HETEROCYCLES, Vol. 88, No. 1, 2014, pp. 441 - 452. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 26th June, 2013, Accepted, 19th July, 2013, Published online, 23rd July, 2013
DOI: 10.3987/COM-13-S(S)50

HIGHLY EFFICIENT, ENANTIOCONTROLLED TOTAL SYNTHESES OF (+)-HELIANNUOL D AND (–)-HELIBISABONOL A†

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Abstract – Enantiocontrolled total syntheses of (+)-heliannuol D (**1**) and (–)-helibisabonol A (**2**) have been accomplished efficiently from a common intermediate **9**, derived from the optically pure aryl allyl ether **7** *via* a chirality transfer through a Lewis acid-mediated Claisen rearrangement and asymmetric dihydroxylation.

INTRODUCTION

Heliannuol D (**1**),[1] a representative helianane-type sesquiterpenoid, and helibisabonol A (**2**),[2] an aromatic bisabolene-type sesquiterpenoid, were isolated by Macías and co-workers from the extracts of fresh leaves of *Helianthus annuus* L. var. SH-222 and dried leaves of *Helianthus annuus* L. cv. Predovick®, respectively. These natural products have been reported to exhibit allelopathic activity, with potential for becoming lead compounds for a new type of agrochemicals. Furthermore, helibisabonol A (**2**) is believed to represent the biogenic precursor of **1** and other helianane families.[3] The structural features of **1** are a characteristic bicyclic core, an oxepane fused to the aryl ring, and two *syn*-oriented tertiary stereogenic centers at C7 and C10 on the oxepane ring. The absolute configuration has been established to be (7*R*,10*R*) by our enantioselective total synthesis of (–)-**1**.[4a] The structure of **2**, on the other hand, possesses a hydroquinone moiety and two stereogenic centers at C7 and C10, the absolute configurations of which have been established to be (7*R*,10*R*) by our enantioselective total synthesis of (–)-**2**.[5b] Although several syntheses of these allelochemicals have been published so far,[4,5] more efficient and practical processes have still been required to develop new agrochemicals. In this report, we describe highly efficient, enantiocontrolled total syntheses of (+)-heliannuol D (**1**) and (–)-helibisabonol A (**2**) (Figure 1).

† This paper is dedicated to Professor Victor Snieckus on the occasion of his 77th birthday.

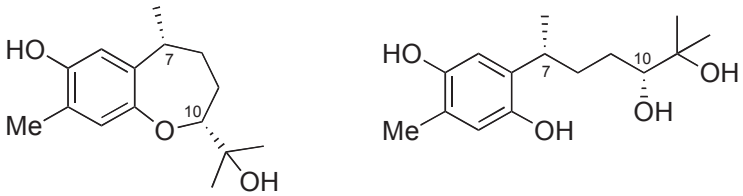
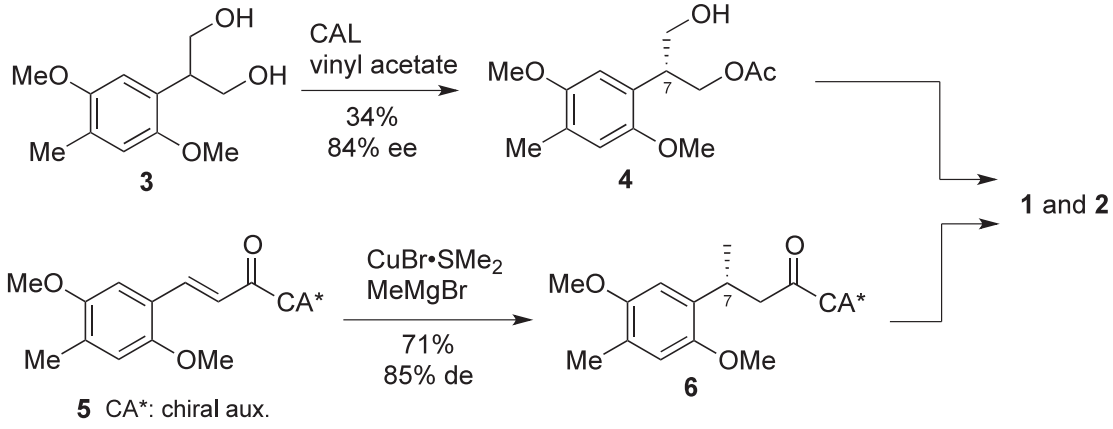


Figure 1. Structures of heliannuol D and helibisabonol A

RESULTS AND DISCUSSION

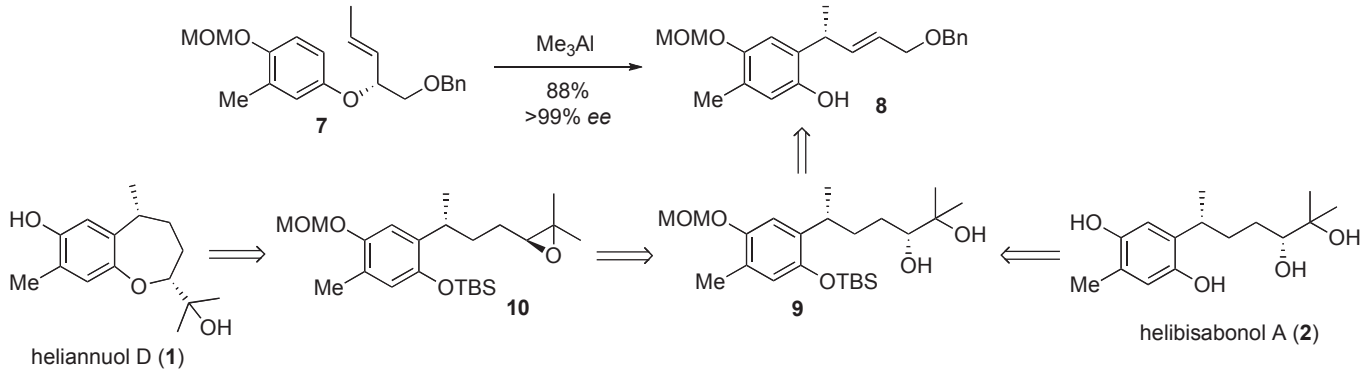
During the course of our enantioselective syntheses of heliannuol D (**1**) and helibisabonol A (**2**), we have developed two general strategies for the construction of the tertiary benzylic stereogenic center at C7.[4a,b,d,5b] A lipase-mediated desymmetrization of σ-symmetrical diol **3**[6] provided the acetate **4** in 34% yield with 84% ee and a diastereoselective conjugate addition of a methyl group to the enone **5**, which possesses a chiral auxiliary (i.e., the Evans' oxazolidinone),[7] produced **6** in 71% yield with 85% de. While the chiral building blocks **4** and **6** thus prepared have been successfully converted to **1** and **2**, a couple of issues, namely slightly lower enantio-(or diastereo-)selectivities and longer reaction steps, for more efficient access to the natural products **1** and **2** have remained to be overcome (Scheme 1).



Scheme 1. Chiral building blocks for accessing heliannuol D and helibisabonol A

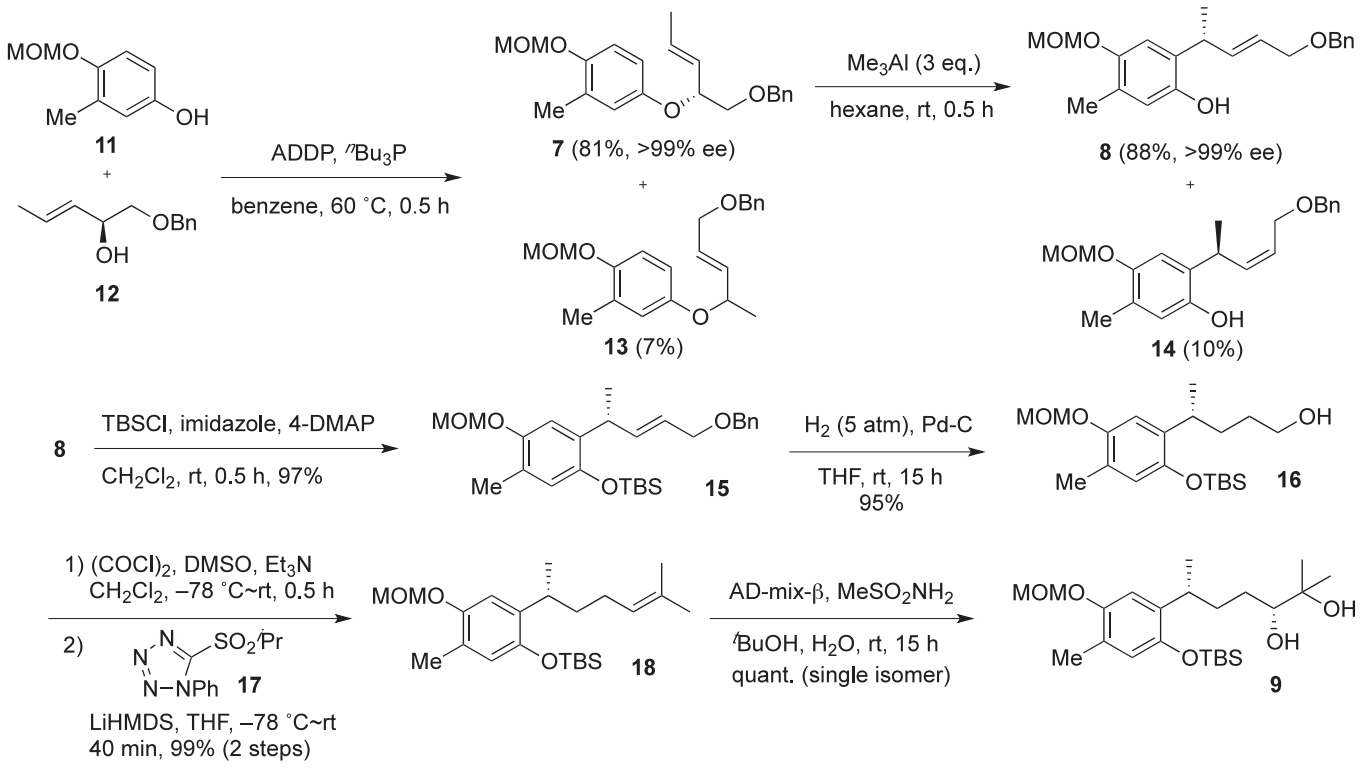
Recently, we reported a strategy for accessing a chiral building block **8** that can serve for the synthesis of helianane allelochemicals, heliannuols A and K, by using a substrate-controlled chirality transfer in Claisen rearrangement (**7** → **8**).[8] Since the phenol **8** can be obtained in good yield with high enantiomeric excess, it was expected to be useful as a starting chiral building block for the efficient syntheses of **1** and

2. Our retrosynthetic analysis is shown in Scheme 2. For the syntheses of both **1** and **2**, we chose the diol **9** as a common intermediate, because it has been successfully converted to heliannuol D (**1**) by sequential epoxidation, K_2CO_3-mediated desilylative [7-*exo*] cyclization of **10**, and deprotection of the methoxymethyl (MOM) ether in our laboratories.[4d] On the other hand, helibisabonol A (**2**) might be obtained from **9** by a simple acidic hydrolysis. The key diol **9** can be derived from **8** through a three-carbon elongation[9] and an asymmetric dihydroxylation[10] (Scheme 2).



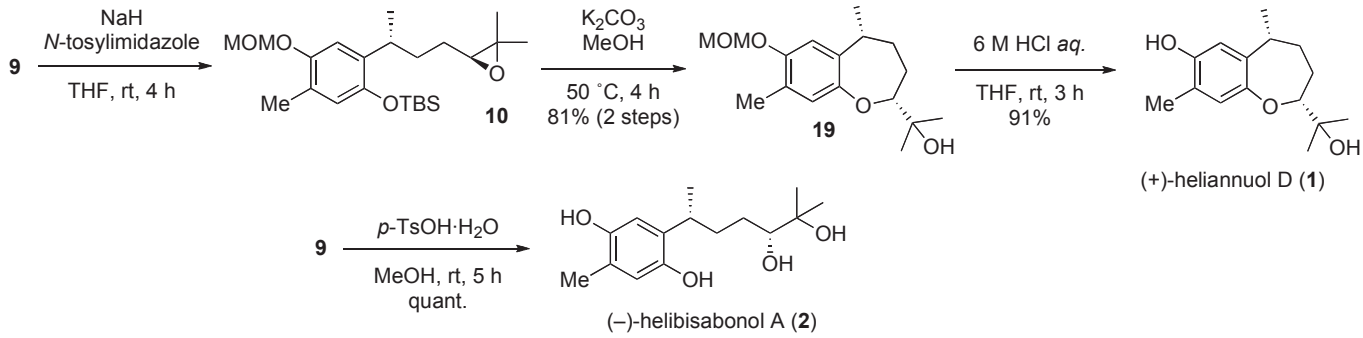
Scheme 2. Retrosynthetic analysis of heliannuol D and helibisabonol A

The chiral building block **8** was prepared from 3-methyl-4-(methoxymethoxy)phenol (**11**) and (*S*,*E*)-1-(benzyloxy)pent-3-en-2-ol (**12**) as previously described.[8] The Mitsunobu reaction between **11** and **12** in the presence of 1,1-(azodicarbonyl)dipiperidine (ADDP) and $^nBu_3P$ provided a chromatographically separable mixture of **7** (81%, >99% ee; by HPLC analysis) and the regioisomer **13** (7%), which was derived *via* S_N2' process. The Claisen rearrangement of **7** was carried out with 3 equiv. of Me_3Al in hexane at room temperature for 0.5 h; the requisite **8** was obtained in 88% yield (>99% ee; by HPLC analysis), along with **14** (10%), which would be generated *via* the disfavored boat-like transition state. The phenolic hydroxyl function was protected as the TBS ether to give **15**, which was exposed to catalytic hydrogenation conditions to produce the alcohol **16**. It was then oxidized under Swern conditions, and the resulting aldehyde was subjected to Kocienski-Julia olefination with the sulfone **17**[11] to give the trisubstituted alkene **18** in good overall yield. On exposure of **18** to an asymmetric dihydroxylation protocol using AD-mix-β and $MeSO_2NH_2$, the diol **9**, a common key intermediate, was obtained quantitatively as a single product[12] (Scheme 3).



Scheme 3. Synthesis of the key diol **9**

The diol **9** was then exposed to *N*-tosylimidazole in the presence of NaH[13] to provide the epoxide **10**, which without purification was treated with K_2CO_3 in methanol at 50 °C[14] and provided the oxepane **19** in 81% yield for the two steps through deprotection of TBS ether and spontaneous 7-*exo* cyclization sequence.[4d] Finally, acidic hydrolysis of **19** with 6 M aqueous hydrochloric acid in THF at room temperature produced heliannuol D (**1**) in 91% yield, of which the spectroscopic (^{1}H and ^{13}C NMR) properties as well as optical rotation, {$[\alpha]_D^{25}$ = +18.1 (*c* 0.38, $CHCl_3$); lit.[1] $[\alpha]_D^{26}$ = +16 (*c* 0.1, $CHCl_3$)}, were identical with those of the natural product. Thus, our fourth-generation enantioselective total synthesis of heliannuol D (**1**) has been accomplished, with the longest linear sequence having ten steps, in 48% yield from the phenol **11**. For the synthesis of helibisabonol A (**2**), the diol **9** was treated with *p*-TsOH·H_2O in methanol at room temperature to give **2** quantitatively. The spectroscopic (^{1}H and ^{13}C NMR) properties as well as optical rotation, {$[\alpha]_D^{30}$ = –7.8 (*c* 0.40, acetone); lit.[5b] $[\alpha]_D^{26}$ = –6.9 (*c* 0.33, acetone)}, were identical with those of the synthesized helibisabonol A.[5b] Thus, the second-generation enantioselective total synthesis of helibisabonol A (**2**) has also been accomplished, with the longest linear sequence having eight steps, in 65% yield from the phenol **11** (Scheme 4).



Scheme 4. Syntheses of (+)-heliannuol D and (–)-helibisabonol A

In conclusion, we have accomplished alternative enantiocontrolled total syntheses of (+)-heliannuol D (**1**) and (–)-helibisabonol A (**2**) from a common intermediate **9**, which was derived from **8**, a chiral building block prepared *via* a chirality transfer through a Lewis acid-mediated Claisen rearrangement of the optically pure aryl allyl ether **7**. In particular, synthesis of heliannuol D was achieved employing a highly efficient K_2CO_3-mediated desilylative biomimetic [7-*exo*] cyclization of the epoxide **10** as the key step. These syntheses were efficiently completed with the longest linear sequence having ten steps in 48% yield for **1,** and eight steps in 65% for **2,** from 3-methyl-4-(methoxymethoxy)phenol (**11**), respectively. The synthetic route developed herein is general and efficient and would be applicable to the synthesis of other helianane-type sesquiterpenoids.

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.

(2*R*,3*E*)-4-[1-(Benzyloxy)pent-3-en-2-yloxy]-1-(methoxymethoxy)-2-methylbenzene (7)[8] and (3*E*)-4-[5-(Benzyloxy)pent-3-en-2-yloxy]-1-(methoxymethoxy)-2-methylbenzene (13)[8]: To a stirred solution of 3-methyl-4-(methoxymethoxy)phenol (**11**) (2.02 g, 12.0 mmol), (*S*,*E*)-1-(benzyloxy)pent-3-en -2-ol (**12**) (3.00 g, 15.6 mmol) and $^{n}Bu_3P$ (4.49 ml, 18.0 mmol) in benzene (34 mL) was added 1,1-(azodicarbonyl)dipiperidine (4.54 g, 18.0 mmol) at 0 °C. After being stirred for 30 min at 60 °C, the reaction mixture was diluted with hexane, and then filtered through a pad of silica gel and concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (33:1 v/v) as eluent to afford aryl allyl ether **7** (3.33 g, 81%, >99% ee) as a colorless oil and the regio isomer **13** (282 mg, 7%) as a colorless oil.

Compound 7: $[\alpha]_D^{25}$ –12.99 (*c* 3.29, $CHCl_3$); IR (neat) 2917, 1498, 1218, 1152, 1011, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.69 (d, *J* = 6.4 Hz, 3H), 2.21 (s, 3H), 3.49 (s, 3H), 3.59 (dd, *J* = 4.4 and 10.4 Hz, 1H), 3.67 (dd, *J* = 7.2 and 10.8 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.69 (dt, *J* = 5.2 and 6.4 Hz, 1H), 5.11 (s, 2H), 5.45 (ddd, *J* = 1.6, 6.4 and 15.6 Hz, 1H), 5.77 (dq, *J* = 6.4 and 15.6 Hz, 1H), 6.69 (dd, *J* = 2.8 and 9.2 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4 (CH_3), 17.9 (CH_3), 55.9 (CH_3), 72.9 (CH_2), 73.4 (CH_2), 78.7 (CH), 95.4 (CH_2), 113.9 (CH), 115.3 (CH), 119.3 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.3 (CH), 128.6 (C), 129.3 (CH), 138.3 (C), 149.8 (C), 152.9 (C); HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{27}O_4$ $[M+H]^+$ 343.1909, found 343.1904; Enantiomeric excess was determined by HPLC analysis [Chiralcel OD column, 1.0% isopropanol/hexane, 1.0 mL/min, λ=254 nm, retention times 22.8 min (*S*) and 30.6 min (*R*)].

Compound 13: $[\alpha]_D^{26}$ +26.31 (*c* 0.68, $CHCl_3$); IR (neat) 2926, 2363, 1498, 1218, 1151, 1075, 1010, 738, 698 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 1.36 (d, *J* = 6.5 Hz, 3H), 2.17 (s, 3H), 3.42 (s, 3H), 3.99 (dd, *J* = 5.5 and 12.5 Hz, 1H), 4.02 (dd, *J* = 5.5 and 12.5 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.83 (quint., *J* = 6.0 Hz, 1H), 5.10 (s, 2H), 5.79 (dd, *J* = 5.5 and 16.0 Hz, 1H), 5.84 (dt, *J* = 5.0 and 15.5 Hz, 1H), 6.70 (dd, *J* = 3.0 and 9.0 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 7.25-7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.4 (CH_3), 17.9 (CH_3), 55.9 (CH_3), 72.9 (CH_2), 73.4 (CH_2), 78.7 (CH), 95.4 (CH_2), 113.9 (CH), 115.3 (CH), 119.3 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.3 (CH), 128.6 (C), 129.3 (CH), 138.3 (C), 149.8 (C), 152.9 (C); HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{27}O_4$ $[M+H]^+$ 343.1909, found 343.1904.

(2*R*,3*E*)-2-[5-(Benzyloxy)pent-3-en-2-yl]-4-(methoxymethoxy)-5-methylphenol (8)[8] and (2*S*,3*Z*)-2-[5-(Benzyloxy)pent-3-en-2-yl]-4-(methoxymethoxy)-5-methylphenol (14)[8]: To a stirred solution of aryl allyl ether **7** (500 mg, 1.46 mmol) in hexane (10 mL) was added Me_3Al (1.08 M in hexane, 4.0 mL, 4.38 mmol) at 0 °C. After being stirred for 30 min 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 **8** (441 mg, 88%, >99% ee) as a colorless oil and the *Z*-isomer **14** (48.5 mg, 10%) as a colorless oil.

Compound 8: $[\alpha]_D^{25}$ –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, $CDCl_3$) δ 1.38 (d, *J* = 6.8 Hz, 3H), 2.18 (s, 3H), 3.49 (s, 3H), 3.66 (quint., *J* = 7.2 Hz, 1H), 4.02 (d, *J* = 6.0 Hz, 2H), 4.50 (s, 2H), 4.60 (s, OH, D_2O exchangeable, 1H), 5.09 (s, 2H), 5.71 (ddt, *J* = 1.2, 6.0 and 15.6 Hz, 1H), 5.94 (dd, *J* = 6.0 and 15.6 Hz, 1H), 6.61 (s, 1H), 6.82

(s, 1H), 7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8 (CH_3), 19.3 (CH_3), 36.1 (CH), 56.0 (CH_3), 70.6 (CH_2), 71.9 (CH_2), 95.8 (CH_2), 114.9 (CH), 118.3 (CH), 125.7 (CH), 126.8 (C), 127.6 (CH), 127.8 (CH), 128.3 (CH), 128.8 (CH), 138.0 (CH), 138.2 (C), 148.1 (C), 149.5 (C); HRMS (ESI-TOF) *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 25.3min (*S*)].

Compound 14: $[\alpha]_D^{25}$ +154.1 (*c* 2.59, $CHCl_3$); IR (neat) 3365, 2960, 2927, 1513, 1454, 1398, 1190, 1149, 1007, 738, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, *J* = 7.2 Hz, 3H), 2.18 (s, 3H), 3.50 (s, 3H), 3.93 (dd, *J* = 6.0 and 11.2 Hz, 1H), 4.03 (dq, *J* = 2.8 and 6.8 Hz, 1H), 4.23 (dd, *J* = 4.4 and 11.2 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 5.10 (s, 2H), 5.55 (dd, *J* = 8.4 and 10.8 Hz, 1H), 5.60 (dt, *J* = 6.4 and 10.8 Hz, 1H), 6.42 (s, OH, D_2O exchangeable, 1H), 6.64 (s, 1H), 6.87 (s, 1H), 7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8 (CH_3), 19.8 (CH_2), 31.5 (CH), 56.0 (CH_2), 65.1 (CH_3), 72.8 (CH_3), 95.9 (CH_3), 113.5 (CH), 118.9 (CH), 122.9 (CH), 127.0 (C), 127.0 (C), 127.9 (CH), 128.2 (CH), 128.5 (CH), 137.3 (C), 140.0 (CH), 148.8 (C), 149.5 (C); HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{27}O_4$ $[M+H]^+$ 343.1909, found 343. 1895.

(2*R*,3*E*)-{2-[5-(Benzyloxy)pent-3-en-2-yl]-4-(methoxymethoxy)-5-methylphenoxy}(*tert*-butyl)-dimethylsilane (15): To a stirred solution of phenol **8** (200 mg, 0.584 mmol) in CH_2Cl_2 (3.25 mL) were added imidazole (159 mg, 2.34 mmol), TBSCl (211 mg, 1.40 mmol) and 4-DMAP (14.3 mg, 0.117 mmol) at 0 °C. After being stirred for 30 min at room temperature, the resultant mixture was quenched 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 (5:1 v/v) as eluent to afford TBS ether **15** (258 mg, 97%) as a colorless oil; $[\alpha]_D^{26}$ +14.6 (*c* 1.08, $CHCl_3$); IR (neat) 2929, 1501, 1391, 1193, 1151, 1012, 838, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21 (s, 3H), 0.22 (s, 3H), 1.00 (s, 9H), 1.28 (d, *J* = 6.8 Hz, 3H), 2.17 (s, 3H), 3.47 (s, 3H), 3.87 (sext., *J* = 6.0 Hz, 1H), 4.01 (d, *J* = 5.6 Hz, 2H), 4.49 (s, 2H), 5.08 (s, 2H), 5.61 (ddd, *J* = 1.6, 5.6 and 15.6 Hz, 1H), 5.90 (dd, *J* = 5.6 and 15.6 Hz, 1H), 6.57 (s, 1H), 6.80 (s, 1H), 7.28-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.1 (CH_3), 16.1 (CH_3), 18.3 (C), 20.1 (CH_3), 25.9 (CH_3), 34.4 (CH), 56.0 (CH_3), 71.0 (CH_2), 71.8 (CH_2), 93.4 (C), 95.7 (CH_2), 100.6 (C), 114.5 (CH), 120.7 (CH), 124.9 (CH), 126.0 (C), 127.5 (C), 127.8 (C), 128.3 (C), 133.9 (C), 138.7 (CH), 147.1 (C); HRMS (ESI-TOF) *m/z* calcd for $C_{27}H_{41}O_4Si$ $[M+H]^+$ 457.2774, found 457.2754.

(4*R*)-4-[2-(*tert*-Butyldimethylsilyloxy)-5-(methoxymethoxy)-4-methylphenyl]pentan-1-ol (16): A suspension of benzyl ether **15** (463 mg, 1.17 mmol) and Pd-C (46.3 mg, 10% w/w) in THF (9.26 mL)

was stirred under 5 atm of hydrogen gas. After being stirred for 15 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 (4:1 v/v) as eluent to afford alcohol **16** (360 mg, 95%) as a colorless oil; $[\alpha]_D^{28}$ +10.7 (*c* 1.02, $CHCl_3$); IR (neat) 3361, 2930, 2858, 1502, 1472, 1391, 887, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 3H), 0.21 (s, 3H), 1.00 (s, 9H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.17-1,29 (m, 1H), 1.40-1.63 (m, 5H), 2.17 (s, 3H), 3.02-3.20 (m, 1H), 3.50 (s, 3H), 3.58 (t, *J* = 6.0 Hz, 1H), 5.09 (d, *J* = 6.4 Hz, 1H), 5.13 (d, *J* = 6.4 Hz, 1H), 6.56 (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), 18.2 (C), 21.3 (CH_3), 25.8 (CH_3), 30.9 (CH_2), 31.4 (CH), 33.3 (CH_2), 56.0 (CH_3), 63.1 (CH_2), 95.6 (CH_2), 113.6 (CH), 120.6 (CH), 125.4 (C), 135.4 (C), 147.4 (C), 149.8 (C); HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{36}O_4SiNa$ $[M+Na]^+$ 391.2281, found 391.2272.

(2*R*)-*tert*-Butyl[4-(methoxymethoxy)-5-methyl-2-(6-methylhept-5-en-2-yl)phenoxy]dimethylsilane (18): To a stirred solution of oxalyl chloride (0.248 mL, 2.93 mmol) in CH_2Cl_2 (7.00 mL) was added DMSO (0.333 mL, 4.69 mmol) at −78 °C, and then a solution of alcohol **16** (360 mg, 0.978 mmol) in CH_2Cl_2 (3.00 mL) was added dropwise. After being stirred for 30 min at −78 °C, Et_3N (0.825 mL, 5.87 mmol) was added and then stirring was continued for 10 min at the same temperature. The reaction mixture was allowed to warm to room temperature, and the stirring was continued for 30 min. The resultant mixture was diluted with H_2O and extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was the corresponding aldehyde (430 mg), a yellow oil, which was used to the next reaction without further purification; ^1H NMR (400 MHz, $CDCl_3$) δ 0.19 (s, 3H), 0.22 (s, 3H), 1.00 (s, 9H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.81-1.91 (m, 2H), 2.17 (s, 3H), 2.25-2.39 (m, 2H), 3.15 (sext, *J* = 7.2 Hz, 1H), 3.45 (s, 3H), 5.10 (s, 2H), 6.57 (s, 1H), 6.81 (s, 1H), 9.68 (t, *J* = 1.2 Hz, 1H).

To a stirred solution of HMDS (0.51 ml, 2.45 mmol) in THF (15.0 mL) was added ^{n}BuLi (1.6 M in hexane, 1.53 mL, 2.45 mmol) at 0 °C. After being stirred for 15 min at 0 °C, the solution was cooled to −78 °C, and then a solution of sulfone **17** (617 mg, 2.45 mmol) in THF (5 mL) was added dropwise. After being stirred for 30 min at −78 °C, a solution of crude aldehyde (0.978 mmol) in THF (5 mL) was added at −78 °C, and then stirring was continued for 10 min at the same temperature. The resultant mixture was allowed to warm to room temperature. After being stirred for 40 min at the room temperature, the reaction mixture was quenched with H_2O and extracted with Et_2O. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel hexane/AcOEt (15:1 v/v) as eluent to afford the trisubstituted alkene **18** (379 mg, 99% for two steps) as a colorless oil; $[\alpha]_D^{26}$ −19.2 (*c* 1.14, $CHCl_3$); IR (neat) 2957, 2928, 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 (C), 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 (C), 131.1 (C), 136.0 (C), 147.4 (C), 149.9 (C); HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{41}O_3Si$ $[M+H]^+$ 393.2825, found 393.2823.

(3*R*,6*R*)-6-[2-(*tert*-Butyldimethylsilyloxy)-5-(methoxymethoxy)-4-methylphenyl]-2-methyl-heptane-2,3-diol (9): To a stirred solution of AD-mix-β (319 mg, 0.407 mmol) and $CH_3SO_2NH_2$ (19.4 mg, 0.204 mmol) in ^{t}BuOH/H_2O (1/1, 2 mL) was added alkene **18** (80.0 mg, 0.204 mmol) at 0 °C. After being stirred at room temperature for 15 h, the reaction mixture was quenched with Na_2SO_3 (0.15 ml, 1.73 mmol) at 0 °C. The resultant mixture was stirred for 1 h at room temperature before being extracted with AcOEt. The combined extracts were washed with 1 M aqueous KOH and brine, and the residue upon workup was chromatographed on silica gel with hexane/AcOEt (3:2 v/v) as eluent to afford diol **9** (86.9 mg, quant.) as a colorless oil; $[\alpha]_D^{28}$ +1.0 (*c* 1.26, $CHCl_3$); IR (neat) 3422, 2859, 1502, 1463, 1391, 1255, 1194, 1151, 1075, 1012 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 0.20 (s, 3H), 0.22 (s, 3H), 1.03 (s, 9H), 1.06 (s, 3H), 1.10 (s, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.25-1.34 (m, 1H), 1.45-1.56 (m, 2H), 1.80-1.89 (m, 1H), 2.15 (s, 3H), 3.13-3.19 (m, 1H), 3.19-3.29 (m, 1H), 3.47 (s, 3H), 5.10 (dd, *J* = 6.4 and 8.2 Hz, 2H), 6.59 (s, 1H), 6.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.2 (CH_3), −4.1 (CH_3), 16.0 (CH_3), 18.2 (C), 21.3 (CH_3), 23.1 (CH_3), 25.8 (CH_3), 26.4 (CH_3), 30.0 (CH_2), 31.9 (CH), 34.6 (CH_2), 56.0 (CH_3), 73.0 (C), 78.9 (CH), 95.6 (CH_2), 113.6 (C), 120.7 (C), 125.5 (C), 135.5 (C), 147.4 (C), 149.9 (C); HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{42}O_5NaSi$ $[M+Na]^+$ 449.2699, found 449.2710.

2-(2*R*,5*R*)-(7-Methoxymethoxy-5,8-dimethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepin-2-yl)propan-2-ol (19): To a stirred suspension of NaH (14.0 mg, 0.352 mmol) in THF (0.40 mL) was added a solution of diol **9** (30.0 mg, 70.3 μmol) in THF (0.40 mL) at 0 °C. After being stirred for 30 min, the reaction mixture was cooled to −78 °C, and then *N*-tosylimidazole (18.8 mg, 84.4 μmol) was added at the same temperature. After being stirred for 4 h at room temperature, 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 the corresponding epoxide **10** (32.3 mg), a colorless oil, which was used to the next reaction without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 3H), 0.21 (s, 3H), 1.00 (s, 9H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.19 (s, 3H), 1.26 (s, 3H), 1.40-1.65 (m, 3H), 1.68-1.83 (m, 1H), 2.17 (s, 3H), 2.69 (t, *J* = 6.4 Hz, 1H), 3.17 (sext, *J* = 7.2 Hz, 1H), 3.50 (s, 3H), 5.10 (s, 2H), 6.56 (s, 1H), 6.82 (s, 1H).

To a stirred solution of crude epoxide **10** (70.3 μmol) in MeOH (2.30 mL) was added K_2CO_3 (97.2 mg, 0.703 mmol) at room temperature. After being stirred for 4 h at 50 °C, the reaction mixture was diluted with Et_2O. The resultant mixture was quenched with H_2O, 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 (7:3 v/v) as eluent to afford *O*-MOM-heliannuol D (**19**) (16.8 mg, 81% for two steps) as a colorless oil; $[\alpha]_D^{27}$ +19.0 (*c* 0.40, $CHCl_3$); IR (neat) 3450, 2928, 1500, 1452, 1397, 1212, 1197, 1180, 1151, 1067, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.28 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.70-1.81 (m, 2H), 1.87-1.94 (m, 1H), 2.00-2.11 (m, 1H), 2.17 (s, 3H), 2.64 (brs, OH, D_2O exchangeable, 1H), 2.93-2.97 (m, 1H), 3.30 (d, *J* = 11.2 Hz, 1H), 3.50 (s, 3H), 5.14 (dd, *J* = 6.8 and 12.0 Hz, 2H), 6.75 (s, 1H), 6.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7 (CH_3), 18.6 (CH_3), 24.5 (CH_3), 25.6 (CH_2), 26.1 (CH_3), 31.8 (CH_2), 38.9 (CH), 56.0 (CH_3), 72.6 (C), 90.5 (CH), 95.2 (CH_2), 115.6 (CH), 123.5 (CH), 126.2 (C), 137.8 (C), 151.5 (C), 152.6 (C); HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{27}O_4$ $[M+H]^+$ 295.1909, found 295.1916.

(+)-Heliannuol D (1)[4]: To a stirred solution of MOM ether **19** (9.5 mg, 32.3 μmol) in THF (0.2 mL) was added 6 M aqueous HCl (0.5 mL) at room temperature. After being stirred for 3 h at room temperature, 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 concentrated in vacuo to afford heliannuol D (**1**) (7.4 mg, 91%) as a colorless crystalline solid; mp 157-158 °C (lit.[4f,4h] 161-162 °C); $[\alpha]_D^{25}$ +18.1 (*c* 0.38, $CHCl_3$); IR (neat) 3365, 2931, 1508, 1417, 1192, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 6H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.70-1.79 (m, 2H), 1.88-1.92 (m, 1H), 1.99-2.09 (m, 1H), 2.16 (s, 3H), 2.70 (brs, OH, D_2O exchangeable, 1H), 2.90 (brs, 1H), 3.30 (d, *J* = 10.8 Hz, 1H), 4.55 (brs, OH, D_2O exchangeable, 1H), 6.54 (s, 1H), 6.73 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3 (CH_3), 18.6 (CH_3), 24.4 (CH_3), 25.5 (CH_3), 26.1 (CH_2), 31.8 (CH_2), 38.5 (CH), 72.7 (C), 90.5 (CH), 115.8 (CH) 122.1 (C), 123.5 (CH), 138.1 (C), 149.6 (C), 151.7 (C); HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1647, found 251.1643.

(−)-Helibisabonol A (2)[5b]: To a stirred solution of diol **9** (18.2 mg, 42.7 μmol) in MeOH (0.9 mL) was added *p*-TsOH·H_2O (20.3 mg, 0.107 mmol) at room temperature. After being stirred for 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 with hexane/AcOEt (1:1 v/v) as eluent to afford helibisabonol A (**2**) (11.9 mg, quant.) as a colorless oil; $[\alpha]_D^{30}$ –7.8 (*c* 0.40 in acetone); IR (neat): 3367, 2963, 1703, 1419, 1193 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6)

δ 1.06 (s, 6H), 1.14 (d, *J*=7.0 Hz, 3H), 1.22-1.31 (m, 1H), 1.50 (dddd, *J*=15.5, 10.0, 5.5 and 2.0 Hz, 1H), 1.58 (dddd, *J*=13.5, 10.0, 7.5 and 5.5 Hz, 1H), 1.78 (dddd, *J*=13.5, 10.0, 7.0 and 5.5 Hz, 1H), 2.08 (s, 3H), 3.11 (sext, *J*=7.0 Hz, 1H), 3.27 (s, D_2O exchangeable, 1H), 3.27 (ddd, *J*=10.0, 5.0 and 2.0 Hz, 1H), 3.59 (d, *J*=5.0 Hz, D_2O exchangeable, 1H), 6.55 (s, 1H), 6.60 (s, 1H), 7.26 (s, D_2O exchangeable, 1H), 7.36 (s, D_2O exchangeable, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 15.7 (CH_3), 21.4 (CH_3), 24.7 (CH_3), 25.8 (CH_3), 30.0 (CH_2), 32.3 (CH), 35.8 (CH_2), 72.7 (C), 79.5 (CH), 113.7 (CH), 118.3 (CH), 122.2 (C), 132.4 (C), 147.8 (C), 149.1 (C); HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{25}O_4$ $[M+H]^+$ 269.1753, found 269.1758.

ACKNOWLEDGEMENT

This work was supported financially by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Sciences (JSPS) and a Grant-in-Aid from the Program for the Promotion of Basic and Applied Research for Innovations in the Bio-oriented Industry (BRAIN).

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