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A new, convenient synthesis of the chiral auxiliary (+)-8-phenyl*iso*menthol

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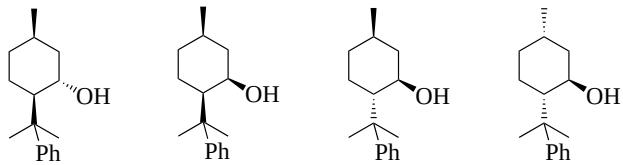
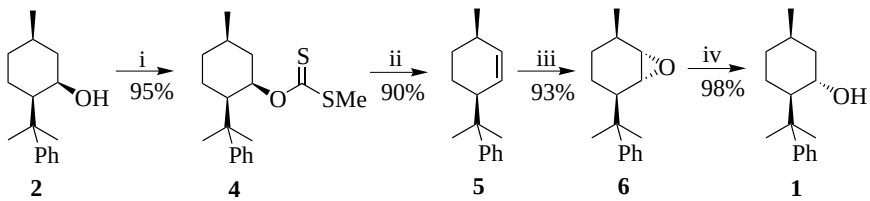
Abstract—A new, straitghtforward and efficient method for preparing (+)-8-phenyl*iso*menthol **1** from its diastereomer (+)-8-phenyl*isoneo*menthol **2** is described. Conversion of **2** to (+)-8-phenyl-2-menthene **5**, followed by oxidation to the corresponding (+)-*trans*-epoxide **6** and reduction of **6** with $LiBEt_3H$ afforded **1** in 78% overall yield. © 2001 Elsevier Science Ltd. All rights reserved.

(−)-8-Phenylmenthol (**3**) is one of the most widely employed recoverable chiral auxiliaries, being used to achieve enantioselectivity in numerous syntheses.[1] Its popularity is due both to the good enantiomeric excesses it affords (especially in face differentiation processes, in which its capacity for faceselective stacking via π interactions is decisive) and to its ready availability (it can be prepared in good yields from the inexpensive reagent (*R*)-(+)-pulegone).[2] By contrast, the high cost of its enantiomer (+)-8-phenylmenthol, *ent*-**3**, which in principle is just as attractive as **3** as a chiral auxiliary, has resulted in its only rarely having been used as such.

Whitesell noted in 1986 that since the configuration of *ent*-**3** in the region responsible for chiral induction (C1 and C2) is the same as that of its diastereomer (+)-8-phenyl*iso*menthol **1**, **1** ought to have the same effects as *ent*-**3** when used as a chiral auxiliary; and he verified this prediction for Diels–Alder and ene reactions.[3] Until recently, however, **1** has only been obtained as a side-product in the standard preparation of **3** from (*R*)-(+)-pulegone, and hence, in very low yield (6%) and only after tiresome separation of diastereomers.



Our interest in the preparation of 3-substituted 2-azabicyclo[2.2.1]hept-5-enes, which are important intermediates in the syntheses of compounds of pharmaceutical and/or biological relevance,[4] has led us to investigate the efficiencies of all the various stereomers of 8-phenylmenthol as chiral auxiliaries in aza-Diels–Alder reactions. To this end we recently developed efficient syntheses affording (−)-8-phenyl*isoneo*menthol (**2**) and



Scheme 1. *Reagents and conditions*: (i) CS_2, Me_2SO_4, ^{n}BuLi, THF; (ii) 200°C; (iii) *m*-CPBA 70%, Cl_2CH_2; (iv) $LiBEt_3H$ 1 M, THF.

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(+)-8-phenyl*neo*menthol in 40% yields from (*R*)-(+)-pulegone, and we obtained **1** in 20% yield from **2** by isolation from the mixture of four diastereomeric 8-phenylmenthols produced by Sarett oxidation of **2** and reduction of the resulting (+)-8-phenyl*iso*menthone with Na in ^{i}PrOH.[5] We have now developed the following new, very efficient stereospecific route from **2** to **1**.

8-Phenylmenthol **2** was easily converted to the *S*-methyl xanthate **4**,[6] which was then transformed into 8-phenyl-2-menthene **5** by pyrolytic *syn* elimination.[7] *trans*-Epoxide **6** was obtained in good yield by oxidation of **5** with *m*-CPBA,[8] which took place with high facial stereoselectivity because of the great difference in steric hindrance between the two faces of the C=C bond. Finally, clean reduction of **6** with $LiBEt_3H$ (Super-Hydride®), which occurs at the less-hindered position, gave (+)-8-phenyl*iso*menthol **1** (Scheme 1).[9]

Acknowledgements

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6. **(1*R*,2*R*,5*R*)-*S*-Methyl-*O*-[5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl]dithiocarbonate, 4**: To a solution of **2** (1 g, 4.3 mmol) in THF (10 mL) at −60°C under argon was added a 2.5 M solution of butyllithium in hexanes (1.89 mL, 1.1 equiv.) followed by CS_2 (2.15 mL) and Me_2SO_4 (0.45 mL, 1.1 equiv.). The mixture was allowed to warm to room temperature and after a further 4 h was washed with Et_2O (80 mL) and H_2O (80 mL). The combined organic phases were washed again with water (100 mL) and brine (80 mL), and after drying (Na_2SO_4) the solvents were removed in vacuo, leaving a solid that upon purification by flash chromatography [silica gel 60; 9:1 hexane/Et_2O] afforded **4** as a white solid (1.20 g; 95%). Mp 71–73°C. $[\alpha]_D^{23}$ +41.0 (*c* 1.0, $CHCl_3$). IR (KBr) ν_{max}: 2921, 1495, 1455, 1383, 1292, 1220, 1146, 1111, 1050, 768, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 0.98 (d, 3H, $J=7.4$ Hz, 5-CH_3), 1.33 and 1.35 (2s, 6H, C-$(CH_3)_2$), 1.39–2.08 (m, 8H), 2.52 (s, 3H, SCH_3), 5.68 (s, 1H, 1-H), 7.15–7.20 (m, 1H, ArH), 7.28–7.32 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): 18.06 (CH_2), 19.25 (SCH_3), 20.74 (CH_3), 26.35 (CH_3), 26.45 (CH_3), 26.92 (CH), 32.38 (CH_2), 35.61 (CH_2), 40.61 (C-8), 52.54 (C-2), 82.29 (C-1), 126.02 (C-4′), 126.51 (C-2′+C-6′), 128.50 (C-3′+C-5′), 149.63 (C-1′), 214.47 (C(S)).
7. **(3*R*,6*S*)-3-Methyl-6-(1-methyl-1-phenylethyl)-1-cyclohexene, 5**: Compound **4** (1.1 g, 3.79 mmol) was heated for 1 h at 200°C (without any solvent). The residue was purified by flash chromatography [silica gel 60; hexane] affording **5** as an oil (0.73 g; 90%). $[\alpha]_D^{23}$ +71.5 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3019, 2958, 2867, 1559, 1495, 1457, 1365, 1311, 1240, 1098, 1030, 961, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 0.95 (d, 3H, $J=7.1$ Hz, 3-CH_3), 1.29 and 1.31 (2s, 6H, C-$(CH_3)_2$), 1.33–1.42 (m, 3H), 1.61–1.66 (m, 1H), 2.14–2.15 (m, 1H), 2.38–2.40 (m, 1H), 5.47 (d×t, 1H, $J_d=10.3$ Hz, $J_t=1.7$ Hz, 2-H), 5.66 (d×t, 1H, $J_d=10.3$ Hz, $J_t=3.2$ Hz, 1-H), 7.17–7.22 (m, 1H, ArH), 7.26–7.39 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): 20.65 (CH_3), 21.36 (CH_2), 25.60 (CH_3), 25.77 (CH_3), 29.13 (CH), 29.65 (CH_2), 40.64 (C-8), 46.70 (CH), 125.83 (C-4′), 126.54 and 126.61 (C-2′+C-6′), 128.30 and 128.35 (C-3′+C-5′), 134.75 (C-1+C-2), 150.17 (C-1′).
8. **(1*R*,2*S*,3*R*,6*R*)-1,2-Epoxy-3-methyl-6-(1-methyl-1-phenylethyl)cyclohexane, 6**: A solution of **5** (0.59 g, 2.75 mmol) in dry Cl_2CH_2 (4 mL) was added dropwise under argon to a solution of 70% *m*-CPBA (0.85 g, 3.40 mmol) in dry Cl_2CH_2 (10 mL) at 0°C. After stirring for 3 h at room temperature the mixture was treated with a saturated aqueous solution of $NaSO_3H$ (80 mL) and extracted with Cl_2CH_2 (3×80 mL). The combined organic phases were washed with saturated K_2CO_3 (3×90 mL) and brine (80 mL), and after drying (Na_2SO_4) the solvents were removed in vacuo, affording **6** as a colourless oil (0.59 g; 93%). $[\alpha]_D^{23}$ +30.2 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3057, 2962, 1598, 1496, 1444, 1369, 1128, 1032, 930, 800, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 1.00 (d, 3H, $J=7.2$ Hz, 3-CH_3), 1.03–1.27 (m, 3H), 1.33 and 1.41 (2s, 6H, C-$(CH_3)_2$), 1.54–1.63 (m, 1H), 2.14–2.27 (m, 2H, 3-H and 6-H), 2.79–2.87 (m, 2H, 1-H and 2-H), 7.16–7.22 (m, 1H, ArH), 7.29–7.41 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): 15.80 (CH_3), 17.31 (CH_2), 24.74 (CH_2), 25.53 (CH_3), 26.27 (CH_3), 27.23 (CH), 40.60 (C-8), 44.71 (CH), 54.36 (CH), 58.19 (CH), 126.19 (C-4′), 126.49 (C-2′+C-6′), 128.60 (C-3′+C-5′), 149.16 (C-1′).
9. **(1*S*,2*R*,5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexanol, 1**: A 1.0 M solution of lithium triethylborohydride in dry THF (4.3 mL, 10 equiv.) was added under argon, at room temperature and in one dose, to a solution of **6** (100 mg, 0.43 mmol) in 5 mL of the same solvent. The mixture was cooled to 0°C, treated with 50 mL of 5% NaOH solution followed by 25 mL of 3% H_2O_2, and extracted with Et_2O (3×50 mL). The combined organic phases were washed with brine (80 mL), and after drying (Na_2SO_4) the solvents were removed in vacuo, leaving an oil that upon purification by flash chromatography [silica gel 60; 9:1 hexane/Et_2O] afforded **1** as a colourless oil (98 mg; 98%). $[\alpha]_D^{23}$ +11.5 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3566, 3402, 3087, 3057, 2921, 1601, 1495, 1444, 1380, 1343, 1155, 1061, 1031, 1014, 972, 763, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 0.93 (d, 3H, $J=7.2$ Hz, 5-CH_3), 1.31 and 1.43 (2s, 6H, C-$(CH_3)_2$), 1.20–1.55 (m, 5H), 1.61–1.77 (m, 2H), 1.97–2.05 (m, 1H), 3.76 (d×t, $J_t=9.7$ Hz, $J_d=4.3$ Hz, 1_{ax}-H), 7.15–7.21 (m, 1H, 4′-H), 7.29–7.34 (m, 2H, 3′-H+5′-H), 7.38–7.41 (m, 2H, 2′-H+6′-H). ^{13}C NMR ($CDCl_3$): 19.08 (CH_3), 21.65 (CH_2), 24.91 (CH_3), 28.06 (CH), 28.83 (CH_3), 31.88 (CH_2), 40.30 (C-8), 42.24 (CH_2), 55.39 (CH), 69.18 (C-1), 126.18 (C-4′+C-2′+C-6′), 128.80 (C-3′+C-5′), 150.70 (C-1′).