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Preliminary communication

Synthesis of 7-[3-amino-2,3,6-trideoxy-4-*O*-(2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)-α-L-*lyxo*-hexopyranosyl]daunomycinone

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This paper deals with the synthesis of an anthracycline analog having a class I anthracycline[1] aglycon, namely, daunomycinone[2], and a class II sugar moiety[3], namely, the disaccharide 4-*O*-(2,6-dideoxy-L-*lyxo*-hexopyranosyl)-L-daunosamine. The rationale for preparing such an analog is to impart to a member of class I anthracyclines, daunorubicin[4], some of the better characteristics inherent in class II anthracyclines, namely, lessened cardiotoxicity[5].

Attempts to prepare a disaccharide glycoside of an anthracyclinone by treating the natural anthracycline with a glycosyl halide have invariably resulted in transglycosylation, and formation of a new monosaccharide glycoside of the anthracyclinone[6]. It was, therefore, decided to prepare first the needed oligosaccharide and then combine it with the anthracyclinone. We have previously described a daunosamine-containing disaccharide[6] having a terminal daunosamine residue attached to a deoxy sugar. However, if this disaccharide were linked to an anthracyclinone, the daunosamine would be separated from the aglycon by a deoxy sugar residue.

As this is an unnatural sequence in class II anthracyclines, an attempt was made to synthesize a disaccharide glycoside of daunomycinone having the natural sequence of monosaccharides, found in a class II anthracycline[3], namely 2,6-dideoxy-L-*lyxo*-hexose, linked to the daunosamine. To prepare this, we first synthesized methyl 2,3,6-trideoxy-4-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyso*-hexopyranosyl)-3-(trifluoroacetamido)-β-L-*lyxo*-hexofuranoside (**4**) by treating, for 24 h at room temperature, 2-deoxy-L-*lyxo*-hexopyranosyl chloride (**1**) with methyl *N*-(trifluoroacetyl)-β-L-daunosaminide (**2**) in dichloromethane in the presence of mercuric bromide, yellow mercuric oxide, and 4A molecular sieves. The desired disaccharide (**4**) was obtained in 35% yield after chromatography on silica gel with 1:2 ethyl acetate–hexane, m.p. 155–157°, $[\alpha]_D$ −123° (chloroform).

Attempts to convert disaccharide **4** into a glycosyl halide, either directly or *via* acetolysis, resulted in degradation, and formation of monosaccharide derivatives. It was, therefore, decided to alter the synthesis, and to use, as the starting material, a benzyl glycoside of daunosamine, instead of a methyl glycoside, so that the benzyl group could

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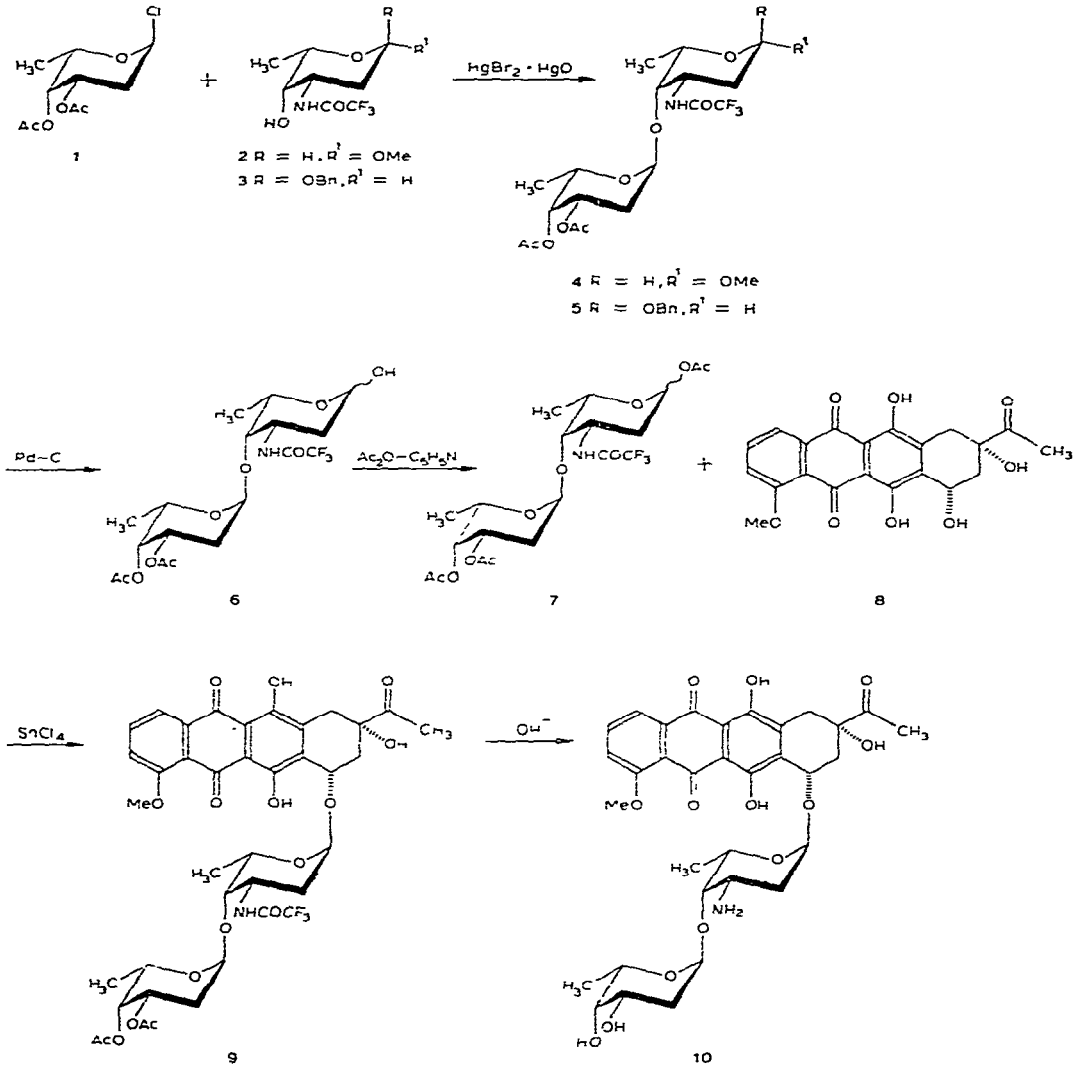
be readily removed from the disaccharide by hydrogenolysis, without affecting the interglycosidic bond.

1,4-Di-*O*-acetyl-*N*-(trifluoroacetyl)-L-daunosamine[7] was accordingly treated with bromotrimethylsilane[8] in 1,2-dichloroethane at 0°, to yield 4-*O*-acetyl-*N*-(trifluoroacetyl)-L-daunosaminyl bromide, which reacted with an excess of benzyl alcohol in the presence of mercuric bromide, yellow mercuric oxide, and powdered 4A molecular sieves for 15 min at 0°, and 2 h at room temperature, to give, after chromatography on silica gel with 1:1 hexane–ether, anomerically pure, crystalline benzyl 4-*O*-acetyl-3-(trifluoroacetyl)-α-L-daunosamide, m.p. 140–144°, $[\alpha]_D$ −179° (chloroform) in 82% yield. This was treated with sodium methoxide in dry methanol to remove the acetyl group attached to O-4, and gave, quantitatively, compound 3, which was treated with 1 under the Koenigs–Knorr conditions in the presence of mercuric bromide, yellow mercuric oxide, and finely powdered 4A molecular sieves. The reaction was complete in 30 min, and, after chromatography on silica gel with 1:2 ethyl acetate–hexane, the desired disaccharide (5) was obtained as a colorless syrup, $[\alpha]_D$ −209° (chloroform) in 72% yield.

The higher yield of this benzyl disaccharide, compared to that for the methyl disaccharide (4) described earlier, was probably due to its less-hindered, 4-hydroxyl group, which is *trans* to the benzyl group on O-1, whereas, in the methyl glycoside 4, the arrangement is *cis* between the 4-OH group and the OMe group attached to C-1. The benzyl disaccharide 5 was hydrogenolyzed in ethanol, with 10% palladium-on-charcoal, at 70 lb. in.$^{-2}$, to remove the benzyl group. The reaction was stopped when 10–20% of the starting material remained unreacted. At that time, there began to form a by-product that appeared as a fast-moving spot in t.l.c. The debenzylated disaccharide (6) was obtained as a syrup, $[\alpha]_D$ −207° (chloroform), in 78% yield after chromatography on silica gel with 40:1 dichloromethane–methanol. Compound 6 was treated with acetic anhydride in pyridine at 0°, to give, quantitatively, the per-*O*-acetylated disaccharide (7) as a syrupy, anomeric mixture, $[\alpha]_D$ −206° (chloroform).

Coupling of disaccharide 7 with daunomycinone (8) presented some difficulties. Thus, for example, attempts to prepare a glycosyl bromide from the disaccharide 7 using bromotrimethylsilane[8] as the brominating agent resulted in splitting of the interglycosidic bond. It was, therefore, decided to use the acetylated disaccharide (7) directly for coupling in the presence of a Lewis catalyst. In our laboratory, we had been able to cause maltose octaacetate to react with ε-rhodimycinone, in the presence of boron trifluoride etherate, in good yield, but, in view of the labile nature of disaccharide 7, an even milder Lewis acid was now used, namely, tin tetrachloride. One equivalent each of the per-*O*-acetylated disaccharide (7) and daunomycinone (8) were dissolved in dry benzene. All traces of moisture were removed by distilling off the benzene; the residue was dissolved in dichloromethane, and powdered 4A molecular sieves and tin tetrachloride (0.2 equiv.) were added. After stirring for 45 min at room temperature, t.l.c. showed that ~50% of the daunomycinone had reacted. Prolongation of the reaction time did not increase the yield of the glycoside, but, instead, caused aromatization of the daunomycinone. The reaction was quenched with triethylamine, the suspension filtered,



the filtrate evaporated, and the residue chromatographed on a column of silica gel with 50:1 dichloromethane–methanol, affording the blocked disaccharide glycoside (**9**) of daunomycinone as a red precipitate, $[\alpha]_D$ +73.8° (chloroform); yield 57%. The desired disaccharide, namely, 7-[3-amino-2,3,6-trideoxy-4-*O*-(2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)-α-L-*lyxo*-hexopyranosyl]daunomycinone (**10**), was obtained in quantitative yield by treating compound **9** with 0.1M NaOH in oxolane for 7 h at 0°, neutralizing the base with 0.1M citric acid, washing a chloroform solution of the product with saturated sodium hydrogencarbonate, and evaporating. The desired product (**10**) was isolated as a red powder.

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