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Facile total synthesis of the (−)-Heliconol A

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Abstract—The facile total synthesis of the (−)-Heliconol A (*ent*-**1**) as well as its diastereoisomer **18** is described, in which different reaction sequences lead to different results. The osmylation of **15** followed by hydrolysis afforded a single isomer **18**, otherwise, a mixture of *ent*-**1** and **18** resulted. Other important processes include the catalytic asymmetric CBS reduction and induced osmylation. The synthesis proceeded with a sequence of 11 steps, affording *ent*-**1** in 9.0% and **18** in 22% overall yield, respectively.

1. Introduction

Heliconols A–C (**1**–**3**), three new polyketide-derived hemiketals containing an unusual reduced furano-cyclopentane unit, were isolated from the freshwater aquatic fungus *Helicodendron giganteum* Glen-Bott (Helotiaceae) that were collected from a sample of submerged wood in Alaska by Gloer et al.[1] Heliconols A–C (**1**–**3**) were tested against *Candida albicans* (ATCC 14053), *Staphylococcus aureus* (ATCC 29213), *Bacillus subtilis* (ATCC 6051), *Escherichia coli* (ATCC 25922),[2] *Aspergillus flavus* (NRRL 6541), and *Fusarium verticillioides* (NRRL 25457).[3] Heliconol A (**1**) was found to inhibit the growth of *F. verticillioides* and exhibited activity against *C. albicans*, *S. aureus*, and *B. subtilis*.[1] The absolute configuration of Heliconol A was assigned by single-crystal X-ray crystallographic analysis of its dibromobenzoate derivative.[1] To the best of our knowledge, no total synthesis of Heliconol A has been reported. In order to study the relationship between the structure and the bioactivity of the compound, we describe the first total synthesis of (−)-Heliconol A (*ent*-**1**) and its diastereoisomer **18** in this paper (Fig. 1).

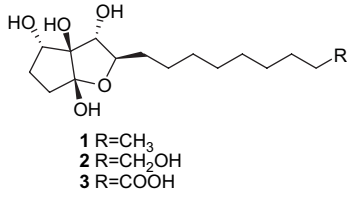
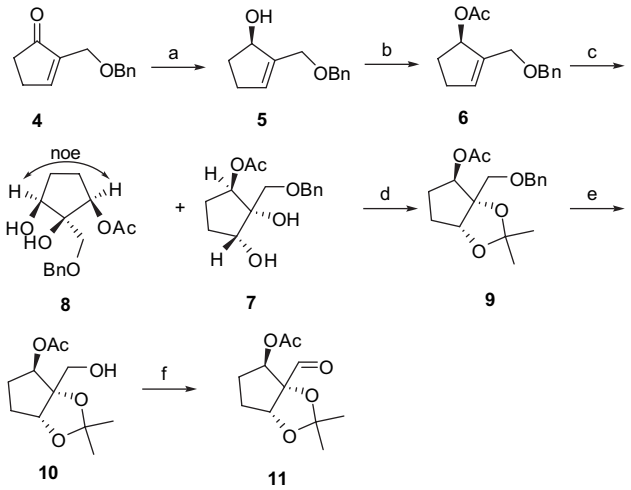


Figure 1.

2. Results and discussion

The synthesis began with the known enone **4** (Scheme 1), which was readily available from cyclopentenone in three steps according to the literature.[4] Reduction of **4** with (*S*)-*n*Bu-CBS afforded alcohol **5** in 93% yield.[5] The ee of **5** was determined as 87% by HPLC analysis, while its configuration was anticipated to be *R*. This was confirmed by converting **5** to compound *ent*-**1** and comparing its optical rotation to that reported for natural (+)-Heliconol A (**1**). Acetylation of **5** provided acetate **6** in 98% yield. Dihydroxylation of **6** using OsO_4 generated an easily separable



Scheme 1. Reagents and conditions: (a) (*S*)-*n*Bu-CBS, BMS, THF, −10 °C, 93%; (b) Ac_2O, pyridine, DMAP, rt, 98%; (c) OsO_4, NMO, THF/H_2O, rt, 90%; (d) DMP, CH_2Cl_2, *p*-TSA, rt, 99%; (e) 5% Pd/C, EtOH, H_2, 98%; (f) Swern oxidation, 90%.

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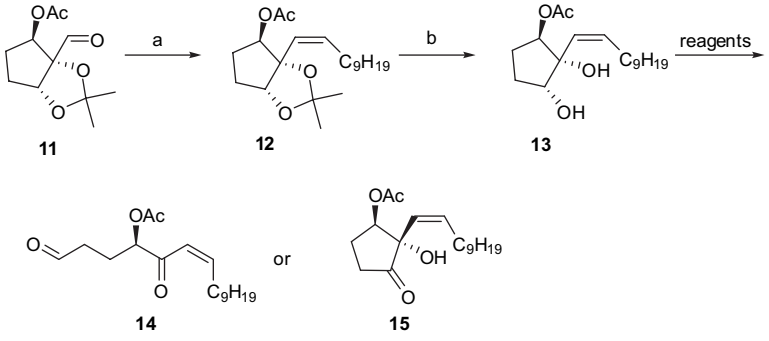
mixture of **7** and **8** in 90% yield and with 14:1 diastereoselectivity.[6] The configurations of the newly formed C1 and C5 stereocenters in **7** and **8** were confirmed by NOE difference experiment of compound **8**. Protection of diol **7** with 2,2-dimethoxypropane in the presence of catalytic *p*-TSA followed by Pd/C cleavage of benzyl ether provided the acetonide-protected alcohol **10** in essentially quantitative yield. Oxidation of **10** with standard Swern oxidation condition furnished aldehyde **11** in 92% yield.[7]

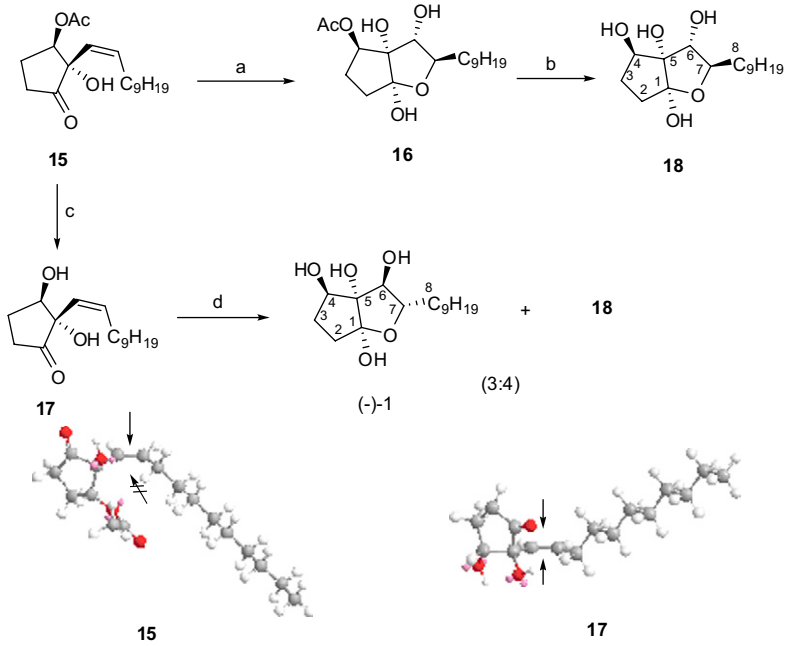
With the intermediate **11** in hand, the stage was set for the synthesis of ketone **15** (Scheme 2). Wittig olefination of **11** with the ylide derived from *n*-decatriphenylphoshonium bromide led to **12** as a single (Z)-isomer in 65% yield. Treatment of **12** with 80% aqueous acetic acid afforded diol **13** in 89% yield. In the process of the oxidation of compound **13**, three methods were tried. However, Dess–Martin periodinane[8] and IBX reagent[9] gave an oxidative cleavage product **14**. Only Swern oxidation gave our desired ketone **15** in 80% yield.[7]

As shown in Scheme 3, osmium-mediated dihydroxylation of β,γ-unsaturated ketone **15** directly gave a single isomer **16**. Basic hydrolysis of **16** led to compound **18**, of which the spectral data did not completely match the data of the natural Heliconol A (**1**). C6 and C7 stereocenters of **18** were opposite to those of the natural Heliconol A (**1**), which was confirmed by NOESY experiment of compound **18** in



Entry	reagents	Yield (%)	product
1	IBX, DMSO	93%	14
2	Dess-Martin periodinane,CH_2Cl_2	98%	14
3	Swern oxidation	80%	15

Scheme 2. Reagents and conditions: (a) *n*-BuLi, $C_{10}H_{21}PPh_3^+Br^-$, THF, 65%; (b) 80% AcOH, rt, 89%.



Scheme 3. Reagents and conditions: (a) OsO_4, NMO, THF/H_2O, 30 h, rt, 75%; (b) K_2CO_3, MeOH, rt, 95%; (c) K_2CO_3, MeOH, rt, 98%; (d) OsO_4, NMO, THF/H_2O, 48 h, rt, 70%.

the NMR spectrum. Namely, osmylation of **15** did not furnish our expected product. In general, regardless of the double bond substitution pattern and geometry, the relative stereochemistry between the pre-existing hydroxyl or alkoxyl group and the adjacent newly formed hydroxyl group of the major diastereomer will be *erythro* (i.e. *anti* if the carbon chain is drawn in the zig-zag convention).[10] It was an unusual phenomenon that the osmylation of **15** provided the triol with a *syn* arrangement between the tertiary alcohol and the newly installed 1,2-diol unit. The stereochemical outcome of dihydroxylation could be rationalized by considering that the attack of OsO_4 on the C=C double bond occurs preferentially from the less hinder β-face of the molecule under the influence of the C4 acetoxyl. To our surprise, if the reaction sequences of osmylation/hydrolysis were changed, a mixture of *ent*-**1** and **18** with 3:4 diastereoselectivity was afforded. The formation of the two products can be explained as follows: because the steric influence of both sides of C6 alkene is similar, compounds *ent*-**1** and **18** can be afforded by attack of OsO_4 on the α- and β-faces of the C6 alkene, respectively. The spectroscopic properties (^1H and ^{13}C NMR, HRMS) of the synthetic target *ent*-**1** were fully identical with those of the natural product Heliconol A (**1**), but the optical rotation of the synthetic *ent*-**1** ($[\alpha]_D^{25}$ −24 (*c* 0.2, acetone)) was opposite to that of natural Heliconol A (**1**) ($[\alpha]_D^{25}$ +21 (*c* 1.6, acetone)). The synthetic *ent*-**1** was the enantiomer of natural Heliconol A and its absolute configuration was shown as (1*S*,4*R*,5*R*,6*S*,7*S*).

In conclusion, we have accomplished the first total synthesis of (−)-Heliconol A (*ent*-**1**) and its diastereoisomer **18** starting from the known enone **4**. The synthesis proceeded with a longest linear sequence of 11 steps, affording *ent*-**1** in 9.0% overall yield and **18** in 22% overall yield. Key steps include a catalytic asymmetric CBS reduction and twice induced dihydroxylation.

3. Experimental

3.1. General

Melting points were measured on a Kofler apparatus and were uncorrected. The ^1H and ^{13}C NMR data are recorded in $CDCl_3$ and DMSO-*d* solutions with a Varian Mercury 300, 400 and 600 BB spectrometer. The chemical shifts are reported in parts per million relative to TMS. The optical rotations were determined with a JASCO J-20C polarimeter with 0.2 dm tube. The mass spectra were measured with EI (70 eV) technique. Column chromatographies were generally performed on silica gel (200–300 meshes) eluting with petroleum ether and ethyl acetate.

3.2. (+)-2-(Benzyloxymethyl)cyclopent-2-enol (5)

(*S*)-Bu-CBS reagent (9.2 mL, 2.3 mmol, 0.25 M in toluene solution) was transferred into a freshly flame-dried flask and toluene was completely removed in vacuo. After the CBS reagent was diluted with THF (55 mL), the resulting solution was transferred to a flask containing compound enone **4** (4.659 g, 23 mmol) at room temperature and the reaction temperature cooled to −10 °C. $BH_3\cdot Me_2S$ (BMS) (2.0 M in THF, 6.9 mL, 0.6 equiv) was slowly added over 10 min. After addition of BMS, TLC analyses indicated completion of the reaction. Methanol (4.3 mL) was slowly added until gas evolution was no longer evident. The mixture was warmed to room temperature, treated with 1 N NaOH (2.88 mL), and stirred for an additional 15 min. The mixture was then poured into a separatory funnel containing ether and brine. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with 1 N HCl, saturated $NaHCO_3$, and brine, then dried with $NaSO_4$. The solvents were evaporated. The residue was flash chromatographed using petroleum ether and ethyl acetate (10:1, v/v) to give compound **5** (4.363 g, 93%) as a colorless oil. (87% ee; Chiralcel OD, hexane/*i*-PrOH=90:10, flow rate=0.7 mL/min, 254 nm.) $[\alpha]_D^{20}$ +26 (*c* 3.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.28–7.36 (m, 5H), 5.84 (br s, 1H), 4.85 (br s, 1H), 4.54 (s, 2H), 4.20 (q, *J*=11.7 Hz, 2H), 2.53 (br s, 1H), 2.47–2.53 (m, 1H), 2.25–2.31 (m, 2H), 1.78–1.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0, 137.9, 131.8, 128.4, 127.7, 127.6, 77.6, 72.5, 67.6, 33.3, 30.0. IR (KBr): 3397, 1656, 1604; HRMS calcd for $C_{13}H_{16}O_2Na$ (M+Na): 227.1048. Found $(M+Na)^+$: 227.1050.

3.3. (+)-2-(Benzyloxymethyl)cyclopent-2-enyl acetate (6)

The alcohol **5** (4.363 g, 21.4 mmol) was dissolved in dry acetic anhydride (10.2 mL, 5 equiv) and cooled to 0 °C. To the stirred solution were added dry pyridine (3.3 mL, 42.8 mmol, 2 equiv) and *N*,*N*-dimethylaminopyridine (261 mg, 2.14 mmol, 0.1 equiv). After stirring for 10 min, the reaction was allowed to warm to room temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4. The solvents were evaporated. The residue was flash chromatographed using petroleum ether and ethyl acetate (20:1, v/v) to give compound **6** (5.159 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ +6 (*c* 3.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.35 (m, 5H), 6.03 (d, *J*=1.2 Hz, 1H), 5.76 (t, *J*=3.8 Hz, 1H), 4.50 (q, *J*=12 Hz, 2H), 4.08 (s, 2H), 2.47–2.53 (m, 1H), 2.32–2.43 (m, 2H), 1.99 (s, 3H), 1.81–1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 139.2, 138.1, 134.2, 128.3, 127.6, 127.5, 79.4, 72.4, 66.4, 30.9, 30.2, 21.2. IR (KBr): 1733, 1370, 1241, 1033; HRMS calcd for $C_{15}H_{18}O_3Na$ (M+Na): 262.1148. Found $(M+Na)^+$: 262.1144.

3.4. (−)-*anti*-2-(Benzyloxymethyl)-2,3-dihydroxycyclopentyl acetate (7) and (−)-*syn*-2-(benzyloxymethyl)-2,3-dihydroxycyclopentyl acetate (8)

A sample of *N*-methylmorpholine-*N*-oxide (2.219 g, 18.9 mmol) and OsO_4 (0.1 M in H_2O, 7.9 mL, 0.79 mmol) were sequentially added to a solution of acetate **6** (3.887 g, 15.8 mmol) in THF/H_2O (4:1, 50 mL) at room temperature. After stirring at room temperature for 12 h, the reaction was quenched by the addition of Na_2SO_3 (2 g) and EtOAc (200 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2×50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give a residue. This crude material was purified by column chromatography using

petroleum ether and ethyl acetate (5:1, v/v) to afford diol **7** (3.716 g, 84%) as a colorless oil and diol **8** (265 mg, 6%) as a colorless oil. (**7**: R_f=0.25; **8**: R_f=0.22 (petroleum ether/ethyl acetate=4:1; v/v).)

Compound **7**: $[\alpha]_D^{20}$ −32 (*c* 3.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–7.37 (m, 5H), 5.05 (dd, *J*=6.9, 4.2 Hz, 1H), 4.56 (d, *J*=11.7 Hz, 1H), 4.51 (d, *J*=11.7 Hz, 1H), 4.04 (dd, *J*=12.9, 6.9 Hz, 1H), 3.61 (d, *J*=9.3 Hz, 2H), 3.52 (d, *J*=9.3 Hz, 2H), 3.46 (s, 1H), 2.72 (d, *J*=5.4 Hz, 1H), 2.27–2.33 (m, 1H), 2.03–2.10 (m, 1H), 1.94 (s, 3H), 1.62–1.73 (m, 1H), 1.46–1.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 137.5, 128.4, 127.8, 127.7, 79.7, 79.0, 74.5, 73.7, 71.5, 28.9, 27.3, 21.0; IR (KBr): 3433, 1732, 1371, 1242, 1096, 1032; HRMS calcd for $C_{15}H_{20}O_5Na$ (M+Na): 303.1203. Found $(M+Na)^+$: 303.1204.

Compound **8**: $[\alpha]_D^{20}$ −2.3 (*c* 3.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.27–7.37 (m, 5H), 4.99 (t, *J*= 7.4 Hz, 1H), 4.56 (d, *J*=11.6 Hz, 1H), 4.49 (d, *J*=11.6 Hz, 1H), 4.03 (dd, *J*=12.8, 6.8 Hz, 1H), 3.53 (d, *J*=9.2 Hz, 1H), 3.48 (d, *J*=9.2 Hz, 1H), 3.07 (s, 1H), 2.65 (d, *J*=5.6 Hz, 1H), 2.05 (s, 3H), 1.76–2.04 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 137.6, 128.4, 127.8, 127.7, 77.8, 74.9, 73.7, 73.4, 73.3, 28.9, 26.6, 21.0; IR (KBr): 3442, 1733, 1370, 1245, 1099, 1070, 1043; HRMS calcd for $C_{15}H_{20}O_5Na$ (M+Na): 303.1203. Found $(M+Na)^+$: 303.1201.

3.5. (−)-3a-(Benzyloxymethyl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl acetate (9)

2,2-Dimethoxypropane (11.456 g, 110 mmol) and *p*-toluenesulfonic acid (100 mg, 0.526 mmol) both were added to a solution of diol **7** (3.079 g, 11 mmol) in CH_2Cl_2 (25 mL) at room temperature. The reaction mixture was stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ (20 mL) and ether (100 mL) were sequentially added. The organic phase was separated and the aqueous phase was extracted with ether (2×50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude oil. This crude material was purified by column chromatography using petroleum ether and ethyl acetate (20:1, v/v) to afford **9** (3.484 g, 99%) as a colorless oil. $[\alpha]_D^{20}$ −37.5 (*c* 4.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.27–7.36 (m, 5H), 5.18 (dd, *J*=3.2, 2.0 Hz, 1H), 4.60 (d, *J*=12 Hz, 1H), 4.54 (d, *J*=12 Hz, 1H), 4.51 (br s, 1H), 3.67 (s, 2H), 2.21–2.25 (m, 1H), 1.93 (s, 3H), 1.83–1.88 (m, 1H), 1.76–2.04 (m, 4H), 1.70 (m, 1H), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 138.0, 128.3, 127.5, 111.4, 92.8, 82.5, 79.6, 73.7, 70.3, 30.2, 29.7, 26.7, 21.0; IR (KBr): 1739, 1451, 1373, 1238, 1103, 1209; HRMS calcd for $C_{18}H_{24}O_5Na$ (M+Na): 343.1516. Found $(M+Na)^+$: 343.1515.

3.6. (−)-3a-(Hydroxymethyl)-2,2-dimethyl-tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl acetate (10)

Compound **9** (3.484 g, 10.9 mmol) was hydrogenated using 10% Pd/C (300 mg) in dry EtOH (70 mL) for 8 h at room temperature and atmospheric pressure. The catalyst was filtered off by silica gel column chromatography using EtOH. The solvent was distilled off to afford **10** (2.478 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ −50 (*c* 1.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.14 (d, *J*=5.1 Hz, 1H), 4.50 (dd, *J*=4.2, 3.0 Hz, 1H), 3.76 (d, *J*=7.2 Hz, 1H), 3.74 (d, *J*=7.2 Hz, 1H), 2.21–2.80 (m, 1H), 2.04 (s, 3H), 1.83–1.91 (m, 2H), 1.66–1.73 (m, 1H), 1.44 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 111.3, 93.5, 82.5, 79.8, 62.7, 30.2, 29.8, 27.6, 26.9, 21.1; IR (KBr): 3484, 1739, 1374, 1240, 1029; HRMS calcd for $C_{11}H_{18}O_5Na$ (M+Na): 253.1046. Found $(M+Na)^+$: 253.1051.

3.7. (−)-3a-Formyl-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl acetate (11)

To a solution of oxalyl chloride (2.284 g, 18 mmol) in dry CH_2Cl_2 (30 mL) at −78 °C was added dropwise dry DMSO (2.807 g, 2.55 mL, 36 mmol) in CH_2Cl_2 (5 mL). After 30 min, alcohol **10** (2.760 g, 12 mmol) in CH_2Cl_2 (5 mL) was added over 10 min giving copious white precipitate. After stirring for 1 h at −78 °C the reaction mixture was brought to −60 °C and Et_3N (6.7 mL, 48 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (30 mL) and CH_2Cl_2 (100 mL). The organic layer was separated and washed with water and brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give the crude oil. This crude material was purified by column chromatography using petroleum ether and ethyl acetate (10:1, v/v) to afford aldehyde **11** (2.462 g, 90%) as a colorless crystal. Mp: 56–58 °C; $[\alpha]_D^{20}$ −55 (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.70 (s, 1H), 5.01 (d, *J*=4.5 Hz, 1H), 4.75 (d, *J*=3.9 Hz, 1H), 2.12–2.20 (m, 1H), 1.93–2.03 (m, 2H), 1.93 (s, 3H), 1.77–1.89 (m, 1H), 1.45 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.4, 170.5, 111.6, 95.7, 82.6, 80.1, 31.4, 29.3, 26.2, 24.8, 20.9; IR (KBr): 2985, 2942, 2721, 1740, 1376, 1237, 1213; HRMS calcd for $C_{11}H_{16}O_5Na$ (M+Na): 251.0890. Found $(M+Na)^+$: 251.0891.

3.8. (−)-2,2-Dimethyl-3a-((*Z*)-undec-1-enyl)tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl acetate (12)

To a solution of *n*-decatriphenylphoshonium bromide (3.388 g, 7 mmol) in THF (30 mL), *n*-BuLi (1.4 M, 4.7 mL) was added dropwise and stirred for 30 min under a stream of argon at 0 °C. Compound **11** (998 mg, 4.38 mmol) in THF (10 mL) was added dropwise to the above solution at −40 °C and stirred for 1 h. The reaction mixture was stirred for another 30 min at 0 °C. After quenching the reaction with brine, it was extracted with ethyl acetate, dried, and evaporated. The residue was flash chromatographed using petroleum ether and ethyl acetate (30:1, v/v) to give compound **12** (1.00 g, 65%) as a colorless oil. $[\alpha]_D^{20}$ −56 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.45 (dt, *J*=12.0, 6.8 Hz, 1H), 5.41 (d, *J*=12.0 Hz, 1H), 5.17 (d, *J*=3.9 Hz, 1H), 4.52 (d, *J*=4.8 Hz, 1H), 2.10–2.25 (m, 3H), 1.95 (s, 3H), 1.91–2.03 (m, 1H), 1.84 (dd, *J*=13.2, 6.3 Hz, 1H), 1.70 (dd, *J*=13.2, 6.0 Hz, 1H), 1.41 (s, 3H), 1.29 (s, 3H), 1.25 (m, 14H), 0.86 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 134.4, 128.9, 110.1, 92.6, 86.9, 80.5, 31.9, 31.0, 29.7, 29.6, 29.5, 29.3, 29.1, 26.7, 25.3, 22.6, 21.2, 14.1; IR (KBr): 2926, 2854, 1748, 1653, 1461,

1373, 1236, 1209, 1029; HRMS calcd for $C_{21}H_{36}O_4Na$ (M+Na): 375.2506. Found $(M+Na)^+$: 375.2512.

3.9. (+)-2,3-Dihydroxy-2-((*Z*)-undec-1-enyl)cyclopentyl acetate (13)

Compound **12** (600 mg, 1.92 mmol) was dissolved in 8 mL of AcOH and 2 mL of water and stirred at 85–90 °C for 24 h. The reaction was quenched with solid saturated $NaHCO_3$ and extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4. The solvents were evaporated. The residue was flash chromatographed using petroleum ether and ethyl acetate (8:1, v/v) to give compound **13** (533 mg, 89%) as a colorless crystal. Mp: 49–50 °C; $[\alpha]_D^{20}$ +6 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.56 (dt, *J*=11.7, 7.2 Hz, 1H), 5.32 (d, *J*=11.7 Hz, 1H), 5.05 (dd, *J*=8.4, 6.0 Hz, 1H), 4.04 (br s, 1H), 3.96 (dd, *J*=5.4, 3.6 Hz, 1H), 3.07 (br s, 1H), 2.25–2.34 (m, 3H), 2.04 (s, 3H), 1.94–2.01 (m, 1H), 1.63–1.74 (m, 2H), 1.24 (m, 14H), 0.86 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 137.1, 126.1, 83.1, 82.6, 77.8, 31.8, 29.9, 29.5, 29.3, 29.2, 28.7, 27.9, 26.6, 22.6, 21.0, 14.0; IR (KBr): 3447, 2924, 2854, 1721, 1653, 1462, 1373, 1242, 1033; HRMS calcd for $C_{18}H_{32}O_4Na$ (M+Na): 335.2193. Found $(M+Na)^+$: 335.2187.

3.10. (*Z*)-1,5-Dioxohexadec-6-en-4-yl acetate (14)

IBX (220 mg, 0.785 mmol) was dissolved in DMSO (2 mL) at room temperature. After 20 min, compound **13** (123 mg, 0.394 mmol) was added. TLC analyses indicated completion of the reaction. Work-up was easily performed by dilution of the reaction mixture with water. The white precipitate was filtered and the reaction mixture was extracted with ethyl acetate (3×20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude oil. The residue was flash chromatographed using petroleum ether and ethyl acetate (5:1, v/v) to give compound **14** (113 mg, 93%) as a colorless oil. $[\alpha]_D^{20}$ +10 (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.76 (s, 1H), 6.29 (dt, *J*=11.1, 6.8 Hz, 1H), 6.20 (d, *J*=11.1 Hz, 1H), 5.04 (dd, *J*=8.1, 4.8 Hz, 1H), 2.53–2.63 (m, 4H), 2.15–2.21 (m, 1H), 2.12 (s, 3H), 2.00 (m, 1H), 1.40 (m, 2H), 1.24 (m, 12H), 0.85 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.4, 196.1, 170.1, 153.3, 121.9, 77.4, 39.2, 31.8, 29.9, 29.5, 29.4, 29.3, 29.2, 28.9, 22.8, 22.6, 20.6, 20.5, 14.1; IR (KBr): 2925, 2854, 1746, 1702, 1617, 1373, 1236, 1050; HRMS calcd for $C_{18}H_{30}O_4Na$ (M+Na): 333.2036. Found $(M+Na)^+$: 333.2038.

3.11. (+)-2-Hydroxy-3-oxo-2-((*Z*)-undec-1-enyl)cyclopentyl acetate (15)

To a solution of oxalyl chloride (141 mg, 1.11 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C was added dropwise dry DMSO (170 mg, 0.15 mL, 2.172 mmol) in CH_2Cl_2 (1 mL). After 30 min, alcohol **14** (226 mg, 0.724 mmol) in CH_2Cl_2 (1 mL) was added over 2 min giving copious white precipitate. After stirring for 30 h at −78 °C the reaction mixture was brought to −60 °C and Et_3N (0.41 mL, 2.91 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (5 mL) and CH_2Cl_2 (50 mL). The organic layer was separated and washed with water and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude oil. This crude material was purified by column chromatography using petroleum ether and ethyl acetate (10:1, v/v) to afford ketone **15** (179 mg, 80%) as a colorless oil. $[\alpha]_D^{20}$ +73 (*c* 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.75 (dt, *J*=11.7, 7.8 Hz, 1H), 5.46 (d, *J*=11.7 Hz, 1H), 5.05 (dd, *J*=8.4, 6.3 Hz, 1H), 3.28 (s, 1H), 2.51–2.61 (m, 1H), 2.21–2.43 (m, 4H), 2.10 (s, 3H), 1.73–1.97 (m, 1H), 1.24 (m, 14H), 0.86 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.3, 170.9, 140.7, 121.1, 80.9, 79.3, 32.6, 31.8, 29.49, 29.46, 29.28, 29.26, 28.9, 23.3, 22.6, 20.9, 14.1; IR (KBr): 3463, 2925, 2854, 1750, 1462, 1371, 1237, 1042; HRMS calcd for $C_{18}H_{31}O_4$ (M+H): 311.2217. Found $(M+H)^+$: 311.2214.

3.12. (+)-3,3a,6a-Trihydroxy-2-nonylhexahydro-2*H*-cyclopenta[*b*]furan-4-ylacetate (16)

A sample of *N*-methylmorpholine-*N*-oxide (54.8 mg, 0.468 mmol) and OsO_4 (0.1 M in H_2O, 0.78 mL, 0.078 mmol) were sequentially added to a solution of acetate **15** (121 mg, 0.39 mmol) in THF/H_2O (3:1) (4 mL) at room temperature. After stirring at room temperature for 30 h, the reaction was quenched by addition of Na_2SO_3 (55 mg) and EtOAc (30 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2×20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give a residue. This crude material was purified by column chromatography using petroleum ether and ethyl acetate (2:1, v/v) to afford product **16** (94 mg, 75%) as a colorless oil. $[\alpha]_D^{20}$ +60 (*c* 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.85 (dd, *J*=11.1, 6.9 Hz, 1H), 4.82 (br s, 1H), 4.41 (s, 1H), 3.49–3.57 (m, 2H), 2.49 (d, *J*=9.3 Hz, 1H), 2.10–2.17 (m, 1H), 2.11 (s, 3H), 1.92–1.98 (m, 1H), 1.62–1.74 (m, 3H), 1.36–1.59 (m, 3H), 1.24 (m, 12H), 0.86 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 107.5, 82.5, 81.5, 80.2, 74.8, 33.6, 32.1, 31.8, 29.7, 29.5, 29.4, 29.3, 25.5, 25.1, 22.6, 20.6, 14.1; IR (KBr): 3421, 2926, 2855, 1726, 1462, 1376, 1252; HRMS calcd for $C_{18}H_{32}O_6Na$ (M+Na): 367.2091. Found $(M+H)^+$: 367.2092.

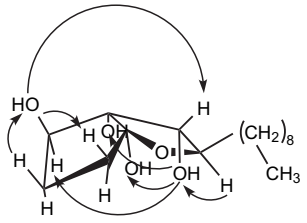
3.13. (+)-2,3-Dihydroxy-2-((*Z*)-undec-1-enyl)cyclopentanone (17)

To a solution of **15** (111 mg, 0.36 mmol) in dry CH_3OH (7 mL) at room temperature was added K_2CO_3 (4.9 mg, 0.036 mmol). After 2 h, the reaction mixture was diluted with EtOAc (3×20 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give the crude oil. This crude material was purified by column chromatography using petroleum ether and ethyl acetate (3:1, v/v) to afford product **17** (95 mg, 98%) as a colorless oil. $[\alpha]_D^{20}$ +31 (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.85 (dt, *J*=11.7, 7.8 Hz, 1H), 5.60 (d, *J*=11.7 Hz, 1H), 4.14 (dd, *J*=7.2, 6.3 Hz, 1H), 2.87 (br s, 1H), 2.50–2.61 (m, 1H), 2.16–2.36 (m, 5H), 1.89–1.97 (m, 1H), 1.24 (m, 14H), 0.87 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 214.3, 140.9, 121.7, 81.8, 76.7, 32.5, 31.9, 29.53, 29.52, 29.49, 29.32, 29.29, 29.2, 25.3, 22.6, 14.1; IR (KBr): 3408, 2924, 2853, 1747, 1462; HRMS calcd for

$C_{16}H_{32}O_3N$ (M+NH_4): 286.2377. Found (M+NH_4)$^+$: 286.2381.

3.14. (+)-2-Nonylhexahydro-2*H*-cyclopenta[*b*]furan-3,3a,4,6a-tetraol (18)

To a solution of **16** (28 mg, 0.08 mmol) in dry CH_3OH (2 mL) at room temperature was added K_2CO_3 (1.1 mg, 0.008 mmol). After 2 h, the reaction mixture was diluted with EtOAc (3×20 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give the crude oil. This crude material was purified by column chromatography using petroleum ether and ethyl acetate (1:2, v/v) to afford product **18** (23 mg, 95%) as a colorless oil. $[\alpha]_D^{20}$ +20 (*c* 0.4, acetone); ^{1}H NMR (300 MHz, DMSO): δ 5.63 (s, 1H), 4.90 (d, *J*=4.8 Hz, 1H), 4.78 (d, *J*=6.6 Hz, 1H), 4.43 (s, 1H), 3.73 (dt, *J*=11.1, 6.9, 4.8 Hz, 1H), 3.56 (dd, *J*=8.1, 6.6 Hz, 1H), 3.42 (t-like, *J*=8.1 Hz, 1H), 1.68 (dd, *J*=12, 6.9 Hz, 1H), 1.58 (m, 2H), 1.34 (m, 2H), 1.24 (m, 13H), 1.09–1.16 (m, 1H), 0.87 (t, *J*=5.7 Hz, 3H); ^{13}C NMR (75 MHz, DMSO): δ 108.2, 82.6, 79.0, 78.0, 72.9, 33.3, 32.3, 31.4, 29.3, 29.1, 28.8, 28.1, 25.5, 22.2, 14.1; IR (KBr): 3378, 2924, 2854; HRMS calcd for $C_{16}H_{30}O_5N$ (M+NH_4): 320.2431. Found (M+NH_4)$^+$: 320.2429. The stereostructure of **18** was confirmed by NOESY experiment in the 300 Hz ^{1}NMR spectra. The key NOESY correlation is depicted in the following figure:



NOESY **18**

3.15. (−)-Heliconol A (*ent*-1)

A sample of *N*-methylmorpholine-*N*-oxide (39 mg, 0.331 mmol) and OsO_4 (0.1 M in H_2O, 1.3 mL, 0.13 mmol) were sequentially added to a solution of **17** (74 mg, 0.276 mmol) in THF/H_2O (4:1, 5 mL) at room temperature. After stirring at room temperature for 48 h, the reaction was quenched by addition of Na_2SO_3 (56 mg) and EtOAc (40 mL). The organic phase was separated and the aqueous phase extracted with EtOAc (2×20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give a residue. This crude material was purified by column chromatography using petroleum ether and ethyl acetate (1:2, v/v) to afford compound **18** (33 mg, 40%) and product *ent*-**1** (25 mg, 30%) as a colorless oil. (*ent*-**1**: R_f=0.10; **18**: R_f=0.08 (petroleum ether/ethyl acetate=2:1; v/v)). $[\alpha]_D^{20}$ −24 (*c* 0.2, acetone); ^{1}H NMR (600 MHz, DMSO): δ 5.82 (s, 1H), 5.56 (d, *J*=7.2 Hz, 1H), 5.47 (d, *J*=4.2 Hz, 1H), 4.57 (s, 1H), 4.03 (dt, *J*=7.2, 4.2 Hz, 1H), 3.72 (t-like, *J*=7.2 Hz, 1H), 3.55 (dt, *J*=7.8, 4.8 Hz, 1H), 1.87 (ddd, *J*=12, 6.6, 5.4 Hz, 1H), 1.80 (ddt, *J*=12, 7.2, 4.8 Hz, 1H), 1.58 (ddd, *J*=12, 9.6, 7.2 Hz, 1H), 1.48–1.53 (m, 2H), 1.34–1.40 (m, 2H), 1.24 (m, 12H), 0.85 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO): δ 108.5, 84.0, 83.2, 81.4, 80.0, 35.1, 34.0, 31.3, 30.5, 29.1, 29.0, 28.9, 28.7, 25.3, 22.1, 14.0; IR (KBr): 3374, 2923, 2853; HRMS calcd for $C_{16}H_{30}O_5N$ (M+NH_4): 320.2431. Found (M+NH_4)$^+$: 320.2432.

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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.2007.07.053.

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