A Synthesis of 1-Azabicyclo[2.2.1]heptane-3-carboxylic Acid Esters in Enantiomerically Pure Form

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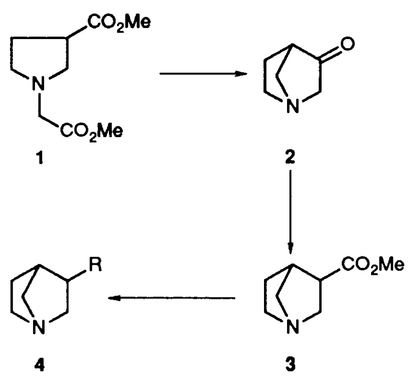
A novel synthesis of ethyl 1-azabicyclo[2.2.1]heptane-3-carboxylate *via* 1-benzylperhydropyrano-[3,4-*c*]pyrrol-4-one and 1-benzyl-3-(2-bromoethyl)-4-ethoxycarbonylpyrrolidinium bromide is described. Modification of the method, by incorporation of a chiral substituted benzyl group on the nitrogen atom, has led to the first reported process for the preparation of these esters in enantiomerically pure form. The absolute configuration of the bicyclic esters was deduced by X-ray crystallography of an intermediate, 2-[(*S*)-1-phenylethyl]perhydropyrano[3,4-*c*]pyrrole-4-one.

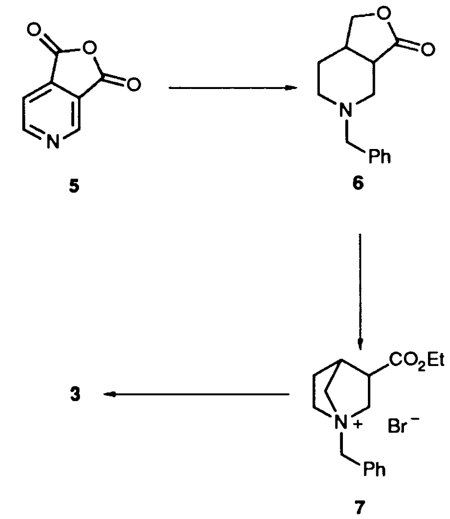
Heterocyclic derivatives of the 1-azabicyclo[2.2.1]heptane system have been shown to be potent muscarinic agonists with potential for the treatment of senile dementia of the Alzheimer type.[1-3] Key intermediates in one approach for the preparation



Scheme 1 R = heterocycle

of the heterocyclic derivatives are 1-azabicyclo[2.2.1]heptane-3-carboxylic acid esters (*e.g.* **3**).[1,2] Two routes for the preparation of the racemic esters have been reported. In one, Scheme 1,[1] Dieckmann cyclisation of the pyrrolidine diester **1** afforded the azabicyclic ketone **2** which was converted into the ester **3** in two steps. However, this approach was unsuitable for development because poor variable yields were obtained during scale up of the Dieckmann reaction. The alternative route, Scheme 2,[3] of acid catalysed cyclisation of 4-benzylperhydro-7*H*-furo[3,4-*c*]-pyridin-2-one **6** was also unsuitable for scale up, due to the very poor yields of intermediates obtained at the initial stages of the reaction sequence from pyridine-3,4-dicarboxylic acid anhydride **5**.

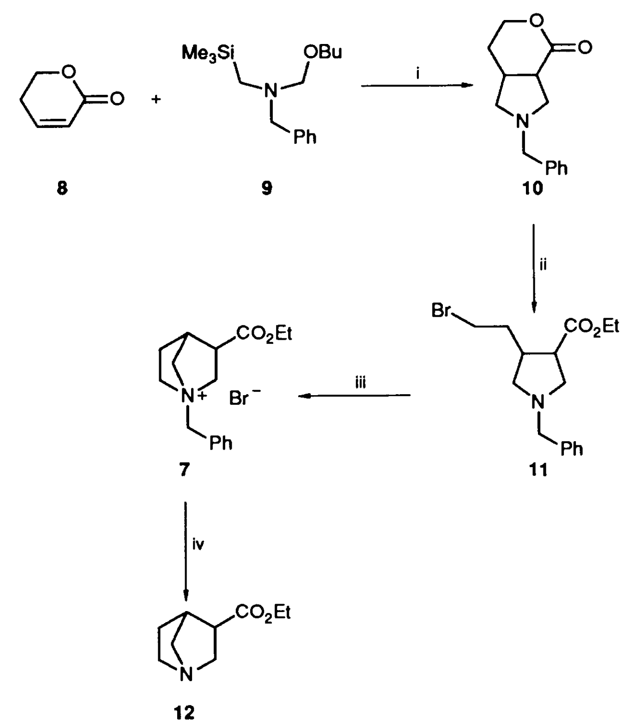
We now report a new method for the preparation of the 1-azabicyclo[2.2.1]heptane-3-carboxylic acid derivatives, in which a two carbon bridge is formed across a pyrrolidine ring onto the nitrogen atom, Scheme 3. Following the procedure of Achiwa,[4] for the preparation of 3,4-disubstituted pyrrolidines, treatment of *N*-benzyl-*N*-methoxymethyltrimethylsilylmethylamine **9**[5] with trifluoroacetic acid in the presence of 5,6-dihydropyran-2-one **8** gave the perhydropyrano[3,4-*c*]pyrrole **10** in 97% yield. Opening of the lactone ring with hydrogen bromide in ethanol gave the bromoethylpyrrolidinium bromide **11** (92% yield), which cyclised spontaneously on conversion into the free base to give the bicyclic quaternary salt **7** in high yield (94%). Debenzylation then gave ethyl (±)-1-azabicyclo-[2.2.1]heptane-3-carboxylate **12** in 82% yield.



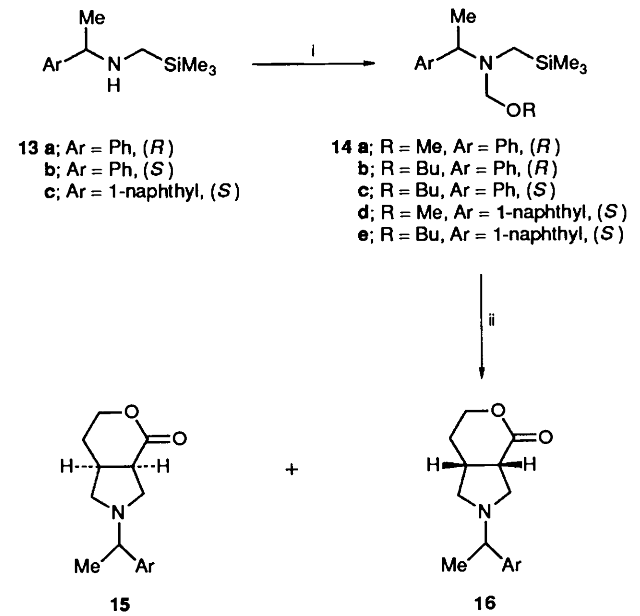
Scheme 2

Results and Discussion

There are no reports of the synthesis of enantiomerically pure 1-azabicyclo[2.2.1]heptane-3-carboxylic acid esters. In a development of the new process, we have now shown that incorporation of a chiral auxiliary on the nitrogen of the aminoacetal silane affords separable diastereoisomers at two stages of the synthesis, allowing preparation of enantiomerically pure products. Padwa[6] has demonstrated encouraging diastereoselectivity in the cycloaddition of azomethine ylides, generated from *N*-cyanomethyl-*N*-trimethylsilylmethylamines bearing a chiral substituent on the nitrogen atom, with nitroalkenes to give 3-aryl-4-nitropyrrolidines. Following this lead we investigated the diastereoselectivity of 1,3-dipolar addition of ylides to the dihydropyranone **8**. Reaction of (*R*)- and (*S*)-*N*-1-phenylethyl-*N*-trimethylsilylmethylamines **13a** and **b** with formaldehyde and butan-1-ol (and methanol with the *R*-isomer) gave the crude amino acetals **14a–c** in good yields, Scheme 4. The amino acetals (*ca.* 85% pure) were not purified, but were used crude to generate the ylide for reaction with 5,6-dihydropyran-2-one **8** yielding mixtures of the *cis*-lactones **15/16 a** and **b**. However, cycloaddition had occurred with no stereo bias as the products were 1:1 mixtures of diastereoisomers. Increasing the size of the chiral auxiliary by preparation of the (*S*)-1-naphthyl derivatives **14d** and **e** followed by reaction with the pyranone **8** failed to improve the isomer ratio of the derived lactones **15c/16c**.



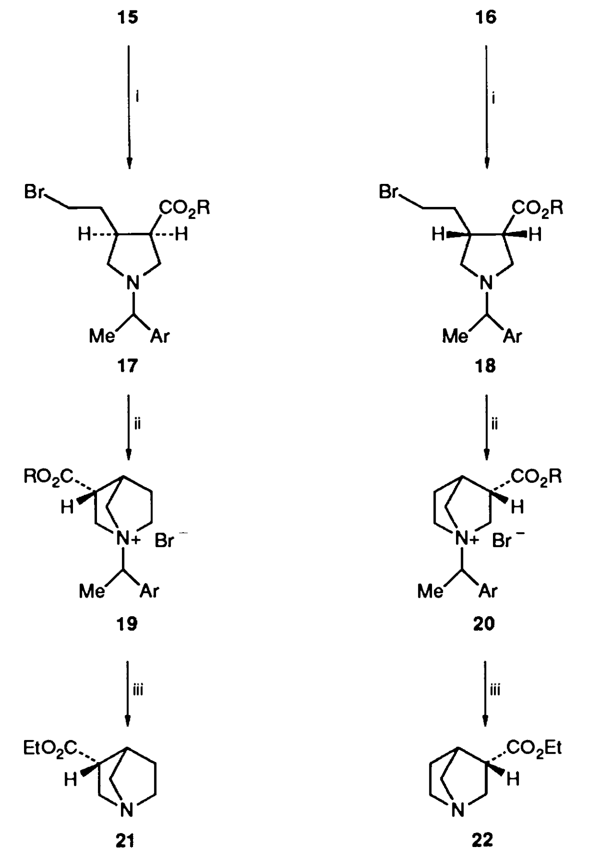
Scheme 3 *Reagents:* i, CF_3CO_2H, EtOAc; ii, HBr, EtOH; iii, $NaHCO_3$, H_2O; iv, cyclohexene, Pd–C



a; Ar = Ph, (*R*)
b; Ar = Ph, (*S*)
c; Ar = 1-naphthyl, (*S*)

Scheme 4 *Reagents:* i, CH_2O, ROH; ii, CF_3CO_2H, **8**, CH_2Cl_2

Separation of the diastereoisomeric lactones (**15**/**16 a** and **b**) was achieved by crystallisation from diethyl ether, the lactones bearing the (*R*)-1-phenylethyl substituent gave the pure (3a*S*,7a*R*) diastereoisomer **16a** in 39% yield and the (*S*)-1-phenylethyl compounds gave pure (3a*R*,7a*S*) diastereoisomer **15b** in 41% yield. The pure lactones **15b** and **16a** were treated with hydrogen bromide in ethanol and the bromoethyl derivatives **17a** and **18b**, which were not isolated, cyclised to give the 3*R*,4*S* and 3*S*,4*R* bicyclic quaternary compounds **19a** and **20b**, respectively, Scheme 5.



a; R = Et, Ar = Ph (*S*)
b; R = Et, Ar = Ph (*R*)
c; R = Pr, Ar = Ph (*R*)
d; R = Bu, Ar = Ph (*R*)
e; R = Et, Ar = 1-naphthyl, (*S*)

Scheme 5 *Reagents:* i, HBr, ROH; ii, $NaCO_3$, H_2O; iii, H_2 or cyclohexene, Pd–C

More conveniently for large scale work, the mixture of lactones **15a**/**16a** was treated with hydrogen bromide in ethanol and the solution concentrated. Neutralisation of the residue gave a mixture of diastereoisomeric quaternary salts **19b**/**20b** which were readily separable by crystallisation to give the pure salt **20b** in 32% yield. Attempts to improve the recovery of crystalline diastereoisomer from the mixture, by conversion of the lactones **15a**/**16a** into the propyl ester **20c** (30%) and butyl ester **20d** (27%) were unsuccessful. The mixture of naphthyl substituted lactones **15c**/**16c** was also treated with hydrogen bromide in ethanol to give the bromoethylpyrrolidines **17e**/**18e** which cyclised on neutralisation to give the quaternary salts **19e**/**20e** in 80% yield. However, the mixture could not be separated by crystallisation and the crude product was hydrogenated to give the racemic ester **12**.

Hydrogenation of the pure diastereoisomeric quaternary salts **19a** and **20b** gave enantiomerically pure ethyl (3*R*,4*S*)- and (3*S*,4*R*)-1-azabicyclo[2.2.1]heptane-3-carboxylates **21** and **22** in 84% and 100% yields, respectively.

X-Ray crystallographic analysis established the 3a*R*,7a*S* configuration of the (*S*)-1-phenylethyl substituted lactone **15b**, a computer generated drawing showing the stereochemistry and conformation is shown in Fig. 1. The azabicycloheptane ester **21** derived from this lactone **15b** therefore has the 3*R*,4*S* configuration. The isomeric *cis*-lactone **16a** was assigned the 3a*S*,7a*R* stereochemistry which leads to the 3*S*,4*R* configuration for the bicycloheptane ester **22**.

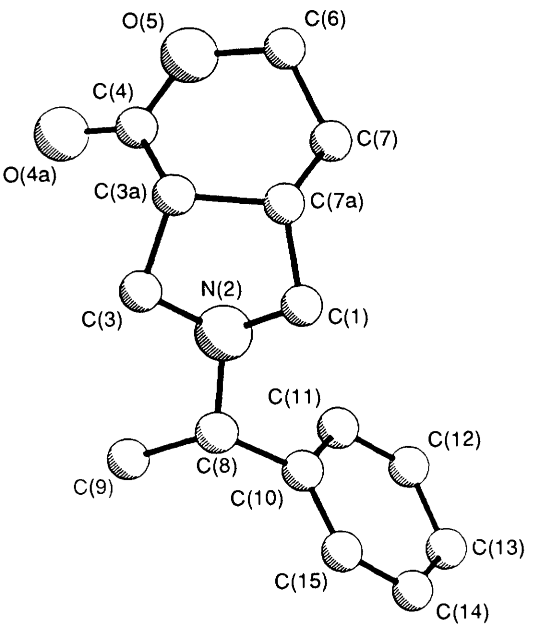


Fig. 1 X-Ray molecular structure of the lactone **15b** with the crystallographic numbering system

Experimental

M.p.s were determined on a Buchi 510 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-250 spectrometer with tetramethylsilane as internal standard in [$^2H_6$]acetone unless otherwise stated. All *J* values are in Hz.

2-Benzyl-4-oxoperhydropyrano[3,4-c]*pyrrolium Hydrogen Maleate* **10**·$HO_2CCH{=}CHCO_2H$.—*N*-Benzyl-*N*-(butoxymethyl)trimethylsilylmethylamine[5] (41.6 g, 0.127 mol) was added over 10 min to a stirred solution of 5,6-dihydropyran-2-one[7] (15.2 g, 0.155 mol) and trifluoroacetic acid (0.1 cm^3) in ethyl acetate (280 cm^3) at 5 °C. The mixture was warmed to 30 °C, whereupon an exothermic reaction carried the temperature to 55 °C before being moderated by an ice bath. The reaction mixture was allowed to cool from 55 to 20 °C during 2 h. Saturated aqueous sodium hydrogen carbonate (80 cm^3) was added, the mixture stirred for 10 min and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 × 80 cm^3) and the organic phases were combined, dried and evaporated to dryness. The crude base was dissolved in ethyl acetate (100 cm^3) and added to a hot solution of maleic acid (17.5 g, 0.15 mol) in ethyl acetate (250 cm^3). The resulting suspension of an oily precipitate was stirred vigorously for 18 h to complete crystallisation. The crystalline solid was collected to give the salt of the *pyrrole* **10** (42.7 g, 97%), m.p. 143–145 °C (Found: C, 62.25; H, 6.1; N, 4.05. $C_{14}H_{17}NO_2{\cdot}C_4H_4O_4$ requires C, 62.25; H, 6.1; N, 4.05%); $\delta_H(CD_3OD)$ 1.62 (1 H, m, 7-H_{ax}), 1.98 (1 H, dddd, *J* 2.2, 5.5, 6.5 and 14.5, 7-H_{eq}), 2.32 (1 H, dd, *J* 4.5 and 8, 1-H_β), 2.67 (1 H, m, 7a-H), 2.72 (1 H, t, *J* 8, 1-H_α), 2.82 (1 H, dd, *J* 8.5 and 10, 3-H_α), 2.91 (1 H, dd, *J* 5.5 and 10, 3-H_β), 3.05 (1 H, ddd, *J* 5.5, 8.5 and 10, 3a-H), 3.52 (1 H, d, *J* 13, NCH_A), 3.61 (1 H, d, *J* 13, NCH_B), 4.18 (1 H, ddd, *J* 2.2, 9.5 and 11, 6-H_α), 4.35 (1 H, ddd, *J* 3.2, 5.5, 11, 6-H_β) and 7.1–7.4 (5 H, m, Ph).

1-Benzyl-3-(2-bromoethyl)-4-ethoxycarbonylpyrrolidinium Bromide **11**·HBr.—Hydrogen bromide gas was bubbled into a solution of pyranopyrrole **10** (13.6 g, 59 mmol) in ethanol (300 cm^3) at 5 °C. The mixture crystallised, but the solid redissolved as more hydrogen bromide was absorbed. The saturated solution was stirred at 20 °C for 18 h and then evaporated under reduced pressure at 40 °C. The residue was triturated with ethanol (100 cm^3) to give the *bromoethylpyrrolidine* **11** as the crystalline hydrobromide salt (22.9 g, 92%), m.p. 180–182 °C (Found: C, 45.65; H, 5.45; Br, 38.0; N, 3.3. $C_{16}H_{22}BrNO_2{\cdot}HBr$ requires C, 45.65; H, 5.5; N, 3.35; Br, 37.95%); $\delta_H(CD_2Cl_2)$ 1.31 (3 H, t, *J* 6.5, Me), 1.92 (2 H, m, CH_2), 2.75–3.1 (2 H, m, 3- and 4-H), 3.25 (3 H, m, 2-H_2 and 5-H), 3.63 (1 H, dd, *J* 6 and 10, 5-H), 3.87 (2 H, dd, *J* 8 and 13.9, CH_2Br), 4.22 (2 H, 2 × q, *J* 6.5, CH_2O), 4.38 (1 H, d, *J* 13, NCH_A), 4.46 (1 H, d, *J* 13, NCH_B) and 7.4–7.6 (5 H, m, Ph).

1-Benzyl-3-ethoxycarbonyl-1-azoniabicyclo[2.2.1]*heptane Bromide* **7**.—Pyrrolidinium bromide **11**·HBr (10 g, 24 mmol) was slurried in chloroform (70 cm^3) and the mixture treated with saturated aqueous sodium hydrogen carbonate (70 cm^3). The mixture was stirred vigorously at 20 °C for 15 min, the phases were separated and the aqueous phase was extracted with chloroform (3 × 70 cm^3). The organic phases were combined, dried (Na_2SO_4) and evaporated under reduced pressure. The residual oil was stirred with ethyl acetate–chloroform (100 cm^3; 9:1) at 5 °C for 16 h. The crystalline product was filtered off under nitrogen and dried *in vacuo* at 55 °C for 48 h to give the extremely hygroscopic quaternary salt **7** (7.6 g, 94%), m.p. 94–102 °C (Found: M^+, 260.1662. $C_{16}H_{22}NO_2{}^+$ requires M^+, 260.1650); $\delta_H(CD_2Cl_2)$ 1.98 (3 H, t, *J* 6.5, Me), 1.64 and 2.2 (2 H, m, 5-H_2), 3.0–3.25 (2 H, m, 3- and 4-H), 3.48 and 3.62 (2 H, m, 7-H_2), 3.9–4.6 (4 H, m, 2- and 6-H_2), 4.18 (2 H, q, *J* 6.5, CH_2O), 5.25 (2 H, s, CH_2) and 7.4–7.7 (5 H, m, Ph).

3-Ethoxycarbonyl-1-azoniabicyclo[2.2.1]*heptane Bromide* **12**·HBr.—(*a*) *From the bromide* **7**. A solution of the bromide **7** (2.0 g, 5 mmol) and cyclohexene (8 cm^3) in ethanol (40 cm^3) was heated under reflux with 10% Pd/C (0.2 g) for 4 h. The catalyst was filtered off and the filtrate evaporated to give the racemic *ester* **12** as the extremely hygroscopic hydrobromide salt (1.2 g, 82%), m.p. 171–173 °C; $\delta_H(CD_3OD)$ 1.1 (3 H, t, *J* 6.5, Me), 1.53, 1.92 (2 H, m, 5-H_2), 3.0–3.6 (8 H, m, 2-, 6-, 7-H_2 and 3-, 4-H) and 4.04 (2 H, 2 × q, *J* 6.5, CH_2O). A sample of the HBr salt was converted into the non-hygroscopic hydrogen oxalate, m.p. 132–133 °C (isopropyl alcohol) (Found: C, 50.95; H, 6.6; N, 5.4. $C_9H_{15}NO_2{\cdot}C_2H_2O_4$ requires C, 50.95; H, 6.6; N, 5.4%).

(*b*) *From* 1-[(S)-1-(1-*naphthyl*)*ethyl*]-3-*ethoxycarbonyl*-1-*azoniabicyclo*[2.2.1]*heptane Bromide* (**19e**/**20e**). A solution of bromide **19e**/**20e** (0.72 g, 1.8 mmol) and cyclohexene (5 cm^3) in ethanol (30 cm^3) was heated under reflux with 10% Pd/C (70 mg) for 24 h. The catalyst was filtered off and the filtrate evaporated to give the *ester* **12**·HBr (0.34 g, 76%), m.p. 168–170 °C identical (NMR) with previous sample.

(S)-(−)-N-(*1-Phenylethyl*)-N-*trimethylsilylmethylamine* **13b**.—This compound was prepared by the method used by Padwa[6] for the preparation of the *R*-isomer **13a**. The *S* amine **13b** was obtained as an oil, b.p. 84–85 °C/0.3 mbar* in 71% yield (Found: C, 69.5; H, 10.1; N, 6.65. $C_{12}H_{21}NSi$ requires C, 69.5; H, 10.2; N, 6.75%); $\delta_H(CDCl_3)$ 0.0 (9 H, s, $SiMe_3$), 1.31 (3 H, d, *J* 7, Me), 1.84 (1 H, d, *J* 13.5, NCHSi), 1.91 (1 H, d, *J* 13.5, NCHSi), 3.63 (1 H, q, *J* 7, PhCH) and 7.17–7.35 (5 H, m, Ph); $[\alpha]_D$ −50.0° (*c* 0.5 in $CHCl_3$).

(S)-(−)-N-(*1-Naphthyl*)*ethyl*-N-*trimethylsilymethylamine* **13c**.—(*S*)-(−)-1-(1-Naphthyl)ethylamine (12.5 g, 0.073 mol) and chloromethyltrimethylsilane (6.0 g, 0.049 mol) were gently heated together under reflux (*ca.* 105 °C) and under a nitrogen atmosphere. Heating was continued for 4 h, the oil bath

* 1 mbar = 100 Pa.

temperature reaching 185 °C. The reaction mixture was cooled in a water bath, toluene (50 cm^3) and 15% aqueous potassium hydroxide (45 cm^3) were added and the mixture was stirred vigorously. The layers were separated and the aqueous layer was extracted with toluene (2 × 50 cm^3). The organic phases were combined, dried (K_2CO_3) and evaporated under reduced pressure to give an orange oil. Chromatography of the oil on silica gel with ethyl acetate followed by distillation (Kugelrohr) gave the *amine* **13c** (as a colourless oil (8.4 g, 67%), b.p. 100 °C/0.3 mbar (Found: C, 74.7; H, 9.05; N, 5.4. $C_{16}H_{23}NSi$ requires C, 74.65; H, 9.0; N, 5.45%); $\delta_C(CD_2Cl_2)$ − 1.9 ($SiMe_3$), 24.2 (Me), 39.2 (NCH_2Si), 59.1 (CH), 124.0, 124.4, 126.2, 126.6, 126.8, 127.9, 129.8, 130.8, 135.5 and 142.7 (naphthyl).

(R)-(+)-N-1-*Phenylethyl*-N-*(methoxymethyl)trimethylsilylmethylamine* **14a**.—(R)-(+)-*N*-1-Phenylethyl-*N*-trimethylsilylmethylamine[6] (5.61 kg, 27.1 mol) was added to an ice-cooled mixture of methanol (1.29 dm^3, 3.18 mol) and aqueous formaldehyde (37–40% w/v, 2.49 dm^3) during 45 min. The heterogeneous mixture was stirred at 0 °C for 2 h and then anhydrous potassium carbonate (1.08 kg) was added and the mixture stirred for 30 min at 0 °C. The layers were separated and the aqueous phase extracted with methyl *tert*-butyl ether (2 × 5 dm^3). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure at < 30 °C to give the *acetal* **14a** as a colourless oil (6.76 kg, 99%) (85% pure); δ_C (CD_2Cl_2) − 1.1 ($SiMe_3$), 19.61 (Me), 40.38 (NCH_2Si), 54.91 (OMe), 62.51 (CH), 86.41 (NCH_2O), 127.13, 128.16, 128.61 and 146.07 (Ph).

(R)-(+)-N-1-*Phenylethyl*-N-*(butoxymethyl)trimethylsilylmethylamine* **14b**. The title compound was prepared from (*R*)-(+)-*N*-1-phenylethyl-*N*-trimethylsilylmethylamine by reaction with butan-1-ol and aqueous formaldehyde following the general procedure to give the *acetal* **14b** (85% pure) as a colourless oil (34.2 g, 84%); $\delta_C(CD_2Cl_2)$ − 1.09 ($SiMe_3$), 14.35, 20.16, 24.72, 67.38 (OBu), 19.57 (CMe), 40.30 (NCH_2Si), 62.30 (CH), 84.73 (NCH_2O), 127.01, 128.15, 128.51 and 146.15 (Ph).

(S)-(−)-N-1-*Phenylethyl*-N-*(butoxymethyl)trimethylsilylmethylamine* **14c**. The title compound was prepared from (*S*)-(−)-N-1-phenylethyl-*N*-trimethylsilylmethylamine by reaction with butan-1-ol and aqueous formaldehyde following the general procedure to give the *acetal* **14c** (85% pure) as a colourless oil (7.1 g, 80%). The NMR spectrum was identical with the above (*R*)-isomer.

(S)-(−)-N-[1-(1-*Naphthyl)ethyl*]-N-*methoxymethyltrimethylsilylmethylamine* **14d**. The title compound was prepared from (*S*)-(−)-*N*-1-(1-naphthyl)ethyl-*N*-trimethylsilylmethylamine by reaction with methanol and aqueous formaldehyde following the general procedure to give the *acetal* **14d** (85% pure) as a colourless oil (3.6 g, 93%); δ_H 0.0 (9 H, s, $SiMe_3$), 1.57 (3 H, d, *J* 7, Me), 2.18, 2.40 (2 H, ABq, *J* 15, NCH_2Si), 3.17 (3 H, s, OMe), 4.15, 4.30 (2 H, ABq, *J* 10, NCH_2O), 4.72 (1 H, q, *J* 7, CH) and 7.4–8.5 (7 H, m, naphthyl).

(S)-(−)-N-[1-(1-*Naphthyl)ethyl*]-N-*butoxymethyltrimethylsilylmethylamine* **14e**. The title compound was prepared from (*S*)-(−)-*N*-1-(1-naphthyl)ethyl-*N*-trimethylsilylmethylamine by reaction with butan-1-ol and aqueous formaldehyde following the general procedure to give the *acetal* **14e** (80% pure) as a pale yellow oil (5.5 g, 82%); δ_H 0.1 (9 H, s, $SiMe_3$), 0.93 (3 H, t, *J* 7, Me), 1.2–1.7 (7 H, m, Me and $[CH_2]_2$), 2.22, 2.45 (2 H, ABq, *J* 15, NCH_2Si), 3.25 (2 H, t, *J* 7, CH_2O), 4.22, 4.35 (2 H, ABq, *J* 10, NCH_2O), 4.78 (1 H, q, *J* 7, CH) and 7.3–8.5 (7 H, m, naphthyl).

2-[(R)-1-*Phenylethyl*]-*perhydropyrano*[3,4-c]*pyrrol-4-one* **15a/16a**.—(*a*) *From methyl acetal* **14a**. Crude amine **14a** (3.42 kg. 11.6 mol) was added during 10 min to a cooled, stirred solution of 5,6-dihydropyran-2-one (1.29 kg, 13.16 mol) and trifluoroacetic acid (6 cm^3) in ethyl acetate (73 dm^3) at 15 °C. Cooling was discontinued and an exothermic reaction carried the reaction temperature to 45 °C. The solution was stirred for 1.5 h its temperature being allowed to fall to 27 °C. Aqueous sodium hydrogen carbonate (3.1 dm^3) was added and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 × 3 dm^3) and the extracts were combined, washed with water and dried (Na_2SO_4). The solution was evaporated under reduced pressure and the residue dissolved in hot ethyl acetate (9.6 dm^3). A solution of maleic acid (1.52 kg, 13.13 mol) in hot ethyl acetate (16.8 dm^3) was added with stirring and then hexane (4.8 dm^3) was added to complete the crystallisation. The crystalline solid was collected to give the *lactones* **15a/16a** as the maleate salt (3.57 kg, 85%), m.p. 123–125 °C. A sample recrystallised from isopropyl alcohol resulted in some separation of diastereoisomers to give the salt, m.p. 160–161 °C (Found: C, 63.1; H, 6.45; N, 3.85. $C_{16}H_{19}NO_2 \cdot C_4H_4O_4$ requires C, 63.15; H, 6.4; N, 3.9%).

The maleate salt (3.57 kg) was added portionwise to a stirred mixture of ethyl acetate (8.5 dm^3) and aqueous sodium hydrogen carbonate (23 dm^3). The mixture was stirred at 20 °C for a further 30 min and then the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 5.5 dm^3) and the organic layers were combined and dried (Na_2SO_4). The solution was evaporated under reduced pressure to afford the mixture of *diastereoisomers* **15a/16a** as a yellow oil (2.31 kg, 96% recovery) which crystallised. The NMR spectrum showed the product to be a 1:1 mixture of the diastereoisomers. δ_C 23.53, 23.70 (C-7), 27.53, 27.70 (Me), 35.64, 35.76 (C-7a), 42.65, 42.67 (C-3a), 56.30, 58.86 (C-1), 59.79, 59.82 (C-3), 65.50, 65.59 (CH), 67.61, 67.68 (C-6), 127.74, 127.83, 129.17, 129.24, 146.5 (Ph), 173.40 and 173.42 (CO).

(*b*) *From butyl acetal* **14b**. Similarly reaction of amine **14b** with 5,6-dihydropyran-2-one in the presence of trifluoroacetic acid gave the *lactone* **15a/16a** (18.5 g, 72% yield) with a NMR spectrum identical to the above free base.

Separation of diastereoisomeric lactones **15a/16a**. The 1:1 mixture of diastereoisomers **15a/16a** (20 g) was crystallised from diethyl ether (50 cm^3) and the product recrystallised twice from diethyl ether (20 cm^3) to give the more polar diastereoisomer (3a*S*,7a*R*)-2-[(*R*)-1-phenylethyl]perhydropyrano[3,4-*c*]pyrrol-4-one **16a** (3.9 g, 39%), m.p. 85–87 °C (Found: C, 73.35; H, 7.8; N, 5.7. $C_{15}H_{19}NO_2$ requires C, 73.5; H, 7.8; N, 5.7%); δ_C 23.70 (C-7), 27.70 (Me), 35.76 (C-7a), 42.67 (C-3a), 58.86 (C-1), 59.79 (C-3), 65.59 (CH), 67.68 (C-6), 127.83, 129.24, 146.5 (Ph) and 173.4 (CO); $[\alpha]_D$ +30.9° (*c* 1 in EtOAc).

Separation of diastereoisomeric lactones **15b/16b**. A mixture of lactones **15b/16b** was obtained from amine **14b** and 5,6-dihydropyran-2-one as above. The mixture of diastereoisomers (10.9 g) was crystallised from diethyl ether (30 cm^3) and the product recrystallised from diethyl ether (10 cm^3) to give the more polar diastereoisomer (3aR,7aS)-2-[(S)-1-*phenylethylperhydropyrano*[3,4-c]*pyrrol-4-one* **15b** (2.2 g, 41%) m.p. 86–87 °C (Found: C, 73.35; H, 7.8; N, 5.65. $C_{15}H_{19}NO_2$ requires C, 73.5; H, 7.8; N, 5.7%; δ_C 23.53 (C-7), 27.53 (Me), 35.64 (C-7a), 42.65 (C-3a), 56.30 (C-1), 59.82 (C-3), 65.50 (CH), 67.61 (C-6), 127.74, 129.17, 146.5 (Ph) and 173.42 (CO); $[\alpha]_D$ −30.1° (*c* 1 in EtOAc).

2-[(S)-(−)-1-(1-*Naphthyl)ethyl*]*perhydropyrano*[3,4-c]*pyrrol-4-one* **15c/16c**.—(*a*) *From methyl acetal* **14d**. A solution of trifluoroacetic acid in dichloromethane (1 mol dm^{-3}; 1 cm^3) was added to a stirred solution of crude (*S*)-(−)-*N*-[1-(1-naphthyl)-ethyl]-*N*-methoxymethyltrimethylsilylmethylamine (3.5 g, 9.9 mmol) and 5,6-dihydropyran-2-one (1.3 g, 13.3 mmol) in dichloromethane (15 cm^3) at 0 °C. The cooling bath was removed and a slight exotherm was noted. After 20 min no acetal remained. The reaction mixture was washed with saturated aqueous sodium hydrogen carbonate (10 cm^3) and the aqueous solution back-extracted with dichloromethane (2 × 10 cm^3). The combined extracts were washed with saturated brine (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give an orange oil. Chromatography on silica with ethyl acetate followed by Kugelrohr distillation gave the *lactones* **15c/16c** as an oil (2.2 g, 76%), b.p. 70 °C/0.2 mbar; δ_C 22.72 (C-7), 27.70 (Me), 35.84, 36.93 (C-7a), 42.74, 42.84 (C-3a), 56.97, 57.08 (C-1), 59.83, 60.06 (C-3), 67.70 (C-6), 124.90, 125.09, 125.37, 125.80, 126.22, 126.55, 128.19, 128.29, 129.22, 129.75 and 147.80 (naphthyl). The lactone (1.8 g, 6.1 mmol) was dissolved in *tert*-butyl methyl ether (18 cm^3) and treated with maleic acid (0.7 g, 6.0 mmol) in ethyl acetate (7 cm^3) to give the mixture of diastereoisomers as the maleate salt (1.9 g, 76% recovery), m.p. 87–98 °C (Found: C, 67.0; H, 6.15; N, 3.4. $C_{19}H_{21}NO_2 \cdot C_4H_4O_4$ requires C, 67.15; H, 6.1; N, 3.4%).

(*b*) *From butyl acetal* **14e**. Similarly reaction of (*S*)-(−)-*N*-[1-(1-naphthyl)ethyl]-*N*-butoxymethyltrimethylsilylmethylamine with 5,6-dihydropyran-2-one in the presence of trifluoroacetic acid gave the *lactones* **15c/16c** (2.2 g, 59%) with a NMR spectrum identical with that of the above product.

(3R,4S)-3-*Ethoxycarbonyl*-1-[(S)-1-*phenylethylazoniabicyclo*-[2.2.1]*heptane Bromide* **19a**.—A solution of the perhydropyrano[3,4-*c*]pyrrole **15b** (80 mg, 0.03 mmol) in ethanol (5 cm^3) was saturated with hydrogen bromide gas at 0 °C, and the solution allowed to warm to 20 °C during 48 h. The solution was evaporated and the residue basified by addition of saturated aqueous sodium hydrogen carbonate. The mixture was extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated. The gummy residue was triturated with acetone to give the quaternary salt **19a** (0.11 g, 95%), m.p. 159–160 °C (from ethanol–ethyl acetate) (Found: C, 56.3; H, 6.9; Br, 22.0; N, 3.8. $C_{17}H_{24}BrNO_2 \cdot 0.5H_2O$ requires C, 56.2; H, 6.9; Br, 22.0; N, 3.8%); $[\alpha]_D$ −25.2° (*c* 1 in MeOH); δ_C 16.15, 62.09 (EtO), 14.41 (Me), 24.80 (C-5), 38.87 (C-4), 43.19 (C-3), 57.89 (C-2), 59.94 (C-6), 66.29 (CHN^+), 66.61 (C-7), 129.27, 130.75 and 130.84 (Ph).

(3S,4R)-3-*Ethoxycarbonyl*-1-[(R)-1-*phenylethyl*]-1-*azoniabicyclo*[2.2.1]*heptane Bromide* **20b**.—(*a*) *From diastereoisomer* **16a**. A solution of the perhydropyrano[3,4-*c*]pyrrole **16a** (120 mg, 0.045 mmol) in ethanol (5 cm^3) was saturated with hydrogen bromide gas at 0 °C. The solution was allowed to warm to 20 °C during 24 h and then evaporated to give the salt of the *bromoethylpyrrolidine* **18b**; δ_C(CD_3OD) 12.58, 60.89 (EtO), 18.06 (Me), 29.08 (CH_2), 31.03 (CH_2Br), 39.16 (C-4), 43.93 (C-3), 53.66 (C-2), 55.26 (C-5), 66.47 (CHN), 127.18, 128.57, 128.82, 136.02 (Ph) and 171.20 (CO). The gum was stirred with aqueous sodium hydrogen carbonate and chloroform. The organic phase was dried (Na_2SO_4) and evaporated and the residue triturated with acetone to give the quaternary salt **20b** (0.17 g, 95%), m.p. 160–162 °C (from ethanol–ethyl acetate) (Found: C, 57.3; H, 6.85; Br, 22.55; N, 3.95. $C_{17}H_{24}BrNO_2$ requires C, 57.65; N, 6.85; Br, 22.55; N, 3.95%); $[\alpha]_D$ +22.8° (*c* 1 in MeOH); δ_C 16.15, 62.09 (EtO), 14.41 (Me), 28.80 (C-5), 38.87 (C-4), 43.19 (C-3), 57.89 (C-2), 59.94 (C-6), 66.29 (CHN^+), 66.61 (C-7), 129.27, 130.75 and 130.84 (Ph).

(*b*) *From a mixture of diastereoisomers* **15a/16a**. In a similar manner a solution of a 1:1 mixture of the (3a*R*,7a*S*)- and (3a*S*,7a*R*)-pyrano[3,4-*c*]pyrroles (**15a**, **16a**) (139 g, 0.57 mol) in ethanol (1.39 dm^3) were saturated with hydrogen bromide and then neutralised with aqueous sodium hydrogen carbonate to give a mixture of the 3*S*,4*R* and 3*R*,4*S* quaternary salts (189 g) in 94% yield. The crude mixture was dissolved in boiling ethanol (90 cm^3), and ethyl acetate (810 cm^3) was added to the hot solution. Cooling gave a crystalline solid (69.0 g) which was suspended in boiling acetone (640 cm^3) for 1 h. The suspension was cooled to 5 °C for 2 h and then filtered to give the 3S,4R *quaternary salt* **20b** as a colourless solid (64.0 g, 32%), m.p. 160–161 °C identical (NMR) with the previous sample.

(3S,4R)-3-*Propoxycarbonyl*-1-[(R)-1-*phenylethyl*]-1-*azoniabicyclo*[2.2.1]*heptane Bromide* **20c**.—A solution of the pyrano[3,4-*c*]pyrrole isomers **15a/16a** (5.8 g) in propan-1-ol (116 cm^3) was saturated with hydrogen bromide gas and heated under reflux overnight. The solvent was removed under reduced pressure and the residue treated with saturated aqueous sodium hydrogen carbonate (150 cm^3). The mixture was extracted with chloroform (3 × 100 cm^3) and the extract dried (Na_2SO_4) and evaporated. The residue was crystallised from acetone–ethyl acetate (1:1) to give a 4:1 diastereoisomeric mixture (3*S*,4*R*:3*R*,4*S*) of the quaternary salts. Recrystallisation from acetone afforded the pure 3*S*,4*R* *isomer* **20c** as a colourless crystalline solid (1.3 g, 30%), m.p. 144–146 °C (Found: C, 56.1; H, 7.15; Br, 20.8; N, 3.8. $C_{18}H_{26}BrNO_2 \cdot H_2O$ requires C, 55.95; H, 7.3; Br, 20.7; N, 3.65%); $[\alpha]_D$ +22.6° (*c* 0.5 in EtOH), δ_C(CD_2Cl_2) 10.48, 22.25, 66.56 (PrO), 16.45 (Me), 24.83 (C-5), 38.66 (C-4), 45.12 (C-3), 57.91 (C-2), 59.70 (C-6), 66.36 (CHN^+), 67.75 (C-7), 129.70, 130.41, 130.78, 132.21 (Ph) and 170.90 (CO).

(3*S*,4*R*)-3-*Butoxycarbonyl*-1-[(R)-1-*phenylethyl*]-1-*azoniabicyclo*[2.2.1]*heptane Bromide* **20d**.—A solution of the pyrano[3,4-*c*]pyrrole isomers **15a/16a** (5.0 g) in butan-1-ol (100 cm^3) was saturated with hydrogen bromide gas and heated under reflux overnight. The solvent was removed under reduced pressure and the residue treated with aqueous sodium hydrogen carbonate (150 cm^3) and extracted with chloroform (3 × 100 cm^3). The extract was dried (Na_2SO_4) and evaporated. The crude product was chromatographed on silica gel eluting with ethyl acetate–methanol (3:1) then crystallised from ethyl acetate–acetone (4:1) to give the 3S,4R *salt* **20d** as a colourless solid (1.06 g, 27%), m.p. 92–94 °C (Found: C, 56.75; H, 7.45; Br, 19.8; N, 3.65. $C_{19}H_{28}NO_2Br \cdot H_2O$ requires C, 57.0; H, 7.55; Br, 19.95; N, 3.5%); $[\alpha]_D$ +22.9° (*c* 0.5 in EtOH); δ_C(CD_2Cl_2) 13.81, 19.45, 30.69, 66.08 (BuO), 16.42 (Me), 24.83 (C-5), 38.62 (C-4), 45.17 (C-3), 57.86 (C-2), 59.75 (C-6), 66.22 (CHN^+), 66.52 (C-7), 129.67, 130.36, 130.76, 134.15 (Ph) and 170.81 (CO).

3-*Ethoxycarbonyl*-1-[(S)-1-(1-*naphthyl*)*ethyl*]-1-*azoniabicyclo*[2.2.1]*heptane Bromide* **19e/20e**.—2-[(S)-1-(1-Naphthyl)-ethyl]-4-oxoperhydropyrano[3,4-*c*]pyrrolium hydrogen maleate (**15/16e**·$HO_2CCH{=}CHCO_2H$ 4.4 g, 10.7 mmol) was slurried in ethyl acetate (50 cm^3) and treated with aqueous sodium hydrogen carbonate (50 cm^3). The mixture was stirred until all the solid had dissolved, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 50 cm^3). The organic phases were combined, dried and evaporated. The pale brown oil (3.2 g) was dissolved in absolute ethanol (60 cm^3) and the solution cooled to 5 °C. The mixture was saturated with hydrogen bromide gas (temperature ⩽15 °C) during 2 h. The solution was stirred at 20 °C for 16 h and then the solvent removed under reduced pressure to give the crude *bromoethyl diastereoisomers* **17e/18e** as the hydrobromide salt (4.5 g, 87%); δ_H(CD_2Cl_2) 1.28 and 1.32 (3 H, t, *J* 6.5, Me), 1.7 and 2.05 (2 H, m, CH_2), 1.91 and 1.97 (3 H, d, *J* 6.5, Me), 2.4–3.85 (6 H, m, CH_2Br, C-2, -3 and -4), 3.9–4.4 (4 H, m, CH_2O and C-5), 5.6 (1 H, m, CHN) and 7.0–8.8 (7 H, m, naphthyl).

The salt (4.2 g, 8.7 mmol) in chloroform (50 cm^3) was stirred vigorously with aqueous sodium hydrogen carbonate (25 cm^3) and the phases were separated. The aqueous phase was extracted with chloroform (3 × 25 cm^3). The organic phases were combined, dried (Na_2SO_4) and evaporated to a mixture of diastereoisomeric quaternary salts **19e/20e** (3.2 g, 80%) (Found:

Table 1 Bond lengths (Å)[a] for compound **15b**

C(1)–N(2)	1.45(2)	C(6)–C(7)	1.516(3)
C(1)–C(7a)	1.531(7)	C(7)–C(7a)	1.505(3)
N(2)–C(3)	1.470(2)	C(8)–C(9)	1.511(2)
N(2)–C(8)	1.466(2)	C(8)–C(10)	1.523(2)
C(3)–C(3a)	1.520(2)	C(10)–C(11)	1.384(2)
C(3a)–C(4)	1.511(3)	C(10)–C(15)	1.374(2)
C(3a)–C(7a)	1.560(2)	C(11)–C(12)	1.384(2)
C(4)–O(4a)	1.203(3)	C(12)–C(13)	1.385(3)
C(4)–O(5)	1.335(3)	C(13)–C(14)	1.375(3)
O(5)–C(6)	1.442(3)	C(14)–C(15)	1.383(2)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 2 Bond angles (°)[a] for compound **15b**

N(2)–C(1)–C(7a)	104(1)	C(1)–C(7a)–C(3a)	102.9(3)
C(1)–N(2)–C(3)	103.0(2)	C(1)–C(7a)–C(7)	113.9(7)
C(1)–N(2)–C(8)	113.1(6)	C(3a)–C(7a)–C(7)	111.0(2)
C(3)–N(2)–C(8)	113.8(1)	N(2)–C(8)–C(9)	111.7(1)
N(2)–C(3)–C(3a)	103.3(1)	N(2)–C(8)–C(10)	110.8(1)
C(3)–C(3a)–C(4)	111.2(2)	C(9)–C(8)–C(10)	109.0(1)
C(3)–C(3a)–C(7a)	104.7(1)	C(8)–C(10)–C(11)	121.1(1)
C(4)–C(3a)–C(7a)	116.4(2)	C(8)–C(10)–C(15)	119.7(1)
C(3a)–C(4)–O(4a)	122.9(2)	C(11)–C(10)–C(15)	119.1(1)
C(3a)–C(4)–O(5)	119.1(2)	C(10)–C(11)–C(12)	120.4(2)
O(4a)–C(4)–O(5)	117.9(2)	C(11)–C(12)–C(13)	119.8(2)
C(4)–O(5)–C(6)	119.8(2)	C(12)–C(13)–C(14)	120.0(1)
O(5)–C(6)–C(7)	109.9(2)	C(13)–C(14)–C(15)	119.6(2)
C(6)–C(7)–C(7a)	109.4(2)	C(10)–C(15)–C(14)	121.1(2)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 3 Fractional co-ordinates of atoms[a] for compound **15b**

Atom	*x*	*y*	*z*
C(1)	0.7905(2)	0.0852	0.8327(2)
N(2)	0.7168(1)	0.2434(4)	0.7391(1)
C(3)	0.5697(2)	0.2277(6)	0.7300(2)
C(3a)	0.5818(2)	0.2510(5)	0.8505(2)
C(4)	0.5495(2)	0.5053(6)	0.8757(2)
O(4a)	0.4622(2)	0.6301(6)	0.8082(2)
O(5)	0.6155(2)	0.5935(5)	0.9785(1)
C(6)	0.7286(3)	0.4585(8)	1.0594(2)
C(7)	0.8179(2)	0.3414(7)	1.0031(2)
C(7a)	0.7320(2)	0.1536(5)	0.9215(2)
C(8)	0.7369(2)	0.1756(5)	0.6366(1)
C(9)	0.6494(2)	0.3307(7)	0.5387(2)
C(10)	0.8914(2)	0.1965(4)	0.6524(1)
C(11)	0.9707(2)	0.3958(6)	0.7041(2)
C(12)	1.1079(2)	0.4203(7)	0.7105(2)
C(13)	1.1661(2)	0.2443(8)	0.6651(2)
C(14)	1.0884(2)	0.0440(7)	0.6153(2)
C(15)	0.9515(2)	0.0217(6)	0.6094(2)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

M^+, 324.1945. $C_{21}H_{26}NO_2^+$ requires M^+, 324.1963); $\delta_H(CD_2Cl_2)$ 1.23 and 1.98 (3 H, t, *J* 6.5, Me), 1.7, 1.95 and 2.47 (2 H, m, 5-H_2), 1.95 and 2.03 (3 H, d, *J* 6.5, Me), 3.0–3.4 (2 H, m, 3- and 4-H), 3.4–5.2 (6 H, m, 2-, 6- and 7-H_2), 4.12 and 4.18 (2 H, q, *J* 6.5, CH_2O), 6.52 (1 H, 2 × q, *J* 6.5, CHN), 7.4–8.1 (6 H, m, naphthyl) and 9.19 (1 H, br d, *J* 9, naphthyl 8-H).

(3R,4S)-3-*Ethoxycarbonyl*-1-*azoniabicyclo*[2.2.1]*heptane Hydrogen Oxalate* **21**·HO_2CCO_2H.—The 1-azoniabicyclo-[2.2.1]heptane **19a** (4.8 g, 13.5 mmol) in ethanol (200 cm^3) containing acetic acid (3 cm^3) was shaken with 10% palladium on carbon (0.6 g) under a hydrogen atmosphere (150 psi) for 48 h at 20 °C. The catalyst was filtered off and washed with ethanol (3 × 50 cm^3). The combined filtrates were evaporated under reduced pressure at ⩽40 °C. The solid residue was cooled in an ice bath and basified by addition of saturated aqueous sodium hydrogen carbonate (20 cm^3). Chloroform (100 cm^3) was added, followed by sufficient water (10 cm^3) to give two clear layers. The layers were separated and the aqueous phase was extracted with chloroform (2 × 100 cm^3). The combined extracts were dried (Na_2SO_4), evaporated to dryness under reduced pressure, and flushed with isopropyl alcohol (20 cm^3). A solution of anhydrous oxalic acid (1.22 g, 13.5 mmol) in isopropyl alcohol (20 cm^3) was added and the mixture heated to give a clear solution. The solution was allowed to cool and crystallise to give *ester* **21** as the hydrogen oxalate salt (2.9 g, 84%), m.p. 130–132 °C (Found: C, 50.8; H, 6.6; N, 5.4. $C_9H_{15}NO_2 \cdot C_2H_2O_4$ requires C, 50.95; H, 6.6; N, 5.4%); $[\alpha]_D$ −32° (*c* 0.5 in EtOH); δ_C (free base) 13.52, 59.67 (EtO), 24.88 (C-5), 40.72 (C-4), 46.12 (C-3), 53.25 (C-6), 55.86 (C-7), 59.67 (C-2) and 173.64 (CO).

Ethyl (3S,4R)-1-*Azabicyclo*[2.2.1]*heptane*-3-*carboxylate* **22**.—10% Palladium on charcoal (120 g) was suspended in ethanol (11 dm^3) at <0 °C in a 30 gallon glass lined vessel under nitrogen. A solution of (3*S*,4*R*)-3-ethoxycarbonyl-1-[(*R*)-1-phenylethyl]-1-azoniabicyclo[2.2.1]heptane bromide **20b** (1.2 kg, 3.39 mol) in ethanol (19 dm^3) was added followed by cyclohexene (5 dm^3). The mixture was heated under reflux at 74 °C for 4 h and then allowed to cool. The catalyst was filtered off and the filtrate evaporated to give *ester* **22** as the crystalline hydrobromide salt (850 g, 100%), m.p. 168–170 °C (Found: C, 43.35; H, 6.4; N, 5.55. $C_9H_{15}NO_2 \cdot HBr$ requires C, 43.2; H, 6.45; N, 5.6%); $[\alpha]_D$ +30.1° (*c* 0.5 in EtOH); $\delta_C(CD_3OD)$ 12.54 (Me), 22.55 (C-5), 38.50 (C-4), 43.09 (C-3), 51.70 (C-6), 53.58 (C-7), 60.77 (CH_2O) and 169.94 (CO).

X-Ray Crystal Structure of (3aR,7aS)-2-[(S)-1-*phenylethyl*]-*perhydropyrano*[3,4-c]*pyrrol*-4-*one* **15b**.—*Crystal data.* $C_{15}H_{19}NO_2$, *M* = 245.32. Monoclinic, *a* = 10.255(2), *b* = 5.540(1), *c* = 12.930(1) Å, β = 112.28(2)°, *V* = 679.7 Å^3, space group $P2_1$, *z* = 2, D_x = 1.199 g cm^{-3}, μ = 5.96 cm^{-1}, *F*(000) = 264. Lattice parameters determined from 21 reflections with 34 < 2θ < 40°.

Data collection and processing. CAD4 diffractometer; radiation, Cu-*K*α (λ = 1.541 84 Å); temp. 23 °C; monochromator, graphite, incident beam; scan type, ω; scan rate, 20.1–2.1° min^{-1}; scan width, 1.00 + 0.14 tan (θ)°; aperture (horiz.), 2.00 + 1.00 tan (θ) mm; aperture (vert.), 4.0 mm; data 2θ limit, 140°; data index range, +*h*, +*k*, ±*l*; reflections measured, 1435; unique reflections, 1435; observed data, 1320, [$I > 3\sigma(I)$].

Min., max., mean change (%) in 3 intensity standards = −0.5, −1.0, −0.8 (0.3). Data corrected for Lorentz effect, polarization and background.

Structure analysis and refinement. Application of a multi-solution tangent formula approach to phase solution gave an initial model for the structure which was subsequently refined with least squares and Fourier methods.[8] Hydrogens were added with isotropic temperature factors which were not refined. The function $\Sigma\omega(|F_o| - |F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$ was minimized with full matrix least squares to give an unweighted residual of 0.048. Reflection weighting $\omega = 4F_o/\sigma(F_o)$ and $\sigma(I)$ from counting statistics with *p* = 0.04. *R* = 0.048, R_w = 0.063, *S* = 2.64, $(\Delta/\sigma)_{max}$ = 0.02. The maximum peak in final difference Fourier is 0.16(7) eÅ^{-3}.

Fig. 1 is a computer generated drawing from the final X-ray co-ordinates showing the stereochemistry and conformation. All bond lengths (Table 1) and bond angles (Table 2) are within reasonable limits. The fractional atomic co-ordinates are collected in Table 3. The Crystallographic data has been deposited at the Cambridge Crystallographic Data Centre.*

* For details of the CCDC deposition scheme see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1991, issue 1.

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