# Synthesis of the selective muscarinic agonist (3*R*)-3-(6-chloropyrazin-2-yl)-1-azabicyclo[2.2.2]octane

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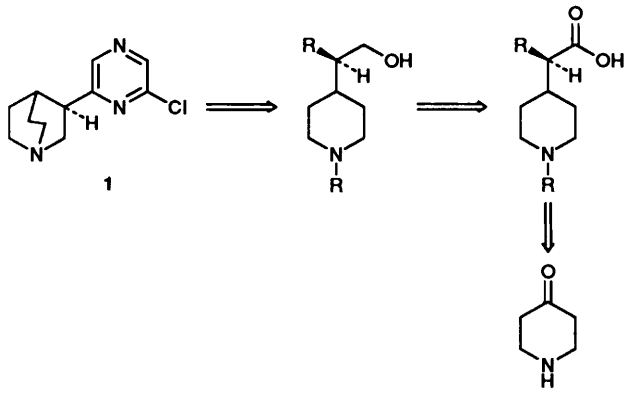
The synthesis of the functionally selective muscarinic agonist (3*R*)-3-(6-chloropyrazin-2-yl)-1-azabicyclo-[2.2.2]octane is described commencing from readily available 4-piperidone. The key feature of this novel process is the preparation and resolution of a piperidin-4-ylacetic acid, with the advantage that high yields of the pure (*S*)-enantiomer may be obtained by epimerisation of the unwanted enantiomer for further resolution. The reaction sequence is completed by reduction to a chiral 4-hydroxyethylpiperidine and intramolecular *N*-alkylation to the bicycle **1**.

3-Substituted quinuclidine derivatives have been identified as muscarinic agonists with potential for the treatment of Alzheimer's disease,[1,2] and (*R*)-3-(6-chloropyrazin-2-yl)-1-azabicyclo[2.2.2]octane **1** was selected for further biological evaluation, creating a need for large quantities of this material. The small scale method[2] used to obtain the pyrazine **1** in moderate yield involved the reaction of the enolate of methyl quinuclidine-3-carboxylate with 2,6-dichloropyrazine at −50 °C followed by hydrolysis, decarboxylation and resolution. Other pyrazine derivatives[1,2] were prepared by a more general method from reaction of 2-lithiopyrazines with quinuclidin-2-one at −45 to −100 °C to give a methanol, followed by chlorination and reduction. Unfortunately the methods were not amenable to scale up due to the high cost of the quinuclidines and the low temperatures involved.

Chiral 3-substituted quinuclidines have been obtained by intramolecular *N*-alkylation of 4-hydroxyethylpiperidine derivatives derived from natural products, *e.g.* (*R*)-3-vinylquinuclidine was prepared[3] from 4-(2-bromoethyl)-3-vinylpiperidine obtained from cinchonine, and (*S*)-3-hydroxyquinuclidine was prepared[4] from a hydroxyethylpiperidine methanesulfonate obtained from glucose. Our strategy involved the preparation of a hydroxyethylpiperidine from a piperidinylacetic acid which could be resolved. The anticipated advantages of this approach were that either isomer of the acid could be obtained, and the unwanted enantiomer would be available for racemisation due to the acidic proton at the chiral centre, thereby increasing the yield of the resolved product. In addition the starting material was the readily available and inexpensive 4-piperidone (Scheme 1).




**Scheme 1** Retrosynthetic scheme

**Table 1** Horner–Wittig reaction of ketone **3**

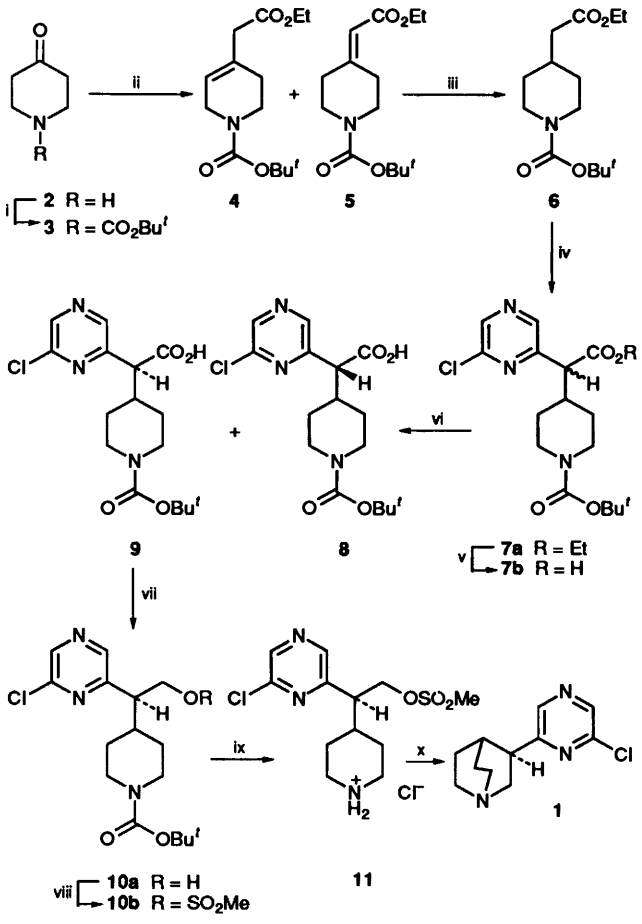
| Base | Solvent | *T*/°C | *t*/h | Product (%)[a] | |
|---|---|---|---|---|---|
| | | | | **4** | **5** |
| Bu$^t$OK | DMF | 20 | 1 | 59[b] | 38[b] |
| $K_2CO_3$ | DMF | 90 | 5 | 7 | 92 |
| $K_2CO_3$ | DMF | 70 | 22 | < 1 | 97 |

[a] Isolated yields. [b] By GLC.

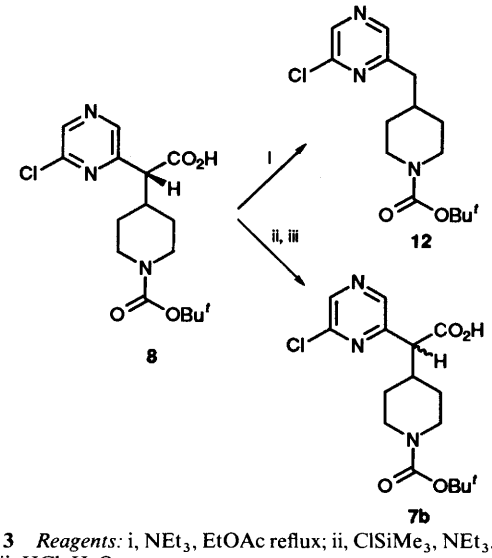
## Results and discussion

4-Piperidone **2** in water was treated with di-*tert*-butyl dicarbonate to give the crystalline *tert*-butoxycarbonyl derivative **3** in quantitative yield (Scheme 2). The ketone **3** was treated with the anion derived from diethyl ethoxycarbonylmethylphosphonate in dimethylformamide (DMF) to give a mixture of the unsaturated esters **4** and **5**, addition of water to the reaction mixture gave the isomer **5** as a crystalline solid, and isomer **4** could be extracted from the aqueous DMF solution. However, in order to eliminate the need for an extractive work-up, the reaction conditions were modified to minimise the generation of isomer **4** to < 1%, thus enabling the isolation of the ester **5** as a solid in 97% yield (Table 1). The unsaturated ester **5** was reduced by catalytic transfer hydrogenation using ammonium formate[5] to give the piperidinylacetic acid ester **6** in 98% yield.

Alkylation of the ester **6** with 2,6-dichloropyrazine was investigated using a number of bases to generate the enolate. Lithium diisopropylamide and both lithium and potassium hexamethyldisilazide gave significant amounts of by-products, whereas with sodium hexamethyldisilazide (1 equiv.) reaction proceeded smoothly to give the product **7a**, but stopped after 50% conversion because the proton α to the ester group is more acidic in the product **7a** than in the starting material **6**. However, the use of 2.25 equiv. of sodium hexamethyldisilazide at −15 °C gave essentially quantitative yields of the ester **7a**, which was hydrolysed to the pyrazinylacetic acid **7b**. Resolution of the acid gave pure enantiomer **9** as the 1-phenylethylamine salt in 40% yield (*i.e.* 80% of theory). In order to increase the efficiency of the process, base catalysed racemisation of the unwanted isomer **8** was attempted, but decarboxylation occurred. However, a simple one pot procedure was developed, whereby the acid in ethyl acetate was protected *in situ* as the trimethylsilyl ester by treatment with chlorotrimethylsilane and



**Scheme 2** *Reagents:* i, $(Bu^tOCO)_2O$, $NaHCO_3$, $H_2O$; ii, $(EtO)_2POCH_2CO_2Et$, $K_2CO_3$, DMF; iii, $NH_4{}^+HCO_2{}^-$, $H_2O$, EtOH, Pd/C; iv, $NaN(SiMe_3)_2$, THF, 2,6-dichloropyrazine; v, NaOH, $H_2O$, EtOH; vi, (*S*)-(−)-1-phenylethylamine, EtOAc; vii, $BH_3$, THF; viii, $MeSO_2Cl$, $NEt_3$, EtOAc; ix, HCl, EtOAc; x, $K_2CO_3$, $H_2O$



**Scheme 3** *Reagents:* i, $NEt_3$, EtOAc reflux; ii, $ClSiMe_3$, $NEt_3$, EtOAc, reflux; iii, HCl, $H_2O$

excess triethylamine (Scheme 3). Heating the solution of the ester effected the racemisation, and an aqueous hydrochloric acid work-up gave the racemic acid **7b** in quantitative yield for further resolution. In this manner the yield of the diastereoisomeric salt of the desired acid **9** was increased to > 65% after one recycle.

Reduction of the acid **9** to the alcohol **10a** with borohydride or aluminium hydride reagents was more difficult than expected, presumably due to complex formation with the pyrazine. Attempted reduction of the acid, after conversion to the ethyl ester, with diisobutylaluminium hydride[6] or sodium bis(2-methoxyethoxy)aluminium hydride[7] only gave decomposition products, whereas with sodium borohyride[8] reactions were very slow and failed to give good yields of the alcohol **10a**. Conversion of the acid **9** into a mixed anhydride with ethyl chloroformate followed by treatment with sodium borohydride[9] also gave low yields of the alcohol. Finally reduction of the acid **9** with excess borane as the tetrahydrofuran (THF) complex[10] gave the alcohol **10a** in moderate yield (57%). The loss in yield at this step is due primarily to reduction of the pyrazine ring to form polar piperazine derivatives which were removed by a silica pad. Reaction of the alcohol **10a** with methanesulfonyl chloride and triethylamine gave the methanesulfonate ester **10b** in almost quantitative yield. Removal of the *tert*-butoxycarbonyl group from this derivative by treatment with hydrogen chloride,[11] followed by treatment of the resulting amine hydrochloride **11** with excess potassium carbonate gave the 1-azabicyclo[2.2.2]octane derivative **1** isolated as the tartrate salt in 61% yield.

The preparation of this compound demonstrates a novel procedure for the preparation of a chiral 3-substituted quinuclidine from a prochiral piperidinylacetic acid, which should be applicable to the synthesis of other quinuclidines of biological interest.

## Experimental

Mps were determined on a Büchi 510 apparatus and are uncorrected. $^1H$ NMR spectra were obtained on a Bruker AM-250 spectrometer with tetramethylsilane as internal standard. All *J* values are in Hz. $[\alpha]_D$ Values are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. The chiral purity of the final product was determined by HPLC using a Technicol Cyclobond I acetylated column (250 × 4.0 mm) with 45% aqueous methanol as solvent at 1 $cm^3$ $min^{-1}$.

### *N-tert*-Butoxycarbonylpiperidin-4-one 3

To a slurry of sodium hydrogen carbonate (476 g, 5.67 mol) in water (545 $cm^3$) at room temperature was added a solution of 4-piperidone hydrochloride monohydrate (727 g, 4.73 mol) in water (2.47 $dm^3$) over 20 min. Di-*tert*-butyl dicarbonate (1.05 kg, 4.8 mol) was added in portions to the mixture over 30 min the mixture warmed to 35 °C over 1 h, left to stand for 1 h, and then heated at 50 °C for 2.5 h. The mixture was cooled to 25 °C and ethyl acetate (700 $cm^3$) added. The aqueous layer was separated, re-extracted with ethyl acetate (300 $cm^3$) and the organic extracts combined. The organic solution was washed with saturated aqueous brine (300 $cm^3$) and then evaporated to give the butoxycarbonyl derivative **3** as a solid (946 g, 100%), mp 74–75 °C (Found: C, 59.9; H, 8.5; N, 7.0. $C_{10}H_{17}NO_3$ requires C, 60.3; H, 8.6; N, 7.05%); $\delta_H(CD_2Cl_2)$ 1.38 (9 H, s, $CMe_3$), 2.39 (4 H, t, *J* 7, $CH_2CO$) and 3.64 (4 H, t, *J* 7, $CH_2N$).

### Ethyl 2-(*N-tert*-Butoxycarbonylpiperidin-4-ylidene)acetate 5

Diethyl ethoxycarbonylmethylphosphonate (1.42 kg, 6.35 mol) was added to a stirred slurry of milled anhydrous potassium carbonate (2.02 kg, 14.66 mol) in DMF (9.7 $dm^3$). The piperidone **3** (972 g, 4.88 mol) was added to the mixture which was then heated at 70 °C under a nitrogen atmosphere for 22 h. The reaction mixture was cooled to 30 °C, water (30 $dm^3$) added dropwise and the slurry stirred at 0 °C overnight. The product was collected by filtration, washed with water (6

$dm^3$) and dried at 22 °C to give the ester **5** as a crystalline solid (1.28 kg, 97%), mp 84–86 °C (Found: C, 62.5; H, 8.55; N, 5.15. $C_{14}H_{23}NO_4$ requires C, 62.45; H, 8.6; N, 5.2%); $\delta_H(CD_2Cl_2)$ 1.25 (3 H, t, *J* 7, Me), 1.44 (9 H, s, $CMe_3$), 2.26 (2 H, m, $CH_2C$=), 2.91 (2 H, m, $CH_2C$=), 4.12 (2 H, q, *J* 7, $CH_2O$) and 5.70 (1 H, m, CH=C).

**Ethyl 2-(*N*-*tert*-Butoxycarbonylpiperidin-4-yl)acetate 6**

Ammonium formate in water (10 mol $dm^{-3}$; 930 $cm^3$) was added over 30 min to a slurry of unsaturated ester **5** (1.285 kg, 4.77 mol) and palladium on carbon (10%, 128 g) in ethanol (12.8 $dm^3$) and water (400 $cm^3$) at 18 °C under an atmosphere of nitrogen. The mixture was stirred for 1 h and then the catalyst removed by filtration. The filtrate was evaporated under reduced pressure and the residue partitioned between hexane (500 $cm^3$) and water (1 $dm^3$). The organic layer was separated, washed with water (2 × 500 $cm^3$) and evaporated under reduced pressure to give the ester **6** as an oil, which crystallised to a solid (1.268 kg, 98%), mp 31 °C (Found: C, 61.75; H, 9.2; N, 5.25. $C_{14}H_{25}NO_4$ requires C, 61.95; H, 9.3; N, 5.15%); $\delta_H(CD_2Cl_2)$ 1.12 (2 H, ddd, *J* 4.5, 12 and 16, 3- and 5-$H_{ax}$) 1.23 (3 H, t, *J* 7, Me), 1.42 (9 H, s, $CMe_3$), 1.67 (2 H, br d, *J* 16, 3- and 5-H eq), 1.9 (1 H, m, 4-H), 2.21 (2 H, d, *J* 6.5, $CH_2CO$), 2.68 (2 H, br t, *J* 12, 2- and 6-$H_{ax}$), 4.02 (2 H, br d, *J* 12, 2- and 6-H eq) and 4.09 (2 H, q, *J* 7, $CH_2O$).

**(*S*)-2-(*N*-*tert*-Butoxycarbonylpiperidin-4-yl)-2-(6-chloropyrazin-2-yl)acetic acid 9**

**(a) From ester 6.** To a stirred solution of sodium bis(trimethylsilyl)amide in THF (1 mol $dm^{-3}$; 13.1 mol) under a nitrogen atmosphere was added, over 30 min, a solution of 2,6-dichloropyrazine (861 g, 5.78 mol) and ester **6** (1.49 kg, 5.49 mol) in THF (3 $dm^3$) maintaining the temperature < −15 °C. The mixture was stirred at −10 °C for 1.5 h and then added to a mixture of aqueous hydrochloric acid (2 mol $dm^{-3}$; 7.5 $dm^3$) and hexane (4 $dm^3$). The organic phase was separated, washed with aqueous hydrochloric acid (2 mol $dm^{-3}$; 5 $dm^3$) and then water (2 × 5 $dm^3$). The hexane solution was evaporated under reduced pressure to give the crude ester **7a** as an oil, which was dissolved in ethanol (12 $cm^3$). Sodium hydroxide (341 g, 8.5 mol) in water (12 $cm^3$) was added to the solution of the ester and the mixture stirred at 25 °C for 2 h. The solution was concentrated under reduced pressure at < 25 °C to remove most of the ethanol and the aqueous residue extracted with ethyl acetate–hexane (1:1, 4 $dm^3$) then ethyl acetate (2 × 4 $dm^3$) to remove non-acidic material. The aqueous solution was acidified with conc. hydrochloric acid (750 $cm^3$) and extracted with ethyl acetate (2 × 3 $dm^3$). The solution of the acid **7b** was dried by azeotropic distillation at 25 °C and treated with a solution of (*S*)-(−)-1-phenylethylamine (399 g, 3.29 mol) in ethyl acetate (4 $dm^3$). The slurry of the salt was stirred at 25 °C for 30 min, heated to 60 °C for 1 h and cooled to 20 °C for 2 h. The partially resolved acid salt (1.196 kg) $[\alpha]_D$ +10 (*c* 0.25 in $CH_2Cl_2$) was collected by filtration and suspended in boiling ethyl acetate (12 $dm^3$) for 1 h. The suspension was cooled to 20 °C for 2 h and filtered to give the salt (1.124 kg) $[\alpha]_D$ +13.3 (*c* 0.25 in $CH_2Cl_2$). The solid was resuspended in boiling ethyl acetate (11.5 $dm^3$) for 1 h and cooled to 20 °C. The solid was collected by filtration to give the pure (*S*)-acid **9** as the (*S*)-(−)-1-phenylethylamine salt (1.08 kg, 41.5%), mp 178 °C (Found: C, 60.25, H, 6.95; N, 11.7. $C_{16}H_{22}ClN_3O_4{\cdot}C_8H_{11}N$ required C, 60.45; H, 6.95; N, 11.75%) $[\alpha]_D$ +13.0 (*c* 0.25 in $CH_2Cl_2$). The salt was partitioned between ethyl acetate (3.5 $dm^3$) and aqueous hydrochloric acid (1 mol $dm^{-3}$; 2.5 $dm^3$). The aqueous layer was separated and extracted with ethyl acetate (2 $dm^3$). The combined extract was washed with aqueous hydrochloric acid (1 mol $dm^{-3}$, 1 $dm^3$) then with water (2 × 1.5 $dm^3$) and dried ($MgSO_4$). The solution was evaporated under reduced pressure to give the (*S*)-acid **9** as a crystalline solid (777 g, 40%), mp 148 °C (Found: C, 53.95; H, 6.25; N, 11.75. $C_{16}H_{22}ClN_3O_4$ requires C, 54.0; H, 6.25; N, 11.8%); $[\alpha]_D$ +59.3 (*c* 0.8 in MeOH); $\delta_H(CD_2Cl_2)$ (two conformers) 1.12 and 1.32 (2 H, ddd, *J* 4, 12 and 16, 3- and 5-$H_{ax}$), 1.43 (9 H, s, $CMe_3$), 1.90 and 2.40 (2 H, br d, *J* 15, 3- and 5-H eq), 2.39 (1 H, m, 4-H), 2.68 and 2.78 (2 H, br t, *J* 15, 2- and 6-$H_{ax}$), 3.65 (1 H, d, *J* 10, CHCO), 4.03 and 4.13 (2 H, br d, *J* 12, 2- and 6-H eq), 8.58 (1 H, s, py-H), 8.60 (1 H, s, py-H) and 9.82 (1 H, br s, $CO_2H$).

The ethyl acetate liquors from the salt formation were washed with aqueous hydrochloric acid and evaporated under reduced pressure to give recovered (*R*) enantiomer enriched acid **8** (1.095 kg, 56%).

**(b) From enantiomer 8.** A solution of the (*R*)-enantiomer enriched acid **8** (540 g, 1.52 mol) and triethylamine (637 $cm^3$, 4.56 mol) in ethyl acetate (5.4 $dm^3$) was treated with chlorotrimethylsilane (233 $cm^3$, 1.8 mol) maintaining the temperature at 20–30 °C. The mixture was heated under reflux for 7.5 h and then cooled to 20 °C. Aqueous hydrochloric acid (2 mol $dm^{-3}$; 2 $dm^3$) was added to the mixture and the two phases mixed well before being allowed to separate. The ethyl acetate solution was washed with aqueous hydrochloric acid 2 mol $dm^{-3}$; 500 $cm^3$) then brine (2 × 1 $dm^3$) and evaporated under reduced pressure to give the racemic acid **7b** (543 g, 100%) $[\alpha]_D$ 0 (*c* 1 in MeOH). Resolution of the acid as before gave the (*S*)-enantiomer acid **9** as the (*S*)-(−)-1-phenylethylamine salt (328 g, 45%) $[\alpha]_D$ +13.4 (*c* 0.25 in $CH_2Cl_2$).

**(*R*)-(+)-2-(*N*-*tert*-Butoxycarbonylpiperidin-4-yl)-2-(6-chloropyrazin-2-yl)ethanol 10a**

A solution of the acid **9** (1.4 kg, 3.94 mol) in dry THF (2.8 $dm^3$) was cooled to 10 °C and a solution of borane in THF (1 mol $dm^{-3}$; 12 $dm^3$, 12 mol) was added maintaining the temperature < 15 °C. The solution was allowed to warm to room temperature and stirred for 1.5 h. The solution was added to water (20 $dm^3$) at 2 °C with vigorous stirring over 1 h. The mixture was allowed to warm to room temperature and stirred for 2 h to complete hydrolysis of the borate esters. The solution was concentrated under reduced pressure at < 24 °C and the aqueous residue extracted with ethyl acetate (3 × 4 $dm^3$). The extract was washed with water (4 $dm^3$) and then evaporated under reduced pressure. The residue was dissolved in ethyl acetate, absorbed onto silica gel (3 kg) and placed on top of the same amount of silica gel in a 12 in diameter column. Elution of the column with ethyl acetate–hexane (1:1, 70 $dm^3$) and evaporation of the eluate gave the alcohol **10a** as an oil (766 g, 57%) (Found: C, 56.1; H, 7.1; N, 12.0. $C_{16}H_{24}ClN_3O_3$ requires C, 56.2; H, 7.1; N, 12.3%); $[\alpha]_D$ +55.6 (*c* 1 in MeOH); $\delta_H(CD_2Cl_2)$ (two conformers) 1.2 (2 H, m, 3- and 5-$H_{ax}$), 1.45 (9 H, s, $CMe_3$), 1.98 (2 H, m, 3- and 5-H eq), 2.0 (1 H, m, 4-H), 2.45–2.75 (2 H, m, 2- and 6-$H_{ax}$), 2.77 (1 H, m, CH), 3.9–4.2 (4 H, m, $CH_2O$, 2- and 6-H eq), 8.37 (1 H, s, py-H) and 8.50 (1 H, s, py-H).

**(*R*)-(+)-2-(*N*-*tert*-Butoxycarbonylpiperidin-4-yl)-2-(6-chloropyrazin-2-yl)ethyl Methanesulfonate 10b**

A solution of the alcohol **10a** (766 g, 2.24 mol) and triethylamine (947 $cm^3$, 6.77 mol) in ethyl acetate (7.6 $dm^3$) was cooled to −20 °C and treated with methanesulfonyl chloride (245 $cm^3$, 3.16 mol) added over 1 h. The mixture was stirred for 30 min at −15 °C and then aqueous hydrochloric acid (1 mol $dm^{-3}$; 6 $dm^3$) was slowly added maintaining the temperature < 0 °C. The organic layer was separated, washed with aqueous hydrochloric acid (3 $dm^3$), brine (2 × 3 $dm^3$) and dried ($MgSO_4$). The solution was evaporated under reduced pressure to give the methanesulfonate **10b** as an oil (934 g, 99%). A sample was chromatographed on silica with ethyl acetate–hexane (1:1) to give the pure product as an oil (Found: C, 48.85;

H, 6.3; Cl, 8.2; N, 9.8; S, 7.65. $C_{17}H_{26}ClN_3O_5S$ requires C, 48.6; H, 6.25; Cl, 8.45; N, 10.0; S, 7.65%); $[\alpha]_D$ +26.9 (*c* 1 in MeOH); $\delta_H(CD_2Cl_2)$ (two conformers) 1–1.35 (4 H, m, 3- and 5-H), 1.42 (9 H, s, $CMe_3$), 1.95 (1 H, m, 4-H), 2.6 (2 H, m, 2- and 6-$H_{ax}$), 2.89 (3 H, s, $MeSO_2$), 3.11 (1 H, dt, *J* 5.5 and 10, CH), 4.02 and 4.12 (2 H, br d, *J* 14, 2- and 6-H eq), 4.59 and 4.61 (2 H, dd, *J* 10 and 16, $CH_2O$), 8.38 (1 H, s, py-H) and 8.52 (1 H, s, py-H).

**(*R*)-(−)-3-(6-Chloropyrazin-2-yl)-1-azabicyclo(2.2.2)octane 1**

The methanesulfonate **10b** (933 g, 2.24 mol) was dissolved in ethyl acetate (9.3 $dm^3$) and the solution was saturated with dry hydrogen chloride at 25–30 °C. The mixture was stirred for 2 h to complete the deprotection. Water (3.5 $dm^3$) was added to the mixture containing the amine hydrochloride **11** followed by careful addition of potassium carbonate (2.25 kg) in water (2.25 $dm^3$). The two phase mixture was heated with stirring at 60 °C for 2 h and then cooled to 25 °C. The aqueous layer was separated, extracted with ethyl acetate (2 × 2 $dm^3$) and the extract evaporated under reduced pressure to give the crude base **1** as an oil (455 g, 92%). The oil was dissolved in isopropyl alcohol (2 $dm^3$) and added to a warm solution (40 °C) of L-tartaric acid (305 g, 2 mol) in isopropyl alcohol (3 $dm^3$). The mixture was allowed to cool to room temperature overnight. The solid (685 g) was collected, dissolved in methanol (21 $dm^3$) and the solution concentrated to 6.6 $dm^3$ to crystallise the solid. The solid was resuspended in methanol (5.5 $dm^3$), stirred under reflux for 1 h and then cooled to 20 °C to give the pure enantiomer **1** as a crystalline salt (505 g, 61%), mp 189 °C (Found: C, 48.2; H, 5.4; 5.4; N, 11.25. $C_{11}H_{14}ClN_3 \cdot C_4H_6O_6$ requires C, 48.2; H, 5.4; N, 11.3%); $[\alpha]_D$ +24.2 (*c* 1 in $H_2O$); 98.3% ee; $\delta_H(CD_3OD)$ 1.7–2.3 (5 H, m, 4-CH, 5-$CH_2$ and 8-$CH_2$), 2.34 (1 H, m, 2-CH), 3.2–3.75 (5 H, m, 2-CH, 6-$CH_2$ and 7-$CH_2$), 3.93 (1 H, dd, *J* 4 and 11, 3-CH), 6.43 (2 H, s, tartaric acid CH), 8.55 (1 H, s, py-H) and 8.56 (1 H, s, py-H).

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