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Total syntheses of the sesquiterpenoids (+)-*trans*-dracunculifoliol and (+)-4-hydroxyoppositan-7-one

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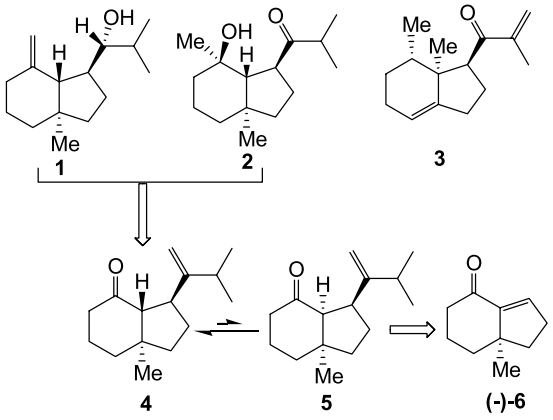
Abstract—Sesquiterpenoids (+)-*trans*-dracuncuflifoliol (**1**) and (+)-4-hydroxyoppositan-7-one (**2**) were prepared stereoselectively from enantiomerically pure (7a*R*)-7a-methyl-1,2,5,6,7,7a-hexahydro-4*H*-inden-4-one ((−)-**6**), whose synthesis was described herein. Conjugate addition of the organocopper (I) reagent **10** to (−)-**6**, followed by epimerization of the ring junction, generated 3 of the 4 contiguous chiral centers of both natural products.

1. Introduction

The sesquiterpenoid (+)-*trans*-dracunculifoliol (**1**) was isolated from Vassoura oil and was previously synthesized as a racemate in eighteen linear steps with an overall yield of 1.8%.[1] A structurally related natural product, (+)-4-hydroxyoppositan-7-one (**2**) was isolated from the liverworts *Chiloscyphus pallescens*[2] and *C. rivularis*[3] and has not yet been synthesized. While the absolute stereochemistry of either **1** or **2** has not been reported, the natural product chiloscyphone (**3**), isolated from *C. polyanthus*, was elucidated by an X-ray crystallographic study.[4] One of the goals of this synthetic study is to determine if the absolute stereochemistry of **1** and **2** is as shown in Scheme 1.

Natural products **1** and **2** share a common *trans*-fused [4.3.0] bicyclo skeleton and it was envisaged that three of the four contiguous chiral centres could be created by the conjugate addition of an organocopper (I) reagent to enone (−)-**6**, to generate **5** which, after epimerization of the centre alpha to the carbonyl, gives the common intermediate **4** (Scheme 1). The stereochemical outcome of the key conjugate addition reaction was predicted to parallel those obtained in the previously reported 1,4-addition reactions to bicyclo[4.3.0]non-9-en-2-ones.[5,6] Conjugate addition of organocoper (I) reagents to enones of general structure **6** proceeds stereoselectively, with the group being introduced *trans* to the angular methyl group (i.e., **5**). In addition, a



Scheme 1.

predominant *cis*-fused ring junction is obtained.[6] However, equilibration of structurally related compounds generally dictates that the *cis*-fused isomer can be equilibrated with base to produce a mixture of epimers in which the *trans*-fused isomer, the thermodynamically more stable of the two epimers, predominates.[7]

2. Results and discussion

2.1. Synthesis of chiral enone (−)-6

Ohkubo et al.[8] reported an enantioselective synthesis of (+)-**6**, but the route is laborious (8 steps from a non-commercial starting material) with an overall yield of 38%.

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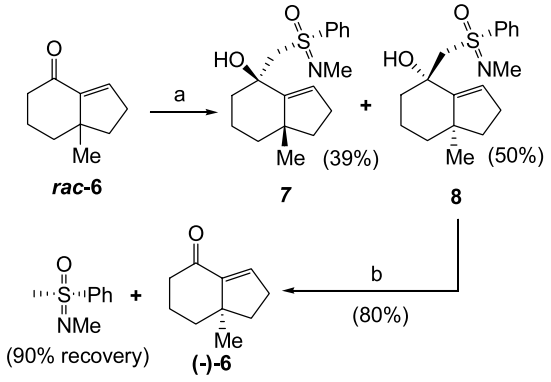
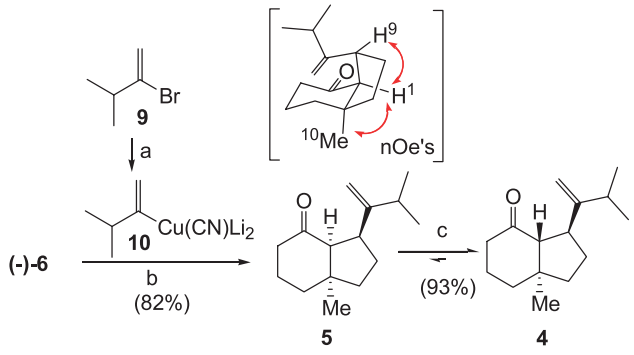
The synthesis of the chiral enone (−)-**6** was readily accomplished via the route outlined in Scheme 2. The racemic enone **6**[9] was resolved by condensation with the anion of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine.[10] These conditions delivered a readily separable mixture of diastereomers **7** (39%) and **8** (50%). Sulfoximine-mediated resolution of ketones is ideally suited for bicyclic enones which exhibit diastereoface specificity towards the addition of the anion of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine. Lastly, thermolysis of **8** regenerated the sulfoximine and the optically pure (−)-**6**. The absolute stereochemistry was assigned based on the comparison of the sign of rotation to that of the reported (+)-**6**,[8] in which the absolute stereochemistry is known.



Scheme 2. (a) (*S*)-(+)-PhS(O)(NMe)CH_3, *n*-BuLi, THF, −78 °C; (b) toluene, 110–120 °C.

2.2. Synthesis of keto-alkene 4

For the synthesis of the key intermediate **4**, the stereoselective conjugate addition of the organocopper (I) reagent **10** to the bicyclic enone (−)-**6** was required (Scheme 3). Reagent **10** was prepared by sequential treatment of **9**[11] with *t*-BuLi and LiCl/CuCN. The conjugate addition of reagent **10** to the bicyclic enone (−)-**6** in the presence of TMSBr provided, after hydrolysis of the resultant silyl enol ether, one single diastereomer **5** in 82% yield. It was gratifying to find that the conjugate addition had proceeded stereoselectively, as expected (vide supra). The relative configuration of **5** was confirmed by the following ^{1}H NMR nOe difference experiments. Irradiation of the signal due to Me-10 caused an enhancement of the signal for H-1 and vice versa (Scheme 3) and this confirmed the *cis*-fused nature of the ring junction. Irradiation of the signal due to H-9 caused an enhancement of the signal for H-1, thereby verifying that reagent **10** had introduced the vinyl group *trans* to the angular methyl group (Me-10), as predicted.

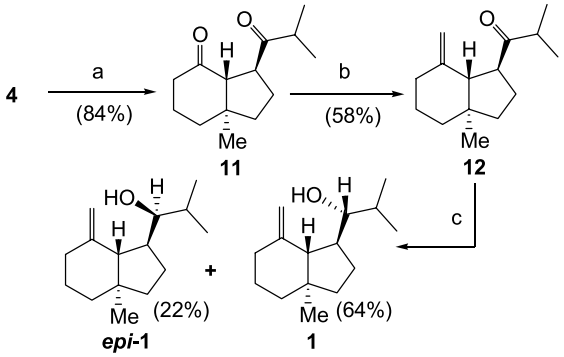


Scheme 3. (a) *t*-BuLi, THF, −78 °C; LiCl/CuCN. (b) TMSBr, THF, −78 °C; H_2O, NH_4OH–NH_4Cl. (c) NaOMe, MeOH, 55 °C.

A *trans*-fused ring junction was required for the synthesis of natural products **1** and **2**. According to previous studies[5,6] and results reported by Dana and co-workers,[7] epimerization of **5** should lead to a mixture of compounds in which the *trans*-fused epimer **4** is thermodynamically favored. In fact, treatment of **5** with NaOMe in MeOH at 55 °C resulted in a 33:1 mixture of epimers **4** and **5** (Scheme 3). These two epimers were readily separated by flash chromatography on silica gel, and the desired synthetic intermediate **4** was obtained in 93% yield.

2.3. Synthesis of (+)-*trans*-dracunculifoliol (1)

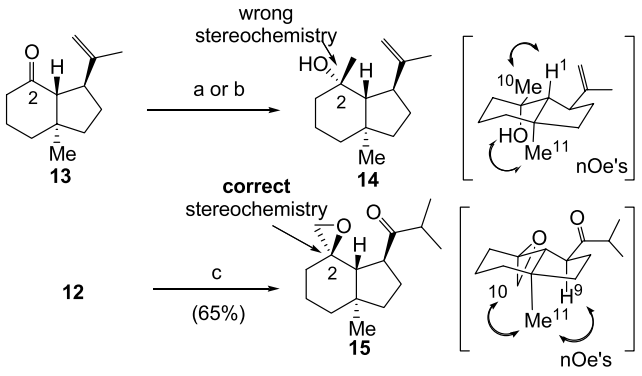
Elaboration of intermediate **4** to (+)-*trans*-dracunculifoliol (**1**) involved ozonolysis of the exocyclic alkene to afford, after treatment with triphenylphosphine, the diketone **11** (Scheme 4). A regioselective Wittig reaction was then attempted and complete selectivity was obtained to generate the desired keto alkene **12** in 58% yield. This regioselective Wittig reaction on the sterically less hindered ketone eliminated the need for a protection/deprotection strategy. Interestingly, even when 1.5 equiv of ylide were used, no *bis*-olefinated product was detected. Reduction of **12** with Super Hydride® afforded a mixture of **1** and *epi*-**1** in a 3:1 ratio.[12] The ^{1}H NMR and ^{13}C NMR data derived from the synthetic **1** are identical with those of the natural product **1**.[1] The absolute configuration of the natural product was confirmed by the fact that the sign of the specific optical rotation of the synthetic material ($[\alpha]^{20}_D = +54.4$ (*c* 0.8, $CHCl_3$)) is the same as that reported for the natural product ($[\alpha]^{20}_D = +19$ (*c* 0.4, $CHCl_3$), 85% pure by GC[1]). Thus, the synthesis of **1** was accomplished in a concise (5 steps) and enantioselective manner. The overall yield of **1** from (−)-**6** was 24%.



Scheme 4. (a) O_3, CH_2Cl_2, −78 °C; PPh_3, rt; (b) Ph_3PCH_3Br, *n*-BuLi, THF, 0 °C; (c) $LiEt_3BH$, THF, −78 °C to rt.

2.4. Synthesis of (+)-4-hydroxyoppositan-7-one (2)

Elaboration to (+)-4-hydroxyoppositan-7-one (**2**) required the formation of a quaternary center at C-2. The first attempt involved the addition of a methyl group to the ketone of the

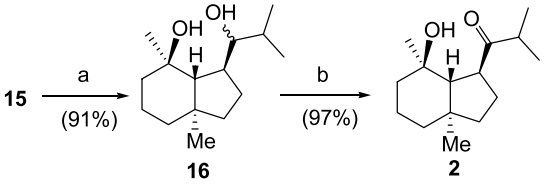


Scheme 5. (a) MeMgBr, TMSBr, Et_2O, −78 to 0 °C; (b) MAD, MeLi, PhMe, −78 to −25 °C; (c) *m*-CPBA, CH_2Cl_2, 0 °C.

model compound **13** (Scheme 5). Reaction of **13** with MeMgBr provided the tertiary alcohol **14** in 55% yield with exclusively one stereoisomer at C-2. The following ^{1}H NMR nOe difference experiments confirmed that the methyl group added from the less sterically hindered face of the molecule to provide the undesired stereochemistry at C-2 (axial OH). Irradiation of the signal due to Me-11 caused an enhancement of the signal for the tertiary alcohol proton (Scheme 5) and irradiation of the signal due to the newly introduced Me-10 caused an enhancement of the signal for H-1, thereby verifying that the Grignard reagent had delivered the methyl group *trans* to the axial angular methyl group (Me-11). Even treatment with MAD (methyl aluminum-*bis*-(2,6-di-*tert*-butyl-4-methylphenoxide)), a Lewis acid known to complex with the less hindered face of carbonyls, gave exclusively **14** upon addition of MeLi.

Knowing that the face opposite to the angular axial methyl group is more accessible, we decided to add the equatorial alcohol functionality of **2** to the alkene of **12** from the less hindered face. This transformation firstly required the epoxidation of **12** with *m*-CPBA which did, indeed, provide the desired epoxide **15** in which the stereochemistry was confirmed by the following ^{1}H NMR nOe difference experiments (Scheme 5). Irradiation of the signal due to Me-11 caused an enhancement of the signals for H-9 and the epoxide protons on C-10 and vice versa.

The reductive opening of the epoxide **15** was accomplished with $LiEt_3BH$ to generate the desired tertiary alcohol with concomitant reduction of the ketone to provide the diol **16** in 91% yield (Scheme 6). The secondary alcohol of **16** was oxidized to the ketone with TPAP, thereby completing the first total synthesis of (+)-4-hydroxyoppositan-7-one (**2**) in 7 steps and 25% overall yield from (−)-**6**. The ^{1}H NMR and ^{13}C NMR data derived from the synthetic **2** are identical with those of natural **2**.[2] The absolute configuration of the



Scheme 6. (a) $LiEt_3BH$, THF, rt; (b) TPAP, NMO, 4A mol. sieves, CH_2Cl_2, rt.

natural product was confirmed by the fact that the sign of the specific optical rotation of the synthetic material ($[\alpha]^{20}_D = +73.6$ (*c* 0.65, $CHCl_3$)) is the same as that reported for the natural product ($[\alpha]^{20}_D = +76.1$ (*c* 0.28, $CHCl_3$)[2]).

3. Conclusion

The work described in this paper culminated in the first total synthesis of (+)-4-hydroxyoppositan-7-one (**2**) and the first enantiopure synthesis of (+)-*trans*-dracunculifoliol (**1**). These syntheses started with the enantiomerically pure bicyclic enone (−)-**6**, whose efficient synthesis is described herein. The key step used to generate the advanced common intermediate **4** involved a stereoselective conjugate addition of the organocopper (I) reagent **10** to enone (−)-**6**, followed by equilibration of the ring junction to the thermodynamically more stable *trans*-fused isomer **4**. This sequence efficiently generated 3 of the 4 contiguous chiral centers required in the natural products. Intermediate **4** was elaborated in a straightforward manner to the keto alkene **12** which was then used to complete the syntheses of both natural products **1** and **2**. The absolute stereochemistries of **1** and **2** were also confirmed by these syntheses.

4. Experimental

4.1. General

All substrates and reagents were obtained commercially and used without further purification unless otherwise noted. All glassware was dried in an oven overnight and flame dried under dry nitrogen. Reactions were carried out with continuous stirring under a positive pressure of nitrogen except where noted. Flash chromatography was carried out with silica gel 60, 230–400 mesh. Anhydrous solvents were purchased from Aldrich and used without further purification. TSMBr was distilled from CaH_2 immediately before use and LiCl was flame dried under vacuum. Proton (^{1}H NMR) and carbon (^{13}C NMR) magnetic resonance spectra were recorded on a Bruker AMX spectrometer at 300 and 75.3 MHz, respectively, unless otherwise noted. All spectra were recorded in $CDCl_3$ using residual solvent ($CHCl_3$) as internal standard. Signal multiplicity was designated according to the following abbreviations: s=singlet, d=doublet, dd=doublet of doublets, ddd=doublet of doublet of doublets, t=triplet, q=quartet, dt=doublet of triplets, dq=doublet of quartets, m=multiplet, br s=broad singlet, br d=broad doublet. Elemental analyses were provided by Oneida Research Services Inc., Whitesboro, NY. High resolution mass spectra (HRMS-FAB$^+$) were obtained at the Biomedical Mass Spectrometry Unit, McGill University, Montreal, Quebec, Canada. Rotations were measured on a Perkin Elmer polarimeter (model #241).

4.1.1. (4*S*,7a*R*)-7a-Methyl-4-[(*N*-methyl-*S*-phenylsulfonimidoyl)methyl]-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-ol (8). To a cold (−30 °C) solution of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (13.6 mL, 15.8 g, 93.3 mmol, 2 equiv) in dry THF (230 mL) was slowly added *n*-butyllithium (37.3 mL, 2.5 M in hexanes,

93.3 mmol, 2 equiv). The reaction was then warmed to room temperature and stirred for 15 min. Once formation of the sulfoximine ylide was complete, the mixture was cooled to −78 °C and a solution of 6-methylbicyclo[4.3.0]non-9-en-2-one (*rac*-**6**)[9] (7.0 g, 47 mmol, 1 equiv) in THF (50 mL) was added via cannula, rinsing with THF (2×5 mL). The reaction was allowed to stir at −78 °C for 1 h, then poured into a 1:2 mixture of aqueous saturated ammonium chloride and diethyl ether (200 mL). The aqueous phase was extracted with diethyl ether (4×200 mL) and the combined organic extracts were washed with brine (150 mL) and dried over sodium sulfate. Gradient flash chromatography of the crude residue (90/10→80/20 hexane/ethyl acetate) afforded, in order of elution, diastereomers **8** (7.1 g, 47 or 50% yield based on recovered starting material) and **7** (5.4 g, 36 or 39% yield based on recovered starting material).

Compound **8**. $[\alpha]^{20}_{D}=+21.5$ (*c* 1.185, $CHCl_3$); ^{1}H NMR: δ 7.87 (2H, d), 7.58 (3H, m), 5.83 (1H, br s), 3.38 (2H, q), 2.65 (3H, s), 2.19 (2H, m), 1.20–1.75 (9H, m), 0.80 (3H, s); ^{13}C NMR: δ 150.9, 138.2, 133.0, 129.3, 129.2, 128.8, 125.7, 72.8, 62.2, 46.2, 43.9, 40.7, 39.5, 31.4, 28.6, 24.4, 22.4, 20.7; HRMS (FAB+) *m*/*z* Calcd for $C_{18}H_{25}NO_2S$ 320.1606, found: 320.1685. Anal. Calcd for $C_{18}H_{25}NO_2S$: C, 67.67; H, 7.89; N, 4.38, found: C, 67.64; H, 7.51; N, 4.33.

4.1.2. (4*R*,7a*S*)-7a-Methyl-4-[(*N*-methyl-*S*-phenylsulfonimidoyl)methyl]-2,4,5,6,7,7a-hexahydro-1*H*-inden-4-ol (7). $[\alpha]^{20}_{D}=+36.3$ (*c* 1.075, $CHCl_3$); ^{1}H NMR: δ 7.81 (2H, d), 7.62 (3H, m), 5.87 (1H, br s), 3.35 (2H, br s), 2.61 (3H, s), 2.20–2.45 (2H, m), 1.20–1.85 (9H, m), 0.98 (3H, s). ^{13}C NMR: δ 149.4, 138.9, 132.9, 129.3, 128.9, 128.8, 126.4, 72.1, 62.7, 60.2, 46.4, 43.6, 41.5, 40.9, 28.8, 28.7, 24.1, 20.0; HRMS (FAB+) *m*/*z* Calcd for $C_{18}H_{25}NO_2S$ 320.1606, found: 320.1685. Anal. Calcd for $C_{18}H_{25}NO_2S$: C, 67.67; H, 7.89; N, 4.38, found: C, 67.10; H, 7.70; N, 4.32.

4.1.3. (7a*R*)-7a-Methyl-1,2,5,6,7,7a-hexahydro-4*H*-inden-4-one ((−)-6). A solution of **8** (10.1 g, 31.6 mmol, 1 equiv) in toluene (200 mL) was refluxed overnight (oil bath temperature 110–120 °C). Since it was difficult to remove the toluene by rotary evaporation without also evaporating the product (−)-**6**, the reaction mixture was loaded directly onto a silica gel column and flushed with hexane to elute the toluene. This was followed by gradient elution (100/0→90/10 hexane/diethyl ether) to afford (−)-**6** (3.7 g, 79% yield). $[\alpha]^{20}_{D}=-114.5$ (*c* 1.135, $CHCl_3$). ^{1}H NMR identical to that reported for *rac*-**6**.[9] In order to recover the (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine, the column was eluted with ethyl acetate/acetone (50/50) to afford the sulfoximine (3.6 g, 90% recovery) in an unchanged state of optical purity.

4.1.4. (3*S*,3a*S*,7a*R*)-3-(1-Isopropylvinyl)-7a-methyloctahydro-4*H*-inden-4-one (5). To a cold (−78 °C), yellow solution of *t*-butyllithium (1.7 M in pentane, 31 mL, 53 mmol, 6 equiv) in THF (200 mL) was slowly added 2-bromo-3-methylbut-1-ene (**9**)[11] (4.0 g, 27 mmol, 3 equiv) in THF (50 mL) over 30 min. To the resultant clear, cold (−78 °C) solution was added, via cannula, a solution of LiCl (2.3 g, 53 mmol, 6 equiv) and CuCN (2.6 g, 29 mmol, 3.2 equiv) in THF (80 mL) followed by TMSBr (4.5 mL, 34 mmol, 3.9 equiv). This was immediately followed by the addition of a solution of (−)-**6** (1.3 g, 8.8 mmol, 1 equiv) in THF (10 mL), via cannula. The orange solution was stirred at −78 °C for 4 h followed by quenching with aqueous HCl (1%, 200 mL). After warming to room temperature, the mixture was poured into diethyl ether (400 mL) and sat. aq. NH_4Cl/NH_4OH (pH 8, 400 mL) and stirred vigorously overnight. The deep blue aqueous phase was extracted with diethyl ether (4×150 mL) and the combined organic extracts were washed with water (2×150 mL) and brine (200 mL), then dried over $MgSO_4$. Upon concentration, the residual oil was subjected to flash column chromatography (95/5 hexane/ethyl acetate) to yield **5** (1.4 g, 70% yield or 82% based on recovered starting material) followed by recovered starting material (−)-**6** (190 mg). ^{1}H NMR: δ 4.91 (1H, s), 4.84 (1H, s), 3.07 (1H, dt, $J=10.9$, 7.3 Hz), 2.59 (1H, d, $J=10.6$ Hz), 2.11–2.28 (3H, m), 1.97–2.08 (1H, m), 1.85–1.93 (1H, m), 1.65–1.84 (4H, m), 1.45–1.54 (2H, m, 5d), 1.12 (3H, s), 0.98 (6H, dd, $J=12.4$, 6.8 Hz); ^{13}C NMR (100.4 MHz): δ 213.9, 156.9, 106.0, 62.7, 47.2, 46.2, 41.2, 39.4, 34.8, 33.6, 29.4, 29.0, 23.0, 21.4, 20.8.

4.1.5. (3*S*,3a*R*,7a*R*)-3-(1-Isopropylvinyl)-7a-methyloctahydro-4*H*-inden-4-one (4). A solution of **5** (0.8 g, 3.5 mmol, 1 equiv) and NaOMe (6 mL, 0.5 M in MeOH, 3 mmol, 0.9 equiv) was stirred for 1 week at 55 °C. The reaction was quenched with 30 mL of water, and the residual methanol was removed by rotary evaporation. Diethyl ether (60 mL) and sat. aq. $NaHCO_3$ (60 mL) were added and the aqueous phase was extracted with diethyl ether (4×60 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (125 mL), brine (125 mL) and dried over $MgSO_4$. The ^{1}H NMR ratio of the crude material indicated a 33:1 ratio of epimers **4** and **5**. The mixture was subjected to flash column chromatography (gradiant elution of 95/5→90/10 hexane/ethyl acetate) to yield **4** (0.72 g, 93% yield). $[\alpha]^{20}_{D}=+53.4$ (*c* 0.825, $CHCl_3$); ^{1}H NMR: δ 4.70 (1H, s), 4.58 (1H, s), 2.83 (1H, dt, $J=10.9$, 6.6 Hz), 2.56 (1H, d, $J=11.1$ Hz), 2.21–2.32 (3H, m), 1.75–2.13 (4H, m), 1.51–1.69 (3H, m), 1.36–1.47 (1H, m), 1.03 (6H, dd, $J=6.8$, 5.5 Hz), 0.74 (3H, s); ^{13}C NMR: δ 210.5, 160.0, 104.1, 64.8, 49.1, 41.4, 39.9, 39.2, 38.5, 33.5, 29.6, 24.2, 22.4, 18.5; HRMS (FAB+) *m*/*z* Calcd for $C_{15}H_{24}O$ 221.1827, found: 221.1904. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98; found: C, 81.04; H, 10.40.

4.1.6. (3*S*,3a*R*,7a*R*)-3-Isobutyryl-7a-methyloctahydro-4*H*-inden-4-one (11). A solution of **4** (0.7 g, 3.3 mmol, 1 equiv) in CH_2Cl_2 (73 mL) was cooled to −78 °C. O_3 was bubbled through the solution until it turned pale blue in colour (5–10 min). N_2 was then bubbled through the solution to remove the excess O_3, rendering the reaction mixture colourless. Triphenylphosphine (1.8 g, 6.8 mmol, 2.1 equiv) was added and the mixture was allowed to warm to room temperature. The reaction was stirred for 3 h, followed by removal of the solvent by rotary evaporation. The crude mixture was flash chromatographed (gradient elution of 95/5→90/10 hexane/ethyl acetate) to afford the diketone **11** (0.6 g, 84% yield), a colourless oil. $[\alpha]^{20}_{D}=+58.8$ (*c* 0.585, $CHCl_3$); ^{1}H NMR: δ 3.35 (1H, dt, $J=10.5$, 5.7 Hz), 2.83 (1H, d, $J=10.7$ Hz), 2.76 (1H, septet, $J=6.9$ Hz), 2.24 (2H, m), 1.80–2.06 (4H, m), 1.52–1.71 (4H, m), 1.09 (6H, t, $J=7.2$ Hz), 0.73 (3H, s); ^{13}C

NMR: δ 209.5, 216.8, 62.6, 48.7, 44.0, 41.0, 40.5, 39.8, 37.6, 26.1, 23.7, 18.4, 17.9, 17.8; HRMS (FAB+) *m/z* Calcd for $C_{14}H_{22}O$ 223.1620, found: 223.1697. Anal. Calcd for $C_{14}H_{22}O$: C, 75.63; H, 9.97; found: C, 75.03; H, 9.30.

4.1.7. 2-Methyl-1-[(1*S*,3a*R*,7a*S*)-3a-methyl-7-methylene-octahydro-1*H*-inden-1-yl]propan-1-one (12). To a cold (0 °C), stirred solution of bromomethyltriphenylphosphine (0.36 g, 1.0 mmol, 1 equiv) in THF (5.7 mL) was added dropwise *n*-BuLi (2.5 M in hexanes, 0.4 mL, 1.0 mmol, 1 equiv). The resultant bright yellow solution was stirred at 0 °C for 45 min, followed by the addition of a solution of diketone **11** (0.23 g, 1.0 mmol, 1 equiv) in THF (6 mL). The reaction mixture was allowed to warm slowly to room temperature for 1 h. At this time another 0.25 equiv of ylide was prepared using the above procedure. Since all the starting material had not been consumed after 1 h, the 0.25 equiv of prepared ylide was added to the reaction mixture. After an additional h, the reaction was quenched with sat. aq. NH_4Cl (25 mL). The aqueous phase was extracted with diethyl ether (4×40 mL) and the combined organic extracts were washed with brine (3×40 mL) and then dried over $MgSO_4$. After removal of the solvent by rotary evaporation, the crude mixture was flash chromatographed (gradient elution of 95/5→90/10 hexane/diethyl ether) to afford product **12** (0.13 g, 58% yield). $[\alpha]^{20}_D$ = +100.7 (*c* 3.1, $CHCl_3$); ^{1}H NMR: δ 4.68 (1H, s), 4.31 (1H, s), 3.08 (1H, dt, *J*=11.2, 6.3 Hz), 2.71 (1H, septet, *J*=6.9 Hz), 2.35 (1H, d, *J*=11.3 Hz), 2.22 (1H, ddd, *J*=13.5, 2.9, 1.5 Hz), 1.89–2.10 (2H, m), 1.30–1.78 (7H, m), 1.07 (6H, dd, *J*=6.9, 3.0 Hz), 0.65 (3H, s); ^{13}C NMR: δ 217.2, 147.8, 104.8, 55.5, 47.5, 44.1, 40.4, 39.4, 38.8, 35.3, 26.5, 23.3, 18.3, 18.3, 17.9; HRMS (FAB+) *m/z* Calcd for $C_{15}H_{24}O$ 221.1827, found: 221.1904. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98; found: C, 81.30; H, 10.85.

4.1.8. 2-Methyl-1-[(1*S*,3a*R*,7a*S*)-3a-methyl-7-methylene-octahydro-1*H*-inden-1-yl]propan-1-ol (1). To a cold (−78 °C), stirred solution of **12** (26 mg, 0.12 mmol, 1 equiv) in THF (1.5 mL) was added Super Hydride® (1 M in THF, 0.3 mL, 2.5 equiv). The mixture was allowed to warm to 0 °C and stirred for 1.5 h followed by the addition of another aliquot of Super Hydride® (1 M in THF, 0.3 mL, 2.5 equiv). The mixture was warmed to rt and stirred for 1.5 h. Water was added and the product was extracted with diethyl ether (2×20 mL), washed with brine (1×10 mL) and dried over $MgSO_4$. After removal of the solvent by rotary evaporation, the crude mixture was purified by flash chromatography (90/10 hexane/diethyl ether) to afford the desired natural product **1** (16.8 mg, 64% yield) followed by the corresponding diastereomer at C-12, *epi*-**1** (5.7 mg, 22% yield).

Compound **1**. $[\alpha]^{20}_D$ = +54.4 (*c* 0.80, $CHCl_3$); natural **1**: $[\alpha]^{20}_D$ = +19 (*c* 0.4, $CHCl_3$) 85% pure by GC.[1] ^{1}H NMR (500 MHz): δ 4.86 (1H, d, *J*=1.3 Hz), 4.71 (1H, d, *J*=1.4 Hz), 3.22 (1H, dd, *J*=9.9, 2.4 Hz), 2.27 (1H, dd, *J*=13.0, 4.9 Hz), 2.21 (1H, dq, *J*=10.3, 5.0 Hz), 1.96 (1H, dt, *J*=13.0, 5.6 Hz), 1.5–1.86 (8H, m), 1.22–1.35 (3H, m), 0.97 (3H, d, *J*=6.9 Hz), 0.88 (3H, d, *J*=6.8 Hz), 0.64 (3H, s); ^{13}C NMR: δ 151.2, 105.7, 82.9, 58.6, 45.4, 39.4, 39.19, 39.16, 36.6, 31.2, 25.6, 24.0, 20.4, 18.0, 14.6; HRMS (FAB+) *m/z* Calcd for $C_{15}H_{26}O$ 223.1984, found: 223.2063. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79; found: C, 81.94; H, 12.20.

Compound epi-**1**. $[\alpha]^{20}_D$ = +49.4 (*c* 0.32, $CHCl_3$); ^{1}H NMR (400 MHz): δ 4.76 (1H, d, *J*=1.5 Hz), 4.39 (1H, d, *J*=1.6 Hz), 3.36 (1H, d, *J*=7.9 Hz), 2.24 (2H, dq, *J*=9.4, 1.7 Hz), 1.97 (1H, d, *J*=11.7 Hz), 1.91 (1H, dt, *J*=13.1, 6.0 Hz),1.48–1.69 (7H, m), 1.21–1.35 (3H, m), 0.97 (3H, d, *J*=6.6 Hz), 0.90 (3H, d, *J*=6.7 Hz), 0.64 (3H, s); ^{13}C NMR: δ 148.5, 104.3, 54.1, 44.1, 39.5, 39.2, 38.5, 36.2, 33.3, 23.9, 19.9, 19.5, 19.2, 17.8; HRMS (FAB+) *m/z* Calcd for $C_{15}H_{26}O$ 223.1984, found: 223.2024. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79; found: C, 81.01; H, 12.16.

4.1.9. (3*S*,3a*R*,7a*R*)-3-Isopropenyl-7a-methyloctahydro-4*H*-inden-4-one (13). Synthesized as reported by Piers and Boulet.[13]

4.1.10. (3*S*,3a*R*,4*S*,7a*R*)-3-Isopropenyl-4,7a-dimethyl-octahydro-1*H*-inden-4-ol (14). To a cold (−78 °C), stirred solution of MeMgBr (1.4 M in 3:1 toluene:THF, 1.1 mL, 1.5 mmol, 9 equiv) in diethyl ether (2 mL) was added, via cannula, a solution of **13** (32.3 mg, 0.17 mmol) and TMSBr (100 μl, 0.76 mmol, 4.5 equiv) in diethyl ether (1 mL). The mixture was stirred at −78 °C for 30 min, −43 °C for 3 h then 0 °C for 2 h. The reaction was quenched with water (1 mL) and treated with aqueous HCl (10%, 0.5 mL) for 1 h at room temperature. Water (10 mL) was added and the product was extracted with diethyl ether (3×5 mL). The combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. After rotary evaporation of solvents, the product was flash chromatographed over silica (95/5 hexane/ethyl acetate) to yield **14** (19.5 mg, 55% yield). ^{1}H NMR (500 MHz): δ 4.82 (1H, s), 4.63 (1H, s), 2.80 (1H, dt, *J*=11.4, 5.5 Hz), 1.89–1.98 (1H, m), 1.78 (1H, tq, *J*=13.7, 3.9 Hz), 1.69 (4H, br s), 1.59 (1H, br d, *J*=14.1 Hz), 1.45 (1H, br d, *J*=13.9 Hz), 1.34–1.40 (2H, m), 1.29 (1H, td, *J*=13.8, 4.8 Hz), 1.26 (1H, d, *J*=11.9 Hz), 1.17 (3H, s), 1.08–1.20 (2H, m), 1.05 (1H, s), 1.02 (3H, s). ^{13}C NMR (100.4 MHz): δ 149.9, 110.8, 72.6, 55.3, 44.1, 42.1, 41.4, 41.2, 39.3, 29.6, 28.0, 19.9, 19.0, 17.7.

4.1.11. 2-Methyl-1-[(3*S*,3a*R*,4*R*,7a*R*)-7a-methyloctahydrospiro[indene-4,2′-oxiran]-3-yl]propan-1-one (15). To a cold (0 °C), stirred solution of **12** (23 mg, 0.11 mmol, 1 equiv) in CH_2Cl_2 (2 mL) was added *m*-chloroperbenzoic acid (*m*-CPBA, 70% pure, 31 mg, 0.13 mmol, 1.2 equiv) and the reaction was allowed to stir at 0 °C for 30 min. The reaction was then warmed to room temperature and an additional aliquot of *m*-CPBA (44 mg, 1.7 equiv) was added and the mixture was stirred for 45 min. Excess *m*-CPBA was destroyed by the addition of sat. aq. $Na_2S_2O_3$ (1 mL). The aqueous layer was extracted with diethyl ether (2×25 mL) and the combined organic extracts were washed with sat. aq. $NaHCO_3$ (2×25 mL) and then dried over $MgSO_4$. After removal of solvents by rotary evaporation, the residue was flash chromatographed on silica gel (95/5 hexane/ethyl acetate) to yield epoxide **15** (18.5 mg, 75% yield). $[\alpha]^{20}_D$ = +63.2 (*c* 0.85, $CHCl_3$); ^{1}H NMR: δ 2.80 (1H, br s), 2.66 (1H, dt, *J*=11.1, 5.6 Hz), 2.56 (2H, m), 2.26 (1H, d, *J*=11.4 Hz), 1.94 (1H, m), 1.47–1.83 (7H, m), 1.22–1.32 (2H, m), 1.02 (6H, t, *J*=7.4 Hz), 0.82 (3H, s); ^{13}C NMR: δ 217.1, 59.2, 54.5, 49.8, 45.5, 45.4, 41.2, 40.1, 37.9,

34.4, 27.2, 22.2, 18.4, 18.0, 17.5; HRMS (FAB+) *m/z* Calcd for $C_{15}H_{24}O_2$ 237.1776, found: 237.1854.

4.1.12. (3*S*,3a*R*,4*R*,7a*R*)-3-(1-Hydroxy-2-methylpropyl)-4,7a-dimethyloctahydro-1*H*-inden-4-ol (16). To a stirred solution of **15** (16 mg, 0.07 mmol, 1 equiv) in THF (1.5 mL) was added Super Hydride® (1 M in THF, 0.3 mL, 4 equiv) and the mixture was stirred at rt for 40 min. An additional aliquot of Super Hydride® (1 M in THF, 0.3 mL, 4 equiv) was added and the reaction mixture was stirred for 2 h at rt. The reaction was then cooled to 0 °C and quenched with 10% HCl (~5 mL). The solution was neutralized with sat. aq. $NaHCO_3$. The mixture was extracted with ethyl acetate (3×25 mL) and the combined organic extracts were washed with brine (1×25 mL) and dried over $MgSO_4$. After rotary evaporation of solvents, the residue was flash chromatographed on silica gel (gradient elution of 90/10→80/20 hexane/ethyl acetate) to afford the diol **16** (14.7 mg, 91% yield) as a white powder. ^{1}H NMR: δ 3.84 (2H, br s), 3.30 (1H, dd, J=9.5, 1.7 Hz), 2.04 (1H, m), 1.68–1.91 (3H, m), 1.27–1.62 (8H, m), 1.23 (3H, s), 1.01–1.22 (1H, m), 0.99 (3H, d, J=6.9 Hz), 0.86 (3H, d, J=7.0 Hz), 0.85 (3H, s).

4.1.13. 1-[(1*S*,3a*R*,7*R*,7a*R*)-7-Hydroxy-3a,7-dimethyloctahydro-1*H*-inden-1-yl]-2-methylpropan-1-one (2). To a stirred mixture of the diol **16** (12.5 mg, 0.05 mmol, 1.0 equiv), 4-methylmorpholine-*N*-oxide, NMO (9 mg, 0.08 mmol, 1.5 equiv) and powdered 4 Å molecular sieves (20 mg) in CH_2Cl_2 (1.5 mL) was added tetrapropylammoniumperruthenate, TPAP (4.6 mg, 0.01 mmol, 0.25 equiv). The reaction was allowed to stir at rt for 3 h. The reaction mixture was then filtered through a short column of silica. After rotary evaporation of the solvents, the residue was flash chromatographed on silica gel (80/20 hexane/ethyl acetate) to yield the desired natural product **2** (12.1 mg, 97% yield). $[\alpha]^{20}_D$=+73.6 (*c* 0.65, $CHCl_3$); natural **2**: $[\alpha]^{20}_D$=+76.1 (*c* 0.28, $CHCl_3$)[2] and +84 (*c* 0.31, $CHCl_3$)[3]; ^{1}H NMR: δ 3.07 (1H, dt, J=11.4, 5.8 Hz), 2.75 (1H, septet, J=6.9 Hz), 2.00 (1H, m), 1.86 (1H, d, J=11.7 Hz), 1.79 (2H, br d), 1.63 (2H, dd, J=12.6, 2.5 Hz), 1.31–1.58 (4H, m), 1.13–1.26 (2H, m), 1.09 (9H, s and d), 0.86 (3H, s); ^{13}C NMR: δ 220.5, 72.4, 60.6, 46.1, 43.7, 43.6, 42.1, 41.7, 38.5, 27.0, 21.6, 21.3, 20.1, 18.3, 18.1; HRMS (FAB M+H+Na) *m/z* Calcd for $C_{15}H_{26}O_2$ 261.1833, found: 261.1830. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99; found: C, 74.93; H, 10.75.

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