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SYNTHESIS OF (±)-HELIANNUOL D BASED ON PLATINUM CATALYZED REGIOSELECTIVE ADDITION OF ARYLBORONIC ACIDS TO ALLENES[†]

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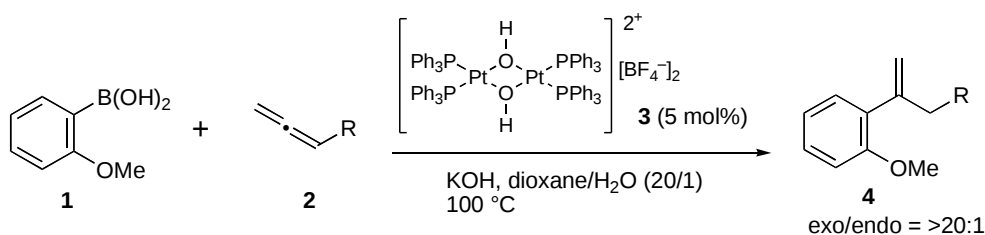
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Abstract – An alternative total synthesis of (±)-heliannuol D has been achieved in 13 steps and 6.9% overall yield from the arylboronic acid **9**. The synthesis applies the previously developed regiocontrolled addition of arylboronic acids to allenes using a platinum catalyst to install the C5 carbon chain on the aryl ring.

INTRODUCTION

In our previous paper, we reported the regiocontrolled addition of arylboronic acids **1** to allenes **2** using the platinum catalyst **3** leading to the formation of *exo*-olefinic products **4** with high yields and regioselectivity (>20:1).¹ The procedure would be useful for the synthesis of natural products with a tertiary stereogenic center at the benzylic position by hydrogenation of the products. (Scheme 1)

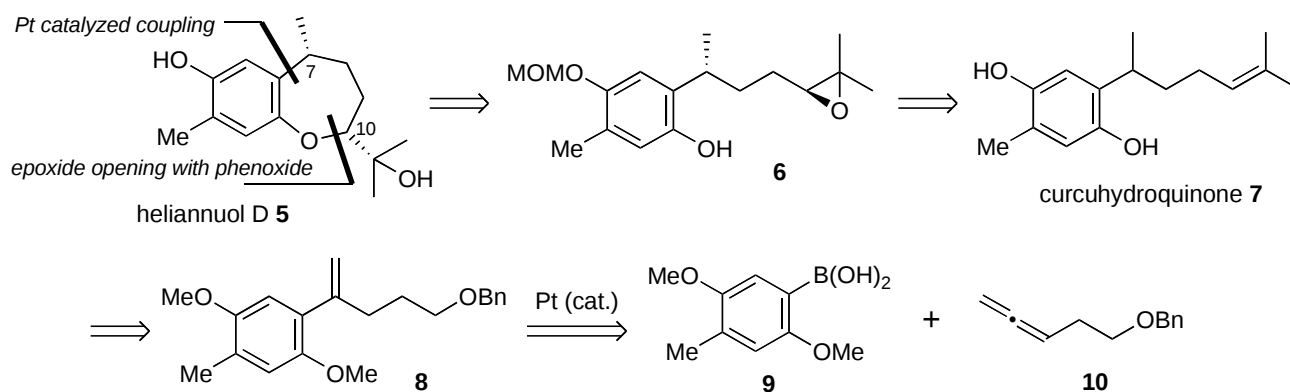


Scheme 1. Regiocontrolled addition of arylboronic acids to allenes using platinum catalyst

[†] This paper is dedicated to Dr. Akira Suzuki on the occasion of his 80th birthday.

RESULTS AND DISCUSSION

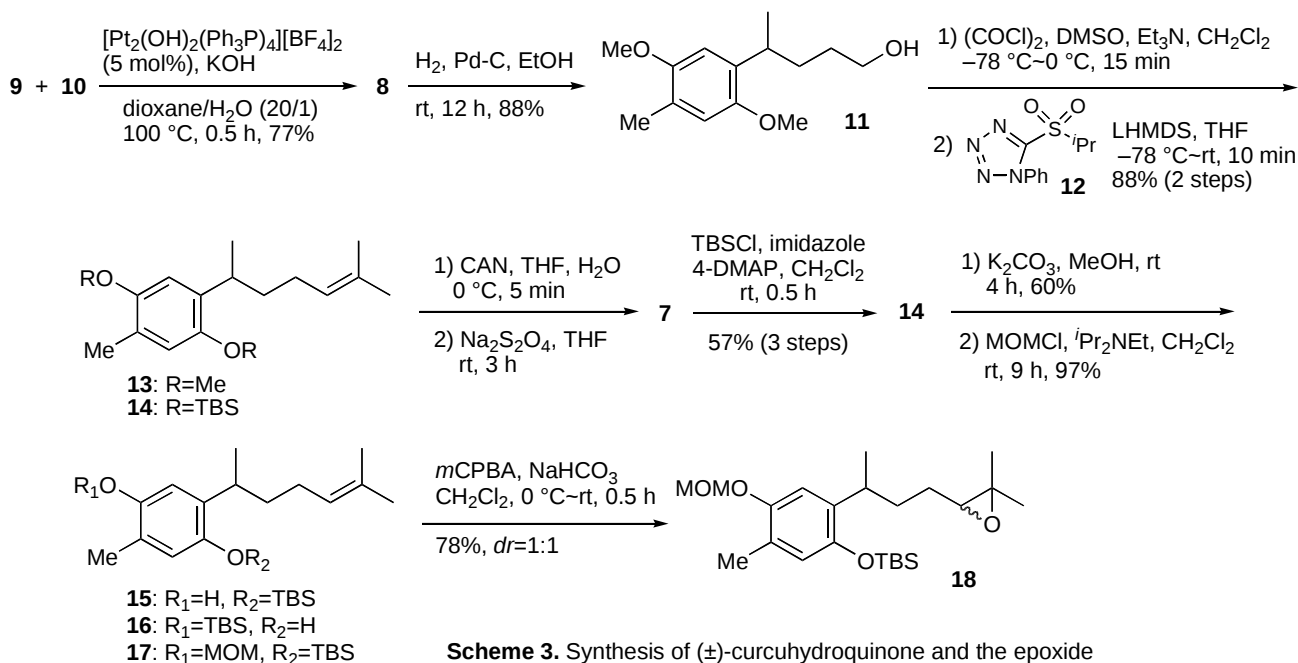
During the course of our projects directed towards an efficient synthesis of allelochemicals for the development of a new type of environmentally benign herbicides,² we planned to apply this cross coupling reaction to the synthesis of heliannuol type sesquiterpenoids isolated from the aqueous extracts of fresh sunflower leaves (*Helianthus annuus* var. SH-222).³ As a target allelochemical, we chose heliannuol D (**5**),^{3b} which has a unique carbon skeleton made up of an oxygen-containing seven-membered heterocycle fused to the aryl ring and two stereogenic centers whose absolute configurations were determined to be *C*-7*R* and *C*-10*R*, respectively, by our enantioselective total synthesis of (–)-**5**.^{4a} Because of the intriguing structural features and the allelopathic activity of **5**, three enantioselective total syntheses⁴ and six racemic syntheses⁵ have been reported so far. Herein we report a new approach to the total synthesis of (±)-heliannuol D using the cross coupling methodology for the application to the allelochemical synthesis. Approaching the synthesis from a retrosynthetic perspective, we envisioned the following scheme: (±)-**5** would be derived from the phenolic epoxide **6** employing the intramolecular etherification we previously developed. The epoxide **6** would be prepared *via* curcuhydroquinone **7**,⁶ which can be made by catalytic hydrogenation followed by demethylation of **8**. The *exo*-olefinic compound **8** could in turn be synthesized by the platinum catalyzed cross coupling reaction of the boronic acid **9** with the allene **10**. (Scheme 2)



Scheme 2. Retrosynthetic Analysis

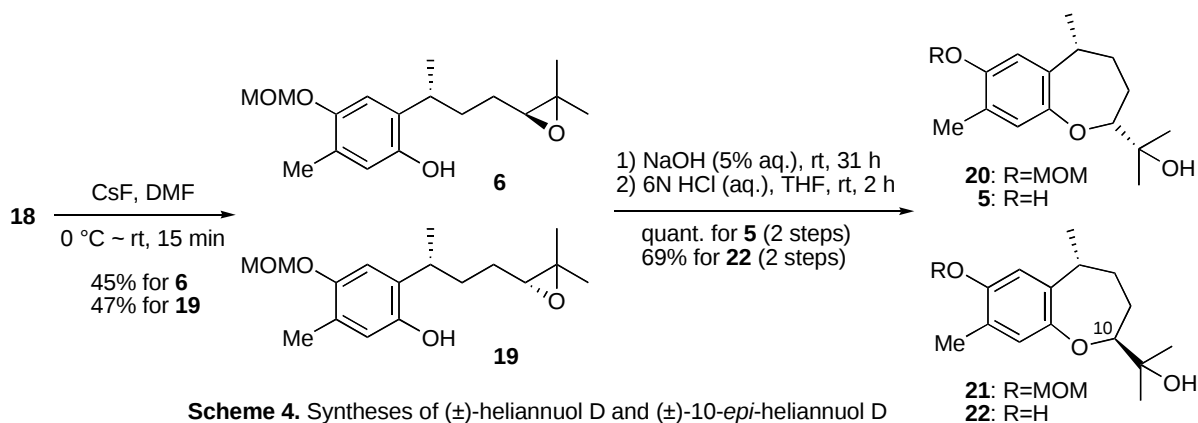
Treatment of a mixture of the boronic acid **9**⁷ and the allene **10**⁸ with a catalytic amount of the platinum complex, $[\text{Pt}_2(\text{OH})_2(\text{Ph}_3\text{P})_4][\text{BF}_4]_2$ (**3**),¹ and KOH in dioxane/ H_2O (20/1) at 100 °C for 0.5 h furnished in 77% yield the coupled product **8**, which was subjected to catalytic hydrogenation to give the alcohol **11**.⁹ Swern oxidation and Julia-Kocienski olefination of the aldehyde with the sulfone **12**¹⁰ in the presence of LHMDS provided the alkene **13**^{4a} in good overall yield. Oxidation of **13** with ceric ammonium nitrate (CAN) in aqueous THF followed by immediate reduction of the resulting quinone with $\text{Na}_2\text{S}_2\text{O}_4$ provided (±)-curcuhydroquinone (**7**),⁶ which was treated with TBSCl, imidazole and 4-DMAP to give the bis-TBS

ether **14**^{4a} in 57% yield for the 3 steps. Desilylation of **14** with K₂CO₃ in MeOH furnished a separable mixture of the mono-TBS ethers **15** (the desired), **16** (the undesired but which can be recycled¹¹) and the recovered **14** in 60%, 17% and 12% yield, respectively. The desired **15** was converted to the methoxymethyl (MOM) ether **17**, which was oxidized with *m*CPBA to give the epoxide **18**^{4a} as an inseparable 1:1 mixture of diastereomers. (Scheme 3)



Scheme 3. Synthesis of (±)-curcuhydroquinone and the epoxide

Deprotection of the TBS ether in **18** was realized by treatment with CsF in DMF at 0 °C to give a chromatographically separable mixture of the phenolic epoxides **6**^{4a} and **19** in 45% and 47% yield, respectively. Finally, **6** was treated with 5% aqueous NaOH to produce the 7-membered cyclized product **20**, which was hydrolyzed with 6N HCl (aq.) to give (±)-heliannuol D (**5**) quantitatively. The spectroscopic properties of the synthesized compound **5** were completely identical with those for the natural product.³⁻⁵ Similarly, **19** was transformed to (±)-10-*epi*-heliannuol D (**22**)^{5a,c} in 69% yield for the 2 steps. (Scheme 4)



Scheme 4. Syntheses of (±)-heliannuol D and (±)-10-*epi*-heliannuol D

In conclusion, an alternative total synthesis of ($\pm$)-heliannuol D (**5**) has been achieved in 13 steps and 6.9% overall yield from the arylboronic acid **9**. This synthesis highlights the utility of the regiocontrolled addition of arylboronic acids to allenes using platinum catalyst developed in our laboratories. The synthetic route developed here is efficient and flexible for obtaining a variety of derivatives (*e.g.* 10-*epi*-heliannuol D), which can be supplied for evaluation of the allelopathic activity.

EXPERIMENTAL

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.

1-{5-(Benzyloxy)pent-1-en-2-yl}-2,5-dimethoxy-4-methylbenzene (**8**)

To a stirred solution of 5-benzyloxy-1,2-pentadiene **10**⁸ (222 mg, 1.28 mmol) in 1,4-dioxane (12.3 mL) and H_2O (0.61 mL) were added 2,5-dimethoxy-4-methylphenylboronic acid **9**⁷ (500 mg, 2.55 mmol), $[\text{Pt}_2(\text{OH})_2(\text{PPh}_3)_4][\text{BF}_4]_2$ (**3**)¹ (105 mg, 0.064 mmol) and KOH (358 mg, 0.37 mmol) at rt, and stirring was continued at 100 °C for 0.5 h. The reaction mixture was diluted with minimum amount of AcOEt and dried over MgSO_4 . After filtration through a pad of silica gel, the residue upon workup was chromatographed on silica gel with hexane-AcOEt (97:3, v/v) as eluent to give **8** (320 mg, 77%, *exo:endo* = >20:1) as a colorless oil. IR (neat): 2935, 2852, 1503, 1465, 1396, 1211, 1104, 1045, 901, 737, 698 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.70 (quint., J = 6.8 Hz, 2H), 2.21 (s, 3H), 2.57 (t, J = 7.6 Hz, 2H), 3.47 (t, J = 6.4 Hz, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 4.47 (s, 2H), 5.02 (s, 1H), 5.13 (s, 1H), 6.61 (s, 1H), 6.68 (s, 1H), 7.26-7.33 (m, 5H); ^{13}C -NMR (100 MHz, CDCl_3) δ 16.1 (CH_3), 28.2 (CH_2), 32.9 (CH_2), 55.9 (CH_3), 56.2 (CH_3), 70.0 (CH_2), 72.7 (CH_2), 112.6 (CH), 114.0 (CH_2), 114.4 (CH), 126.1 (Cq), 127.4 (CH), 127.5 (CH), 128.2 (CH), 129.7 (Cq), 138.7 (Cq), 148.5 (Cq), 150.1 (Cq), 151.5 (Cq); HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{26}\text{O}_3\text{Na}$ [$\text{M}^+ + \text{Na}^+$] 349.1780, found 349.1780.

4-(2,5-Dimethoxy-4-methylphenyl)pentan-1-ol (**11**)⁹

To a stirred suspension of Pd-C (79.4 mg, 25 wt%) in EtOH (2.3 mL) was added ether **8** (317 mg, 0.97 mmol) at rt, and stirring was continued for 12 h at the same temperature under 5 atm of hydrogen gas. The resulting solution was filtered and the solvent was evaporated to give a residue, which was chromatographed on silica gel with hexane-AcOEt (75:25, v/v) as eluent to give the alcohol **11** (203 mg, 88%) as a colorless oil. IR (neat): 3363, 2937, 1505, 1464, 1398, 1209, 1046 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.21 (d, J = 6.8 Hz, 3H), 1.44 (s, 1H, OH, D_2O exchangeable), 1.44-1.65 (m, 2H), 2.20 (s, 3H), 3.17 (sext., J = 6.8 Hz, 1H), 3.61 (t, J = 6.4 Hz, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 6.67 (s, 1H), 6.68 (s, 1H);

^{13}C -NMR (100 MHz, CDCl_3) δ 16.0 (CH_3), 21.0 (CH_3), 30.7 (CH_2), 31.5 (CH), 33.4 (CH_2), 56.1 (CH_3), 56.3 (CH_3), 62.9 (CH_2), 109.6 (CH), 114.3 (CH), 124.3 (Cq), 133.5 (Cq), 150.6 (Cq), 151.9 (Cq); HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{14}\text{ONa}$ [$\text{M}^+ + \text{Na}^+$] 261.1467, found 261.1467.

1-(1,5-Dimethylhex-4-enyl)-2,5-dimethoxy-4-methylbenzene (**13**)^{4a}

To a solution of oxalyl chloride (1.63 mL, 18.7 mmol) in CH_2Cl_2 (17.6 mL) was added DMSO (1.8 mL, 23 mmol) in CH_2Cl_2 (8.8 mL) at -78°C . A solution of **11** (1.78 g, 7.5 mmol) in CH_2Cl_2 (17.6 mL) was added dropwise, and after 30 min, Et_3N (8.14 mL, 58.4 mmol) was added. After being stirred for 10 min at -78°C , the reaction mixture was allowed to warm to 0°C over 15 min and the reaction mixture was diluted with water and concentrated *in vacuo*. The residue was extracted with Et_2O and the combined extracts were washed with brine. The residue upon workup was the corresponding aldehyde, a colorless oil, which was used to the next reaction without further purification. To a solution of sulfone **12** ¹⁰ (4.3 g, 17 mmol) in THF (100 mL) at -78°C was added dropwise LHMDs (1.6 M in THF, 10.8 mL, 17 mmol). The yellow solution was stirred at -78°C for 30 min and the solution was added in one portion with a precooled syringe to a solution of the crude aldehyde in THF (100 mL) at -78°C . The reaction mixture was stirred at -78°C for 3 h, then the mixture was slowly warmed to rt and stirred for 10 min. The reaction mixture was quenched with H_2O and concentrated *in vacuo*. The residue was extracted with Et_2O and the extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (95:5, v/v) as eluent to give **13** (1.73 g, 88% for the 2 steps) as a colorless oil. IR (neat): 2927, 2852, 1504, 1465, 1398, 1208, 1049 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.18 (d, $J = 7.2$ Hz, 3H), 1.54 (s, 3H), 1.48-1.67 (m, 2H), 1.67 (s, 3H), 1.92 (dt, $J = 16.6$ Hz and 8.4 Hz, 2H), 2.20 (s, 3H), 3.14 (sext., $J = 7.6$ Hz, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 5.12 (t, $J = 7.2$ Hz, 1H), 6.67 (s, 2H); ^{13}C -NMR (100 MHz, CDCl_3) δ 16.0 (CH_3), 17.5 (CH_3), 21.2 (CH_3), 25.6 (CH_3), 26.3 (CH_2), 31.9 (CH), 37.3 (CH_2), 55.9 (CH_3), 56.2 (CH_3), 109.7 (CH), 114.2 (CH), 124.1 (Cq), 124.8 (CH), 130.9 (Cq), 133.9 (Cq), 150.8 (Cq), 151.9 (Cq); HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{26}\text{O}_2\text{Na}$ [$\text{M}^+ + \text{Na}^+$] 285.1831, found 285.1839.

1,4-Bis-(*tert*-butyldimethylsiloxy)-2-(1,5-dimethylhex-4-enyl)-5-methylbenzene (**14**)^{4a}

To a solution of **13** (31.7 mg, 0.121 mmol) in THF (1.12 mL) and H_2O (0.38 mL) was added CAN (159 mg, 0.29 mmol) at 0°C . After being stirred at the same temperature for 5 min, the reaction mixture was diluted with H_2O and extracted with Et_2O . The combined extracts were washed with brine and the residue upon workup was curcquinone,⁶ a yellow oil, which was used to the next reaction without further purification. To a solution of curcquinone in THF (0.6 mL) was added and $\text{Na}_2\text{S}_2\text{O}_4$ (63.5 mg, 0.36 mmol) in H_2O at 0°C . After being stirred at rt for 3 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O . The extracts were washed with brine and the residue upon

workup was curcuhydroquinone **7**⁶, a yellow oil, which was used to the next reaction without further purification. To a solution of curcuhydroquinone, imidazole (29.6 mg, 0.435 mmol) and TBSCl (40.1 mg, 0.27 mmol) in CH₂Cl₂ (0.6 mL) was added 4-DMAP (1.5 mg, 12.1 mmol) at 0 °C. After being stirred for 0.5 h at rt, the reaction mixture was quenched with water and extracted with CH₂Cl₂. The extracts were washed with brine and the residue upon workup was chromatographed on silica gel with hexane-AcOEt (95:5, v/v) as eluent to give **14** (31.9 mg, 57% for the 3 steps) as a colorless oil. IR (neat): 2958, 2930, 2859, 1499, 1472, 1463, 1399, 1255, 1203 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.16-0.19 (m, 12H), 1.00 (s, 18H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.46-1.53 (m, 5H), 1.66 (s, 3H), 1.88-1.96 (m, 2H), 2.11 (s, 3H), 3.10 (sext., *J* = 7.2 Hz, 1H), 5.09 (t, *J* = 6.4 Hz, 1H), 6.53 (s, 1H), 6.55 (s, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ -4.3 (CH₃), -4.1 (CH₃), 16.6 (CH₃), 17.6 (CH₃), 18.2 (Cq), 18.2 (Cq), 21.3 (CH₃), 25.7 (CH₃), 25.8 (CH₃), 26.1 (CH₂), 30.8 (CH), 37.4 (CH₂), 116.8 (CH), 120.6 (CH), 124.8 (CH), 125.8 (Cq), 131.1 (Cq), 135.7 (Cq), 146.6 (Cq), 147.8 (Cq); HRMS (ESI) *m/z* calcd for C₂₉H₅₈O₂NaSi₂ [M⁺+Na⁺] 517.3873, found 517.3872.

4-(tert-Butyldimethylsiloxy)-5-(1,5-dimethylhex-4-enyl)-2-methylphenol (15) and 4-(tert-Butyldimethylsiloxy)-2-(1,5-dimethylhex-4-enyl)-5-methylphenol (16)

To a solution of **14** (40.7 mg, 87.9 μmol) in MeOH (2.9 mL) was added K₂CO₃ (36.5 mg, 0.26 mmol) at rt. After being stirred for 4 h, the reaction mixture was quenched with water and extracted with AcOEt. The extracts were washed with brine and the residue upon workup was chromatographed on silica gel with CHCl₃ as eluent to give the recovered **14** (9.2 mg, 22%), compound **16** (5.3 mg, 17%) as a colorless oil, and compound **15** (18.5 mg, 60%) as a colorless oil.

Compound **16**: IR (neat): 3414, 2958, 2928, 2857, 1510, 1412, 1256, 1195 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.17 (s, 6H), 1.01 (s, 9H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.53 (s, 3H), 1.53-1.60 (m, 2H), 1.68 (s, 3H), 1.93 (q, *J* = 7.2 Hz, 2H), 2.12 (s, 3H), 2.92 (sext., *J* = 7.2 Hz, 1H), 4.31 (s, 1H, OH, D₂O exchangeable), 5.11 (t, *J* = 7.2 Hz, 1H), 6.55 (s, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ -4.2 (CH₃), -4.2 (CH₃), 16.4 (CH₃), 17.7 (CH₃), 18.2 (Cq), 21.2 (CH₃), 25.7 (CH₃), 25.8 (CH₃), 26.0 (CH₂), 31.4 (CH), 37.4 (CH₂), 117.0 (CH), 117.8 (CH), 124.6 (CH), 126.6 (Cq), 130.8 (Cq), 132.0 (Cq), 146.8 (Cq), 147.7 (Cq); HRMS (ESI) *m/z* calcd for C₂₁H₃₇O₂Si [M⁺+H⁺] 349.2563, found 349.2559.

Compound **15**: IR (neat): 3353, 2958, 2928, 2858, 1503, 1462, 1408, 1196 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.19 (s, 3H), 0.20 (s, 3H), 1.00 (s, 9H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.47-1.60 (m, 2H), 1.54 (s, 3H), 1.66 (s, 3H), 1.86-2.00 (m, 2H), 2.16 (s, 3H), 3.10 (sext., *J* = 6.8 Hz, 1H), 4.26 (s, 1H, OH, D₂O exchangeable), 5.09 (tt, *J* = 7.2 Hz and 1.2 Hz, 1H), 6.53 (s, 1H), 6.58 (s, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ -4.2 (CH₃), -4.1 (CH₃), 15.6 (CH₃), 17.6 (CH₃), 18.2 (Cq), 21.2 (CH₃), 25.7 (CH₃), 25.8 (CH₃), 26.1 (CH₂), 30.9 (CH), 37.4 (CH₂), 113.3 (CH), 120.6 (CH), 121.0 (Cq), 124.7 (CH), 131.1 (Cq), 136.6

(Cq), 146.4 (Cq), 147.8 (Cq); HRMS (ESI) m/z calcd for $C_{21}H_{37}O_2Si$ [$M^+ + H^+$] 349.2563, found 349.2560.

1,4-Bis-(*tert*-butyldimethylsiloxy)-2-(1,5-dimethylhex-4-enyl)-5-methylbenzene (14)^{4a}

To a solution of **16** (5.1 mg, 14.63 μ mol) and TBSCl (3.3 mg, 21.95 μ mol) in CH_2Cl_2 (0.1 mL) was added 4-DMAP (0.2 mg, 1.46 μ mol) at rt. After being stirred for 10 min, the reaction mixture was quenched with water and extracted with CH_2Cl_2 . The extracts were washed with brine and the residue upon workup was chromatographed on silica gel with hexane-AcOEt (98:2, v/v) as eluent to give the olefin **14** (5.9 mg, 87%) as a colorless oil.

6-(2-*tert*-Butyldimethylsiloxy-5-methoxymethoxy-4-methylphenyl)-2-methyl-2-heptene (17)

To a solution of **15** (57.9 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) was added iPr_2NEt (0.35 mL, 1.99 mmol) and methoxymethyl chloride (0.13 mL, 1.66 mmol) at rt. The reaction mixture was stirred for 9 h at the same temperature, then quenched with water and extracted with Et_2O . The extracts were washed with brine and the residue upon workup was chromatographed on silica gel with hexane-AcOEt (92.5:7.5, v/v) as eluent to give the MOM ether **17** (63.1 mg, 97%) as a colorless oil. IR (neat): 2957, 2928, 2857, 1501, 1391, 1255, 1215, 1193, 1151 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 3H), 0.21 (s, 3H), 1.01 (s, 9H), 1.13 (d, $J = 6.8$ Hz, 3H), 1.48-1.60 (m, 2H), 1.54 (s, 3H), 1.66 (s, 3H), 1.93 (quint., $J = 7.2$ Hz, 2H), 2.17 (s, 3H), 3.11 (sext., $J = 6.8$ Hz, 1H), 3.50 (s, 3H), 5.08-5.12 (m, 1H), 5.10 (s, 2H), 6.55 (s, 1H), 6.82 (s, 1H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ -4.2 (CH_3), -4.1 (CH_3), 16.0 (CH_3), 17.6 (CH_3), 18.2 (Cq), 21.2 (CH_3), 25.7 (CH_3), 25.8 (CH_3), 26.2 (CH_2), 31.2 (CH), 37.2 (CH_2), 56.0 (CH_3), 95.8 (CH_2), 113.7 (CH), 120.5 (CH), 124.8 (CH), 125.2 (Cq), 131.1 (Cq), 136.0 (Cq), 147.4 (Cq), 149.9 (Cq); HRMS (ESI) m/z calcd for $C_{23}H_{41}O_3Si$ [$M^+ + H^+$] 393.2825, found 393.2823.

6-(2-*tert*-Butyldimethylsiloxy-5-methoxymethoxy-4-methylphenyl)-2-methyl-2,3-epoxyheptane (18)^{4a}

To a mixture of **17** (19.9 mg, 50.7 μ mol) and sodium bicarbonate (21.3 mg, 0.25 mmol) in CH_2Cl_2 (0.5 mL) was added *m*CPBA (20.2 mg, 76.0 μ mol) at 0 °C. After being stirred at rt for 0.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and concentrated *in vacuo*. The residue was extracted with CH_2Cl_2 , the extracts were washed with brine and the residue upon workup was chromatographed on silica gel with hexane-AcOEt (90:10, v/v) as eluent to give a 1:1 diastereomeric mixture of **18** (16.2 mg, 78%) as a colorless oil. IR (neat): 2958, 2930, 2859, 1503, 1391, 1255, 1215, 1194, 1151 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ 0.19-0.21 (m, 6H), 1.00 (s, 4.5H), 1.00 (s, 4.5H), 1.17 (d, $J = 6.8$ Hz, 3H), 1.19 (s, 3H), 1.25 (s, 1.5H), 1.26 (s, 1.5H), 1.35-1.73 (m, 4H), 2.17 (s, 3H), 2.65-2.71 (m, 1H), 3.16 (sext., $J = 6.4$ Hz, 1H), 3.49 (s, 1.5 H), 3.50 (s, 1.5H), 5.08-5.12 (m, 2H), 6.56 (s, 1H), 6.82 (s, 0.5H), 6.83 (s, 0.5H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ -4.2 (CH_3), -4.0 (CH_3), 16.1 (CH_3), 18.3 (Cq), 18.6

(CH₃), 21.1 (CH₃), 21.4 (CH₃), 24.9 (CH₃), 25.9 (CH₃), 27.0 (CH₂), 27.4 (CH₂), 31.5 (CH), 31.7 (CH), 33.7 (CH₂), 34.1 (CH₂), 56.0 (CH₃), 58.2 (Cq), 64.3 (CH), 64.6 (CH), 95.7 (CH₂), 113.5 (CH), 113.6 (CH), 120.6 (CH), 120.7 (CH), 125.5 (Cq), 135.2 (Cq), 147.4 (Cq), 150.0 (Cq); HRMS (ESI) m/z calcd for C₂₃H₄₀O₄NaSi [M⁺+Na⁺] 431.2594, found 431.2596.

6-(2-Hydroxy-5-methoxymethoxy-4-methylphenyl)-2-methyl-2,3-epoxyheptane (6)^{4a} and 3-*epi*-6-(2-hydroxy-5-methoxymethoxy-4-methylphenyl)-2-methyl-2,3-epoxyheptane (19)

To a mixture of CsF (6.8 mg, 0.04 mmol) in DMF (0.62 mL) was added **18** (15.3 mg, 37.4 mmol) in DMF (0.62 mL) at 0 °C. The reaction mixture was stirred at rt for 15 min, then quenched with water and extracted with Et₂O. The extracts were washed with brine and the residue upon workup was chromatographed on silica gel with hexane-AcOEt (90:10, v/v) as eluent to give **19** (5.2 mg, 47%) as a colorless oil and **6** (4.9 mg, 45%) as a colorless oil.

Compound 19: IR (neat): 3379, 2960, 2927, 1514, 1455, 1399, 1191, 1150 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.06-1.17 (m, 1H), 1.21 (s, 3H), 1.25 (d, 6.8 Hz, 3H), 1.33 (s, 3H), 1.67-1.76 (m, 2H), 1.80-1.87 (m, 1H), 2.17 (s, 3H), 2.85 (dd, J = 9.2 Hz and 1.6 Hz, 1H), 3.14-3.18 (m, 1H), 3.50 (s, 3H), 5.08-5.11 (m, 2H), 6.61 (s, 1H, OH, D₂O exchangeable), 6.66 (s, 1H), 6.80 (s, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 15.9 (CH₃), 18.4 (CH₃), 22.4 (CH₃), 24.7 (CH₃), 25.9 (CH₂), 30.5 (CH), 36.4 (CH₂), 56.0 (CH₃), 58.9 (Cq), 66.2 (CH), 95.9 (CH₂), 113.3 (CH), 119.3 (CH), 126.4 (Cq), 130.5 (Cq), 148.3 (Cq), 149.9 (Cq); HRMS (ESI) m/z calcd for C₁₇H₂₇O₄ [M⁺+H⁺] 295.1909, found 295.1913.

Compound 6: IR (neat): 3375, 2960, 1456, 1191, 1149, 1058 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.21 (s, 3H), 1.24 (d, J = 7.2 Hz, 3H), 1.28 (s, 3H), 1.44-1.69 (m, 3H), 1.77-1.86 (m, 1H), 2.17 (s, 3H), 2.72 (t, J = 6.4 Hz, 1H), 3.07 (sext., J = 6.8 Hz, 1H), 3.50 (s, 3H), 4.58 (s, 1H, OH, D₂O exchangeable), 5.10 (s, 2H), 6.56 (s, 1H), 6.83 (s, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 15.8 (CH₃), 18.6 (CH₃), 20.8 (CH₃), 24.8 (CH₃), 26.7 (CH₂), 32.0 (CH), 33.6 (CH₂), 56.0 (CH₃), 58.8 (Cq), 64.6 (CH), 95.9 (CH₂), 114.2 (CH), 117.8 (CH), 126.1 (Cq), 130.9 (Cq), 147.9 (Cq), 149.6 (Cq); HRMS (ESI) m/z calcd for C₁₇H₂₇O₄ [M⁺+H⁺] 295.1909, found 295.1911.

(±)-Heliannuol D (5)⁵

A solution of **6** (10.1 mg, 34 μmol) in 5% aqueous NaOH (1.1 mL) was stirred at rt for 31 h. The reaction mixture was diluted with CHCl₃, acidified with 1% aqueous HCl (pH < 7) and extracted with CHCl₃. The extracts were washed with brine and the residue upon workup was the alcohol **20**, a colorless oil, which was used to the next reaction without further purification. To a solution of the crude **20** in THF (0.1 mL) was added 6 N HCl aq. (0.1 mL). After being stirred at rt for 2 h, the mixture was extracted with Et₂O. The extracts were washed with brine and the residue upon workup was chromatographed on silica gel

with hexane-AcOEt (70:30, v/v) as eluent to give the ($\pm$)-heliannuol D **5** (8.7 mg, quant. for 2 steps) as a colorless crystalline solid. mp 157-158 °C (lit., [5a,c](#) 161-162 °C); IR (KBr): 3362, 2931, 2360, 1508, 1456, 1417, 1375, 1192, 1065 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.27-1.29 (m, 9H), 1.72-2.05 (m, 4H), 2.16 (s, 3H), 2.66 (s, 1H, OH, D_2O exchangeable), 2.88-2.91 (m, 1H), 3.30 (dd, $J = 11.2$ Hz and 1.2 Hz, 1H), 4.54 (s, 1H, OH, D_2O exchangeable), 6.54 (s, 1H), 6.73 (s, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 15.3 (CH_3), 18.6 (CH_3), 24.5 (CH_3), 25.6 (CH_2), 26.1 (CH_3), 31.8 (CH_2), 38.5 (CH), 72.6 (Cq), 90.5 (CH), 115.8 (CH), 122.1 (Cq), 123.5 (CH), 138.2 (Cq), 149.6 (Cq), 151.7 (Cq); HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{23}\text{O}_3$ [$\text{M}^+ + \text{H}^+$] 251.1647, found 251.1643.

($\pm$)-10-*epi*-Heliannuol D (**22**)[5a,c](#)

According to the same procedure as for the preparation of **5**, **22** was obtained from **19** as a colorless crystalline solid in 69% yield for the 2 steps. mp 155-157 °C (lit., [5c](#) 158-159 °C); IR (KBr): 3262, 2973, 1506, 1456, 1374, 1187, 1152, 1062 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ 1.27 (s, 3H), 1.28 (s, 3H), 1.30 (d, $J = 7.2$ Hz, 3H), 1.87-1.93 (m, 3H), 2.18 (s, 3H), 2.63 (s, 1H, OH, D_2O exchangeable), 3.02 (quint., $J = 8.0$ Hz, 1H), 3.24 (dd, $J = 10.0$ Hz and 3.2 Hz, 1H), 4.62 (s, 1H, OH, D_2O exchangeable), 6.61 (s, 1H), 6.76 (s, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 15.3 (CH_3), 20.2 (CH_3), 24.4 (CH_3), 26.3 (CH_3), 30.9 (CH_2), 34.3 (CH), 65.9 (CH_2), 72.5 (Cq), 89.7 (CH), 112.7 (CH), 121.5 (Cq), 122.8 (CH), 138.5 (Cq), 149.8 (Cq), 152.6 (Cq); HRMS (ESI) m/z calcd for $\text{C}_{15}\text{H}_{23}\text{O}_3$ [$\text{M}^+ + \text{H}^+$] 251.1647, found 251.1645.

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