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Efficient and enantioselective total syntheses of heliannuols A and K

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ABSTRACT

The second-generation enantioselective synthesis of heliannuol A and the first enantioselective total synthesis of heliannuol K (via two routes) have both been accomplished efficiently; (heliannuol A, nine steps and 25% yield; heliannuol K, seven steps and 47% yield). Highlights of our synthetic strategy include a substrate-controlled chirality transfer in the Lewis acid mediated Claisen rearrangement of the allyl aryl ether for the key construction of a tertiary stereogenic center at the benzylic position followed by, for heliannuol A, ring-closing metathesis, diastereoselective epoxidation, and regioselective cleavage of the epoxide; and for heliannuol K, ring-closing metathesis and conjugate reduction of the eight-membered enone.

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1. Introduction

Heliannuol A (**1**),[1] the first member of a class of bioactive sesquiterpenes, and heliannuol K (**2**)[2] were isolated from the moderately polar bioactive fractions of the fresh leaf aqueous extracts of the cultivar *Helianthus annuus* L. var. SH-222 in 1993 and in 1999, respectively, by Macías et al. These natural products have been reported to exhibit significant allelopathic activity against several dicotyledon (*Lactuca sativa* and *Lepidium sativum*) and monocotyledon species (*Hordeum vulgare* and *Triticum aestivum*) at concentrations of 10^{-4}–10^{-9} M.[3] The structure of **1**, including the relative stereochemistry, was determined by single crystal X-ray diffraction analysis. This intriguing compound contains an aryl ring fused to the eight-membered oxygen heterocycle with two tertiary stereogenic centers at the C7 and C10 positions. Its absolute structure was established to be (7*R*,10*S*) by our enantioselective total synthesis of the unnatural enantiomer of (+)-heliannuol A,[4a] while the structure of heliannuol K (**2**) was elucidated mainly by ^{1}H NMR and found to have the same carbon framework as heliannuol A except for the presence of a C10 carbonyl function. Although the absolute stereochemistry at C7 has never been established, it can be deduced to be *R* based on the biogenetic parallelism with heliannuol A. Because of the interesting structural features and phytotoxic properties of these compounds, several reports on the total synthesis of the heliannuols A (**1**) and K (**2**) have been published.[5] During the course of our studies directed toward the enantioselective synthesis of helianane-type terpenoids with allelopathic activity,[6] we reported the first enantioselective total synthesis of the natural enantiomer (−)-heliannuol A (**1**),[4b] which was completed in seventeen steps from 2,5-dimethoxy-4-methyliodobenzene with an overall yield of 5%. The obvious challenge was to improve both the low yield and the many reaction steps. Herein we describe the efficient and enantioselective total syntheses of heliannuols A (**1**) and K (**2**) (Fig. 1).

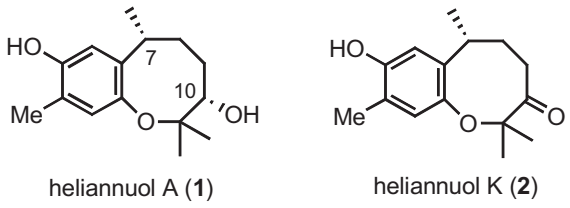

Fig. 1. Structures of heliannuols A and K.

2. Results and discussion

2.1. The second-generation synthesis of (−)-heliannuol A (1) and the first enantioselective synthesis of (−)-heliannuol K (2)

Our retrosynthetic analysis of **1** is shown in Scheme 1. For the synthesis of **1**, we chose the dihydrobenzoxocine **3**[7] with a stereogenic center at C7 as the key compound, because it has been converted efficiently to **1** by sequential diastereoselective epoxidation, regioselective cleavage of the epoxide, and deprotection of the phenolic hydroxyl function in good overall yield.[4b] The MOM protected heliannuol A, the penultimate intermediate of **1**, would be transformed to heliannuol K (**2**) by a simple two-step sequence; oxidation followed by deprotection. The eight-membered heterocycle fused to the aryl ring can be assembled by ring-closing

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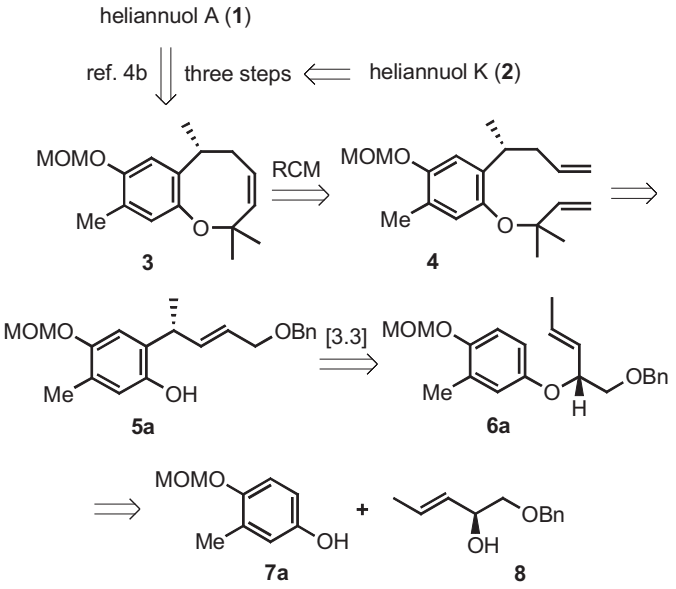
metathesis of the diene **4**, which would be prepared from the phenol **5a** via Pd-catalyzed dimethylallyl etherification.[4b,8] For the key construction of the tertiary stereogenic center at the benzylic position, we planned to use a substrate-controlled chirality transfer in the Claisen rearrangement[9,10] of the allyl aryl ether **6a** prepared from the phenol **7a** and *S*-(*E*)-1-(benzyloxy)pent-3-en-2-ol (**8**)[11] by the Mitsunobu coupling[12] (Scheme 1).



Scheme 1. Retrosynthetic analysis.

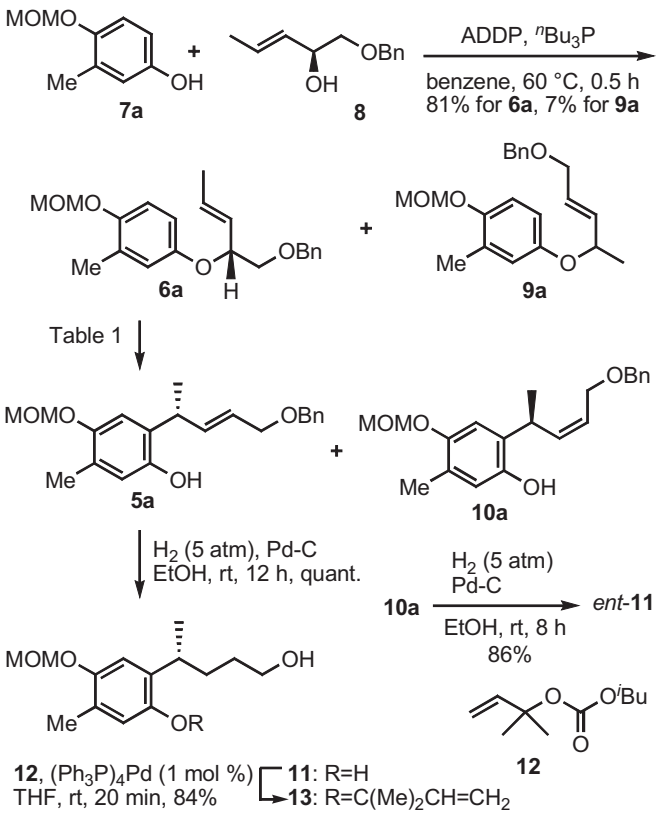
The Mitsunobu reaction between 4-(methoxymethoxy)-3-methylphenol (**7a**), prepared from 3-hydroxy-4-methylacetophenone in two steps, and the allylic alcohol **8**, derived from *S*-(+)-benzyl glycidyl ether in two steps, in the presence of 1,1-(azodicarbonyl)dipiperidine (ADDP)[13] and $^{n}Bu_3P$ provided a chromatographically separable mixture of the requisite ether **6a** (>99% ee; by HPLC analysis using a Chiralcel OD column) and the regioisomer **9a**, which was derived via the S_N2' process, in 81% and 7% yield, respectively. The key Claisen rearrangement of **6a** was examined and the results are shown in Table 1. Treatment of

Table 1
Claisen rearrangement of **6a**

Entry	Conditions	Yield, %	(% ee)[a]
		5a	**10a**
1	$Eu(fod)_3$ (8 mol %) $ClCH_2CH_2Cl$, 90 °C, 24 h	92 (90)	7
2	Et_2AlCl (1.5 equiv), hexane 0 °C, 4 h	27 (>99)	5
3	Me_3Al (3 equiv), hexane rt, 0.5 h	85 (>99)	4

[a] HPLC (Chiralcel AD column).

a solution of **6a** in dichloroethane with 8 mol % of $Eu(fod)_3$[9d] at 90 °C for 24 h gave a separable mixture of *R*-**5a** and the *Z*-isomer **10a** with the *S* configuration in 92% and 7% yield, respectively. However, the enantiomeric excess of **5a** was 90% (determined by HPLC analysis using a Chiralcel AD column) (entry 1). When the reaction was conducted with 1.5 equiv of Et_2AlCl in hexane at 0 °C for 4 h, the enantiomerically pure **5a** was obtained in only 27% yield along with 5% of **10a** (entry 2). The optimized reaction conditions call for 3 equiv of Me_3Al[14] in hexane at room temperature for 0.5 h; the requisite **5a** was obtained in 85% yield (>99% ee), together with **10a** (4%) (entry 3). On exposure of **5a** to hydrogenation conditions, the phenolic alcohol **11** {$[\alpha]_D^{27}$ −17.3 (*c* 2.65, $CHCl_3$)} was obtained quantitatively. As for the absolute configuration of the stereogenic center in **10a**, it was determined to be *S* by hydrogenation providing *ent*-**11** {$[\alpha]_D^{27}$ +18.0 (*c* 1.48, $CHCl_3$)} in 86% yield. Treatment of **11** with the mixed carbonate **12** in the presence of catalytic $(Ph_3P)_4Pd$ (1 mol %)[8] provided the alkenyl alcohol **13** in 84% yield (Scheme 2).



Scheme 2. Preparation of **13**.

The alcohol **13** was exposed to the dehydration protocol of Nishizawa–Grieco[15] to give the diene **4** (R=MOM), which was identical with the authentic material prepared previously, in 76% yield for the two steps. It was then treated with the Grubbs' second-generation catalyst **14** (0.5 mol %)[16] in refluxing methylene chloride to give the dihydrobenzoxocine **3** in 93% yield. Attempts at a substrate-controlled diastereoselective epoxidation of **3** using *m*CPBA provided a lower yield (73%) of the product **15**. However reaction of **3** with methyl(trifluoromethyl)dioxirane[17] generated in situ from methyl trifluoromethyl ketone and Oxone® in the presence of $Na_2{\cdot}EDTA{\cdot}2H_2O$ and sodium hydrogen carbonate in acetonitrile provided only the epoxide **15** in 83% yield. The stereochemistry was confirmed by the observation of a distinct NOE correlation between the Ha (δ 3.11) and Hb (δ 2.55) protons. $LiAlH_4$ reduction of the epoxide occurred at the sterically less congested carbon (C9) regioselectively to give the alcohol **16** in 91% yield as a single product. Finally, acidic hydrolysis of the MOM ether produced heliannuol A (**1**), whose spectroscopic (^1H and ^{13}C NMR) properties as well as optical rotation, {$[\alpha]_D^{26}$ −78.0 (*c* 2.4, MeOH) {lit.[1a] $[\alpha]_D$ −55.4 (*c* 0.3, MeOH)}, were identical with those of the natural product. Thus, the second-generation enantioselective total synthesis of heliannuol A (**1**) has been accomplished in a longest linear sequence of nine steps in 25% yield from the phenol **7a**. For the synthesis of heliannuol K (**2**), the penultimate intermediate **16** was oxidized with Dess–Martin periodinane to give the ketone **17**, which was exposed to the acidic hydrolysis conditions producing **2** in 99% yield for the two steps. The spectroscopic properties (^1H and

^{13}C NMR) of the synthetic **2** were identical with those of the natural heliannuol K. However, the optical rotation of the synthetic **2**, $\{[\alpha]_D^{28}$ −5.70 (*c* 0.71, $CHCl_3$), was completely different[18] from that reported for the natural product {lit.[2] $\{[\alpha]_D^{28}$ +90.0 (*c* 0.1, $CHCl_3$)}. To confirm its structure, the synthetic **2** was converted to the crystalline carbamate **18** by treatment with 4-bromophenyl isocyanate and Et_3N. X-ray crystallographic analysis of **18**[19] (Fig. 2) revealed that our synthetic material was found to possess the structure shown in Fig. 1. Thus, the first enantioselective total synthesis of heliannuol K (**2**) was accomplished in a longest linear sequence of ten steps in 26% yield from **7a** (Scheme 3).

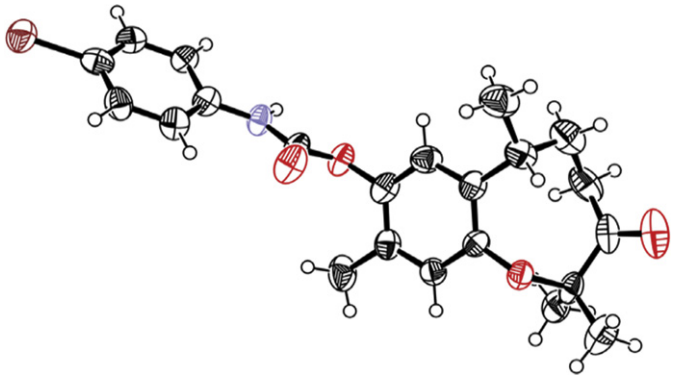
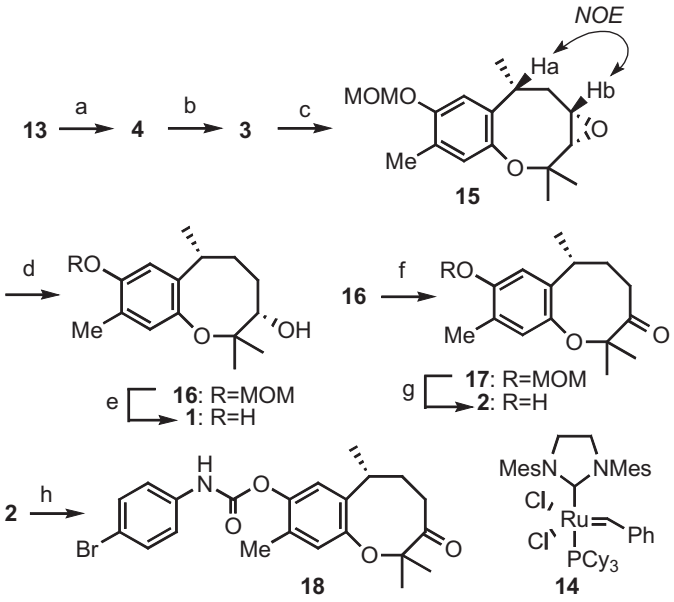


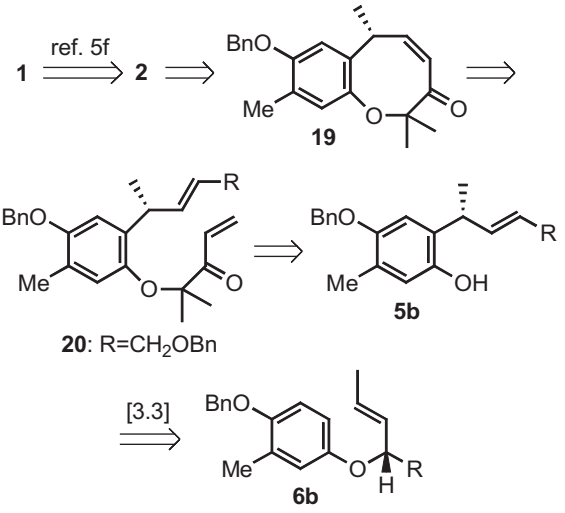
Fig. 2. ORTEP drawing of **18**.



Scheme 3. Syntheses of heliannuols A (**1**) and K (**2**). Reagents and conditions: (a) *o*-$NO_2C_6H_4SeCN$, $^nBu_3P$, THF, rt, 4 h then 30% H_2O_2 (aq), $NaHCO_3$, THF, rt, 4 h, 91%; (b) **14** (0.5 mol %), CH_2Cl_2, reflux, 0.5 h, 93%; (c) CF_3COCH_3, Oxone®, $Na_2{\cdot}EDTA{\cdot}2H_2O$, $NaHCO_3$, MeCN, 0 °C, 83%; (d) $LiAlH_4$, THF, 50 °C, 4 h, 91%; (e) 6 M HCl (aq), THF, rt, 15 h, 96%; (f) DMP, CH_2Cl_2, rt, 0.5 h, 99%; (g) 6 M HCl (aq), THF, rt, 3 h, quant.; (h) 4-bromophenyl isocyanate, Et_3N, THF, rt, 0.5 h, quant.

2.2. An alternative synthesis of (−)-heliannuol K (2)

Although we had achieved an efficient synthesis of heliannuols A and K, we wanted to find an environmentally benign synthetic route that avoided the use of an excess amount of the toxic selenium reagent (**13**→**4** in Scheme 3). Our retrosynthetic analysis is illustrated in Scheme 4.



Scheme 4. Retrosynthetic analysis.

Heliannuol K (**2**) would be obtained by the conjugate reduction of the enone in **19**, which could be constructed by ring-closing metathesis of **20**. The diene **20** with the enone and the allyl ether moieties could be accessed from the phenol **5b**, which can be prepared by the same procedure as for **5a** using a Lewis acid mediated Claisen rearrangement of **6b**. Since the conversion of heliannuol K to A by the diastereoselective reduction of **2** with $NaBH_4$ has been reported in the literature,[5f] the elaboration of **19** to **2** represents a formal synthesis of heliannuol A (Scheme 4).

The Mitsunobu reaction of **7b**[20] and **8** produced a separable mixture of **6b**, the substrate for the Claisen rearrangement, and the regioisomer **9b** in 78% and 17% yield, respectively. The Claisen rearrangement was examined using two kinds of Lewis acids, $Eu(fod)_3$ and Me_3Al, and it was revealed that the requisite **5b** was obtained with high enantiomeric excess in both cases. The conditions using a catalytic amount of $Eu(fod)_3$ provided **5b** in a higher yield of 91% (Table 2).

Table 2
Claisen rearrangement of **6b**

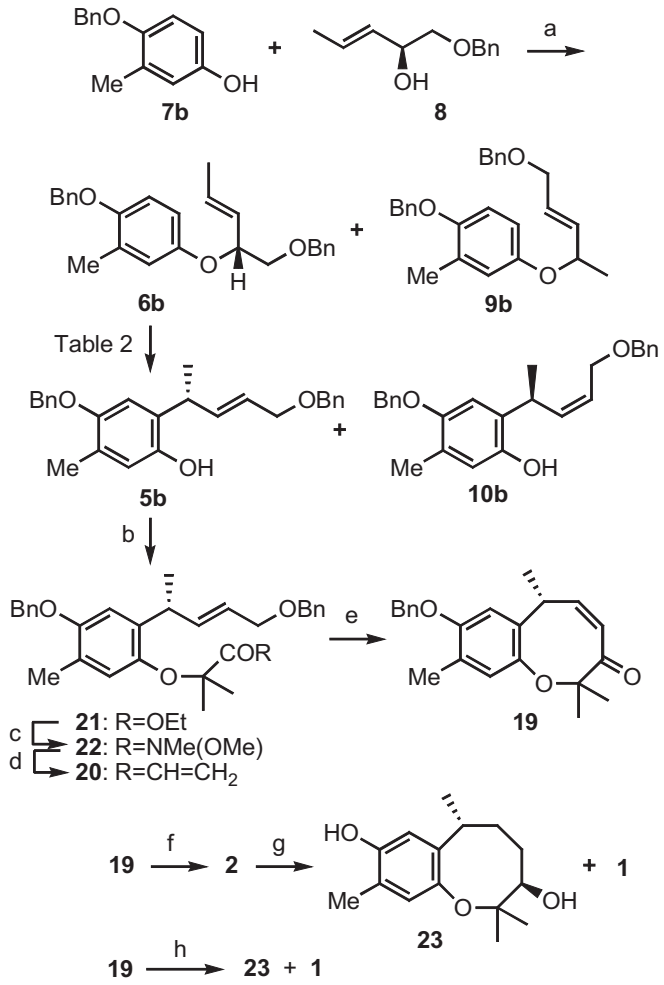
Entry	Conditions	Yield, %	(% ee)[a]
		5b	**10b**
1	$Eu(fod)_3$ (7 mol %) $ClCH_2CH_2Cl$, 90 °C, 12 h	91 (>99)	8
2	Me_3Al (3 equiv), hexane rt, 0.5 h	81 (>99)	7

[a] HPLC (Chiralcel AD column).

Treatment of **5b** with ethyl 2-bromo-2-methylpropanoate and potassium carbonate provided the ester **21**, which was converted to the Weinreb amide **22** in 95% yield for the two steps. It was then treated with vinylmagnesium chloride to give quantitatively the diene **20**, which was subjected to the ring-closing metathesis with the Grubbs' second-generation catalyst **14** (6 mol %) in the presence of benzoquinone (10 mol %)[21] in refluxing toluene to afford the eight-membered enone **19** in 80% yield. Catalytic hydrogenation of **19** with Pd/C in EtOH produced heliannuol K (**2**) quantitatively via a chemoselective reduction of the olefin and simultaneous debenzylation of the phenolic ether. However, the enantiomeric excess of **2** was only 94%,[22] which was determined by HPLC analysis on Chiralcel OD-H column. Therefore, we searched for a procedure that would prevent the partial racemization. After numerous attempts, we found that using Raney-nickel (W-2) in EtOH at room temperature for 0.5 h[23] provided heliannuol K (**2**) in 87% yield without racemization (>99% ee). The spectroscopic properties as

well as optical rotation {$[\alpha]_D^{30}$ −6.4 (*c* 1.81, $CHCl_3$)} of the synthetic material was identical with those of the authentic sample prepared in **2.1**. Thus, a highly efficient and enantioselective total synthesis of heliannuol K (**2**) has been accomplished in a longest linear sequence of seven steps in a greatly improved yield of 47% from the phenol **7b**.

Since the direct conversion of (±)-heliannuol K (**2**) to (±)-heliannuol A (**1**) has been reported to proceed with complete diastereoselectivity by Venkateswaran, we examined the conversion using the same reaction conditions. Thus, treatment of **2** with $NaBH_4$ in MeOH at 0 °C for 0.5 h produced unexpectedly an inseparable 3.8:1 mixture (by ^{1}H NMR) of 10-*epi*-heliannuol A (**23**)[5d] and heliannuol A (**1**) quantitatively. Interestingly, on exposure of **19** to Raney-nickel (W-2) in EtOH under hydrogen atmosphere, a 3.7:1 mixture of **23** and **1** was obtained in 84% yield (Scheme 5).



Scheme 5. Alternative synthesis of heliannuol K (**2**). Reagents and conditions: (a) ADDP, ^{n}Bu$_3$P, benzene, rt, 0.5 h, 78% for **6b**, 17% for **9b**; (b) ethyl 2-bromo-2-methylpropanoate, K_2CO_3, MeCN/DMF=18/1, 100 °C, 12 h, 95%; (c) LHMDS, (MeO)MeNH·HCl, THF, rt, 4 h, quant.; (d) vinylmagnesium chloride, THF, rt, 1 h, quant.; (e) **14** (6 mol %), benzoquinone (10 mol %), toluene, reflux, 7 h, 80%; (f) Raney-Ni (W-2), EtOH, rt, 0.5 h, 87%; (g) $NaBH_4$, MeOH, 0 °C, 0.5 h, quant. (**23**/**1**=3.8/1); (h) H_2 (5 atm), Raney-Ni (W-2), EtOH, rt, 2 h, 84% (**23**/**1**=3.7/1).

3. Conclusion

In summary, we have completed the second-generation enantiocontrolled total syntheses of heliannuol A (**1**) using the chirality transfer that occurred with high selectivity during the Lewis acid mediated Claisen rearrangement for the construction of the C7 stereogenic center as the key step. The synthesis was efficiently completed in a longest linear sequence of nine steps from 4-(methoxymethoxy)-3-methylphenol with an overall yield of 25%. In addition, the first enantioselective total synthesis of heliannuol K (**2**) was achieved from the penultimate intermediate for **1** via a two-step sequence. An alternative and efficient total synthesis of heliannuol K (**2**) was also accomplished via the Claisen rearrangement, ring-closing metathesis and a conjugate reduction of the eight-membered enone as the key reaction step in a longest linear sequence of seven steps from the known 4-benzyloxy-3-methylphenol with an overall yield of 47%. It has been also revealed that the optical rotation of the natural heliannuol K was not identical to that of the compound with the assigned structure **2** by the present total synthesis.

4. Experimental

4.1. General

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 except 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. Column chromatography was performed on silica gel, and flash column chromatography was performed on silica gel using the indicated solvent.

4.2. The second-generation synthesis of (−)-heliannuol A (1) and the first enantioselective synthesis of (−)-heliannuol K (2)

*4.2.1. 4-(Methoxymethoxy)-3-methylphenol (**7a**).* To a stirred solution of 4-hydroxy-3-methylacetophenone (25.0 g, 166 mmol) in CH_2Cl_2 (500 mL) were added ^{i}Pr$_2$NEt (130 mL, 749 mmol) and MOMCl (28.2 mL, 375 mmol) at 0 °C. After being stirred for 0.5 h at rt, the reaction mixture was diluted with Et_2O and water. The resultant solution was extracted with Et_2O. The combined extracts were washed with brine, and dried over $MgSO_4$, filtered and concentrated to give MOM ether as a colorless oil, which was used to the next reaction without further purification. To a stirred solution of crude MOM ether in CH_2Cl_2 (625 mL) was added *m*CPBA (43.8 g, 70%, 416 mmol) at 0 °C. After being stirred for 20 h at rt, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The combined extracts were washed with brine. To the residue upon workup was added a solution of 10% KOH in MeOH (pH 9–10) at rt. After being stirred for 30 min at the same temperature, the reaction mixture was concentrated and added water. The resultant mixture was acidified with 10% aqueous HCl and extracted with AcOEt. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (1:4 v/v) as eluent to give phenol **7a** (26.2 g, 93%) as a colorless oil; IR (neat) 3389, 2953, 1505, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (3H, s), 3.49 (3H, s), 5.11 (2H, s), 6.59 (1H, dd, *J*=3.2 and 8.8 Hz), 6.65 (1H, d, *J*=3.2 Hz), 6.92 (1H, d, *J*=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (CH_3), 55.8 (CH_3), 95.4 (CH_2), 113.0 (CH), 116.2 (CH), 117.8 (CH), 129.1 (Cq), 149.1 (Cq), 150.3 (Cq); HRMS (ESI) *m*/*z* calcd for $C_9H_{13}O_3$ 169.0865 $[M+H]^+$, found 169.0869.

*4.2.2. (R,E)-4-(1-(Benzyloxy)pent-3-en-2-yloxy)-1-(methoxymethoxy)-2-methylbenzene (**6a**) and (E)-4-(5-(benzyloxy)pent-3-en-2-yloxy)-1-(methoxymethoxy)-2-methylbenzene (**9a**).* To a stirred solution of phenol **7a** (2.02 g, 12.0 mmol), alcohol **8** (3.00 g, 15.6 mmol), and ^{n}Bu$_3$P (4.49 mL, 18.0 mmol) in benzene (34 mL) was

added 1,1-azodicarbonyldipiperizine (4.54 g, 18.0 mmol) at 0 °C. After being stirred for 15 min at rt, the reaction mixture was diluted with hexane and then filtered through a pad of Celite and concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (19:1 v/v) as eluent to afford allyl aryl ether **6a** (3.33 g, 81%, >99% ee) as a colorless oil and the region isomer **9a** (281 mg, 7%) as a colorless oil; **6a**; $\{[\alpha]_D^{25}$ −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 (3H, d, *J*=6.4 Hz), 2.21 (3H, s), 3.49 (3H, s), 3.59 (1H, dd, *J*=4.4 and 10.4 Hz), 3.67 (1H, dd, *J*=7.2 and 10.8 Hz), 4.59 (1H, d, *J*=12.0 Hz), 4.64 (1H, d, *J*=12.0 Hz), 4.69 (1H, dt, *J*=5.2 and 6.4 Hz), 5.11 (2H, s), 5.45 (1H, ddd, *J*=1.6, 6.4 and 15.6 Hz), 5.77 (1H, dq, *J*=6.4 and 15.6 Hz), 6.69 (1H, dd, *J*=2.8 and 9.2 Hz), 6.76 (1H, d, *J*=2.4 Hz), 6.92 (1H, d, *J*=8.8 Hz), 7.27–7.31 (5H, m); ^{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 (Cq), 129.3 (CH), 138.3 (Cq), 149.8 (Cq), 152.9 (Cq); HRMS (ESI) *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*)]; **9a**; $\{[\alpha]_D^{26}$ +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 (3H, d, *J*=6.5 Hz), 2.17 (3H, s), 3.42 (3H, s), 3.99 (1H, dd, *J*=5.5 and 12.5 Hz), 4.02 (1H, dd, *J*=5.5 and 12.5 Hz), 4.42 (1H, d, *J*=12.0 Hz), 4.45 (1H, d, *J*=12.0 Hz), 4.83 (1H, quint, *J*=6.0 Hz), 5.10 (2H, s), 5.79 (1H, dd, *J*=5.5 and 16.0 Hz), 5.84 (1H, dt, *J*=5.0 and 15.5 Hz), 6.70 (1H, dd, *J*=3.0 and 9.0 Hz), 6.77 (1H, d, *J*=2.5 Hz), 6.93 (1H, d, *J*=9.0 Hz), 7.25–7.34 (5H, m); ^{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 (Cq), 129.3 (CH), 138.3 (Cq), 149.8 (Cq), 152.9 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{27}O_4$ $[M+H]^+$ 343.1909, found 343.1904.

*4.2.3. (R,E)-2-(5-(Benzyloxy)pent-3-en-2-yl)-4-(methoxymethoxy)-5-methylphenol (**5a**) and (S,Z)-2-(5-(benzyloxy)pent-3-en-2-yl)-4-(methoxymethoxy)-5-methylphenol (**10a**).* To a stirred solution of allyl aryl ether **6a** (1.01 g, 2.95 mmol) in hexane (20 mL) was added Me_3Al (8 mL, 1.10 M solution in hexane, 8.85 mmol) at 0 °C. After being stirred for 30 min at rt, the reaction mixture was quenched with water. After being stirred for 1 h at the same temperature, the resultant mixture was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (9:1 v/v) as eluent to afford phenol **5a** (894 mg, 88%, >99% ee) as a colorless oil and the *Z*-isomer **10a** (162 mg, 4%) as a colorless oil; **5a**; $\{[\alpha]_D^{25}$ −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 (3H, d, *J*=6.8 Hz), 2.18 (3H, s), 3.49 (3H, s), 3.66 (1H, quint, *J*=7.2 Hz), 4.02 (2H, d, *J*=6.0 Hz), 4.50 (2H, s), 4.60 (1H, s, OH, D_2O exchangeable), 5.09 (2H, s), 5.71 (1H, dtd, *J*=1.2, 6.0 and 15.6 Hz), 5.94 (1H, dd, *J*=6.0 and 15.6 Hz), 6.61 (1H, s), 6.82 (1H, s), 7.26–7.36 (5H, m); ^{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 (Cq), 127.6 (CH), 127.8 (CH), 128.3 (CH), 128.8 (CH), 138.0 (CH), 138.2 (Cq), 148.1 (Cq), 149.5 (Cq); 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*)]; **10a**; $\{[\alpha]_D^{25}$ +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, $CDCl_3$) δ 1.32 (3H, d, *J*=7.2 Hz), 2.18 (3H, s), 3.50 (3H, s), 3.93 (1H, dd, *J*=6.0 and 11.2 Hz), 4.03 (1H, dq, *J*=2.8 and 6.8 Hz), 4.23 (1H, dd, *J*=4.4 and 11.2 Hz), 4.58 (1H, d, *J*=12.0 Hz), 4.62 (1H, d, *J*=12.0 Hz), 5.10 (2H, s), 5.55 (1H, dd, *J*=8.4 and 10.8 Hz), 5.60 (1H, dt, *J*=6.4 and 10.8 Hz), 6.42 (1H, s, OH, D_2O exchangeable), 6.64 (1H, s), 6.87 (1H, s), 7.29–7.37 (5H, m); ^{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 (Cq), 127.0 (Cq), 127.9 (CH), 128.2 (CH), 128.5 (CH), 137.3 (Cq), 140.0 (CH), 148.8 (Cq), 149.5 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{27}O_4$ $[M+H]^+$ 343.1909, found 343. 1895.

*4.2.4. (R)-2-(5-Hydroxypentan-2-yl)-4-(methoxymethoxy)-5-methylphenol (**11**).* To a stirred suspension of Pd/C (7.5 mg, 5 wt %) in EtOH (0.3 mL), which was preactivated at rt under 1 atm of hydrogen gas, was added phenol **5a** (75 mg, 0.193 mmol) in EtOH (1.2 mL) at rt, and the stirring was continued for 12 h at the same temperature under 5 atm of hydrogen gas. The resulting solution was filtered and concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (7:3 v/v) as eluent to afford diol **11** (52.7 mg, quant.) as a colorless oil; $\{[\alpha]_D^{27}$ −17.25 (*c* 2.65, $CHCl_3$); IR (neat) 3378, 2954, 1514, 1454, 1190, 1149, 1050, 1007 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, d, *J*=6.8 Hz), 1.49–1.56 (2H, m), 1.59–1.73 (2H, m), 2.18 (3H, s), 3.08 (1H, quint, *J*=6.8 Hz), 3.50 (3H, s), 3.68–3.74 (2H, m), 5.09 (1H, d, *J*=8.0 Hz), 5.11 (1H, d, *J*=8.0 Hz), 5.27 (1H, br s, OH, D_2O exchangeable), 6.60 (1H, s), 6.83 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8 (CH_3) 20.9 (CH_3), 29.7 (CH_2), 31.5 (CH), 34.5 (CH_2), 56.0 (CH_3), 63.3 (CH_2), 95.9 (CH_2), 114.0 (CH), 118.1 (CH), 126.2 (Cq), 131.1 (Cq), 148.0 (Cq), 149.6 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{14}H_{22}O_4Na$ $[M+Na]^+$ 277.1416, found 277.1410.

*4.2.5. (S)-2-(5-Hydroxypentan-2-yl)-4-(methoxymethoxy)-5-methylphenol (ent-**11**).* By following the same procedure described for **11**, *ent*-**11** was prepared from **10a**: yield 86%; colorless oil; $\{[\alpha]_D^{27}$ +18.00° (*c* 1.48, $CHCl_3$). Other spectral data coincides with those of the enantiomer *ent*-**11**.

*4.2.6. (R)-4-(5-(Methoxymethoxy)-4-methyl-2-(2-methylbut-3-en-2-yloxy)phenyl)pentan-1-ol (**13**).* To a stirred solution of diol **11** (23 mg, 0.090 mmol) in THF (1 mL) were added mixed carbonate **12** (23 mg, 0.123 mmol) and $(Ph_3P)_4Pd$ (1.2 mg, 1.02 μmol) at rt. After being stirred for 20 min at the same temperature, the reaction mixture was filtered through a pad of silica gel and concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (6:4 v/v) as eluent to afford alcohol **13** (24.6 mg, 84%) as a colorless oil; $\{[\alpha]_D^{27}$ −7.56 (*c* 3.62, $CHCl_3$); IR (neat) 3419, 2931, 1499, 1391, 1190, 1150, 1008, 922, 890 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, d, *J*=6.8 Hz), 1.30 (1H, br s, OH, D_2O exchangeable), 1.41 (3H, s), 1.43 (3H, s), 1.46–1.62 (4H, m), 2.15 (3H, s), 3.19 (1H, sext., *J*=6.8 Hz), 3.50 (3H, s), 3.60 (2H, t, *J*=6.0 Hz), 5.10 (1H, d, *J*=11.2 Hz), 5.11 (1H, d, *J*=10.0 Hz), 5.12 (1H, d, *J*=11.2 Hz), 5.18 (1H, d, *J*=17.6 Hz), 6.13 (1H, dd, *J*=10.8 and 17.6 Hz), 6.82 (1H, s), 6.83 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (CH_3) 21.3 (CH_3), 26.8 (CH_3), 27.4 (CH_3), 30.8 (CH_2), 31.7 (CH), 33.9 (CH_2), 56.0 (CH_3), 63.1 (CH_2), 79.3 (Cq), 95.5 (CH_2), 112.8 (CH_2), 113.0 (CH), 122.6 (CH), 124. 6 (Cq), 137.7 (Cq), 145.0 (CH), 147.9 (Cq), 150.7 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{31}O_4$ $[M+H]^+$ 323.2222, found 323.2220.

*4.2.7. (R)-1-(Methoxymethoxy)-2-methyl-4-(2-methylbut-3-en-2-yloxy)-5-(pent-4-en-2-yl)benzene (**4**).* To a stirred solution of alcohol **13** (30 mg, 93 μmol) in THF (0.3 mL) were added 2-nitrophenyl selenocyanate (32 mg, 0.14 mmol) and $^nBu_3P$ (0.052 mL, 0.21 mmol) at 0 °C. After being stirred for 5 min at rt, and then cooled to 0 °C. To the reaction mixture was added $NaHCO_3$ (78 mg, 0.93 mmol) and 30% aqueous H_2O_2 (0.28 mL, 1.03 mmol) at 0 °C. After being stirred for 4 h at rt, the resultant mixture was diluted with Et_2O and filtered through a pad of Celite and concentrated. The residue was extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (19:1 v/v) as eluent to give diene **4** (25.8 mg, 91%) as a colorless oil; $\{[\alpha]_D^{27}$ −6.19 (*c* 1.49, $CHCl_3$); IR (neat) 3076, 2976, 1639, 1499, 1151 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 1.16 (3H, d, J=6.8 Hz), 1.43 (3H, s), 1.43 (3H, s), 2.15 (3H, s), 2.20(1H, m), 2.35 (1H, m), 3.23 (1H, ddq, J=6.6, 6.8 and 7.1 Hz), 3.51 (3H, s), 4.94 (1H, ddt, J=1.0, 2.2, and 10.0 Hz), 5.01 (1H, m), 5.11 (2H, s), 5.11 (1H, dd, J=0.8 and 10.8 Hz), 5.19 (1H, dd, J=1.0 and 17.8 Hz), 5.76 (1H, dddd, J=6.7, 7.6, 9.5, and 16.9 Hz), 6.13 (1H, dd, J=10.8 and 17.8 Hz), 6.83 (1H, s), 6.83 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2 (CH_3), 20.4 (CH_3), 27.2 (CH_3), 27.3 (CH_3), 32.2 (CH), 41.8 (CH_2), 56.0 (CH_3), 79.1 (Cq), 95.5 (CH_2), 112.7 (CH_2), 113.3 (CH), 115.4 (CH_2), 122.1 (CH), 124.5 (Cq), 137.3 (Cq), 137.6 (CH), 145.0 (CH), 147.8 (Cq), 150.3 (Cq); MS (EI) m/z 304 $[M]^+$; HRMS (EI) m/z calcd for $C_{19}H_{28}O_3$ $[M]^+$ 304.2038, found 304.2010.

*4.2.8. (R,Z)-8-(Methoxymethoxy)-2,2,6,9-tetramethyl-5,6-dihydro-2H-benzo[b]oxocine (**3**).* To a stirred solution of diene **4** (13 mg, 0.043 mmol) in CH_2Cl_2 (2.1 mL) was added Grubbs' second-generation catalyst **14** (0.18 mg, 0.21 μmol) at rt, and then the mixture was heated to reflux. After being stirred for 30 min, the reaction mixture was cooled to rt. After being stirred for 1 h at the same temperature under air, the resultant mixture was concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (97:3 v/v) as eluent to give oxocine **3** (11.0 mg, 93%) as a colorless oil; {$[\alpha]_D^{27}$ −56.5 (c 0.34, $CHCl_3$); IR (neat) 2960, 1652, 1503, 1147 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (1H, d, J=7.1 Hz), 1.36 (3H, s), 1.57 (3H, s), 2.00–2.10 (1H, br s), 2.16 (3H, s), 2.90 (1H, br s), 3.26 (1H, br s), 3.49 (3H, s), 5.13 (2H, s), 5.26 (1H, d, J=11.0 Hz), 5.67 (1H, ddd, J=8.0, 10.0, and 10.5 Hz), 6.69 (1H, s), 6.72 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9 (CH_3), 25.4 (CH_3), 28.4 (CH_3), 29.4 (CH_3), 33.9 (CH_2), 40.2 (CH), 56.0 (CH_3), 80.9 (Cq), 95.0 (CH_2), 116.1 (CH), 124.8 (Cq), 128.7 (CH), 130.0 (CH), 134.8 (CH), 137.9 (Cq), 146.5 (Cq), 152.0 (Cq); MS (EI) m/z 276 $[M]^+$; HRMS (EI) m/z calcd for $C_{17}H_{24}O_3$ $[M]^+$ 276.1725, found 276.1725.

*4.2.9. (1aS,8R,9aS)-6-(Methoxymethoxy)-2,2,5,8-tetramethyl-2,8,9,9a-tetrahydro-1aH-benzo[b]oxireno[2,3-f]oxocine (**15**).* To a stirred solution of **3** (12.7 mg, 0.046 mmol), $Na_2{\cdot}EDTA{\cdot}2H_2O$ (0.21 mL), CF_3COCH_3 (0.05 mL, 0.51 mmol) and $NaHCO_3$ (29.9 mg, 0.357 mmol) in MeCN (0.5 mL) was added Oxone® (141.4 mg, 0.23 mmol) over a period of 1 h at 0 °C. After being stirred for 1.5 h at the same temperature, the reaction mixture was added water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (95:5 v/v) as eluent to give epoxide **15** (11.1 mg, 83%) as a colorless oil; {$[\alpha]_D^{26}$ −80.0 (c 0.43, $CHCl_3$); IR (neat) 2925, 1503, 1385, 1147 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, d, J=6.8 Hz), 1.46 (3H, s), 1.56 (3H, s), 2.18 (3H, s), 2.20–2.33 (2H, m), 2.55 (1H, d, J=4.0 Hz), 2.96 (1H, dq, J=6.4 and 6.5 Hz), 3.11 (1H, ddd, J=3.6, 4.0 and 11.2 Hz), 3.51 (3H, s), 5.15 (2H, dd, J=6.4 and 10.2 Hz), 6.75 (1H, s), 6.77 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (CH_3), 25.0 (CH_3), 27.4 (CH_3), 29.4 (CH_3), 34.1 (CH_2), 37.2 (CH), 56.1 (CH_3), 57.7 (CH), 59.3 (CH), 79.7 (Cq), 95.0 (CH_2), 116.2 (CH), 125.4 (Cq), 128.6 (CH), 137.7 (Cq), 146.3 (Cq), 152.2 (Cq); MS (EI) m/z 292 $[M]^+$; HRMS (EI) m/z calcd for $C_{17}H_{24}O_4$ $[M]^+$ 292.1675, found 292.1658.

*4.2.10. (3S,6R)-8-(Methoxymethoxy)-2,2,6,9-tetramethyl-3,4,5,6-tetrahydro-2H-benzo[b]oxocin-3-ol (**16**).* To a stirred suspension of $LiAlH_4$ (63.7 mg, 1.68 mmol) in THF (1.5 mL) was added a solution of epoxide 15 (44.6 mg, 0.152 mmol) in THF (1.0 mL) at 0 °C. After being stirred for 4 h at 50 °C, the reaction mixture was cooled to 0 °C and then added water. After being stirred for 1 h at the same temperature, the resultant mixture was filtered through a pad of Celite and concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (9:1 v/v) as eluent to give alcohol **16** (40.6 mg, 91%) as a colorless oil; {$[\alpha]_D^{26}$ −67.0 (c 0.36, $CHCl_3$); IR (neat) 3446, 2930, 1499, 1010 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, s), 1.26 (3H, s), 1.26 (3H, d, J=6.8 Hz), 1.46 (2H, br s), 1.69 (2H, m), 1.84 (1H, br s), 1.97 (1H, s, D_2O exchangeable, OH), 2.18 (3H, s), 3.50 (3H, s), 3.66 (1H, br s), 3.70 (1H, dd, J=7.0 and 7.0 Hz), 5.14 (2H, s), 6.71 (1H, s), 6.79 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (CH_3), 19.5 (CH_3), 25.0 (CH_3), 28.8 (CH_3), 30.2 (CH_2), 36.2 (CH_2), 39.1 (CH), 56.0 (CH_3), 78.0 (CH), 94.5 (CH_2), 110.2 (CH), 124.2 (Cq), 126.2 (CH), 137.2 (Cq), 146.7 (Cq), 151.8 (Cq); MS (EI) m/z 294 $[M]^+$; HRMS (EI) m/z calcd for $C_{17}H_{26}O_4$ $[M]^+$ 294.1831, found 294.1837.

*4.2.11. (−)-Heliannuol A (**1**).* To a stirred solution of MOM ether **16** (35.4 mg, 0.12 mmol) in THF (0.6 mL) was added 6 M aqueous HCl (0.6 mL) at 0 °C. After being stirred for 15 h at rt, the reaction mixture was quenched with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (8:2 v/v) as eluent to give (−)-heliannuol A (**1**) (28.7 mg, 96%) as a colorless prism; mp 83.8–85.2 (recrystallized from benzene/hexane); {$[\alpha]_D^{26}$ −78.0 (c 2.4, MeOH) {lit.[1a] $[\alpha]_D$ −55.4 (c 0.3, MeOH)}; IR (neat) 3375, 2928, 1507, 1134 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD, −30 °C) δ 1.15, 1.31 (3H, s), 1.31, 1.44 (3H, s), 1.36 (2H, m), 1.22, 1.27 (3H, d, J=6.8 Hz), 1.65, 1.88 (2H, m), 2.08, 2.10 (3H, s), 3.23 (1H, m), 3.47, 3.56 (1H, m), 6.46, 6.51 (1H, s), 6.60, 6.65 (1H, s); ^{13}C NMR (100 MHz, CD_3OD, −30 °C) δ 16.1 (CH_3), 16.3 (CH_3), 18.2 (CH_3), 29.7 (CH_3), 30.1 (CH), 31.5 (CH_2), 38.5 (CH_2), 78.9 (CH), 82.9 (Cq), 114.7 (CH), 122.3 (Cq), 127.5 (CH), 138.2 (Cq), 146.3 (Cq), 153.1 (Cq); MS (EI) m/z 250 $[M]^+$; HRMS (EI) m/z calcd for $C_{15}H_{22}O_3$ $[M]^+$ 250.1569, found 250.1587.

*4.2.12. (R)-8-(Methoxymethoxy)-2,2,6,9-tetramethyl-5,6-dihydro-2H-benzo[b]oxocin-3(4H)-one (**17**).* To a stirred solution of alcohol **16** (6.0 mg, 0.020 mmol) in CH_2Cl_2 was added Dess–Martin periodinane (13.0 mg, 0.031 mmol) at 0 °C. After being stirred for 0.5 h at rt, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (9:1 v/v) as eluent to give ketone (**17**) (5.8 mg, 99%) as a colorless oil; {$[\alpha]_D^{25}$ −14.30 (c 0.70, $CHCl_3$); IR (neat) 2931, 1713, 1499, 1187, 1147, 1008 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, d, J=7.2 Hz), 1.45 (3H, s), 1.48 (3H, s), 1.64–1.74 (1H, m), 1.97 (1H, ddt, J=7.2, 10.0, and 14.4 Hz), 2.17 (3H, s), 2.45 (1H, ddd, J=3.2, 8.0 and 11.2 Hz), 2.53–2.59 (1H, m), 3.09 (1H, ddq, J=3.2, 10.0, and 10.8 Hz), 3.49 (3H, s), 5.14 (2H, s), 6.73 (1H, s), 6.81 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (CH_3), 20.4 (CH_3), 23.6 (CH_3), 24.4 (CH_3), 34.4 (CH_2), 34.7 (CH), 36.1 (CH_2), 56.0 (CH_3), 86.0 (Cq), 95.1 (CH_2), 113.3 (CH), 125.4 (Cq), 127.5 (CH), 137.4 (Cq), 147.2 (Cq), 152.8 (Cq), 212.9 (Cq); HRMS (ESI) m/z calcd for $C_{17}H_{25}O_4$ $[M+H]^+$ 293.1753, found 293.1743.

*4.2.13. (−)-Heliannuol K (**2**).* By following the same procedure described for (−)-heliannuol A (**1**), (−)-heliannuol K (**2**) was prepared from ketone (**17**): yield quant.; white solid; mp 125.4–126.3 °C (recrystallized from benzene); {$[\alpha]_D^{28}$ −5.70 (c 0.71, $CHCl_3$) {lit.[2] {$[\alpha]_D^{25}$ +90.0 (c 0.1, $CHCl_3$)}; IR (neat) 3404, 2962, 2932, 1710, 1408, 1188, 1143, 909, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, d, J=7.2 Hz), 1.43 (3H, s), 1.49 (3H, s), 1.58–1.66 (1H, m), 1.93–2.00 (1H, m), 2.18 (3H, s), 2.46–2.49 (2H, m), 3.08 (1H, ddq, J=3.6, 10.4, and 10.8 Hz), 4.47 (1H, s, OH, D_2O exchangeable), 6.57 (1H, s), 6.72 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5 (CH_3), 20.4 (CH_3), 23.3 (CH_3), 24.6 (CH_3), 34.0 (CH), 34.6 (CH_2), 36.2 (CH_2), 86.0 (Cq), 113.5 (CH), 121.5 (Cq), 127.5 (CH), 137.9 (Cq), 146.3 (Cq), 151.0 (Cq), 213.0 (Cq); HRMS (ESI) m/z calcd for $C_{15}H_{20}O_3Na$ $[M+Na]^+$ 271.1310, found 271.1301.

*4.2.14. (R)-2,2,6,9-Tetramethyl-3-oxo-3,4,5,6-tetrahydro-2H-benzo[b]oxocin-8-yl 4-bromophenyl carbamate (**18**).* To a stirred solution

of (−)-heliannuol K (**2**) (3.3 mg, 13 μmol) in THF (0.5 mL) were added Et_3N (4.0 μL, 26 μmol) and 4-bromophenyl isocyanate (3.2 mg, 16 μmol) at 0 °C. After being stirred for 0.5 h at rt, the reaction mixture was concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (4:1 v/v) as eluent to give carbamate (**18**) (7.5 mg, quant.) as a white solid; mp 155.2–156.4 °C (recrystallized from benzene); $\{[\alpha]_D^{25}$ −7.48 (*c* 0.48, $CHCl_3$); IR (neat) 3316, 2929, 1715, 1538, 1492, 1395, 1211, 1169, 1008, 826, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, d, *J*=7.2 Hz), 1.46 (3H, s), 1.52 (3H, s), 1.55–1.64 (1H, m), 1.95–2.05 (1H, m), 2.19 (3H, s), 2.46–2.50 (2H, m), 3.12 (1H, ddq, *J*=3.8, 10.4, and 10.8 Hz), 6.83 (1H, s), 6.92 (1H, s), 7.35 (1H, d, *J*=6.0 Hz), 7.45 (1H, d, *J*=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (CH_3), 20.2 (CH_3), 23.2 (CH_3), 24.6 (CH_3), 33.7 (CH), 34.5 (CH_2), 36.0 (CH_2), 86.4 (Cq), 120.3 (CH), 120.8 (CH), 127.6 (CH), 128.5 (Cq), 128.5 (Cq), 132.1 (CH), 136.6 (Cq), 138.3 (Cq), 145.0 (Cq), 150.7 (Cq), 151.3 (Cq), 212.3 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{25}NO_4Br$ $[M+H]^+$ 446.0967, found 446.0984.

4.3. An alternative synthesis of (−)-heliannuol K (2)

*4.3.1. 4-(Benzyloxy)-3-methylphenol (**7b**).* To a stirred solution of 4-hydroxy-3-methylacetophenone (3.0 g, 19.98 mmol) in acetone (60 mL) were added K_2CO_3 (13.8 g, 99.89 mmol) and BnBr (8.3 mL, 69.92 mmol) at 0 °C. After being stirred for 1 h under reflux condition, the reaction mixture was cooled to rt, and then added water. The resultant solution was extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (1:4 v/v) as eluent to give benzyl ether (5.01 g, quant.) as a white solid; mp 75.8 °C (recrystallized from benzene); IR (neat) 1675, 1601, 1502, 1263, 1143, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s), 2.55 (3H, s), 5.16 (2H, s), 6.90 (1H, d, *J*=8.4 Hz), 7.32–7.44 (5H, m), 7.79 (1H, d, *J*=2.4 and 8.8 Hz), 7.80 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4 (CH_3), 26.3 (CH_3), 69.9 (CH_2), 110.5 (CH), 127.0 (CH), 127.1 (Cq), 127.9 (CH), 128.3 (CH), 128.6 (CH), 130.1 (Cq), 131.0 (CH), 136.6 (Cq), 160.8 (Cq), 197.0 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{16}O_2Na$ $[M+Na]^+$ 263.1048, found 263.1053; To a stirred solution of benzyl ether (4.91 g, 20.43 mmol) in CH_2Cl_2 (100 mL) were added $NaHCO_3$ (3.43 g, 40.86 mmol) and *m*CPBA (5.88 g, 70%, 24.52 mmol) at 0 °C. After being stirred for 6 h at rt, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The combined extracts were washed with brine. To the residue upon workup was added a solution of 10% KOH in MeOH (pH 9–10) at rt. After being stirred for 30 min at the same temperature, the reaction mixture was concentrated and added water. The resultant mixture was acidified with 10% aqueous HCl and extracted with AcOEt. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (7:3 v/v) as eluent to give phenol **7b** (4.57 g, quant.) as a white solid; mp 58.1 °C (recrystallized from benzene); IR (neat) 3311, 1697, 1505, 1454, 1217, 1020, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.24 (3H, s), 4.30 (1H, br s, D_2O exchangeable, OH), 5.01 (2H, s), 6.59 (1H, dd, *J*=2.8 and 8.4 Hz), 6.67 (1H, d, *J*=3.2 Hz), 6.75 (1H, d, *J*=8.4 Hz), 7.29–7.44 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4 (CH_3), 70.9 (CH_2), 112.6 (CH), 113.3 (CH), 118.0 (CH), 127.2 (CH), 127.7 (CH), 128.4 (CH), 128.8 (Cq), 137.7 (Cq), 149.3 (Cq), 151.1 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{14}H_{14}O_2Na$ $[M+Na]^+$ 237.0891, found 237.0882.

*4.3.2. (R,E)-1-(Benzyloxy)-4-(1-(benzyloxy)pent-3-en-2-yloxy)-2-methylbenzene (**6b**) and (E)-1-(benzyloxy)-4-(5-(benzyloxy)pent-3-en-2-yloxy)-2-methylbenzene (**9b**).* By following the same procedure described for **6a** and **9a**, **6b** and **9b** were prepared from **7b** and **8**: yield 78% for **6b**; colorless oil; $\{[\alpha]_D^{25}$ −13.34 (*c* 2.26, $CHCl_3$); IR (neat) 1499, 1454, 1379, 1215, 1100, 1026, 966, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.70 (3H, d, *J*=6.4 Hz), 2.24 (3H, s), 3.59 (1H, dd, *J*=4.0 and 10.4 Hz), 3.67 (1H, dd, *J*=6.8 and 10.4 Hz), 4.59 (1H, d, *J*=12.0 Hz), 4.64 (1H, d, *J*=12.0 Hz), 4.68 (1H, dt, *J*=5.2 and 6.0 Hz), 5.01 (2H, s), 5.50 (1H, dd, *J*=1.6 and 15.6 Hz), 5.77 (1H, dq, *J*=6.4 and 15.2 Hz), 6.69 (1H, dd, *J*=2.8 and 8.8 Hz), 6.76 (1H, d, *J*=8.8 Hz), 6.79 (1H, d, *J*=2.4 Hz), 7.27–7.74 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5 (CH_3), 17.9 (CH_3), 70.6 (CH_2), 72.9 (CH_2), 73.3 (CH_2), 78.8 (CH), 112.5 (CH), 113.8 (CH), 119.6 (CH), 127.1 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.2 (Cq), 128.3 (CH), 128.4 (CH), 129.3 (CH), 137.7 (Cq), 138.3 (Cq), 151.4 (Cq), 152.1 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{29}O_3$ $[M+H]^+$ 389.2117, found 389.2105: yield 17% for **9b**; colorless oil; $\{[\alpha]_D^{25}$ +31.78 (*c* 2.71, $CHCl_3$); IR (neat) 2856, 1498, 1454, 1216, 1027, 968, 737, 696 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 1.35 (3H, d, *J*=6.4 Hz), 2.19 (3H, s), 3.97 (1H, dd, *J*=4.8 and 12.4 Hz), 4.01 (1H, dd, *J*=5.2 and 12.4 Hz), 4.42 (2H, s), 4.81 (1H, quint, *J*=6.0 Hz), 5.03 (2H, s), 5.77 (1H, dd, *J*=4.8 and 15.6 Hz), 5.83 (1H, dt, *J*=4.8 and 15.6 Hz), 6.70 (1H, dd, *J*=3.2 and 8.8 Hz), 6.78 (1H, d, *J*=2.8 Hz), 6.86 (1H, d, *J*=8.8 Hz), 7.23–7.47 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5 (CH_3), 21.4 (CH_3), 70.0 (CH_2), 70.6 (CH_2), 71.9 (CH_2), 74.6 (CH), 112.6 (CH), 113.8 (CH), 119.6 (CH), 127.1 (CH), 127.6 (CH), 127.7 (CH), 127.7 (CH), 127.8 (CH), 128.3 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 137.7 (Cq), 138.2 (Cq), 151.4 (Cq), 151.8 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{29}O_3$ $[M+H]^+$ 389.2117, found 389.2121.

*4.3.3. (R,E)-4-(Benzyloxy)-2-(5-(benzyloxy)pent-3-en-2-yl)-5-methylphenol (**5b**) and (S,Z)-4-(benzyloxy)-2-(5-(benzyloxy)pent-3-en-2-yl)-5-methylphenol (**10b**).* To a stirred solution of allyl aryl ether **6b** (3.52 g, 9.06 mmol) in 1,2-dichloroethane (70 mL) was added tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionaic) europium (700 mg, 0.67 mol) at rt. After being stirred at 100 °C for 12 h, the reaction mixture was filtered through a pad of silica gel and concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (17:3 v/v) as eluent to afford phenol **5b** (3.19 g, 91%, >99% ee) as a colorless oil and the *Z*-isomer **10b** (292 mg, 8%) as a white solid; **5b**; $\{[\alpha]_D^{25}$ −6.15 (*c* 2.44, $CHCl_3$); IR (neat) 3363, 2926, 2863, 1508, 1453, 1414, 1377, 1192, 974, 737, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, d, *J*=6.8 Hz), 2.21 (3H, s), 3.69 (1H, quint, *J*=6.8 Hz), 4.02 (2H, d, *J*=5.6 Hz), 4.51 (2H, s), 4.51 (1H, br s, OH, D_2O exchangeable), 4.99 (2H, s), 5.69 (1H, dt, *J*=6.4 and 15.2 Hz), 5.92 (1H, dd, *J*=6.0 and 15.6 Hz), 6.62 (1H, s), 6.66 (1H, s), 7.28–7.43 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (CH_3), 19.4 (CH_3), 36.1 (CH), 70.6 (CH_2), 71.1 (CH_2), 72.1 (CH_2), 112.4 (CH), 118. 6 (CH), 125.9 (CH), 126.5 (Cq), 127.3 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.3 (Cq), 128.4 (CH), 128.4 (CH), 137.7 (CH), 138.3 (Cq), 138.8 (Cq), 147.1 (Cq), 151.1 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{29}O_3$ $[M+H]^+$ 389.2117, found 389.2125. Enantiomeric excess was determined by HPLC analysis [Chiralcel AD column, 5.0% isopropanol/hexane, 1.0 mL/min, λ=254 nm, retention times 44.7 min (*R*) and 51.0 min (*S*)]; **10b**; mp 70.2 °C; $\{[\alpha]_D^{25}$ −128.06 (*c* 0.87, $CHCl_3$); IR (neat) 3361, 2866, 1507, 1455, 1417, 1192, 1066, 1026, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, d, *J*=7.2 Hz), 2.21 (3H, s), 3.93 (1H, dd, *J*=6.0 and 11.6 Hz), 4.03 (1H, dq, *J*=6.8 and 9.2 Hz), 4.21 (1H, ddd, *J*=1.2, 4.8, and 10.8 Hz), 4.57 (1H, d, *J*=12.0 Hz), 4.61 (1H, d, *J*=12.0 Hz), 5.00 (2H, s), 5.53 (1H, ddd, *J*=1.2, 10.0, and 10.8 Hz), 5.59 (1H, dt, *J*=6.0 and 10.8 Hz), 6.25 (1H, s, OH, D_2O exchangeable), 6.66 (1H, s), 6.70 (1H, s), 7.29–7.45 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8 (CH_3), 19.9 (CH_3), 31.6 (CH), 65.2 (CH_2), 71.3 (CH_2), 72.8 (CH_2), 111.1 (CH), 119.2 (CH), 123.0 (CH), 126.6 (Cq), 127.3 (CH), 127.7 (CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 137.4 (Cq), 137.8 (Cq), 139.9 (CH), 147.8 (Cq), 147.1 (Cq), 151.0 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{26}H_{29}O_3$ $[M+H]^+$ 389.2117, found 389.2136.

*4.3.4. (E)-1-(Benzyloxy)-4-(5-(benzyloxy)pent-3-en-2-yloxy)-2-methylbenzene (**21**).* To a stirred solution of phenol **5b** (1.67 g, 4.29 mmol) and ethyl 2-bromo-2-methylpropanoate (5.0 g,

25.71 mmol) in MeCN/DMF (18 mL, 18/1 v/v) was added K_2CO_3 (3.6 g, 25.71 mmol) at rt. After being stirred for 12 h at 107 °C, the reaction mixture was cooled to 0 °C, and then diluted with Et_2O and 1 M aqueous HCl. The resultant mixture was extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (4:1 v/v) as eluent to give ester **18** (2.04 g, 95%) as a colorless oil; $\{[\alpha]_D^{25}$ −5.55 (*c* 3.14, $CHCl_3$); IR (neat) 2932, 1733, 1500, 1454, 1382, 1197, 1176, 1138, 1019, 972, 737, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t, *J*=7.2 Hz), 1.29 (3H, d, *J*=8.4 Hz), 1.53 (3H, s), 1.56 (3H, s), 2.17 (3H, s), 3.96 (1H, quint, *J*=6.8 Hz), 4.00 (2H, d, *J*=6.0 Hz), 4.26 (2H, q, *J*=6.8 Hz), 4.50 (2H, s), 4.98 (2H, s), 5.62 (1H, dt, *J*=6.4 and 15.6 Hz), 5.86 (1H, dd, *J*=5.6 and 15.6 Hz), 6.57 (1H, s), 6.67 (1H, s), 7.24–7.41 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 16.2 (CH_3), 20.1 (CH_3), 25.1 (CH_3), 25.7 (CH_3), 34.5 (CH), 61.3 (CH_2), 70.5 (CH_2), 71.9 (CH_2), 79.3 (Cq), 111.6 (CH), 120.5 (CH), 124.8 (CH), 125.1 (Cq), 127.3 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 128.3 (CH), 128.4 (CH), 135.0 (Cq), 137.6 (Cq), 138.5 (Cq), 138.5 (Cq), 138.7 (CH), 146.1 (Cq), 152.0 (Cq), 174.7 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{32}H_{38}O_5Na$ $[M+Na]^+$ 525.2617, found 525.2625.

*4.3.5. (R,E)-2-(4-(Benzyloxy)-2-(5-(benzyloxy)pent-3-en-2-yl)-5-methylphenoxy)-N-methoxy-N,2-dimethylpropanamide (**22**).* To a stirred solution of ester **18** (1.99 g, 3.96 mmol) and (MeO)MeNH·HCl (1.16 g, 11.87 mmol) in THF (26 mL) was added LHMDS (12 mL, 1.0 M solution in THF, 34.4 mmol) at 0 °C. After being stirred for 4 h at rt, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (4:1 v/v) as eluent to give Weinreb amide **22** (2.84 g, 98%) as a colorless oil; $\{[\alpha]_D^{25}$ −8.71 (*c* 3.56, $CHCl_3$); IR (neat) 2932, 1655, 1500, 1454, 1382, 1198, 1151, 1017, 738, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, d, *J*=6.8 Hz), 1.56 (3H, s), 1.58 (3H, s), 2.17 (3H, s), 3.33 (3H, s), 3.63 (3H, s), 3.89 (1H, quint, *J*=6.8 Hz), 4.00 (2H, d, *J*=6.4 Hz), 4.50 (2H, s), 4.98 (2H, s), 5.62 (1H, dt, *J*=6.4 and 15.2 Hz), 5.87 (1H, dd, *J*=6.0 and 15.6 Hz), 6.57 (1H, s), 6.69 (1H, s), 7.27–7.42 (10H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2 (CH_3), 20.1 (CH_3), 25.2 (CH_3), 25.2 (CH_3), 35.1 (CH), 60.5 (CH_3), 70.5 (CH_2), 70.9 (CH_2), 72.0 (CH_2), 77.2 (CH_3), 79.9 (Cq), 111.7 (CH), 119.3 (CH), 124.9 (CH), 125.3 (Cq), 127.3 (CH), 127.5 (CH), 127.7 (CH), 127.7 (CH), 128.3 (CH), 128.4 (CH), 134.1 (Cq), 137.6 (Cq), 138.4 (Cq), 138.5 (CH), 146.1 (Cq), 151.7 (Cq), 173.6 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{32}H_{39}NO_5Na$ $[M+Na]^+$ 540.2726, found 540.2744.

*4.3.6. (R,E)-4-(4-(Benzyloxy)-2-(5-(benzyloxy)pent-3-en-2-yl)-5-methylphenoxy)-4-methylpent-1-en-3-one (**20**).* To a stirred solution of amide **22** (30 mg, 0.058 mmol) in THF (0.6 mL) was added vinylmagnesium chloride (0.13 mL, 1.36 M solution in THF, 34.4 mmol) at 0 °C. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with 1 M aqueous HCl and extracted with AcOEt. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (9:1 v/v) as eluent to give diene **20** (31.8 mg, quant.) as a colorless oil; $\{[\alpha]_D^{25}$ −9.17 (*c* 2.45, $CHCl_3$); IR (neat) 2937, 2857, 1700, 1609, 1500, 1455, 1401, 1379, 1196, 1154, 1066, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, d, *J*=6.8 Hz), 1.45 (3H, s), 1.47 (3H, s), 2.12 (3H, s), 3.93 (1H, quint, *J*=6.4 Hz), 4.01 (2H, d, *J*=6.0 Hz), 4.51 (2H, s), 4.97 (2H, s), 5.63 (1H, dt, *J*=6.0 and 15.6 Hz), 5.74 (1H, dd, *J*=1.6 and 10.4 Hz), 5.89 (1H, dd, *J*=6.0 and 15.6 Hz), 6.31 (1H, s), 6.51 (1H, dd, *J*=2.0 and 17.2 Hz), 6.69 (1H, s), 7.04 (1H, dd, *J*=10 and 17.2 Hz), 7.28–7.41 (10H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.1 (CH_3), 20.0 (CH_3), 23.8 (CH_3), 23.9 (CH_3), 35.0 (CH), 70.6 (CH_2), 71.0 (CH_2), 72.0 (CH_2), 83.3 (Cq), 111.9 (CH), 119.4 (CH), 125.0 (CH), 125.2 (Cq), 127.3 (CH), 127.5 (CH), 127.7 (CH), 127.7 (CH), 128.3 (CH), 128.4 (CH), 129.8 (CH_2), 130.4 (CH), 134.2 (Cq), 137.6 (Cq), 137.6 (Cq), 138.5 (CH), 146.0 (Cq), 151.8 (Cq), 202.6 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{32}H_{36}O_4Na$ $[M+Na]^+$ 507.2511, found 507.2526.

*4.3.7. (R,Z)-8-(Benzyloxy)-2,2,6,9-tetramethyl-2H-benzo[b]oxocin-3(6H)-one (**19**).* To a stirred solution of diene **20** (20 mg, 0.041 mmol) in toluene (2 mL) were added benzoquinone (1.0 mg, 4.1 μmol) and Grubbs' second-generation catalyst **14** (3.0 mg, 2.5 μmol) at rt, and then the mixture was heated to reflux. After being stirred for 7 h, the reaction mixture was cooled to rt. After being stirred for 1 h at the same temperature under air, the resultant mixture was concentrated. The residue was chromatographed on silica gel with benzene as eluent to give eight-membered enone **19** (11.1 mg, 80%, >99% ee) as a white solid; mp 131.4 °C; $\{[\alpha]_D^{25}$ −83.29 (*c* 1.46, $CHCl_3$); IR (neat) 2984, 1685, 1503, 1456, 1377, 1197, 1152, 1016, 737, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (3H, d, *J*=7.6 Hz), 1.53 (3H, s), 1.54 (3H, s), 2.20 (3H, s), 3.85 (1H, br m), 4.99 (2H, s), 5.76 (1H, dd, *J*=1.6 and 12.8 Hz), 6.22 (1H, dd, *J*=4.8 and 12.8 Hz), 6.61 (1H, s), 6.87 (1H, s), 7.29–7.42 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.1 (CH_3), 19.5 (CH_3), 24.6 (CH_3), 25.5 (CH), 70.4 (CH_2), 87.4 (Cq), 110.9 (CH), 126.0 (Cq), 126.1 (CH), 126.8 (CH), 127.2 (CH), 127.8 (CH), 128.5 (CH), 135.5 (Cq), 137.4 (Cq), 144.4 (CH), 147.6 (Cq), 153.9 (Cq), 206.3 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{24}O_3Na$ $[M+Na]^+$ 356.1623, found 359.1624. Enantiomeric excess was determined by HPLC analysis [Chiralcel OD-H column, 1.0% isopropanol/hexane, 1.0 mL/min, λ=254 nm, retention times 46.3 min (*S*) and 62.6 min (*R*)].

*4.3.8. (−)-Heliannuol K (**2**).* To a stirred solution of eight-membered enone **19** (11.2 mg, 0.033 mmol) in EtOH (0.5 mL) was added Raney-Ni (W-2) (10 mg) at rt. After being stirred for 30 min at the same temperature, the reaction mixture was filtered and concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (4:1 v/v) as eluent to give (−)-Heliannuol K (**2**) (7.1 mg, 87%, >99% ee) as a white solid; $\{[\alpha]_D^{30}$ −6.4 (*c* 1.81, $CHCl_3$); Other spectral data matched with those of the authentic sample prepared in Section 4.2.13. Enantiomeric excess was determined by HPLC analysis [Chiralcel AS-H column, 5.0% isopropanol/hexane, 1.0 mL/min, λ=254 nm, retention times 50.2 min (*S*) and 60.0 min (*R*)].

*4.3.9. (−)-Heliannuol A (**1**) and 10-epi-heliannuol A (**23**). 4.3.9.1. Reduction of (−)-heliannuol K (**2**).* To a stirred solution of (−)-heliannuol K (**2**) (34.2 mg, 0.138 mmol) in MeOH (0.5 mL) was added $NaBH_4$ (10.4 mg, 0.275 mmol) at 0 °C. After being stirred for 10 min at the same temperature, the reaction mixture was added water and extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane/AcOEt (17:8 v/v) as eluent to give (−)-heliannuol A (**1**) and 10-*epi*-heliannuol A (**23**) (35.0 mg, quant. as a 1:3.8 mixture) as a white solid; IR (neat) 3396, 2935, 1507, 1459, 1407, 1189, 1135, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14–1.37 (0.42H, m), 1.22–1.58 (0.79H, br m), 1.23 (3H, d, *J*=7.5 Hz), 1.28, 1.47 (0.63H, br s), 1.37–1.55 (0.21H, br m), 1.38 (2.37H, s), 1.43 (2.37H, s), 1.47, 1.63 (0.63H, br s), 1.56–1.61 (0.79H, br m), 1.84 (0.21H, br m), 1.98 (0.79H, ddt, *J*=3.0, 8.0 and 14.0 Hz), 2.06–2.15 (0.79H, m), 2.18 (3H, s), 2.82, 3.26 (0.21H, br m), 3.11–3.20 (0.79H, m), 3.42 (0.79H, dd, *J*=6.5 and 8.5 Hz), 3.66 (0.21H, br s), 4.61–4.68 (1H, br m, OH, D_2O exchangeable), 6.56 (0.21H, s), 6.59 (0.79H, s), 6.70 (0.21H, s), 6.73 (0.79H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.5 (CH_3), 18.8 (CH_3), 19.7 (CH_3), 20.9 (CH_3), 23.1 (CH_3), 25.6 (CH_3), 29.0 (CH_3), 29.8 (CH), 30.7 (CH_2), 31.9 (CH), 32.4 (CH_2), 36.0 (CH_2), 36.8 (CH_2), 75.7 (CH), 78.5 (CH), 82.1 (Cq), 82.6 (Cq), 111.8 (CH), 112.1 (CH), 120.8 (Cq), 121.1 (Cq), 126.8 (CH), 138.5 (Cq), 139.5 (Cq), 145.9 (Cq), 146.8 (Cq), 150.4 (Cq), 150.5 (Cq); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1647, found 251.1641.

*4.3.9.2. Reduction of eight-membered enone (**19**).* To a stirred solution of eight-membered enone **19** (9.0 mg, 27 μmol) in EtOH (0.5 mL) was added Raney-Ni (W-2) (10 mg) at rt. After being stirred for 2 h at the same temperature under 5 atm of hydrogen gas, the reaction mixture was filtered and concentrated. The residue was chromatographed on silica gel with hexane/AcOEt (4:1 v/v) as eluent to give (−)-heliannuol A (**1**) and 10-*epi*-heliannuol A (**23**) (5.7 mg, 84% as a 1:3.7 mixture) as a white solid; The spectral data matched with those of the sample prepared in Section 4.3.9.1.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.05.034. These data include MOL files and InChiKeys of the most important compounds described in this article.

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18. Since we were not able to obtain the sample of natural heliannuol K, the discrepancy with the optical rotation of synthetic product with that reported for the natural product could not be explained.
19. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 816717. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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