Synthesis of 3-Amino-2,3-dideoxy-α-D-*arabino*-hexopyranosyl Gentamine C_1

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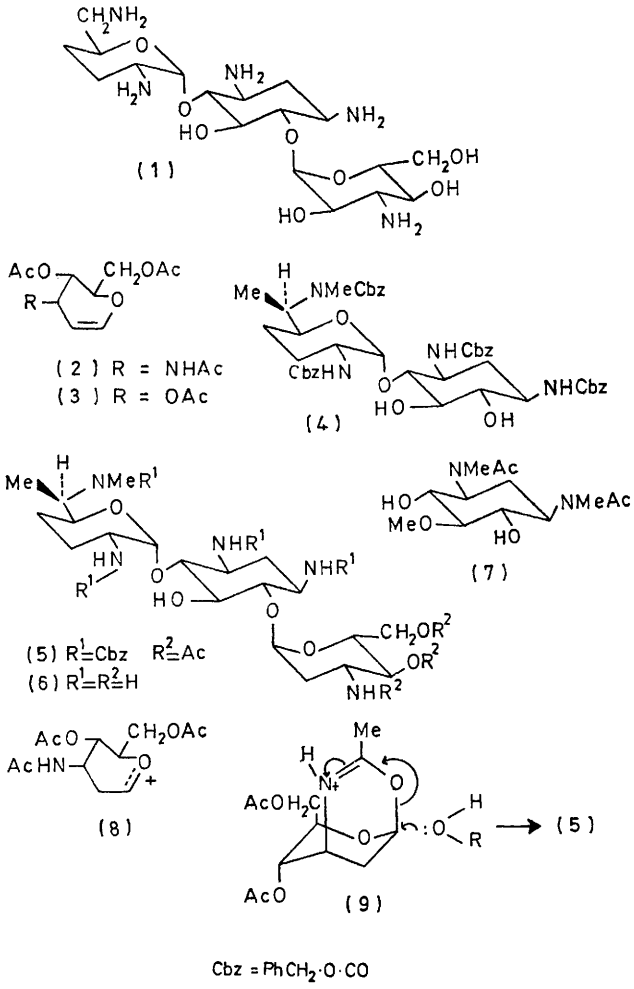
Summary Acid catalysed addition of 3-acetamido-3-deoxy-4,6-di-*O*-acetyl-D-glucal (**2**) to the relatively complex pseudodisaccharide (**4**) resulted in regio- and stereoselective formation of the 2-deoxy-α-glycoside (**5**).

IMPORTANT recent trends in aminoglycoside chemistry have focused on a synthetic modification, or elimination of sites within the antibiotic molecule which have been shown to be targets for inactivation by enzymes present in resistant organisms. A number of such modifications have recently been remarkably successful.[1] The discovery that antibiotics of the kanamycin–gentamicin class, *e.g.* 3′,4′-dideoxykanamycin B (**1**), can be inactivated by adenylylation at the 2″-position by certain resistant bacteria[2] has made the efficient synthesis of 3-amino-2,3-dideoxy-α-glycopyranosides of particular importance. The acid catalysed condensation of an alcohol with the glucal[3] (**2**) provides such a method.

The acid catalysed addition of alcohols to glycals to afford 2-deoxyglycosides is well known. This reaction, however, has usually required a large excess of the alcohol to be condensed and has suffered from the further limitation that accompanying allylic rearrangements occur when the substituent at C-3 is an acetoxy-group as, for example, in the case of tri-*O*-acetyl-D-glucal[4] (**3**). Yields from such reactions have consequently been typically low. It was reasoned, however, that compound (**2**), having a poorer leaving group at the 3-position should undergo addition of alcohols without rearrangement and this was proved to be the case. Condensation of tetra-*N*-benzyloxycarbonylgentamine C_1 (**4**) (2·2 equiv.), prepared by standard methods from the free amine,[5] with the glucal (**2**) (4·0 equiv.) in the presence of toluene-*p*-sulphonic acid hydrate (0·27 equiv.) in dry benzene at 45—50° for 36 h gave (**5**) (88%) together with some unchanged glycal. Removal of the benzyloxycarbonyl and acetate groups was effected with sodium in liquid ammonia, followed by dilute aqueous alkali, to give, after chromatography, 3-amino-2,3-dideoxy-α-D-*arabino*-hexopyranoside (**6**), $[\alpha]_D$ + 101·5° (*c* 0·4, H_2O), in 48% overall yield from (**4**). Although two hydroxy-groups are in principal available for condensation in compound (**4**), reaction takes place only at the least hindered site. This was demonstrated by an *N*-acetylation, permethylation, and hydrolysis sequence[6] which gave symmetrical *N*,*N*′-diacetyl-2-deoxy-*N*,*N*′-5-*O*-trimethylstreptamine (**7**), m.p.



221—223°, identical with authentic material, as the sole product. The ^{1}H n.m.r. spectrum of (**6**) showed two doublets, a somewhat broadened signal at δ 5·11 (*J* 3·5 Hz), and a sharper absorption at δ 5·05 (*J* 3·5 Hz), which could be assigned to the anomeric H_1'' and H_1' protons, respectively, of the two α-glycosides. All other ^{1}H n.m.r. signals could be assigned in accordance with structure (**6**). Irradiation of the 2″-methylene protons at δ 1·6 resulted in collapse of the doublet at δ 5·11 into a singlet. The fragmentation pattern in the mass spectrum of (**6**) was consistent with the assigned structure and fitted well into the pattern observed for related compounds.[7] The ^{13}C n.m.r. spectrum of (**6**) was also consistent with the assigned structure.

Compound (**5**) was the only product of the condensation reaction. The reaction was therefore cleanly regio- and stereo-selective. Such high yielding, stereoselective, α-glycoside syntheses from alcohols as complex as (**4**) are relatively rare. The exclusive formation of the α-anomer may reflect simply the stereoelectronic requirements in addition of the alcohol to a cationic intermediate such as (**8**). Alternatively the reaction may proceed *via* the protonated bicyclic intermediate (**9**) in which participation of the 3-acetamido-group would dictate exclusive α-glycoside formation. A similar bicyclic intermediate has recently been proposed to account for reactions of another 3-acetamido sugar.[8] Experiments are in progress to clarify the mechanism of this reaction.

The 2″-deoxyaminoglycoside (**6**) was essentially inactive as an antibacterial which was surprising in view of the interesting antibacterial activity found for the related 2″-deoxygentamicin C_2.[9]

During the progress of this work a report appeared describing the acid catalysed addition of heterocyclic bases to the related glycal (**2**; R = $NHCOOC_2H_5$),[10] which afforded nucleoside analogues in high yields without rearrangement.

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