A New Route to (±)-Daunosamine and Related Amino-sugars

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1-(2-Furyl)ethanol has been converted into (±)-daunosamine by use of a modified Mitsunobu reaction.

Several syntheses of the important amino-sugar, daunosamine, have been described, starting from both carbohydrate precursors[1] and non-sugar substrates.[2] Many of these routes are lengthy and proceed in low overall yields. One of the most efficient was reported by Hauser *et al.*[2f] and requires nine steps, commencing with penta-1,3-diene, producing a 10% overall yield of *N*-benzoyl-L-daunosamine.

Herein we describe an eight-step process which proceeds in overall yields of greater than 30%.

Preparation of the methyl acetal (**3**) from 1-(2-furyl)ethanol (**1**) was achieved by known methods in overall 74% yield. Thus bromination in methanol gave the dimethoxy derivative (**2**)[3] which could be converted into the acetal (**3**) using methanol with formic acid as catalyst.[4] ^{1}H N.m.r. analysis of the initial acetal product indicated a 3 : 1 mixture of the α- and β-anomers; these could either be separated by column chromatography before further reaction or be used as a mixture.

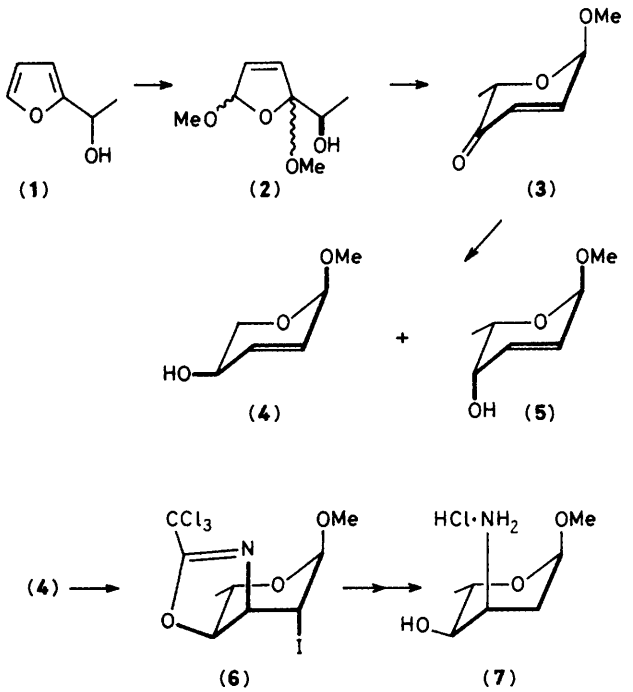
Reduction of the ketone group in the pyranulose (**3**) with sodium borohydride afforded, in high yield, a 9 : 1 mixture of the two alcohols (**4**) and (**5**). Although attempts to improve the ratio of alcohols formed, to give solely either isomer, have so far failed, the two alcohols are readily separated by silica gel column chromatography to give the pure major alcohol (**4**).

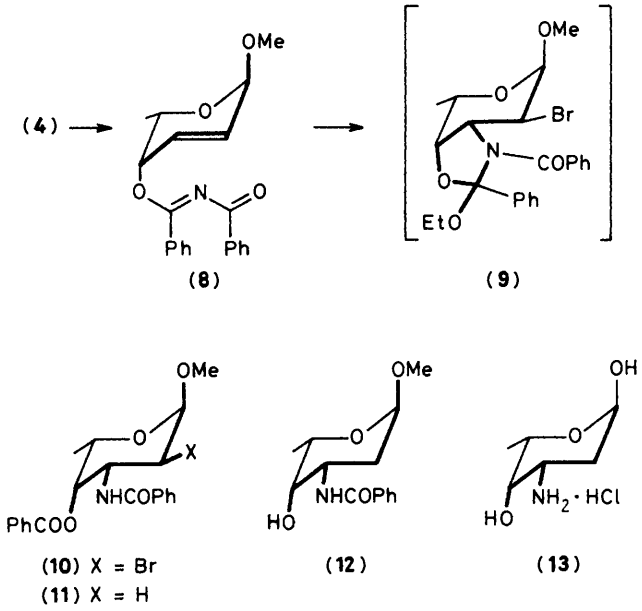
Conversion of the alcohol (**4**) into the ristosamine derivative (**7**) was achieved by a method similar to that which was described by Fraser-Reid *et al.*[1g] after this part of our work had been carried out. Thus, reaction of the alcohol (**4**), first with trichloroacetonitrile and then *N*-iodosuccinimide, afforded the cyclic imidate (**6**). Reduction with tributyltin hydride, followed by hydrolysis with 5 M-sodium hydroxide, gave (±)-ristosamine methyl ether, isolated as the hydrochloride (**7**).

In order to obtain the daunosamine series of derivatives one has either to use the minor alcohol (**5**) or to effect an inversion about the C(OH) centre of the major alcohol (**4**). Previous workers[1g] have chosen the latter course, for example, using triphenylphosphine–diethyl azodicarboxylate reagent in the presence of benzoic acid, in order to obtain the epimeric benzoate ester, followed by hydrolysis to the required epimeric alcohol (**5**) which was then further processed in a manner similar to that described above for the ristosamine derivatives.[1g]

It was argued that a more direct route would involve a modified Mitsunobu reaction,[5] using a nucleophile that would generate an imidate species directly. Thus, the alcohol (**4**) was treated with triphenylphosphine and diethyl azodicarboxylate in the presence of dibenzoylimide, a reagent known to attack preferentially *via* an oxygen atom.[6] The product, isolated in 93% yield, was the required imidate (**8**), m.p. 87—90 °C.†

Careful reaction of the imidate (**8**) with *N*-bromosuccinimide in chloroform containing ethanol produced the ortho-amide (**9**), which was readily hydrolysed *in situ*, under acidic conditions, to give the benzoate–amide (**10**), m.p. 212—214 °C, in 86% yield. Removal of the bromine by tributyltin hydride reduction and base-catalysed hydrolysis of the ester (**11**), m.p. 182—183 °C, gave the amide (**12**), m.p. 171—172 °C. The overall yield from the alcohol (**1**) to the *N*-benzoyl-(±)-daunosamine (**12**) was 38%. Acid hydrolysis of the benzamide (**12**) produced daunosamine (41%), isolated as its hydrochloride (**13**), m.p. 148—150 °C. Since it is known





† All new compounds gave satisfactory microanalytical and spectroscopic data.

that the enantioselective reduction of 2-furyl methyl ketone can produce pure enantiomers of the alcohol (**1**)[7] and that oxidation of the alcohol (**1**) to give the pyranulose (**3**) can be effected with very little epimerisation,[8] the route can also be adapted to produce optically active material.

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