A Short, Efficient Route to a Protected Daunosamine from L-Rhamnose†

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The imidate ester obtained from the reaction of methyl 2,3,6-trideoxy-α-L-*threo*-hex-2-enopyranoside with trichloroacetonitrile undergoes iodonium ion-induced cyclisation, and the dihydroxazole product is subjected to reductive dehalogenation to give a protected form of daunosamine.

Daunosamine (**1a**) is an essential component of the chemically important antitumour anthracycline antibiotics, and not surprisingly, its synthesis has been the focus of considerable recent attention.[1] The need for optically active material has been met by the transformation of amino acids,[1a] and more accessible sugars.[2] The last approach is hampered by the presence of the *cis* vicinal hydroxy-amino component which is traditionally problematic, usually requiring many more

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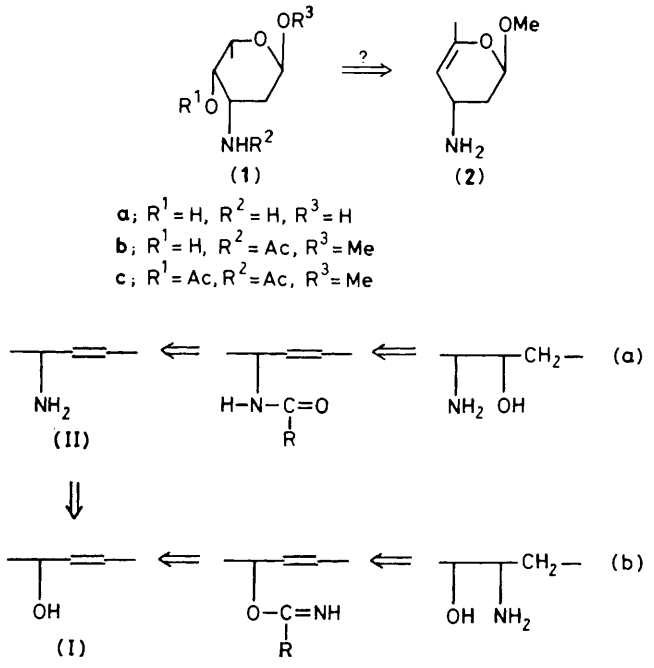


Scheme 1

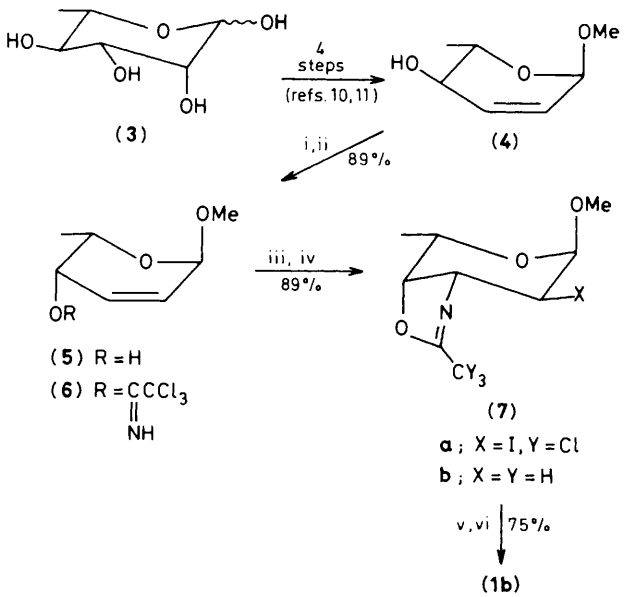
'additional steps' than the corresponding *trans* counterpart.[3] However, the cost of naturally-occurring L-rhamnose, (**3**) a plausible precursor for (**1**), precludes the application of these 'additional steps'. As a result, a synthesis of (**1a**), beginning with D-mannose has been developed even though the generic change, D→L, alone requires three steps.[2] Here we outline a short route from L-rhamnose to (**1**).

Scheme 1, equation (a) shows the use of an allylic amine (II) as a fulcrum for introducing the vicinal oxygen, and is the key process in our recent syntheses of garosamine,[4] holacosamine,[5] and 4-epi-sibirosamine.[6] Application of this method to daunosamine would require the currently unknown hex-4-enopyranoside (**2**).

Here we report the synthesis of daunosamine *via* the complementary plan shown in equation (b), Scheme 1, in which an allylic alcohol (I) is the fulcrum for introducing the vicinal nitrogen. This is achieved by the iodocyclization of an imidate ester.§ Thus, methyl *N*-acetyl-α-L-daunosaminide (**1b**) was obtained in six steps from a known compound.

The alcohol (**4**)[9] [available from L-rhamnose (**3**) *via* the Ferrier reaction[10] of di-*O*-acetyl-L-rhamnal[11]] was epimerised by means of the Mitsunobo reaction,[12] and the resulting benzoate gave (**5**) in 89% overall yield. The trichloromethyl imidate ester (**6**), prepared by modification of the method of Overman,[13] was chosen because of the highly nucleophilic nitrogen atom.[7] Iodonium ion-induced cyclization[14] of (**6**) was comparatively slow, requiring 3—5 days at room temperature, before the product (**7a**) was obtained (89% yield for the two steps). Exhaustive dehalogenation proceeded smoothly by use of excess of tri-n-butyltin hydride, and the resulting crude dihydroxazole (**7b**) was hydrolysed to the known acetamide (**1b**) in 75% overall yield: m.p. 179—180 °C, $[\alpha]_D^{20}$ −220° (MeOH); lit.[15] m.p. 176—178 °C, $[\alpha]_D^{20}$ −230° (MeOH). For the diacetate (**1c**): m.p. 186—187 °C, $[\alpha]_D^{20}$ −208° ($CHCl_3$); lit.[13] m.p. 188—189 °C, $[\alpha]_D^{20}$ −202° ($CHCl_3$).

§ This reaction was recently introduced by us in a synthesis of ristosamine, (ref. 7) and independently by Cardillo *et al.* who have examined acyclic systems as potential precursors for amino sugars (ref. 8).



Scheme 2. i, Ph_3P, diethyl azodicarboxylate, $PhCO_2H$, tetrahydrofuran (dry), 0 °C, 1.5 h. ii, NaOMe, MeOH, room temp., 18 h. iii, NaH, Cl_3CCN, CH_2Cl_2, 0 °C → room temp., 3 h. iv, I(2,4,6-trimethylpyridine)$_2ClO_4$ (3 equiv.), dry MeCN, room temp., 3—5 days. v, tri-n-butyltin hydride (5 equiv.), benzene (reflux), azobisisobutyronitrile, *ca.* 3 h. vi, Me-*p*-$C_6H_4SO_2OH$ in pyridine–H_2O, 4 : 1, 100 °C, 2.5 h.

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