0; HRMS (*m*/*z*) calcd for $C_{12}H_{16}O_3Na$, 231.0997 [M+Na]$^+$; found, 231.1001.

4.1.3. 1-(But-3-en-2-yl)-2,5-dimethoxy-4-methylbenzene (9). To a suspension of methyltriphenylphosphonium iodide (8.02 g, 19.85 mmol) in dry THF (50 mL) at 0 °C was added *n*-BuLi (10.5 mL, 1.8 M in hexanes, 18.91 mmol). The reaction mixture was stirred for 15 min at 0 °C and was then warmed to rt while stirring was continued for 45 min. The solution was then recooled to 0 °C, and a solution of aldehyde **8** (3.276 g, 15.75 mmol) in dry THF (20 mL) was added slowly via syringe. The reaction mixture was then warmed to rt and stirred for an additional 2 h. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O (3×50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 50:1) to give alkene **9** (2.828 g, 87%) as a colorless oil. IR (KBr) 3388, 2970, 1505, 1208, 1047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J=7.2 Hz, 3H), 2.23 (s, 3H), 3.80 (s, 3H), 3.80 (s, 3H), 3.92 (dq, J=7.2, 6.0 Hz, 1H), 5.05–5.11 (m, 2H), 6.07 (ddd, J=16.1, 10.3, 6.0 Hz, 1H), 6.67 (s, 1H), 6.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 19.5, 35.5, 56.0, 56.3, 110.2, 112.8, 114.3, 124.7, 131.9, 142.9, 150.4, 151.7; HRMS (*m*/*z*) calcd for $C_{13}H_{19}O_2$, 207.1386 [M+H]$^+$; found, 207.1384.

4.1.4. 2-(But-3-en-2-yl)-5-methylcyclohexa-2,5-diene-1,4-dione (10). To a solution of **9** (2.794 g, 13.56 mmol) in CH_3CN (34 mL) at rt was added a solution of CAN (18.58 g, 33.91 mmol) in H_2O (34 mL) in one portion with stirring. After 5 min, H_2O (120 mL) and CH_2Cl_2 (120 mL) were added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3×80 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was

purified by column chromatography (hexanes/EtOAc, 50:1) to give **10** (2.339 g, 98%) as a yellow oil. IR (KBr) 3073, 2850, 1660, 1244, 1112; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, J=7.2 Hz, 3H), 1.99 (s, 3H), 3.55–3.60 (m, 1H), 5.03–5.11 (m, 2H), 5.79 (ddd, J=16.5, 10.5, 7.2 Hz, 1H), 6.46 (s, 1H), 6.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 18.3, 35.0, 115.4, 131.5, 133.6, 139.2, 145.2, 152.0, 186.8, 188.2; HRMS (*m*/*z*) calcd for $C_{11}H_{12}O_2$, 176.0837 $[M]^+$; found, 176.0833.

4.1.5. 2-(But-3-en-2-yl)-4-[(*tert*-butyldiphenyl)oxyl]-5-methylphenol (4). To the quinone **10** (2.328 g, 13.23 mmol) in Et_2O (50 mL) at rt was added an aqueous solution of $Na_2S_2O_4$ (9.22 g, 52.91 mmol, in 50 mL H_2O) in one portion with rapid stirring. After 20 min more $Na_2S_2O_4$ solution (50 mL) was added. Fifteen minutes later the layers were separated, and the aqueous phase was extracted with Et_2O (3×50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4 containing $Na_2S_2O_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes/EtOAc, 6:1) to give accordingly 1,4-dihydroquinone **11** (2.284 g, 97%) as a colorless oil. This dihydroquinone was used for the next step immediately.

Under Ar, to a stirred solution of compound **11** (2.273 g, 12.77 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C were added imidazole (1.04 g, 15.23 mmol) followed by TBDPSCl (3.69 g, 13.41 mmol) and DMAP (78 mg, 0.64 mmol). After stirring overnight at 0 °C, the reaction mixture was quenched with H_2O and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/CH_2Cl_2, 2:1) to give **4** (3.875 g, 73%) as a colorless oil. IR (KBr) 3398, 2931, 1507, 1410, 1197, 1111, 910, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J=7.2 Hz, 3H), 1.18 (s, 9H), 2.35 (s, 3H), 3.33–3.42 (m, 1H), 4.67 (s, 1H), 4.88–4.94 (m, 2H), 5.68 (ddd, J=16.4, 10.6, 6.8 Hz, 1H), 6.24 (s, 1H), 6.64 (s, 1H), 7.37–7.48 (m, 6H), 7.74–7.77 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 18.5, 19.6, 26.7, 36.8, 113.7, 117.8, 118.2, 126.9, 127.6, 127.7, 129.7, 133.3, 135.5, 142.2, 146.9, 147.7; HRMS (*m*/*z*) calcd for $C_{27}H_{32}O_2Si$, 416.2172 $[M]^+$; found, 416.2177.

4.1.6. Dialkene 3. Under Ar, to a solution of PPh_3 (2.405 g, 9.16 mmol), phenol **4** (3.812 g, 9.16 mmol) and (*S*)-1-[(*tert*-butyldimethyl)oxyl] but-3-en-2-ol **5** (1.680 g, 8.33 mmol) in dry THF (40 mL) at 0 °C was added dropwise DIAD (1.853 g, 9.06 mmol). The reaction mixture was warmed to rt and stirred overnight. The solvent was then evaporated and the residue was purified by column chromatography (hexanes/EtOAc, 100:1) to give **3** (3.546 g, 71%) as a colorless oil. This product is a mixture of two diastereoisomers at C-7.

4.1.7. Compounds 13 and 14. To a solution of **3** (1.356 g, 2.26 mmol) in degassed CH_2Cl_2 (230 mL) at rt was added the second-generation Grubbs catalyst **12** (192 mg, 0.226 mmol). The reaction mixture was stirred at rt for 15 h. The solvent was then evaporated and the residue was purified by column chromatography (hexanes/CH_2Cl_2, 15:1) to give both (7*R*,10*R*)-**13** (609 mg, 47%) and (7*S*,10*R*)-**14** (553 mg, 43%) as colorless oils. Compound **13**: $[\alpha]_D^{25}$: −10 (*c* 0.7, $CHCl_3$); IR (KBr) 2930, 1500, 1201, 1112, 839, 704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 1.04 (d, J=7.8 Hz, 3H), 1.10 (s, 9H), 2.30 (s, 3H), 2.85 (dq, J=7.6, 6.5 Hz, 1H), 3.60 (dd, J=10.2, 5.7 Hz, 1H), 3.78 (dd, J=10.5, 7.4 Hz, 1H), 4.31–4.33 (m, 1H), 5.34 (dd, J=12.0, 5.6 Hz, 1H), 5.67 (ddd, J=11.7, 6.3, 2.4 Hz, 1H), 6.08 (s, 1H), 6.83 (s, 1H), 7.32–7.43 (m, 6H), 7.67–7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, 16.7, 18.3, 19.6, 22.3, 25.9, 26.6, 38.2, 65.9, 80.5, 117.8, 124.3, 126.5, 126.7, 127.6, 127.7, 129.8, 133.5, 135.4, 135.5, 137.4, 150.0; HRMS (*m*/*z*) calcd for $C_{35}H_{48}O_3Si_2$, 572.3142 $[M]^+$; found, 572.3151. Compound **14**: $[\alpha]_D^{25}$: +31 (*c* 1.1, $CHCl_3$); IR (KBr) 2930, 1499, 1199, 1111, 839, 704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.80 (d, J=7.2 Hz, 3H), 0.94 (s, 9H), 1.12 (s, 9H), 2.32 (s, 3H), 3.59 (dq, J=7.4, 3.2 Hz, 1H), 3.63 (dd, J=10.4, 4.8 Hz, 1H), 3.78 (dd, J=10.4, 7.2 Hz, 1H), 4.37 (dd, J=4.4, 2.4 Hz, 1H), 5.25 (dd, J=12.4, 2.4 Hz, 1H), 5.47 (ddd, J=12.6, 8.0, 4.0 Hz), 6.16 (s, 1H), 6.87 (s, 1H), 7.34–7.44 (m, 6H), 7.69–7.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, 16.6, 18.4, 18.7, 19.6, 25.9, 26.7, 32.7, 40.1, 65.3, 81.1, 115.4, 124.0, 126.2, 126.6, 127.7, 129.8, 133.4, 134.8, 135.5, 138.2, 149.7; HRMS (*m*/*z*) calcd for $C_{35}H_{48}O_3Si_2$, 572.3142 $[M]^+$; found, 572.3149.

4.1.8. {(7*R*,10*R*)-7,10-Dihydro-5-[(*tert*-butyldiphenyl)-oxyl]-4,7-dimethylbenzo[*b*]oxepin-2-yl}methanol (15). To a solution of **12** (561 mg, 0.98 mmol) in 10:1 THF/H_2O (11 mL) was added $TsOH\cdot 2H_2O$ (19 mg, 0.10 mmol). The resulting solution was stirred at rt for 24 h. Saturated $NaHCO_3$ was added, and the mixture was extracted with EtOAc (4×15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 10:1) to give **15** (409 mg, 91%) as a white foam. $[\alpha]_D^{25}$: −8 (*c* 0.5, $CHCl_3$); IR (KBr) 2959, 1500, 1200, 1110, 923, 705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, J=7.2 Hz, 3H), 1.12 (s, 9H), 2.33 (s, 3H), 2.37 (br s, 1H), 2.80 (dq, J=7.2, 6.9 Hz, 1H), 3.67–3.71 (m, 2H), 4.38–4.42 (m, 1H), 5,22 (dd, J=11.7, 1.1 Hz, 1H), 5.75 (ddd, J=11.7, 6.9, 2.4 Hz, 1H), 6.10 (s, 1H), 6.85 (s, 1H), 7.33–7.45 (m, 6H), 7.68–7.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 19.6, 22.7, 26.6, 38.7, 65.6, 80.9, 118.3, 123.9, 125.2, 127.1, 127.6, 129.8, 132.8, 133.1, 134.4, 135.4, 137.1, 149.9; HRMS (*m*/*z*) calcd for $C_{29}H_{34}O_3SiNa$, 481.2175 $[M+Na]^+$; found, 481.2178.

4.1.9. (7*R*,10*R*)-7,10-Dihydro-5-[(*tert*-butyldiphenyl)-oxyl]-4,7-dimethylbenzo[*b*]oxepin-carbaldehyde (16). A mixture of alcohol **15** (376 mg, 0.82 mmol) and IBX (1.152 g, 4.11 mmol) in THF/DMSO (9:1, 24 mL) was stirred for 4 h at rt, diluted with hexanes, filtered through Celite, and rinsed with hexanes/EtOAc (3:1). The filtrate was transferred to a separated funnel and washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give the crude aldehyde **16**. This crude aldehyde was used directly in the following step without further purification.

4.1.10. Compound 17. To a solution of MeMgI in Et_2O (0.5 M, 3.96 mL, 1.98 mmol) at 0 °C was added a solution

of the above crude aldehyde **16** (374 mg, 0.82 mmol) in dry Et_2O (5 mL). The reaction mixture was warmed to rt and stirred for 30 min. The reaction was quenched with saturated NH_4Cl and the layers were separated. The aqueous phase was extracted with Et_2O (3×10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 10:1) to give **17** (324 mg, 84% over 2 steps) as a colorless oil. This product is a mixture of two diastereoisomers at C-11.

4.1.11. 2-{(7*R*,10*R*)-7,10-Dihydro-5-[(*tert*-butyldiphenyl)-oxyl]-4,7-dimethylbenzo[*b*]oxepin-2-yl}propan-2-ol (19). Alcohol **17** (289 mg, 0.61 mmol) was subjected to the same oxidation/MeMgI attack operation as described above for alcohol **15**. Workup as above and column chromatography (hexanes/EtOAc, 30:1) afforded alcohol **19** (242 mg, 81% over 2 steps) as a colorless oil. $[\alpha]_D^{25}$: −5 (*c* 0.5, $CHCl_3$); IR (KBr) 2961, 1489, 1197, 923, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.11 (d, *J*=6.6 Hz, 3H), 1.27 (s, 6H), 2.32 (s, 3H), 2.62–2.72 (m, 1H), 2.77 (br s, 1H), 4.05 (d, *J*=1.1 Hz, 1H), 5.41 (dd, *J*=11.7, 1.1 Hz, 1H), 5.77 (ddd, *J*=11.7, 7.5, 2.4 Hz, 1H), 6.08 (s, 1H), 6.83 (s, 1H), 7.32–7.47 (m, 6H), 7.66–7.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 19.6, 24.5, 25.2, 26.6, 26.7, 39.4, 72.3, 86.9, 118.4, 123.6, 125.2, 127.2, 127.6, 127.8, 129.8, 132.8, 133.9, 135.4, 137.0, 149.8; HRMS (*m*/*z*) calcd for $C_{31}H_{38}O_3SiNa$, 509.2488 $[M+Na]^+$; found, 509.2483.

4.1.12. Heliannuol B (1). Under Ar, to a solution of **19** (183 mg, 0.38 mmol) in THF at rt was added $TBAF\cdot 3H_2O$ (356 mg, 1.13 mmol) in one portion. After stirring at rt for 12 h, the solvent was evaporated in vacuo and the residue was purified by column chromatography (hexanes/EtOAc, 5:1) to give heliannuol B (**1**) (89 mg, 96%) as a colorless oil. $[\alpha]_D^{25}$: −22 (*c* 0.7, $CHCl_3$); IR (KBr) 3386, 1630, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.32 (s, 3H), 1.43 (d, *J*=7.2 Hz), 2.18 (s, 3H), 2.86 (br s, 1H), 3.14 (dq, *J*=7.5, 7.3 Hz, 1H), 4.11 (br s, 1H), 5.48 (dd, *J*=12.0, 1.2 Hz, 1H), 5.97 (ddd, *J*=12.0, 7.6, 2.4 Hz, 1H), 6.51 (s, 1H), 6.82 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 23.2, 24.5, 25.2, 39.6, 72.5, 87.2, 114.7, 122.6, 124.0, 125.5, 133.8, 138.2, 150.0; HRMS (*m*/*z*) calcd for $C_{15}H_{20}O_3$, 248.1412 $[M]^+$; found, 248.1416.

4.1.13. Heliannuol D (2). A mixture of heliannuol B (**1**) (47 mg, 0.19 mmol) and Pd/C (5%) (10 mg, 2.5 mol %) in EtOAc (5 mL) at rt was hydrogenated under a H_2 atmosphere. After stirring at rt for 2.5 h, the reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 4:1) to give heliannuol D (**2**) (46 mg, 98%) as colorless crystals. Mp 160–161 °C; $[\alpha]_D^{25}$: +23 (*c* 0.7, $CHCl_3$); IR (KBr) 3372, 2955, 2924, 1620, 1266 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.27 (s, 3H), 1.27 (s, 3H), 1.28 (d, *J*=7.2 Hz, 3H), 1.69–1.73 (m, 1H), 1.74–1.78 (m, 1H), 1.85–1.90 (m, 3H), 2.01–2.05 (m, 1H), 2.16 (s, 3H), 2.87–2.90 (m, 1H), 3.29 (dd, *J*=11.1, 1.5 Hz), 4.54 (br s, 1H), 6.54 (s, 1H), 6.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 18.6, 24.4, 25.5, 26.1, 31.7, 38.5, 72.6, 90.5, 115.7, 121.9, 123.5, 138.1, 149.5, 151.7; HRMS (*m*/*z*) calcd for $C_{15}H_{22}O_3$, 250.1569 $[M]^+$; found, 250.1573.

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