

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

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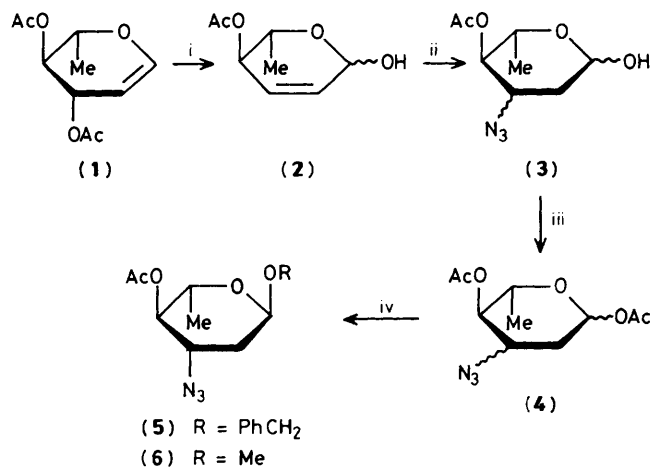
A stereoselective synthesis of methyl (or benzyl) 3-azido-2,3,6-trideoxy- α -L-arabino-hexopyranoside from di-O-acetyl-L-rhamnal is reported; it proceeds *via* addition of hydrazoic acid to a hex-2-enopyranose, followed by acetylation and glycosidation with the appropriate alcohol, in the presence of 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 HN₃ in acetic acid and water, at room temperature, to an

α,β -unsaturated carbonyl system such as hex-3-enopyranosid-2-ulose⁴ or hex-2-enopyranosid-4-ulose⁵ 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 HN₃ 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

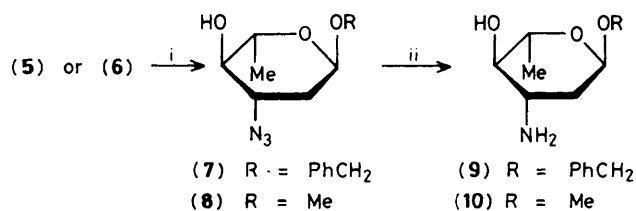


Scheme 1. Reagents: i, H₂O, 80 °C, 2 h; ii, H₂O, AcOH, NaN₃, 24 h; iii, CH₂Cl₂, C₅H₅N, Ac₂O, 18 h; iv, ROH, K₁₀ montmorillonite, reflux, 24 h.

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 alcohols⁷ or daunosynone⁸ can be performed in the presence of toluene-*p*-sulphonic acid as catalyst. On the other hand, a recent publication⁹ 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*-MeC₆H₄SO₃H 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.) (PhCH₂OH or MeOH). This led stereoselectively, after 24 h, to the benzyl acosamide (5) (syrup, [α]_D²⁰ –10°) or to the methyl acosamide (6) (syrup, [α]_D²⁰ –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, [α]_D²⁰ –19°), β-L-arabino (1%, syrup, [α]_D²⁰ +70°), and α-L-ribo (3.5%, [α]_D²⁰ –186°) isomers in the case of the benzyl glycosides; in the case of the methyl glycosides, although the corresponding β-L-ribo pro-

† 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 [α]_D²⁰ were measured in chloroform solution (*c* 1), except where indicated.



Scheme 2. Reagents: i, NaOMe, MeOH; ii, Et₃N, EtOH, Pd/C

duct (10%, [α]_D²⁰ –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; [α]_D²⁰ –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, [α]_D²⁰ –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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