Complex Quinuclidines (1-Azabicyclo[2.2.2]octanes) from Sugars: Synthesis of (1α,3α,4α,5α)-Quinuclidine-3,5-diol from D-Glucose

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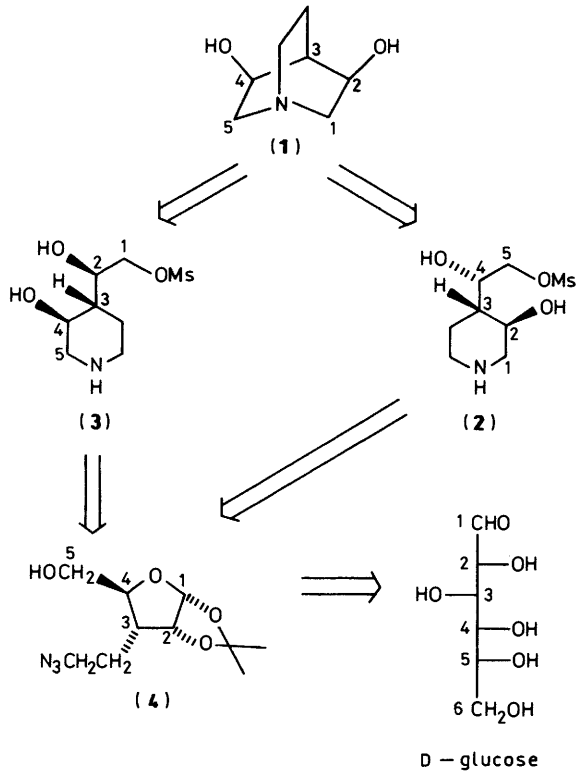
The synthesis of (1α,3α,4α,5α)-quinuclidine-3,5-diol from D-glucose by two alternative ring closures is described.

Few strategies have been delineated for the stereocontrolled synthesis of multisubstituted quinuclidines.[1] However, recently two alternative approaches to the enantiospecific synthesis of chiral quinuclidines from sugars have been exemplified in the synthesis of (*S*)-quinuclidin-3-ol from glucose.[2,3] The potential of sugars for the synthesis of complex quinuclidines is further illustrated in this paper by the synthesis of the *meso*-quinuclidinediol (**1**) from glucose; the accompanying paper reports the synthesis of a chiral quinuclidine diol from arabinose.[4]

The azido alcohol (**4**) is a key divergent intermediate for the synthesis of the *meso*-quinuclidinediol (**1**) from D-glucose. Formation of a piperidine ring by closure of the amine derived from the azide onto C-1 of the sugar allows the development of a suitably protected derivative of the amino mesylate (**2**) from



which the second six-membered ring may be formed by intramolecular displacement of mesylate by nitrogen. Alternatively, the first piperidine ring may be obtained by closing the nitrogen function onto C-5 of the sugar, leading to a protected derivative of (**3**) which is the enantiomer of the amino mesylate (**2**).

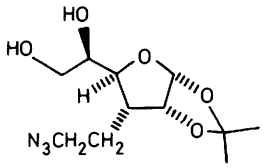
The synthesis of (**4**) from glucose requires the introduction of a two carbon chain with a terminal nitrogen function at C-3 of glucose, followed by degradation of the sugar to remove C-6. Diacetone glucose (1,2;5,6-di-isopropylidene-D-glucose) was converted in six steps as previously described[3] into the azido diol (**5**) in an overall yield of 68%. Oxidation of (**5**) with sodium periodate, followed by reduction of the resulting aldehyde with sodium borohydride in ethanol gave the azido alcohol (**4**),* m.p. 59—62 °C, $[\alpha]_D^{20}$ +85.3° (*c*, 1.0 in $CHCl_3$), in 85% yield. Thus 20 g amounts of the easily crystallised compound (**4**) may readily be prepared from diacetone glucose in an overall yield of 58%.

The piperidine mesylate (**2**) was prepared by a sequence leading to closure of an azide-derived amine onto C-1 of the sugar. Hydrolysis of the acetonide (**4**) with 50% aqueous trifluoroacetic acid gave 3-(2-azidoethyl)-3-deoxy-D-ribose (**6**) as a mixture of lactols (86% yield); hydrogenation of (**6**) in aqueous methanol in the presence of 10% palladium on carbon at 50 °C and 250 p.s.i. caused intramolecular reductive amination to give, after protection of the amino function *via* benzyl chloroformate, the carbamate (**7**), $[\alpha]_D^{20}$ −2.1° (*c*, 1.0 in $CHCl_3$), in 62% yield. Selective esterification of the primary hydroxy group in the triol (**7**) by methanesulphonyl chloride in pyridine at −30 °C gave the primary mesylate (**8**), $[\alpha]_D^{20}$ +8.5° (*c*, 1.0 in $CHCl_3$) in 61% yield. Hydrogenation of (**8**) gave the amino mesylate (**2**); however, treatment of (**2**) with sodium acetate gave intramolecular cyclisation by a hydroxy group—rather than by the piperidine nitrogen—to give a tetrahydrofuran. Accordingly, compound (**2**) was converted into the bis-silyl ether (**9**) by treatment with t-butyldimethylsilyl trifluoromethanesulphonate in the presence of 2,6-lutidine (86% yield). Removal of the benzyloxycarbonyl protecting group by hydrogenolysis of (**9**) in the presence of palladium black, followed by cyclisation catalysed by sodium acetate, afforded the quinuclidine bis-silyl ether (**10**), m.p. 64—66 °C, $[\alpha]_D^{20}$ zero (*c*, 1.0 in $CHCl_3$), in 88% yield. Removal of the silyl protecting groups with aqueous trifluoroacetic acid gave (1α,3α,4α,5α)-quinuclidine-3,5-diol (**1**), which sublimes above 205 °C, $[\alpha]_D^{20}$ zero (*c*, 0.5 in H_2O), in 64% yield [17% overall yield from (**4**)]. The ^1H n.m.r. spectrum (D_2O) of (**1**)† is very much simpler than that of the chiral quinuclidine-3,5-diol reported in the accompanying paper and ^{13}C n.m.r. spectrum (D_2O) of (**1**) shows only five non-equivalent carbons: δ_C 9.1 (t, C-8), 33.3 (d, C-4), 44.3 (t, C-7), 52.7 (t, C-2 and C-6), and 63.5 (d, C-3 and C-5).

The alternative synthesis of compound (**1**) from the azido alcohol (**4**) involves initial closure of the nitrogen function onto

* Satisfactory microanalytical and spectral data have been obtained for all new compounds reported in this paper.

† δ_H 1.58 (m, 2 H, 8-H and 8′-H), 1.87 (quin., 1 H, 4-H, *J* 3.1 Hz), 2.27 (m, 2 H, 2-H and 6-H), 2.64 (m, 2 H, 7-H and 7′-H), 2.82 (m, 2 H, 2′-H and 6′-H), and 3.78 (m, 2 H, 3-H and 5-H).



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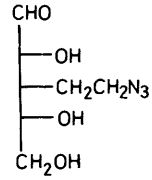

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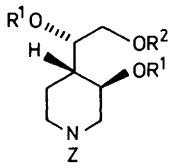
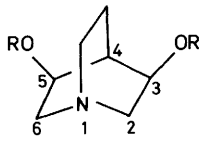
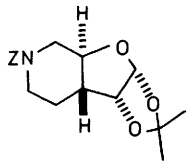


(7) $R^1 = R^2 = H$
(8) $R^1 = H; R^2 = Ms$
(9) $R^1 = [Si]; R^2 = Ms$



(1) R = H
(10) R = [Si]
(11) R = Bn



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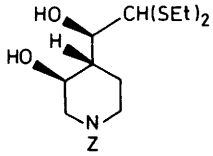

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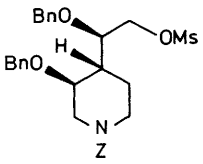

(14)

Ms = SO_2Me
Z = CO_2CH_2Ph
[Si] = $SiBu^tMe_2$
Bn = CH_2Ph

C-5 of the sugar. Esterification of the primary hydroxy function in (**4**) with methanesulphonyl chloride gave the corresponding azidomesylate (83% yield) which on hydrogenation in ethanol in the presence of 10% palladium on carbon, followed by sodium acetate-catalysed cyclisation and subsequent reaction with benzyl chloroformate, afforded the fully protected piperidine (**12**), m.p. 79—81 °C (lit.,[3] 79—81 °C), (66% yield) which with ethanethiol in aqueous trifluoroacetic acid gave the dithioacetal (**13**), m.p. 104—105 °C, $[\alpha]_D^{20}$ −48° (*c*, 1.0 in $CHCl_3$) (92% yield). Sequential dibenzylation, mercuric chloride-catalysed hydrolysis, sodium borohydride reduction, and mesylation gave the mesylate (**14**) in 52% overall yield. Selective hydrogenolysis of the carbamate protecting group in (**14**) in the presence of palladium black in ethanol followed by cyclisation of the resulting amino mesylate in the presence of sodium acetate gave the dibenzylquinuclidine (**11**) in 64% yield. Subsequent hydrogenolysis of the dibenzyl ether (**11**) in the presence of palladium black in acetic acid gave the *meso*-quinuclidienediol (**1**), identical with the diol (**1**), prepared above, in 81% yield [14% overall yield from (**4**)].

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3 G. W. J. Fleet, K. James, R. J. Lunn, and C. J. Mathews, *Tetrahedron Lett.*, 1986, **27**, 3057.
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