A New Route to 4-*epi*-L-Daunosamine containing Disaccharides

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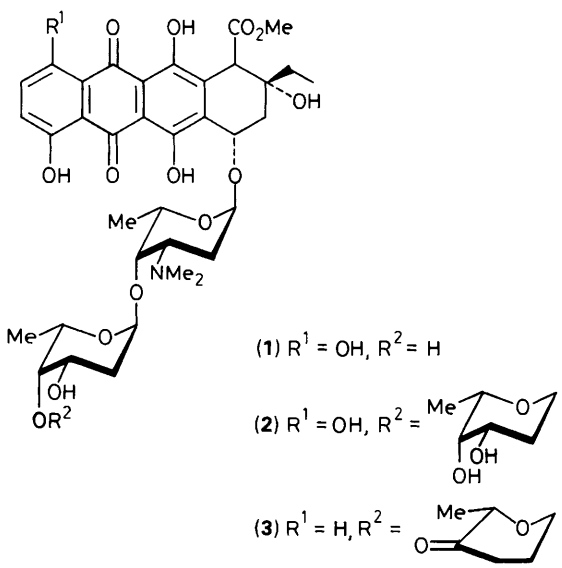
The methyl 4-*O*-(2,6-dideoxy-2-iodo-α-L-mannopyranosyl)-α-L-acosaminide (**11**) and the methyl 4-*O*-(2,6-dideoxy-α-L-arabinopyranosyl)-α-L-acosaminide analogue (**12**) have been stereoselectively synthesized in seven and eight steps, respectively, from di-*O*-acetyl-L-rhamnal (**4**) and methyl 2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (**5**); the key step involved a 1,4-addition of hydrazoic acid to a corresponding hex-2-enopyranose.

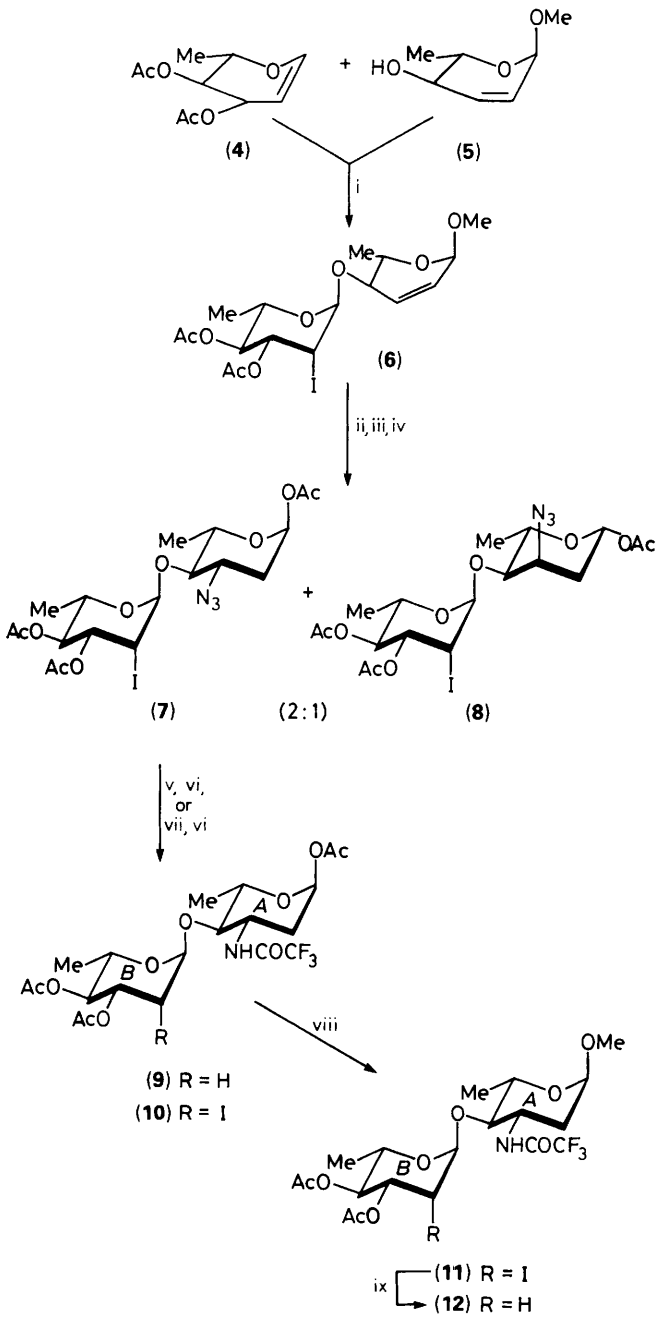
Polydeoxygenated di- or tri-saccharides which contain 3-dimethylamino-2,3,6-trideoxy-L-*lyxo*-hexose (or L-rhodosamine) as a reductive unit occur naturally in several anthracycline antibiotics such as musettamycin (**1**),[1] marcellomycin (**2**),[2] and aclacinomycin (**3**).[2] The total synthesis of these oligosaccharides has been achieved recently in our laboratory[3] as well as the synthesis of 4'-*epi*-L-rhodosamine containing disaccharide.[4]

On the other hand, two years ago, we reported[5] that 3-amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranoside (or methyl-α-L-acosaminide) can be synthesized stereoselectively after transformation of di-*O*-acetyl-L-rhamnal into the corresponding pseudo-glucal followed by a 1,4-addition of HN_3 to this α,β-unsaturated aldehyde equivalent, as the key step.

Advantage of this strategy was taken for the synthesis of analogues of the oligosaccharide moieties present in anthracyclines (**1**)—(**3**). This method avoids the need for the synthesis of the fully functionalized and totally protected unit *A*, prior to the elaboration of the interglycosidic bond.

As depicted in Scheme 1, condensation of 3,4-di-*O*-acetyl-α-L-*arabino*-hex-1-enitol (or di-*O*-acetyl-L-rhamnal) (**4**)[6] with methyl 2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (**5**) in the presence of *N*-iodosuccinimide[7] afforded, after flash chromatography (hexane–EtOAc, 4:1), the 2'-iodo-disaccharide (**6**) {syrup, $[\alpha]_D^{20}$ −126° (*c* 1, $CHCl_3$)} in 64% yield. Acid hydrolysis of (**6**) under mild conditions (AcOH–H_2O, 4:3, 72 h, room temp.) was followed by addition of HN_3 to the crude mixture and stirring for 36 h at room temperature. After





Scheme 1. *Reagents and conditions*: i, *N*-iodosuccinimide, MeCN; ii, AcOH–H_2O; iii, NaN_3; iv, Ac_2O; v, H_2, Pd–C (10%), Et_3N; vi, $(CF_3CO)_2O$, CH_2Cl_2; vii, Ph_3P–H_2O; viii, TMSOTf, MeOH, −78 °C; ix, Bu_3SnH, AIBN, benzene.

conventional acetylation, disaccharides (**7**)† {m.p. 112 °C (CH_2Cl_2);‡ $[\alpha]_D^{20}$ −94° (*c* 1, $CHCl_3$)} and (**8**) {m.p. 58 °C (CH_2Cl_2); $[\alpha]_D^{20}$ −30° (*c* 1, $CHCl_3$)} were separated by column chromatography in 42 and 21% overall yields from (**6**), respectively.

Catalytic hydrogenation of (**7**) (Pd–charcoal 10%, Et_3N, EtOAc, 15 min) followed by *N*-trifluoroacetylation gave the disaccharide (**9**) {55%, syrup; $[\alpha]_D^{20}$ −12° (*c* 1, $CHCl_3$)} whereas the corresponding 2′-iodo-disaccharide (**10**) {m.p. 215—216° (hexane–acetone); $[\alpha]_D^{20}$ −84° (*c*1, $CHCl_3$)} was obtained in 50% overall yield by reduction of the azide function of (**9**) under modified Staudinger conditions[8] (Ph_3P–H_2O–THF) (THF = tetrahydrofuran) followed by *N*-trifluoroacetylation of the amino-derivative. Moreover, glycosidation of (**10**) with methanol in the presence of trimethylsilyltrifluoromethanesulphonate (TMSOTf) afforded stereospecifically the methyl-α-L-glycoside (**11**) {syrup; $[\alpha]_D^{20}$ −54° (*c* 1, $CHCl_3$)} in 75% yield.

Obtention of the valuable intermediate 2′-iodo-disaccharide (**10**), ready to be glycosylated, is of great interest since the presence of iodine at C-2′ enhances the stabilization of the interglycosidic bond. This avoids the usual problems of transglycosidation generally observed[9,10] during the coupling of the corresponding 2′-deoxy disaccharides. For example, an attempt to glycosylate compound (**9**) under the same conditions as used with (**10**) (MeOH, TMSOTf) led to a complex mixture of four compounds which were not analysed in detail.

Although the C–I bond can be removed easily after glycosidation as shown by radical transformation [Bu_3SnH, azoisobutyronitrile (AIBN), benzene, reflux] of (**11**) into (**12**) {syrup, $[\alpha]_D^{20}$ −81° (*c*1, $CHCl_3$)}, the 2″-iodo anthracycline derivatives are also worthy of antitumor evaluation if we keep in mind the results reported with other 2′-iodo-monosaccharide glycosides.[11]

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† Selected ^1H NMR data ($CDCl_3$) for (**7**): δ 6.09 (dd, 1-H), 5.41 (d, 1′-H), 5.08 (t, 4′-H), 4.62 (dd, 2′-H), 4.51 (dd, 3′-H), 4.05—3.70 (m, 3-H, 5-H, 5′-H), 3.12 (dd, 4-H), 2.22 (dd, 2e-H), 1.86 (m, 2a-H), 2.13, 2.10, 2.05 (3s, 3 OAc), 1.30, 1.25 (2d, 2 Me); for (**8**): δ 6.00 (dd, 1-H), 5.30 (d, 1′-H), 5.14 (t, 4′-H), 4.62 (dd, 2′-H), 4.54 (dd, 3′-H), 4.20 (m, 3-H), 4.12 and 4.00 (2 qd, 5-H and 5′-H), 3.62 (dd, 4-H), 2.09, 2.06 (2s, 3 OAc), 1.87 (m, 2a-H), 1.34, 1.23 (2d, 2 Me); for (**11**): δ 6.61 (d, NH), 5.25 (d, 1-′H), 5.18 (d, 1-H), 5.05 (t, 4′-H), 4.66 (dd, 2′-H), 4.46 (dd, 3′-H), 4.20 (m 3-H), 3.95, 3.74 (2 qd, 5-H and 5′-H), 3.36 (t, 4-H), 3.29 (s, OMe), 2.02, 2.00 (2s, 2 OAc), 1.28, 1.20 (2d, 2 Me); for (**12**): δ 6.50 (d, NH), 5.12 (m, 3′-H), 5.04 (dd, 1′-H), 4.72 (t, 4′-H), 4.72 (d, 1-H), 4.29 (m, 3-H), 3.92, 3.79 (2 qd, 5-H, 5′-H), 3.39 (t, 4-H), 3.34 (s, OMe), 2.17—1.75 (m, CH_2, CH_2'), 1.33, 1.17 (2d, 2 Me).

‡ Characterization data, including microanalyses, mass spectra, and ^1H NMR are in excellent agreement with the proposed structures for the new compounds.

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