The Synthesis of 5- and 6-Substituted Quinuclidine-3-carboxylic Esters: Intermediates for Novel Muscarinic Ligands[1]

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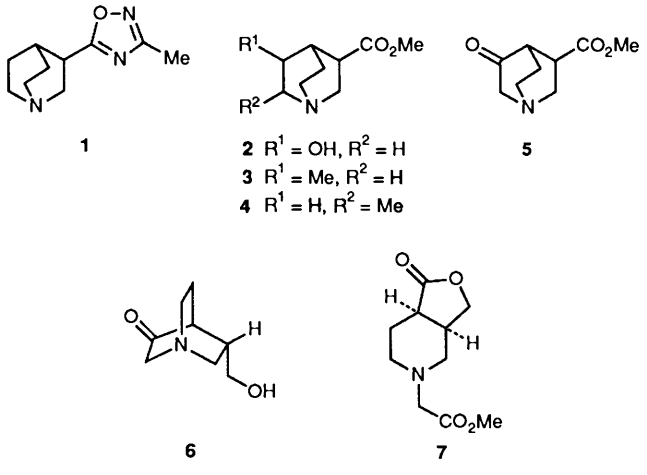
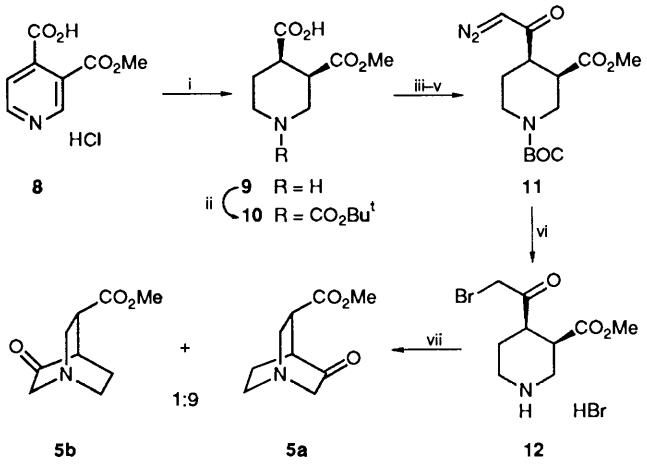
Quinuclidine-3-carboxylic esters bearing 5-hydroxy, 5-methyl and 6-methyl substituents are of interest as precursors to novel muscarinic ligands. All diastereoisomers of these disubstituted quinuclidines have been prepared, in each case using an appropriately substituted quinuclidin-3-one as the key intermediate. The keto ester **5a** was obtained stereoselectively, either by intramolecular alkylation of a bromoacetylpiperidine, or by Dieckmann cyclisation of the differentially protected piperidine **18**. 5-Methylquinuclidin-3-one was formed as a single isomer **24b** by Dieckmann cyclisation. Piperidine-2,4-diester **33**, in contrast, yielded a mixture of 2,5-disubstituted quinuclidine isomers **34** on cyclisation. Elaboration of the quinuclidinones gave the required esters, in several cases with high stereoselectivity. The stereochemical outcome of the Dieckmann cyclisation has been rationalised on the basis of molecular mechanics calculations.

Recently we reported synthesis of the oxadiazole **1** as part of a novel series of muscarinic agonists containing the quinuclidine ring system.[2,3] In the course of this work we wished to study the effect of introducing substituents into different positions of the quinuclidine ring. Initially methyl and, where possible, hydroxy groups were chosen; syntheses of the corresponding ester precursors were therefore required. Substitution at the 2-position using the condensation of quinuclidinone with aldehydes[4] is well known. The 3-hydroxy ester is a known compound[5] and the methyl analogue may be obtained by direct alkylation of the ester enolate. Examples of 4-substituted quinuclidinones have also been described,[6,7] and these can be homologated to the required ester. However very few examples of quinuclidine-3-carboxylates with substituents in the 5- or 6-position (compounds **2**–**4**) have appeared previously. For our purpose we required all four possible diastereoisomers in each case. It was clear that a stereorandom synthesis, followed by separation of isomers, would be impractical. We therefore chose the strategy of defining the configuration of one substituent before introducing the final stereocentre, with separation of a mixture of only two isomers at the final step where necessary. The most useful approach for constructing the quinuclidine ring was found to be the Dieckmann cyclisation, which in several cases gave good stereoselectivity. We now report the synthesis of all diastereoisomers of 5-hydroxy- **2**, 5-methyl- **3** and 6-methyl-quinuclidine-3-carboxylic ester **4**.





Scheme 1 *Reagents and conditions:* i, H_2, PtO_2, MeOH; ii, BOC_2O, Na_2CO_3, aq. dioxane; iii, NaH, THF; iv, $SOCl_2$, THF, reflux; v, excess of CH_2N_2; vi, HBr, HOAc, CH_2Cl_2; vii, Pr^i_2NEt, MeCN, reflux, high dilution. BOC = CO_2Bu^t

Results and Discussion

1. *The 5-Hydroxy Series.*—The key intermediate for the 5-hydroxy series was the keto ester **5**. The only example of this type of 3,5-disubstituted system in the literature is the hydroxymethyl ketone **6**,[8] obtained by Dieckmann cyclisation of lactone **7**, which would yield compound **5** on oxidation and esterification. However, in our hands several of the steps leading to lactone **7** were low yielding. In view of this, an alternative approach was chosen which began from pyridine monoester **8**[9] and involved intramolecular alkylation of the nitrogen by bromo ketone **12** (Scheme 1). Regiospecific introduction of the required bromo ketone was achieved *via* the diazo ketone **11**. Previously, reported cyclisations of 4-bromoacetylpiperidines to quinuclidinones used aqueous alkali or alcohol solvents,[6] but only suceeded when a geminal 4-substituent was present. No cyclisation of bromo ketone **12** could be observed under these

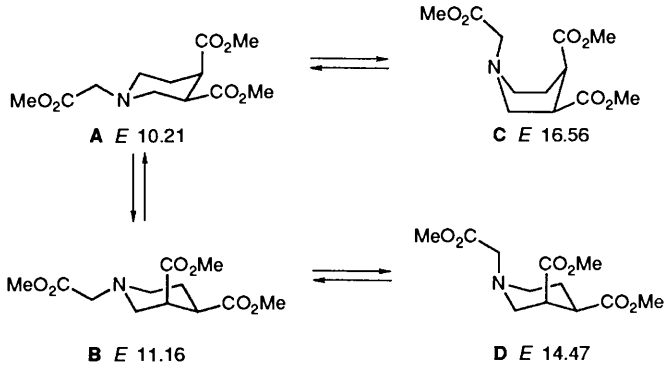
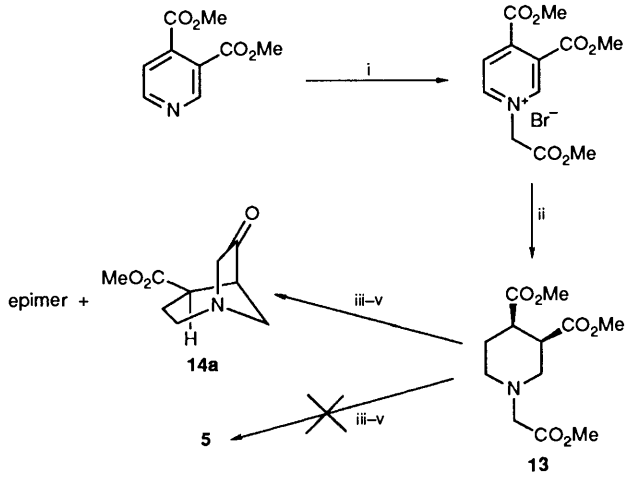


Fig. 1 Calculated energies for conformations of the triester **13**. Energies (kcal mol^{-1}) calculated using the molecular mechanics programme OPTIMOL. Rotatable bonds were adjusted to the minimum-energy conformer, using a rigid-rotor procedure, and the resulting molecule was minimised in OPTIMOL. For the boat form, carbons 2, 3, 5 and 6 were constrained to lie in a plane: otherwise this conformer minimises to a twist-boat.

conditions, but on addition of a solution of the salt in acetonitrile to a refluxing solution of diisopropylethylamine in the same solvent under high-dilution conditions, the desired ketone **5** was formed in 54% overall yield from diazo ketone **11**. The product was mainly diastereoisomer **5a** (9:1), which could be freed from *anti*-isomer **5b** by medium-pressure liquid chromatography (MPLC) or by crystallisation of the hydrochloride. The stereochemistry of compound **5a** was inferred from the *cis* orientation of the substituents in compound 11, and confirmed by NOE measurements. This approach provides a short, stereoselective synthesis of the required quinuclidine in satisfactory yield, but the hazards of handling large quantities of diazomethane, coupled with the need to perform the cyclisation under high dilution, make it impractical for preparing multigram quantities of compound **5**. In view of these limitations we turned our attention to Dieckmann cyclisation, which is one of the most useful routes to quinuclidines.[10] The formal precursor to compound **5** by this method is the readily available triester **13** (Scheme 2), but



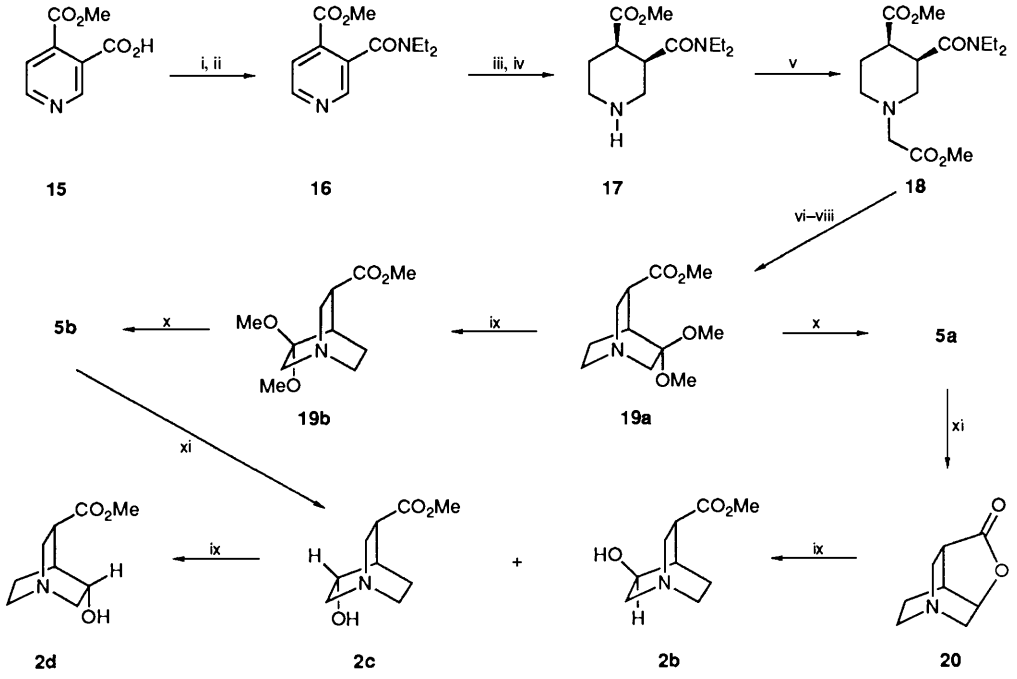
Scheme 2 *Reagents and conditions:* i, $BrCH_2CO_2Me$, MeOH, reflux; ii, H_2, Pd/C, water; iii, $KOBu^t$, PhMe, reflux; iv, conc. HCl, reflux; v, $SOCl_2$, MeOH

cyclisation to the 3-position was expected to be more favourable. The two chair conformers **A** and **B** (Fig. 1) differ in energy by less than 1 kcal,* from molecular mechanics calculations, but whereas the correct conformation **D** for cyclisation to C-3 can be achieved by a simple inversion at nitrogen from **B**, the ring must flip into the boat form **C** in order to cyclise to C-4. Conformer **D** is favoured by 2 kcal over **C**, and cyclisation should occur preferentially from this form. This prediction was confirmed by treating triester **13** with potassium t-butoxide in toluene followed by hydrolysis and re-esterification to give a 27% yield of the [3.2.1] system **14** and no trace of the desired quinuclidine.

The problem of differentiating the esters was solved in the reported synthesis of compound **6** by reduction of the C-3 ester, but it would be preferable to maintain the correct oxidation level by using a suitable protecting group to direct cyclisation to the 4-position. We reasoned that the diethylamide **18** would be appropriate, since the lower reactivity of the amide should ensure reaction at the ester, and the increased bulk would favour the conformer **A**, with the ester group at C-4 axial as required for cyclisation. The preparation of amide **18** (Scheme 3) commenced from pyridine monoester **15**.[9] Hydrogenation of compound **16** as the hydrochloride produced predominantly the *cis* piperidine **17**. With compound **18** available in quantity the cyclisation was carried out using potassium t-butoxide in refluxing toluene, followed by complete hydrolysis with hydrochloric acid and re-esterification, but only small amounts of the keto ester **5** were formed. Instead the major product was the dimethyl ketal **19**, predominantly (8–9:1) the diastereoisomer **19a** resulting from the *cis* piperidine, which apparently cyclises without significant epimerisation. To our knowledge, this is the first instance of acetalisation of quinuclidinones under these conditions. Gratifyingly, the cyclised material was exclusively the quinuclidine, and none of the [3.2.1] system was observed. Evidently, the diethylamide was sufficient to direct cyclisation in the required direction. Formation of the acetal proved fortuitous, since the diastereoisomers were now readily separable by flash chromatography. In addition the presence of the bulky acetal group meant that epimerisation of compound **19a** gave a 6:1 mixture favouring isomer **19b**, which could not be obtained in any quantity by the earlier route. In this way the cyclised product could be obtained in 64% yield on a 120 g scale, and either diastereoisomer could be produced selectively.

Completion of the synthesis of the required hydroxy esters involved deprotection of the separated acetals, which were surprisingly inert, requiring 70% perchloric acid in a two-phase system[11] to liberate the ketone. All the quinuclidinone salts were prone to hydrate formation, and both forms were observed when the NMR spectrum was run in deuterium oxide. As expected, reduction of keto ester **5b** with sodium borohydride gave little selectivity, forming a 40:60 mixture of hydroxy esters **2b** and **2c** which were separated by MPLC. With keto ester **5a** however, attack occurs mainly from the face opposite to the ester to give product **2a**. This closes to the lactone **20** on work-up, and is isolated after rapid chromatography on alumina in 55% yield. The selectivity is somewhat higher than the yield implies, since the lactone decomposes during chromatography. The formation of lactone **20** offered an alternative, selective, route to hydroxy ester **2b**: heating of lactone **20** with sodium methoxide caused ring opening and epimerisation of the resulting hydroxy ester. By NMR spectroscopy the crude product was an 85:15 mixture of compounds **2b** and **20**, from which pure ester **2b** is obtained simply. The remaining diastereoisomer, **2d**, could be isolated only in trace amounts from the reduction of keto ester **5a**, and the preferred procedure was to epimerise compound **2c**. Separation of the resulting 1:1 mixture of isomers **2c** and **2d** was achieved using column chromatography on alumina. With all four isomers in hand the stereochemistry of each was confirmed by COSY NMR spectroscopy. The protons in these quinuclidines showed W-couplings, which though small in magnitude

* 1 cal = 4.184 J.

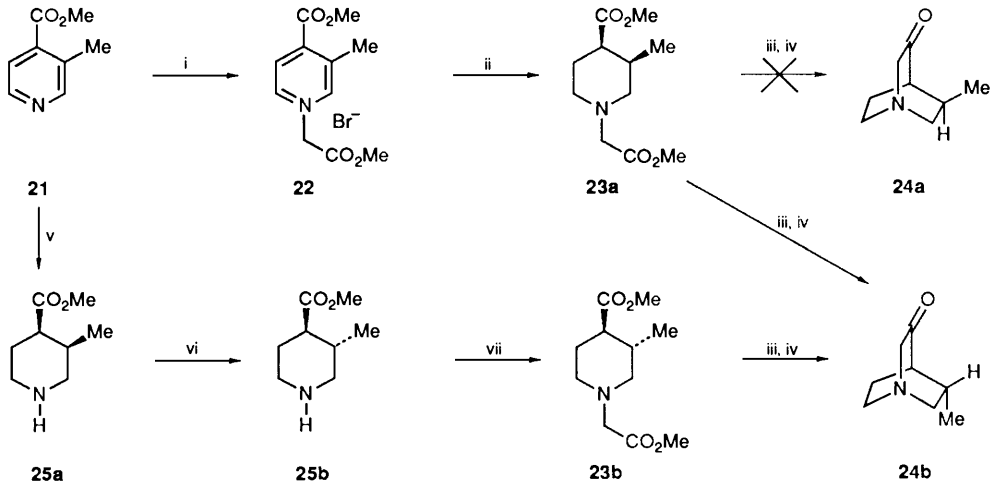


Scheme 3 *Reagents and conditions:* i, $(COCl_2)$, CH_2Cl_2; ii, Et_2NH; iii, HCl, Et_2O; iv, H_2, PtO_2, MeOH; v, $BrCH_2CO_2Me$, K_2CO_3, PhMe, 60 °C; vi, $KOBu^t$, PhMe, reflux; vii, conc. HCl, reflux; viii, MeOH, HCl, $(MeO)_3CH$; ix, NaOMe, MeOH, reflux; x, $HClO_4$, CH_2Cl_2; xi, $NaBH_4$, MeOH, −30 °C

were clearly visible in the COSY45 spectrum. The proton adjacent to the hydroxy group may be assigned from its chemical shift, and the bridgehead proton, which has only small couplings, is very characteristic in these systems. From this the coupling pattern allowed full assignment of the proton spectrum. Each isomer showed all the expected W-couplings. Since only one isomer can form a lactone, conversion of lactone **20** into ester **2b**, which must be epimeric with compound **2c** at the hydroxy group, established the stereochemistry of all the isomers by chemical means.

2. *The 5-Methyl Series.*—With the keto ester **5a** available, the most rapid entry to the 5-methyl series was by homologation to the corresponding exo-methylene compound **32** (see Scheme 5), which reaction occurred in moderate yield. Hydrogenation of this isomer occurred exclusively from the face opposite the ester to yield compound **3a** as the only product. This enabled one methyl epimer to be obtained selectively, and proved the most efficient way of producing this particular isomer of compound **3**. An alternative approach which was expected to give both methyl epimers selectively was based on Dieckmann cyclisation of the *cis*- and *trans*-3-methylpiperidine **23a** and **23b** give the 5-methylquinuclidinone epimers **24a** and **25b** respectively (Scheme 4). The required piperidines were derived from the pyridine ester **21**.[12] Quaternisation followed by hydrogenation yielded the *cis*-piperidine **23a**. To obtain its isomer **23b**, the hydrochloride of substrate **21** was hydrogenated to give piperidine **25a**, which equilibrated to the *trans*-isomer **25b** before introduction of the acetate side-chain. On subjection of the *cis*-piperidine **23a** to the standard Dieckmann cyclisation conditions, 5-methylquinuclidinone was isolated as very largely (>95%) one isomer (42% yield). To our surprise, when the *trans*-piperidine **23b** was treated in the same way, an identical product was obtained and clearly **23a** undergoes complete epimerisation to **23b** prior to ring closure. In each case a minor peak (3–5%) was observed in the gas chromatogram of the crude product, which was shown to be the other diastereoisomer by GC–MS. At this stage the stereochemistry of the major product could not be assigned unambiguously by NMR spectroscopy, due to overlapping signals but, after elaboration to the esters, was shown to be that of isomer **23b**. This provided the methyl epimer which could not be obtained cleanly by the Wittig route. In order to confirm the stereochemistry of the ketone by chemical means, and to provide a better route to the other methyl epimer, we sought an unambiguous synthesis of compound **24a**. This could be achieved starting from **19a** (Scheme 5), which has the correct configuration, by reducing the ester to a methyl group; compound **19a** was converted smoothly to the alcohol **26**, but attempts to reduce the derived chloride or mesyl ester with hydride reagents failed. However, the Ireland procedure[13] involving reduction of the phosphoramidate **27** with lithium in ethylamine led to the required acetal **28**. Deprotection yielded compound **24a**, which was identical (GLC) with the minor product from the Dieckmann cyclisation.

To complete the synthesis of the esters, the ketones were elaborated *via* the ketene dithioacetals **29**.[14] For compound **24b** this proceeded in good yield, but with isomer **24a** the reaction occurred in only 30% conversion, probably due to competing enolisation of the more hindered ketone. Most of the unchanged **24a** was recovered and recycled, however. Methanolysis of dithioacetal **29b** gave the expected 1:1 mixture of products **3c** and **3d**, but compound **29a** yielded compound **3b** as virtually the only product, with less than 5% of other isomers. To facilitate the separation, the mixture of products **3c** and **3d** was first converted into the borane complex **30**. This has been used[15] as a protecting group in related compounds and here had the advantage of greatly reducing the polarity and thus permitting chromatography on silica in non-polar solvents. Pure complexes **30c** and **30d** were isolated by MPLC, and the amine was liberated by mild acid treatment. The stereochemical assignment was carried out on the oxalate salts, and as with the hydroxy series, COSY NMR analysis allowed a complete assignment of the proton spectrum and revealed most of the expected long-range couplings. In a few cases the W-couplings were obscured by overlapping cross-peaks, but the stereochemistry could be assigned unambiguously from the vicinal coupling constants. In this way all four diastereoisomers of the 5-methylquinuclidine ester were obtained in a pure form, two of them with a high degree of stereoselectivity.



Scheme 4 *Reagents and conditions:* i, $BrCH_2CO_2Me$, MeOH, reflux; ii, H_2, Pd/C, MeOH; iii, KOBu^t, PhMe, reflux; iv, conc. HCl, reflux; v, HCl, H_2, PtO_2, HOAc; vi, NaOMe, MeOH, reflux; vii, $BrCH_2CO_2Me$, K_2CO_3, PhMe, 60 °C

3. *The 6-Methyl Series.*—The 6-methyl series, which contains the substitution pattern found in the *Cinchona* alkaloids, has received slightly more attention. Dieckmann cyclisation of both the 2-methyl analogue of compound **23**[16] and the triester **33**[17] have been previously reported, but the stereochemistry of the product was not assigned. We elected to construct the key intermediate **38** from triester **33**, since introduction of the 6-substituent as the ester would allow interconversion of the isomers, irrespective of the stereochemical outcome of the cyclisation, and thus provide access to both intermediates **38a** and **38b**. In the event, cyclisation of predominantly *cis* **33**, which was expected to give mainly *exo*-product **34b**, yielded both isomers in roughly equal amounts. These were isolated after re-esterification as the dimethyl acetals **34a** and **34b**. This is in contrast to the two earlier Dieckmann cyclisations and is discussed further below. The diastereoisomers were separated using a Waters Prep 500 liquid chromatograph to provide multigram quantities of each. Complete reduction of the ester in *endo*-compound **34a** was best achieved *via* the alcohol **35a** and chloride **36a** (Scheme 5). In this series, reaction of chloride **36a** with lithium aluminium hydride in the presence of sodium iodide and crown ether gave the 6-methyl acetal **37a** by reduction of the iodide formed *in situ*. Deprotection then yielded the required ketone **38a** as a single isomer. An exactly analogous sequence starting from *exo*-compound **34b** led to ketone **38b**.

The ketones **38** were homologated to the esters as for the 5-methyl series. In this case reaction with the silyldithiane was satisfactory for both isomers, presumably because the ketone is less hindered. Methanolysis of the ketone dithioacetals **39b** and **39a**, in contrast to isomer **29a**, gave a *ca.* 50:50 mixture of esters in each case. Partial separation of each pair was obtained by column chromatography on alumina, but for complete separation the borane complexes were again used. In this instance no separation could be seen by MPLC, but preparative HPLC readily provided the pure single diastereoisomers. These were deprotected and the stereochemistry was assigned in the same way as for the 5-methyl series.

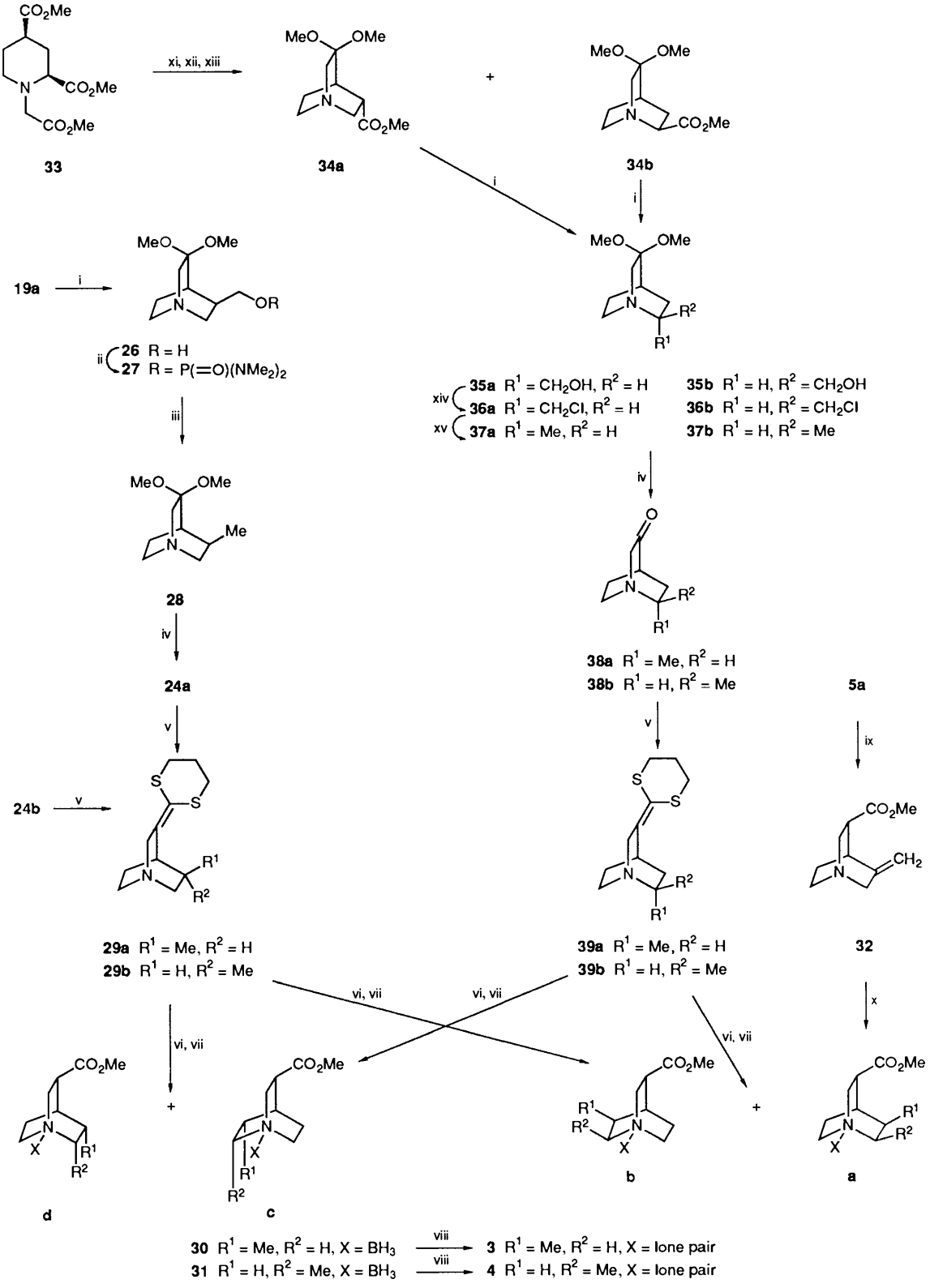
4. *Conformational Analysis.*—We sought to account for the differing stereochemical outcome of the Dieckmann cyclisations by calculating the energies of the various conformers of the piperidines. For each conformer, a conformational search using a rigid-rotor procedure was applied to all rotatable bonds, and the resulting minimum-energy form was optimised using a molecular mechanics force-field.* The results are shown in Table 1. In the case of the *cis*-methylpiperidine **23a** the two chair forms have the same energy. This is *ca.* 2 kcal higher than that of the *trans*-isomer **23b**, and the observed product arises simply from epimerisation to the more stable form. The amide **18** has the ester axial in the minimum-energy conformer, as expected with the bulky amide group, and this is much lower in energy than the alternative chair form. However, in this case the *trans*-isomer is higher in energy than the *cis*. Evidently the *trans*-form suffers a considerable repulsive *gauche* interaction between the large substituents. The cost of placing a substituent in an axial position is relatively small for a group joined through an sp^2 atom: 1.1 kcal for CO_2Et in cyclohexane,[18] *cf.* 1.8 kcal for a methyl group,[19] making the *cis* the preferred isomer of compound **19**, which cyclises without epimerisation to give the observed product. A similar effect is seen with the 2,4-diester **33**. Here the *cis*-isomer was expected to be the more stable, since both esters occupy equatorial positions. However, there is a repulsive interaction between the 2-ester and the nitrogen side-chain, which is relieved on moving the ester to the axial site, and this form is almost 2 kcal lower in energy. The *gauche* interactions can also be relieved by inversion at nitrogen to place the acetete side-chain in an axial position (not shown). However, the acetate methylene now has unfavourable 1,3-interactions with the axial ring protons, and this form is slightly higher in energy (18.2 kcal) than the all-equatorial form. It appears in this case that the difference in energies may not be as large as the calculations suggest, since a mixture of products is obtained, though this may also be due to differing rates of cyclisation for the two isomers.

In conclusion, the Dieckmann cyclisation of disubstituted piperidines occurs with equilibration to the more stable isomer. In the case of the 3,4-disubstituted piperidines studied there is sufficient difference between the *cis*- and *trans*-isomers to provide synthetically useful stereoselection, though which isomer is obtained depends on the nature of the substituents. The biological activity of compounds derived from all the series discussed here will be presented in a forthcoming publication.

Experimental

General Directions.—M.p.s were determined on a Büchi 512 apparatus and are uncorrected; IR spectra were recorded on a Perkin-Elmer 782 instrument, and refer to solutions in chloroform unless otherwise stated. ^1H NMR spectra were

* Using the OPTIMOL programme based on an MM2 force field, within the Merck Molecular Modelling System, T. Halgren, Rahway, unpublished.

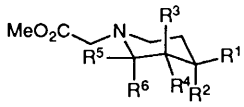


Scheme 5 *Reagents and conditions:* i, $LiAlH_4$, THF; ii, BuLi, $(Me_2N)_2P(=O)Cl$, THF; iii, Li, $EtNH_2$, Bu^{t}OH, THF; iv, $HClO_4$, CH_2Cl_2; v, BuLi, 2-trimethylsilyl-1,3-dithiane, THF, −60 °C; vi, MeOH, HCl, 55 °C; vii, BH_3•THF, THF, −70 °C; viii, 3 mol dm^{-3} HCl, acetone (1 : 3); ix, Ph_3PMeBr, BuLi, Et_2O–THF; x, H_2, Pd/C, MeOH; xi, KOBu^t, PhMe, reflux; xii, conc. HCl, reflux; xiii, $SOCl_2$, MeOH; xiv, $SOCl_2$, Et_3N. CH_2Cl_2, −50 °C; xv, $LiAlH_4$, NaI, 15-crown-5, THF, reflux

obtained on a Bruker AM360 spectrometer, operating at 360 MHz. Unless otherwise indicated, deuteriochloroform was used as solvent. Mass spectra were run on a VG 70-250 machine operating in alternating CI/EI (ACE) mode; data refer to the electron-impact spectrum unless otherwise stated.

Analytical TLC was performed on commercial plates coated with silica gel (Merck Art. 5719) or on aluminium foil coated with neutral alumina (Merck Art. 5550). Silica column chromatography under gravity was carried out on Merck Kieselgel 60 (63–200 μm); the same absorbent from Fluka (40–63 μm) was used for flash chromatography. Alumina for column chromatography was Woelm Grade III neutral. MPLC was

Table 1 Calculated energies for chair conformations of the Dieckmann precursors



Compound	Stereochem.	R^1	R^2	R^3	R^4	R^5	R^6	Energy[a]
23a	*cis*	H	CO_2Me	H	Me	H	H	16.85
23a	*cis*	CO_2Me	H	Me	H	H	H	16.65
23b	*trans*	CO_2Me	H	H	Me	H	H	14.76
18	*cis*	H	CO_2Me	H	$CONEt_2$	H	H	−1.20
18	*cis*	CO_2Me	H	$CONEt_2$	H	H	H	6.84
18	*trans*	CO_2Me	H	H	$CONEt_2$	H	H	3.28
33	*cis*	CO_2Me	H	H	H	CO_2Me	H	17.47
33	*trans*	CO_2Me	H	H	H	H	CO_2Me	15.49
33	*trans*	H	CO_2Me	H	H	CO_2Me	H	18.57

[a] Energies (kcal mol^{-1}) were calculated as described in Fig. 1.

carried out on pre-packed 'Lobar' silica columns (Merck Art. 10402), size C, operating at a flow rate of 6 cm^3 min^{-1}. A Spherisorb 5 μm silica column, 25 cm × 10 mm, was used for preparative HPLC. Capillary GC analysis was performed on a Perkin-Elmer 8320 instrument with helium as carrier gas and flame ionisation detection, using either a 12 m SE30 (column A) or 25 m BP1 (column B) at inlet pressures of 11 and 15 psi respectively.

Organic solutions which had been in contact with water were dried over anhydrous magnesium sulphate prior to evaporation, which has carried out in a Büchi rotary evaporator at 20 mmHg. Ether refers to diethyl ether. Hyflo (BDH Ltd.) was used as a filter aid where necessary.

1. 5-Hydroxy Series

cis-*Piperidine*-3,4-*dicarboxylic Acid* 3-*Methyl Ester Hydrochloride* **9** HCl.—A solution of pyridine-3,4-dicarboxylic acid 3-methyl ester[9] (5.0 g, 27.6 mmol) in methanol (50 cm^3) was treated with excess of ethereal hydrogen chloride and evaporated to dryness. The resulting salt **8** in methanol (100 cm^3) was hydrogenated over platinum oxide (500 mg) at 50 psi for 24 h. The catalyst was removed by filtration through Hyflo, and the filtrate was evaporated to give the *piperidine* **9**·HCl (6.17 g, 100%), m.p. 180–184 °C (decomp.) (Found: C, 42.1; H, 6.2; N, 6.2. $C_8H_{13}NO_4$·HCl·0.25H_2O requires C, 42.1; H, 6.4; N, 6.1%); $\delta_H(D_2O)$ 2.10–2.20 (2 H, m, 5-H_2), 3.19–3.25 (2 H, m, 3- and 4-H), 3.27–3.32 (1 H, m, 6-H_{ax}), 3.34–3.39 (1 H, m, 6-H_{eq}), 3.51 (1 H, dd, *J* 4 and 13 Hz, 2-H_{eq}) and 3.60 (1 H, dd, *J* 7.5 and 13 Hz, 2-H_{ax}); *m/z* 185 (M^+ − 2).

cis-*Piperidine*-1,3,4-*tricarboxylic Acid* 1-*t-Butyl* 3-*Methyl Diester* **10**.—The foregoing piperidine salt **9** (7.16 g, 32.1 mmol) was dissolved in a solution of sodium carbonate (6.80 g, 64.2 mmol) in water (50 cm^3), and a solution of di-t-butyl dicarbonate (8.39 g, 38.5 mmol) in dioxane (15 cm^3) was added. After being stirred at room temperature for 20 h, the solution was washed with ether, and the aq. layer was acidified with 2 mol dm^{-3} citric acid, and extracted twice with ethyl acetate. The extracts were washed successively with water and brine, dried and evaporated to give the protected *piperidine* **10** (7.78 g, 84%); m.p. 129–136 °C (Found: C, 54.3; H, 7.2; N, 4.9. $C_{13}H_{21}NO_6$ requires C, 54.35; H, 7.4; N, 4.9%); ν_{max}/cm^{-1} 3200 br, 1740, 1700 and 1655; δ_H 1.44 (9 H, s, Bu^t), 1.89 (1 H, br, 5-H), 2.13 (1 H, br, 5-H), 2.84–2.89 (1 H, m, 4-H), 2.93–2.96 (1 H, m, 3-H), 3.12–3.21 (1 H, m, 6-H), 3.43–3.48 (1 H, m, 6-H), 3.68–3.75 (1 H, m, 2-H), 3.69 (3 H, s, OMe) and 4.07–4.14 (1 H, m, 2-H); *m/z* (CI) (−ve) 286 (M − H^- 100%).

1-*t-Butyl* 3-*Methyl* 4-*Diazoacetylpiperidine*-1,3-*dicarboxylate* 11.—A solution of the piperidine diester **10** (2.0 g, 6.97 mmol) in dry tetrahydrofuran (THF) (15 cm^3) was stirred with sodium hydride (250 mg of 80% dispersion, 8.3 mmol) at room temperature for 2 h. Thionyl chloride (0.60 cm^3, 8.3 mmol) was added and the mixture heated to 60 °C for 1 h. The cooled mixture was added dropwise to an ice-cooled, ethanol-free solution of diazomethane in ether (~35 mmol). The solution was stirred at 0 °C for 1.5 h, then acetic acid was added to destroy any residual diazomethane. The solvent was evaporated off and the residue was partitioned between aq. sodium hydrogen carbonate and dichloromethane. Column chromatography of the material from the organic layer on silica in dichloromethane–ethyl acetate (4:1) afforded the pure diazo ketone 11 as a yellow gum (1.55 g, 72%); ν_{max}/cm^{-1} 2120 (diazo ketone), 1740, 1690 and 1640; δ_H 1.44 (9 H, s, Bu^t), 1.76 (1 H, br, 5-H), 2.01–2.14 (1 H, m, 5-H), 2.81 (1 H, br) and 2.88–2.98 (2 H, m, 3- and 4-H), 3.22–3.34 (1 H, m, 6-H), 3.50–3.71 (2 H, m, 2- and 6-H), 3.68 (3 H, s, OMe), 4.02–4.11 (1 H, m, 2-H) and 5.36 (1 H, s, CH=N_2); *m/z* (CI) 312 (M + H^+, 80%), 284 (M + H − N_2, 22), 256 (100), 212 (100) and 184 (78).

(3R*,4R*)-*Methyl* 5-*Oxo*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate Hydrochloride* **5a**·HCl.—A stirred solution of the diazo ketone 11 (4.85 g, 15.5 mmol) in dichloromethane (250 cm^3) at 0 °C was treated with hydrogen bromide in acetic acid (10 cm^3 of 48% w/v) for 30 min. The solvent was removed using a toluene azeotrope to give methyl 4-(2-bromoacetyl)piperidine-3-carboxylate hydrobromide **12** as a gum, $\delta_H(D_2O)$ 2.01–2.22 (2 H, m, 5-H_2), 3.16–3.33 (2 H, m, 3- and 4-H), 3.40–3.58 (3 H, m, 2-H, 6-H_2), 3.72–3.78 (1 H, m, 2-H), 3.73 (3 H, s, OMe) and 4.46 (2 H, s, CH_2Br).

A solution of this material in dry acetonitrile (280 cm^3) was added slowly *via* a syringe pump to refluxing acetonitrile (1500 cm^3) containing diisopropylethylamine (29 cm^3, 167 mmol) during 5 h and the mixture was heated for a further 1 h. The solvent was evaporated off and the residue was partitioned between 2 mol dm^{-3} aq. potassium carbonate and dichloromethane. Chromatography of the material from the organic layer on silica in dichloromethane–methanol (95:5) gave the quinuclidine **5** (1.60 g, 56%) as a 9:1 mixture of isomers **5a** and **5b**. The hydrochloride was crystallised from ethanol–ether to give pure **5a** *hydrochloride*, m.p. 171–172 °C (Found: C, 49.1; H, 6.5; N, 6.2; Cl, 15.9. $C_9H_{13}NO_4$·HCl requires C, 49.2; H, 6.4; N, 6.4; Cl, 16.1%); ν_{max}/cm^{-1} (free base) 1740br; δ_H(free base; $CDCl_3$) 2.04 (2 H, dt, *J* 3 and 7.5 Hz, 8-H_2), 2.69 (1 H, q, *J* 3 Hz, 4-H), 2.88–2.97 (2 H, m, 7-H_2), 3.07 (1 H, ddd, *J* 3, 5.5 and 10 Hz, 3-H), 3.14–3.25 (2 H, m, 2-H_2), 3.32 (1 H, dd, *J* 2 and 10 Hz, 6-H), 3.39 (1 H, d, *J* 10 Hz, 6-H) and 3.69 (3 H, s, OMe); *m/z* 183 (M^+,

5%), 155 (30) and 96 (100); GC (free base) t_R 3.93 min (column A; 130 °C).

cis-*Dimethyl* 1-(*Methoxycarbonylmethyl*)*piperidine*-3,4-*dicarboxylate* **13**.—A solution of dimethyl pyridine-3,4-dicarboxylate (58.5 g, 0.30 mol) and methyl bromoacetate (50 g, 0.33 mol) in methanol (300 cm^3) was heated under reflux for 24 h and was then evaporated. The residue in water (200 cm^3) was hydrogenated over palladium on carbon (10%; 5.0 g) at 50 psi for 36 h. The solution was filtered, basified with potassium carbonate, and extracted with dichloromethane. Evaporation of the organic layer yielded virtually pure *piperidine triester* **13** (58.3 g, 71%), b.p. 165–170 °C/0.1 mmHg (Kugelrohr) (Found: C, 52.5; H, 7.05; N, 5.2. $C_{12}H_{19}NO_6$ requires C, 52.7; H, 7.0; N, 5.1%); δ_H 1.92–2.02 (1 H, m, 5-H), 2.12–2.22 (1 H, m, 5-H), 2.57 (2 H, t, *J* 6 Hz, 3- and 4-H), 2.72–2.80 (1 H, m, 6-H), 2.80–2.87 (1 H, m, 6-H), 3.01–3.07 (2 H, m, 2-H_2), 3.23 and 3.30 (each 1 H, d, *J* 17 Hz, NC$H_2$$CO_2$Me), 3.69 (3 H, s, NC$H_2$$CO_2$*Me*) and 3.70 (6 H, s, 2 × CO_2Me); *m/z* (CI) 274 (M + H^+, 100%) and 214 (42).

Methyl 6-*Oxo*-1-*azabicyclo*[3.2.1]*octane*-4-*carboxylate* **14**.—Triester **13** (12.0 g, 44 mmol) was cyclised by the general method for Dieckmann cyclisations described below for compound **19a** and the product was re-esterified. Chromatography on silica, and elution with dichloromethane–methanol (95:5), yielded uncyclised material (1.6 g), isomer A (830 mg) and isomer B (1.30 g). The major product, isomer B, had the 4*R**,5*R** configuration **14a** (Found: M^+, 183.0906. $C_9H_{13}NO_3$ requires M, 183.0895); δ_H 1.76–1.83 (1 H, m, 3-H), 1.95–2.04 (1 H, m, 3-H), 2.66–2.70 (1 H, m, 5-H), 2.89 (1 H, ddd, *J* 2.4, 5.5 and 13 Hz, 4-H), 3.05 (1 H, dd, *J* 3 and 18 Hz, 7-H *anti* to CO_2Me), 3.06–3.17 (3 H, m, 2-H_2, 8-H_{ax}), 3.19 (1 H, d, *J* 18 Hz, 7-H *syn* to CO_2Me), 3.35 (1 H, dd, *J* 4 and 12 Hz, 8-H_{eq}) and 3.73 (3 H, s, OMe).

Methyl 3-(*Diethylcarbamoyl*)*pyridine*-4-*carboxylate Hydrochloride* **16**·HCl.—To a stirred, cooled suspension of pyridine-3,4-dicarboxylic acid 4-methyl ester **15**[9] (421 g, 2.32 mol) in dichloromethane (2.5 dm^3) under nitrogen was added oxalyl dichloride (308 g, 2.43 mmol), while the temperature was kept below 0 °C. After the addition was complete, the solution was stirred at room temperature for 2 h and at reflux for 8 h. The mixture was cooled again and diethylamine (880 cm^3, 8.5 mol) was added dropwise at <0 °C. The mixture was stirred for a further 2 h at room temperature, then a solution of potassium carbonate (138 g, 1.0 mol) in water (1.5 dm^3) was added and the layers were separated. The organic layer was washed with water (2 × 50 cm^3) and evaporated. Methanol (1 dm^3) was evaporated from the residue to remove diethylamine, and the salt was formed by addition of methanolic hydrogen chloride (10 mol dm^{-3}; 250 cm^3). After removal of the solvent, crystallisation from propan-2-ol–ether yielded the *pyridine hydrochloride* **16**·HCl (462 g, 73%), m.p. 111–113 °C (Found: C, 52.6; H, 6.3; N, 10.2. $C_{12}H_{16}N_2O_3$·HCl requires C, 52.85; H, 6.3; N, 10.3%); ν_{max} (free base; film)/cm^{-1} 1740s, 1640s, 1585 and 1560; $\delta_H(D_2O)$ 1.07 and 1.29 (each 3 H, t, *J* 7.2 Hz, 2 × CH_2*Me*), 3.23 and 3.60 (each 2 H, q, *J* 7.2 Hz, 2 × CH_2Me), 4.00 (3 H, s, OMe), 8.43 (1 H, d, *J* 6 Hz, 5-H), 8.96 (1 H, s, 2-H) and 9.00 (1 H, d, *J* 6 Hz, 6-H); *m/z* (CI) 237 (M + H^+, 100%) and 164 (20).

cis-*Methyl* 3-(*Diethylcarbamoyl*)*pyridine*-4-*carboxylate Hydrochloride* **17**·HCl.—A solution of the pyridine hydrochloride **16**·HCl (578 g, 2.21 mmol) in methanol (1 dm^3) was hydrogenated over platinum oxide (2.0 g) in a 2 dm^3 stirred autoclave at 8 bar* for 48 h. The solution was filtered through Hyflo, the solvent was evaporated off, and the residue was partitioned between 4 mol dm^{-3} aq. potassium carbonate and dichloromethane. Evaporation of the organic layer yielded virtually pure piperidine **17** (483 g, 94%) as a 9:1 mixture of *cis* and *trans* isomers, which was routinely used in the next step without purification. An analytical sample of the cis-*piperidine* was obtained by flash chromatography in dichloromethane–methanol–0.88 ammonia (90:10:0.2) to afford the *hydrochloride*, m.p. 145–147 °C (Found: C, 51.6; H, 8.2; N, 10.0. $C_{12}H_{22}N_2O_3$·HCl requires C, 51.7; H, 8.3; N, 10.05%); ν_{max}/cm^{-1} 3600–3200, 1740 and 1630; $\delta_H(D_2O)$ 1.07 and 1.86 (each 3 H, t, *J* 7 Hz, 2 × CH_2*Me*), 2.10 (1 H, dq, *J* 4.5 and 15 Hz, 5-H_{eq}), 2.41 (1 H, dddd, *J* 4, 10, 10 and 15 Hz, 5-H_{ax}), 3.09–3.18 (3 H, m, 2-H_{ax}, 4-H, 6-H_{ax}), 3.30 (1 H, dd, *J* 4 and 13 Hz, 2-H_{eq}), 3.29–3.38 (1 H, m, 6-H_{eq}), 3.47–3.60 (4 H, m, 2 × CH_2Me), 3.64 (1 H, q, *J* 4.5 Hz, 3-H) and 3.71 (3 H, s, OMe); *m/z* 242 (M^+, 25%), 142 (67) and 82 (100).

cis-*Methyl* 3-(*Diethylcarbamoyl*)-1-(*methoxycarbonylmethyl*)*piperidine*-4-*carboxylate* **18**.—Methyl bromoacetate (203 cm^3, 2.15 mol) was added during 20 min to a mechanically stirred solution of the piperidine **17** (495 g, 2.04 mol) in toluene (2 dm^3) containing powdered potassium carbonate (594 g, 4.3 mol). The mixture was then heated to 70 °C for 2.5 h, cooled, and water (500 cm^3) was added. The layers were separated, the aqueous layer was extracted with dichloromethane, and the combined organic layers were evaporated to yield virtually pure *compound* **18**, a 9:1 mixture of *cis* and *trans* isomers (577 g, 90%), as an oil, which was used in the next step without purification (Found: M^+, 314.183. $C_{15}H_{26}N_2O_5$ requires *M*, 314.184); ν_{max}(film)/cm^{-1} 1740 and 1640; δ_H 1.09 and 1.22 (each 3 H, t, *J* 7 Hz, 2 × CH_2*Me*), 1.92–2.01 (1 H, m, 5-H_{ax}), 2.25–2.34 (1 H, m, 5-H_{eq}), 2.60–2.66 (2 H, m, 4- and 6-H), 2.75 (1 H, dd, *J* 4 and 11 Hz, 3-H), 2.84–2.90 (1 H, m, 6-H), 2.99 (1 H, dd, *J* 8 and 11 Hz, 2-H_{ax}), 3.16–3.21 (1 H, m, 2-H_{eq}), 3.28 and 3.35 (each 1 H, d, *J* 7 Hz, NC$H_2$$CO_2$), 3.28–3.43 (4 H, m, 2 × CH_2Me) and 3.66 and 3.70 (each 3 H, s, 2 × OMe).

(3R*,4R*)-*Methyl* 5,5-*Dimethoxy*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate Hydrochloride* **19a**·HCl.—A strongly refluxing solution of potassium t-butoxide (105 g, 0.94 mol) in toluene (1500 cm^3) under nitrogen was stirred very vigorously with a mechanical propeller stirrer. A solution of the piperidine **18** (110 g, 0.35 mol) in toluene (400 cm^3) was added during 1.5 h, and the mixture was heated for a further 1.5 h before being cooled in ice, and conc. hydrochloric acid (600 cm^3) was added. The layers were separated, the organic layer was extracted with more hydrochloric acid, and the combined acid layers were heated under reflux for 24 h. The cooled solution was evaporated to dryness and the residue was dried at 60 °C. Thionyl chloride (130 cm^3, 1.78 mol) was added dropwise to stirred methanol (1000 cm^3) under nitrogen, while the temperature was kept below −20 °C. When the addition was complete, the crude reaction product was added as a slurry in methanol (500 cm^3) and the resulting dark solution was heated at 60 °C for 45 h. The cooled solution was evaporated and the residue was partitioned between 2 mol dm^{-3} aq. potassium carbonate (500 cm^3) and dichloromethane (4 × 500 cm^3). The material from the organic layer was filtered through a plug of silica in dichloromethane–methanol (95:5) to remove baseline material. The eluate was evaporated and purified on a Waters Prep. 500 liquid chromatograph, with dichloromethane–methanol–triethylamine (97:3:0.2) as eluent. The first eluted component was uncyclised material. The second component was the ketone **5** (9.6 g, 15%), followed by the acetal **19** (39.6 h, 49%); overall yield of cyclised product 64%, ratio of diastereoisomers 9:1. The major acetal isomer **19a** was characterised as its *hydrochloride*,

* 1 bar = 10^5 Pa.

m.p. 163–166 °C (from propan-2-ol) (Found: C, 48.6; H, 7.3; N, 5.2. $C_{11}H_{19}NO_4$·HCl·0.25H_2O requires C, 48.9; H, 7.6; N, 5.2%); $\delta_H(D_2O)$ 1.92–2.03 (1 H, m, 8-H), 2.08–2.18 (1 H, m, 8-H), 3.09 (1 H, q, *J* 3 Hz, 4-H), 3.13–3.18 (1 H, m, 3-H), 3.16 and 3.28 [each 3 H, s, $C(OMe)_2$], 3.25–3.36 (3 H, m, 6-H_2, 7-H), 3.44–3.53 (2 H, m, 2- and 8-H), 3.72–3.84 (1 H, m, 2-H) and 3.76 (3 H, s, CO_2Me); *m/z* 229 (M^+, 20%), 214 (100) and 198 (35); GC (free base) t_R 6.34 min (column A; 130 °C).

(3R*,4S*)-*Methyl* 5,5-*Dimethoxy*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate* **19b** *Oxalic Acid Adduct*.—Sodium (0.15 g, 6.5 mmol) was dissolved in dry methanol (100 cm^3) and the acetal free base **19a** (5.14 g, 22.4 mmol) was added. The solution was heated under reflux for 48 h, cooled, neutralised with acetic acid and evaporated. The residue was partitioned between 2 mol dm^{-3} aq. potassium carbonate and dichloromethane and the organic layer was evaporated to yield a 6:1 mixture of acetals **19b** and **19a** (4.4 g). Flash chromatography with dichloromethane–methanol (93:7) yielded pure compound **19b** (2.97 g, 58%) as a gum, along with mixed fractions (0.89 g, 17%). The *oxalate salt* had m.p. 88–91 °C (from propan-2-ol) (Found: C, 48.9; H, 6.5; N, 4.4. $C_{11}H_{19}NO_4$·$C_2H_2O_4$ requires C, 48.9; H, 6.6; N, 4.4%); $\delta_H(D_2O)$ 1.77–1.88 (1 H, m, 8-H), 1.98–2.10 (1 H, m, 8-H), 2.91 (1 H, q, *J* 3 Hz, 4-H), 3.10–3.42 (3 H, m, 3-H, 7-H_2), 3.31 and 3.32 [each 3 H, s, $C(OMe)_2$], 3.43 (2 H, s, 6-H_2), 3.50 (1 H, dt, *J* 2.4 and 12 Hz, 2-H), 3.70 (1 H, dd, *J* 5 and 12 Hz, 2-H) and 3.79 (3 H, s, CO_2Me); *m/z* 229 (M^+, 12%), 214 (100) and 198 (25); GC t_R 6.92 min (Column A; 130 °C).

(3R*,4S*)-*Methyl* 5-*Oxo*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate Hydrochloride* **5b**·HCl.—A stirred solution of the acetal **19b** (2.10 g, 9.17 mmol) in dichloromethane (15 cm^3) was cooled to 0 °C and 70% perchloric acid (8 cm^3) was added. The cooling bath was removed and the mixture was stirred at room temperature for 1 h, cooled again in ice, diluted with dichloromethane (30 cm^3) and water (20 cm^3), and basified with solid sodium carbonate. The layers were separated and the aqueous phase was extracted with more dichloromethane. Evaporation of the combined organic layers yielded the *ketone* **5b** (1.48 g, 88%); the *hydrochloride* had m.p. 181–182 °C (from propan-2-ol) (Found: C, 49.65; H, 6.7; N, 6.0. $C_9H_{13}NO_3$·HCl·0.25C_3H_8O requires C, 49.9; H, 6.9; N, 6.0%); ν_{max}(free base)/cm^{-1} 1740; δ_H (free base) 1.82–1.94 (1 H, m, 8-H), 2.06–2.19 (1 H, m, 8-H), 2.79 (1 H, q, *J* 3 Hz, 4-H), 2.83–2.95 (1 H, m, 7-H), 2.97–3.06 (2 H, m, 2- and 3-H), 3.12 (1 H, dt, *J* 2.4 and 12 Hz, 7-H), 3.28 (2 H, t, *J* 1 Hz, 6-H_2), 3.40 (1 H, dd, *J* 5 and 14 Hz, 2-H) and 3.75 (3 H, s, OMe); *m/z* (CI) 184 ($M + H^+$, 60%), 155 (60) and 96 (100); GC (free base) t_R 3.71 min (column A; 130 °C).

Hexahydro-3H-1,5-*methanofuro*[3,4-c]*pyridin*-3-*one** **20**.—A stirred solution of ketone **5a** (4.80 g, 26.2 mmol) in methanol (200 cm^3) was cooled to −30 °C and sodium borohydride (1.0 g, 26.2 mmol) was added. After 1.5 h, 2 mol dm^{-3} hydrochloric acid was added to destroy excess of borohydride, and the mixture was evaporated. The residue was partitioned between aq. potassium carbonate and dichloromethane. The material isolated from the organic layer (3.54 g) was purified by rapid filtration through a small plug of alumina in dichloromethane–ethyl acetate (1:1) to give the *title lactone* **20** (2.20 g, 55%), m.p. 164–167 °C (from ethyl acetate) (Found: C, 62.7; H, 7.3; N, 9.1. $C_8H_{11}NO_2$ requires C, 62.7; H, 7.2; N, 9.1%); ν_{max}/cm^{-1} 1780; δ_H 1.65–1.75 (1 H, m, 7-H), 1.83–1.93 (1 H, m, 7-H), 2.49 (1 H, dd, *J* 5 and 9 Hz, 3a-H), 2.79–2.84 (1 H, m, 7a-H), 2.90 (2 H, t, *J* 8 Hz, 6-H_2), 2.97–3.08 (2 H, m, 4- and 8-H,both *syn* to lactone), 3.17 (2 H, dd, *J* 5 and 15 Hz, 4- and 8-H, both *anti* to lactone) and 4.55 (1 H, t, *J* 5 Hz, 1-H); *m/z* 153 (M^+, 65%) and 96 (100); GC t_R 4.68 min (column A; 120 °C).

(3R*,4S*,5S*)-*Methyl* 5-*Hydroxy*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate Hydrochloride* **2c**·HCl.—Sodium borohydride (108 mg, 2.85 mmol) was added to a stirred, ice-cooled solution of the keto ester **5b** (1.04 g, 5.7 mmol) in methanol (20 cm^3). After 30 min excess of borohydride was destroyed with 2 mol dm^{-3} hydrochloric acid. The solution was basified with aq. potassium carbonate and extracted with dichloromethane (5 × 60 cm^3). Evaporation of the combined extracts yielded virtually pure alcohol (952 mg, 90%) as a 60:40 mixture of hydroxy esters **2c** and **2b**. A portion of the product (560 mg) was separated by MPLC with dichloromethane–methanol–triethylamine (85:15:0.05) as eluent. The first eluted component was compound **2b** (see below). Fractions containing the pure second component yielded the title alcohol **2c** (170 mg), *hydrochloride* m.p. 174–177 °C (from ethanol) (Found: C, 47.9; H, 7.2; N, 6.2. $C_9H_{15}NO_3$·HCl·0.25H_2O requires C, 47.8; H, 7.35; N, 6.2%); $\delta_H(D_2O)$ 1.72–1.83 (1 H, m, 8-H *syn* to ester), 2.14–2.24 (1 H, m, 8-H *anti* to ester), 2.61 (1 H, quintet, *J* 3 Hz, 4-H), 3.09 (1 H, dt, *J* 3 and 14 Hz, 6-H *syn* to OH), 3.13–3.19 (1 H, m, 3-H), 3.30–3.38 (2 H, t, *J* 8 Hz, 7-H_2), 3.40 (1 H, t, *J* 11 Hz, 2-H *anti* to ester), 3.58–3.73 (2 H, m, 2-H *syn* to ester, 6-H *anti* to OH), 3.79 (3 H, s, OMe) and 4.39 (dt, *J* 3 and 8.5 Hz, 5-H); *m/z* 185 (M^+, 85%), 170 (15), 142 (60), 126 (80) and 82 (100).

(3R*,4S*,5R*)-*Methyl* 5-*Hydroxy*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate Hydrochloride* **2b**·HCl.—The lactone **20** (400 mg, 2.61 mmol) was treated with sodium (60 mg, 2.6 mmol) in methanol (50 cm^3) under reflux for 18 h to give the crude product (367 mg) as an 80:20 mixture of compound **2b** and substrate **20**. Column chromatography on alumina with dichloromethane–methanol (99:1) as eluent yielded the pure alcohol **2b** (260 mg, 54%), *hydrochloride*, m.p. 159–160 °C (from propan-2-ol) (Found: C, 48.3; H, 7.1; N, 6.5. $C_9H_{15}NO_3$·HCl·0.1H_2O requires C, 48.4; H, 7.3; N, 6.4%); $\delta_H(D_2O)$ 1.77–1.97 (2 H, m, 8-H_2), 2.62 (1 H, br quintet, *J* 3 Hz, 4-H), 3.06 (1 H, dt, *J* 3 and 14 Hz, 6-H *syn* to OH), 3.12–3.30 (2 H, m, 7-H_2), 3.41–3.52 (2 H, m, 2-H *anti* to ester, 3-H), 3.62 (1 H, ddd, *J* 2.7, 8.6 and 13.6 Hz, 6-H *anti* to OH), 3.72 (1 H, dt, *J* 2.6 and 8 Hz, 2-H *syn* to ester), 3.79 (3 H, s, OMe) and 4.38 (1 H, ddd, *J* 3, 4 and 8.5 Hz, 5-H); *m/z* 185 (M^+, 45%), 154 (22), 110 (70) and 91 (100).

(3R*,4R*,5R*)-*Methyl* 5-*Hydroxy*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate* **2d** *Oxalic Acid Adduct*.—Hydroxy ester **2c** (645 mg, 3.52 mmol) was treated with sodium (130 mg, 5.65 mmol) in methanol (30 cm^3) under reflux for 18 h, as above, to give the crude product (421 mg) as a 1:1 mixture of isomers **2c** and **2d**. Column chromatography on alumina with dichloromethane–methanol (99:1) as eluent yielded pure compound **2d** (67 mg, 10%), along with mixed fractions, as the *oxalic acid adduct*, m.p. 166–168 °C (Found: C, 47.9; H, 6.2; N, 5.0. $C_9H_{15}NO_3$·$C_2H_2O_4$ requires C, 48.0; H, 6.2; N, 5.1%); $\delta_H(D_2O)$ 1.86–1.96 (1 H, m, 8-H *anti* to OH), 2.27–2.37 (1 H, m, 8-H *syn* to OH), 2.67 (1 H, quintet, *J* 3 Hz, 4-H), 3.07 (1 H, dt, *J* 3 and 14 Hz), 3.27–3.38 (3 H, m, 3-H, 7-H_2), 3.47 (1 H, td, *J* 2.6 and 10 Hz, 2-H *anti* to ester), 3.57–3.66 (2 H, m, 2-H *syn* to ester, 6-H *anti* to OH), 3.79 (3 H, s, OMe) and 4.18 (1 H, dt, *J* 2.4 and 8.7 Hz, 5-H); *m/z* 185 (M^+, 100%), 154 (50), 142 (55) and 126 (72).

2. 5-Methyl Series

cis-*Methyl* 1-(*Methoxycarbonylmethyl*)-3-*methylpiperidine*-4-*carboxylate* **23a**.—A solution of methyl 3-methylpyridine-4-carboxylate[12] **21** (56.7 g, 0.375 mol) and methyl bromoacetate

* Preferred name: Hexahydro-2*H*-3,6-methanofuro[2,3-*c*]pyridin-2-one.

(64 g, 0.42 mol) in methanol (200 cm^3) was stirred at room temperature for 6 h and then heated at reflux for 18 h to form the pyridinium salt **22**; $\delta_H(D_2O)$ 2.72 (3 H, s, CMe), 3.87 (3 H, s, $CH_2CO\mathit{Me}$), 4.05 (3 H, s, CO_2Me), 5.62 (2 H, s, CH_2CO_2), 8.42 (1 H, d, *J* 6 Hz, 5-H), 8.84 (1 H, d, *J* 6 Hz, 6-H) and 8.91 (1 H, s, 2-H).

The solution was hydrogenated over palladium on carbon (10%; 5.0 g) at 50 psi for 3 days. The catalyst was removed by filtration through Hyflo and the filtrate was evaporated. The residue was partitioned between aq. potassium carbonate and dichloromethane and the residue from the organic layer was distilled to give the cis-*piperidine* **23a** along with *ca.* 8% *trans*-isomer **23b** (51.8 g, 60%), b.p. 108–110 °C (0.35 mmHg) (Found: M^+, 229.130. $C_{11}H_{19}NO_4$ requires M, 229.131); δ_H 1.01 (3 H, d, *J* 7 Hz, 3-Me), 1.76 (1 H, dq, *J* 5 and 14 Hz, 5-H_{eq}), 1.92–1.99 (1 H, m, 5-H_{ax}), 2.18–2.29 (1 H, m, 3-H), 2.36 (1 H, dt, *J* 3 and 13 Hz, 4-H), 2.42–2.54 (2 H, m, 2- and 6-H_{ax}), 2.67 (1 H, dd, *J* 5 and 14 Hz, 2-H_{eq}), 2.81 (1 H, dt, *J* 5.5 and 11 Hz, 6-H_{eq}), 3.16 and 3.24 (each 1 H, ABq, *J* 16 Hz, NCH_2CO_2) and 3.67 and 3.71 (each 3 H, s, 2 × CO_2Me); *m/z* 230 ($M + H^+$, 20%), 229 (M^+, 17%) and 170 (100).

cis-*Methyl* 3-*Methylpiperidine*-4-*carboxylate Hydrochloride* **25a**·HCl.—Pyridine ester **21** (17.7 g, 0.117 mol) was converted into the hydrochloride salt and hydrogenated at 50 psi over platinum oxide (1.0 g) in acetic acid (200 cm^3) for 1.5 days. The solution was filtered and evaporated, and the residue was partitioned between aq. potassium carbonate and dichloromethane. Evaporation of the organic layer yielded the piperidine free base (16.2 g, 88%) as a 9:1 mixture of isomers **25a** and **25b**, which was used in the next step without purification. An analytical sample of the *cis*-isomer **25a** was obtained by flash chromatography in dichloromethane–methanol–0.88 ammonia (90:10:0.2); the *hydrochloride* had m.p. 147–150 °C (from methanol–ether) (Found: C, 49.7; H, 8.25; N, 7.3. $C_8H_{15}NO_2$·HCl requires C, 49.6; H, 8.3; N, 7.2%); $\delta_H(D_2O)$ 1.00 (3 H, d, *J* 7 Hz, 3-Me), 1.96–2.15 (2 H, m, 5-H_2), 2.36–2.46 (1 H, m, 3-H), 2.93 (1 H, dt, *J* 4.5 and 7.4 Hz, 4-H), 3.14 (1 H, ddd, *J* 4, 8 and 13 Hz, 6-H_{ax}), 3.20 (1 H, dd, *J* 3 and 13 Hz, 2-H), 3.23 (1 H, dd, *J* 7 and 13 Hz, 2-H), 3.38 (1 H, ddd, *J* 4, 8 and 13 Hz, 6-H_{eq}) and 3.74 (3 H, s, OMe); *m/z* (CI) 158 ($M + H^+$, 100%) and 114 (15).

trans-*Methyl* 3-*Methylpiperidine*-4-*carboxylate Hydrochloride* **25b**·HCl.—The *cis*-piperidine **25a** free base (16.0 g, 0.10 mol) was treated with sodium (2.34 g, 0.10 mol) in methanol (250 cm^3) under reflux for 48 h, as described for the preparation of compound **19b**, to give a 9:1 mixture of stereoisomers **25b** and **25a**. Column chromatography on silica in dichloromethane–methanol (95:5) yielded pure *trans*-isomer **25b** (10.8 g, 68%); the *hydrochloride* had m.p. 151–152 °C (from propan-2-ol) (Found: C, 49.45; H, 8.2; N, 7.1. $C_8H_{15}NO_2$·HCl requires C, 49.6; H, 8.3; N, 7.2%); $\delta_H(D_2O)$ 0.96 (3 H, d, *J* 7 Hz, 3-Me), 1.86 (1 H, dq, *J* 4 and 13 Hz, 5-H_{ax}), 2.02–2.16 (1 H, m, 3-H), 2.15 (1 H, qd, *J* 3 and 13 Hz, 5-H_{eq}), 2.45 (1 H, dt, *J* 4 and 12 Hz, 4-H), 2.73 (1 H, t, *J* 12.5 Hz, 2-H_{ax}), 3.00 (1 H, dt, *J* 3 and 13 Hz, 6-H_{ax}), 3.39 (1 H, dd, *J* 4 and 12.5 Hz, 2-H_{eq}), 3.47 (1 H, dq, *J* 2 and 13 Hz, 6-H_{eq}) and 3.75 (3 H, s, OMe); *m/z* (CI) 158 ($M + H^+$, 100%).

trans-*Methyl* 1-(*Methoxycarbonylmethyl*)-3-*methylpiperidine*-4-*carboxylate* **23b**.—The *trans*-piperidine **25b** was treated with methyl bromoacetate as for the preparation of compound **18** to afford *diester* **23b** (95%) (Found: $M + H^+$, 230.1391. $C_{11}H_{20}NO_4$ requires *m/z*, 230.1392); δ_H 0.89 (3 H, d, *J* 7 Hz, Me), 1.84–2.02 (4 H, m, 2- and 3-H and 4-H_2), 2.03–2.13 (1 H, m, 6-H_{ax}), 2.17–2.28 (1 H, m, 2-H_{ax}), 2.91 (1 H, ddd, *J* 1.5, 3 and 11 Hz, 6-H_{eq}), 2.99 (1 H, br d, *J* 11 Hz, 2-H_{eq}), 3.26 (2 H, s, NCH_2CO_2) and 3.71 and 3.75 (each 3 H, s, 2 × CO_2Me); *m/z* (CI) 230 ($M + H^+$, 100%) and 170 (100).

(4R*,5S*)-5-*Methyl*-1-*azabicyclo*[2.2.2]*octane* 3-*one Hydrochloride* **24b**·HCl.—A solution of potassium t-butoxide (30.6 g, 0.273 mol) in toluene (150 cm^3) was heated to reflux under nitrogen and vigorously stirred with a Hirschberg stirrer. A solution of the *cis*-piperidine **23a** (25.0 g, 0.109 mol) in toluene (120 cm^3) was added during 1 h, and the mixture was heated for a further 2 h. The mixture was cooled in ice, and conc. hydrochloric acid (200 cm^3) was added. The layers were separated and the organic layer was extracted with more acid (50 cm^3). The combined acid extracts were heated under reflux for 16 h, cooled, and evaporated. The dark residue was dissolved in water (300 cm^3), basified with solid potassium carbonate, and extracted with ether (4 × 400 cm^3). Evaporation of the combined ether layers yielded virtually pure *quinuclidinone* **24** as a 95:5 mixture of stereoisomers **24b** and **24a** (6.34 g, 42%). The *hydrochloride* was crystallised from methanol–ether, m.p. 280–295 °C (sublimes) (Found: C, 54.8; H, 7.9; N, 7.95; Cl, 20.2. $C_8H_{13}NO$·HCl requires C, 54.7; H, 8.0; N, 8.0; Cl, 20.2%); δ_H(free base) 1.13 (3 H, d, *J* 7 Hz, Me), 1.75–1.85 (1 H, m, 8-H), 2.15–2.24 (2 H, m, 5- and 8-H), 2.22–2.26 (1 H, m, 4-H), 2.42 (1 H, ddd, *J* 2, 8 and 14 Hz, 6-H), 2.82–2.89 (1 H, m, 7-H), 2.90–3.02 (1 H, m, 7-H), 3.17 (1 H, ddd, *J* 2, 10 and 14 Hz, 6-H) and 3.24 (2 H, ABq, *J* 18 Hz, 2-H_2); *m/z* (CI) 140 ($M + H^+$, 60%), 111 (100) and 96 (40); GC (free base) t_R 5.89 min (column A; 80 °C).

(4R*,5R*)-5-*Hydroxymethyl*-3,3-*dimethoxy*-1-*azabicyclo*-[2.2.2]*octane* **26**.—To a stirred, ice-cooled, dry solution of the acetal ester **19a** (13.2 g, 57.6 mmol) in dichloromethane (50 cm^3)–THF (350 cm^3) under nitrogen was added dropwise a suspension of sodium borohydride in THF (1 mol dm^{-3}; 58 cm^3, 58 mmol). The suspension was stirred at 0 °C for 1 h and then at room temperature for 1 h. The suspension was cooled again in ice and worked up by sequential addition of ethyl acetate (5 cm^3), water (2.2 cm^3), 2 mol dm^{-3} aq. sodium hydroxide (2.2 cm^3), and more water (6.6 cm^3). After 15 min the mixture was filtered through Hyflo, the filter was washed well with dichloromethane, and the combined washings and filtrate were evaporated to yield the *alcohol* **26** as an amorphous solid (9.65 g, 83%), m.p. 58–62 °C (Found: M^+, 201.1356. $C_{10}H_{19}NO_3$ requires M, 201.1365); δ_H 1.31–1.41 (1 H, m, 5-H), 1.78–1.87 (1 H, m, 8-H), 1.91–2.02 (1 H, m, 8-H), 2.22 (1 H, q, *J* 3 Hz, 4-H), 2.50 (1 H, dd, *J* 6 and 13 Hz, 6-H), 2.76 (2 H, t, *J* 8.5 Hz, 7-H_2), 2.80 and 2.89 (each 1 H, ABq, *J* 14 Hz, 2-H_2), 2.95 (1 H, dd, *J* 2 and 13 Hz, 6-H), 3.22 (6 H, s, 2 × OMe), 3.54 (1 H, dd, *J* 8 and 11 Hz, C*H*HOH) and 3.61 (1 H, dd, *J* 6 and 11 Hz, CH*H*OH); *m/z* 201 (M^+, 10%), 186 (100) and 170 (28).

(4R*,5R*)-3,3-*Dimethoxy*-5-*methyl*-1-*azabicyclo*[2.2.2]-*octane* **28** *Oxalic Acid Adduct*.—Butyllithium (12.5 cm^3 of 2.5 mol dm^{-3} solution in hexane, 31.4 mmol) was added to a stirred, ice-cooled solution of the alcohol **26** (5.72 g, 28.5 mmol) in THF (120 cm^3) under nitrogen. The cooling bath was removed and the solution was stirred for 1 h. *N,N,N',N'*-tetramethylphosphorodiamidic chloride (8.3 cm^3, 57 mmol) was added and the mixture was stirred at room temperature for 20 h. The solvent was evaporated off and the residue was partitioned between aq. potassium carbonate and dichloromethane. Evaporation of the organic layer gave the crude phosphoramidate **27** (9.93 g). A portion of this (1.1 g) was purified by column chromatography on alumina to give pure compound **27** (460 mg); δ_H 1.36–1.45 (1 H, m, 8-H), 1.79–1.86 (1 H, m, 8-H), 2.08–2.17 (1 H, m, 5-H), 2.16–2.19 (1 H, m, 4-H), 2.50 (1 H, dd, *J* 7 and 13 Hz, 6-H), 2.63 and 2.66 (each 6 H, s, 2 × NMe_2), 2.60–2.80 (2 H, m, 7-H_2), 2.80 and 2.90 (each 1 H, ABq, *J* 15 Hz, 2-H_2), 3.09 (1 H, t, *J* 13 Hz, 6-H), 3.15 and 3.16 (each 3 H, s, 2 × OMe), 3.91 (1 H, dd, *J* 7.6 and 16 Hz, CHOP) and 4.00 (1 H, dd, *J* 6 and 16 Hz, CHOP); *m/z* (CI) 336 ($M + H^+$, 10%), 320 (40) and 304 (100).

A solution of the crude phosphoramidate (8.74 g) in THF (30 cm^3) containing 2-methylpropan-2-ol (5.77 g, 78 mmol) was added to ice-cooled ethylamine (250 cm^3) which had been freshly distilled from potassium hydroxide. The flask was flushed with nitrogen, and lithium wire (1.8 g, 257 mol) was added in portions to the stirred contents. After *ca.* 1.5 h a deep blue colour developed, and the mixture was stirred for a further 1 h. Water (100 cm^3) was added dropwise with caution, and the product was extracted with dichloromethane. Chromatography of the residue from the organic layer on alumina with dichloromethane–methanol (99:1) as eluent yielded the 5-*methyl acetal* **28** (3.93 g, 75% from **26**), as its *oxalic acid adduct*, m.p. 104–107 °C (Found: C, 51.4; H, 7.6; N, 5.1. $C_{10}H_{19}NO_2{\cdot}C_2H_2O_4{\cdot}0.25H_2O$ requires C, 51.5; H, 7.7; N, 5.0%); $\delta_H(D_2O)$ 1.70 (3 H, d, *J* 7 Hz, 5-Me), 1.80–1.90 (1 H, m, 8-H), 2.01–2.11 (1 H, m, 5-H), 2.28–2.36 (1 H, m, 8-H), 2.40 (1 H, q, *J* 2.5 Hz, 4-H), 2.82 (1 H, dd, *J* 8 and 12.5 Hz, 6-H), 3.23–3.30 (2 H, m, 7-H_2), 3.27 (6 H, m, 2 × OMe), 3.34 (1 H, dd, *J* 2 and 13.5 Hz, 2-H), 3.43 (1 H, d, *J* 13.5 Hz, 2-H) and 3.56 (1 H, dt, *J* 2 and 12.5 Hz, 6-H); *m/z* (CI) 186 ($M + H^+$, 66%), 170 (25), 154 (70) and 141 (100).

(4R*,5R*)-5-*Methyl*-1-*azabicyclo*[2.2.2]*octan*-3-*one Hydrochloride* **24a**·HCl.—Acetal **28** (4.90 g, 26.5 mmol) was deprotected as described for compound **5b** (60%) to give the title *hydrochloride*, m.p. 226–229 °C (decomp.) (from propan-2-ol) (Found: C, 53.0; H, 7.8; N, 8.1. $C_8H_{13}NO{\cdot}HCl{\cdot}0.25H_2O$ requires C, 53.3; H, 8.1; N, 7.8%); δ_H (free base) 0.96 (3 H, d, *J* 7 Hz, 5-Me), 1.95–2.01 (2 H, m, 8-H_2), 2.20–2.28 (1 H, m, 5-H), 2.27–2.30 (1 H, m, 4-H), 2.38 (1 H, dd, *J* 5.5 and 13 Hz, 6-H), 2.84–2.96 (2 H, m, 7-H_2), 3.15 (1 H, d, *J* 19 Hz, 2-H), 3.22–3.28 (1 H, m, 6-H) and 3.26 (1 H, d, *J* 19 Hz, 2-H); *m/z* 139 (M^+, 25%), 111 (100) and 96 (95); GC (free base) t_R 5.11 min (column A; 80 °C).

(4R*,5S*)-3-(1,3-*Dithian*-2-*ylidene*)-5-*methyl*-1-*azabicyclo*[2.2.2]-*octane* **29b**.—A solution of the quinuclidinone **24b** (2.77 g, 19.9 mmol) in dry THF (25 cm^3) was dried over magnesium sulphate for 2 h. Meanwhile, butyllithium (11.9 cm^3 of 2.5 mol dm^{-3} solution in hexane, 29.8 mmol) was added to a stirred solution of 2-trimethylsilyl-1,3-dithiane (5.73 g, 29.8 mmol) in THF (60 cm^3), with the temperature kept below −60 °C. After 1.5 h, the ketone solution was added, and the mixture was stirred for 1.5 h at −70 °C and allowed to warm slowly to room temperature. Water (100 cm^3) was added and the product was extracted with dichloromethane. Flash chromatography in dichloromethane–methanol (95:5) gave recovered starting material (0.35 g) and pure *dithiane* **29b** (2.99 g, 71% based on consumed ketone) as an oil (Found: M^+, 241.0988. $C_{12}H_{19}NS_2$ requires M, 241.0959); δ_H 1.06 (3 H, d, *J* 7 Hz, 5-Me), 1.43–1.54 (1 H, m, 8-H), 1.82–2.02 (2 H, m, 5- and 8-H), 2.13–2.21 (2 H, m, $SCH_2CH_2CH_2S$), 2.35 (1 H, ddd, *J* 2, 6 and 13 Hz, 6-H), 2.73–2.82 (1 H, m, 7-H), 2.83–2.94 (6 H, m, 4- and 7-H, $SCH_2CH_2CH_2S$), 3.09 (1 H, ddd, *J* 2, 10 and 13 Hz, 6-H), 3.48 (1 H, dd, *J* 2 and 18 Hz, 2-H) and 3.55 (1 H, dd, *J* 2 and 18 Hz, 2-H); *m/z* 241 (M^+, 100%), 226 (10) and 199 (25).

(4R*,5R*)-3-(1,3-*Dithian*-2-*ylidene*)-5-*methyl*-1-*azabicyclo*[2.2.2]*octane* **29a**.—Prepared in 69% yield from compound **24a** (24% conversion) (Found: M^+, 241.0975. $C_{12}H_{19}NS_2$ requires M, 241.0959); δ_H 0.92 (3 H, d, *J* 7 Hz, 5-Me), 1.69–1.80 (2 H, m, 8-H_2), 1.95–2.04 (1 H, m, 5-H), 2.17 (2 H, quintet, *J* 6 Hz, $SCH_2CH_2CH_2S$), 2.28 (1 H, dd, *J* 6 and 13 Hz, 6-H), 2.79–2.96 (6 H, m, 7-H_2, $SCH_2CH_2CH_2S$), 3.01 (1 H, q, *J* 3 Hz, 4-H), 3.18 (1 H, ddd, *J* 2, 10 and 13 Hz, 6-H), 3.49 (1 H, dd, *J* 2 and 17.6 Hz, 2-H) and 3.58 (1 H, d, *J* 17.6 Hz, 2-H); *m/z* 241 (M^+, 100%), 226 (10) and 199 (22).

Methyl 5-*Methylene*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate* **32**.—Keto ester **5a** (1.17 g, 6.39 mmol) was treated with the ylide of methyltriphenylphosphonium bromide (4.57 g, 12.8 mmol) under standard conditions.[20] Flash chromatography in ethyl acetate–methanol (9:1) gave recovered ketone (177 mg), pure isomer A of **32** (50 mg) (first eluted), pure isomer B of **32** (225 mg) and mixed fractions (184 mg) (40% combined yield). Isomer B was converted into the oxalate salt for characterisation, but this was hygroscopic and could not be crystallised. This *isomer* has the 3*R**,4*R** configuration **32a** (Found: M^+, 181.1106. $C_{10}H_{15}NO_2$ requires M, 181.1103); $\delta_H(D_2O)$ 2.05–2.25 (2 H, m, 8-H_2), 3.13 (1 H, q, *J* 3 Hz, 4-H), 3.29–3.46 (3 H, m, 3-H, 7-H_2), 3.55 (1 H, ddd, *J* 2, 10 and 13 Hz, 2-H *anti* to CO_2Me), 3.72–3.79 (1 H, m, 2-H *syn* to CO_2Me), 3.74 (3 H, s, OMe), 4.02 (2 H, ABq, *J* 16 Hz, 6-H_2) and 5.03 and 5.14 (each 1 H, t, *J* 2 Hz, C=CH_2); *m/z* 181 (M^+, 93%), 166 (29), 150 (21) and 122 (100).

(3R*,4S*,5S*)-*Methyl* 5-*Methyl*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate* **3a** *Oxalic Acid Adduct*.—A solution of compound **32** as the oxalate (280 mg, 1.03 mmol) in methanol (20 cm^3) was hydrogenated over 10% palladium on carbon (80 mg) at 50 psi for 3 h. The solution was filtered and evaporated, and the residue was crystallised from propan-2-ol to yield the *title compound* **3a** as a *single isomer oxalate* (196 mg, 69%), m.p. 117–119 °C (Found: C, 52.2; H, 6.9; N, 5.1. $C_{10}H_{17}NO_2{\cdot}C_2H_2O_4{\cdot}0.2H_2O$ requires C, 52.05; H, 7.1; N, 5.1%); $\delta_H(D_2O)$ 0.95 (3 H, d, *J* 7 Hz, 5-Me), 1.98–2.05 (2 H, m, 8-H_2), 2.20–2.32 (1 H, m, 5-H), 2.56–2.60 (1 H, m, 4-H), 2.84 (1 H, dd, *J* 7 and 12.7 Hz, 6-H *syn* to Me), 3.14–3.21 (1 H, m, 3-H), 3.29 (2 H, t, *J* 8 Hz, 7-H_2), 3.45 (1 H, ddd, *J* 2.6, 11 and 14 Hz, 2-H, *anti* to CO_2Me), 3.52 (1 H, dt, *J* 2.6 and 13 Hz, 6-H *anti* to Me), 3.78 (3 H, s, OMe) and 3.82 (1 H, dd, *J* 7 and 14 Hz, 2-H *syn* to CO_2Me); *m/z* 183 (M^+, 95%), 168 (54), 154 (30) and 124 (100); GC (free base) t_R 7.32 min (column B; 140 °C).

(3R*,4R*,5S*)-*Methyl* 5-*Methyl*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate* **3c** *Oxalic Acid Adduct*.—The dithiane **29b** (2.55 g, 10.6 mmol) was heated in a freshly prepared solution of dry hydrogen chloride in methanol (*ca.* 40 g in 100 cm^3) at 55 °C for 16 h. Basification and extraction yielded the quinuclidine ester as a 1:1 mixture of diastereoisomers (1.07 g, 55%). A portion of this material (643 mg, 3.5 mmol) in dichloromethane (5 cm^3)–THF (10 cm^3) was cooled to −70 °C under nitrogen and a 1 mol dm^{-3} solution of borane–THF (10.5 cm^3, 10.5 mmol) was added. After 30 min the reaction was quenched by addition of water (2 cm^3) at −70 °C, warmed to room temperature, and partitioned between dichloromethane and aq. sodium hydrogen carbonate. Column chromatography of the residue from the organic layer on silica in dichloromethane–ethyl acetate (97:3) gave pure borane complex **30** (602 mg, 87%). The isomers were separated by MPLC with hexane–propan-2-ol (95:5) as eluent using several recycles.

The first eluted borane complex **30c** was deprotected by the method of Stotter[15] (87%) and product **3c** was characterised as the oxalic acid adduct, m.p. 89–92 °C (from methanol–ether) (Found: C, 50.9; H, 6.7; N, 4.8. $C_{10}H_{17}NO_2{\cdot}1.25C_2H_2O_4$ requires C, 50.8; H, 6.65; N, 4.7%); $\delta_H(D_2O)$ 1.13 (3 H, d, *J* 7 Hz, 5-Me), 1.64–1.74 (1 H, m, 8-H *anti* to Me), 2.01–2.11 (1 H, m, 8-H *syn* to Me), 2.27–2.36 (2 H, m, 4- and 5-H), 2.78 (1 H, ddd, *J* 2.5, 7 and 13 Hz, 6-H *syn* to Me), 3.18–3.29 (3 H, m, 3-H, 7-H_2), 3.40 (1 H, ddd, *J* 2, 10.5 and 13 Hz, 2-H *syn* to CO_2Me), 3.50 (1 H, ddd, *J* 2, 10 and 13 Hz, 6-H *anti* to Me), 3.72 (1 H, ddd, *J* 2.6, 5 and 13 Hz, 2-H *anti* to CO_2Me) and 3.78 (3 H, s, OMe); *m/z* 183 (M^+, 61%), 168 (49), 124 (77) and 96 (100); GC (free base) t_R 7.15 min (column B; 140 °C).

(3R*,4S*,5R*)-*Methyl* 5-*Methyl*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate* **3d** *Oxalic Acid Adduct*.—The second eluted borane complex **30d** (41 mg, 0.208 mmol) was deprotected as above

(81%) to give the *oxalate* of *compound* **3d**, m.p. 141–143 °C (Found: C, 52.5; H, 6.9; N, 5.0. $C_{10}H_{17}NO_2 \cdot C_2H_2O_4$ requires C, 52.7; H, 7.0; N, 5.1%); $\delta_H(D_2O)$ 1.07 (3 H, d, *J* 7 Hz, 5-Me), 1.86–1.97 (1 H, m, 8-H *syn* to CO_2Me), 2.08–2.18 (1 H, m, 5-H), 2.17–2.26 (1 H, m, 8-H *anti* to CO_2Me), 2.33–2.37 (1 H, m, 4-H), 2.76 (1 H, ddd, *J* 2.5, 7 and 13 Hz, 6-H *syn* to Me), 3.16–3.37 (3 H, m, 3-H, 7-H_2), 3.44–3.53 (2 H, m, 2-H *syn* to CO_2Me, 6-H *anti* to Me), 3.63 (1 H, ddd, *J* 2.5, 7 and 13 Hz, 2-H *anti* to CO_2Me), and 3.77 (3 H, s, OMe); *m/z* 183 (M^+, 65%), 168 (47), 154 (30), 124 (94) and 82 (100); GC (free base) t_R 6.81 min (column B; 140 °C).

(3R*,4R*,5R*)-*Methyl* 5-*Methyl*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate* **3b**.—Methanolysis of the dithiane **29a** gave the title ester (75%) as its *oxalate*, m.p. 110–112 °C (from propan-2-ol–ether) (Found: C, 51.7; H, 6.8; N, 5.1. $C_{10}H_{17}NO_2 \cdot 1.1C_2H_2O_4$ requires C, 51.9; H, 6.9; N, 5.0%); $\delta_H(D_2O)$ 1.14 (3 H, d, *J* 7 Hz, 5-Me), 1.89 (2 H, dt, *J* 3 and 8 Hz, 8-H_2), 2.27–2.38 (2 H, m, 4- and 5-H), 2.74 (1 H, ddd, *J* 2, 7 and 13 Hz, 6-H *syn* to Me), 3.17–3.26 (1 H, m, 7-H *anti* to Me), 3.26–3.36 (2 H, m, 3- and 7-H *syn* to Me), 3.45 (1 H, ddd, *J* 2.5, 10 and 13 Hz, 2-H *anti* to CO_2Me), 3.52 (1 H, ddd, *J* 2.5, 10.5 and 13 Hz, 6-H *anti* to Me), 3.63 (1 H, ddd, *J* 2.6, 7 and 13 Hz, 2-H *syn* to CO_2Me) and 3.78 (3 H, s, OMe); *m/z* 183 (M^+, 100%), 168 (44), 154 (29) and 124 (100); GC (free base) t_R 6.86 min (column B; 140 °C).

3. 6-Methyl Series

Methyl 5,5-*Dimethoxy*-1-*azabicyclo*[2.2.2]*octane*-2-*carboxylate* **34a** *and* **34b**.—*cis*-Dimethyl 1-(methoxycarbonylmethyl)-piperidine-2,4-dicarboxylate **33**[17] (185 g, 0.68 mol) was cyclised and esterified as described for the preparation of compound **19a**. The crude product was purified on a Waters prep 500 liquid chromatograph with ethyl acetate–methanol (95:5) as eluent. The first eluted component was the 2*R**,4*R** -isomer **34a** (22 g, 14%). An analytical sample was converted into the *sesquioxalate*, m.p. 105–106 °C (from acetone–ether) (Found: C, 46.1; H, 6.1; N, 3.9. $C_{11}H_{19}NO_4 \cdot 1.5C_2H_2O_4$ requires C, 46.1; H, 6.1; N, 3.8%); $\delta_H(D_2O)$ 1.88–2.12 (3 H, m, 3-H, 7-H_2), 2.37–2.46 (1 H, m, 3-H), 2.60–2.63 (1 H, m, 4-H), 3.27 and 3.28 [each 3 H, s, $C(OMe)_2$], 3.30–3.40 (1 H, m) and 3.47–3.65 (3 H, m, 8- and 6-H_2), 3.86 (3 H, s, CO_2Me) and 4.37–4.43 (1 H, m, 2-H); *m/z* 229 (M^+, 17%), 214 (100), 198 (23) and 154 (50). The second eluted component was a mixture of diastereoisomers (7:1) (**34b**:**34a**) (20 g, 13%). A pure example of the 2*R**,4*S** -isomer **34b** was obtained by converting the mixture into the *fumarate salt* and crystallisation twice from propan-2-ol–ether, m.p. 108–109 °C (Found: C, 52.0; H, 6.6; N, 4.0. $C_{11}H_{19}O_4 \cdot C_4H_4O_4$ requires C, 52.2; H, 6.7; N, 4.1%); $\delta_H(D_2O)$ 1.93–1.99 (1 H, m, 7-H), 2.05–2.09 (1 H, m, 7-H), 2.24–2.40 (2 H, m, 3-H_2), 2.60–2.63 (1 H, m, 4-H), 3.23 and 3.31 [each 3 H, s, $C(OMe)_2$], 3.34–3.62 (4 H, m, 6- and 8-H_2), 3.86 (3 H, s, CO_2Me), 4.45 (1 H, dd, *J* 1 and 7 Hz, 2-H) and 6.68 (2 H, s, fumarate); *m/z* (CI) 230 ($M + H^+$, 85%) and 214 (100).

(2R*,4R*)-2-*Hydroxymethyl*-5,5-*dimethoxy*-1-*azabicyclo*[2.2.2]*octane* **35a**.—Ester **34a** was treated as for the preparation of **26** and the *product* was distilled (94%), b.p. 150–155 °C (0.4 mmHg) (Found: C, 58.2; H, 9.6; N, 6.8. $C_{10}H_{19}NO_3 \cdot 0.25H_2O$ requires C, 58.4; H, 9.6; N, 6.8%); δ_H 0.80 (1 H, ddd, *J* 2, 7.7 and 9.8 Hz, 3-H), 1.29–1.37 (1 H, m, 7-H), 1.70–1.87 (2 H, m, 3- and 7-H), 2.08–2.11 (1 H, m, 4-H), 2.54–2.63 (1 H, m, 8-H), 2.83–3.00 (4 H, m, 6-H_2, 2- and 8-H), 3.12 and 3.13 [each 3 H, s, $C(OMe)_2$], and 3.41–3.49 (2 H, m, CH_2OH); *m/z* (CI) 202 ($M + H^+$, 100%), 186 (78) and 170 (30).

(2R*,4S*)-2-*Hydroxymethyl*-5,5-*dimethoxy*-1-*azabicyclo*[2.2.2]*octane* **35b**.—Ester **34b** was treated as above and the *product* was crystallised from cyclohexane (56%), m.p. 92–93 °C (Found: C, 59.7; H, 9.3; N, 7.0. $C_{10}H_{19}NO_3$ requires C, 59.7; H, 9.5; N, 6.7%); δ_H 1.21–1.27 (1 H, m), 1.42–1.59 (2 H, m) and 1.73–1.80 (1 H, m, 3- and 8-CH_2), 2.09–2.12 (1 H, m, 4-H), 2.62 (1 H, d, *J* 14.5 Hz, 6-H), 2.75–2.88 (3 H, m, 2-H and 7-CH_2), 2.97 (1 H, dd, *J* 2 and 14.5 Hz, 6-H), 3.16 and 3.19 [each 3 H, each s, $C(OMe)_2$], 3.41 (1 H, dd, *J* 6 and 11 Hz, C*H*OH) and 3.46 (1 H, t, *J* 11 Hz, C*H*OH); *m/z* 201 (M^+, 14%), 186 (100) and 170 (22).

(2R*,4S*)-5,5-*Dimethoxy*-2-*methyl*-1-*azabicyclo*[2.2.2]*octane* **37a**.—A solution of the alcohol **35a** (11.6 g, 58 mmol) in dichloromethane (500 cm^3) containing triethylamine (7.02 g, 69 mmol) was cooled to −60 °C and thionyl chloride (7.6 g, 64 mmol) was added. The mixture was allowed to warm to room temperature and was stirred for 16 h. Saturated aq. sodium carbonate was added, the product was extracted with dichloromethane, and the extract was evaporated to yield the chloride **36a** as an oil (12.1 g, 95%). This was dissolved in THF (200 cm^3), and sodium iodide (18 g, 120 mmol) and 15-crown-5 (1 cm^3) were added. A 1 mol dm^{-3} suspension of lithium aluminium hydride in THF (55 cm^3, 55 mmol) was added dropwise and the reaction mixture was stirred for 1 h at room temperature and then heated to reflux. After 4 h, reaction was complete by TLC and water (3.0 cm^3), 2 mol dm^{-3} aq. sodium hydroxide (3.0 cm^3), and more water (9.0 cm^3) were added sequentially to the cooled mixture, which was then filtered and evaporated, and the residue was purified by chromatography on alumina with dichloromethane–methanol (97.5:2.5) to yield pure *compound* **37a** as an oil (4.2 g, 41%) (Found: M^+, 185.1418. $C_{10}H_{19}NO_2$ requires M, 185.1416); δ_H 0.96 (1 H, ddd, *J* 2, 7 and 13 Hz, 3-H), 1.15 (3 H, d, *J* 7 Hz, 2-Me), 1.34–1.42 (1 H, m, 8-H), 1.67–1.74 (1 H, m, 8-H), 1.91–1.97 (1 H, m, 3-H), 2.05–2.08 (1 H, m, 4-H), 2.59–2.67 (1 H, m, 7-H), 2.90–3.03 (2 H, m, 2- and 7-H), 2.90 (2 H, d, *J* 1 Hz, 6-H_2) and 3.19 and 3.20 [each 3 H, each s, $C(OMe)_2$]; *m/z* 185 (M^+, 15%), 170 (100) and 154 (32).

(2R*,4R*)-5,5-*Dimethoxy*-2-*methyl*-1-*azabicyclo*[2.2.2]*octane Hydrochloride* **37b**·HCl.—Alcohol **35b** (9.8 g, 49 mmol) was treated with thionyl chloride (6.5 g, 55 mmol) as described in the preceding preparation to yield the chloride **36b** as an oil (10.5 g, 96%). This material, in dry THF (200 cm^3) containing sodium iodide (18 g, 120 mmol) and 15-crown-5 (5 cm^3), was treated with a 1 mol dm^{-3} suspension of lithium aluminium hydride in THF (47 cm^3, 47 mmol) as described for compound **37a** to yield its isomer **37b** as an oil (5.6 g, 64%). An analytical sample was converted into the *hydrochloride*, m.p. 153–154 °C (Found: C, 54.0; H, 9.0; N, 6.3. $C_{10}H_{19}NO_2 \cdot HCl$ requires C, 54.2; H, 9.1; N, 6.3%); δ_H(free base) 1.12 (3 H, d, *J* 7 Hz, 2-Me), 1.37–1.43 (2 H, m) and 1.62–1.75 (2 H, m) (3- and 8-H_2), 2.05–2.08 (1 H, m, 4-H), 2.66 (1 H, d, *J* 14 Hz, 6-H), 2.75–2.90 (3 H, m, 2-H, 7-H_2), 3.07 (1 H, d, *J* 14 Hz, 6-H) and 3.11 and 3.13 [each 3 H, each s, $C(OMe)_2$]; *m/z* 185 (M^+, 18%), 170 (100) and 154 (40).

(4R*,6S*)-6-*Methyl*-1-*azabicyclo*[2.2.2]*octan*-3-*one* **38a**.—Acetal **37a** was deprotected as for the preparation of compound **5b** (94%) to give ketone **38a**; *hydrochloride*, m.p. 250–260 °C (decomp.) (Found: C, 53.8; H, 7.8; N, 7.75. $C_8H_{13}NO \cdot HCl \cdot 0.2H_2O$ requires C, 53.6; H, 8.1; N, 7.8%); δ_H(free base) 1.47 (3 H, d, *J* 7 Hz, 6-Me), 1.53 (1 H, ddd, *J* 2, 7 and 13 Hz, 5-H), 1.84–1.98 (2 H, m, 8-H_2), 2.15–2.25 (1 H, m, 5-H), 2.35–2.41 (1 H, m, 4-H), 2.73–2.84 (1 H, m, 7-H), 2.98–3.01 (1 H, m, 7-H), 3.28 (1 H, d, *J* 19 Hz, 2-H), 3.37 (1 H, d, *J* 19 Hz, 2-H) and 3.20–3.32 (1 H, m, 6-H); *m/z* 139 (M^+, 18%) and 111 (100).

(4R*,6R*)-6-*Methyl*-1-*azabicyclo*[2.2.2]*octan*-3-*one* **38b**.—Acetal **37b** was deprotected as above (95%) to give ketone **38b** as its *hydrochloride*, m.p. 290–291 °C (from propan-2-ol) (Found: C, 54.7; H, 7.9; N, 7.95. $C_8H_{13}NO \cdot HCl$ requires C, 54.7; H, 8.0;

N, 8.0%); δ_H(free base) 1.17 (3 H, d, *J* 7 Hz, 6-Me), 1.49 (1 H, ddt, *J* 2, 6.5 and 14 Hz, 5-H), 1.88–2.03 (2 H, m, 5- and 8-H), 2.17–2.26 (1 H, m, 8-H), 2.40–2.43 (1 H, m, 4-H), 2.90–2.99 (1 H, m, 7-H), 3.02–3.13 (2 H, m, 6- and 7-H), 3.07 (1 H, d, *J* 18 Hz, 2-H) and 3.50 (1 H, d, *J* 18 Hz, 2-H); *m/z* 139 (M^+, 19%), 111 (100) and 96 (97).

(4R*,6R*)-3-(1,3-*Dithian*-2-*ylidene*)-6-*methyl*-1-*azabicyclo*-[2.2.2]*octane* **39b**.—The quinuclidinone **38b** was treated as described for compound **29b** to give *compound* **39b** (54%) (Found: M^+, 241.0947. $C_{12}H_{19}NS_2$ requires M, 241.0959); δ_H 1.13 (3 H, d, *J* 7 Hz, Me), 1.54–1.70 (2 H, m, 5- and 8-H), 1.84–1.96 (2 H, m, 5- and 8-H), 1.91 (2 H, quintet, *J* 4 Hz, $SCH_2CH_2CH_2S$), 2.81–3.00 (7 H, m, 6-H, 7-H_2, SCH_2CH_2-CH_2S), 3.07–3.13 (1 H, m, 4-H), 3.37 (1 H, d, *J* 18 Hz, 2-H) and 3.68 (1 H, dd, *J* 2 and 18 Hz, 2-H); *m/z* 241 (M^+, 100%) and 198 (20).

(4R*,6S*)-3-(1,3-*Dithian*-2-*ylidene*)-6-*methyl*-1-*azabicyclo*-[2.2.2]*octane* **39a**.—This was prepared from the quinuclidinone **38a** (77%) (Found: M^+, 241.0968); δ_H 1.20 (3 H, d, *J* 7 Hz, Me), 1.50–1.68 (2 H, m, 5- and 8-H), 1.78–1.98 (2 H, m, 5- and 8-H), 2.16 (2 H, quintet, *J* 6 Hz, $SCH_2CH_2CH_2S$), 2.66 (1 H, ddd, *J* 4, 11 and 15 Hz, 7-H), 2.80–2.92 (5 H, m, 6-H, $SCH_2CH_2CH_2S$), 3.06–3.16 (2 H, m, 4- and 7-H), 3.53 (1 H, d, *J* 18 Hz, 2-H) and 3.60 (1 H, dd, *J* 2 and 18 Hz, 2-H); *m/z* 241 (M^+, 100%) 198 (20) and 185 (30).

(3R*,4R*,6R*)-*Methyl* 6-*Methyl*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate* **4b** *Oxalic Acid Adduct*.—Methanolysis of the dithiane **39b** (519 mg, 2.15 mmol) as described for the preparation of compound **3c** yielded the crude ester as a mixture of isomers (352 mg, 89%). The diastereoisomers were separated as the borane complex **31a** and **31b** by preparative HPLC with hexane–propan-2-ol (95:5) as eluent. The second eluted component **31b** was deprotected to give the title compound free base (80%), whose *oxalate salt* had m.p. 105–106 °C (from acetone–ether) (Found: C, 52.3; H, 6.9; N, 5.2. $C_{10}H_{17}NO_2 \cdot C_2H_2O_4 \cdot 0.1H_2O$ requires C, 52.4; H, 7.0; N, 5.1%); $\delta_H(D_2O)$ 1.38 (3 H, d, *J* 7 Hz, 6-Me), 1.56 (1 H, ddt, *J* 2, 7 and 14 Hz, 5-H *syn* to Me), 1.74–1.91 (2 H, m, 8-H_2), 2.26 (1 H, ddd, *J* 4, 10 and 18 Hz, 5-H *anti* to Me), 2.49–2.55 (1 H, m, 4-H), 3.13–3.20 (1 H, m, 3-H), 3.33 (2 H, t, *J* 9 Hz, 7-H_2), 3.56–3.68 (1 H, m, 6-H), 3.61 (2 H, d, *J* 7 Hz, 2-H_2) and 3.78 (3 H, s, OMe); *m/z* 183 (M^+, 65%), 168 (50), 142 (26) and 124 (100).

(3R*,4S*,6S*)-*Methyl* 6-*Methyl*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate* **4a** *Oxalic Acid Adduct*.—The first eluted borane complex from the preceding experiment, compound **31a**, was deprotected to give the title compound free base (81%), whose *oxalate salt* showed m.p. 83–86 °C (from acetone–ether) (Found: C, 50.4; H, 6.6; N, 4.8. $C_{10}H_{17}NO_2 \cdot 1.3C_2H_2O_4$ requires C, 50.4; H, 6.6; N, 4.7%); $\delta_H(D_2O)$ 1.36–1.45 (1 H, m, 5-H *syn* to Me), 1.38 (3 H, d, *J* 7 Hz, 6-Me), 1.93–2.06 (2 H, m, 8-H_2), 2.06–2.14 (1 H, m, 5-H *anti* to Me), 2.49–2.55 (1 H, m, 4-H), 3.13 (1 H, ddt, *J* 2, 7.5 and 11 Hz, 3-H), 3.26–3.35 (1 H, m, 7-H), 3.35–3.47 (2 H, m, 2-H *anti* to CO_2Me, 7-H), 3.55–3.66 (1 H, m, 6-H), 3.78 (3 H, s, OMe) and 3.81 (1 H, ddd, *J* 2.6, 7.5 and 13.6 Hz, 2-H *syn* to CO_2Me); *m/z* 183 (M^+, 70%), 168 (48), 142 (29) and 124 (100).

(3R*,4R*,6S*)-*Methyl* 6-*Methyl*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate* **4c** *Oxalic Acid Adduct*.—Methanolysis of the dithiane **39a** (800 mg, 3.32 mmol) on treatment with methanolic hydrogen chloride as described for compound **3c** gave the title ester as a 1:1 mixture of isomers (444 mg, 73%). The isomers were separated as the borane complex by preparative HPLC with hexane–propan-2-ol (95:5) as eluent. The first eluted isomer had the 3*R**,4*R**,6*S** configuration **31c**. This was deprotected (85%) and converted into the *oxalate salt*, which was hygroscopic and did not crystallise (Found: M^+, 183.1257. $C_{10}H_{17}NO_2$ requires M, 183.1259); $\delta_H(D_2O)$ 1.40 (3 H, d, *J* 7 Hz, 6-Me), 1.57 (1 H, ddd, *J* 2, 7 and 14 Hz, 5-H *syn* to Me), 1.76–1.91 (2 H, m, 8-H_2), 2.20–2.30 (1 H, m, 5-H *anti* to Me), 2.46–2.53 (1 H, m, 4-H), 3.15–3.24 (2 H, m, 3- and 7-H *syn* to CO_2Me), 3.43–3.52 (1 H, m, 7-H *anti* to CO_2Me), 3.52–3.57 (1 H, m, 2-H *anti* to CO_2Me), 3.57–3.68 (1 H, m, 6-H), 3.71 (1 H, dd, *J* 7 and 13 Hz, 2-H *syn* to CO_2Me) and 3.77 (3 H, s, OMe); *m/z* 183 (M^+, 15%), 138 (20) and 91 (100).

(3R*,4S*,6R*)-*Methyl* 6-*Methyl*-1-*azabicyclo*[2.2.2]*octane*-3-*carboxylate* **4d** *Oxalic Acid Adduct*.—The second eluted borane complex **31d** from the preceding experiment was deprotected as above (82%), and the *oxalate salt* showed m.p. 118–121 °C (from acetone–ether) (Found: M^+, 183.1250); $\delta_H(D_2O)$ 1.37 (3 H, d, *J* 7 Hz, 6-Me), 1.45 (1 H, ddt, *J* 2, 7 and 14 Hz, 5-H *syn* to Me), 1.90–2.02 (2 H, m, 8-H_2), 2.02–2.09 (1 H, m, 5-H *anti* to Me), 2.50–2.56 (1 H, m, 4-H), 3.12–3.22 (2 H, m, 2- and 7-H *anti* to Me), 3.45–3.54 (1 H, m, 7-H *syn* to Me), 3.50 (1 H, dd, *J* 10.5 and 13 Hz, 2-H *anti* to CO_2Me), 3.57–3.68 (1 H, m, 6-H), 3.77 (3 H, s, OMe) and 3.78 (1 H, ddd, *J* 2, 7 and 13 Hz, 2-H *syn* to CO_2Me); *m/z* 183 (M^+, 77%), 168 (56), 152 (20) and 124 (100).

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