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A chiral pool based approach to antipodes of α-cuparenone

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ABSTRACT

A synthetic route to both antipodes of α-cuparenone was achieved from the readily available chiral pool starting material L-malic acid and involved cyclopentannulation as the key step.

1. Introduction

α-Cuparenone **1** is a bicyclic sesquiterpene, which is found in two isomeric forms. (+)-α-Cuparenone was isolated from the wood of *Thuja orientallis* (mayurpankhi) by Dev et al.[1] whereas (−)-α-cuparenone was isolated from the liverwort *Mannia fragrans* by Benesova et al.[2]. This sesquiterpene is a synthetic challenge to organic chemists due to the presence of two contiguous quaternary centers, one of which is stereogenic in the cyclopentane ring. The quaternary stereogenic center has been constructed in a variety of ways.[3]

Recently, Natarajan et al. reported the synthesis of cuparenone **1** by employing a photoinduced decarbonylation of a ketone.[4] For enantiomerically pure natural products, they carried out the resolution via diastereoisomers. Tsunoda et al. used asymmetric aza-Claisen rearrangements for the enantioselective construction of the quaternary stereogenic centers.[5] Moreover, the Pd-catalyzed cross coupling of tertiary allylic carbonates and allylboronates was described by Morken and Zhang to construct quaternary stereogenic centers.[6] To date, approximately 20 asymmetric syntheses have been reported.

As part of our interest in cyclopentane rings in naturally occurring pentanoids,[7] we undertook the synthesis of α-cuparenone **1** (see Fig. 1).

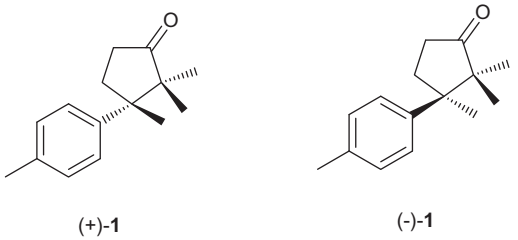

Figure 1.

We have recently accomplished a short synthesis of α-cuparenone **1**[8] in which the carbon-bearing aryl group acts as a nucleophile, and which involves simple dialkylation to construct a cyclopentene ring.

As it is obvious from the retrosynthesis outlined in (Scheme 1), our tactic was to prepare the key intermediate **2** by dialkylation. From our previous results,[8] we expected that cyclopentannulation of 4-methyl-benzyl cyanide **4** with the help of (*S*)-(((1,4-diiodobutan-2-yl)oxy)methyl)benzene **3** as a chiral auxiliary would provide the required stereogenic center of **2**. Herein we wish to report a new synthesis of **1** employing (*S*)-(((1,4-diiodobutan-2-yl)oxy)methyl)benzene **3** as a source of chirality, which can be accessed from the commercially available cheap starting material like L-malic acid.

2. Result and discussion

The enantiomerically pure (*S*)-(((1,4-diiodobutan-2-yl)oxy)methyl)benzene **3** was obtained in four steps from L-malic acid.[9] Accordingly, L-malic acid **5** upon treatment with thionyl chloride and methanol gave the methyl ester. The secondary hydroxy group was protected using benzyl bromide, and silver oxide in ethyl acetate as the solvent to furnish the *O*-benzyl ether **6** in 90% yield over two steps. The reduction of diester **6** was carried out using calcium borohydride to afford the dihydroxy compound **7** in 95% yield. Both hydroxy groups were converted into a mesylate derivative and the mesylate was treated with sodium iodide in acetone at 65 °C to furnish the corresponding di-iodo compound **3** in 85% yield over two steps (Scheme 2).

With the di-iodo compound **3** in hand, our next task was to construct the cyclopentane ring. Thus 4-methyl benzyl cyanide was treated with sodium hydride in DMF as the solvent at 0 °C followed by the addition of **3**, and afforded **2** as a diastereomeric mixture (50:50) in 90% yield, which was separated by column chromatography using hexane/ethyl acetate (98:2) as eluent to give pure **2a** and **2b** (Scheme 3).

Fortunately, one of these two diastereomers **2b** was solid (mp = 82 °C). After recrystallization (pet ether/ethylacetate),

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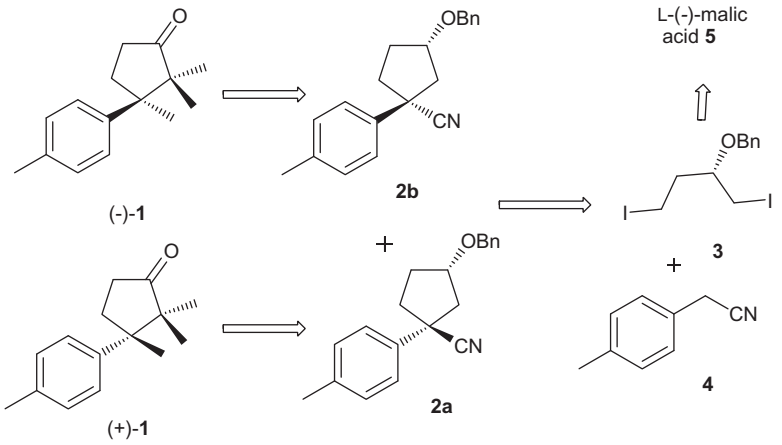
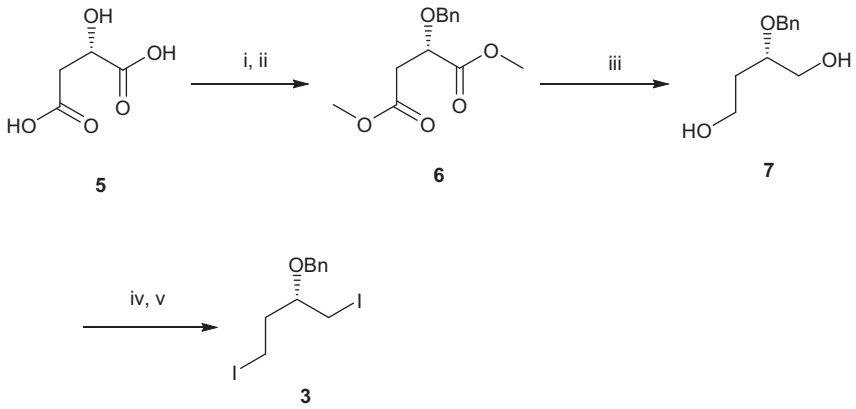
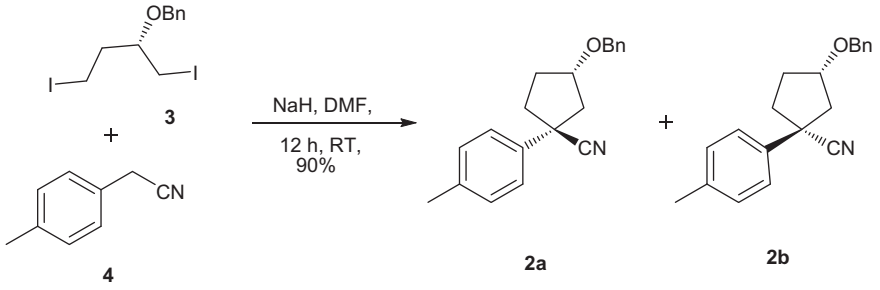


Scheme 1.



Scheme 2. Reagents and conditions: (i) $SOCl_2$, MeOH, RT, 24 h; (ii) Ag_2O, BnBr, EtOAc, RT, 6 h, 90%; (iii) $NaBH_4$, $CaCl_2$, EtOH, 2 h, 0 °C, 95%; (iv) Et_3N, MsCl, DCM, 0 °C, 6 h; (v) NaI, acetone, reflux, 4 h, 85% (over two steps).



Scheme 3.

colorless X-ray quality crystals were obtained. Since we knew that the absolute configuration of the L-malic acid used was (*S*), from single-crystal X-ray diffraction analysis[10] we could clearly ascertain that the absolute stereochemistry of the quaternary carbon of **2b** had an (*R*)-configuration (Fig. 2).

With the (*R,S*)-**2** configuration assigned for the polar diastereomer, the configuration of the other less polar isomer was assigned as (*S,S*)-**2**. This was confirmed by nOe experiments.[11]

Next, a set of functional group transformations were carried out separately on both diastereomers. Thus, cyanide **2a** was subjected to reduction using DIBAL-H to furnish the aldehyde, which was used as such for the next reaction without further purification. The crude aldehyde was subjected to Huang-Minlon[12] reaction conditions to give **8a** in 70% yield. Hydrogenolysis of **8a** was carried out using Pd/C as the catalyst to furnish the hydroxyl compound. The hydroxy compound was oxidized by using IBX in dry DMSO as a solvent to furnish 3,3-disubstituted cyclopentanone **9a** in 95% yield.[13] Finally, cyclopentanone **9a** was dimethylated using LiHMDS and methyliodide[3a,f,8] to afford (+)-α-cuparenone **1** in 70% yield (Scheme 4).

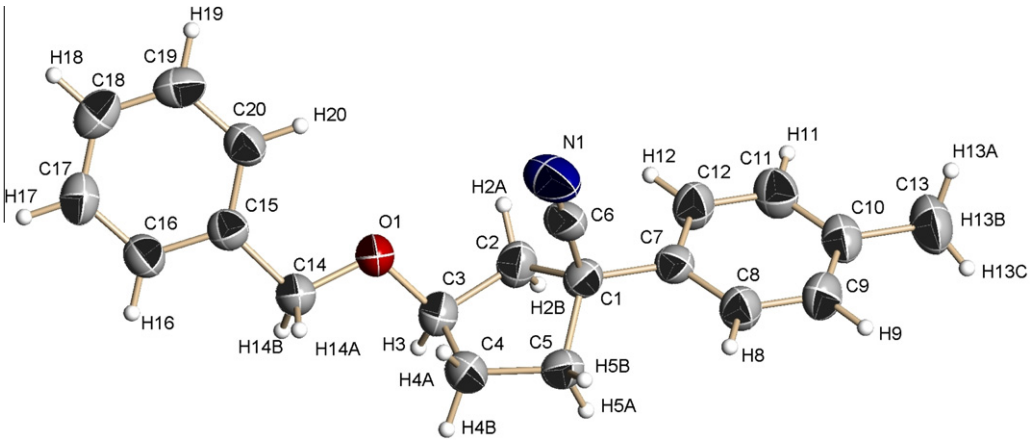
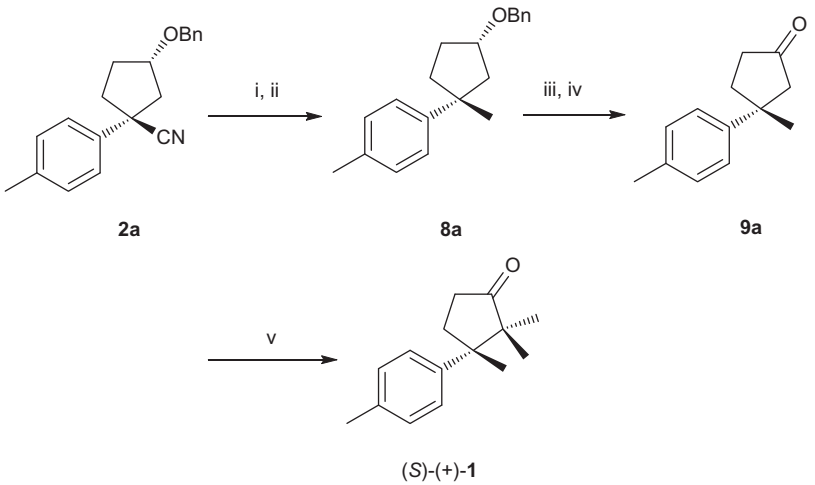


Figure 2. X-ray structure of polar diastereomer 2b.



Scheme 4. Reagents and conditions: (i) DIBAL-H, DCM, −78 °C, 1 h; (ii) NaOH, NH_2NH_2, ethylene glycol, 180 °C, 24 h, 70%; (iii) Pd-C, H_2, 60 psi, 1 h, MeOH; (iv) IBX, dry DMSO, 4 h, 95%; (v) LiHMDS, MeI, DME, HMPA, 3 h,70%.

3. Conclusion

The synthesis of both enantiomers of α-cuparenone was achieved in ten steps involving one diastereomeric separation, starting from L-malic acid **5** and 4-methyl benzyl cyanide **4**, to give (*S*)-(+)-**1** and (*R*)-(−)-**1** in ⩾99% ee and 15% overall yield.

4. Experimental section

4.1. General

Melting points were recorded using a Buchi B-540 or M-560 melting point apparatus in capillary tubes and are uncorrected; temperatures are in centigrade. IR spectra were recorded on a Perkin–Elmer Infrared Spectrophotometer Model 68B or on a Perkin–Elmer 1615 FT Infrared spectrophotometer. ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded on a Bruker spectrometer, using a 2:1 mixture of $CDCl_3$ and CCl_4 as solvent. The chemical shifts (δ ppm) and coupling constants (Hertz) are reported in the standard fashion with reference to chloroform, δ 7.26 (for ^1H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT-135 spectra. Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 elemental analyzer. Enantiomeric excesses of the products were determined by HPLC (Agilent) employing a chiralcel OD-H column (250 × 4.6 mm) or comparing the specific rotation of known compounds. The reaction progress was monitored by TLC analysis using thin layer plates precoated with silica gel 60 F_{254} (Merck) and visualized by fluorescence quenching or iodine or by charring after treatment with *p*-anisaldehyde. Merck's flash silica gel (200–400 mesh) was used for column chromatography. All small scale dry reactions were carried out using standard syringe-septum techniques. Low temperature reactions were carried out using a bath made of sodium chloride and ice. Dry DCM was prepared by distillation over phosphorous pentoxide or calcium hydride. Dry acetone was obtained by distillation over anhydrous potassium carbonate. Dry DMF and DMSO were prepared by distillation over calcium hydride. All other reagents and solvents were used as received from the manufacturer, unless otherwise specified. All air and water sensitive reactions were performed in flasks that were flame dried under a positive flow of argon and conducted under an argon atmosphere.

4.1.1. (*S*)-Dimethyl 2-(benzyloxy)succinate 6

L-(*S*)-Malic acid (5 g, 37.31 mmol) was dissolved in methanol (100 mL) and cooled to 0 °C. Thionyl chloride (5.95 mL, 82.08 mmol) was added dropwise over 30 min and then the solution was stirred at room temperature for 24 h. The solvent was evaporated almost to dryness and the residue was partitioned between dichloromethane (50 mL) and a saturated sodium bicarbonate solution (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, to give a colorless oil, which was used without further purification.

To a stirred solution of (*S*)-malate (6 g, 37.03 mmol) in EtOAc was added Ag_2O (12.83 g, 55.55 mmol) after which benzyl bromide (5.42 mL, 44.44 mmol) was added dropwise and the reaction mixture was stirred for 6 h. After completion the reaction mixture was filtered through a Celite pad, and the solution was concentrated under reduced pressure and purified by flash column chromatography using (10% EtOAc/hexane) as a eluent to furnish **6** (8.43 g, 90%) as a colorless oil. R_f (30% EtOAc/hexane) 0.5; $[\alpha]_D^{25} = -70.4$ (*c* 1.08, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3028, 2954, 1746, 1217, 756; ^1H NMR ($CDCl_3 + CCl_4$, 200 MHz): δ 2.78–2.81 (m, 2H), 3.69 (s, 3H), 3.78 (s, 3H), 4.39 (dd, *J* = 5.68 Hz, 1H), 4.54 (dd, *J* = 11.4 Hz, 1H), 4.78 (d, *J* = 11.4 Hz, 1H), 7.29–7.35 (m, 5H); ^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz): δ 37.67, 51.76, 52.01, 72.95, 74.38, 127.85, 128.0 (2C), 128.28 (2C), 137.2, 170.2, 171.53; MS (EI): *m*/*z* = 275 $(M+Na)^+$.

4.1.2. (*S*)-2-(Benzyloxy) butane-1,4-diol 7

Compound **6** (8.4 g, 33.20 mmol) was dissolved in ethanol (100 mL) and cooled to 0 °C. Calcium chloride was then added (14.74 g, 132.8 mmol) followed by the portionwise addition of sodium borohydride (4.91 g, 132.8 mmol) over 30 min. After the addition was complete, the reaction mixture was stirred for an additional 2 h. After completion, the reaction mixture was quenched by a 10% HCl solution and evaporated almost to dryness, then extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine solution and then dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash column chromatography using (50% EtOAc/hexane) as a eluent to furnish **7** (6.18 g, 95%). R_f (50% EtOAc/hexane) 0.3; $[\alpha]_D^{25} = -14.3$ (*c* 1.26, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3393, 2933, 2873, 1716, 1278; ^1H NMR ($CDCl_3 + CCl_4$, 200 MHz): δ 1.76–1.85 (m, 2H), 3.27 (br s, 2H), 3.53–3.77 (m, 5H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz): δ 33.99, 58.95, 63.60, 71.46, 77.56, 127.78 (3C), 128.42 (2C), 138.16; MS (EI): *m*/*z* = 219 $(M+Na)^+$.

4.1.3. (*S*)-(((1,4-Diiodobutan-2-yl)oxy)methyl)benzene 3

To a stirred solution of dihydroxy **7** (6 g, 30.61 mmol) in dry DCM (60 mL) was added Et_3N (14.37 mL, 101.02 mmol) at 0 °C, followed by the dropwise addition of mesyl chloride (6.23 mL, 76.52 mmol). The reaction mixture was stirred at 0 °C for 6 h under a nitrogen atmosphere. After completion of the reaction, the reaction mixture was diluted with dichloromethane and washed with a saturated solution of sodium bicarbonate (50 mL) and water. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the *O*-mesyl compound (10.8 g, crude).

To a solution of the *O*-mesyl compound (10 g, 28.40 mmol) in anhydrous acetone (150 mL) was added sodium iodide (21.16 g, 142.04 mmol) and the reaction mixture was heated at 70 °C for 4 h under a nitrogen atmosphere. After completion of the reaction (monitored by TLC), it was cooled to room temperature, evaporated almost to dryness then extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, and purified by flash column chromatography using (20% EtOAc/hexane) as eluent to furnish **3** (10.04 g, 85%). R_f (20% EtOAc/hexane) 0.6; $[\alpha]_D^{25} = -62.7$ (*c* 1.02, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3029, 2861, 1087, 1062, 737, 697; ^1H NMR ($CDCl_3 + CCl_4$, 200 MHz): δ 2.08–2.18 (m, 2H), 3.25-3.33 (m, 4H), 3.42–3.53 (m, 1H), 4.50 (d, *J* = 11.2 Hz, 1H), 4.72 (d, *J* = 11.2 Hz, 1H), 7.31–7.39 (m, 5H); ^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz): δ 2.12, 8.69, 38.72, 71.76, 76.90, 127.94, 127.98 (2C), 128.47 (2C), 137.53.

4.1.4. (1*S*,3*S*)-3-(Benzyloxy)-1-(*p*-tolyl)cyclopentanecarbonitrile 2a

To a solution of 60% NaH (458 mg, 19.08 mmol) (washed with dry petroleum ether, 2–3 times) in dry DMF was added 4-methyl benzyl cyanide **4** (1 g, 7.63 mmol) in dry DMF (10 mL) at 0 °C and stirred for 30 min. Next, 1,4-diiodo compound **3** (3.16 g, 7.63 mmol) in DMF (15 mL) was added dropwise over 20 min. and then the reaction was stirred for 12 h at room temperature. Upon completion of the reaction, it was quenched by the addition of saturated ammonium chloride solution, extracted with ethyl acetate (3 × 40 mL), and washed with water then brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to furnish **2a** and **2b** as a diastereomeric mixture (1:1) in 90% yield. The diastereoisomers were separated by column chromatography using (2% EtOAc/hexane) as eluent to afford compound **2a** (0.95 g, 45%) as an oil and compound **2b** (0.95 g, 45%) as a solid (melting point 82 °C). R_f (10% EtOAc/hexane) of 0.4 and 0.3 respectively; $[\alpha]_D^{25} = -3.5$ (*c* 1.73, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 2924, 2233, 1274, 813,755; ^1H NMR ($CDCl_3 + CCl_4$, 200 MHz): δ 2.12–2.32 (m, 4H), 2.42–2.51(m,1H), 2.85 (m,1H), 3.07 (s, 3H), 4.31–4.41 (m, 1H), 4.5 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 7.16–7.44 (m, 9H); ^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz): δ 20.98, 31.92, 39.49, 46.53, 47.21, 71.15, 79.12, 124.27, 125.87, 127.57, 127.7, 128.43, 129.51, 136.77, 137.43, 138.07; MS (EI): *m*/*z* = 292 $(M+H)^+$, 314 $(M+Na)^+$; Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81%. Found: C, 83.14; H, 7.74; N, 4.64%.

4.1.5. (1*R*,3*S*)-3-(Benzyloxy)-1-(*p*-tolyl)cyclopentanecarbonitrile 2b

$[\alpha]_D^{25} = +8.4$ (*c* 6.68, $CHCl_3$); ^1H NMR ($CDCl_3 + CCl_4$, 200 MHz): δ 2.11–2.23 (m, 3H), 2.37 (s, 3H), 2.28–2.38 (m, 1H), 2.63–2.75 (m, 2H), 4.20–4.29 (m, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 7.16–7.38 (m, 9H); ^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz): δ 20.86, 32.18, 38.84, 44.76, 46.15, 70.81, 79.01, 124.26, 125.5(2C), 127.49(2C), 128.3(2C), 129.49(2C), 137.28, 137.42, 138.10.

4.1.6. 1-((1*R*,3*S*)-3-(Benzyloxy)-1-methylcyclopentyl)-4-methylbenzene 8a

Compound **2a** (0.9 g, 3.09 mmol) was taken in dry DCM (10 mL) under an argon atmosphere and the temperature was lowered to −78 °C. Next, DIBAL-H (6.18 mmol, 6.14 mL, 1 M, solution in toluene) was added dropwise and left to stir at the same temperature until completion of the reaction (1 h). After completion of the reaction, it was quenched at −78 °C by the dropwise addition of 2 M HCl and then warmed to room temperature. The organic layer was separated and the aqueous layer extracted with DCM (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the aldehyde, which was used as such without further purification.

To a stirred solution of crude aldehyde (0.9 g, 3.07 mmol) in diethylene glycol (10 mL) were added hydrazine monohydrate (0.59 mL, 12.28 mmol) and sodium hydroxide (0.49 g, 12.28 mmol). The reaction mixture was heated at reflux for 24 h. After completion of the reaction, it was diluted with water (10 mL) and extracted using ethyl acetate (3 × 10 mL). The com-

bined organic layers were then washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford a residue which was purified by flash column chromatography using 2% EtOAc/hexane as eluent to give compound **8a** (0.6 g, 70%) yield. R_f (5% EtOAc/hexane) 0.5; $[\alpha]_D^{25} = -29.7$ (*c* 1.82, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 2956, 1515, 1454, 815, 734; ^1H NMR ($CDCl_3 + CCl_4$, 200 MHz): δ 1.29 (s, 3H), 1.85–2.36 (m, 6H), 2.38 (s, 3H), 4.23–4.34 (m, 1H), 4.54 (s, 2H), 7.12–7.38 (m, 9H); ^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz): δ 20.95, 30.20, 31.25, 38.12, 45.64, 46.82, 70.86, 80.18, 125.70(2C), 127.34, 127.53(2C), 128.27(2C), 128.78(2C), 134.69, 138.84, 148.14; MS (EI): $m/z = 303$ $(M+Na)^+$; Anal. Calcd for $C_{20}H_{24}O$: C, 85.67; H, 8.63%. Found: C, 85.85; H, 9.03%.

4.1.7. 1-((1*S*,3*S*)-3-(Benzyloxy)-1-methylcyclopentyl)-4-methylbenzene 8b

$[\alpha]_D^{25} = +18.1$ (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3 + CCl_4$, 200 MHz): δ 1.43 (s, 3H), 1.93–2.06 (m, 5H), 2.34 (s, 3H), 2.28–2.39(m, 1H), 4.08–4.15 (m, 1H), 4.50 (s, 2H), 7.08-7.22 (m, 4H), 7.27–7.36 (m, 5H); ^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz): δ 20.91, 31..02, 31.79, 38.34, 45.84, 46.29, 71.04, 80.36, 125.65(2C), 127.37, 127.55(2C), 128.32(2C), 128.85(2C), 134.80, 138.87, 147.74.

4.1.8. (*R*)-3-Methyl-3-(*p*-tolyl)cyclopentanone 9a

To a well stirred solution of compound **8** (500 mg, 1.78 mmol) in MeOH (10 mL), was added 10% Pd/C (20 mg). The resulting reaction mixture was kept on a shaker at 60 psi under a hydrogen atmosphere for 1 h. After the disappearance of the starting material, the reaction mixture was filtered on Celite and the residue was washed with MeOH (3 × 20 mL). The solvent was removed under reduced pressure to afford the alcohol, which was used as such without further purification.

To a stirred solution of alcohol (330 mg, 1.78 mmol) in dry DMSO (10 mL) was added IBX (982 mg, 3.56 mmol) and left to stir at room temperature for 4 h. After completion of the reaction, the reaction mixture was diluted with water and extracted using diethylether (3 × 20 mL). The combined organic layers were then washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford a residue which was purified by using flash column chromatography using (10% EtOAc/hexane) as eluent to afford compound **9** (310 mg, 95%) as a white solid, melting point 56–58 °C. R_f (10% EtOAc/hexane) 0.3; $[\alpha]_D^{25} = +12.3$ (*c* 1.62, $CHCl_3$) {lit. $[\alpha]_D^{25} = +13.3$ (*c* 4.00, $CHCl_3$)};[3f] IR ($CHCl_3$, cm^{-1}): 3019, 1720, 1614, 1246, 815,; ^1H NMR ($CDCl_3 + CCl_4$, 200 MHz): δ 1.39 (s, 3H), 2.21–2.29 (m, 2H), 2.35 (s, 3H), 2.35–2.37 (m, 2H), 2.46 (d, *J* = 17. 7 Hz, 1H), 2.65 (d, *J* = 17.7 Hz, 1H), 7.12–7.22 (m, 4H); ^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz): δ 20.7, 29.3, 35.8, 36.5, 43.3, 52.1, 125.1, 129.0, 135.5, 145.3, 217.8; MS (EI): $m/z = 211$ $(M+Na)^+$.

4.1.9. (*S*)-3-Methyl-3-(*p*-tolyl)cyclopentanone 9b

$[\alpha]_D^{25} = -10.0$ (*c* 1.05, $CHCl_3$)

4.1.10. (*S*)-2,2,3-Trimethyl-3-*p*-tolylcyclopentanone 1

To a stirred solution of ketone **9** (200 mg, 1.0 mmol) in dry DME (10 mL) was added LiHMDS (371 mg, 2.2 mmol) and a catalytic amount of HMPA (0.25 mL). This mixture was stirred for a few minutes after which methyl iodide (0.325 mL, 5.0 mmol) in dry DME (2 mL) was added dropwise and the reaction mixture was stirred for 3 h. After completion, the reaction mixture was quenched by a saturated ammonium chloride solution, extracted with ethyl acetate (3 × 10 mL) washed with a brine solution and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure and purified by flash column chromatography using (5% EtOAc/hexane) as eluent to furnish the desired target molecule **1** (152 mg, 70%) as a solid, melting point 56 °C (lit. 52–53 °C). R_f (10% EtOAc/hexane) 0.4; $[\alpha]_D^{25} = +170.1$ (*c* 1.08, $CHCl_3$)[14]; IR ($CHCl_3$, cm^{-1}): 2960, 1725, 1510, 1460, 815; ^1H NMR ($CDCl_3 + CCl_4$, 200 MHz): δ 0.61 (s, 3H), 1.17 (s, 3H), 1.26 (s, 3H), 1.86–1.97 (m, 1H), 2.35 (s, 3H), 2.41–2.52 (m, 2H), 2.58-2.71 (m, 1H), 7.14–7.30 (m, 4H); ^{13}C NMR ($CDCl_3 + CCl_4$, 50 MHz): δ 18.3, 20.8, 22.1, 25.3, 29.6, 33.7, 48.3, 53.2, 126.3, 128.9, 135.8, 141.9, 222.7; MS (EI): $m/z = 216$ $(M+H)^+$.

4.1.11. (*R*)-2,2,3-Trimethyl-3-*p*-tolylcyclopentanone 1

$[\alpha]_D^{25} = -162.7$ (*c* 1.02, $CHCl_3$).[14]

Acknowledgments

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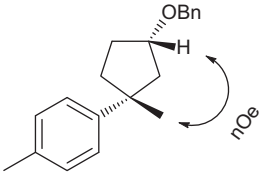
10. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 897216. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +044 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
11. The stereochemistry of compound **8a** was confirmed by 2D NOESY spectroscopic analysis



(1*R*,3*S*)-**8a**

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12. (a) Huang-Minlon *J. Am. Chem. Soc.* **1946**, *68*, 2487; (b) Huang-Minlon *J. Am. Chem. Soc.* **1949**, *71*, 3301.
13. Confirmed by comparing the specific rotation with the literature values. 3f HPLC on a CHIRALCEL OD-H column was used to determine the enantiomeric purity of (+)-**9** and (−)-**9** by comparison with racemic **9**, which was synthesized using the same reaction sequence using DL-malic acid.
14. The specific rotations for both enantiomers matches with the literature values; the reported specific rotations for natural (+) and (−)-α-cuparenone[1,2] in $CHCl_3$ are +177.1 and −169.9, respectively.