Enantiospecific Synthesis of the (4*R*)-1-Azabicyclo[2.2.1]heptane Ring System

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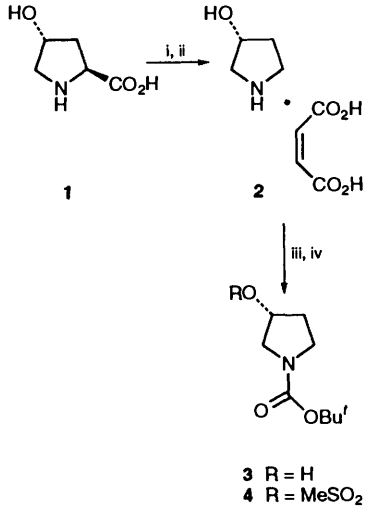
An enantioselective synthesis of (4*R*)-1-azabicyclo[2.2.1]heptane derivatives is described commencing from readily available *trans*-4-hydroxy-L-proline which is converted into the key intermediate (3*R*)-*N*-(*tert*-butoxycarbonyl)-3-methylsulfonyloxypyrrolidine **4**. Reaction of the sulfonate ester **4** with an enolate anion yields a mixture of (3*R*)-pyrrolidinylacetic esters **8** and **9** which are reduced to the corresponding alcohols **10** and **11**. Conversion of the alcohols into the sulfonate esters **12** and **13** followed by deprotection of the pyrrolidine nitrogen leads to cyclisation yielding the (4*R*)-1-azabicyclo[2.2.1]heptane derivatives **14** and **15**.

Heterocyclic derivatives of 1-azabicyclo[2.2.1]heptane are potent muscarinic agonists and have potential for the treatment of senile dementia of the Alzheimer type.[1,2] Investigation of a number of agonists identified (3*R*,4*R*)-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane as a new drug candidate,[3] and thus larger quantities of material for further biological evaluation were required. The large scale preparation of chiral intermediates for this type of heterocycle has been reported in an earlier communication,[4] which described a novel route to 1-azabicyclo[2.2.1]heptane-3-carboxylic acid ester enantiomers involving resolution assisted by a chiral auxiliary. However, unless the unwanted isomer can be epimerised, the resolution of diastereoisomers is not a very efficient method for the preparation of a chiral compound. We now report an enantiospecific synthesis of the oxadiazole derivative taking advantage of a chiral pool starting material to introduce the 4*R* asymmetric bridgehead carbon atom of the 1-azabicyclo[2.2.1]heptane ring system.

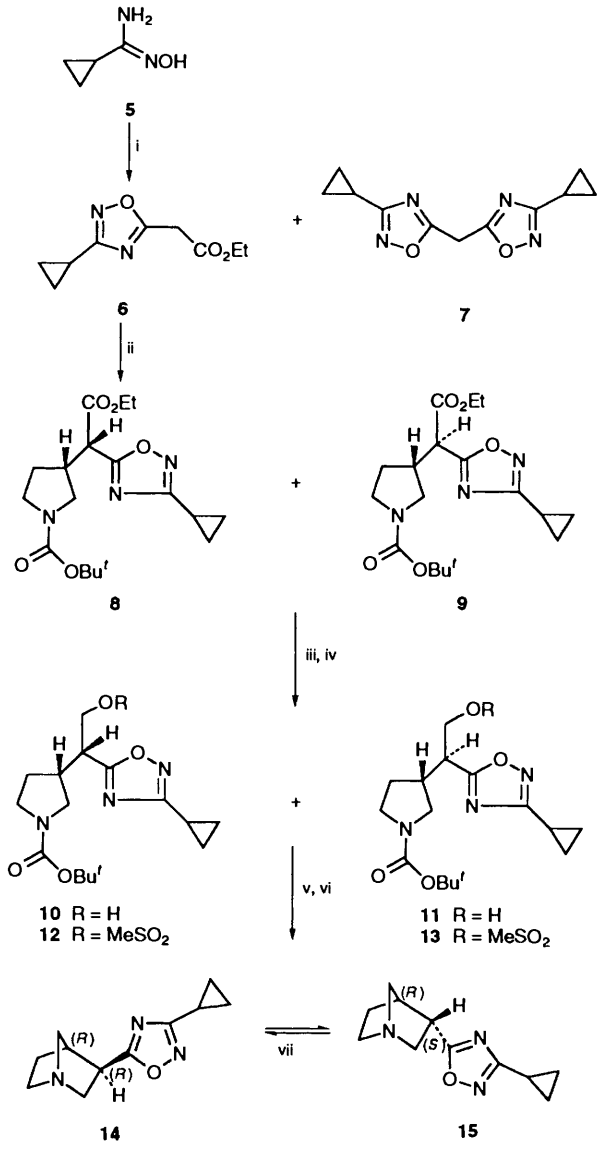


Scheme 1 *Reagents:* i, cyclohexanol, 2-cyclohexen-1-one; ii, maleic acid, Me_2CHOH; iii, $(Bu^tOCO)_2O$, $NaHCO_3$, H_2O; iv, $MeSO_2Cl$, NEt_3, EtOAc

Results and Discussion

As in our earlier method, the azabicyclic ring system is constructed by forming a two-carbon bridge across a pyrrolidine ring onto the nitrogen atom. However in this new method the stereochemistry at the bridgehead is established by stereospecifically introducing the side chain by displacement, with inversion, of methanesulfonate ion from a chiral pyrrolidinyl alcohol derivative. X-ray crystallography[3] had established the absolute configuration of the *exo*-isomer **14**, and thus the key intermediate for this approach is (3*R*)-(−)-3-hydroxypyrrolidine obtained by decarboxylation of readily available *trans*-4-hydroxy-L-proline **1** by the method of Hashimoto.[5] In our hands we found isolation of the pyrrolidine as the crystalline hydrogen maleate salt **2** (74% yield) was more practicable than the hygroscopic hydrochloride, which was difficult to handle on the large scale. Protection of the pyrrolidine as the *tert*-butoxycarbonyl derivative **3** and conversion into the methanesulfonate ester **4** proceeded in 98% overall yield (Scheme 1).

Reaction of cyclopropanecarboxamide oxime **5** with an excess of diethyl malonate gave a mixture containing the oxadiazole acetic ester **6** with a little of the bis by-product **7** (Scheme 2). Distillation gave recovered diethyl malonate and then the product **6** in 69% yield. Generation of the enolate of the ester **6** by treatment with sodium hydride or potassium *tert*-butoxide in dimethylformamide (DMF) followed by heating with the methanesulfonate **4** at 100 °C gave the alkylated products **8** and **9**, but with up to 23% of the product formed by elimination of methanesulfonic acid from the pyrrolidine sulfonate. Attempts to use the organic bases diisopropylethylamine or tributylamine were unsuccessful as no reaction occurred on heating the reactants with the amines in 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU) at 80 °C. However, heating the reactants in DMPU with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 80 °C gave the products **8** and **9** with < 15% of the eliminated product. Better results were obtained by stirring the methanesulfonate **4** and DBU with an excess of ester **6** at 55 °C without solvent to give the alkylated products **8** and **9**, containing only 6% of the eliminated product, as an oil in 97% crude yield. Some diastereoselection occurred in this reaction generating another chiral centre, as the two isomers **8** and **9** were obtained in the ratio 1.6:1. A sample was purified by column chromatography for analysis, but the bulk of the crude ester was reduced to the alcohols **10** and **11**. The ester was recovered unchanged after attempted reduction with sodium bis(2-methoxyethoxy)aluminium hydride, and reduction of the ester with diisobutylaluminium hydride gave the corresponding aldehyde. Reduction of the ester with sodium borohydride activated by methanol,[6] a method well suited for large scale work, gave the alcohols **10** and **11** in 85% yield. GC/MS analysis showed the product to be 95% pure with diastereoisomers **10** and **11** in a ratio of 1.9:1. A sample of the pure (2*R*, 3'*S*) enantiomer **10** was isolated by



Scheme 2 *Reagents:* i, $CH_2(CO_2Et)_2$, toluene; ii, **4**, DBU; iii, $NaBH_4$, THF, MeOH; iv, $MeSO_2Cl$, NEt_3, EtOAc; v, CF_3CO_2H, Me_3COH; vi, Na_2CO_3, H_2O, Me_3COH; vii, KOBu', EtOH

column chromatography for analysis. The crude alcohols **10** and **11** were converted into the methanesulfonate esters **12** and **13** in quantitative yield, and an analytical sample of the (2*R*,3'*S*) enantiomer **12** obtained by chromatography.

Deprotection of the pyrrolidine under acid conditions followed by neutralisation of the solution gave a mixture of the bicyclic products **14** and **15** in a ratio of 2:1 in 69% yield. Separation of the desired *exo*-isomer **14** may be achieved by chromatography, or more conveniently for large scale work by fractional crystallisation of the toluene-*p*-sulfonate salts. The pure (3*R*,4*R*)-azabicyclo[2.2.1]heptane **14** was obtained in 27% yield, and a sample of the pure *endo*-isomer **15** isolated by chromatography for identification. The yield of the *exo*-isomer **14** was increased further by epimerisation[3] of the *endo*-isomer **15** followed by crystallisation of the toluene-*p*-sulfonate salt from the thermodynamic equilibrium mixture of 3:1 *exo*:*endo* isomers.

The preparation of the oxadiazole derivatives **14** and **15** demonstrates this novel process which clearly has wider application in the synthesis of other (4*R*)-azabicyclo[2.2.1]heptanes.

Experimental

M.p.s were determined on a Büchi 510 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-250 spectrometer with tetramethylsilane as internal standard. All *J* values are in Hz. GC analyses were carried out with a Hewlett Packard 5790 gas chromatograph with a cool on-column injector (Column CPSIL5CB, 75 °C for 2 min and then 10 °C min^{-1} to 300 °C). GC/MS analyses were carried out with a Finnegan Mat TSQ70 spectrometer. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}.

(3R)-3-*Hydroxypyrrolidinium Hydrogen Maleate* **2**.—(2*S*,4*R*)-(−)-4-Hydroxypyrrolidine-2-carboxylic acid (1.0 kg, 7.6 mol) suspended in cyclohexanol (5.0 dm^3) and cyclohex-2-en-1-one (100 cm^3) was heated under reflux at 155 °C for 5.5 h until all the solid had dissolved. The clear red solution was cooled to 25 °C and maleic acid (885 g, 7.6 mol) added over 30 min maintaining the temperature < 35 °C. On complete addition crystallisation occurred and the mixture was stirred at 25 °C for 30 min. Ethyl acetate (10 dm^3) was added over 1 h and then the suspension stirred at 20 °C for 2 h. The crystalline solid was collected, washed with a mixture of ethyl acetate (2 dm^3) and cyclohexanol (1 dm^3) and then ethyl acetate (3 dm^3) to give the pyrrolidine salt **2** (1.14 kg, 74%), m.p. 90–91 °C (Found: C, 47.25; H, 6.4; N, 6.9. $C_4H_9NO \cdot C_4H_4O_4$ requires C, 47.3; H, 6.45; N, 6.9%); $[\alpha]_D$ −5.4 (*c* 1 in H_2O), $\delta_H(CD_3OD)$ 2.05 (2 H, m, CCH_2C), 3.2–3.6 [4 H, m, $(NCH_2)_2$], 4.57 (1 H, m, OCH) and 6.29 (2 H, s, CH=CH).

(3R)-N-(tert-*Butoxycarbonyl*)-3-*hydroxypyrrolidine* **3**.—A solution of the pyrrolidinium hydrogen maleate **2** (3.6 kg, 17.7 mol) in water (10.8 dm^3) was added over 15 min to a suspension of sodium hydrogen carbonate (7.42 kg, 88.3 mol) in water (29 dm^3) at 20 °C. Di-*tert*-butyl dicarbonate (4.64 kg, 21.3 mol) was added to the solution and the mixture stirred for 65 h. Ethyl acetate (10 dm^3) was added and the mixture filtered. The aqueous layer was separated from the filtrate and extracted with ethyl acetate (10 dm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the hydroxypyrrolidine **3** as an oil (3.3 kg, 100%), which crystallised, m.p. 62–65 °C (Found: C, 57.8; H, 9.1; N, 7.5. $C_9H_{17}NO_3$ requires C, 57.7; H, 9.15; N, 7.5%); $[\alpha]_D$ −22.7 (*c* 1 in CH_2Cl_2); $\delta_H[(CD_3)_2SO$ at 60 °C] 1.40 (9 H, s, CMe_3), 1.73 (1 H, m, 4-H), 1.95 (1 H, dtd, *J* 5.0, 9.0 and 11.0, 4-H), 3.11 (1 H, ddd, *J* 1.8, 2.5 and 11.0, 2-H), 3.3 (3 H, m, 2-H and 5-H_2) and 4.21 (1 H, m, 3-H); GC analysis 99% R_t 7.9 min.

(3R)-N-(tert-*Butoxycarbonyl*)-3-*methylsulfonyloxypyrrolidine* **4**.—Methanesulfonyl chloride (1.68 dm^3, 21.7 mol) was added over 1 h to a solution of the alcohol **3** (3.39 kg, 18.1 mol) and triethylamine (5.1 dm^3, 36.5 mol) in ethyl acetate (50 dm^3) maintained at −5 °C. The mixture was stirred at −5 °C for 30 min and then quenched with water (20 dm^3) added over 10 min. The organic phase was separated and washed sequentially with hydrochloric acid (10 dm^3, 1 mol dm^{-3}) and saturated sodium hydrogen carbonate solution (10 dm^3). The solution was dried (Na_2SO_4) and evaporated to give the methanesulfonate **4** as an oil (4.725 kg, 98%) (Found: C, 45.1; H, 7.2; N, 5.2; S, 12.0. $C_{10}H_{19}NO_5S$ requires C, 45.25; H, 7.2; N, 5.3, S, 12.1%); $[\alpha]_D$ −27 (*c* 1 in CH_2Cl_2); $\delta_H[(CD_3)_2SO$ at 60 °C] 2.1 (2 H, m, 4-H_2), 3.20 (3 H, s, SO_2CH_3), 3.25 (1 H, m, 5-H), 3.4 (1 H, m, 5-H), 3.45 (1 H, dd, *J* 3.4 and 12.5, 2-H), 3.55 (1 H, dd, *J* 4.0 and 12.5, 2-H) and 5.24 (1 H, m, 3-H); GC analysis 99% R_t 3.1 min.

Ethyl 2-(3-*Cyclopropyl*-1,2,4-*oxadiazol*-5-*yl*)*acetate* **6**.—A solution of cyclopropanecarboxamide oxime[7] (5.39 kg, 53.9 mol) and diethyl malonate (24.5 kg, 160 mol) in toluene (54 dm^3) was heated under reflux for 21 h. The aqueous ethanol layer

which separated from the condensate was periodically removed. GC analysis of reaction mixture 64% R_t 2.4 min (diethyl malonate), 33% R_t 7.6 min (oxadiazole **6**), 3% R_t 12.3 min (by-product 7). The reaction mixture was cooled to 20 °C, washed with brine (3 × 5 dm^3) and evaporated under reduced pressure. The residue was distilled through a short fractionating column to give recovered diethyl malonate (19.9 kg), b.p. 60–70 °C/2 mbar* and oxadiazole **6** as an oil (7.26 kg, 69%), b.p. 90–100 °C/1 mbar (Found: C, 54.85; H, 6.2; N, 14.0. $C_9H_{10}N_2O_3$ requires C, 55.1; H, 6.15; N, 14.3%); $\delta_H(CD_2Cl_2)$ 1.0 (4 H, m, cyclopropyl, CH_2CH_2), 1.28 (3 H, t, *J* 7.0, Me), 2.09 (1 H, m, cyclopropyl CH), 3.93 (2 H, s, CH_2CO) and 4.20 (2 H, q, *J* 7.0, CH_2); GC analysis 98% R_t 7.6 min.

Ethyl (2R,3'R)- *and* (2S,3'R)-2-(3-*Cyclopropyl*-1,2,4-*oxadiazol*-5-*yl*)-2-(N-tert-*butoxycarbonylpyrrolidin*-3-*yl*)*acetates* **8** *and* **9**.—Diazabicyclo[5.4.0]undec-7-ene (4.6 kg, 30 mol) was added over 20 min to a mixture of mesylate **4** (4.22 kg, 15.9 mol) and oxadiazole **6** (6.24 kg, 31.8 mol). The temperature increased from 20 °C to 45 °C during this time, and then the mixture was heated at 54 °C for 30 h. The mixture was cooled to 20 °C and partitioned between ethyl acetate (12.5 dm^3) and hydrochloric acid (8 dm^3, 1 mol dm^{-3}). The organic phase was washed sequentially with hydrochloric acid (4 dm^3, 1 mol dm^{-3}) then brine (2 × 5 dm^3) and dried (Na_2SO_4). The solution was evaporated under reduced pressure to an oil (8.89 kg) GC analysis 42% R_t 7.6 min (ester **6**) and 51% R_t 18.2 min (products **8** and **9**). The oil was passed through a short-path distillation apparatus at 130 °C 0.5 mbar to recover the oxadiazole ester **6** and to give products **8** and **9** as a red oil (5.66 kg, 97%). GC analysis 92% R_t 18.2 min. A sample was chromatographed on silica with ethyl acetate–hexane (1:9) to give the pure products **8** and **9** as a colourless oil (Found: C, 59.25; H, 7.5; N, 11.45. $C_{18}H_{27}N_3O_5$ requires C, 59.15; H, 7.45; N, 11.5%); $\delta_H(CD_2Cl_2)$ 0.9–1.1 (4 H, m, cyclopropyl CH_2CH_2), 1.19 (3 H, 2 × t, *J* 7.0, Me), 1.3–1.4 (9 H, s, CMe_3), 2.05 (1 H, m, cyclopropyl CH), 3.73 (1 H, d, *J* 9.0, CHCO) and 4.13 (2 H, 2 × q, *J* 7.0, OCH_2).

(2R,3'R)- *and* (2S,3'R)-2-(3-*Cyclopropyl*-1,2,4-*oxadiazol*-5-*yl*)-2-(N-tert-*butoxycarbonylpyrrolidin*-3-*yl*)*ethanol* **10** *and* **11**.—Sodium borohydride (2.57 kg, 67.9 mol) was added to a solution of the esters **8** and **9** (6.2 kg, 16 mol) in tetrahydrofuran (THF) (18.6 dm^3) at −5 °C. Methanol (13.8 dm^3) was added to the suspension over 1 h maintaining the temperature at 0 °C. The reaction mixture was stirred at −5 °C for 3 h, cooled to −20 °C and added to a mixture of ethyl acetate (30 dm^3) and hydrochloric acid (146 dm^3, 2 mol dm^{-3}) at < −5 °C. The mixture was stirred for 15 min then the aqueous layer separated and extracted with ethyl acetate (5 × 15 dm^3). The combined organic phases were washed sequentially with hydrochloric acid (13 dm^3, 2 mol dm^{-3}) and brine (3 × 13 dm^3) and dried (Na_2SO_4). The solution was evaporated under reduced pressure to give alcohols **10** and **11** as an oil (4.65 kg, 85%), GC/MS analysis 95% ratio of **10** and **11** (1.9:1). A sample was chromatographed on silica with diethyl ether–hexane (3:2) to give the pure less polar (2*R*,3*R'*) enantiomer **10** as a solid, m.p. 71–74 °C (Found: C, 59.3; H, 7.75; N, 12.8. $C_{16}H_{25}N_3O_4$ requires C, 59.45; H, 7.8; N, 13.0%), $[\alpha]_D$ +1.7 (*c* 1 in CH_2Cl_2); $\delta_H[(CD_3)_2SO$ at 60 °C] 0.90 and 1.02 (4 H, m, cyclopropyl CH_2CH_2), 1.39 (9 H, s, Me_3), 1.50 (1 H, m, pyrrolidine 4-H), 1.75 (1 H, m, pyrrolidine 4-H), 2.08 (1 H, m, cyclopropyl CH), 2.50 (1 H, m, pyrrolidine 3-H), 3.14 (2 H, m, CH and pyrrolidine 5-H), 3.28 (1 H, ddd, *J* 2.8, 9.0 and 11.0, pyrrolidine 5-H), 2.98 (1 H, dd, *J* 10.5 and 19.5, pyrrolidine 2-H), 3.56 (1 H, dd, *J* 7.5 and 10.5, pyrrolidine 2-H) and 3.71 (2 H, d, *J* 6.0, CH_2O); δ_C 27.92 (Me_3), 28.52 (pyrrolidine 4-CH_2), 37.64 (pyrrolidine 3-CH), 43.76 (CH), 44.60 (pyrrolidine 5-CH_2), 49.00 (pyrrolidine 2-CH_2), 61.74 (CH_2O), 77.94 (C–O), 153.17 (C=O), 171.23 (oxadiazole C-3) and 179.31 (oxadiazole C-5).

(2R,3'R)- *and* (2S,3'R)-2-(3-*Cyclopropyl*-1,2,4-*oxadiazol*-5-*yl*)-2-(N-tert-*butoxycarbonylpyrrolidin*-3-*yl*)*ethyl Methanesulfonate* **12** *and* **13**.—Triethylamine (3.97 dm^3, 28.4 mol) was added to a solution of the alcohols **10** and **11** (4.6 kg, 14.2 mol) in ethyl acetate (46 dm^3) cooled at −20 °C. Methanesulfonyl chloride (1.32 dm^3, 17.1 mol) was added to the solution over 30 min maintaining the temperature at −20 to −15 °C. The reaction mixture was stirred at −20 °C for 45 min and then quenched by slow addition of hydrochloric acid (14.1 dm^3, 2 mol dm^{-3}). The aqueous layer was separated and extracted with ethyl acetate (3 × 3 dm^3). The combined organic phases were washed with brine (4 × 6.4 dm^3) and concentrated. Some solid which separated was removed by filtration and the filtrate evaporated under reduced pressure to give the methanesulfonates **12** and **13** as an oil (5.8 kg, 100%). A sample was chromatographed on silica with diethyl ether–hexane (9:4) to give less polar (2*R*,3'*R*) enantiomer **12** as a solid, m.p. 85–88 °C (Found: C, 50.9; H, 6.8; N, 10.4; S, 8.0. $C_{17}H_{27}N_3O_6S$ requires C, 50.85; H, 6.8; N, 10.45; S, 8.0%); $[\alpha]_D$ −25.3 (*c* 1 in CH_2Cl_2); $\delta_H(CD_2Cl_2)$ 0.85–1.05 (4 H, m, cyclopropyl CH_2CH_2), 1.35 (9 H, br s, CMe_3), 1.51 (1 H, m, pyrrolidine 4-H), 1.79 (1 H, m, pyrrolidine 4-H), 2.01 (1 H, dt, *J* 5.0 and 8.5 cyclopropyl CH), 2.47 (1 H, m, pyrrolidine 3-H), 2.89 (3 H, s, $MeSO_2$), 2.98–3.31 (4 H, m, pyrrolidine 2-H_2 and 5-H_2), 3.58 (1 H, q, *J* 9.5, CH) and 4.38 and 4.4 (2 H, m, CH_2O); $\delta_C[(CD_3)_2SO$ at 60 °C] 27.87 (Me_3), 28.22 (pyrrolidine 4-CH_2), 36.62 ($MeSO_2$), 37.64 (pyrrolidine 3-CH), 40.10 (CH), 44.57 (pyrrolidine 5-CH_2), 48.58 (pyrrolidine 2-CH_2), 68.76 (CH_2O), 78.06 (C–O), 153.11 (C=O), 171.56 (oxadiazole C-3) and 177.15 (oxadiazole C-5).

(3R,4R)-3-(3-*Cyclopropyl*-1,2,4-*oxadiazol*-5-*yl*)-1-*azabicyclo*[2.2.1]*heptane* **14**.—(a) *From methanesulfonates* **12** and **13**. Trifluoroacetic acid (12.0 dm^3) was added dropwise over 1 h to a solution of the methanesulfonates **12** and **13** (5.9 kg, 14.7 mol) in *tert*-butyl alcohol (3.0 dm^3) at 20–25 °C. The reaction mixture was stirred at 20 °C for 1 h, diluted with *tert*-butyl alcohol (24 dm^3), and aqueous sodium carbonate (80 dm^3, 10%) was added to adjust the pH to 7.5. The mixture was heated to 40 °C for 1.5 h maintaining the pH at 7.5 by addition of sodium carbonate solution. Heating at 40 °C was continued for a further 1.5 h maintaining the pH at 8.5. The pH was finally increased to 9.5 and the reaction mixture extracted with toluene (20 dm^3 and 4 × 10 dm^3). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give the bicyclo[2.2.1]heptanes **14** and **15** as an oil (2.08 kg). GC analysis 65% R_t 11.0 min (product **14**) and 28% R_t 10.6 min (product **15**). The crude product was chromatographed on silica with ethyl acetate–methanol (5:1) and then methanol to give the pure enantiomer **14** as a crystalline solid (803 g, 27%), m.p. 60–61 °C (Found: C, 64.35; H, 7.4; N, 20.45. $C_{11}H_{15}N_3O$ requires C, 64.35; H, 7.35; N, 20.45%); $[\alpha]_D$ −1.7 (*c* 1 in H_2O); $\delta_H(CD_2Cl_2)$ 0.9–1.1 (4 H, m, cyclopropyl CH_2CH_2), 1.25 (1 H, m, 5-H), 1.67 (1 H, dt, *J* 4.5 and 11.2, 5-H), 2.02 (1 H, dt, *J* 5.5 and 8.0, cyclopropyl CH), 2.35 (1 H, d quin, *J* 1.0 and 10.0, 7-H), 2.49 (1 H, dddd, *J* 2.2, 5.0, 10.5 and 13.0, *exo* 6-H), 2.69 (1 H, ddd, *J* 1.0, 2.0 and 10.0, 7-H), 2.7–2.85 (3 H, m, 3-H, 4-H and *endo* 6-H), 2.90 (1 H, ddd, *J* 2.5, 8.0 and 12.0, 2-H) and 3.02 (1 H, ddd, *J* 2.5, 7.8 and 12.0, 2-H); $\delta_C(CD_2Cl_2)$ 7.73 (cyclopropyl CH), 8.4 (cyclopropyl CH_2), 31.07 (5-CH_2), 41.35 (4-CH), 43.77 (3-CH), 54.76 (6-CH_2), 59.68 (7-CH_2), 61.39 (2-CH_2), 173.03 (oxadiazole C-3) and 182.20 (oxadiazole C-5); Chiral HPLC analysis (Bakerbond Chiral AGP) >98.5% e.e. Latter

* 1 bar = 10^5 Pa.

fractions from the column gave an *exo–endo* mixture of products **14** and **15** (406 g, 14%) GC analysis 17% R_t 11.0 min (product **14**) and 83% R_t 10.6 min (product **15**).

(b) *From methanesulfonate* **12**. The methanesulfonate **12** (200 mg, 0.5 mmol) in *tert*-butyl alcohol (5 cm^3) was treated as above to give the crude enantiomer **14** (60 mg, 60%) GC analysis single peak R_t 11.0 min.

(c) *By epimerisation of* endo-*enantiomer* **15**. A solution of the *endo* enantiomer enriched mixture of products **14** and **15** (120 g, ratio 17:83) and potassium *tert*-butoxide (7.5 g) in ethanol (600 cm^3) was heated under reflux for 30 min. GC analysis 76% R_t 11.0 min (product **14**) and 24% R_t 10.6 min (product **15**). The solution was evaporated and the residue partitioned between ethyl acetate (400 cm^3) and water (50 cm^3). The aqueous phase was separated and extracted with ethyl acetate (3 × 50 cm^3). The combined organic phases were dried (Na_2SO_4) and evaporated to an oil (118 g). A solution of toluene-*p*-sulfonic acid monohydrate (109 g, 0.57 mol) in ethyl acetate (500 cm^3) was distilled to give a solution (350 cm^3) of the anhydrous acid, which was diluted with isopropyl alcohol (120 cm^3). The *exo*-enantiomer enriched oil, in a mixture of ethyl acetate (260 cm^3) and isopropyl alcohol (116 cm^3), was added to the acid solution and the solution stirred at 20 °C for 2 h to crystallise. The mixture was cooled to 5 °C for 1 h and the solid collected by filtration. GC analysis 98.4% R_t 11.0 min (product **14**). The solid was suspended in boiling ethyl acetate (1.2 dm^3) for 2 h and then cooled to 20 °C. The solid was collected to give the enantiomer **14** as the crystalline toluene-*p*-sulfonate salt (117 g, 51%), m.p. 132–133 °C (Found: C, 57.0; H, 6.15; N, 11.2; S, 8.5. $C_{11}N_{15}N_3O \cdot C_7H_8O_3S$ requires C, 57.3; H, 6.15; N, 11.15; S, 8.5%); $[\alpha]_D$ −2.4 (*c* 1 in H_2O); GC analysis 99.5% R_t 11.0 min (3*R*,4*R*)-enantiomer.

(3S,4R)-3-(3-*Cyclopropyl*-1,2,4-*oxadiazol*-5-*yl*)-1-*aza*-*bicyclo*[2.2.1]*heptane* **15**.—A sample of the *exo–endo* mixture of products **14** and **15**, obtained from the column in the preparation of the *exo* enantiomer **14**, was chromatographed on silica with ethyl acetate–methanol (5:1) and then methanol to give the *endo* enantiomer **15** as an oil. The oil (1.1 g, 5.4 mmol) was dissolved in ethyl acetate (20 cm^3) and treated with a solution of toluene-*p*-sulfonic acid monohydrate (1.0 g, 5.3 mmol) in ethyl acetate (30 cm^3) at 20 °C. The crystalline solid was collected to give the enantiomer **15** as the toluene-*p*-sulfonate salt (1.8 g, 89%), m.p. 138–139 °C (Found: C, 57.3; H, 6.15; N, 11.35; S, 8.5. $C_{11}H_{15}N_3O \cdot C_7H_8O_3S$ requires C, 57.3; H, 6.15; N, 11.15; S, 8.5%); $[\alpha]_D$ +35.8 (*c* 1 in H_2O); δ_H(free base in CD_2Cl_2) 0.95–1.05 (4 H, m, cyclopropyl CH_2CH_2), 1.11 (1 H, m, 5-H), 1.41 (1 H, m, 5-H), 2.03 (1 H, dt, *J* 5.0 and 8.0, cyclopropyl CH), 2.45–2.65 (3 H, m, 6-H and 7-H_2), 2.7–3.0 (3 H, m, 3-H, 4-H and 6-H), 3.15 (1 H, ddd, *J* 2.5, 11.0 and 12.5, 2-H) and 3.31 (1 H, dddd, *J* 2.0, 5.0, 9.0 and 11.0, 2-H); δ_C(free base in CD_2Cl_2) 7.71 (cyclopropyl CH), 8.42 (cyclopropyl CH_2), 26.02 (5-CH_2), 40.44 (4-CH), 43.36 (3-CH), 55.17 (6-CH_2), 59.33 (7-CH_2), 62.83 (2-CH_2), 173.08 (oxadiazole C-3) and 181.29 (oxadiazole C-5); GC analysis 99.0% R_t 10.6 min (3*S*,4*R*)-enantiomer.

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References

1 J. Saunders, A. M. MacLeod, K. J. Merchant, G. A. Showell, R. J. Snow, L. J. Street and R. Baker, *J. Chem. Soc., Chem. Commun.*, 1988, 1618; L. J. Street, R. Baker, T. Book, C. O. Kneen, A. M. MacLeod, K. J. Merchant, G. A. Showell, J. Saunders, R. H. Herbert, S. B. Freedman and E. A. Harley, *J. Med. Chem.*, 1990, **33**, 2690; G. A. Showell, R. Baker, J. Davis, R. Hargreaves, S. B. Freedman, K. Hoogsteen, S. Patel and R. J. Snow, *J. Med. Chem.*, 1992, **35**, 911.

2 B. S. Orlek, F. E. Blaney, F. Brown, M. S. G. Clark, M. S. Hadley, J. Hatcher, G. J. Riley, H. E. Rosenberg, H. J. Wadsworth and P. Whyman, *J. Med. Chem.*, 1991, **34**, 2726.

3 R. Baker, G. A. Showell, L. J. Street, J. Saunders, K. Hoogsteen, S. B. Freedman and R. J. Hargreaves, *J. Chem. Soc., Chem. Commun.*, 1992, 817.

4 I. F. Cottrell, D. Hands, D. J. Kennedy, K. J. Paul, S. H. B. Wright and K. Hoogsteen, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1091.

5 M. Hashimoto, Y. Eda, Y. Osanai, T. Iwai and S. Aoki, *Chem. Lett.*, 1986, 893.

6 K. Soai, H. Oyamada and A. Ookawa, *Synth. Commun.*, 1982, **12**, 463.

7 W. J. Fanshawe, V. J. Bauer, S. R. Safir, D. A. Blickens and S. J. Riggi, *J. Med. Chem.*, 1969, **12**, 381.

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