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Anticholinergic Agents 4.* Stereocontrolled Synthesis of Fluorinated Acetylcholine Antagonists; Syntheses of the Two 1-Cyclohexyl-1-(4-fluorophenyl)-3-piperidyl-1-propanols and their Methiodides

Peter Sjö and Arne Jørgen Aasen

Department of Pharmacy, University of Oslo, P.O. Box 1068, Blindern, N-0316 Oslo 3, Norway

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Four new putative muscarinic antagonists, (*R*)-(−)- and (*S*)-(+)-1-cyclohexyl-1-(4-fluorophenyl)-3-piperidyl-1-propanol and their methiodides, have been synthesised. Absolute configurations have been assigned on the basis of the anticipated chirality of the products of the Sharpless asymmetric epoxidation reaction.

At least four subtypes of muscarinic receptor (M_1, M_2, M_3, and M_4) can now be discriminated on the basis of radioligand binding experiments[1–3] and pharmacological studies employing a number of selective antagonists.[4,5] Data obtained during recent years suggest that the muscarinic receptor subtypes can exert a high degree of stereoselectivity.[5–12] Fluorinated muscarinic antagonists have proved to be valuable tools in muscarinic receptor research. Several racemic compounds are available and have found widespread use in the classification of such receptor subtypes.[13]

The enantiomers of the drug trihexyphenidyl hydrochloride (**14**) have been used extensively for muscarinic receptor studies.[14] Its 4-fluorophenyl analogues possess a more acidic hydroxy group and would be expected to exhibit binding properties different from the four-binding site receptor model postulated by Waelbroeck *et al.*[8] In this paper we describe the syntheses of the two antipodes of 1-cyclohexyl-1-(4-fluorophenyl)-3-piperidyl-1-propanol and their methiodides.

Results and discussion

So far, the synthesis of muscarinic antagonists possessing crowded, enantiomerically pure quaternary carbinolic centres, has been performed by fractional crystallisation of racemates employing various chiral amines or acids as resolving agents.[15] In this paper we describe the synthesis of such compounds using chelation-controlled addition of a Grignard reagent to an optically active epoxy ketone.[16]

Synthesis. The intermediate epoxy ketone **4** was prepared in four steps from cyclohexanecarbaldehyde. This aldehyde reacted with lithium trimethylsilylacetylide to the racemic propargylic alcohol **1** which was stereospecifically reduced to the corresponding allylic alcohol (*E*)-**2** by treatment with Red-Al in diethyl ether (Scheme 1).[17] The racemic allylic alcohol (*E*)-**2**, was kinetically resolved by Sharpless asymmetric epoxidation[18,19] with (+)-diisopropyl L-tartrate as chiral auxiliary, to a mixture of (*R*)-(−)-**2** and the optically active epoxy alcohol (1*S*,2*S*,3*S*)-(+)-**3**. The mixture was readily separated by flash chromatography on triethylamine-deactivated silica. Swern oxidation[20] furnished the epoxy ketone (2*S*,3*S*)-(+)-**4**, which was converted with 4-fluorophenylmagnesium bromide into the epoxy alcohol (1*R*,2*S*,3*S*)-(−)-**5**. Owing to coordination of magnesium to the epoxy and the carbonyl oxygens the Grignard reagent adds to the carbonyl group in a diastereoselective manner in agreement with Cram's rule, see Fig. 2.[16,21] The diastereomeric alcohol was not detected on analysis of the crude reaction mixture with capillary-GC. The enantiomeric epoxy alcohol (1*S*,2*R*,3*R*)-(+)-**5** was prepared in the same manner from the allylic alcohol (*R*)-(−)-**2** with (−)-diisopropyl D-tartrate as chiral auxiliary.

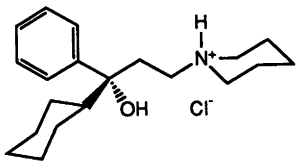

Fig. 1. (*R*)-(−)-Trihexyphenidyl hydrochloride [(*R*)-(−)-**14**].

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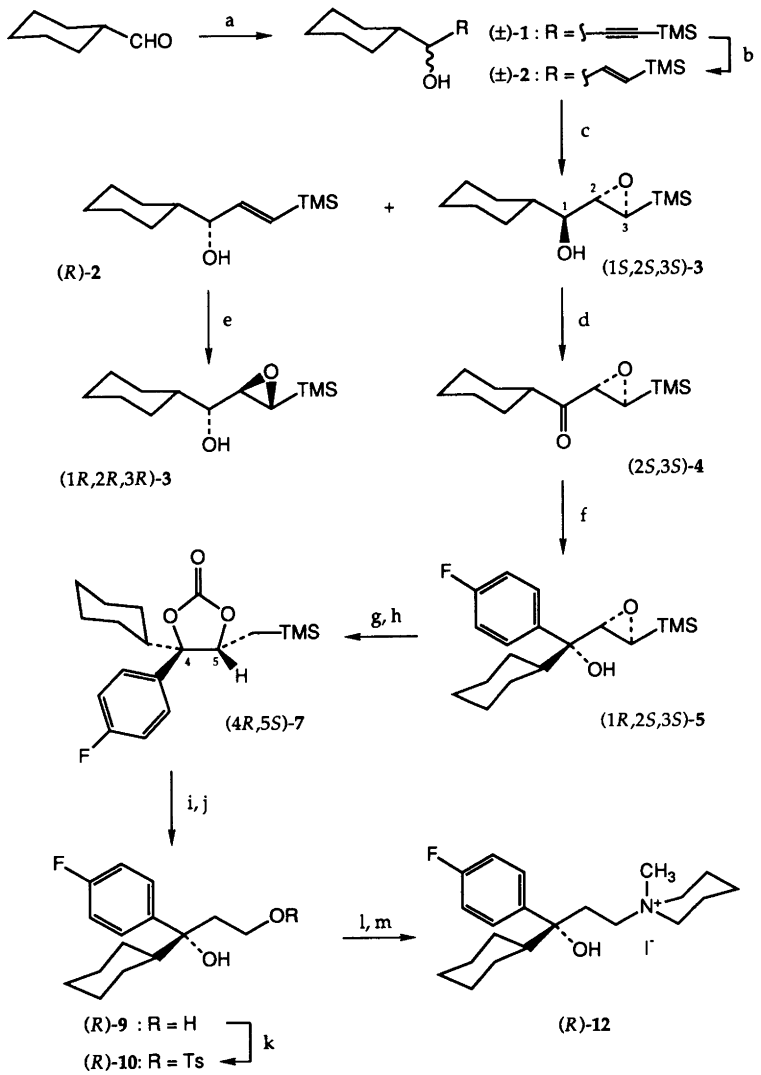


Scheme 1. (a) Lithium trimethylsilylacetylide, diethyl ether, −40°C to r.t.; (b) Red-Al, diethyl ether, reflux; (c) (+)-diisopropyl L-tartrate, $Ti(O^iPr)_4$, ^{t}BuOOH, CH_2Cl_2, −23°C; (d) oxalyl chloride, DMSO, triethylamine, CH_2Cl_2, −70 to −15°C; (e) (−)-diisopropyl D-tartrate, $Ti(O^iPr)_4$, ^{t}BuOOH, CH_2Cl_2, −23°C; (f) 4-fluorophenylmagnesium bromide, diethyl ether, −70 to 0°C; (g) $LiBH_4$, $Ti(O^iPr)_4$, toluene, r.t.; (h) $COCl_2$, pyridine, THF, r.t.; (i) TBAF, THF, r.t.; (j) 9-BBN, THF, reflux; H_2O_2, NaOH, 50°C; (k) TsCl, triethylamine, DMAP, CH_2Cl_2, r.t.; (l) piperidine, DMF, r.t.; (m) MeI, acetone, 50°C.

Reduction of the epoxy alcohol **5** to the 1,2-diol **6** with $LiAlH_4$ gave a complex mixture of products. The diol **6** was, however, obtained in fair yield on regioselective reduction with $Ti(O^iPr)_4$–$LiBH_4$.[22] Attemps to transform **6** directly into the allylic alcohol **8** via the Peterson elimination of trimethylsilanol, with KHMDS or KH as bases, furnished **8** in low yield. The use of KH and 18-crown-6 gave 1-cyclohexyl-1-(4-fluorophenyl)propane-1,2-diol (**13**) as the main product via a protiodesilylation pathway[23,24] (Scheme 2). This product was not observed when KHMDS was used. The conversion of the diol **6** into the alkenol **8** was, instead, performed by a two-step procedure: (a) the 1,2-diol **6** was converted with phosgene into the cyclic carbonate **7** which on (b) treatment with tetrabutylammonium fluoride in THF furnished the allylic alcohol **8**.

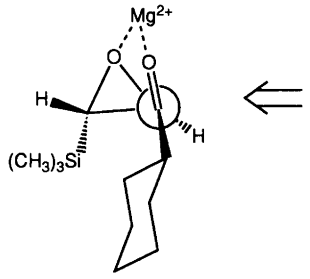
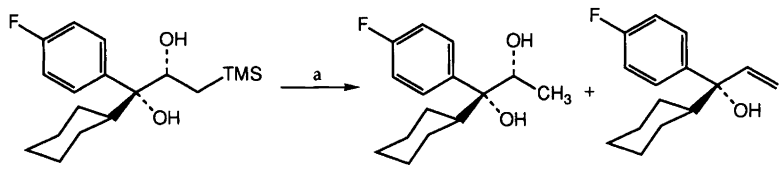


Fig. 2. Preferred direction of attack of the Grignard reagent on the epoxy ketone (2*S*,3*S*)-**4**; cf. Cram's phase selection rule.[16]

Hydroboration of the alkenol **8** with 9-BBN followed by oxidative work-up with alkaline hydrogen peroxide afforded the 1,3-diol **9** which was transformed into the tertiary amine **11** via the tosylate **10**. *N*-Methylation with methyl iodide in acetone gave the target molecule **12**.



Scheme 2. Protiodesilylation using KH, 18-crown-6, THF, 0°C followed by H^+, H_2O (a).

Unsuccessful attempts were made to determine the optical purities of the enantiomers of the amine **11**. However, based on the optical purities of the intermediate epoxy alcohols **3**, the (*R*)-MPTA esters of which were analysed by gas chromatography,[25,26] the enantiomeric purities of the amine **11** and the corresponding methiodide **12** were assumed to be at least 91 % ee and 98 % ee for the (*R*)- and (*S*)-enantiomers, respectively.

Absolute configuration. The chirality induced by the tartaric acid ester in the Sharpless asymmetric epoxidation is predictable and, thus, allows configurational assignments of the intermediate epoxy alcohols **3**.[27] The configurations attributed to the final products follow from the diastereoselective addition of the Grignard reagent to the epoxy ketones **4**; cf. Cram's rule and Fig. 2.[16,21] NOESY experiments performed on the intermediate dioxolane **7** confirmed the relative stereochemistry; see Fig. 3.

Experimental

General methods. Optical rotations were recorded with a Perkin-Elmer 241 polarimeter with chloroform as the solvent unless otherwise stated. Melting points were determined on a Büchi melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini-200 or XL-300 instruments. The solvent peak of chloroform (δ_H 7.26), dichloromethane (δ_H 5.32) and the central solvent peak of chloroform-*d* (δ_C 77.0), acetonitrile-d_3 (δ_C 1.3) or dichloromethane-d_2 (δ_C 53.8) were used as internal references. All couplings are given in Hz. Approximate values for shifts and couplings of ABX spin systems were obtained with the LAOCOON spin simulation program included in the software of the Varian Gemini-200 instrument.

Diethyl ether and THF distilled from sodium–benzophenone, DMF and triethylamine distilled from CaH_2, DMSO, toluene and dichloromethane dried over 4 A molecular sieves were used when anhydrous conditions were required. The reagents were used as received. All reactions were run in a nitrogen atmosphere.

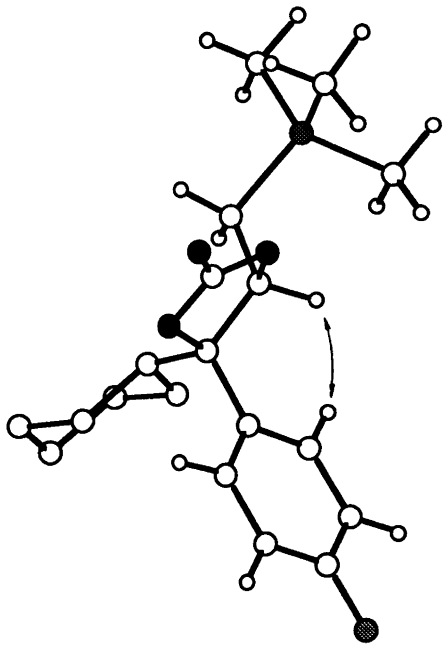


Fig. 3. Observed NOESY interaction for the intermediate dioxolane (4*R*,5*S*)-**7**.

(±)-*1-Cyclohexyl-3-(trimethylsilyl)-2-propynol* [(±)-**1**]. Trimethylsilylacetylene (10.0 g, 102 mmol) was dissolved in diethyl ether (200 ml) and the solution cooled on ice. Butyllithium (70 ml, 1.6 M in hexane, 112 mmol) was slowly added and the temperature was maintained below 5°C for 40 min. The solution was cooled to −40°C and cyclohexanecarbaldehyde (11.42 g, 102 mmol) was slowly added. The temperature was allowed to reach room temperature and sat. aq. NH_4Cl (100 ml) was added. The phases were separated and the organic phase was washed with brine (50 ml), dried over Na_2SO_4, and concentrated *in vacuo* to an oil which, on distillation, yielded (±)-**1**, 19.1 g (89 %), as a colourless oil. B.p. 90–95°C/3 Torr. ^1H NMR (200 MHz, $CDCl_3$): δ 0.18 (9 H, s), 0.90–1.40 (5 H, m), 1.45–1.95 (6 H, m), 4.13 (1 H, d, *J* 6.1). ^{13}C NMR (50 MHz, $CDCl_3$): δ 0.8, 26.5, 27.0, 28.7, 29.1, 44.4, 67.6, 89.9, 105.6. Anal. $C_{12}H_{22}OSi$: C, H.

(E)-(±)-*1-Cyclohexyl-3-(trimethylsilyl)-2-propenol* [(E)-(±)-**2**]. Sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) (41.6 ml, 3.5 M in toluene, 145 mmol) was slowly added to an ice-cooled solution of (±)-**1** (18.0 g, 85.7 mmol) in dry diethyl ether (400 ml). After the gas evolution had ceased the solution was refluxed for 16 h. Water (14 ml) and hydrochloric acid (200 ml, 1 M) were successively added to the ice-cooled reaction mixture. Phase separation, sequential washing of the organic phase with water (50 ml), sat. $NaHCO_3$ (50 ml)

and brine (50 ml) followed by drying over Na_2SO_4, evaporation of the solvent and distillation yielded (*E*)-(±)-**2**, 15.7 g (86%), as a colourless oil. B.p. 99–101°C/0.6 Torr. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (9 H, s), 0.80–1.45 (5 H, m), 1.50–1.95 (6 H, m), 3.84 (1 H, t, *J* 5.8), 5.82 (1 H, dd, *J* 18.8, 1.0), 6.04 (1 H, ddd, *J* 18.8, 5.5, 1.0). ^{13}C NMR (50 MHz, $CDCl_3$): δ 0.3, 26.7, 26.8, 27.1, 28.8, 29.5, 43.9, 79.1, 129.7, 146.4. Anal. $C_{12}H_{24}OSi$: C, H.

*(1*S,*2*S,*3*S)-(+)-*1-Cyclohexyl-2,3-epoxy-3-(trimethylsilyl)-1-propanol* [(*1*S,*2*S,*3*S)-(+)-**3**]. $Ti(O^iPr)_4$ (5.03 g, 17.7 mmol) was dissolved in dry dichloromethane (250 ml) containing 4 A molecular sieves (15 g). The solution was cooled to −23°C and (+)-diisopropyl L-tartrate (4.97 g, 21.2 mmol) was added. The solution was aged for 20 min before the addition of (*E*)-(±)-**2** (7.50 g, 35.4 mmol). Stirring was continued for another 20 min and *tert*-butyl hydroperoxide (6.4 ml, 3.3 M in isooctane. 21.2 mmol) was added. GC analysis showed approximately 50% conversion after 17.5 h at −23°C. The reaction was quenched by addition of dimethyl sulfide (0.7 ml) and stirring for 30 min at −23°C. The reaction mixture was worked up by addition of aqueous L-(+)-tartaric acid (10%, 7.5 ml), diethyl ether (200 ml), LiF (7 g) and Celite (15 g) followed by stirring for 30 min at room temperature. Filtration, evaporation and flash chromatography yielded (*R*)-(*E*)-(−)-**2**, 3.07 g (41%) on elution with heptane–ethyl acetate–triethylamine (95 : 5 : 1). $[\alpha]_D^{20}$ −12.0°, *c* 1.00, and (*1S,2S,3S*)-(+)-**3**, 2.81 g (35%). Data for (*1S,2S,3S*)-(+)-**3**: $[\alpha]_D^{20}$ +1.6°, *c* 1.00. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 (9 H, s), 1.00–1.40 (5 H, m), 1.45–1.90, (6 H, m), 2.37 (1 H, d, *J* 4.8), 2.93 (1 H, t, *J* 4.7), 3.61–3.71 (1 H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.7, 26.7, 26.8, 27.1, 29.1, 29.4, 42.4, 47.5, 57.2, 72.9. Anal. $C_{12}H_{24}O_2Si$: C, H.

The optical purity of the product was found to be 91.2% ee on capillary GC[25] of the (*R*)-MPTA ester.[26]

*(1*R,*2*R,*3*R)-(−)-*1-Cyclohexyl-2,3-epoxy-3-(trimethylsilyl)-1-propanol* [(*1*R,*2*R,*3*R)-(−)-**3**]. (*1R,2R,3R*)-(−)-**3** was prepared from (*R*)-(*E*)-(−)-**2** (2.75 g, 13.0 mmol, *vide supra*), $Ti(O^iPr)_4$ (3.69 g, 13.0 mmol), (−)-diisopropyl D-tartrate (3.64 g, 15.6 mmol) and *tert*-butyl hydroperoxide (4.7 ml, 3.3 M in isooctane, 15.6 mmol), essentially as described above. Yield: 2.43 g (82%), $[\alpha]_D^{20}$ −2.0°, *c* 1.37. Anal. $C_{12}H_{24}O_2Si$: C, H. Optical purity: 98.5% ee.

*(2*S,*3*S)-(+)-*1-Cyclohexyl-2,3-epoxy-3-(trimethylsilyl)-1-propanone* [(*2*S,*3*S)-(+)-**4**]. DMSO (2.33 ml, 32.8 mmol) was added dropwise to a solution of oxalyl chloride (1.44 ml, 16.4 mmol) in dry dichloromethane (50 ml) at −70°C. The solution was stirred for 10 min whereupon (*1S,2S,3S*)-(+)-**3** (2.50 g, 10.9 mmol) dissolved in dichloromethane (2 ml) was added. The reaction was allowed to proceed for 20 min at −70°C before the addition of triethylamine (7.63 ml, 54.7 mmol). The temperature was slowly raised to −15°C and water (20 ml) was added. The phases were separated and the organic phase washed with brine (20 ml), dried over Na_2SO_4, evaporated and filtered through silica to yield (*2S,3S*)-(+)-**4**, 2.21 g (89%), as a clear, faintly yellow oil. $[\alpha]_D^{20}$ +24.0°, *c* 0.98. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.11 (9 H, s), 1.15–1.45 (5 H, m), 1.50–1.95 (5 H, m), 2.31 (1 H, dd, *J* 3.5, 0.6), 2.36–2.52 (1 H, m), 3.29 (1 H, dd, *J* 3.5, 0.6). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.8, 25.8, 26.4, 26.4, 28.3, 29.8, 44.4, 51.3, 56.5, 209.7. Anal. $C_{12}H_{22}O_2Si$: C, H.

*(2*R,*3*R)-(−)-*1-Cyclohexyl-2,3-epoxy-3-(trimethylsilyl)-1-propanone* [(*2*R,*3*R)-(−)-**4**]. (*2R,3R*)-(−)-**4** was prepared as described above from (*1R,2R,3R*)-(−)-**3**. $[\alpha]_D^{20}$ −29.7°, *c* 1.16. Anal. $C_{12}H_{22}O_2Si$: C, H.

*(1*R,*2*S,*3*S)-(−)-*1-Cyclohexyl-2,3-epoxy-1-(4-fluorophenyl)-3-(trimethylsilyl)-1-propanol* [(*1*R,*2*S,*3*S)-(−)-**5**]. 4-Fluorophenylmagnesium bromide (5.5 ml, 2 M in diethyl ether, 11.0 mmol) was added to a solution of (*2S,3S*)-(+)-**4** (2.00 g, 8.8 mmol) in dry diethyl ether at −70°C. The temperature was allowed slowly to rise to 0°C and sat. aq. NH_4Cl (20 ml) added. The phases were separated and the ethereal phase was washed with brine (20 ml), dried over Na_2SO_4 and evaporated. Flash chromatography furnished 2.36 g (83%) of (*1R,2S,3S*)-(−)-**5** as a semi-solid. $[\alpha]_D^{20}$ −17.8°, *c* 1.76. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.12 (9 H, s), 0.80–1.40 (5 H, m), 1.45–1.85 (6 H, m), 2.59 (1 H, d, *J* 3.7), 3.30 (1 H, d, *J* 3.7), 6.97–7.10 (2 H, m), 7.37–7.49 (2 H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ −2.6, 27.0, 27.1, 27.2, 27.7, 28.2, 45.0, 49.7, 60.3, 75.3, 114.4 ($^2J_{CF}$ 20.9), 126.7 ($^3J_{CF}$ 7.8), 140.1 ($^4J_{CF}$ 3.1), 160.8 ($^1J_{CF}$ 242.3). Anal. $C_{18}H_{27}FO_2Si$: C, H.

*(1*S,*2*R,*3*R)-(+)-*1-Cyclohexyl-2,3-epoxy-1-(4-fluorophenyl)-3-(trimethylsilyl)-1-propanol* [(*1*S,*2*R,*3*R)-(+)-**5**]. (*1S,2R,3R*)-(+)-**5** was prepared as described above from (*2R,3R*)-(−)-**4**. $[\alpha]_D^{20}$ +18.7°, *c* 1.44. Anal. $C_{18}H_{27}FO_2Si$: C, H.

*(4*R,*5*S)-(−)-*4-Cyclohexyl-4-(4-fluorophenyl)-5-(trimethylsilyl)methyl-1,3-dioxolan-2-one* [(*4*R,*5*S)-(−)-**7**]. (*1R,2S,3S*)-(−)-**5** (2.00 g, 6.2 mmol) was added to a solution of $Ti(O^iPr)_4$ (2.99 g, 10.5 mmol) in dry toluene (20 ml) and stirred at ambient temperature for 45 min. $LiBH_4$ (0.40 g, 18.6 mmol) was quickly transferred to the reaction mixture after cooling to approximately 10°C. After 1 h at room temperature the reaction was quenched by the addition of a mixture of potassium oxalate (20 ml, 1 M) and citric acid (20 ml, 2 M). The biphasic mixture was stirred for ca. 1 h until clear phases were obtained. Phase separation and drying over Na_2SO_4 followed by evaporation and filtration through a short silica column yielded the intermediate diol (*1R,2S*)-(+)-1-cyclohexyl-1-(4-fluorophenyl)-3-(trimethylsilyl)propane-1,2-diol [(*1R,2S*)-(+)-**6**] as a colourless oil. A small aliquot was

chromatographed on silica and the following spectral data were obtained: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.08 (9 H, s), 0.40–0.60 (1 H, m), 0.80–1.40 (6 H, m), 1.45–2.00 (6 H, m), 4.25–4.45 (1 H, m), 6.90–7.10 (2 H, m), 7.40–7.50 (2 H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ −0.3, 18.1, 26.9, 27.0, 27.2, 27.8, 28.0, 44.8, 72.6, 80.8, 114.2 ($^2J_{CF}$ 20.8), 127.8 ($^3J_{CF}$ 7.7), 137.7 ($^4J_{CF}$ 3.1), 160.9 ($^1J_{CF}$ 242.4). $[\alpha]_D^{20}$ +2.2°, *c* 0.85. Anal. $C_{18}H_{29}FO_2Si$: C, H.

The major portion of the crude product was dissolved in THF (50 ml) and pyridine (2.00 ml, 24.8 mmol). The reaction mixture was cooled on ice and phosgene (6.4 ml, 1.93 M in toluene, 12.4 mmol) was added dropwise. The reaction was quenched by the addition of water (50 ml) and diethyl ether (50 ml). The phases were separated and the aqueous phase extracted with diethyl ether (50 ml) which was dried over Na_2SO_4 and evaporated. Recrystallisation from ethanol–water yielded 1.38 g (4*R*,5*S*)-(−)-**7** (63%). M.p. 137°C, $[\alpha]_D^{20}$ −26.5°, *c* 1.39. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.08 (9 H, s), 0.40–0.60 (1 H, m), 0.80–1.40 (6 H, m), 1.45–2.00 (6 H, m), 4.25–4.45 (1 H, m), 6.90–7.10 (2 H, m), 7.40–7.50 (2 H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ −0.1, 16.8, 26.5, 26.6, 26.9, 27.7, 28.3, 43.1, 85.5, 91.0, 115.1 ($^2J_{CF}$ 21.3), 125.6 ($^3J_{CF}$ 7.9), 134.9 ($^4J_{CF}$ 3.3), 153.1, 161.3 ($^1J_{CF}$ 244.5). Anal. $C_{19}H_{27}FO_3Si$: C, H.

(4S,5R)-(+)-4-Cyclohexyl-4-(4-fluorophenyl)-5-(trimethylsilyl)methyl-1,3-dioxolan-2-one [(4S,5R)-(+)-**7**]. (4*S*,5*R*)-(+)-**7** was prepared as described above from (1*S*,2*R*,3*R*)-(+)-**5**. M.p. 137°C. $[\alpha]_D^{20}$ +27.3°, *c* 1.09. Anal. $C_{19}H_{27}FO_3Si$: C, H.

(R)-(−)-1-Cyclohexyl-1-(4-fluorophenyl)-2-propenol [(R)-(−)-**8**]. Tetrabutylammonium fluoride (TBAF) (3.8 ml, 1 M in THF, 3.8 mmol) was added to a solution of (4*R*,5*S*)-(−)-**7** (1.10 g, 3.1 mmol) in dry THF (20 ml). The reaction was worked up after 3 h by addition of water (20 ml) and heptane–ethyl acetate (95 : 5) (20 ml). The organic phase was dried over Na_2SO_4, evaporated and filtered through silica. Yield: 0.74 g (100%) of (*R*)-(−)-**8**, as a colourless oil. $[\alpha]_D^{20}$ −33.9°, *c* 1.29. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.80–1.35 (5 H, m), 1.40–1.90 (6 H, m), 5.21 (1 H, B part of an ABX system, J_{AB} 1.2, J_{BX} 10. 7), 5.28 (1 H, A part of an ABX system, J_{AX} 17.2), 6.27 (1 H, X part of an ABX system), 6.95–7.10 (2 H, m), 7.35–7.45 (2 H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.0, 27.1, 27.2, 27.4, 27.8, 48.2, 78.9, 112,4, 114.3 ($^2J_{CF}$ 20.8), 126.6 ($^3J_{CF}$ 7.8), 140.5 ($^4J_{CF}$ 3.0), 142.4, 160.6 ($^1J_{CF}$ 241.9). Anal. $C_{15}H_{19}FO$: C, H.

(S)-(+)-1-Cyclohexyl-1-(4-fluorophenyl)-2-propenol (S)-(+)-**8**]. (*S*)-(+)-**8** was prepared as described above from (4*S*,5*R*)-(+)-**7**. $[\alpha]_D^{20}$ +33.5°, *c* 0.99. Anal. $C_{15}H_{19}FO$: C, H.

(R)-(−)-3-Cyclohexyl-3-(4-fluorophenyl)-3-hydroxypropyl toluenesulfonate [(R)-(−)-**10**]. 9-Borabicyclo[3.3.1]-nonane (9-BBN) (1.18 g, 9.7 mmol) was added to a solution of (*R*)-(−)-**8** (0.65 g, 2.7 mmol) in THF (45 ml) and refluxed. Another portion of 9-BBN (6.94 g, 6.89 mmol) was added after 2.5 h and the heating was continued for 7.5 h. The solution was cooled to room temperature and a mixture of aq. NaOH (9.0 ml, 1 M) and aq. H_2O_2 (4.2 ml, 30%) was carefully added. The mixture was then heated to 50°C for 2 h. The reaction mixture was cooled after which heptane–ethyl acetate (95 : 5) (45 ml) and water (45 ml) were added. The organic phase was dried over Na_2SO_4, evaporated and filtered though silica. The crude diol was dissolved in dry dichloromethane (20 ml) containing triethylamine (0.37 g, 3.65 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP). Tosyl chloride (0.52 g, 2.74 mmol) was added to this solution which was then stirred for 4 h at room temperature. Water (10 ml) was then added and the phases were separated. The organic phase was dried over Na_2SO_4, evaporated and flash chromatographed. Recrystallisation from heptane–ethyl acetate afforded (*R*)-(−)-**10**, 0.50 g (45%). M.p. 80°C (decomp.). $[\alpha]_D^{20}$ −17.4°, *c* 0.84. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.75–1.35 (5 H, m), 1.45–1.95 (6 H, m), 2.10–2.40 (2 H, m), 2.45 (3 H, s), 4.15–4.75 (2 H, m), 6.90–7.00 (2 H, m), 7.15–7.25 (2 H, m), 7.29 (2 H, d, *J* 8.1), 7.64 (2 H, d, *J* 8.4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2, 26.8, 27.0, 27.0, 27.1, 27.5, 38.8, 49.3, 67.9, 77.2, 114.3 ($^2J_{CF}$ 21.0), 126.5 ($^3J_{CF}$ 7.8), 127.2, 129.1, 132.2, 138.6 ($^4J_{CF}$ 3.2), 143.9, 160.5 ($^1J_{CF}$ 242.2). Anal. $C_{22}H_{27}FO_4S$: C, H.

(S)-(+)-3-Cyclohexyl-3-(4-fluorophenyl)-3-hydroxypropyl toluenesulfonate [(S)-(+)-**10**]. (*S*)-(+)-**10** was prepared as described above from (*S*)-(+)-**8**. M.p. 81°C (decomp.). $[\alpha]_D^{20}$ +17.7°, *c* 0.99. Anal. $C_{22}H_{27}FO_4S$: C, H.

(R)-(−)-1-Cyclohexyl-1-(4-fluorophenyl)-3-piperidyl-1-propanol [(R)-(−)-**11**]. (R)-(−)-**10** (0.38 g, 0.93 mmol) was dissolved in dry DMF (10 ml) and piperidine (0.49 ml, 4.92 mmol). The solution was stirred at 40°C overnight. Water (10 ml) was added and the aqueous phase extracted with diethyl ether (3 × 10 ml). Drying over Na_2SO_4 and evaporation followed by recrystallisation from acetonitrile furnished 0.21 g (68%) of (*R*)-(−)-**11**. M.p. 137°C. $[\alpha]_D^{20}$ −34.6°, *c* 1.49. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85–1.85 (19 H, m) 1.90–2.35 (6 H, m), 6.95–7.05 (2 H, m), 7.30–7.43 (2 H, m). ^{13}C NMR (50 MHz, CD_2Cl_2): δ 25.0, 26.9, 27.4, 27.5, 27.5, 27.6, 27.9, 33.5, 49.6, 54.8, 55.8, 79.5, 113.7 ($^2J_{CF}$ 20.6), 127.4 ($^3J_{CF}$ 7.7), 142.7 ($^4J_{CF}$ 2.8), 160.3 ($^1J_{CF}$ 239.6). Anal. $C_{20}H_{30}FNO$: C, H.

(S)-(+)-1-Cyclohexyl-1-(4-fluorophenyl)-3-piperidyl-1-propanol [(S)-(+)-**11**]. (*S*)-(+)-**11** was prepared as described above from (*S*)-(+)-**10**. M.p. 136°C. $[\alpha]_D^{20}$ +35.0°, *c* 0.93. Anal. $C_{20}H_{30}FNO$: C, H.

(R)-(−)-1-Cyclohexyl-1-(4-fluorophenyl)-3-piperidyl-1-propanol methiodide [(R)-(−)-**12**]. (*R*)-(−)-**11** (0.075 g, 0.23 mmol) and methyl iodide (0.13 g, 0.94 mmol) were dissolved in acetone (3 ml) and heated to 50°C for 1.5 h when TLC showed no remaining starting material. The reaction mixture was evaporated. Recrystallisation of the residue from acetone–hexane yielded (*R*)-(−)-**12**, 0.11 g (100%), as white crystals. M.p. 204°C. $[\alpha]_D^{20} - 6.1°$, *c* 0.94 (MeOH). ^{1}H NMR (200 MHz, CD_3CN): δ 0.80–1.42 (6 H, m), 1.48–1.90 (10 H, m), 2.19–2.38 (2 H, m), 2.65–2.87 (1 H, m), 2.98 (3 H, s), 3.10–3.46 (6 H, m), 7.05–7.18 (2 H, m), 7.34–7.47 (2 H, m). ^{13}C NMR (50 MHz, CD_3CN): δ 20.4, 21.2, 26.8, 26.9, 27.0, 27.3, 27.7, 31.7, 48.2, 49.4, 60.7, 61.3, 77.4, 114.1 ($^2J_{CF}$ 21.1), 127.3 ($^3J_{CF}$ 7.8), 139.0 ($^4J_{CF}$ 3.1), 160.7 ($^1J_{CF}$ 239.8). Anal. $C_{21}H_{33}FINO$: C, H.

(S)-(+)-1-Cyclohexyl-1-(4-fluorophenyl)-3-piperidyl-1-propanol methiodide [(S)-(+)-**12**]. (*S*)-(+)-**12** was prepared as described above from (*S*)-(+)-**11**. M.p. 203°C. $[\alpha]_D^{20} + 6.0°$, *c* 0.89 (MeOH). Anal. $C_{21}H_{33}FINO$: C, H.

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