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Synthesis of (3S,5S)-Quinuclidine-3,5-diol and of [3S-(3α,3aα,7aα)]-Octahydro-2-furo[2,3-c]pyridinol from D-Arabinose

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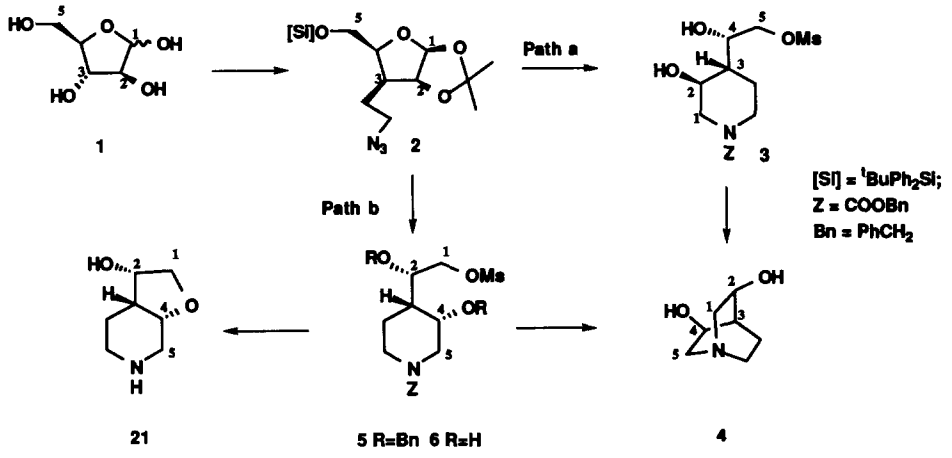
Abstract: The synthesis of (3S,5S)-quinuclidine-3,5-diol is achieved by an introduction of a 2 carbon chain at C-3 of D-arabinose, followed by joining the terminus of the chain extension to C-1 and C-5 of the sugar; the synthesis of [3S-(3α,3aα,7aα)]-octahydro-2-furo[2,3-c]pyridinol, a potential muscarine mimic, is described.

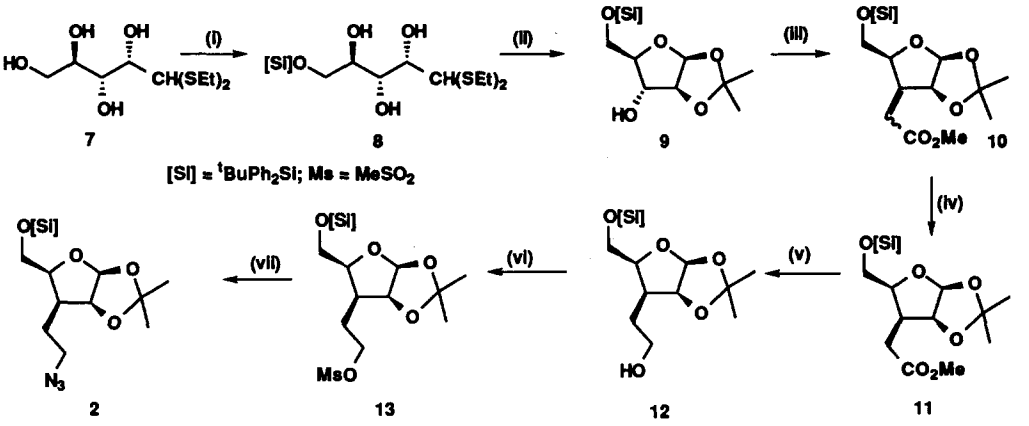
Carbohydrates have been widely used for the synthesis of bicyclic nitrogen heterocycles such as indolizidines[1] and pyrrolizidines,[2] but only a few examples of the use of sugars in the synthesis of bridgehead heterocycles have been reported. Preliminary reports on the synthesis of monohydroxy[3] and dihydroxy-quinuclidines[4,5] from D-glucose have appeared. A number of rigid bicyclic analogues of muscarine have been investigated as muscarinic agonists which may be potential chemotherapeutic agents in the treatment of Alzheimer's disease.[6] Chiral quinuclidines yielded highly potent and selective non-peptide antagonists of the substance P (NK_1) receptor;[7,8] they have also been demonstrated to be potentially useful for the study of interactions of ligands with specific muscarinic receptors;[9,10] the novel octahydrofuropyridinol ring system, exemplified by **21**, may also provide a series of rigid muscarine analogues which might allow a greater understanding of the structural requirements of individual muscarinic receptors. Additionally, other recently identified potential chemotherapeutic uses for complex and highly functionalised quinuclidines[11] include anti-emesis,[12] squalene synthase inhibition[13], and 5-HT_3 receptor antagonist and 5-HT_4 receptor agonist activities.[14] Complex chiral quinuclidines have been used as ligands in the asymmetric hydroxylation of alkenes by osmium tetraoxide;[15] the availability of simpler chiral quinuclidine structures may be useful in elucidating aspects of the mechanism of this reaction.[16]

The value of pentoses in the synthesis of these highly functionalised homochiral bicyclic nitrogen heterocycles is illustrated in this paper by the synthesis of (3S,5S)-quinuclidine-3,5-diol (**4**) and of [3S-(3α,3aα,7aα)]-octahydro-2-furo[2,3-c]pyridinol (**21**) from a key intermediate azide **2** in which a two carbon chain has been introduced at the C-3 of D-arabinose; a preliminary report of some aspects of this work has appeared.[17] The chiral centres of (3S,5S)-quinuclidine-3,5-diol (**4**) and of the tetrahydrofuran **21** were derived from the C-2 and C-4 hydroxyl groups of D-arabinose, shown in a furanose form **1**. The synthesis [Scheme 1] required the introduction of a two carbon chain at C-3 of arabinose with a nitrogen function at its terminus. The quinuclidine nucleus was then formed by connecting the nitrogen function to carbons derived from both C-1 and C-5 of arabinose. Initial formation of the piperidine ring between the nitrogen and C-1 of the sugar [path a] permitted the development of the piperidine **3**; hydrogenolytic removal of the Z-protecting group gave an aminodiol in which efficient displacement of the mesylate by the piperidine nitrogen gave the quinuclidine **4**.



Scheme 1. All numbering in this scheme refers to the original carbon atoms in arabinose

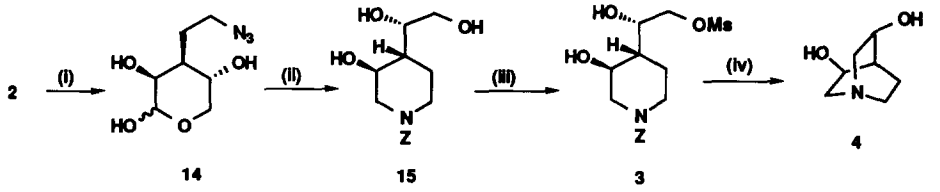
The creation of the first piperidine ring by connection to C-5 of arabinose [path b] would give access to the piperidine **6**, epimeric at C-3 with that formed in path a. However, the aminodiol derived from **6** shut to give, as the major product, the tetrahydrofuran **21**. In this case, the ring hydroxyl group of the piperidine has successfully competed with the amine as the internal nucleophile. Accordingly, it was necessary to prepare the dibenzyl ether **5** in order to complete the synthesis of the quinuclidine nucleus by this strategy.



Scheme 2 (i) $^{t}BuPh_2SiCl$, imidazole, DMF (ii) HgO, $HgCl_2$, Me_2CO; then $CuSO_4$, Me_2CO, H^+ (iii) PCC, CH_2Cl_2; then $Ph_3P{=}CHCO_2Me$ (iv) H_2, Pd/C, EtOAc (v) $LiAlH_4$, THF (vi) MsCl, pyridine (vii) NaN_3, DMF

For the synthesis of the divergent intermediate azide **2**, D-arabinose dithioacetal (**7**)[18] was treated with *tert*-butyldiphenylsilyl chloride in dimethylformamide in the presence of imidazole resulting in highly selective protection of the primary hydroxyl group to afford the silyl ether **8** in 95% yield. Deprotection of the thioacetal moiety in **8** by treatment with mercury(II) in acetone, followed by acetonation in the presence of acid gave the

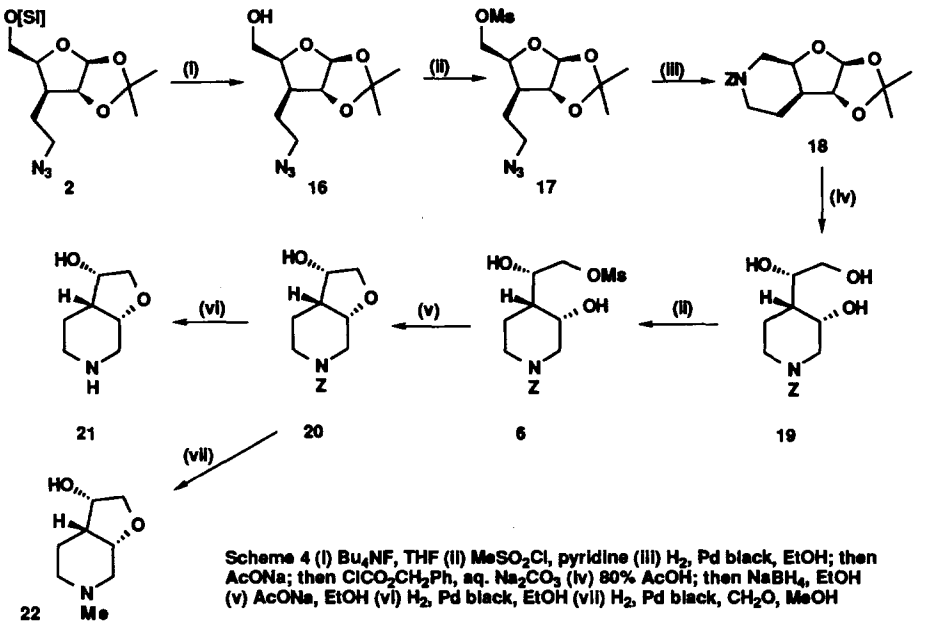
arabinofuranose **9** with only the C-3 hydroxyl group unprotected [71% yield]. Oxidation of the secondary alcohol **9** with pyridinium chlorochromate in dichloromethane in the presence of powdered molecular sieve gave an intermediate ketone which with the stabilised Wittig reagent, $Ph_3P{=}CHCO_2Me$, gave a mixture of the unsaturated esters **10** in an overall yield of 81% from **9**. Hydrogenation of the mixture of alkenes **10** in ethyl acetate in the presence of palladium on carbon gave only the saturated ester **11** [quantitative yield], arising from a highly stereoselective reduction of the double bond. The ester **11** on treatment with lithium aluminum hydride in tetrahydrofuran was reduced to the primary alcohol **12** [88% yield] which was esterified with methanesulfonyl chloride to afford the mesylate **13** [98% yield]. Subsequent nucleophilic displacement of the mesylate in **13** by sodium azide in dimethyl formamide gave silyl azide **2** in 96% yield. The key intermediate **2** may thus be readily prepared in large amounts from arabinose diethyldithioacetal (**7**) in an overall yield of 45%.



Scheme 3 (i) aq. CF_3COOH (ii) H_2, 10% Pd/C, 260 psi, MeOH/H_2O; then $ClCO_2CH_2Ph$, aq. Na_2CO_3 (iii) $MeSO_2Cl$, pyridine (iv) Pd black, EtOH; then AcONa

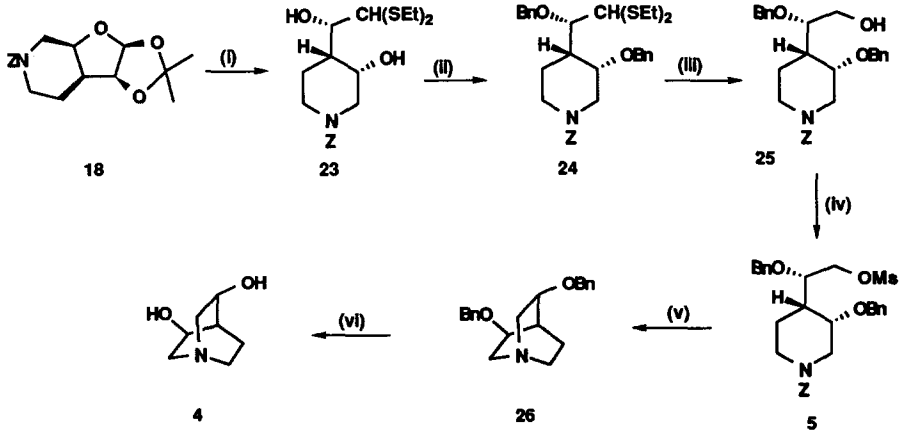
The quinuclidine **4** was first synthesised by initial formation of a piperidine ring between the nitrogen function of the C-3 side chain and the aldehyde at C-1 of the sugar [Scheme 3]. Removal of the silyl ether and isopropylidene protecting groups from **2** was achieved by treatment with aqueous trifluoroacetic acid to give the unprotected lyxopyranose derivative **14** in 80% yield. Hydrogenation of **14** in the presence of palladium on carbon in methanol:water caused reduction of the azide to the corresponding amine followed by intramolecular reductive amination between the amine and C-1 of the sugar to form the piperidine triol which was isolated as the benzyl carbamate **15** in 77% overall yield. Reaction of **15** with methanesulfonyl chloride in pyridine resulted in a selective esterification of the primary hydroxyl group to afford the mesylate **3** in 87% yield. Hydrogenolysis of the Z protecting group in **3** in the presence of a palladium catalyst, followed by treatment with sodium acetate in ethanol to induce the second cyclisation gave (3S,5S)-quinuclidine-3,5-diol (**4**) in 78% yield [42% overall yield from the silyl azide **2**; 19% from dithioacetal **7**].

The alternative strategy (Scheme 1, path b), in which the first piperidine ring is formed between the nitrogen function and C-5 of the sugar is shown is Scheme 4. The silyl protecting group in **2** was removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran to give the primary alcohol **16** [95% yield] which was esterified by methanesulfonyl chloride in pyridine to afford the mesylate **17** [94% yield]. Subsequent hydrogenation of **17** in the presence of palladium black gave an amine which spontaneously cyclised in the presence of sodium acetate to a piperidine isolated, after treatment with benzyl chloroformate, as the carbamate **18** in an overall yield of 96% from the azidomesylate **17**. The isopropylidene group could be removed from **18** by hydrolysis with aqueous acetic acid to give a lactol which underwent reduction on treatment with sodium borohydride in ethanol to afford the piperidine triol **19** [82% yield]. The primary hydroxyl group in **19** was selectively esterified by methanesulfonyl chloride in pyridine to form the primary mesylate **6** in 81% yield.



Scheme 4 (I) Bu_4NF, THF (II) $MeSO_2Cl$, pyridine (III) H_2, Pd black, EtOH; then AcONa; then $ClCO_2CH_2Ph$, aq. Na_2CO_3 (IV) 80% AcOH; then $NaBH_4$, EtOH (V) AcONa, EtOH (VI) H_2, Pd black, EtOH (VII) H_2, Pd black, CH_2O, MeOH

Hydrogenolysis of the carbamate **6** by palladium black gave the corresponding aminomesylate which spontaneously cyclised to give a mixture of the quinuclidine **4** and the tetrahydrofuran **21** in which the latter was the major component; it was not easy to separate these two products and so **6** was treated with sodium acetate in ethanol to give the closure to the furopiperidine **20** in 84% yield. The Z group could be removed by hydrogenolysis in the presence of palladium black in ethanol to give pure **21** [88% yield]; hydrogenation of **20** in the presence of formaldehyde afforded the N-methyl derivative **22** in 96% yield. Thus, this route provides relatively easy access to the octahydro-2-furo[2,3-c]pyridinol ring system and has allowed the study of such compounds as potential ligands to muscarinic receptors.[19]



Scheme 5 (I) aq. CF_3CO_2H, EtSH (II) BnBr, NaH, Bu_4NI cat., THF (III) Hg(II), aq. Me_2CO; then $NaBH_4$, EtOH (IV) $MeSO_2Cl$, pyridine (V) H_2, 10% Pd/C, EtOH; then NaOAc (VI) H_2, Pd black, AcOH/EtOH

The different ring closures shown (Scheme 1) by the two epimeric piperidine mesylates **3** and **6** were not anticipated. Both compounds could cyclise to the same quinuclidine diol **4**, so that if developing product stability is important in the transition state for the alternative closures, the greater thermodynamic stability of the *cis*-fused system **21** in contrast to the trans-fused system that would be generated by closure of the oxygen at C-3 onto the mesylate may explain the differing nucleophilicities of oxygen and nitrogen observed in the two closures. It may be that other kinetic factors account for the difference in products of the two reactions.

Whatever the reason for the contrasting behaviour of **3** and **6**, it is clearly necessary to protect the secondary hydroxyl groups in **6** in order to generate the quinuclidine nucleus. Thus it was considered that **5**, in which the cyclisation by the oxygen to a tetrahydrofuran was blocked by protection of the hydroxyl groups as the corresponding dibenzyl ether, would allow closure to the dibenzylquinuclidine **25**. However, all attempts to benzylate **6** directly to give **5** were unsuccessful, so that a different route from **18** to **5** was developed (Scheme 5).

The isopropylidene protecting group was removed from **18** by treatment with aqueous trifluoroacetic acid to give a lactol, which in the presence of ethanethiol gave the dithioacetal **23** in 89% yield. The secondary hydroxyl functionalities in **23** were converted to the corresponding dibenzyl ether **24** by reaction with sodium hydride and benzyl bromide in tetrahydrofuran in the presence of tetrabutylammonium iodide [70% yield]. The dithioacetal in **24** was removed by treatment with mercury(II) oxide and mercury(II) chloride and the resulting aldehyde was reduced by sodium borohydride in ethanol to give the primary alcohol **25** in 88% yield. Esterification of **25** with methanesulphonyl chloride in pyridine gave the mesylate **5** [99% yield]. Hydrogenolytic removal of the Z protecting group in **5** in the presence of a catalyst of 10% palladium on carbon in ethanol, followed by treatment with sodium acetate afforded the dibenzyl quinuclidine **26** in 78% yield. Further hydrogenolysis of the benzyl protecting groups in **26** in the presence of a catalyst of palladium black in ethanol-acetic acid gave the unprotected quinuclidine-3,5-diol [98% yield] identical in all respects to that obtained by the alternative cyclisation.

In summary, this paper describes the relatively short synthesis of complex bicyclic heterocycles from a pentose in which the functionality and/or the stereochemistry at each of the five carbons of the sugar have been utilised in assembling the targets. On the basis of the work reported, it appears that an intramolecular oxygen nucleophile under some structural circumstances may successfully compete with an internal nitrogen nucleophile to produce a tetrahydrofuran, rather than a quinuclidine. A quinuclidine is formed in preference to either an epoxide or a *trans*-fused tetrahydrofuran; but a *cis*-fused tetrahydrofuran may be formed in preference to a quinuclidine.

EXPERIMENTAL Melting points were recorded on a Kofler block. Infra red spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra were run at 300 MHz on a Bruker WH 300 spectrometer (500 MHz on a Bruker AM 500 spectrometer); ^{13}C NMR spectra were recorded on a Bruker AM 250 (62.9 MHz) or a Bruker AM 500 (125.0 MHz) spectrometer. Mass spectra were recorded on VG Micromass ZAB 1F or MM 30F spectrometers. Microanalyses were recorded by the microanalytical services of the Dyson Perrins Laboratory. TLC was performed on glass plates coated with silica gel Blend 41, and compounds were visualised with a spray of 5% v/v sulphuric acid in methanol or a solution of 5%

dodecamolybdophosphoric acid in ethanol or a solution of 0.5% ninhydrin in ethanol or Dragendorff reagent. Flash chromatography was carried out using Merck Kieselgel 60, 230-400 mesh; the petroleum ether used was that fraction with b. p. 60°-80°C. Tetrahydrofuran and benzene were distilled from a solution dried with sodium in the presence of benzophenone under dry nitrogen; dichloromethane was distilled from phosphorous pentoxide, dimethylformamide from calcium hydride and stored over 4Å molecular sieves and pyridine from potassium hydroxide. D-Arabinose diethyl dithioacetal (**7**) was prepared from D-arabinose as previously described.[14]

5-O-(tert-Butyldiphenylsilyl)-D-arabinose Diethyldithioacetal (8). *tert*-Butylchlorodiphenylsilane (22.3 ml, 85.4 mmol) was added to a solution of D-arabinose diethyldithioacetal (**7**) (20 g, 78.1 mmol) and imidazole (10.6 g, 156 mmol) in dry dimethylformamide (100 ml) at 0°C and left overnight. The solvent was evaporated and the residue dissolved in chloroform, washed with water (3 x 100 ml) and the organic layer was dried (sodium sulfate). The solution was filtered and the solvent removed to give *5-O-(tert-butyldiphenylsilyl)-D-arabinose diethyldithioacetal (8)* (36.8 g, 95%), m. p. 53-54°C (dichloromethane:petroleum ether), $[\alpha]^{20}$ -45.9 (*c*, 1.18 in $CHCl_3$), ν_{max} (film): 3450 (OH), 1430, 1110, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.67 (4H, m, ArH), 7.42 (6H, m, ArH), 4.12 (1H, d, J 8.5 Hz), 4.06 (1H, d, J 9.3 Hz), 3.88 (3H, m), 3.80 (1H, m), 3.34 (1H, m, OH), 2.80 (5H, m, SCH_2 and OH), 2.45 (1H, d, OH, J 9.4 Hz), 1.30 (6H, t, $CH_2\underline{CH_3}$), 1.09 (9H, s, Me_3C). ^{13}C NMR ($CDCl_3$) δ 14.44 and 14.54 (2q, $\underline{CH_3}CH_2$), 19.19 (s, $Me_3\underline{C}$), 23.70 and 25.43 (2t, $CH_3\underline{CH_2}$), 26.84 (q, $C\underline{Me_3}$), 55.60 (d, C-1), 65.12 (t, C-5), 70.03, 70.76 and 72.35 (3d, C-2, C-3 and C-4), 127.26, 127.74, 129.41, 129.78, 132.93, 133.02, 135.16 and 135.51 (Ar). m/z (DCI, NH_3): 512 ($M+NH_4^+$, 23%), 450 (100%). (Found C, 60.44; H, 7.83; S, 13.09. $C_{25}H_{38}O_4S_2Si$ requires C, 60.69; H, 7.74; S, 12.96%).

5-O-(tert-Butyldiphenylsilyl)-1,2-O-isopropylidene-β-D-arabinofuranose (9). 5-O-(*tert*-Butyldiphenylsilyl)-D-arabinose diethyldithioacetal (**8**) (29.0 g, 58.7 mmol) was dissolved in aqueous acetone (250 ml, 10% water) and, with efficient stirring, red mercury (II) oxide (25.4 g, 117 mmol) followed by mercury (II) chloride (39.8 g, 147 mmol) were added. After 6 h, the mixture was filtered through celite and the residue was washed with acetone. After removal of the solvent, the residue was purified by filtration through a silica gel plug (eluted with ethyl acetate-hexane, 7:3), the resulting oil was dissolved in acetone (250 ml), and the pH of the solution adjusted to 2 by treatment with *dl*-camphorsulfonic acid and anhydrous copper (II) sulfate (30 g). The reaction mixture was stirred at room temperature with exclusion of moisture for 4 h, after which time the solution was neutralised with sodium carbonate and filtered through celite. Removal of the solvent *in vacuo* gave a syrupy residue which was extracted with chloroform (4 x 50 ml). The resulting suspension was filtered through celite and the filtrate washed with water (2 x 100 ml), dried (magnesium sulfate) and concentrated to an oil, which was purified by flash chromatography (ethyl acetate:hexane, 3:7) to yield *5-O-(tert-butyldiphenylsilyl)-1,2-O-isopropylidene-β-D-arabinofuranose (9)* (17.8 g, 71%) as a clear oil, $[\alpha]^{20}$ +5.8 (*c*, 1.12 in $CHCl_3$), ν_{max} (film): 3450 (OH), 1430, 1120, 700 cm^{-1}. ^1H NMR ($CDCl_3$ + D_2O) δ 7.77 (4H, m, ArH). 7.41 (6H, m, ArH), 5.89 (1H, d, H-1, $J_{1,2}$ 4.0 Hz), 4.55 (1H, d, H-2, $J_{2,1}$ 4.1 Hz), 4.43 (1H, d, H-3, $J_{3,4}$ 2.4 Hz), 4.07 (1H, ddd, H-4, $J_{4,3}$ 2.5 Hz, $J_{4,5}$= $J_{4,5'}$= 6.8 Hz), 3.83 (2H, m, H-5), 1.34 (3H, s, CMe_2), and 1.30 (3H, s, CMe_2), 1.08 (9H, s, Me_3C). ^{13}C NMR ($CDCl_3$) δ 19.13 (s, $Me_3\underline{C}$) 26.02 and 26.80 (2q, $\underline{Me_3}C$), 63.65 (t, C-5), 76.04 (d, C-3), 87.00 and 87.47 (2d, C-2 and C-4), 105.50 (d, C-1),

112.41 (s, $\underline{C}Me_2$), 127.70, 129.70, 133.15, and 135.55 (Ar). m/z (DCI, NH_3): 446 ($M+NH_4^+$, 100%), 388 (76%). (Found C, 67.06; H, 7.70. $C_{24}H_{32}O_5Si$ requires C, 67.26; H, 7.53%).

*5-O-(tert-Butyldiphenylsilyl)-3-C-(E,Z)-carbomethoxymethylene)-3-deoxy-1,2-O-isopropylidene-β-D-arabinofuranose (**10**).* The secondary alcohol **9** (21 g, 49.1 mmol) in dry dichloromethane (100 ml) was stirred at room temperature with pyridinium chlorochromate (21.9 g, 102 mmol) and powdered 3Å molecular sieve (17 g) for 4 h, the reaction mixture was diluted with ether (100 ml) and filtered through a silica plug (eluted with chloroform). The solvent was then removed *in vacuo* to give the ketone, *5-O-(tert-butyldiphenylsilyl)-1,2-O-isopropylidene-3-oxo-β-D-arabinofuranose* as a colourless syrup (ν_{max} 1770 cm^{-1}). The crude ketone was dissolved in dry benzene (100 ml) and treated with (carbomethoxymethylene)triphenylphosphorane (24.6 g, 73.6 mmol) and the reaction mixture was stirred at reflux for 4 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography (ethyl acetate:hexane, 15:85) to give a mixture of *5-O-(tert-butyldiphenylsilyl)-3-C-(E,Z)-carbomethoxymethylene)-3-deoxy-1,2-O-isopropylidene-β-D-arabinofuranose (**10**)* (19.05 g, 81% from the alcohol (8)], as a colourless oil, mixture of E:Z isomers, $[\alpha]^{20}$ +75.4 (*c*, 0.92 in $CHCl_3$), ν_{max} (film): 1720 (CO), 1420, 1370, 1110 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.71 (4H, m, ArH), 7.40 (6H, m, ArH), 6.11 (0.2H, t, CH=C, J 1.5 Hz), 6.05 (0.8H, m, CH=C), 5.93 (d, 0.8H, H-1), 5.86 (0.2H, d, H-1), 5.68 (0.2H, dd, H-2, $J_{2,1}$ 4 Hz, $J_{allylic}$ 1.4 Hz), 5.56 (0.8H, m, H-4), 4.86 (0.8H, d, H-2, $J_{2,1}$ 3.9 Hz), 4.68 (0.2H, m, H-4), 3.92 (2H, m, H-5), 3.80 and 3.70 (3H, 2 x s, COOMe), 1.38, 1.36, 1.30 and 1.25 (6H, 4s, CMe_2), 1.08 (9H, s, Me_3C). ^{13}C NMR ($CDCl_3$) δ 19.18 (s, $\underline{C}Me_3$), 25.95, 26.28, 26.41, 26.72 and 27.04 (Me), 51.53 and 51.62 (2q, OMe), 66.59 (t, CH_2OSi), 77.79, 81.55, 83.26 and 83.82 (4d, C-2 and C-4), 104.54 and 105.88 (2d, C-1), 112.91 and 113.26 (2s, $Me_2\underline{C}$) 117.84 and 118.65 (2d, $\underline{C}HCOOMe$), 127.51, 127.69, 129.38, 129.71, 132.96, 133.44, 133.61, 135.55, 135.66, and 135.75 (Ar), 154.52 and 154.89 (2s, C-3), 164.98 and 165.31 (2s, CO). m/z (DCI, NH_3): 500 ($M+NH_4^+$, 100%), 483 ($M+H^+$, 3%), 425 (98%). (Found C, 67.34; H, 7.27. $C_{27}H_{34}O_6Si$ requires C, 67.19; H, 7.10%).

*5-O-(tert-Butyldiphenylsilyl)-3-C-(carbomethoxymethyl)-3-deoxy-1,2-O-isopropylidene-β-D-lyxofuranose (**11**).* The mixture of the olefins **10** (19.0 g, 40.7 mmol) in ethyl acetate (100 ml) containing 10% palladium on charcoal (2 g) was stirred in an atmosphere of hydrogen at room temperature and pressure for 2 days. The catalyst was removed by filtration through celite and the solvent removed to afford *5-O-(tert-butyldiphenylsilyl)-3-C-(carbomethoxymethyl)-3-deoxy-1,2-O-isopropylidene-β-D-lyxofuranose (**11**)*, as a white solid (19.07 g, quantitative yield), m. p. 96-98°C (hexane), $[\alpha]^{20}$ +13.9 (*c*, 0.78 in $CHCl_3$), ν_{max} (film): 2920, 1690 (CO), 1080, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.66 (4H, m, ArH), 7.41 (6H, m, ArH), 5.77 (1H, d, H-1, $J_{1,2}$ 4.0 Hz), 4.70 (1H, t, H-2, $J_{2,1}$= $J_{2,3}$= 4.3 Hz), 4.35 (1H, ddd, H-4, $J_{4,5'}$ 4.7 Hz, $J_{4,5}$= $J_{4,3}$= 8.4 Hz), 3.96 (1H, dd, H-5, $J_{5,5'}$ 10.3 Hz, $J_{5,4}$ 8.6 Hz), 3.73 (1H, dd, H-5', $J_{5,5'}$ 10.3 Hz, $J_{5',4}$= 4.7 Hz), 3.69 (3H, s, OMe), 2.78 (3H, m, H-3 and $\underline{CH_2}COOMe$), 1.28 (3H, s, Me_2C), 1.24 (3H, s, Me_2C), and 1.06 (9H, s, Me_3C). ^{13}C NMR ($CDCl_3$) δ 19.06 (s, Me_3C), 25.45, 26.33, 26.80 and 28.44 (Me and $\underline{C}H_2COOMe$), 40.52 (d, C-3), 51.61 (q, OMe), 64.36 (t, C-5), 80.93 and 82.49 (2d, C-2 and C-4), 105.75 (d, C-1), 111.71 (s, Me_2C), 127.67, 129.64, 133.08, 133.34 and 135.53 (Ar), 172.78 (s, CO). m/z (DCI,

NH_3): 502 ($M+NH_4^+$, 17%), 427 (100%). (Found C, 66.56; H, 7.47. $C_{27}H_{36}O_6Si$ requires C, 66.91; H, 7.49%).

5-O-(tert-Butyldiphenylsilyl)-3-C-(2'-hydroxyethyl)-3-deoxy-1,2-isopropylidene-β-D-lyxofuranose (12). The ester **11** (19.0 g, 39.3 mmol) was dissolved in dry tetrahydrofuran (200 ml) and cooled to 0°C. Lithium aluminum hydride (1.5 g, 39.5 mmol) was added and the solution stirred at room temperature for 1 h. Careful addition of a saturated aqueous solution of sodium sulfate destroyed unreacted lithium aluminum hydride; the organic layer was separated and the aqueous layer was washed with ethyl acetate. The organic extracts were combined, dried (sodium sulfate) and the solvent removed *in vacuo*. Purification of the residue by flash chromatography (ethyl acetate:petroleum ether, 1:1) afforded *5-O-(tert-butyldiphenylsilyl)-3-C-(2'-hydroxyethyl)-3-deoxy-1,2-isopropylidene-β-D-lyxofuranose (12)* (15.8 g, 88%) as a colourless syrup, $[\alpha]^{20}$ +12.5 (c, 0.8 in $CHCl_3$), ν_{max} (film): 3400 (OH), 1420, 1110, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.68 (4H, m, ArH), 7.41 (6H, m, ArH), 5.75 (1H, d, H-1, $J_{1,2}$ 4.0 Hz), 4.63 (1H, dd, H-2, $J_{1,2}$ 4.1 Hz, $J_{2,3}$ 4.8 Hz), 4.37 (1H, ddd, H-4, $J_{4,5}$= $J_{4,3}$= 8.0 Hz, $J_{4,5'}$ 4.7 Hz), 4.01 (1H, dd, H-5, $J_{5,5'}$ 10.3 Hz, $J_{5,4}$ 8.2 Hz), 3.77 (3H, br dd, H-5' and $\underline{CH_2}OH$, $J_{5,5'}$ 10.3 Hz, $J_{5',4}$ 4.8 Hz, 2.48 (1H, br q, H-3, J 5 Hz), 1.94 (2H, m, $\underline{CH_2}CH_2OH$), 1.25 (3H, s, Me_2C), 1.24 (3H, s, Me_2C), and 1.07 (9H, s, Me_3C). ^{13}C NMR ($CDCl_3$) δ 19.06 (s, Me_3C), 25.41, 26.33 and 26.78 (Me and $\underline{C}H_2CH_2OH$), 42.44 (d, C-3), 61.79 (t, CH_2OH), 64.70 (t, C-5), 81.44 and 83.58 (2d, C-2 and C-4), 105.63 (d, C-1), 111.49 (s, Me_2C), 127.67, 129.64, 133.02, 133.32, and 135.55 (Ar). m/z (DCI, NH_3): 474 ($M+NH_4^+$, 1%), 243 (100%). (Found C, 67.98; H, 8.21. $C_{26}H_{36}O_5Si$ requires C, 68.39; H, 7.95%).

5-O-(tert-Butyldiphenylsilyl)-3-C-(2'-O-methanesulfonyl-2'-hydroxyethyl)-3-deoxy-1,2-isopropylidene-β-D-lyxofuranose (13). Methanesulfonyl chloride (4.0 ml, 51.7 mmol) was added dropwise to a solution of the alcohol **12** (15.8 g, 34.6 mmol) in dry pyridine (100 ml) at 0°C. After 3 h, the solvent was removed *in vacuo* and the residue dissolved in chloroform (150 ml); the solution was washed with 5% hydrochloric acid (30 ml) followed by water (30 ml) and the organic layer was dried (sodium sulfate). The solution was filtered and the solvent removed to give a syrup which was purified by flash chromatography (ethyl acetate:hexane, 3:7) to give *5-O-(tert-butyldiphenylsilyl)-3-C-(2'-O-methanesulfonyl-2'-hydroxyethyl)-3-deoxy-1,2-isopropylidene-β-D-lyxofuranose (13)* (18.1 g, 98%), as a colourless syrup, $[\alpha]^{20}$ +8.1 (c, 1.51 in $CHCl_3$), ν_{max} (film): 1450, 1170, 1110, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.65 (4H, m, ArH), 7.41 (6H, m, ArH), 5.76 (1H, d, H-1, $J_{1,2}$ 4.1 Hz), 4.62 (1H, t, H-2, $J_{2,1}$= $J_{2,3}$= 4.1 Hz), 4.40 (2H, m, CH_2OMs), 4.32 (1H, dd, H-4, $J_{4,5'}$ 4.6 Hz, $J_{4,5}$= $J_{4,3}$= 8.2 Hz), 4.02 (1H, dd, H-5, $J_{5,5'}$ 10.3 Hz, $J_{5,4}$ 8.6 Hz), 3.79 (1H, dd, H-5', $J_{5,5'}$ 10.3 Hz, $J_{5',4}$ 4.5 Hz), 2.53 (1H, m, H-3), 2.16 (2H, m, $\underline{CH_2}CH_2OMs$), 1.28 (3H, s, Me_2C), 1.24 (3H, s, Me_2C), and 1.07 (9H, s, Me_3C). ^{13}C NMR ($CDCl_3$) δ 19.07 (Me_3C), 23.89, 25.42, 26.33, and 26.83 (Me and $\underline{C}H_2CH_2OMs$), 37.36 (q, SO_2Me), 41.12 (d, C-3), 64.42 (t, C-5), 68.70 (t, $\underline{C}H_2OMs$), 80.52 and 82.85 (2d, C-2 and C-4), 105.80 (d, C-1), 111.75 (s, Me_2C), 127.70, 129.70, 132.99, 133.31, and 135.51 (Ar). m/z (DCI, NH_3): 552 ($M+NH_4^+$, 40%), 494 (100%). (Found C, 60.59; H, 7.38. $C_{27}H_{38}O_7SSi$ requires C, 60.65; H, 7.16%).

3-C-(2'-Azidoethyl)-5-O-(tert-butyldiphenylsilyl)-3-deoxy-1,2-isopropylidene-β-D-lyxofuranose (2). The mesylate **13** (18.0 g, 33.7 mmol) was dissolved in dry dimethylformamide (100 ml) and sodium azide (7.0 g, 107.7 mmol) was added. The resulting suspension was then stirred at 50°C for 6 h. The solvent was removed *in vacuo* and the residue dissolved in chloroform, washed with water and then dried (sodium sulfate). Evaporation of the solvent and purification of the residue by flash column (ethyl acetate:hexane, 1:9) gave *3-C-(2'-azidoethyl)-5-O-(tert-butyldiphenylsilyl)-3-deoxy-1,2-isopropylidene-β-D-lyxofuranose (2)* (15.6 g, 96%) as a colourless syrup, $[\alpha]^{20}$ +25.5 (c, 1.11 in $CHCl_3$), ν_{max} (film): 2100 (N_3), 1420, 1110, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.67 (4H, m, ArH), 7.41 (6H, m, ArH), 5.76 (1H, d, H-1, $J_{1,2}$ 4.0 Hz), 4.57 (1H, dd, H-2, $J_{2,1}$ 4.2 Hz, $J_{2,3}$ 4.9 Hz), 4.29 (1H, ddd, H-4, $J_{4,5'}$ 4.8 Hz, $J_{4,5}$= $J_{4,3}$= 7.9 Hz), 3.99 (1H, dd, H-5, $J_{5,5'}$ 10.3 Hz, $J_{5,4}$ 8.1 Hz), 3.77 (1H, dd, H-5', $J_{5,5'}$ 10.4 Hz, $J_{5',4}$ 4.8 Hz), 3.43 (2H, m, N_3CH_2), 2.43 (1H, m, H-3), 1.98 (2H, m, $\underline{CH_2}CH_2N_3$), 1.28 (3H, s, Me_2C), 1.25 (3H, s, Me_2C), and 1.07 (9H, s, Me_3C). ^{13}C NMR ($CDCl_3$) δ 19.07 (s, Me_3C), 23.36, 25.39, 26.31, and 26.80 (Me and $\underline{C}H_2CH_2N_3$), 42.33 (d, C-3), 50.21 (t, CH_2N_3), 64.46 (t, C-5), 80.65 and 83.18 (2d, C-2 and C-4), 105.76 (d, C-1), 111.67 (s, Me_2C), 127.67, 129.64, 133.10, 133.36, and 135.52 (Ar). m/z (DCI, NH_3): 499 ($M+NH_4^+$, 14%), 454 (48%), 396 (100%). (Found C, 65.00; H, 7.54; N, 8.55. $C_{26}H_{35}N_3O_4Si$ requires C, 64.83; H, 7.32; N, 8.72%).

3-C-(2'-Azidoethyl)-3-deoxy-D-lyxose (14). The azidofuranose **2** (2.47 g, 5.31 mmol) was stirred in 60% aqueous trifluoroacetic acid (20 ml) at 0°C for 30 min and then the temperature left to rise to room temperature; after 5 h, the solvent was removed and the crude product was purified by flash chromatography (ethyl acetate:petroleum ether (9:1)-ethyl acetate), to give *3-C-(2'-azidoethyl)-3-deoxy-D-lyxose (14)* (0.866 g, 80%), as a white solid, m. p. 84-87°C (chloroform-methanol), $[\alpha]^{20}$ -39.1 (c, 0.44 in methanol), ν_{max} (film): 3350 (OH), 2100 (N_3), 1050, 880 cm^{-1}. ^1H NMR (CD_3OD) δ 4.90 (1H, m, H-1), 3.90-3.15 (6H, m, H-2, H-4, H-5, H-5', H-7, H-7'), 2.00 (1H, m, H-3), 1.79 (2H, m, H-7 and H-7'). ^{13}C NMR (CD_3OD) δ 24.00, 27.47 and 27.80 (3t, C-6), 40.47, 40.82 and 44.88 (3d, C-3), 50.24, 50.49 and 51.50 (3t, C-7), 61.82, 64.47 and 70.20 (3t, C-5), 66.76, 67.03, 69.88, 70.20, 76.41, and 81.82 (6d, C-2 and C-4), 95.00, 97.20 and 103.52 (3d, C-1). m/z (DCI, NH_3): 221 ($M+NH_4^+$, 25%), 203 (M^+, 11%), 160 (85%), 158 (100%). (Found C, 41.77; H, 6.55; N, 20.24. $C_7H_{13}N_3O_4$ requires C, 41.38; H, 6.45; N, 20.68%).

(3S,4R)-N-Benzyloxycarbonyl-3-hydroxy-4-((S)-1,2-dihydroxyethyl) piperidine (15). The azide **14** (637 mg, 3.14 mmol) was dissolved in methanol-water (3:1, 40 ml), palladium on charcoal 10% (110 mg) was added and the mixture hydrogenated during 4 h under 260 psi at 50°C. The methanol was evaporated, added ethyl acetate (20 ml) and saturated aqueous sodium carbonate (10 ml), cooled with stirring in an ice bath and added benzyl chloroformate (674 μl, 4.72 mmol), the reaction was left at room temperature for 13 h, after cooling with an ice bath another portion of benzylchloroformate was added (600 μl, 4.18 mmol) and the stirring at room temperature was continued for 5 h. The reaction mixture was extracted with ethyl acetate (3 x 50 ml); the combined organic extracts were filtered through a celite plug, dried and the solvent removed *in vacuo*. The residue was purified by flash chromatography (chloroform:ethanol, 9:1) to afford the triol *(3S,4R)-N-benzyloxycarbonyl-3-hydroxy-4-((S)-1,2-dihydroxyethyl) piperidine (15)* (712 mg, 77%) as an oil, $[\alpha]^{20}$ +15.9 (c, 0.87 in $CHCl_3$), ν_{max} (film): 3500 (OH), 1680 (CO), 1440, 1050 cm^{-1}. ^1H NMR

($CDCl_3$) δ 7.35 (5H, m, ArH), 5.12 (2H, br s, $ArCH_2$), 4.33 (1H, m), 4.16 (1H, m), 3.91 (1H, m), 3.72 (3H, m), 3.20 (1H, m), 2.98 (1H, m), 2.74 (1H, m), 2.59 (1H, m), 2.25 (1H, m), 1.66 (2H, m), 1.38 (1H, m). ^{13}C NMR ($CDCl_3$) δ 24.17 (t, C-5), 45.57 (d, C-4), 43.59 and 50.21 (2t, C-2 and C-6), 64.65 (t, C-2'), 67.38 (t, $ArCH_2$), 66.83 and 71.33 (C-3 and C-1'), 127.78, 128.05 and 128.48 (3d, Ar), 136.39 (s, Ar), and 155.33 (s, CO). m/z (ACE, NH_3): 313 ($M+NH_4^+$, 10%), 296 ($M+H^+$, 100%), 278 (32%), 252 (46%), 91 (35%). (Found C, 60.73; H, 7.24; N, 5.21. $C_{15}H_{21}NO_5$ requires C, 61.00; H, 7.17; N, 4.74%).

(2S,3'S,4'R)-2-[4'-(N-Benzyloxycarbonyl-3'-hydroxy)piperidyl]-2-hydroxyethyl methanesulfonate (3). The triol **15** (490 mg, 1.66 mmol) in dry pyridine (5 ml) was treated with methanesulfonyl chloride (141 μl, 1.82 mmol) under nitrogen at -20°C and the temperature was allowed to rise to -10°C. The reaction mixture was stirred for 5 h and the pyridine removed *in vacuo*; the crude product was dissolved in chloroform (30 ml), washed with aqueous diluted hydrochloric acid (5 ml) and brine (5 ml), dried (sodium sulfate) and the solvent removed to give a residue which was purified by flash chromatography (chloroform:ethanol, 94:6) to give *(2S,3'S,4'R)-2-[4'-(N-Benzyloxycarbonyl-3'-hydroxy)piperidyl]-2-hydroxyethyl methanesulfonate (3)* (538 mg, 87%) as an oil, $[\alpha]^{20}$ +6.8 (c, 0.81 in $CHCl_3$), ν_{max} (film): 3500-3350 (OH), 3010, 1680 (CO), 1440, 1170 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.34 (5H, m, ArH), 5.11 (2H, br s, $ArCH_2$), 4.34-4.05 (5H, m), 3.65 (1H, m), 3.06 (3H, s, MeS), 3.02 (2H, br s), 2.75 (1H, m), 2.59 (1H, m), 1.64 (2H, m), 1.48 (1H, m). ^{13}C NMR ($CDCl_3$) δ 24.24 (t, C-5'), 37.47 (q, MeS), 43.45 (t, C-6'), 45.41 (d, C-4'), 50.27 (t, C-2'), 67.42 (t, $PhCH_2$), 66.95 and 68.95 (2d, C-3' and C-2), 72.27 (t, C-1), 127.83, 128.11 and 128.52 (3d, Ar), 136.37 (s, Ar), and 155.19 (s, CO). m/z (DCI, NH_3): 572 ((2M-OMs)+NH_4^+, 0.8%), 555 (2(M-OMs)+H^+, 2%), 391 ($M+NH_4^+$, 5%), 295 (M-OMs+NH_4^+, 84%), 278 (M-OMs+H^+, 100%). (Found C, 51.46; H, 6.21; N, 3.75. $C_{16}H_{23}NO_7S$ requires C, 51.41; H, 6.24; N, 3.65%).

(3S,5S)-Quinuclidine-3,5-diol (4). The mesylate **3** (200 mg, 0.536 mmol) was stirred in an atmosphere of hydrogen in ethanol (10 ml) in the presence of palladium black (30 mg) for 6.5 h. The catalyst was removed by filtration; after the addition of ethanol (10 ml) and sodium acetate (88 mg, 1.07 mmol), the reaction mixture was heated for 12 h at 70°C. The solvent was removed and the crude product purified by flash chromatography (ammonia S. G. 0.88:ethanol:chloroform, 2:9:9); the white solid so obtained was purified by ion exchange chromatography (Dowex-50), eluting with aqueous ammonia, to give *(3S,5S)-quinuclidine-3,5-diol (4)* (60 mg, 78%), m. p. 130°C (subl.) (acetone), $[\alpha]^{20}$ -17.4 (c, 0.31 in H_2O), ν_{max} (KBr): 3340, 3300 (OH), 1030, 750 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ 4.05 (1H, m, H-3), 3.96 (1H, m, H-5), 3.02 (1H, ddd, H-2β, J_{gem} 14.3 Hz, $J_{2\beta,3}$ 8.5 Hz, $J_{2\beta,7\beta}$ 2.4 Hz), 2.92 (1H, ddd, H-6, J_{gem} 14.3 Hz, $J_{6,5}$ 8.5 Hz, $J_{6,2\alpha}$ 2.4 Hz), 2.57 (1H, m, H-7α), 2.44 (1H, m, H-7β), 2.35 (1H, td, H-2α, J_{gem} 14.3 Hz, $J_{2\alpha,6}$= $J_{2\alpha,3}$= 2.8 Hz), 2.23 (1H, td, H-6', J_{gem} 14.3 Hz, $J_{6',5}$= $J_{6',7\alpha}$= 2.9 Hz), 1.96 (1H, m, H-4), 1.77 (1H, m, H-8α), 1.20 (1H, m, H-8β). ^{13}C NMR (D_2O) δ 17.00 (t, C-8), 34.84 (d, C-4), 45.63 (t, C-7), 55.40 and 56.32 (2t, C-2 and C-6), 62.60 and 68.11 (2d, C-3 and C-5). m/z (DCI, NH_3): 144 ($M+H^+$, 100%), 126 (6%). (Found C, 58.87; H, 9.45; N, 9.73. $C_7H_{13}NO_2$ requires C, 58.72%, H, 9.15; N, 9.78%).

3-C(2'-Azidoethyl)-3-deoxy-1,2-isopropylidene-β-D-lyxofuranose (16). The protected azide **2** (5.0 g, 10.4 mmol) in tetrahydrofuran (100 ml) containing tetrabutylammonium fluoride (1M solution in tetrahydrofuran, 20.8 ml, 2 equiv.) was stirred at room temperature for 3 h . The solvent was removed and the residue purified

by flash chromatography (ethyl acetate:hexane, 1:1) to afford *3-C-(2'-azidoethyl)-3-deoxy-1,2-isopropylidene-β-D-lyxofuranose (16)* (2.4 g, 95%) as a colourless oil, $[\alpha]^{20}$ -19.6 (c, 1.26 in $CHCl_3$), ν_{max} (film): 3450 (OH), 2100 (N_3), 1380, 870 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.85 (1H, d, H-1, $J_{1,2}$ 4.0 Hz), 4.64 (1H, dd, H-2, $J_{2,1}$ 4.1 Hz, $J_{2,3}$ 5.3 Hz), 2.28 (1H, ddd, H-4, $J_{4,5}$ 9.4 Hz, $J_{4,3}$ 8.3 Hz, $J_{4,5'}$ 4.3 Hz), 3.93 (1H, dd, H-5, $J_{5,5'}$ 11.4 Hz, $J_{5,4}$ 9.6 Hz), 3.44 (3H, m, H-5 and CH_2N_3), 2.47 (1H, m, H-3), 2.25 (1H, br s, OH), 1.89 (1H, m, $\underline{C}H_2CH_2N_3$), 1.76 (1H, m, $\underline{C}H_2CH_2N_3$), 1.55 (3H, s, Me_2C), and 1.31 (3H, s, Me_2C). ^{13}C NMR ($CDCl_3$) δ 22.83 (t, $\underline{C}H_2CH_2N_3$), 25.39 and 26.35 (2q, 2 x Me), 50.07 (t, CH_2N_3), 62.41 (t, C-5), 80.44 and 83.35 (2d, C-2 and C-4), 105.80 (d, C-1), 112.17 (s, Me_2C). m/z (DCI, NH_3): 261 ($M+NH_4^+$, 21%), 198 (100%), 158 (98%). (Found C, 49.81; H, 7.30; N, 16.96. $C_{10}H_{17}N_3O_4$ requires C, 49.37; H, 7.04; N, 17.27%).

3-C-(2'-Azidoethyl)-3-deoxy-1,2-isopropylidene-5-O-methanesulfonyl-β-D-lyxofuranose (17). Methanesulfonyl chloride (1.05 ml, 13.56 mmol) was added dropwise to a solution of the primary alcohol **16** (2.26 g, 9.3 mmol) in dry pyridine (20 ml) at 0°C. After 3 h the solvent was removed and the residue dissolved in chloroform (100 ml); the resulting solution was washed with dilute aqueous hydrochloric acid (10 ml) followed by water (20 ml) and the organic layer was dried (sodium sulfate). The solution was filtered and the solvent removed to give a syrup which was purified by flash column (ethyl acetate:petroleum ether, 1:1) to give *3-C-(2-azidoethyl)-3-deoxy-1,2-isopropylidene-5-O-methanesulfonyl-β-D-lyxofuranose (17)* (2.82 g, 94%) as a white solid, m. p. 78-79.5°C (ether:dichloromethane), $[\alpha]^{20}$ +7.9 (c, 0.76 in $CHCl_3$), ν_{max} (film): 2100 (N_3), 1460, 1030, 980 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.86 (1H, d, H-1, $J_{1,2}$ 3.9 Hz), 4.67 (1H, dd, H-2, $J_{2,1}$ 4.0 Hz, $J_{2,3}$ 4.8 Hz), 4.61 (1H, dd, H-5, $J_{5,5'}$ 10.9 Hz, $J_{5,4}$ 9.0 Hz), 4.41 (1H, ddd, H-4 $J_{4,5}$= $J_{4,3}$= 8.9 Hz, $J_{4,5'}$ 3.7 Hz), 4.26 (1H, dd, H-5', $J_{5,5'}$ 10.9 Hz, $J_{5,4}$ 3.7 Hz), 3.45 (2H, m, CH_2N_3), 3.13 (3H, s, $MeSO_2$), 2.53 (1H, m, H-3), 1.82 (2H, m, $\underline{C}H_2CH_2N_3$) 1.61 (3H, s, Me_2C), and 1.32 (3H, s, Me_2C). ^{13}C NMR ($CDCl_3$) δ 22.92 (t, $\underline{C}H_2CH_2N_3$), 25.05 and 26.03 (2q, Me_2C), 37.78 (q, $MeSO_2$), 42.15 (d, C-3), 49.63 (t, CH_2N_3), 70.10 (t, CH_2OMs), 79.76 and 79.85 (2d, C-2 and C-4), 105.94 (d, C-1), and 112.08 (s, Me_2C). m/z (DCI, NH_3): 339 ($M+NH_4^+$, 100%). (Found C, 41.50; H, 6.02; N, 13.11; S, 9.92. $C_{11}H_{19}N_3O_6S$ requires C, 41.11; H, 5.96; N, 13.08; S, 9.98%).

(1S,3S,7S,8S)-N-Benzyloxycarbonyl-5,5-dimethyl-11-aza-2,4,6-trioxatricyclo[6.4.0.0^{3,7}]dodecane (18). A solution of the azidomesylate **17** (2.62 g, 8.16 mmol) in ethanol (100 ml) containing palladium black (120 mg) was hydrogenated at room temperature overnight. The catalyst was removed by filtration, sodium acetate (1.33 g, 16.2 mmol) was added and the reaction mixture was heated at reflux for 10 h. The solvent was removed and the residue dissolved in ethyl acetate (50 ml); the resulting solution was treated with saturated aqueous sodium bicarbonate solution (20 ml) and benzyl chloroformate (1.75 ml, 12.2 mmol) added at 0°C and the two phase reaction mixture was stirred overnight. The mixture was extracted with ethyl acetate (3 x 30 ml), dried and the organic layer concentrated to an oil which was purified by flash chromatography (ethyl acetate:hexane, 3:7) to give *(1S,3S,7S,8S)-3-N-benzyloxycarbonyl-5,5-dimethyl-11-aza-2,4,6-trioxatricyclo[6.4.0.0^{3,7}]dodecane (18)* (2.60 g, 96%), as a colourless oil, $[\alpha]^{20}$ +19.33 (c, 0.75 in $CHCl_3$), ν_{max} (film): 1700 (CO), 1420, 1020 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35 (5H, m, ArH), 5.84 (1H, d, H-1, $J_{1,2}$ 3.9 Hz), 5.13 (2H, s, $ArCH_2$), 4.72 (1H, dd, H-7, $J_{7,3}$ 3.9 Hz, $J_{7,8}$ 5.6 Hz), 4.22 (1H, m), 3.85 (1H, m),

3.25 (2H, m), 2.39 (1H, m), 2.00 (2H, m), 1.59 (3H, s, Me_2C), and 1.32 (3H, s, Me_2C). ^{13}C NMR ($CDCl_3$) δ 22.50 (t, C-9), 25.34 and 26.75 (2q, Me_2C), 38.22 (d, C-8), 41.91 and 45.91 (2t, C-12 and C-10), 67.03 (t, $ArCH_2$), 76.50 and 82.76 (2d, C-7 and C-1), 106.66 (d, C-3), 112.60 (s, Me_2C), 127.78, 127.92, 128.43, and 136.72 (Ar), and 155.54 (s, CO). m/z (DCI, NH_3): 351 ($M+NH_4^+$, 50%), 334 (M+1, 16%), 276 (100%). (Found C, 64.71; H, 6.95; N, 4.12. $C_{18}H_{23}NO_5$ requires C, 64.85; H, 6.95; N, 4.20%).

*(3S,4S)-N-benzyloxycarbonyl-3-hydroxy-4-((S)-1,2-dihydroxyethyl) piperidine (**19**).* The tricyclic carbamate **18** (1.12 g, 3.36 mmol) was dissolved in 80% aqueous acetic acid (30 ml) and warmed to 50°C for 12 h. The solvent was removed and codistilled with toluene to remove traces of acetic acid. The resulting syrup was dissolved in ethanol (30 ml), treated with sodium borohydride (250 mg, 6.58 mmol), and the solution stirred overnight. The reaction was quenched by careful addition of 5% hydrochloric acid until moderate acid pH and the reaction mixture concentrated. Purification of the residue by flash chromatography (chloroform:ethanol, 93:7) afforded *(3S,4S)-N-benzyloxycarbonyl-3-hydroxy-4-((S)-1,2-dihydroxyethyl) piperidine (**19**)* (0.81 g, 82%) as a colourless syrup, $[\alpha]^{20}$ -35.2 (c, 1.05 in $CHCl_3$). ^1H NMR ($CDCl_3$ + D_2O) δ 7.33 (5H, m, ArH), 5.11 (2H, br s, $ArCH_2$), 4.20 (3H, m), 3.65 (2H, m), 3.53 (1H, m), 2.78 (2H, m), 1.77 (1H, m, H-4), 1.60 (1H, m, H-5), 1.31 (1H, m, H-5'). ^{13}C NMR ($CDCl_3$) δ 22.83 (t, CH_2-C_4), 41.44 (d, C-4), 43.85 and 50.32 (2t, C-2 and C-6), 64.69 (t, C-2'), 67.31 (t, $ArCH_2$), 64.97 and 73.15 (2d, C-1' and C-3), 127.76, 128.01, 128.49, and 136.60 (Ar), and 156.42 (s, CO). m/z (DCI, NH_3): 313 ($M+NH_4^+$, 29%), 296 ($M+H^+$, 100%). (Found C, 60.85; H, 7.44; N, 4.58. $C_{15}H_{21}NO_5$ requires C, 61.00; H, 7.17; N, 4.74%).

*(2S,3'S,4'S)-2-[4'-(N-Benzyloxycarbonyl-3'-hydroxy)piperidyl]-2-hydroxyethyl methanesulfonate (**6**).* The triol **19** (0.80 g, 2.71 mmol) was dissolved in dry pyridine (20 ml) and methanesulfonylchloride (254 μl, 3.28 mmol) was added, with stirring at -10°C the solution was kept at this temperature for 8 h. The reaction was quenched with methanol, the pyridine removed, and the solution was diluted with chloroform (100 ml) and washed successively with 5% hydrochloric acid (5 ml) and water (20 ml). The organic layer was dried and evaporated to a syrup which was purified by flash chromatography (chloroform:ethanol, 95:5) to give *(2S,3'S,4'S)-2-[4'-(N-benzyloxycarbonyl-3'-hydroxy)piperidyl]-2-hydroxyethyl methanesulfonate (**6**)* (823 mg, 81%) as a syrup, $[\alpha]^{20}$ -26.7 (c, 1.23 in $CHCl_3$), ν_{max} (film): 3400 (OH), 1680 (CO), 1440, 1170 cm^{-1}. ^1H NMR ($CDCl_3$ +D_2O) δ 7.36 (5H, m, ArH), 5.15 (2H, m, $ArCH_2$), 4.31 (5H, m), 3.90 (1H, m), 3.09 (3H, s, $MeSO_2$), 2.86 (2H, m), 2.00-1.42 (3H, m, H-4' and H-5'). ^{13}C NMR ($CDCl_3$) δ 22.64 (t, C-5'), 37.45 (q, SO_2Me), 40.85 (d, C-4'), 43.76 and 50.31 (2t, C-2' and C-6'), 67.33 (t, $ArCH_2$), 64.74 and 70.79 (2d, C-2 and C-3'), 71.59 (t, CH_2OSO_2), 127.72, 128.03, 128.49 and 136.51 (Ar), and 156.38 (s, CO). m/z (DCI, NH_3): 572 (2 x (M-$MeSO_3H$)+NH_4^+, 0.5%), 555 (2 x (M-$MeSO_3H$) + H^+, 0.4 %), 391 ($M+NH_4^+$, 1%), 374 ($M+H^+$, 0.8%), 295 ((M-$MeSO_3H$)+NH_4^+, 30%), 278 (M-$MeSO_3H$+H^+, 100%). (Found C, 51.38; H, 6.21; N, 3.66. $C_{16}H_{23}NO_7S$ requires C, 51.46; H, 6.21; N, 3.75%).

*[3S-(3α,3aα,7aα)]-N-Benzyloxycarbonyl-octahydro-2-furo[2,3-c]pyridinol (**20**).* The mesylate **6** (2.11) (163 mg, 0.43 mmol) was dissolved in ethanol (8 ml) and sodium acetate (119 mg, 1.30 mmol) was added. The suspension was stirred at 50 °C for 5h when t.l.c. (hexane:ethyl acetate 1:7) showed no starting

material (R_f 0.4) and one product (R_f 0.3). The solvent was removed *in vacuo* and the residue was partitioned between brine (10 ml) and dichloromethane (3 x 10 ml). The organic extracts were combined, dried (magnesium sulphate), filtered and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexane:ethyl acetate 1:7) to give *[3S-(3α,3aα,7aα)]-N-benzyloxycarbonyl-octahydro-2-furo[2,3-c]pyridinol (20)* (102 mg, 84%), a colourless oil. $[\alpha]_D^{20}$-7.9 (c, 0.88 in chloroform), ν_{max} (film) 3460 (br) (OH), 1695 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35 (5H, m, ArH), 5.14 (2H, br s, $ArC\underline{H}_2$), 4.54 (1H, t, *J* 6 Hz, H-3), 4.01-3.37 (7H, br m, H-2, H-2', H-7a, H-5, H-5', H-7, H-7'), 2.51 (1H, br s, OH), 2.25-1.71 (3H, br m, H-3a, H-4, H-4'); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.1 (s, C=O), 136.9 (s, ArC), 128.6, 128.3, 128.2, 128.1, 127.9 (5d, ArCH), 74.8 (d, C-3), 73.5 (d, C-7a), 73.0 (t, C-2), 67.1 (t, $Ar\underline{C}H_2$), 45.0, 42.1 (2t, C-5 and C-7), 40.0 (d, C-3a), 20.3 (t, C-4); *m/z* (DCI (NH_3)) 278 ($M+H^+$, 100%); (Found C, 65.12; H, 7.11; N, 4.87. $C_{15}H_{19}NO_4$ requires C, 64.97, H, 6.91; N, 5.05%).

[3S-(3α,3aα,7aα)]Octahydro-2-furo[2,3-c]pyridinol (21). A solution of the protected piperidine **20** (64 mg, 2.30 mmol) in ethanol (6 ml) with a catalytic amount of palladium black (10 mg) was stirred at room temperature, under an atmosphere of hydrogen, for 12h. T.l.c. (hexane:ethyl acetate 1:7) then showed no starting material (R_f 0.3) and t.l.c. (0.88 ammonia:ethanol:chloroform 5:10:85) showed a single product (R_f 0.35). The catalyst was removed by filtering through Celite and the solvent was removed *in vacuo*. Following purification by flash chromatography (0.88 ammonia:ethanol:chloroform 5:10:85) and ion exchange chromatography *[3S-(3α,3aα,7aα)]octahydro-2-furo[2,3-c]pyridinol (21)* (29 mg, 88%) was obtained as a colourless solid. m.p. 68-69°C; $[\alpha]_D^{20}$-9.4° (c, 0.65 in methanol), ν_{max} (KBr disc) 3460 cm^{-1} (br) (OH); ^1H NMR (500 MHz, D_2O) δ 4.54 (1H, dd, $J_{2,3}$7.5 Hz, $J_{3,3a}$14.0 Hz, H-3), 3.97 (1H, t, $J_{2,2'}$8.4 Hz, H-2), 3.85 (1H, dd, $J_{7,7a}$2.8 Hz, $J_{3a,7a}$6.4 Hz, H-7a), 3.59 (1H, dd, H-2'), 2.96 (2H, m, H-5, H-7),2.75 (1H, dd, $J_{7,7'}$14.5 Hz, H-7'), 2.45 (1H, dt, $J_{4,5}$2.8 Hz, $J_{5,5'}$12.6 Hz, H-5), 2.22 (1H, ddd, H-3a), 1.54 (1H, m, H-4), 1.37 (1H, m, H-4'); ^{13}C NMR (50 MHz, D_2O) δ 75.5, 73.4 (2d, C-3 and C-7a), 71.0 (t, C-2), 46.5, 39.5 (2t, C-5 and C-7), 43.5 (d, C-3a), 21.2 (t, C-4); *m/z* (CI (NH_3)) 144 ($M+H^+$, 100%), 125 (M^+-H_2O, 24%). (Found C, 58.60, H, 9.06; N, 9.21. $C_7H_{13}NO_2$ requires C, 58.71, H, 9.45; N, 9.02%).

[3S-(3α,3aα,7aα)] N-Methyl-octahydro-2-furo[2,3-c]pyridinol (22). Aqueous formaldehyde (37% solution, 0.05 ml, 0.6 mmol) was added to a solution of the carbamate **20** (57 mg, 0.19 mmol) in distilled methanol (4 ml). The reaction mixture was stirred at room temperature, under an atmosphere of hydrogen, in the presence of a catalytic amount of palladium black (10 mg) for 24 h. T.l.c. (0.88 ammonia:ethanol:chloroform, 5:10:85) then showed a single product (R_f 0.45). The catalyst was removed by filtration through Celite and the solvent was removed *in vacuo* to give *3S-(3α,3aα,7aα)] N-methyl-octahydro-2-furo[2,3-c]pyridinol (22)* (31 mg, 96%), ν_{max} (KBr disc) 3440 cm^{-1} (br) (OH); ^1H NMR (300 MHz, CD_3OD) δ 4.43 (1H, dd, $J_{2,3}$6.6 Hz, $J_{3,3a}$14.1 Hz, H-3), 3.83 (2H, m, H-2, H-7a), 3.44 (1H, t, $J_{2,2'}$7.7 Hz, H-2'), 2.73 (1H, d, $J_{7,7'}$13.4 Hz, H-7), 2.62 (1H, dt, $J_{4,5}$3.6 Hz, $J_{5,5'}$11.7 Hz, H-5), 2.10 (1H, dd, $J_{7a,7'}$2.8 Hz, H-7'), 2.02 (3H, s NCH_3), 1.93 (2H, m, H-3a, H-5'), 1.45 (2H, m, H-4, H-4'); ^{13}C NMR (50 MHz, CD_3OD) δ 75.9, 73.6 (2d, C-3 and C-7a), 72.2 (t, C-2), 56.9, 54.0 (2t, C-5

and C-7), 44.9 (q, NCH_3), 39.5 (d, C-3a), 21.3 (t, C-4); *m/z* (CI (NH_3)) 158 ($M+H^+$, 100%), 139 (M^+-H_2O, 13%).

(1'S,3S,4S)-N-Benzyloxycarbonyl-3-hydroxy-4-(2',2'-bisthioethyl-1'-hydroxy)ethyl piperidine (23). The isopropylidene derivative **18** (1.17 g, 3.51 mmol) was dissolved in 50% aqueous trifluoroacetic acid (20 ml) at 0°C and ethanethiol (1.07 ml, 14.4 mmol) was added. After 4 h, the solvent was removed and the residue purified by flash column (ethyl acetate:hexane, 2:3) to yield *(1'S,3S,4S)-N-benzyloxycarbonyl-3-hydroxy-4-[2',2'-bisthioethyl-1'-hydroxyethyl] piperidine (23)* (1.25 g, 89%) as a white solid, m. p. 89-90°C (dichloromethane:ether), $[\alpha]^{20}$ -36 (c, 0.57 in $CHCl_3$), ν_{max} (KBr): 3430 (OH), 1685 (CO), 1420, 1230 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.36 (5H, m, ArH), 5.15 (2H, br s, CH_2Ar), 4.28 (3H, m), 3.97 (1H, d, H-2'), 3.71 (1H, m), 2.75 (6H, m), 2.05 (2H, m), 1.43 (1H, m), 1.28 (6H, 2t, Me, J 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ 14.47 and 14.57 (2q, Me), 23.36, 24.13 and 25.39 (3t, C-5 and CH_2S), 41.19 (d, C-4), 44.02 and 50.27 (2t, C-2 and C-6), 67.18 (t, CH_2Ar), 56.03, 65.04, 73.50, 73.97, 79.23, and 89.50 (6d, C-3, C-1' and C-2'), 127.79, 127.90, 128.43, and 136.84 (Ar), and 156.28 (s, CO). m/z (DCI, NH_3): 417 ($M+NH_4^+$, 26%), 400 (M+1, 24%), 338 (100%). (Found C, 57.22; H, 7.40; N, 3.38. $C_{19}H_{29}NO_4S_2$ requires C, 57.11; H, 7.32; N, 3.52%).

(1'S,3S,4S)-N-Benzyloxycarbonyl-3-benzyloxy-4-(2',2'-bisthioethyl-1'-benzyloxy)ethyl piperidine (24). The diol **23** (705 mg, 1.77 mmol) in dry tetrahydrofuran (10 ml) was added to a stirred suspension of sodium hydride (50% dispersion in oil, prewashed with hexane, 254 mg, 5.29 mmol) in tetrahydrofuran (10 ml). Tetrabutylammonium iodide (95 mg) and benzyl bromide (0.84 ml, 7.06 mmol) were added to the suspension. After a day, the solvent was removed and the residue partitioned between chloroform (50 ml) and water (10 ml). The organic layer was dried (sodium sulfate) and concentrated to a syrup which was purified by flash chromatography (ethyl acetate:petroleum ether, 1:9) to afford *(1'S,3S,4S)-N-benzyloxycarbonyl-3-benzyloxy-4-(2',2'-bisthioethyl-1'-benzyloxy)ethyl]piperidine (24)* (717 mg, 70 %), as a clear oil, $[\alpha]^{20}$ -88.1 (c, 0.71 in $CHCl_3$), ν_{max} (film): 1700 (CO), 1450, 1090, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.27 (15H, m, ArH), 5.15-3.84 (11H, m), 2.75 (6H, m), 2.16 (1H, m), 1.75 (1H, m), 1.43 (1H, m), 1.26 (6H, m). ^{13}C NMR ($CDCl_3$) δ 14.50 (q, Me), 23.23, 25.19 and 26.59 (3t, C-5 and CH_2S), 44.37 (d, C-4), 43.97 and 45.19 (2t, C-2 and C-6), 54.50 (d, C-2'), 66.91, 67.20, 69.76, 70.19, and 74.93 (5t, CH_2Ar), 71.47 and 82.82 (2d, C-1' and C-3), 126.82, 127.37, 127.63, 127.87, 128.02, 128.23, 128.39, 136.56, 137.01, 138.58, and 138.64 (Ar), and 155.66 (s, CO). m/z (DCI, NH_3): 597 ($M+NH_4^+$, 4%), 580 (M +1, 1%), 518 (100%). (Found C, 68.59; H, 7.42; N, 2.28. $C_{33}H_{41}NO_4S_2$ requires C, 68.35; H, 7.13; N, 2.43%).

(1'S,3S,4S)-N-Benzyloxycarbonyl-3-benzyloxy-4-(1'-benzyloxy-2'-hydroxy)ethyl piperidine (25). Mercury (II) chloride (826 mg, 3.04 mmol) and red mercury (II) oxide (396 mg, 1.83 mmol) were added to a solution of the thioacetal **24** (705 mg, 1.22 mmol) in acetone-water (9:1, 30 ml), and the resulting suspension was stirred at room temperature. After 1 h, the reaction was filtered through celite and the filter cake washed with acetone. The solvent was removed from the combined filtrates and the residue dissolved in chloroform (100 ml). The chloroform solution was washed with water (2 x 50 ml), dried (sodium sulfate) and evaporated to

give a colourless syrup containing the crude aldehyde [ν_{max}: 1730 (CHO), 1690 (CON) cm^{-1}), ^1H NMR ($CDCl_3$) δ 9.62 (1H) and m/z (DCI, NH_3): 491 ($M+NH_4^+$, 3%), 474 (M+1, 39%)]. Without any further purification the crude aldehyde was dissolved in ethanol (50 ml) and treated with sodium borohydride (92 mg, 2.42 mmol). The reaction mixture was stirred for 4 h, quenched with solid ammonium chloride and the solvent removed. The residue was dissolved in chloroform, washed with water, dried and the solvent removed. The residue was purified by flash chromatography (ethyl acetate:petroleum ether, 1:1) to give *(1'S,3S,4S)-N-benzyloxycarbonyl-3-benzyloxy-4-(1'-benzyloxy-2'-hydroxy)ethyl piperidine (25)* (507 mg, 88%) as a colourless syrup, $[\alpha]^{20}$ -92.9 (c, 0.86 in $CHCl_3$), ν_{max} (film): 3450 (OH), 1690 (CO), 1430, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.27 (15H, m, ArH), 5.14-3.52 (12H, m), 2.80 (2H, m), 2.00-1.40 (3H, m). ^{13}C NMR ($CDCl_3$) δ 22.47 (t, C-5), 41.64 (d, C-4), 43.88 and 45.35 (2t, C-2 and C-6), 66.94, 67.17, 70.09, 70.44, and 72.21 (5t, CH_2Ar and C-2'), 71.23 and 79.47 (2d, C-1' and C-3), 127.00, 127.35, 127.64, 127.79, 128.22, 128.40, 128.49, 138.30, 138.49, and 138.50 (Ar), and 155.70 (s, CO). m/z (DCI, NH_3): 493 ($M+NH_4^+$, 16%), 476 (100%). (Found C, 73.01; H, 7.20; N, 2.72. $C_{29}H_{33}NO_5$ requires C, 73.24; H, 6.99; N, 2.95%).

(1'S,3S,4S)-N-Benzyloxycarbonyl-3-benzyloxy-4-(1'-benzyloxy-2'-hydroxy-2'-O-methanesulphonyl)ethyl piperidine (5). Methanesulfonylchloride (0.105 ml, 1.36 mmol) was added to a solution of the primary alcohol **25** (440 mg, 0.93 mmol) in dry pyridine (10 ml) at 0°C. After 2 h the solvent was evaporated and the residue dissolved in chloroform (50 ml), washed with 5% hydrochloric acid (5 ml), followed by water (10 ml). The organic layer was dried (sodium sulfate) and the solvent removed to give a syrup which was purified by flash column (ethyl acetate:petroleum ether, 2:3) to give *(1'S,3S,4S)-N-benzyloxycarbonyl-3-benzyloxy-4-(1'-benzyloxy-2'-hydroxy-2'-O-methanesulphonyl)ethyl piperidine (5)* (506 mg, 99%) as a colourless oil, $[\alpha]^{20}$ -75.9 (c, 1.1 in $CHCl_3$), ν_{max} (film): 1690 (CO), 1450, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.27 (15H, m, ArH), 5.16-3.76 (12H, m), 2.97 (3H, s, $MeSO_2$), 2.77 (2H, m), 2.00-1.40 (3H, m). ^{13}C NMR ($CDCl_3$) δ 22.56 (t, C-5), 37.81 (q, $MeSO_2$), 42.29 (d, C-4), 43.86 and 45.35 (2t, C-2 and C-6), 67.19, 67.45, 68.37, 68.61, 70.35, and 70.72 (t, CH_2Ar), 72.80 (t, C-2'), 70.96, 77.31 (2d, C-1' and C-3), 127.25, 127.68, 128.08, 128.24, 128.48, 128.65, 136.72, 137.89, and 138.48 (Ar), 155.83 (s, CO). m/z (DCI, NH_3): 571 ($M+NH_4^+$, 4%), 554 ($M+H^+$, 3%), 368 (100%). (Found C, 64.93; H, 6.22; N, 2.15. $C_{30}H_{35}NO_7S$ requires C, 65.08; H, 6.37; N, 2.53%).

(3S,5S)-3,5-Di-O-benzylquinuclidine-3,5-diol (26). The carbamate **5** (185 mg, 0.335 mmol) was dissolved in ethanol (10 ml) and hydrogenated in the presence of 10% palladium on charcoal (45 mg) for 1 day. Sodium acetate (55 mg, 0.67 mmol) was added, the catalyst removed and the resulting mixture heated at 60°C for 4 h. The solvent was removed and the residue purified by a short column of silicagel (chloroform:ethanol:ammonium hydroxide 0.88, 90:10:0.25) to give *(3S,5S)-quinuclidine-3,5-di-O-benzyl ether (26)* (84 mg, 78%) as a colourless oil, $[\alpha]^{20}$ -15.7° (c, 0.51 in $CHCl_3$), ν_{max} (film): 2920, 2860, 1490, 1450 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35 (10H, m, ArH), 4.49 (4H, m, CH_2Ar), 3.96 (1H, m, H-3), 3.76 (1H, m, H-5), 3.27 (1H, ddd, H-2β, J_{gem} 14.2 Hz, $J_{2\beta,3}$ 8.2 Hz, J 2.3 Hz), 3.10 (1H, ddd, H-6β, J_{gem} 14.2 Hz, J 8.1 Hz, J 2.3 Hz), 2.91 (1H, m, H-7), 2.73 (3H, m, H-7, H-2α, H-6α), 2.53 (1H, m, H-4), 2.07 (1H, m, H-8α), 1.21 (1H, m, H-8β). ^{13}C NMR ($CDCl_3$) δ 17.65 (t, C-8), 29.01 (d, C-4), 46.64 (t, C-7), 55.48 and 55.89 (2t, C-2 and C-6), 70.59 (d, CH_2Ar), 70.07 and 75.53 (2d, C-3 and C-5), 127.55, 127.65,

128.42, 130.08, 148.83, and 149.78 (Ar). m/z (DCI, NH_3): 324 (M+1, 92%), 232 (100%), 91 (56%). (Found C, 77.73; H, 7.81; N, 4.09. $C_{21}H_{25}NO_2$ requires C, 77.97; H, 7.79; N, 4.35%).

(3S,5S)-Quinuclidine-3,5-diol (4). The dibenzyl ether **26** (80 mg, 0.25 mmol) was dissolved in acetic acid-ethanol (1:1, 6 ml) containing palladium black (50 mg) and stirred under an atmosphere of hydrogen for 2 d. The catalyst was removed by filtration and the solvent evaporated. Purification of the residue by ion-exchange chromatography (Aldrich 50 x 8-100, H^+ form eluted with aqueous ammonia) and removed of the solvent by freeze drying afforded *(3S,5S)-quinuclidine-3,5-diol (4)* (34.8 mg, 98%), having identical properties to those described above.

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REFERENCES

[1]Fleet, G. W. J., Ramsden, N. G., Nash, R. J., Fellows, L. E., Jacob, G. S., Cenci di Bello, I., and Winchester, B., *Carbohydr. Res* , 1990, **205**, 269 and references therein.
[2]Choi, S., Bruce, I., Fairbanks, A. J., Fleet, G. W. J., Jones, A. H., Nash, R. J., and Fellows, L. E., *Tetrahedron Lett.*, 1991, **32**, 5517 and references cited therein.
[3]Fleet, G. W. J., James, K., and Lunn, R. J.,*Tetrahedron Lett.*, 1986, **27**, 3053; Fleet, G. W. J., James, K., Lunn, R. J., and Mathews, C. J.,*Tetrahedron Lett.*, 1986, **27**, 3057.
[4]Fleet, G. W. J., Mathews, C. J., Seijas, J. A., Tato, M. P. V., Baird, P. D., and Brown, D., *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1067.
[5]Deshpande, P. P., Baker, D. C., CARB 82, *205th ACS National Meeting*, Denver, Colarado, March 28-April 2, **1993**.
[6]Orlek, B. S., Wadsworth, H., Wyman, P., and Hadley, M. S., *Tetrahedron Lett.*, 1991, **32**, 1241; Orlek, B. S., Wadsworth, H., Wyman P., and King, F. D., *Tetrahedron Lett.*, 1991, **32**, 1245.
[7]Snider, R. M., Constantine, J. W., Lowe, J. A., Longo, K. P., Lebel, W. S., Woody, H. A., Drozda, S. E., Desai, M. C., Vinick, F. J., Soencer, R. C., and Hess, H.-J., *Science*, 1991, **251**, 435.
[8]Seward, E. M., Swain, C. J., Merchant, K. J., Owen, S. N., Sabin, V., Cascieri, M. A., Sadowski, S., Strader, C., Baler, R., *Bioorg. Med. Chem. Lett.*, 1993, **3**, 1361.
[9]Fisher, A., Weinstock, M., Gitter, S., and Cohen, S., *Eur. J. Pharmacol.*, 1976, 37, 329; Saunders, J., Showell, G. A., Baker, R., Freedman, S. B., Hill, D., McKnight, A., Newberry, N., Salamone, J. D., Hirshfield, J., and Springer, J. P., *J. Med. Chem.*, 1987, **30**, 969; Rzesortarski, J., McPherson, D. W., Ferkany, J. W., Kinnier, W. J., Noronha-Blob, L., and Kirkien-Rzesortarski, A., *J. Med. Chem.*, 1988, **31**, 1463.
[10]Street, L. J., Baker, R., Book, T., Kneen, C. O., McLeod, A. M., Merchant, K. J., Showell, G. A., Saunders, J., Herbert, R. H., Freedman, S. B., and Harley, E. A., *J. Med. Chem.*, 1990, **33**, 2690; Wadsworth, H. J., Jenkins, S. M., Orlek, B. S., Cassidy, F., Clark, M. S. G., Brown, F., Riley, G. J., Graves, D., Hawkins, J., and Naylor, C. B., *J. Med. Chem.*, 1992, **35**, 1280.
[11]For example: Morgan, T. K., Lis, R., Marisca, A. J., Argentieri, T. M., Sullivan, M. E., and Wong, S. S., *J. Med. Chem.*, 1987, **30**, 2259
[12]Powers, M. R., Golec, F. S., Airey, J., Studt, W., *Abstr. Papers 206th ACS Natl. Meeting*, Chicago, Il, **1993**, ORGN-94.
[13]Scotese, A. C., Neuenschwander, K., Amin, D., Gustafson, S., Needle, S., Rutledge, *Abstr. Papers 206th ACS Natl. Meeting*, Chicago, Il, **1993**, ORGN-95.

[14]Clark, R. D., Weinhardt, K. K., Berger, J., Lee, C.-H., Leung, E., Wong, E. H. F., Smith, W. L., Eglen, R. M., *Bioorg. Med. Chem. Lett.*, 1993, **3**, 1375.
[15]Henteges, S. G., and Sharpless, K. B., *J. Am. Chem. Soc.*, 1980, **102**, 4263.
[16]Sharpless, K. B., Amberg, W., Bennani, Y. L., Crispino, G. A., Hartung, J., Jeong, K.-S., Kwong, H.-L., Morilawa, K., Wang, Z.-M., Xu, D., and Zhang, X.-L., *J. Org. Chem.*, 1992, **57**, 2768.
[17]Fleet, G. W. J., Mathews, C. J., Seijas, J. A., Tato, M. P. V., and Brown, D., *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1065.
[18]Wolfrom, M. L., Weisblat, D. I., Zophy, W. H., and Waisbrot, S. W., *J. Am. Chem. Soc.*, 1941, **63**, 201.
[19]Brownlow, S., Mathews, C. J., Brown, D., Fleet, G. W. J., in preparation

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