Synthesis of α-Linked 3′-Deoxy-cyclitol and -aminocyclitol Glycosides

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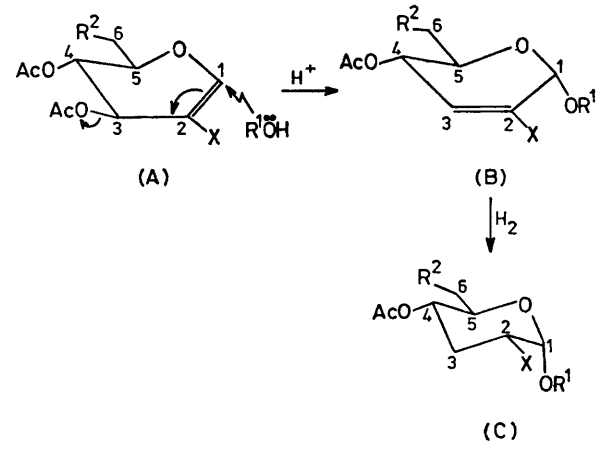
Summary Unsaturated and saturated α-linked cyclitol and aminocyclitol glycosides have been prepared by a boron trifluoride–ether catalysed addition reaction of (**3**) and (**4**) to the appropriately functionalised cyclitol derivatives (**2**), followed by regiospecific hydrogenation from the β face; the structure and conformation of all products have been proved by ^1H and ^{13}C n.m.r. spectroscopy and chemical ionisation mass spectrometry.

THE aminoglycoside antibiotics are effective chemotherapeutic agents,[1–4] particularly against gram-negative bacteria.[4–7] Regrettably they have unwanted toxic side effects and can be subject to enzymatic inactivation.[4–6] There is consequently widespread interest in the synthesis of analogues with improved properties.[6–8] It is essential that any synthetic approach produces α glycosidic linkages with high stereospecificity. The method described here not only fulfils this requirement, but in addition simultaneously yields deoxygenated products at the C-3′ position, a feature that is necessary for the avoidance of a major pathway of enzymatic inactivation and also for enhanced biological activity.[4–7]

The Scheme sets out the basic two-step reaction sequence. The pivotal first step is a 'quasi S_N2' reaction: an acid



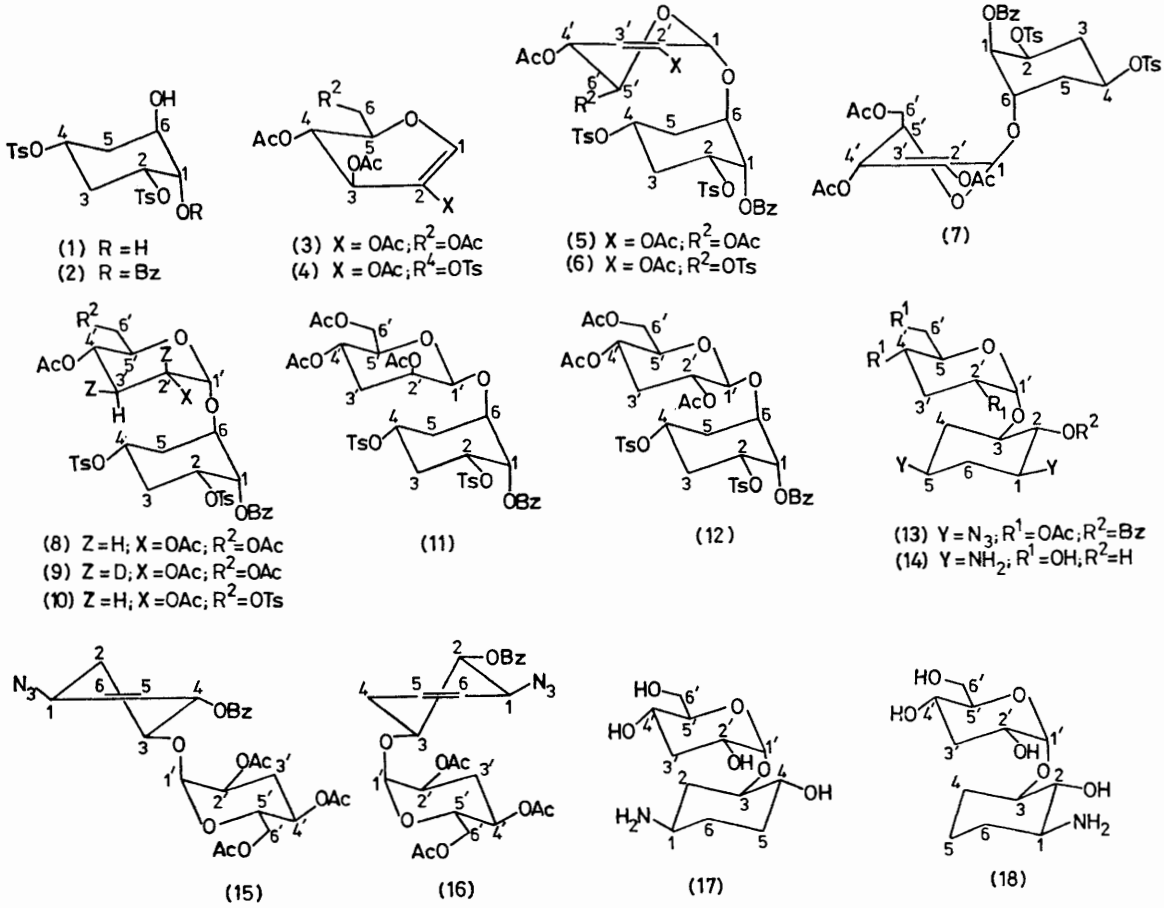
SCHEME

catalysed addition of the 2-substituted glycals (A) to an alcohol. If product (B) could be reduced with high regiospecificity from the β face, the resultant compound (C) would be a 3-deoxy α-glycoside, having the natural D-*ribo*-configuration. Concerted displacement with rearrangement in allylic cyclo-hexenyl[9,10] and cyclic vinyl ether

systems[11,12] (glycals) has been extensively studied. The group R in the Scheme needs to be a suitably protected amino-cyclitol unit, or some easily modified precursor of such a molecule.

The chiral L-2,4-di-*O*-toluene-*p*-sulphonyl-1,2,4/6-cyclohexanetetraol (**1**) described[13] recently by us is such a precursor, particularly since we have subsequently demonstrated that it can be selectively substituted at either hydroxy-group. Thus the reaction of (**1**) with benzoyl chloride in the presence of imidazole gave the benzoyl compound (**2**), m.p. 173—174 °C, $[\alpha]_D$ + 5·5° (*c* 1·6; $CHCl_3$), in 90% yield.

The α-glycoside (**5**) was regiospecifically hydrogenated or deuteriated in quantitative yield using 10% palladium on carbon in ethyl acetate in the presence of a trace of glacial acetic acid to compound (**8**), m.p. 162—163 °C $[\alpha]_D$ + 44° (*c* 1·5; $CHCl_3$) (^{1}H n.m.r.: $J_{1'-2'}$ 5 Hz), and the dideuteriocompound (**9**) (^{1}H n.m.r.: $J_{3'-4'}$ 10 Hz) respectively. The reduction occurred exclusively from the β face of the α-glycoside (**5**). There was no evidence for the formation of the D-*arabino* isomer. In contrast, catalytic reduction of the β-glycoside (**7**), using 10% palladium on carbon in glacial acetic acid, proceeded sluggishly, yielding two products in poor yield which were characterised as com-



Addition of compound (**3**)[11] to a dichloroethane solution of (**2**) (1 equiv.) containing a catalytic amount of boron trifluoride–ether at −20 °C, over 15 min, followed by warming to −15 °C for another 2 h, gave a mixture of two products in 94% yield. The major component (**5**) (82%), m.p. 174—175 °C $[\alpha]_D$ + 34° (*c* 1·1; $CHCl_3$) (^{1}H n.m.r.: $J_{1'-3'}$ 0·5, $J_{4'-5'}$ 9 Hz), was isolated by a single crystallisation from alcohol. The minor product (**7**), m.p. 64—65 °C, $[\alpha]_D$ + 24° (*c* 1·1, $CHCl_3$), was formed in 12% yield (^{1}H n.m.r.: $J_{1'-3'}$ 0·6, $J_{4'-5'}$ 4·5 Hz).

pounds (**11**) (30%), m.p. 60—61 °C, $[\alpha]_D$ −15° (*c* 1·5; $CHCl_3$) (^{1}H n.m.r.: $J_{1'-2'}$ 1·5 Hz), and (**12**) (18%), m.p. 55—57 °C, $[\alpha]_D$ − 5° (*c* 0·8; $CHCl_3$) (^{1}H n.m.r.: $J_{1'-2'}$ 9 Hz). In addition some hydrogenolysed products were also formed which were not examined.

Similarly, the reaction of (**2**) with the toluene-*p*-sulphonyl compound (**4**)[14] under similar conditions gave compound (**6**) (84%), m.p. 153—154 °C, $[\alpha]_D$ + 36° (*c* 1; $CHCl_3$). On catalytic reduction, compound (**6**) furnished compound (**10**) (83%), m.p. 85—86 °C, $[\alpha]_D$ + 36° (*c* 2; $CHCl_3$).

Azidolysis of (**8**), using sodium azide in *NN*-dimethylformamide at 110 °C over 2 h gave a mixture of three products in 81% yield which were separated by silica gel chromatography. The major component (51%) was identified as (**13**), $[\alpha]_D$ + 8° (*c* 2; $CHCl_3$). The two minor components (**15**) (19%) (^{1}H n.m.r.: J_{4-5} 4, J_{4-6} 2, J_{4-3} 8 Hz) and (**16**) (11%) (^{1}H n.m.r.: J_{1-2} 8, J_{2-3} 10 Hz) arose by elimination of toluene-*p*-sulphonic acid in (**8**) from C-2 and C-3, and C-4 and C-3, respectively.

De-esterification of (**13**), (**15**), and (**16**) followed by reduction in the presence of PtO_2 in methanol–water (1 : 1) gave compounds (**14**), $[\alpha]_D$ − 58·6° (*c* 1·55; H_2O), $(M + H)^+$ *m/e* 293; (**17**), $[\alpha]_D$ +21° (*c* 1·27; H_2O), $(M + H)^+$ *m/* 278); and (**18**), $[\alpha]_D$ + 29° (*c* 0·85; H_2O), $(M + H)^+$ *m/e* 278.

The method summarised in the Scheme provides a substantial step forward in approaches to the total synthesis of amino-glycoside antibiotics. Work is in progress utilising compounds of the general type (A), which have a variety of functional groups (X) at C-2, and also have a group (R′) at the C-6 position that allows modification of the final product (C).

We are indebted to Professor R. D. Guthrie for stimulating discussions. Financial assistance from Institut National de la Santé et de la Recherche Médicale (I.N.S.E.R.M.) is gratefully acknowledged.

(*Received*, 1*st June* 1978; *Com.* 574.)

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