Chiral Quinuclidines (1-Azabicyclo[2.2.2]octanes) from Sugars: Synthesis of (3*S*,5*S*)-Quinuclidine-3,5-diol from D-Arabinose

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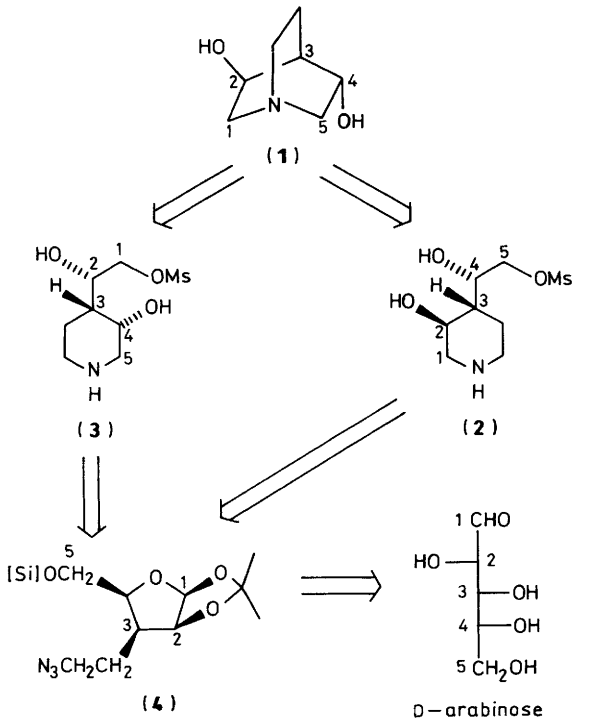
The synthesis of (3*S*,5*S*)-quinuclidine-3,5-diol from D-arabinose by two alternative ring closures is described.

The chemistry of quinuclidines has long been of interest, both in regard to the challenge of the synthesis of the cinchona alkaloids,[1] and in the pharmacological activity of simple quinuclidines.[2] Recently, several reports have highlighted the potential of chiral hydroxylated quinuclidines in probing the active site of muscarinic receptors,[3–5] and these may have a role in the study or treatment of Alzheimer's disease.[6–8] Also, substituted quinuclidines may provide selective Vaughan Williams class III antiarrhythmic agents.[9] Further interest arises from observations of ligand accelerated catalysis by chiral quinuclidines of asymmetric *cis* dihydroxylation of alkenes;[10] the synthesis of relatively simple chiral quinuclidines may allow the identification of mechanistic features of such catalysis. The power of sugars as starting materials for the synthesis of functionalised chiral quinuclidines, previously demonstrated in the synthesis of (*S*)-quinuclidin-3-ol from glucose,[11,12] is illustrated in this paper by the synthesis of (3*S*,5*S*)-quinuclidine-3,5-diol (**1**) from D-arabinose. The synthesis of a *meso*-quinuclidinediol from glucose is described in the accompanying paper.[13]

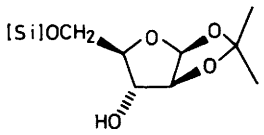
The synthesis of (3*S*,5*S*)-quinuclidine-3,5-diol (**1**) from D-arabinose involves the introduction of a two-carbon chain with inversion of configuation at C-3 to give the protected *lyxo*-furanose (**4**). Subsequent formation of a piperidine ring *via* closure of the amine derived from the azide (**4**) onto C-1 of the sugar permits access to the amino mesylate (**2**) from which the second 6-membered ring may be formed by intramolecular displacement of mesylate to form (**1**). Alternatively, the first piperidine ring may be obtained by closing the side-chain nitrogen function onto C-5 of the sugar, leading to a protected derivative of (**3**) which is a diastereoisomer of the amino-mesylate (**2**).



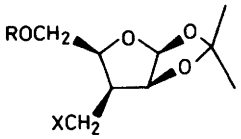
The key intermediate (**4**) may be produced on a multi-gram scale from D-arabinose in eight steps in an overall yield of 41%. The furanoside (**5**), in which only the hydroxy corresponding to C-3 of arabinose is unprotected, was prepared from D-arabinose in an overall yield of 59% *via* formation of the diethyl dithioacetal, silylation of the primary hydroxy group and subsequent hydrolysis by mercury(II) oxide and mercury(II) chloride in aqueous acetone and acetonation. Oxidation of the alcohol (**5**) with pyridinium chlorochromate gave a ketone which was treated with (methoxycarbonylmethylene)triphenylphosphorane to give a mixture of *E*- and *Z*-olefins which on palladium-catalysed hydrogenation afforded the saturated ester (**6**), m.p. 96–98 °C, $[\alpha]_D^{20}$ +13.9° (*c*, 0.8 in $CHCl_3$), in 81% yield. Lithium aluminium hydride reduction of (**6**), followed by mesylation and nucleophilic displacement of the mesylate by azide ion gave the key branched azidoethyl *lyxo*-furanoside (**4**), syrup, $[\alpha]_D^{20}$ +25.5° (*c*, 1.1 in $CHCl_3$) [96% yield from (**6**); 41% from D-arabinose].

The piperidine mesylate (**2**) was prepared by closing the amine derived from the azide (**4**) onto C-1 of the sugar. Acid hydrolysis of the acetonide (**4**) gave 3-(2-azidoethyl)-3-deoxy-D-lyxose (**9**), m.p. 84–87 °C, in 80% yield. Palladium-catalysed hydrogenation of (**9**) caused intramolecular reductive amination which gave, after protection of the amino function *via* benzyl chloroformate, the carbamate (**10**) in 77% yield. Mesylation of the primary hydroxy group in the triol (**10**) gave the mesylate (**11**) in 87% yield. Hydrogenolytic removal of the *Z* protecting group in (**11**) gave the amino mesylate (**2**) which, on treatment with sodium acetate, smoothly cyclised to (3*S*,5*S*)-quinuclidine-3,5-diol (**1**), sublimes above 190 °C, $[\alpha]_D^{20}$ −17.4° (*c*, 0.31 in H_2O), in 79% yield [42% overall yield from (**4**); 17% overall yield from arabinose]. In comparison with the *meso*-quinuclidinediol reported in the accompanying paper[12] the ^1H n.m.r. spectrum of (**1**) was highly complex and the ^{13}C n.m.r. spectrum (D_2O) of (**1**) showed seven non-equivalent carbons: δ_C 17.0 (t, C-8), 34.8 (d, C-4), 45.6 (t, C-7), 55.4 and 56.3 (2 × t, C-2 and C-6), and 62.6 and 68.1 (d, C-3 and C-5).

The formation of a piperidine ring between the nitrogen of the side chain in (**4**) and C-5 of the sugar may be achieved by removal of the silyl protecting group with fluoride ion and subsequent mesylation to afford the azidomesylate (**8**), m.p. 78–79.5 °C, $[\alpha]_D^{20}$ +7.9° (*c*, 0.76 in $CHCl_3$) (94% yield). Hydrogenation of the azide (**8**) formed the corresponding amine which cyclised in the presence of sodium acetate to give,



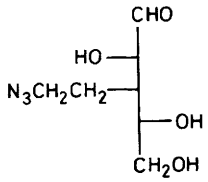
(5)



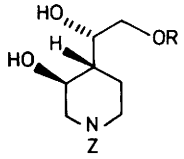
(6) R = [Si]; X = CO_2Me

(7) R = [Si]; X = CH_2N_3

(8) R = Ms; X = CH_2N_3

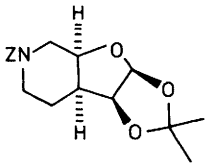


(9)

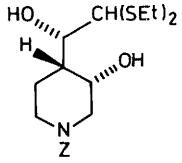


(10) R = H

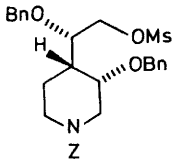
(11) R = Ms



(12)



(13)



(14)

Z = CO_2CH_2Ph

Bn = CH_2Ph

Ms = SO_2Me

[Si] = $SiPh_2Bu^t$

after protection of the amino function with benzyl chloroformate, the protected bicyclic carbamate (**12**), oil, $[\alpha]_D^{20}$ +19.3° (*c*, 0.8 in $CHCl_3$), in 96% yield [86% overall yield from (**4**)]. Treatment of (**12**) with ethanethiol in aqueous trifluoroacetic acid gave the dithioacetal (**13**), m.p. 89–90 °C, $[\alpha]_D^{20}$ −35.9° (*c*, 0.57 in $CHCl_3$) (89% yield). Sequential dibenzylation, mercuric chloride catalysed hydrolysis, sodium borohydride reduction, and mesylation of (**13**) gave the mesylate (**14**), a fully protected equivalent of the amino mesylate (**3**), in 56% overall yield. Selective hydrogenolysis of the carbamate protecting group in (**14**) followed by acetate-induced cyclisation of the resulting amine gave the 3,5-di-*O*-benzyl ether of quinuclidinediol (**1**), oil, $[\alpha]_D^{20}$ −15.7° (*c*, 0.5 in $CHCl_3$), in 78% yield. Hydrogenolytic removal of the benzyl protecting groups gave the quinuclidinediol (**1**), identical with that prepared above, in 98% yield [36% overall yield from (**4**); 15% overall yield from arabinose].

In summary, this paper reports the synthesis of (3*S*,5*S*)-quinuclidine-3,5-diol (**1**) from D-arabinose; since L-arabinose is also readily available, these procedures also provide access to derivatives of (3*R*,5*R*)-quinuclidine-3,5-diol.

Acknowledgements

A Fleming Fellowship from M.E.C./British Council (to J. A. S.), a Fellowship from Xunta de Galicia (to M. P. V. T.), and a C.A.S.E. postgraduate studentship to (C. J. M.) in support of this work are gratefully acknowledged.

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Received 28*th November* 1988; *Paper* 8/04690E