Stereocontrolled Route to 3-Amino-2,3,6-trideoxy-hexopyranoses. K-10 Montmorillonite as a Glycosidation Reagent for Acosaminide Synthesis

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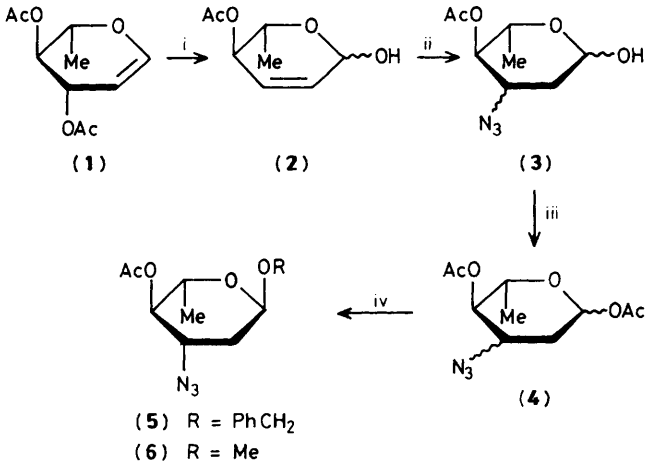
A stereoselective synthesis of methyl (or benzyl) 3-azido-2,3,6-trideoxy-α-L-*arabino*-hexopyranoside from di-*O*-acetyl-L-rhamnal is reported; it proceeds *via* addition of hydrazoic acid to a hex-2-enopyranose, followed by acetylation and glycosidation with the appropriate alcohol, in the presence of K-10 montmorillonite as catalyst.

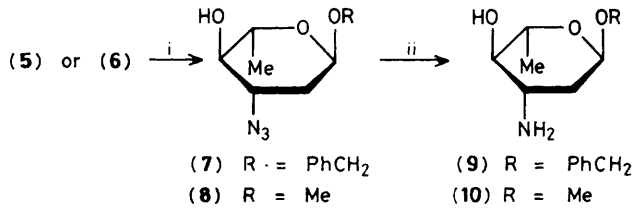
L-Acosamine (3-amino-2,3,6-trideoxy-L-*arabino*-hexopyranose) is the amino sugar component of the vancomycin-type antibiotic, actinoidin.[1] Biological studies on semi-synthetic anthracycline antibiotic analogues have shown that the replacement of L-daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexopyranose) by its L-*arabino* isomer (L-acosamine) leads to second generation drugs, 4′-*epi*-daunorubicin and 4′-*epi*-doxorubicin,[2] which display significant antitumour activity and lower toxicity than the parent compounds. The great interest in L-acosamine results also from the fact that it has often been used as an intermediate in the synthesis of L-daunosamine.[3]

Literature data have shown that conjugate addition of HN_3 in acetic acid and water, at room temperature, to an α,β-unsaturated carbonyl system such as hex-3-enopyranosid-2-ulose[4] or hex-2-enopyranosid-4-ulose[5] gives stereoselectively, under conditions of thermodynamic control, products having the azido group equatorially oriented. However, to our knowledge there are no examples of 1,4-addition to hex-2-enopyranoses, although these can be formally considered as α,β-unsaturated aldehydes and could provide under thermodynamic control 3-azido sugars of L-*arabino* configuration. Therefore addition of HN_3 to 4-*O*-acetyl-6-deoxy-L-*erythro*-hex-2-enopyranose (**2**) was attempted.

To this end, 1,5-anhydro-3,4-di-*O*-acetyl-L-*arabino*-hex-1-enitol (di-*O*-acetyl-L-rhamnal) (**1**) was first converted in 80% yield into the hex-2-enopyranose (**2**) by simple heating in the presence of water.[6] Treatment of (**2**) with sodium azide in



Scheme 1. *Reagents:* i, H_2O, 80 °C, 2 h; ii, H_2O, AcOH, NaN_3, 24 h; iii, CH_2Cl_2, C_5H_5N, Ac_2O, 18 h; iv, ROH, K_{10} montmorillonite, reflux, 24 h.



Scheme 2. *Reagents:* i, NaOMe, MeOH; ii, Et_3N, EtOH, Pd/C

glacial acetic acid and water with stirring for 24 h gave (**3**) in 95% yield. Moreover, when these two reactions were performed without isolation of the intermediate (**2**), the overall yield was increased from 76 to 90%. Conventional acetylation of (**3**) with pyridine–acetic anhydride led quantitatively to the 1-*O*-acetyl hexose (**4**).†

In the 2,6-dideoxy-hexose series, we have previously reported that glycosidation of 1-*O*-acetyl-3-trifluoroacetamido or 1,3-di-*O*-acetyl derivatives with alcohols[7] or daunomycinone[8] can be performed in the presence of toluene-*p*-sulphonic acid as catalyst. On the other hand, a recent publication[9] has shown that tetrahydropyranylation of alcohols or phenols can be achieved cleanly by K-10 montmorillonite, an inexpensive catalyst. Moreover, since the reaction conditions are extremely mild and the work-up involves only filtration before evaporation of the solvent, use of this catalyst rather than *p*-$MeC_6H_4SO_3H$ was attempted to effect glycosidation of the 1-*O*-acetyl hexoses (**4**). Thus, (**4**) was refluxed in anhydrous benzene in the presence of K-10 montmorillonite and of an excess of alcohol (*ca.* 10—20 mol. equiv.) ($PhCH_2OH$ or MeOH). This led stereoselectively, after 24 h, to the benzyl acosamide (**5**) (syrup, $[\alpha]_D^{20}$ −10°) or to the methyl acosamide (**6**) (syrup, $[\alpha]_D^{20}$ −171°), easily isolated by column chromatography (hexane–EtOAc 5:1 and 8:1, respectively) as less polar and major components respectively (44 and 48% yields). Further elution afforded successively the corresponding β-L-*ribo* (8%, syrup, $[\alpha]_D^{20}$ −19°), β-L-*arabino* (1%, syrup, $[\alpha]_D^{20}$ +70°), and α-L-*ribo* (3.5%, $[\alpha]_D^{20}$ −186°) isomers in the case of the benzyl glycosides; in the case of the methyl glycosides, although the corresponding β-L-*ribo* product (10%, $[\alpha]_D^{20}$ −41°) could be isolated, the azido sugars of β-L-*arabino* and α-L-*ribo* configuration (overall yield *ca.* 6%) could not be separated.

Transformation of the 4-*O*-acetyl-3-azido-2,3,6-trideoxy-α-L-*arabino*-hexopyranosides (**5**) or (**6**) into the corresponding benzyl acosaminide (**9**) (m.p. 114—115 °C; $[\alpha]_D$ −108° (*c* 1 in MeOH) or methyl acosaminide (**10**)[10b,c,e,f] was achieved in nearly quantitative yield in two steps by transesterification with MeONa–MeOH, giving (**7**) (syrup, $[\alpha]_D^{20}$ −99°) or (**8**),[10] followed by catalytic hydrogenation in MeOH and in the presence of 10% palladium–charcoal and triethylamine.

In conclusion, this new and highly stereoselective route affords benzyl or methyl acosaminide in five steps from di-*O*-acetyl-L-rhamnal (35% overall yield). Since methyl acosaminide has been previously transformed[10a] into the corresponding methyl daunosaminide, this also formally constitutes a new route to daunosamine.

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† Except for compounds (**3**) and (**4**), obtained as a mixture of α- and β-L-*ribo* and *arabino* isomers, characterisation data, including microanalyses, mass spectra and ^1H n.m.r., are in excellent agreement with the proposed structures for new compounds. Values of $[\alpha]_D^{20}$ were measured in chloroform solution (*c* 1), except where indicated.

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