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A short, efficient synthesis of the chiral auxiliary (+)-8-phenyl*neo*menthol

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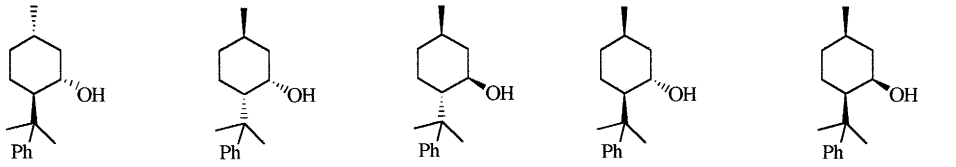
Abstract

(+)-8-Phenyl*neo*menthol **2**, the structure of which was confirmed by X-ray analysis of its 3,5-dinitrobenzoate, was efficiently prepared from commercially available (−)-8-phenylmenthol **3** by oxidation with the Sarett reagent, followed by L-Selectride reduction of the (+)-8-phenylmenthone **6** thus formed.

Keywords: terpene alcohols; chiral auxiliaries; phenyl*neo*menthol; Sarett oxidation; L-Selectride.

Since the introduction of (+)-8-phenylmenthol **1** as a chiral auxiliary,[1] other stereomeric phenylmenthols, among them (+)-8-phenyl*neo*menthol **2**,[2] have also proved useful in asymmetric synthesis.[3]



1 (+)-8-Phenylmenthol; **2** (+)-8-Phenyl*neo*menthol; **3** (-)-8-Phenylmenthol; **4** (+)-8-Phenyl*iso*menthol; **5** (-)-8-Phenyl*isoneo*menthol

In all previously reported syntheses, the crude product is a mixture of compound **2** with diastereomers **3**, **4**, and/or **5**, and isolation of **2** leads to unavoidable loss of the desired product. For instance, $NaBH_4$ reduction of an equilibrium mixture of 8-phenylmenthone and 8-phenyl*iso*menthone[6] yielded a 68:19:13 mixture of **2**, **3** and **5**, and subsequent preparative HPLC separation followed by Kugelrohr distillation afforded the desired pure isomer **2** in 47% yield.[2] More recent preparations also failed to obtain **2** without accompanying stereomers.[7]

We have now found that compound **2** can be rapidly and efficiently obtained in good yield by starting from the (−)-8-phenylmenthol **3** (now commercially available from Aldrich; see Scheme 1). Oxidation of

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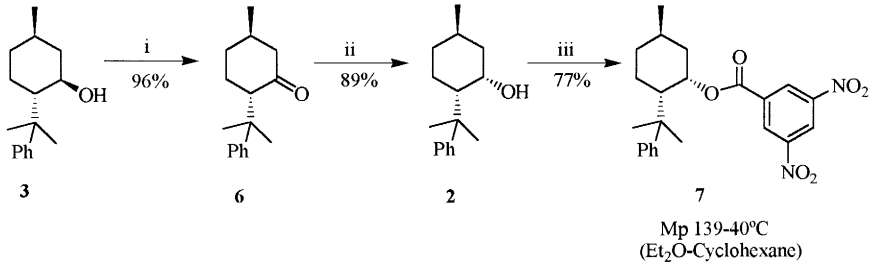
3 in Sarett conditions,[8] followed by reduction of the resulting (+)-8-phenylmenthone **6** with L-Selectride in THF[9] affords **2**, virtually free of diastereomers as shown by ^{1}H NMR spectra. Both **6** and **2** can be used for synthetic purposes without further purification (the chromatographic procedures described below were performed only to obtain analytical samples). The structure of **2** was confirmed via the 3,5-dinitrobenzoate **7**, which was prepared by treatment of the corresponding alcohol with 3,5-dinitrobenzoyl chloride in presence of Et_3N and DMAP.[10] Slow recrystallization of the solid thus obtained from Et_2O in the presence of cyclohexane led to crystals of **7** suitable for X-ray diffractometric analysis.[11,4,5]



Scheme 1. Reagents: (i) CrO_3, py, CH_2Cl_2, 45 min, 0°C; (ii) L-Selectride, THF, 4 h, 0°C; (iii) 3,5-dinitrobenzoyl chloride, Et_3N, DMAP, THF, 5 h, reflux

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3. For use of (−)-8-phenylmenthol **3** and (+)-8-phenyl*iso*menthol **4** see Ref. 4 and 5, respectively
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8. (2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone **6**: To a solution of pyridine (24.9 g, 311 mmol) in CH_2Cl_2 (260 mL) at 0°C were added, in small portions CrO_3 (15.48 g, 155 mmol), then dropwise a solution of **3** (6 g, 25.8 mmol) in CH_2Cl_2 (25 mL). The resulting mixture was stirred for 45 min, filtered on Celite, the solids being washed with Et_2O (4×90 mL). The pooled organic extracts were concentrated to 50 mL, then washed with water (100 mL) and saturated brine (100 mL), and dried (Na_2SO_4). Evaporation of the solvents afforded an oil (6.4 g) which upon flash chromatography [silica gel 60 (210 g); hexane:AcOEt, 9:1] gave **6** as a colourless oil (5.7 g, 96%). $[\alpha]_D^{23}$ −49 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 1709 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 0.97 (d, 3H, *J*=6 Hz, 5-CH_3), 1.41 and 1.47 (2s, 6H, 8-$(CH_3)_2$), 1.50–1.89 (m, 5H), 1.91–2.06 (m, 1H, 6-H), 2.22–2.27 (m, 1H, 6-H), 2.61–2.70 (m, 1H, 2-H), 7.13–7.37 (m, 5H$_{arom}$). ^{13}C NMR (75 MHz,

$CDCl_3$): 22.73, 24.43, 26.91, 29.45, 35.09, 36.69, 39.43 (C-8), 52.76, 59.94, 125.91 (C-4′), 126.16 (C-2′+C-6′), 128.38 (C-3′+C-5′), 150.31 (C-1′), 211.92 (C-1).

9. (1*S*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol **2**: A solution of **6** (8 g, 34.9 mmol) in THF (35 mL) was added dropwise to a 1.0 M solution of L-Selectride in THF (52 mL, 52 mmol) at 0°C, and the resulting mixture was stirred for 4 h at 0°C. Aqueous 3 M NaOH (11 mL, 33 mmol) was then added dropwise followed by slow addition of 30% H_2O_2 (18 mL, 180 mmol). After a further 30 min stirring at room temperature the mixture was extracted with Et_2O (4×30 mL), the combined organic phases being washed with water (2×20 mL) and dried (Na_2SO_4). The solvents were removed in vacuo to leave an oil, which was purified by flash chromatography [silica gel 60 (220 g), hexane:AcOEt, 9:1] to afford **2** as a colourless oil (7.21 g, 89%). $[\alpha]_D^{23}$ +34 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3464 (OH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 0.84 (d, 3H, *J*=6 Hz, 5-CH_3), 0.88–1.11 (m, 2H), 1.38 and 1.40 (2s, 6H, 8-$(CH_3)_2$), 1.43–1.76 (m, 6H), 3.86 (virtual s, 1H, 1_{eq}-H), 7.18 (td, 1H, *J*=7 Hz, 1 Hz, 4′-H), 7.26–7.33 (m, 2H, 3′-H+5′-H), 7.37–7.40 (m, 2H, 2′-H+6′-H). ^{13}C NMR (75 MHz, $CDCl_3$): 21.75 (C-3), 22.63 (C-7), 26.26 (C-9), 26.53 (C-5), 28.05 (C-10), 36.06 (C-4), 40.60 (C-8), 44.26 (C-6), 52.71 (C-2), 68.62 (C-1), 125.92 (C-4′), 126.59 (C-2′+C-6′), 128.42 (C-3′+C-5′), 150.31 (C-1′).
10. (1′*S*,2′*S*,5′*R*)-5′-Methyl-2′-(1-methyl-1-phenylethyl)cyclohexyl 3,5-dinitrobenzoate **7**: 3,5-Dinitrobenzoyl chloride (3.22 g; 14 mmol, freshly recrystallized from CCl_4) was added at once to a solution of **2** (2.30 g, 10.37 mmol), anhydrous Et_3N (1.98 mL, 14 mmol) and DMAP (20 mg) in anhydrous THF (200 mL) and the mixture was refluxed for 5 h with stirring, under an argon atmosphere. After cooling, the resulting mixture was concentrated to 20 mL, diluted with CH_2Cl_2 (80 mL) and washed with saturated $NaHCO_3$ solution (3×100 mL) and saturated brine (100 mL). The organic layer was dried (Na_2SO_4), and the solvents were removed in vacuo to leave an oily residue, which was chromatographed [silica gel 60 (100 g), hexane:AcOEt, 9:1] affording **7** as a white solid (3.25 g, 77%). Mp 139–140°C (Et_2O-cyclohexane). $[\alpha]_D^{23}$ +114 (*c* 1.0, $CHCl_3$). IR (KBr) ν_{max}: 1719 (CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 0.83–0.86 (d, 3H, *J*=7 Hz, 5′-CH_3), 1.02–1.25 (m, 2H), 1.36 and 1.41 (2s, 6H, 8′-$(CH_3)_2$), 1.58–1.99 (m, 6H), 5.45 (virtual s, 1H, $1'_{eq}$-H), 6.91 (t, 1H, *J*=7 Hz, 4′′-H), 7.11 (t, 2H, *J*=8 Hz, 3′′-H+5′-H), 7.24 (d, 2H, *J*=7 Hz, 2′′-H+6′′-H), 8.83 (d, 2H, *J*=2 Hz, 2-H+6-H), 9.18 (t, 1H, *J*=2 Hz, 4-H). ^{13}C NMR (75 MHz, $CDCl_3$): 22.29 (C-3′), 23.26 (C-7′), 26.30 (C-5′), 27.51 (C-9′), 27.88 (C-10′), 35.65 (C-4′), 40.19 (C-6′), 40.34 (C-8′), 52.19 (C-2′), 74.27 (C-1′), 122.47 (C-4), 125.76 (C-4′′), 126.63 (C-2′′+C-6′′), 128.40 (C-3′′+C-5′′), 129.52 (C-2+C-6), 134.80 (C-1), 148.40 (C-1′′), 148.87 (C-3+C-5), 161.71 (C(O)).
11. Results of this analysis will be published elsewhere.