Stereospecific Phenylthio Migrations in the Synthesis of Spirocyclic Lactones and Ethers from *N*-Methyl-4-Piperidone and Quinuclidin-3-one

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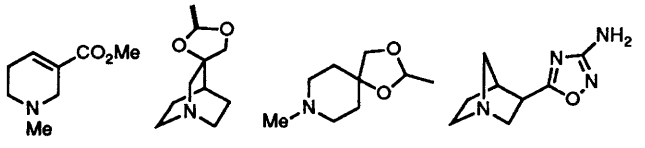
Single diastereoisomers of spirocyclic lactones and ethers have been prepared using intramolecular attack by the oxygen atom of a hydroxy or ester group onto an episulfonium ion. The sulfur group migrates with complete stereospecificity to give the saturated oxygen heterocycle based on the piperidine or quinuclidine ring.

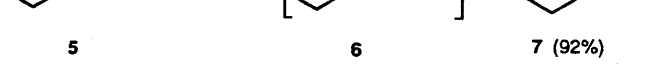
The stereocontrolled synthesis of cyclic and spirocyclic lactones and ethers has been the focus of a great deal of research effort in recent years.[1] One class of such spirocyclic oxygen heterocycles is based on the piperidine, quinuclidine, and azabicycloheptane ring systems. These amines, for example **1**–**4**, have been



1 **2** **3** **4**

prepared as potential muscarinic agonists for the treatment of Alzheimer's disease.[2] In a preliminary communication[3] we outlined the synthesis of a new series of such compounds based on the *N*-methylpiperidine and quinuclidine skeletons.

We have reported the use of stereoselective aldol reactions followed by phenylthio migration to effect the synthesis of spirocyclic lactones and ethers.[4] Rearrangement of the β-hydroxy sulfide **5**[4a] proceeds through the episulfonium ion intermediate **6** which is captured by the hydroxy group to give the spirocyclic ether **7**.

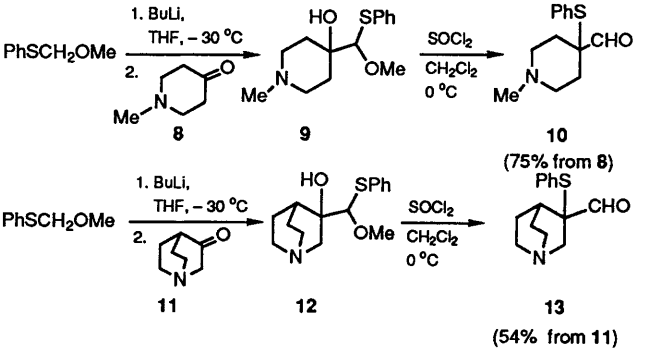


5 **6** **7** (92%)

We wondered if this route to spirocyclic ethers could be applied to the synthesis of spirocyclic amines, partly because of the value of a general approach to spirocyclic amines and partly because this would allow the preparation of structural analogues of known muscarinic agonists such as **2** and **3**.

Following known methodology for the construction of 2-phenylthio aldehydes,[5] the amines **10** and **13** were prepared from *N*-methyl-4-piperidone **8** and quinuclidin-3-one **11**,‡ respectively. Unlike the carbocyclic systems, no base was required for the rearrangement of **9** or **12** as these compounds contain a free nitrogen lone pair and so can themselves act as effective bases for the reaction.

The aldehydes can now be used in aldol reactions. Attempts to prepare the *syn* aldol products with boron enolates of thioethers, as described by Masamune,[6] were unsuccessful. The



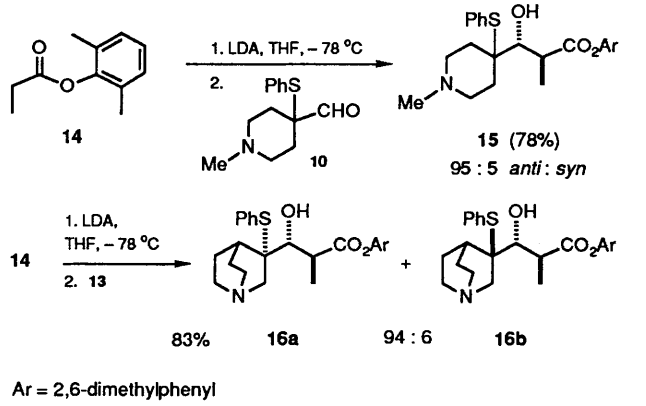
8 **9** **10**

11 **12** **13**

(54% from 11)

reason is probably complexation of the basic nitrogen atom with boron. The *anti*-selective aldol reactions, however, proceeded with good yields according to the method used by Aggarwal.[4] The 2,3-*anti* aldol product **15** was formed in 95:5 ratio as determined by NMR spectroscopy on the crude mixture. Similarly, the aldehyde **13** gave high 2,3-*anti* selectivity. This is in good agreement with other similar aldol reactions with 2-phenylthio aldehydes and the lithium enolate of 2,6-dimethylphenyl propionate **14**.§[4]

To our surprise, the aldol reaction on the prochiral aldehyde group of **13** giving the ester **16** was also highly selective at the centre bearing the phenylthio group. The major product **16a**, isolated in 72% yield, was proved to have this relative stereochemistry by examination of the X-ray crystal structure of the diol **20**.[7] It is not clear why there should be such a large stereoselective preference for the ester **16a** over the ester **16b**. If



Ar = 2,6-dimethylphenyl

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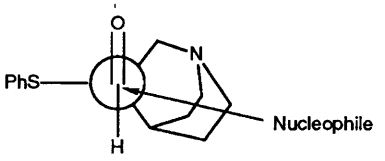
‡ Kindly donated by Glaxo Group Research Ltd, Ware.

§ For the use of the Evan's chiral auxiliary for aldol reactions with 2-phenylthio aldehydes see K. Chibale and S. Warren, *Tetrahedron Lett.*, 1991, **32**, 6645.

we consider the Felkin–Anh model for attack on a carbonyl group then the nucleophile must approach in the direction shown in Fig. 1. We place the phenylthio group perpendicular to the plane of the carbonyl group as this allows maximum σ_{C-S}–$\pi^*_{C=O}$ interaction. This assumption is in agreement with molecular mechanics calculations performed on the aldehyde **13** using Macromodel.[8]

The nitrogen atom of quinuclidinone is an excellent lone pair donor, and it would be expected that the nitrogen atom of the aldehyde **13** would be coordinated to one lithium ion in the solution with the lithium enolate. This would increase the bulk size around the nitrogen atom by solvation and favour attack as shown in Fig. 1. If this is the case, a less bulky ester group

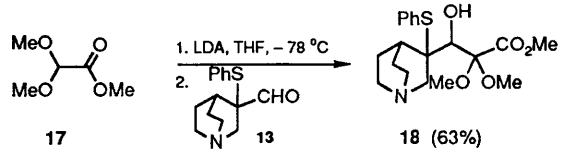


13

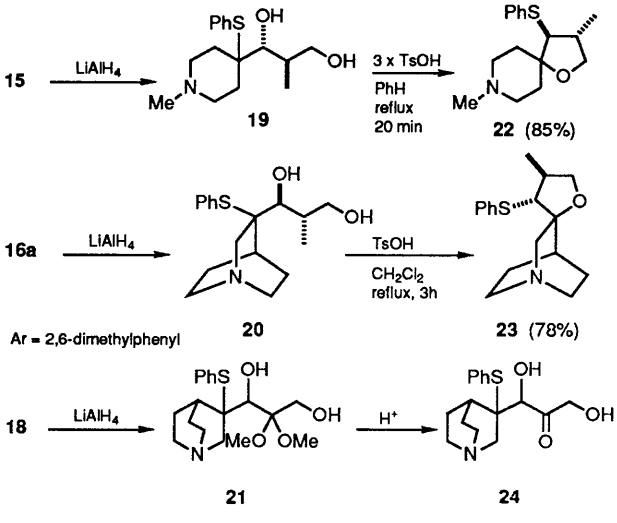
Fig. 1

would give lower selectivity. Indeed, the aldol reaction with the smaller methyl ester **17** gave poor selectivity (1.4:1) at this chiral centre.

Reduction of the esters **15**, **16a** and **18** with $LiAlH_4$ gave the corresponding diols **19**, **20** and **21**, respectively, with no loss of stereochemical purity. On treatment with an excess of toluene-*p*-sulfonic acid (TsOH), the diols **19** and **20** gave good yields of

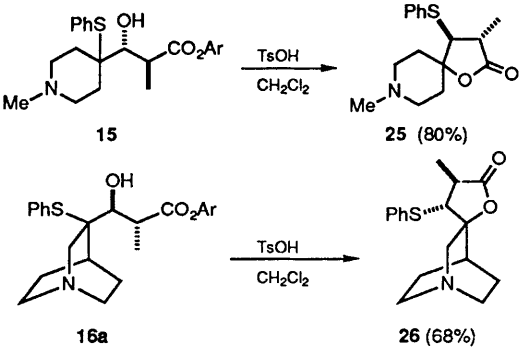


the spirocyclic ethers **22** and **23** respectively. The rearrangement is stereospecific, with inversion of stereochemistry taking place at the migration origin and at the migration terminus. This was verified by NOE experiments and means that the *anti*-diol **19** gives only the *anti* cyclic ether **22**, and that the diol **20** gives ether **23** as the sole product.

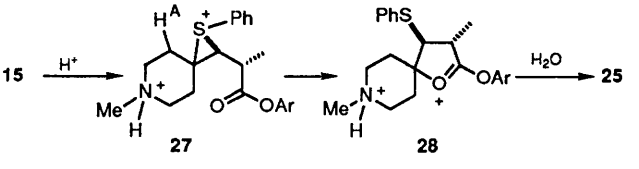


Attempted rearrangement of the diol **21** gave initially the ketone **24** which could be isolated as the hydrochloride salt, but which did not undergo rearrangement with cyclization. The presence of the sp^2 hybridized carbon within the potential ring must be hindering the cyclization, possibly by disfavouring episulfonium ion formation as this would mean the build-up of partial positive charge on the carbon adjacent to the carbonyl group. In addition, the increase in bond angle may be enough to prevent the ring formation which is already an *endo-tet* cyclization.

The spirocyclic ring system can be obtained by treatment of the diols **19** or **20** with TsOH. This ring system could also be prepared simply from the precursor esters **15** and **16a**. Treating these esters with an excess of TsOH gave the spirocyclic

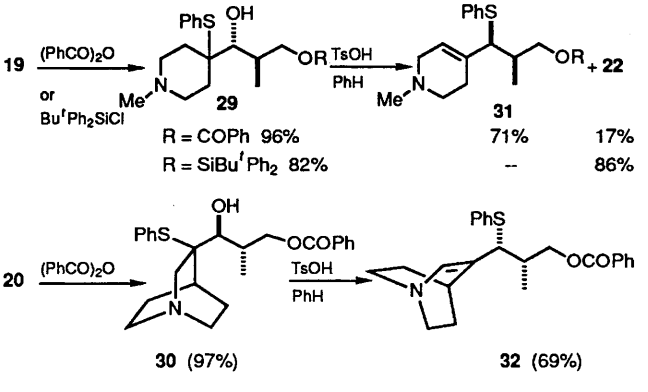


lactones **25** and **26**. The nitrogen atom must be protonated during the rearrangement, which proceeds with complete stereospecificity. No prior hydrolysis of the esters to the corresponding carboxylic acids is needed in order to prevent allylic sulfide formation by loss of H^A from the intermediate **27**.



This is probably because the protonated amine slows down episulfonium ion formation and adjacent proton loss, so giving time for hydrolysis of the intermediate **28**.

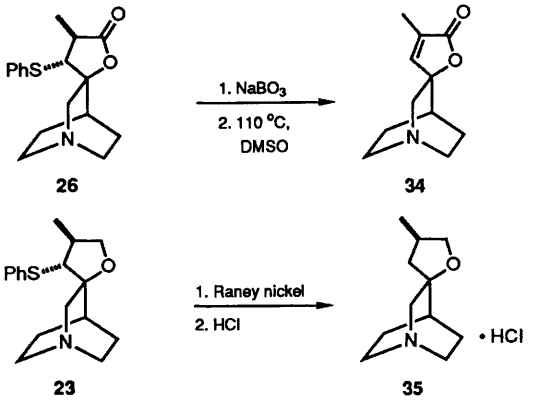
Despite this, the selective preparation of the allylic sulfides is possible by rearrangement of the protected compounds **29** (R = COPh) and **30**. The choice of protecting group is important as the use of a silyl group (R = $SiBu^tPh_2$) gave only a low yield of the allylic sulfide together with a substantial amount of the spirocyclic ether formed presumably by hydrolysis of the silyl group under the reaction conditions. As before,



the phenylthio group rearranges stereospecifically to give exclusively the *syn* allylic sulfides **31** and **32**.

Removal of PhS *from the Rearrangement Products.*—If desired, the phenylthio group can be removed from the spirocyclic compounds, as already described[4a] for the 4-methylpiperidone series. These desulfurizations were extended to the spirocyclic lactone **26** and the spirocyclic ether **23**. Oxidation of the lactone **26** with sodium perborate[9] gives a mixture of the sulfoxides which undergo *syn*-elimination on heating to give the spirocyclic butenolide **34**.

Removal of the sulfur group from the ether **23** with Raney nickel gave the spirocyclic ether **35**, isolated as the hydrochloride salt. Hence, by using a stereoselective aldol reaction



followed by stereospecific phenylthio migration (with concomitant cyclization) in just four steps the spirocyclic ether **35** with 1,3-chirally related centres can be prepared. None of these compounds had any significant activity as muscarinic agonists.

Experimental

3-Phenylthio-1-azabicyclo[2.2.2]octane-3-carbaldehyde **13**.—Butyllithium (1.55 mol dm^{-3} solution in hexane; 110 cm^3, 170 mmol) was slowly added to a solution of methoxymethyl phenyl sulfide[5] (24 cm^3, 163 mmol) in dry tetrahydrofuran (THF) (200 cm^3) under argon at −30 °C. After 30 min, a solution of quinuclidin-3-one (18.5 g, 148 mmol) in dry THF (100 cm^3) was added. After a further 20 min at −30 °C, the solution was poured into saturated aq. ammonium chloride (300 cm^3), acidified with HCl (3 mol dm^{-3}; 100 cm^3), and the organic layer was removed. The aqueous layer was basified (NaOH) and extracted with CH_2Cl_2 (4 × 200 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated to give the alcohol **12**. Thionyl chloride (31 cm^3, 430 mmol) was added to a solution of the alcohol **12** in CH_2Cl_2 (250 cm^3) under argon at 0 °C. After 2 h saturated aqueous potassium carbonate (200 cm^3) was added and the solution was extracted with CH_2Cl_2 (3 × 200 cm^3). The combined extracts were dried, evaporated, and purified by column chromatography on silica gel (500 g), eluting with CH_2Cl_2–EtOH–NH_3 (150:8:1) to give the *aldehyde* **13** (19.9 g, 54%) as needles, m.p. 69–71 °C; R_f [CH_2Cl_2–EtOH–NH_3 (120:8:1)] 0.46; $\nu_{max}(CHCl_3)/cm^{-1}$ 1700 (C=O) and 1580 (Ph); $\delta_H(CDCl_3)$ 7.39–7.27 (5 H, m, Ph), 3.48 (1 H, dd, *J* 14.4 and 2.2, CH_AH_BN), 3.06–2.91 (2 H, m, NCH_2CH_2), 2.82 (1 H, dd, *J* 14.4 and 2.4, CH_AH_BN), 2.39–2.31 (1 H, m, NCH_2CH), 2.06 (1 H, qn, *J* 3.1, NCH_2CH_2CH) and 1.64–1.50 (3 H, m, NCH_2CH_2 and NCH_2CH); $\delta_C(CDCl_3)$ 194.27, 135.82, 129.27, 128.99, 128.88, 60.03, 52.62, 47.45, 45.45, 45.91, 25.35, 24.31 and 21.76 (Found: M^+, 247.1022. $C_{14}H_{17}NOS$ requires *M*, 247.1031); *m/z* 247 (100%, M^+), 218 (91, M − CHO) and 110 (52, PhSH).

(2RS,3SR)-2,6-*Dimethylphenyl* 3-*Hydroxy*-2-*methyl*-3-(3′-*phenylthio*-1′-*azabicyclo*[2.2.2]*octan*-3′-*yl*)*propionoate* **16**.—A solution of 2,6-dimethylphenyl propionate (8.74 g, 49.1 mmol) in THF (90 cm^3) was added dropwise to a solution of lithium diisopropylamide (LDA) (55 mmol) in THF (200 cm^3) under argon at −78 °C. After 1 h, a solution of aldehyde **13** (11.55 g, 46.8 mmol) in THF (50 cm^3) was added and the mixture was stirred for 15 min before being poured into saturated aq. sodium hydrogen carbonate (300 cm^3). The organic layer was separated, and the aqueous layer was basified (NaOH) and extracted with CH_2Cl_2 (3 × 200 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated to give the mixture of esters **16a** and **16b**. The residue was recrystallized from CH_2Cl_2–hexane to give the *ester* **16a** (14.24 g, 72%) as prisms, m.p. 165–166 °C; R_f [CH_2Cl_2–EtOH–NH_3 (120:8:1)] 0.28; $\nu_{max}(CHCl_3)/cm^{-1}$ 3560 (OH), 1735 (C=O) and 1580 (Ph); $\delta_H(CDCl_3)$ 7.73–7.69 (2 H, m, Ph), 7.32–7.29 (3 H, m, Ph), 7.04 (3 H, s, OAr), 4.16 (1 H, t, *J* 7.8, C*H*OH), 3.68 (1 H, qn, *J* 7.3, C*H*Me), 3.01–2.80 [6 H, m, $N(CH_2)_3$], 2.68 (1 H, d, *J* 8.1, CHO*H*), 2.50–2.39 (1 H, m, NCH_2CH), 2.38 (1 H, qn, *J* 3.0, NCH_2CH_2CH), 2.31 (6 H, s, $ArMe_2$), 1.91–1.87 (1 H, m, NCH_2CH), 1.62–1.44 (2 H, m, NCH_2CH_2) and 1.52 (3 H, d, *J* 7.2, CH*Me*); $\delta_C(CDCl_3)$ 174.22, 147.81, 135.11, 132.65, 130.21, 128.87, 128.58, 128.25, 79,45, 60.24, 57.70, 46.77, 46.50, 45.68, 26.47, 24.39, 23.34, 16.44 and 16.31 (Found: M^+, 425.2024. $C_{25}H_{31}NO_3S$ requires *M*, 425.2025); *m/z* 425 (10%, M^+), 248 (72, $C_{14}H_{18}NOS$) and 122 (100, $Me_2C_6H_3OH$) (Found: C, 69.9; H, 7.6; N, 3.3. $C_{25}H_{31}NO_3S$ requires C, 70.55; H, 7.34; N, 3.29%).

Methyl 3-*Hydroxy*-2,2-*dimethoxy*-3-(3′-*phenylthio*-1′-*azabicyclo*[2.2.2]*octan*-3′-*yl*)*propionate* **18**.—In the same way as for the ester **16**, methyl dimethoxyacetate (4.95 ml, 40.5 mmol) and the aldehyde **13** (5.0 g, 20.2 mmol) gave the *ester* **18** (4.83 g, 63%, 1.4:1 mixture of diastereoisomers), purified by column chromatography on silica gel (200 g) eluting with CH_2Cl_2–EtOH–NH_3 (100:8:1), as an oil, R_f [CH_2Cl_2–EtOH–NH_3 (100:8:1)] 0.38; $\nu_{max}(CHCl_3)/cm^{-1}$ 1740 (C=O) and 1580 (Ph); $\delta_H(CDCl_3)$ 7.65–7.61 (2 H, m, Ph), 7.55–7.51 (2 H, m, Ph), 7.32–7.22 (3 H, m, Ph), 4.34 (1 H, d, *J* 5.8, C*H*OH), 4.18 (1 H, d, *J* 8.9, C*H*OH), 3.83 (3 H, s, OMe), 3.72 (3 H, s, OMe), 3.53 (1 H, d, *J* 7.0, CHO*H*), 3.22 (1 H, d, *J* 8.9, CHO*H*), 3.47 (3 H, s, OMe), 3.45 (3 H, s, OMe), 3.42 (3 H, s, OMe), 3.37 (3 H, s, OMe), 2.97–2.57 [6 H, m, $N(CH_2)_3$], 2.57 (1 H, br s, NCH_2CH_2CH) and 2.42–1.25 [4 H, m, $N(CH_2CH_2)_2$]; $\delta_C(CDCl_3)$ 168.88, 168.22, 137.26, 134.50, 133.88, 131.56, 128.79, 128.56, 128.48, 127.27, 102.26, 101.87, 77.90, 77.14, 59.51, 58.05, 57.22, 56.26, 52.66, 51.37, 51.30, 50.16, 49.67, 47.01, 46.76, 46.34, 28.79, 27.54, 24.83, 24.46, 24.05, 23.77 and 18.36 (Found: M^+, 381.1605. $C_{19}H_{27}NO_5S$ requires *M*, 381.1610); *m/z* 381 (6%, M^+), 248 (100, $C_{14}H_{18}NOS$) and 218 (48, $C_{13}H_{16}NS$).

(2RS,3RS,3′SR)-2-*Methyl*-3-(3′-*phenylthio*-1′-*azabicyclo*-[2.2.2]*octan*-3′-*yl*)*propane*-1,3-*diol* **20**.—Lithium aluminium hydride (190 mg, 5.0 mmol) was added to a solution of the ester **16a** (988 mg, 2.32 mmol) in dry THF (20 cm^3) under argon at 0 °C. After 4 h, the mixture was quenched with dilute NaOH (0.01 mol dm^{-3}; 10 cm^3), diluted with sodium potassium tartrate (0.1 mol dm^{-3}; 100 cm^3), and extracted with CH_2Cl_2 (3 × 50 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated and the residue was recrystallized from methanol to give the *diol* **20** (533 mg, 75%) as prisms, m.p. 197–198 °C; R_f [CH_2Cl_2–EtOH–NH_3 (80:8:1)] 0.15; $\nu_{max}(CHCl_3)/cm^{-1}$ 3350 (OH) and 1580 (Ph); $\delta_H(CDCl_3)$ 7.78–7.71 (2 H, m, Ph), 7.31–7.23 (3 H, m, Ph), 3.88 (1 H, dd, *J* 10.7 and 5.2, CH_AH_BO), 3.84 (1 H, d, *J* 6.3, C*H*OH), 3.76 (1 H, dd, *J* 10.7 and 5.4, CH_AH_BO), 3.03–2.74 [6 H, m, $N(CH_2)_3$], 2.44–2.28 (3 H, m, C*H*Me, NCH_2CH and NCH_2CH_2CH), 2.07–1.95 (1 H, m, NCH_2CH), 1.63–1.53 (1 H, m, NCH_2CH), 1.45–1.33 (1 H, m, NCH_2CH) and 1.04 (3 H, d, *J* 7.0, CH*Me*); $\delta_C(CD_3OD)$ 136.01, 130.38, 129.54, 128.61, 80.99, 67.45, 60.65, 59.24, 47.46, 47.32,

41.19, 27.42, 25.16, 24.37 and 16.56 (Found: M^+, 307.1629. $C_{17}H_{25}NO_2S$ requires M, 307.1605); m/z 307 (10%, M^+), 248 (48, $C_{14}H_{18}NOS$), 198 (57, M − PhS), 180 (47, M − PhS − OH_2) and 110 (100, PhSH) (Found: C, 66.1; H, 7.95; N, 4.5. $C_{17}H_{25}NO_2S$ requires C, 66.41; H, 8.20; N, 4.56%).

2,2-*Dimethoxy*-3-(3′-*phenylthio*-1′-*azabicyclo*[2.2.2]*octan*-3′-*yl*)*propane*-1,3-*diol* **21**.—In the same way as for the diol **20**, the ester **18** (4.35 g, 11.4 mmol) and lithium aluminium hydride (1.06 g, 28 mmol) gave the *diol* **21** (3.26 g, 81%, 1:1 mixture of diastereoisomers), purified by column chromatography on silica gel (100 g) eluting with CH_2Cl_2–EtOH–NH_3 (50:8:1), as an oil, R_f [CH_2Cl_2–EtOH–NH_3 (75:8:1)] 0.17 and 0.09; $\nu_{max}(CHCl_3)/cm^{-1}$ 3530 and 3390 (OH) and 1580 (Ph); $\delta_H(CDCl_3)$ 7.74–7.70 (2 H, m, Ph), 7.67–7.63 (2 H, m, Ph), 7.33–7.29 (3 H, m, Ph), 7.27–7.21 (3 H, m, Ph), 4.10 (1 H, s, C*H*OH), 4.05 (1 H, s, C*H*OH), 4.02 (2 H, s, CH_2OH), 3.97 (2 H, s, CH_2OH), 3.60–3.39 (2 H, m, OH), 3.37 (3 H, s, OMe), 3.35 (3 H, s, OMe), 3.35 (3 H, s, OMe), 3.31 (3 H, s, OMe), 2.87–2.60 [7 H, m, $N(CH_2)_3$ and NCH_2CH], 2.44–2.41 (1 H, m, NCH_2CH_2CH), 2.27–2.24 (1 H, m, NCH_2CH_2CH), 2.09–1.81 (1 H, m, NCH_2CH) and 1.60–1.22 (2 H, m, NCH_2CH_2); $\delta_C(CDCl_3)$ 137.07, 134.99, 133.23, 131.43, 128.73, 128.53, 127.03, 102.40, 101.06, 77.30, 75.30, 62.16, 61.68, 59.41, 58.53, 57.78, 56.67, 49.51, 49.37, 48.21, 48.09, 46.91, 46.60, 46.38, 29.33, 27.15, 24.89, 24.75, 24.22 and 24.09 (Found: M^+, 353.1665. $C_{18}H_{27}NO_4S$ requires M, 353.1661); m/z 353 (2%, M^+), 248 (100, $C_{14}H_{18}NOS$) and 105 (37, $C_4H_9O_3$).

(3RS,4SR,3′SR)-4′-*Methyl*-3′-(*phenylthio*)(1-*azabicyclo*-[2.2.2]*octane*)-3-*spiro*-2′-*tetrahydrofuran* **23**.—TsOH (510 mg, 2.7 mmol) was added to a solution of the diol **20** (260 mg, 0.85 mmol) in CH_2Cl_2 (8 cm^3) under argon at room temperature. The solution was heated under refluxed for 4 h after which CH_2Cl_2 (50 cm^3) and water (30 cm^3) were added; the solution was then basified (NaOH) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 cm^3) and the combined extracts were dried (Na_2SO_4), evaporated and purified by column chromatography on silica gel (30 g), eluting with CH_2Cl_2–EtOH–NH_3 (80:8:1) to give the *tetrahydrofuran* **23** (192 mg, 78%) as needles, m.p. 98–100 °C; R_f [CH_2Cl_2–EtOH–NH_3 (80:8:1)] 0.37; $\nu_{max}(CHCl_3)/cm^{-1}$ 1580 (Ph); $\delta_H(CDCl_3)$ 7.44–7.39 (2 H, m, Ph), 7.34–7.20 (3 H, m, Ph), 4.09 (1 H, dd, J 8.7 and 8.0, CH_AH_BO), 3.43 (1 H, dd, J 8.7 and 6.2, CH_AH_BO), 3.21 (1 H, d, J 4.9, C*H*SPh), 3.07 (1 H, d, J 13.9, NCH_ACH_BCO), 3.00–2.76 [5 H, m, NCH_ACH_BCO and $N(CH_2)_2$], 2.48–2.38 (1 H, m, C*H*Me), 2.27–2.20 (1 H, m, NCH_2CH_2CH), 2.19–2.01 (2 H, m, NCH_2CH_2), 1.67–1.51 (1 H, m, NCH_2CH), 1.48–1.39 (1 H, m, NCH_2CH) and 1.07 (3 H, d, J 7.1, CH*Me*); $\delta_C(CDCl_3)$ 135.41, 131.27, 129.12, 127.04, 83.65, 71.37, 62.43, 62.02, 46.67, 46.59, 42.07, 28.05, 22.72, 22.34 and 18.69 (Found: M^+, 289.1483. $C_{17}H_{23}NOS$ requires M, 289.1501); m/z 289 (3%, M^+) and 180 (100, M − PhS).

Rearrangement of 2,2-*Dimethoxy*-3-(3′-*phenylthio*-1′-*azabicyclo*[2.2.2]*octan*-3′-*yl*)*propane*-1,3-*diol* **21**.—In the same way as for the tetrahydrofuran **23**, the diol **21** (53 mg, 0.15 mmol) and TsOH (31 mg, 0.18 mmol) gave the *ketone* **24** (49 mg, 95%, isolated as the HCl salt) as a foam, R_f [CH_2Cl_2–EtOH–NH_3 (75:8:1)] 0.17; $\nu_{max}(CHCl_3)/cm^{-1}$ 2520 (NH^+) and 1710 (C=O); $\delta_H(CDCl_3)$ 10.78 (1 H, s, NH^+), 7.65–7.28 (5 H, m, Ph), 4.84 (1 H, s, C*H*OH), 4.71 (2 H, ABq, J 20.6, CH_2OH), 3.92 (1 H, d, J 14.2, NCH_ACH_BCS), 3.60–2.81 [7 H, m, OH, OH, $N(CH_2)_2$ and NCH_2CH_2CH], 2.68 (1 H, d, J 14.2, NCH_ACH_BCS) and 2.35–1.83 [4 H, m, $N(CH_2CH_2)_2$] (Found: $M^+ - C_2H_3O_2$, 248.1111. $C_{14}H_{18}NOS$ requires $M - C_2H_3O_2$, 248.1109); m/z 248 (4%, $M^+ - C_2H_3O_2$), 218 (12, M − $C_3H_5O_3$) and 110 (100, PhSH).

(3RS,4SR,3′SR)-4′-*Methyl*-3′-(*phenylthio*)(1-*azabicyclo*-[2.2.2]*octane*)-3-*spiro*-2′-(*dihydrofuran*-5′-*one*) **26**.—In the same way as the tetrahydrofuran **23**, the ester **16a** (411 mg, 0.97 mmol) and TsOH (1.3 g, 6.8 mmol) gave the *lactone* **26** (200 mg, 68%), purified by column chromatography on silica gel (40 g), eluting with CH_2Cl_2–EtOH–NH_3 (120:8:1) as an oil, R_f [CH_2Cl_2–EtOH–NH_3 (120:8:1)] 0.27; $\nu_{max}(CHCl_3)/cm^{-1}$ 1760 (C=O) and 1580 (Ph); $\delta_H(CDCl_3)$ 7.46–7.41 (2 H, m, Ph), 7.38–7.29 (3 H, m, Ph), 3.44 (1 H, d, J 6.8, C*H*SPh), 3.12 (1 H, d, J 14.6, NCH_AH_BCO), 2.98–2.72 [5 H, m, NCH_ACH_BCO and $N(CH_2)_2$], 2.33–2.27 (2 H, m, C*H*Me and NCH_2CH_2CH), 2.09–2.00 (1 H, m, NCH_2CH), 1.71–1.59 (1 H, m, NCH_2CH), 1.53–1.43 (2 H, m, NCH_2CH_2) and 1.24 (3 H, d, J 7.5, CH*Me*); $\delta_C(CDCl_3)$ 176.60, 133.35, 132.19, 129.48, 128.12, 86.23, 62.02, 59.17, 46.40, 43.67, 27.89, 22.88, 22.57 and 15.39 (Found: M^+ − PhS, 194.1172. $C_{11}H_{16}NO_2$ requires $M - C_6H_5S$, 194.1181); m/z 194 (100%, M^+ − PhS) and 166 (52, M − PhS − CO).

(2RS,3RS,3′SR)-3-*Hydroxy*-2-*methyl*-3-(3′-*phenylthio*-1′-*azabicyclo*[2.2.2]*octan*-3′-*yl*)*propyl Benzoate* **30**.—A solution of the diol **20** (356 mg, 1.16 mmol), benzoic anhydride (290 mg, 1.28 mmol), pyridine (47 μl, 0.58 mmol) and 4-dimethylaminiopyridine (1 mg, 0.008 mmol) in CH_2Cl_2 (8 cm^3) was stirred at room temperature under argon for 29 h. Water (50 cm^3) and CH_2Cl_2 (50 cm^3) were added, and the solution was neutralized with dilute NaOH (2.5 mol dm^{-3}; 0.5 cm^3) and extracted with CH_2Cl_2 (3 × 40 cm^3). The combined extracts were dried (Na_2SO_4), evaporated and purified by column chromatography on silica gel (40 g), eluting with CH_2Cl_2–EtOH–NH_3 (100:8:1) to give the *ester* **30** (453 mg, 95%) as needles, m.p. 166–169 °C; R_f [CH_2Cl_2–EtOH–NH_3 (100:8:1)] 0.34; $\nu_{max}(CHCl_3)/cm^{-1}$ 3280 (OH), 1705 (C=O), 1600 and 1500 (Ph); $\delta_H(CDCl_3)$ 8.04–8.00 (2 H, m, Ph), 7.69–7.41 (5 H, m, Ph), 7.31–7.26 (2 H, m, Ph), 4.63 (1 H, dd, J 11.0 and 5.1, CH_AH_BO), 4.48 (1 H, dd, J 11.0 and 3.8, CH_AH_BO), 3.73 (1 H, d, J 9.3 Hz, C*H*OH), 3.03–2.70 [7 H, m, $N(CH_2)_3$ and C*H*Me], 2.60–2.50 (1 H, m, NCH_2CH), 2.43–2.40 (1 H, qn, J 3.1, NCH_2CH_2CH), 2.03–1.83 (2 H, m, OH and NCH_2CH), 1.64–1.49 (2 H, m, NCH_2CH_2) and 1.19 (3 H, d, J 7.0, CH*Me*); $\delta_C(CDCl_3)$ 167.09, 135.91, 133.10, 130.04, 129.54, 129.34, 129.24, 128.42, 77.23, 67.91, 54.46, 45.92, 35.70, 26.25, 22.39, 22.06 and 17.63 (Found: M^+, 411.1864. $C_{24}H_{29}NO_3S$ requires M, 411.1868); m/z 411 (4%, M^+), 248 (32, $C_{14}H_{18}NOS$), 122 (67, $PhCO_2H$), 110 (58, PhSH) and 105 (100, PhCO).

(2RS,3SR)-3-(1′-*Azabicyclo*[2.2.2]*oct*-2′-*en*-3′-*yl*)-2-*methyl*-3-(*phenylthio*)*propyl Benzoate* **32**.—TsOH (570 mg, 3.0 mmol) was added to a solution of the ester **30** (411 mg, 1.0 mmol) in benzene (8 cm^3) under argon at room temperature. The solution was heated under refluxed for 15 min after which CH_2Cl_2 (80 cm^3) and water (80 cm^3) were added; the solution was then basified (NaOH) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 cm^3) and the combined extracts were dried (Na_2SO_4), evaporated and purified by column chromatography on silica gel (40 g), eluting with CH_2Cl_2–EtOH–NH_3 (120:8:1) to give the *ester* **32** (272 mg, 69%) as an oil, R_f [CH_2Cl_2–EtOH–NH_3 (100:8:1)] 0.48; $\nu_{max}(CHCl_3)/cm^{-1}$ 1705 (C=O), 1600 and 1500 (Ph); $\delta_H(CDCl_3)$ 8.03–7.99 (2 H, m, Ph), 7.60–7.13 (8 H, m, Ph), 6.33 (1 H, d, J 1.0, HC=C), 4.45 (1 H, dd, J 10.9 and 5.2, CH_AH_BO), 4.21 (1 H, dd, J 10.9 and 6.7, CH_AH_BO), 3.93 (1 H, d, J 7.6 Hz, C*H*SPh), 2.95–2.78 (3 H, m, NCH_2CH_2CH), 2.58–2.51 (1 H, m, NCH), 2.40–2.34 (1 H, m, C*H*Me), 2.30–2.21 (1 H, m, NCH), 1.67–1.50 (3 H, m, NCH_2CH_2 and NCH_2CH), 1.36–1.28 (1 H, m, NCH_2CH) and 1.27 (3 H, d, J 6.9, CH*Me*); $\delta_C(CDCl_3)$ 166.32, 144.84, 138.30, 135.50, 133.03, 130.86, 130.03, 129.51, 128.78, 128.41, 126.64, 67.73, 54.79, 49.32, 49.27, 35.63, 28.40, 28.14, 18.42 and 15.12 (Found: M^+, 393.1791. $C_{24}H_{27}NO_2S$ requires M,

393.1820); *m/z* 393 (4%, M^+), 284 (30, *M* − PhS) and 105 (100, PhCO).

4′-*Methyl*-(1-*azabicyclo*[2.2.2]*octane*)-3-*spiro*-2′-(*furan*)-5′-*one* **34**.—Sodium perborate (143 mg, 0.93 mmol) was added to a solution of the lactone **26** (300 mg, 0.88 mmol) in glacial acetic acid (3 cm^3) under nitrogen at room temperature. After 5 h, water (30 cm^3) and NaOH (2 mol dm^{-3}; 25 cm^3) were added and the solution was extracted with CH_2Cl_2 (4 × 20 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated to give the sulfoxide, which was heated to 110 °C in dimethyl sulfoxide (DMSO) (1 cm^3) for 30 min. Aqueous potassium carbonate (10 cm^3) was added and the aqueous layer was extracted with CH_2Cl_2 (5 × 20 cm^3). The combined extracts were dried (Na_2SO_4), evaporated, and purified by column chromatography on silica gel (25 g), eluting with CH_2Cl_2–EtOH–NH_3 (100:8:1) gave the *butenolide* **34** (46 mg, 27%) as needles, m.p. 90–91 °C; R_f [CH_2Cl_2–EtOH–NH_3 (100:8:1)] 0.28; $\nu_{max}(CHCl_3)/cm^{-1}$ 1740 (C=O) and 1650 (C=C); $\delta_H(CDCl_3)$ 7.18 (1 H, q, *J* 1.5, HC=C), 3.03 (2 H, s, NCH_2CO), 3.00–2.82 [4 H, m, $N(CH_2)_2$], 2.16–2.02 (1 H, m, NCH_2CH), 2.80 (3 H, d, *J* 1.5, Me), 1.82–1.77 (1 H, m, NCH_2CH_2CH), 1.74–1.66 (2 H, m, NCH_2CH_2) and 1.55–1.42 (1 H, m, NCH_2CH); $\delta_C(CDCl_3)$ 173.62, 150.91, 129.03, 86.34, 57.02, 46.40, 46.27, 31.04, 23.19, 21.19 and 10.46 (Found: M^+, 193.1105. $C_{11}H_{15}NO_2$ requires *M*, 193.1103); *m/z* 193 (100%, M^+) and 96 (97, M − $C_5H_4O_2$) (Found: C, 68.1; H, 7.8; N, 6.9. $C_{11}H_{15}NO_2$ requires C, 68.37; H, 7.82; N, 7.25%).

(2RS,4SR)-4′-*Methyl*-(1-*azabicyclo*[2.2.2]*octane*)-3-*spiro*-2′-(*tetrahydrofuran*) **35**.—Raney nickel (50% slurry in water; 1 g) was added to a solution of the sulfide **23** (75 mg, 0.26 mmol) in ethanol (2 cm^3) and the mixture was heated under reflux under nitrogen for 30 min. The suspension was filtered, washed with ethanol, and evaporated to give an oil to which ethereal HCl (2 cm^3) was added. The solvent was then evaporated off to give the tetrahydrofuran hydrochloride **35** (24 mg, 43%) as a foam, R_f [CH_2Cl_2–EtOH–NH_3 (100:8:1)] 0.20; $\nu_{max}(CHBr_3)/cm^{-1}$ 3420 (OH_2); $\delta_H(CDCl_3)$ 12.26 (1 H, s, NH^+), 3.92 (1 H, t, *J* 7.6, CH_AH_BO), 3.37 (1 H, t, *J* 7.6, CH_AH_BO), 3.39–3.07 [6 H, m, $N(CH_2)_3$], 2.38–2.28 (3 H, m, CH_2CO and CHMe), 2.06–1.59 [5 H, m, NCH_2CH_2CH and $N(CH_2CH_2)_2$] and 1.04 (3 H, d, *J* 6.3, $CHMe$) (Found: M^+, 181.1467. $C_{11}H_{19}NO$ requires *M*, 181.1466); *m/z* 181 (4%, M^+), 96 (90, $C_6H_{10}N$) and 84 (87, C_5H_8O).

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