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Synthesis of liverwort sesquiterpene (−)-isocuparene (herbertene) via a Diels–Alder reaction using phenylethylamine as chiral auxiliary

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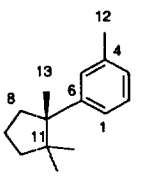
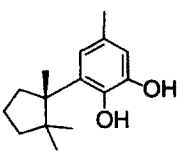
Abstract: The imine of 2-methylcyclopentanone with (*S*)-(−)-phenylethylamine was subjected to reaction with methyl propiolate and the product was transformed into (−)-isocuparene by use of a Diels–Alder reaction to construct the aromatic ring. © 1997 Elsevier Science Ltd

2,2-Disubstituted cyclic chiral keto esters can be easily prepared by the methods of Pfau and d'Angelo using homochiral phenylethylamine,[1] which are widely used and provide the reliable absolute configuration of the quaternary stereogenic center. We have previously developed this reaction with methyl propiolate to prepare α,β-unsaturated keto esters.[2] This has been applied to 2-methylcyclopentanone and the enantiomeric excess is determined. Cuparanes and isocuparanes, for example (−)-isocuparene **1** and (−)-herbertenediol **2**, have been found in liverworts[3] and some complicated dimeric phenols belonging to this class have also been found to be biologically active compounds.[4] We have developed syntheses of these types of monomeric compounds in optically active forms using phenylethylamine methodology.[5]



(-)-isocuparene (herbertene) (1)



(-)-herbertenediol (2)

Since isocuparanes have only one stereogenic center, this can be prepared by phenylethylamine methodology. We planned to prepare the aromatic ring by a Diels–Alder reaction between either the diene (isoprene) and α,β-unsaturated ester or the diene derived from the unsaturated ester and methyl propiolate as illustrated in Scheme 1. The newly created double bond can be oxidized to a diol (R=OH) and therefore this route is also applicable to the herbertenediol system.

The imine of 2-methylcyclopentanone with phenylethylamine was subjected to reaction with methyl propiolate[2] to yield α,β-unsaturated keto ester **5** in 68% yield and 71% ee. When it was carried out with methyl acrylate as reported by Pfau *et al.*,[1] keto ester **3** was obtained in 75% yield and 94% ee. The identity of the absolute configuration of the unsaturated keto ester **5** at the quaternary center was verified by converting **5** into **3** by hydrogenation.

In order to prepare the protected keto ester **6** from **3**, we needed a further three steps as illustrated in Scheme 2. However, the propiolate methodology took only three steps from 2-methylcyclopentanone, although the ee was not so high as that of the acrylate method. This is presumably due to the linearity of the propiolate, while the acrylate is a sickle form.[6]

The next step is to construct the aromatic ring for isocuparene. We first attempted to react ester **6** with isoprene by a Diels–Alder reaction to make an aromatic ring. However after several experiments, it turned out to be difficult, even with the pentafluorophenyl ester of **6**.[7] Therefore, we prepared

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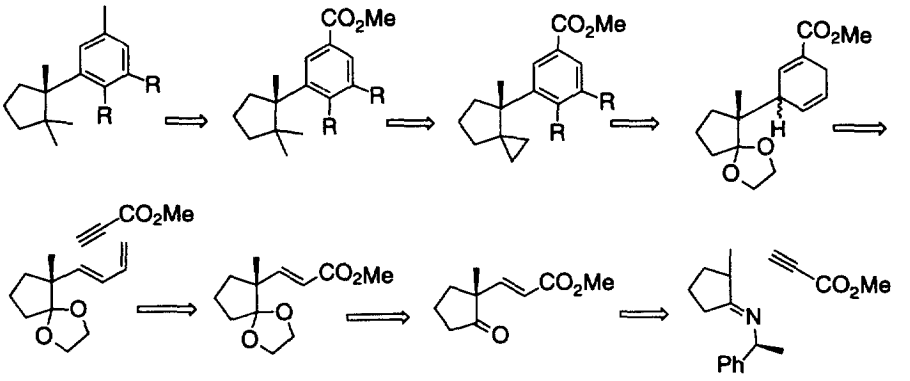
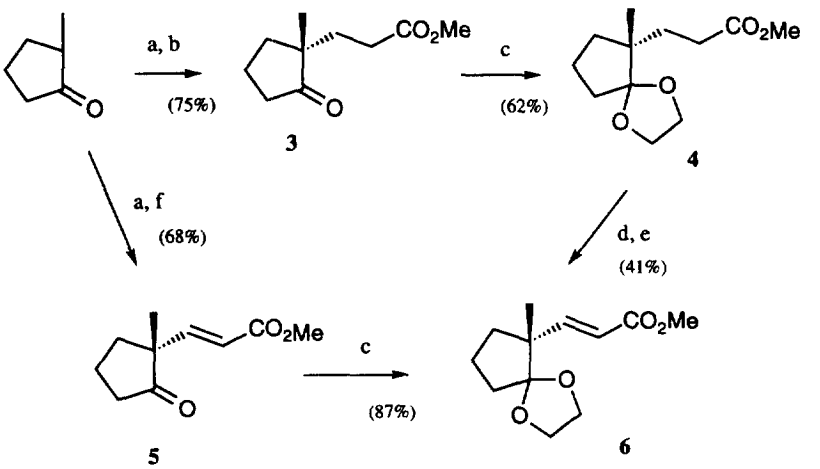


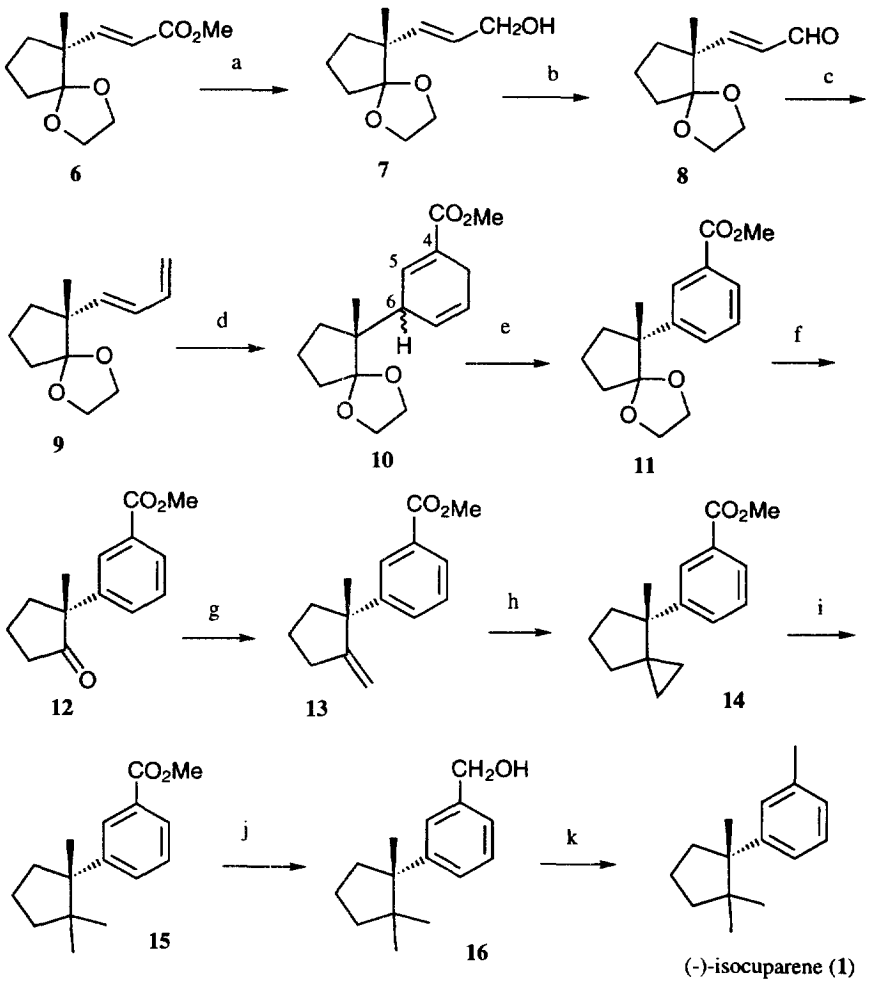
Scheme 1. Synthetic plan.



Scheme 2. Reagents and conditions: (a) (*S*)-(−)-phenylethylamine, $TsOH \cdot H_2O$, C_6H_6; (b) methyl acrylate, 4 days; then $AcOH–H_2O$ (9:1); (c) $HOCH_2CH_2OH$, $TsOH \cdot H_2O$, C_6H_6; (d) LDA, PhSeBr, THF; (e) H_2O_2, THF; (f) methyl propiolate, 4 days; then $AcOH–H_2O$ (9:1).

the diene **9** from the ester **6** in three steps (Scheme 3). The diene **9** was subjected to reaction with methyl propiolate. Because the adduct with the propiolate had two unsaturations in its ring, we chose this derivative for our purpose. The regioselectivity was *ca.* 3.5:1 in favour of the desired product **10**. Because the proton at C-5 of **10** appeared at δ 6.88 as dq (J=3.9 and 1.7 Hz), this isomer was assigned as the desired one. In this case only one diastereoisomer (C-6) was detected, although the stereochemistry was not determined. The ^1H NMR spectrum of the minor regioisomer showed two sets of signals for H-4 at δ 6.80 and 6.94 (each ddd, J=5.0, 4.2, 1.2 Hz), indicating a mixture of two diastereoisomers. The adduct **10** was dehydrogenated by DDQ to give aromatic compound **11** in good yield.

The next thing was to introduce dimethyl groups in the five membered ring. The ketal was removed and exomethylene **13** was obtained by use of the Tebbe reagent.[8] Cyclopropanation using Et_2Zn and diiodomethane cleanly produced the desired compound **14**.[9,10] The opening of the cyclopropane ring into a *gem*-dimethyl group was rather complicated in this case. Hydrogenation in the presence of Pd–C in all ordinary solvents failed. However, by using PtO_2 instead of Pd catalyst, hydrogenation afforded the ring opened *gem*-dimethyl compound **15** by addition of AcOH into the solvent. If this hydrogenation was carried out after conversion of the methoxycarbonyl moiety into the methyl group,



Scheme 3. Reagents and conditions: (a) DIBALH, THF (88%); (b) PDC, CH_2Cl_2 (90%); (c) $Ph_3P^+CH_3Br^-$, BuLi, THF (75%); (d) methyl propiolate, toluene, sealed tube (80%); (e) DDQ, C_6H_6 (95%); (f) $TsOH \cdot H_2O$, acetone–H_2O (90%); (g) Tebbe reagent, toluene (46%); (h) Et_2Zn, CH_2I_2, CH_2Cl_2 (48%); (i) H_2, PtO_2, AcOH–EtOAc; (j) $LiAlH_4$, Et_2O (2 steps 80%); (k) H_2, Pd–C, MeOH (80%).

only the cyclohexane derivative was obtained as a result of over-reduction of the aromatic ring. Thus the hydrogenation must be carried out at the stage of the electron withdrawing functional group (methoxycarbonyl group) at the C-4 position.

The final two steps were straightforward, namely $LiAlH_4$ reduction and hydrogenation of the benzyl alcohol to afford (−)-isocuparene **1**, whose ^1H and ^{13}C NMR spectra were identical with those of the natural product. The specific rotation of the synthetic one was $[\alpha]_D$ −25.3, while the natural one was −48.3.[3,11] This result should solely depend on the ee at the stage of the α,β-unsaturated keto ester **5**.

Thus, we have developed asymmetric synthesis of (−)-isocuparene **1** by use of the slightly modified phenylethylamine technology and Diels–Alder reaction as key steps.

Experimental

General

The IR spectra were measured with a JASCO FT/IR-5300 spectrophotometer. The ^1H and the ^{13}C NMR spectra were taken with a Varian Unity 200 (200 MHz), a JEOL JNM GX400 (400 MHz) or a Varian Unity 600 (600 MHz). The mass spectra including high resolution mass spectra were taken with a JEOL JMS AX-500 spectrometer. The CD spectra were carried out with a JASCO J-500 spectrometer. The optical rotations were measured by a JASCO DIP-140 polarimeter. Chemcopak Nucleosil 50-5 (10×250 mm) was used for HPLC (JASCO pump system). Enantiomeric excess was determined by HPLC using CHIRALCEL OB-H (Daicel, 4×250 mm) or by GC using α-DEX column (SUPELCO, 30 m). Silica gel 60 (70–230 mesh, Merck) was used for column chromatography and silica gel 60 F_{254} plates (Merck) were used for TLC.

Preparation of unsaturated ester 5

(*S*)-(−)-1-Phenylethylamine (67.8 ml, 0.53 mol) and TsOH (5.0 g) were added to a solution of 2-methylcyclopentanone (50.0 g, 0.51 mol) in benzene (200 ml) and the mixture was refluxed for 24 h with the aid of a Dean–Stark water separator. The mixture was washed with water, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and concentrated to afford an imine (91.0 g, 0.46 mol), which was subjected to react with methyl propiolate (45 ml, 0.51 mol) under ice cooling. The mixture was then stirred at rt for 4 days. Acetic acid and water (9:1, 1030 ml) was added to the mixture and kept at 60°C for 1 h. The mixture was extracted with ether and the organic layer was washed with water, saturated $NaHCO_3$ solution, 1 M HCl solution, and brine, dried ($MgSO_4$), and evaporated to afford a residue. Purification by silica gel column chromatography (hexane–EtOAc, gradient) gave unsaturated ester **5** (63.1 g, 68%, 71% ee). $[\alpha]_D^{20}$ = +24.7 (c 1.5, $CHCl_3$). IR (FT): 1740, 1720, and 1650 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.20 (3H, s), 1.8–2.4 (6H, m), 3.73 (3H, s), 5.86 (1H, d, *J*=16.0 Hz), and 6.91 (1H, d, J=16.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.8 (q), 22.0 (t), 36.3 (t), 37.1 (t), 51.6 (q), 120.5 (d), 149.8 (d), 166.6 (s), and 218.1 (s). MS (EI) *m/z*: 182 (M^+), 154, 139, 127, 111, 95 (base), 81, 67, and 55. HRMS (EI) calcd for $C_{10}H_{14}O_3$ (M^+) 182.0943, found: 182.0966.

Preparation of keto ester 3

(*S*)-(−)-1-Phenylethylamine (31 ml, 0.24 mmol) and TsOH (2.3 g) were added to a solution of 2-methylcyclopentanone (23 g, 0.24 mmol) in benzene (250 ml) and the mixture was refluxed for 24 h with the aid of a Dean–Stark water separator. The mixture was washed with water, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and concentrated to afford a residue, which was distilled under reduced pressure to give imine (34 g, bp 110–120°C/7 torr). The imine was subjected to reaction with methyl acrylate (16.2 ml) under ice cooling. The mixture was then stirred at rt for 5 days. Acetic acid and water (9:1, 360 ml) were added to the mixture and kept at 60°C for 1 h. The mixture was extracted with ether and the organic layer was washed with water, saturated $NaHCO_3$ solution, 1 M HCl solution, and brine, dried ($MgSO_4$), and evaporated to afford a residue. Purification by silica gel column chromatography (hexane–EtOAc, gradient) gave ester **3** (32.4 g, total 75%, 94% ee).[1] $[\alpha]_D^{20}$ = +35.0 (c 1.1, $CHCl_3$). IR (FT): 1740 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.01 (3H, s), 1.65–1.95 (6H, m), 2.15–2.45 (4H, m), and 3.66 (3H, s). ^{13}C NMR: δ 18.4, 21.1, 29.0, 31.1, 35.8, 37.3, 47.3, 51.4, 173.7, and 222.3.

Preparation of ketal 4

A solution of keto ester **3** (2 g, 0.11 mol) in benzene (200 ml) was treated with ethylene glycol (6 ml) and TsOH (200 mg) under reflux with the aid of a Dean–Stark water separator for 24 h. The mixture was washed with water, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and evaporated to afford a residue, which was purified by silica gel column chromatography to give ketal **4** (1.54 g, 62%). $[\alpha]_D^{19}$ = −6.3 (c 1.1, $CHCl_3$). IR (FT): 1730 cm^{-1}. MS (EI) *m/z*: 228 (M^+), 197, 185, 155, 113, 99 (base), 55. ^1H NMR (200 MHz, $CDCl_3$): δ 0.96 (3H, s), 1.45–1.85 (8H, m), 2.20–2.45 (2H,

m), 3.66 (3H, s) and 3.90 (4H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.8 (q), 19.9 (t), 30.0 (t), 30.2 (t), 33.3 (t), 35.4 (t), 45.3 (s), 51.5 (q), 64.5 (t), 64.7 (t), 119.3 (s), 174.9 (s). HRMS (EI) calcd for $C_{12}H_{20}O_4$ (M^+) 228.1362, found: 228.1359.

*Preparation of unsaturated ester **6** via phenylselenide*

A solution of ketal **4** (3.19 g, 14.0 mmol) in dry THF (10 ml) was added into a stirred solution of LDA [prepared from nBuLi (1.6 M in hexane; 17.5 ml, 2.0 mmol), diisopropylamine (4.4 ml) in dry THF (30 ml) and HMPA (45 ml)] at −78°C and the mixture was kept at this temperature for 1 h. A solution of phenylselenenyl bromide (5.06 g, 21.4 mmol) in dry THF (10 ml) was added and the mixture was stirred for 0.5 h at −78°C then at 0°C for 0.5 h. Water was added and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue, which was purified by silica gel column chromatography (hexane–EtOAc, gradient) to give seleno ester (2.6 g). The seleno ester was dissolved in THF (100 ml) and treated with 30% H_2O_2 (45 ml) for 12 h. Aqueous $Na_2S_2O_3$ solution was added and the mixture was extracted with ether. The organic layer was washed with brine to afford a residue, which was purified by silica gel column chromatography to give unsaturated ester **6** (1.3 g, total 41%). $[\alpha]_D^{20} = +32.9$ (c 1.3, $CHCl_3$).

*Preparation of ketal **6** via **5***

A solution of unsaturated ester **5** (15.0 g, 0.082 mol) in benzene (200 ml) was treated with ethylene glycol (45.0 ml, 0.81 mol) and TsOH (3.0 g) under reflux with the aid of a Dean–Stark water separator for 24 h. The mixture was washed with water, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and evaporated to afford ketal **6** (16.2 g, 87%). IR (FT): 1730 and 1650 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.12 (3H, s), 1.5–2.0 (6H, m), 3.73 (3H, s), 3.89 (4H, m), 5.84 (1H, d, J=16.0 Hz), and 7.16 (1H, d, J=16.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.2 (t), 19.9 (q), 33.8 (t), 35.5 (t), 49.5 (s), 51.4 (q), 64.9 (t), 65.3 (t), 119.1 (d), 119.4 (s), 153.7 (d), and 167.3 (s). MS (EI) *m/z* 226 (M^+), 195, 183, 167, 153, 125, 113, 99 (base), and 55. HRMS (EI) calcd for $C_{12}H_{18}O_4$ (M^+) 226.1206, found: 226.1220.

*Preparation of alcohol **7***

A stirred solution of ketal **6** (6.50 g, 29 mmol) in dry THF (29 ml) was treated with DIBALH (1 M in hexane, 60 ml, 60 mmol) under Ar for 24 h. Excess reagent was decomposed by wet ether and the solvent was evaporated. The mixture was extracted with ether and the organic layer was washed with water, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and evaporated to afford alcohol **7** (5.57 g, 88%). IR (FT): 3400 and 1660 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.08 (3H, s), 1.5–1.9 (6H, m), 3.89 (4H, s), 4.12 (1H, d, J=5.6 Hz), 5.66 (1H, dt, J=16, 5.6 Hz), and 5.88 (1H, t, J=16.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.0 (t), 20.5 (q), 33.5 (t), 35.6 (t), 48.5 (s), 64.2 (t), 64.9 (t), 65.1 (t), 119.4 (s), 127.1 (d), and 137.3 (d). MS (EI) *m/z*: 198 (M^+), 181, 167, 139, 113, 99 (base), and 55. HRMS (EI) calcd for $C_{11}H_{18}O_3$ (M^+) 198.1256, found: 198.1253.

*Preparation of aldehyde **8***

A solution of alcohol **7** (7.0 g, 35.4 mmol) in CH_2Cl_2 (40 ml) was treated with PDC (20 g, 54.5 mmol) and powdered molecular sieves 4 Å (6.4 g) at rt for 12 h. The mixture was filtered through Celite and silica gel (elution with ether) to afford aldehyde **8** (6.29 g, 90%). IR (FT): 2740, 1690, and 1630 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.17 (3H, s), 1.6–2.1 (6H, m), 3.9 (4H, m), 6.14 (1H, dd, J=16, 7.8 Hz), 7.04 (1H, d, J=16 Hz), and 9.54 (1H, d, 7.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.2 (t), 19.8 (q), 33.8 (t), 35.5 (t), 50.0 (s), 64.9 (t), 65.3 (t), 119.2 (s), 130.9 (d) 163.2 (d), and 194.3 (d). HRMS (EI) calcd for $C_{11}H_{16}O_3$ (M^+) 196.1100, found: 196.1077.

*Preparation of diene **9***

A suspension of methyltriphenylphosphonium bromide (12.0 g, 33.7 mmol) in THF (100 ml) was treated with BuLi (1.63 M in hexane, 16 ml, 26 mmol) under Ar for 1 h. A solution of aldehyde **8**

(3.0 g, 15.3 mmol) in THF (20 ml) was added into the mixture and was kept stirring for 1 h. Water was added and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue, which was purified by silica gel column chromatography (hexane–PhH, gradient) to afford diene **9** (2.40 g, 75%). IR (FT): 1640 and 1600 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.09 (3H, s), 1.5–2.0 (6H, m), 3.90 (4H, s), 4.99 (1H, dd, *J*=10.0, 1.8 Hz), 5.13 (1H, dd, *J*=16.8, 1.8 Hz), 5.89 (1H, d, *J*=15.6 Hz), 6.10 (1H, dd, *J*=15.6, 10.0 Hz), and 6.36 (1H, dt, *J*=16.8, 10.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.0 (t), 20.2 (q), 33.6 (t), 35.8 (t), 48.8 (s), 64.9 (t), 65.1 (t), 115.0 (t), 119.6 (s), 128.8 (d), 137.7 (d), and 139.6 (d). MS (EI) *m/z*: 194 (M^+), 179, 137, 113, 99 (base), 79, 55. HRMS (EI) calcd for $C_{12}H_{18}O_2$ (M^+) 194.1307, found: 194.1307.

*Diels–Alder reaction of **9** with methyl propiolate*

A mixture of diene **9** (700 mg, 3.6 mmol), methyl propiolate (12 ml), hydroquinone (10 mg), and toluene (3 ml) was heated in a sealed tube at 130°C for 2 days. After removal of the solvent, purification by silica gel column chromatography (hexane–EtOAc, 0–30%) afforded adducts **10** (435 mg, 44%) and the mixture of **10** and its regioisomer (550 mg, ratio 2:1). IR (FT): 1720, 1680, and 1640 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (3H, s), 1.6–1.9 (6H, m), 2.8–2.9 (2H, m), 3.32 (1H, m), 3.74 (3H, s), 3.88–4.05 (4H, m), 5.65–5.85 (2H, m), and 6.88 (1H, dq, *J*=3.9, 1.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.7 (t), 18.2 (q), 25.6 (t), 33.2 (t), 35.8 (t), 41.4 (d), 49.1 (s), 51.5 (q), 63.8 (t), 64.0 (t), 119.4 (s), 124.3 (d), 125.7 (d), 129.1 (s), 140.2 (d), and 167.4 (s). MS (CI) *m/z*: 277 $(M-2+H)^+$ (base), 263, 247, 216, 201, 141, and 99. HRMS (EI) calcd for $C_{16}H_{21}O_4$ $(M-2+H)^+$ 277.1440, found: 277.1414.

*Preparation of aromatic ester **11***

A solution of adduct **10** (200 mg, 0.7 mmol) in benzene (20 ml) was treated with DDQ (32.7 mg, 1.44 mmol) under Ar at 60°C for 24 h. Water was added and the mixture was extracted with ether. The organic layer was washed with 1 M NaOH solution and brine, dried ($MgSO_4$), and evaporated to afford aromatic ester **11** (189 mg, 95%). IR (FT): 1720, 1600, and 1580 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.41 (3H, s), 1.75–2.10 (5H, m), 3.35 (1H, m), 3.80 (4H, s), 3.90 (3H, s), 7.34 (1H, t, *J*=7.8 Hz), 7.68 (1H, ddd, *J*=7.8, 1.8, 1.3 Hz), 7.88 (1H, ddd, *J*=7.8, 1.8, 1.3 Hz), and 8.16 (1H. t, *J*=1.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.5 (t), 24.2 (q), 33.7 (t), 34.6 (t), 49.8 (s), 51.9 (q), 64.3 (t), 65.2 (t), 119.4 (s), 127.1 (d), 127.6 (d), 128.3 (d), 129.4 (s), 131.8 (d), 145.6 (s), and 167.5 (s). MS (EI) *m/z*: 276 (M^+), 245, 188, 176, 145, 113, and 99 (base). HRMS (EI) calcd for $C_{16}H_{20}O_4$ (M^+) 276.1362, found: 276.1348.

*Preparation of ketone **12***

Ketal **11** (121 mg, 0.44 mmol) was treated with TsOH (96 mg) in acetone and water (1:2, 7 ml) at rt for 24 h. After removal of acetone, the mixture was extracted with ether. The organic layer was washed with water, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and evaporated to afford ketone **12** (110 mg, 90%). IR (FT): 1740, 1730, 1600, and 1580 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.41 (3H, s), 1.85–2.15 (3H, m), 2.38 (2H, t, *J*=7.8 Hz), 2.58 (1H, m), 3.91 (3H, s), 7.39 (1H, t, *J*=7.7 Hz), 7.58 (1H, dt *J*=7.7, 1.4 Hz), 7.91 (1H, dt, *J*=7.7, 1.4 Hz), and 8.03 (1H, t, *J*=1.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.7 (t), 24.9 (q), 37.6 (t), 38.0 (t), 52.1 (q), 52.8 (s), 127.3 (d), 127.9 (d), 128.5 (d), 130.4 (s), 131.1 (d), 143.2 (s), 166.9 (s), and 220.0 (s). MS (EI) *m/z*: 232 (M^+), 201, 189, 176 (base), 156, 145, 115, and 91. HRMS (EI) calcd for $C_{14}H_{16}O_3$ (M^+) 232.1099, found: 232.1086.

*Preparation of cyclopropane **14***

A solution of ketone **12** (160 mg, 69 mmol) in dry toluene (40 ml) was treated with Tebbe reagent (0.5 M, 10 ml, 20 mmol) at rt for 24 h. The mixture was filtered through Celite. Ether (50 ml), 10% NaOH solution (6 ml), and Na_2SO_4 (4 g) were added and the mixture was filtered. The filtrate was concentrated to afford a residue, which was purified by silica gel column chromatography (hexane–EtOAc, 0–50%) to give exomethylene **13** (73.6 mg, 46%); ^1H NMR (200 MHz, $CDCl_3$): δ 1.45 (3H, s), 2.0–2.6 (6H,

m), 3.91 (3H, s), 4.96 (2H, d, *J*=58.7 Hz), 7.34 (1H, t, *J*=7.8 Hz), 7.58 (1H, dt, *J*=7.8, 1.6 Hz), 7.85 (1H, dt, *J*=7.8, 1.6 Hz), and 8.07 (1H, t, *J*=1.6 Hz). Diethyl zinc (1 M in hexane, 2 ml, 2 mmol) was added into a solution of exomethylene **13** (84 mg, 0.365 mmol) in dry CH_2Cl_2 (10 ml) at 0°C. In 10 min, diiodomethane (0.6 ml, 7.5 mmol) was added slowly and the mixture was stirred at rt for 2 days. Water was added and the mixture was extracted with CH_2Cl_2 and the organic layer was washed with water, 10% H_2SO_4 solution, and brine, dried ($MgSO_4$), and evaporated to afford a residue, which was purified by silica gel column chromatography (hexane–EtOAc, 0–30%) to give cyclopropane **14** (40 mg, 48%). IR (FT): 1720 and 1680 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.26 (2H, m), 0.55 (2H, m), 1.20 (3H, s), 3.92 (3H, s), 7.35 (1H, t, *J*=7.8 Hz), 7.63 (1H, ddd, *J*=7.8, 2.0, 1.0 Hz), 7.84 (1H, ddd, *J*=7.8, 1.6, 1.0 Hz), and 8.09 (1H, dd, *J*=2.0, 1.6 Hz). MS (EI) *m/z*: 244 (M^+), 229, 216 (base), 201, 185, 176, 157, 143, 129, 115, and 91. HRMS (EI) calcd for $C_{16}H_{20}O_2$ (M^+) 244.1463, found: 244.1493.

Preparation of alcohol 15

A solution of cyclopropane **14** (20 mg, 0.082 mmol) in AcOH (18 ml) and EtOAc (9 ml) was treated with H_2 in the presence of PtO_2 (60 mg) for 4 h. After filtration of the catalyst, the solvents were removed to afford ester **15** (32 mg). IR (FT): 1730 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.12 (3H, s), 3.83 (3H, s), 7.26 (1H, t, *J*=7.8 Hz), 7.54 (1H, dt, *J*=7.8, 1.2 Hz), 7.77 (1H, dt, *J*=7.8, 1.2 Hz), and 8.01 (1H, t, *J*=1.2 Hz). MS (EI) *m/z*: 246 (M^+), 215, 190, 176 (base), 163, 145, 131, 115, and 91. HRMS (EI) calcd for $C_{16}H_{22}O_2$ (M^+) 246.1619, found: 246.1620.

A solution of **15** (32 mg, 0.13 mmol) in ether (10 ml) was reduced with $LiAlH_4$ (46 mg, 1.27 mmol) for 3 h. Wet ether and water were added successively and the mixture was extracted with ether. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated to afford a residue, which was purified by silica gel column chromatography (hexane–EtOAc, 0–50%) to give alcohol **16** (16 mg, 80% from **14**). IR (FT): 3400 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.56 (3H, s), 0.79 (3H, s), 1.08 (3H, s), 4.69 (2H, s), and 7.1–7.4 (4H, m). MS (EI) *m/z*: 218 (M^+), 193, 158, 148 (base), 131, 119, and 105. HRMS (EI) calcd for $C_{15}H_{22}O$ (M^+) 218.1671, found: 218.1666.

Preparation of (−)-isocuparene 1

A solution of alcohol **16** (16 mg, 0.073 mmol) in MeOH (6 ml) was treated with H_2 in the presence of Pd–C (20 mg) for 24 h. After filtration of the catalyst, the solvent was evaporated to afford a residue, which was purified by silica gel column chromatography (hexane) to give (−)-isocuparene **1** (12.8 mg, 80%). $[\alpha]_D^{22} = -25.3$ (c 0.47, $CHCl_3$). IR (FT): 2950, 2925, 1610, 1460, and 1380 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.56 (3H, s), 1.07 (3H, s), 1.26 (3H, s), 2.35 (3H, s), 6.99 (1H, m), 7.16 (2H, m), and 7.26 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7 (t), 21.8 (q), 24.3 (q), 24.5 (q), 26.5 (q), 36.8 (t), 39.8 (t), 44.2 (s), 50.5 (s), 124.1 (d), 126.1 (d), 127.3 (d), 127.8 (d), 136.8 (s), and 147.6 (s). MS (EI) *m/z*: 202 (M^+), 187, 159, 145, 132 (base), 120, 105, and 91. HRMS (EI) calcd for $C_{15}H_{22}$ (M^+) 202.1721, found 202.1726.

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10. The yields for these two steps were unexpectedly low despite several trials. This is presumably due to steric hindrance at the C-11 position.
11. The specific rotation of (−)-**1**, $[\alpha]_D$=−25.3, did not correspond with 71% ee determined for compound **5**. This is due to inseparable impurity present in the sample.

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