Synthesis of α-Linked 3′-Deoxy-pseudo-di- and -tri-saccharides Related to Aminocyclitol-glycoside Antibiotics

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Summary The syntheses of the title compounds, precursors of all types of modified aminocyclitol glycoside antibiotics substituted at position 4 or positions 4 and 5 of the aminocyclitol aglycone, are reported.

CHEMOTHERAPY employing aminoglycoside antibiotics is known to be hampered by dose-related toxic side effects[1] and can be subject to enzymatic inactivation.[2] In consequence there is intense current interest in natural or synthetic sources of related compounds having improved therapeutic indices.

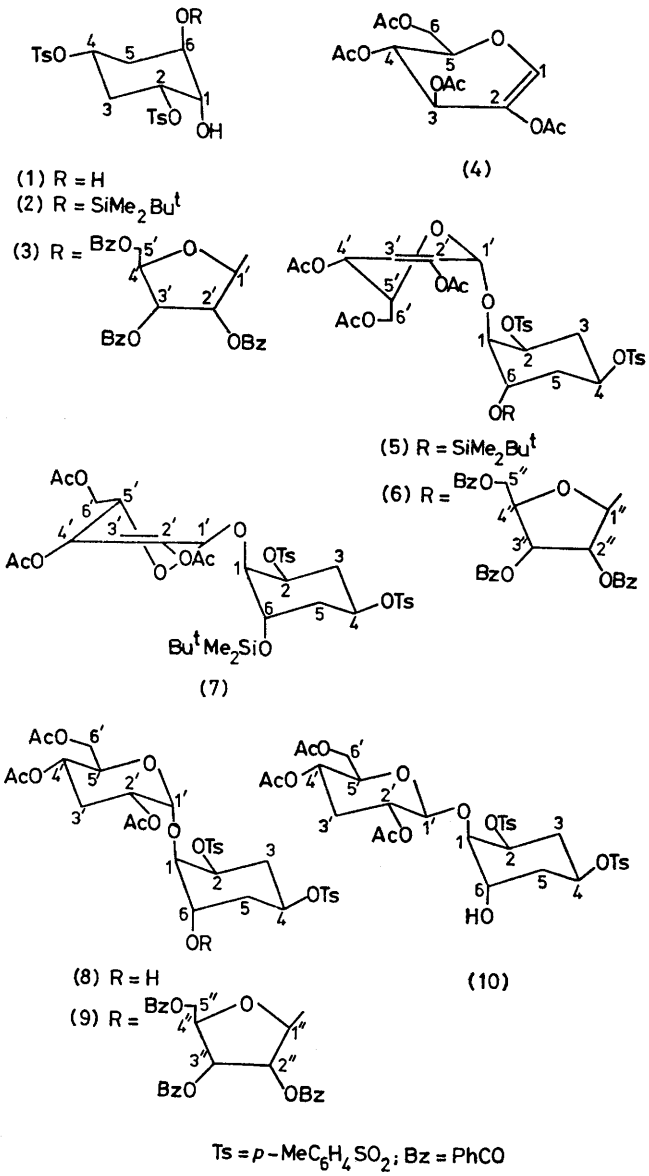
We described in the preceding communication[3] an acid-catalysed addition of 2-substituted glycal derivatives to a suitably protected cyclitol unit, leading to α-linked 3′-deoxy-cyclitol and -aminocyclitol glycosides. Here we report, using the same approach, the synthesis of a variety of 3′-deoxy-pseudo-disaccharides and -pseudo-trisaccharides. In essence, these repeating units are precursors of all types of modified antibiotics substituted at position 4 or positions 4 and 5 of the aminocyclitol nucleus.

Compounds (**2**) and (**3**), readily available from (**1**)[4] by selective silylation and D-ribosylation at C-6, were used as starting materials.

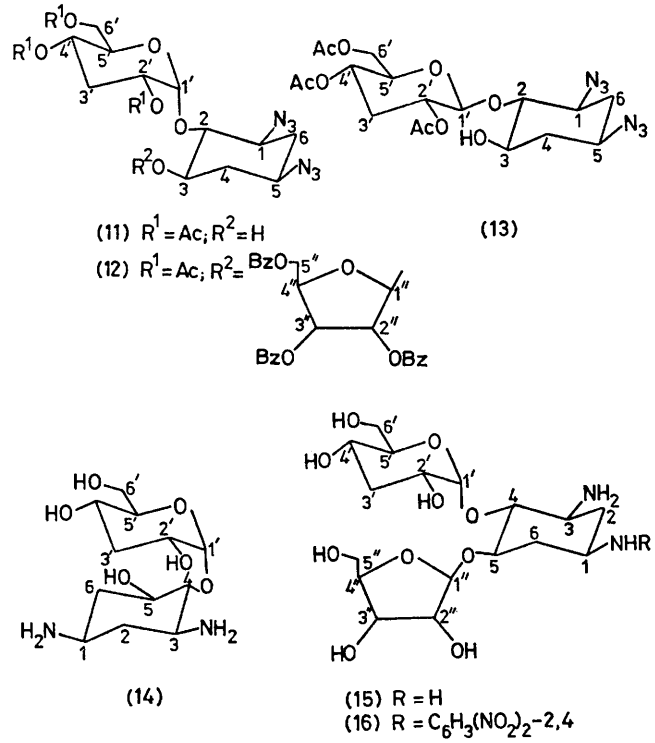
Thus, reaction of (**1**) with t-butyldimethylsilyl chloride in *NN*-dimethylformamide in the presence of imidazole furnished (**2**), m.p. 153—154 °C, $[\alpha]_D$ + 21° (*c* 1·2; $CHCl_3$), in 82% yield, whilst condensation of (**1**) with 2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl chloride in dry chloroform in the presence of mercury(II) bromide and a molecular sieve (4 Å) under reflux over 8 h afforded (**3**) as the major product (56%), m.p. 70—71 °C, $[\alpha]_D$ + 21° (*c* 1·8; $CHCl_3$).

Addition of compound (**4**) to a dichloroethane solution of (**2**) (1 equiv.) containing a catalytic amount of boron

trifluoride–ether at −20 °C, over 20 min, followed by warming to −15 °C for another 2 h furnished two products in 95% yield, having elemental analyses, and ^{1}H and ^{13}C n.m.r. spectra corresponding to a mixture (ratio 70:30) of the stereoisomers (**5**) and (**7**) which could not be separated;



in situ catalytic reduction and desilylation of this mixture by treatment with tetra-n-butylammonium fluoride in tetrahydrofuran gave the required crystalline compounds (**8**), m.p. 71—72 °C, $[\alpha]_D$ + 55·3° (*c* 1·5; $CHCl_3$), and the syrupy β-glycoside (**10**) $[\alpha]_D$ + 30° (*c* 1·4; $CHCl_3$). Azidolysis of the glycosides (**8**) and (**10**) yielded the oily (**11**) (64%), $[\alpha]_D$ + 89° (*c* 0·9; $CHCl_3$), and the crystalline (**13**) (62%), m.p. 139—141 °C, $[\alpha]_D$ − 16° (*c* 1; $CHCl_3$). Catalytic reduction of (**11**) followed by de-acetylation gave compound (**14**) in 85% yield, $[\alpha]_D$ + 27·5° (*c* 1·7; H_2O), $(M + H)^+$ *m/e* 293.



The method was similarly used successfully for the synthesis of a pseudo-trisaccharide. Thus, reaction of the pseudo-disaccharide (**3**) (1 equiv.) and the glycal (**4**) (1·1 equiv.) afforded the crystalline compound (**6**) in 58% yield, m.p. 178—180 °C, $[\alpha]_D$ + 38° (*c* 0·66; $CHCl_3$).

Regiospecific catalytic hydrogenation of (**6**) gave the crystalline compound (**9**) in 85% yield, m.p. 163—165 °C, $[\alpha]_D$ + 30° (*c* 2·2; $CHCl_3$). Azidolysis of the trisaccharide (**9**) gave the crystalline compound (**12**) in 58% yield, m.p. 55—56 °C, $[\alpha]_D$ + 51° (*c* 0·9; $CHCl_3$). Compound (**12**) was sequentially de-*O*-acylated and catalytically hydrogenated, furnishing (**15**), m.p. 204—206 °C, $[\alpha]_D$ + 35° (*c* 0·9; H_2O), which was readily converted into its mono-*N*-2,4-dinitrophenyl derivative (**16**), m.p. 161—162 °C, $[\alpha]_D$ + 136° (*c* 0·6; MeOH).

The compounds described herein all gave ^{1}H and ^{13}C n.m.r. and chemical ionisation mass spectra consistent with the assigned structures.

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[1] A. P. Panwalker, J. B. Malow, V. M. Zimelis, and G. G. Jackson, *Antimicrob. Agents Chemother.*, 1978, **13**, 170.
[2] K. E. Price, J. C. Godfrey, and H. Kawaguchi, 'Structure–Activity Relationships among the Semisynthetic Antibiotics,' ed. D. Perlman, Academic Press, New York, San Francisco, and London, 1977, pp. 239 and 357 (supplement).
[3] J. Cléophax, Do Khac Duc, J. M. Delaumény, S. D. Géro, A. Rolland, and C. Merienne, preceding communication.
[4] J. Cléophax, S. D. Géro, J. Leboul, M. Akhtar, J. E. G. Barnett, and C. J. Pearce, *J. Amer. Chem. Soc.*, 1976, **98**, 7110.