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## Note

# Synthesis of methyl 2,3,6-trideoxy-4-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)-3-(trifluoroacetamido)-β-L-*lyxo*-hexopyranoside

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Several anthracycline antibiotics exist in the form of oligosaccharide glycosides, and these have been extensively studied in the rhodomycin series[1] and in the cinerubin series[2]. It is also known that, during fermentation of the antineoplastic anthracyclines, some minor antibiotics are produced in the form of oligosaccharide glycosides; these are difficult to separate, and are usually partially hydrolyzed to the monosaccharide glycoside stage and then recombined with the main, antibiotic fraction. No detailed study of the activity of oligosaccharide glycosides of adriamycinone, daunomycinone, and carminomycinone has been made. This prompted us to essay the synthesis of some of these compounds. Because attempts to prepare the oligosaccharide glycosides of anthracyclinones by allowing the natural anthracyclines to react with glycosyl halides invariably resulted in transglycosylation, and formation of a new monosaccharide glycoside of the anthracyclinone, we decided to prepare the oligosaccharides first, and then combine these with the desired anthracyclinones.

In a previous publication[3], we described the synthesis of a benzyl 2,3-dideoxy-4-*O*-[*N*-(trifluoroacetyl)daunosaminyl]-D-*glycero*-pentopyranoside. This disaccharide has a terminal, daunosamine residue, which would be separated from an anthracyclinone by a deoxy sugar, whereas, in the rhodomycin and cinerubin series, the *N,N*-dimethyl derivative of daunosamine is directly attached to the anthracyclinone.

We now describe the synthesis of a disaccharide having daunosamine and 2-deoxy-L-fucose in the sequence found naturally in rhodomycins, namely, methyl 2,3,6-trideoxy-4-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)-3-(trifluoroacetamido)-β-L-*lyxo*-hexopyranoside (**3**).

The starting material for the synthesis was 2-deoxy-L-fucopyranosyl chloride[4] (**1**), which was treated with methyl β-L-daunosaminide *N*-trifluoroacetate[5] (**2**) (a sugar that has only one unprotected position through which it can be linked, namely, O-4) in the presence of mercuric bromide and yellow mercuric oxide, to afford the desired disaccharide (**3**) in 35% yield. Compound **3** was accompanied by some di-*O*-

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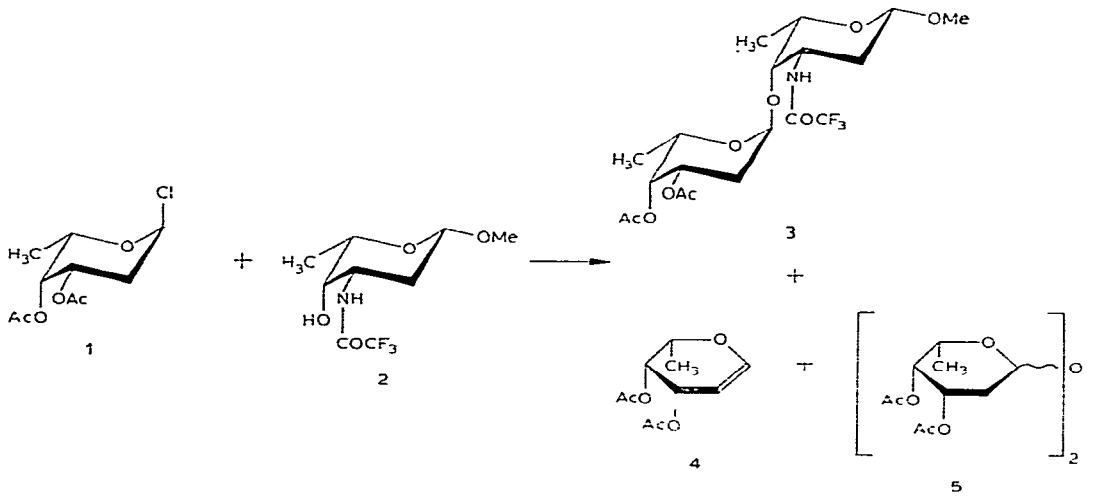

acetyl-L-fucal (**4**), formed by elimination of H-2 from the L-fucopyranosyl chloride. In addition a disaccharide, di-*O*-acetyl-2-deoxy-L-fucopyranosyl di-*O*-acetyl-2-deoxy-L-fucopyranoside (**5**), was isolated in small yield. The structure of disaccharide **3** was confirmed by n.m.r. spectroscopy and mass spectrometry. The n.m.r. spectrum showed signals that could be unequivocally assigned to each of the monosaccharide moieties. Thus, the daunosamine residue showed, at $\delta$ 3.56, a singlet assigned to the methoxyl group on C-1 and a deuteratable N-H proton at $\delta$ 8.48. The 2-deoxy-L-fucopyranosyl group exhibited two *O*-acetyl groups, at $\delta$ 2.01 and 2.18. The C-6-containing methyl groups of the daunosamine residue and the 2-deoxy-L-fucosyl

TABLE I

N.M.R. SPECTRAL DATA FOR THE DISACCHARIDE **3**

| $\delta$ (*p.p.m.*)[a] | | | | | | | |
|---|---|---|---|---|---|---|---|
| *H-1* | *H-2*a,2e | *H-3* | *H-4* | *H-5* | *H-6,6'* | *NH* | *OMe* |
| 4.51(dd) | 1.44–2.34 | 4.0 -(broad m)- | | 3.70(m) | 1.32(d) | 8.84(d) | 3.56 |
| $J_{1,2a}$ 8.5<br>$J_{1,2e}$ 2.1 | | | | $J_{5',6'}$ 6.4 | | $J_{3,NH}$ 8.5 | |
| *H-1'* | *H-2'*a,2'e | *H-3'* | *H-4'* | *H-5'* | *H-6',6"* | *OAc* | |
| 5.09(m) | 1.44–2.34 | 5.5(m) | 5.27(m) | 4.35(m)<br>$J_{5',6'}$ 6.8 | 1.16(d) | 2.01 and 2.18 | |

[a]Key: d, doublet; m, multiplet.

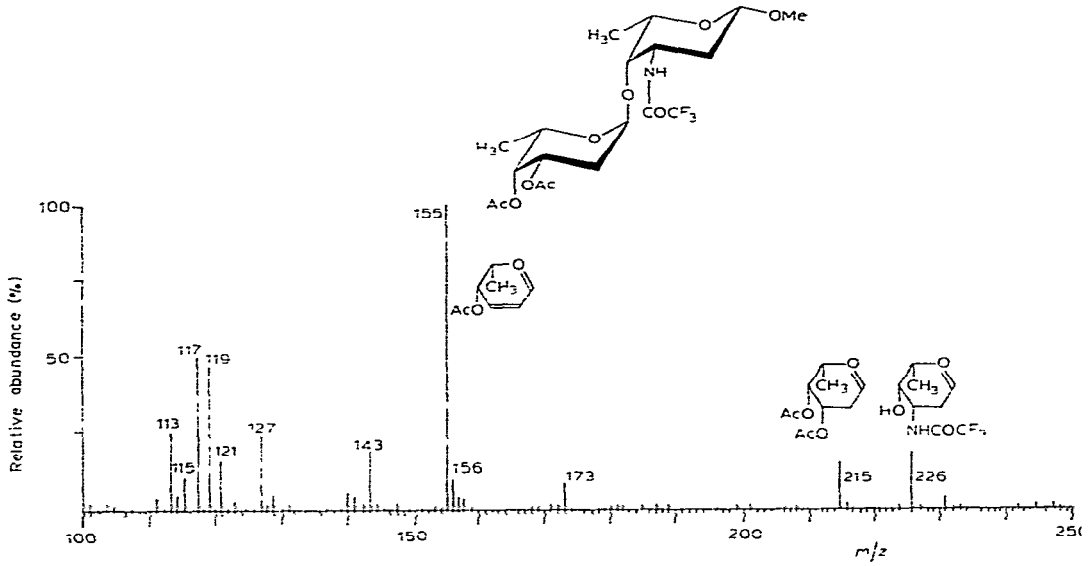


Fig. 1. Mass spectrum of disaccharide 3.

group appeared as two doublets, centered at $\delta$ 1.32 and 1.16, respectively (see Table I).

Although the mass spectrum of disaccharide 3 (see Fig. 1) did not show a molecular peak, it revealed three major fragments that were attributed to the two saccharide moieties. The daunosamine residue gave a peak at *m/z* 226, corresponding to dihydro-2-methyl-5-(trifluoroacetamido)pyran, and the 2-deoxy-L-fucopyranosyl group gave one at *m/z* 215, corresponding to a 3,4-di-*O*-acetyl-2-deoxy-L-fucopyranosyl ion, and a base peak at *m/z* 155, corresponding to an acetoxymethylpyran ion.

## EXPERIMENTAL

*General.* — Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured with a Bendix series 1100 polarimeter. Infrared spectra were recorded with a Perkin–Elmer infrared spectrophotometer, Model 735B, for potassium bromide pellets; n.m.r. spectra with a Varian EM-360 spectrometer, using tetramethylsilane as the internal standard, and $CDCl_3$ as the solvent; and mass spectra with a Hewlett–Packard 5985 B GC-MS System, using positive chemical-ionization, and a direct-insertion mode.

For thin-layer chromatography, plates of silica gel (Eastman Kodak 13181) were used. Chromatographic columns were packed with Sargent–Welch SC 14608 silica gel (60–200 mesh). Microanalyses were performed by Mrs. S. Brotherton in the Department of Chemistry and Chemical Engineering Microanalysis Laboratory.

*Methyl 2,3,6-trideoxy-4-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-*L*-lyxo-hexopyranosyl)-3-(trifluoroacetamido)-β-*L*-lyxo-hexopyranoside* (3). — A mixture of methyl

2,3,6-trideoxy-3-(trifluoroacetamido)-β-L-*lyxo*-hexopyranoside [methyl *N*-(trifluoroacetyl)-daunosaminide; 205 mg], mercuric bromide (30 mg), and yellow mercuric oxide (350 mg) was added to a suspension of finely powdered molecular sieves (3 g) in dry dichloromethane (10 mL), and the mixture was stirred overnight at room temperature in order to dry the reagents. To this mixture was added 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl chloride (410 mg) in dry dichloromethane (2 mL), and the mixture was stirred for 24 h at room temperature. The solids were filtered off and washed with dichloromethane (50 mL), and the filtrate and washing were combined, shaken successively with M potassium iodide solution (50 mL) and water, dried (anhydrous sodium sulfate), and evaporated under diminished pressure to give a syrup (450 mg) that was transferred to a column (60 g, 30 cm) of silica gel. Elution with 7:13 ethyl acetate–hexane gave the desired disaccharide **3** as a crystalline solid (yield 132 mg, 35%); $R_F$ 0.56 (3:7 ethyl acetate–hexane). Recrystallization from anhydrous ether–hexane gave pure compound **3** as fine needles, m.p. 155–157°: $[\alpha]_D^{20}$ −123° (*c* 1.0, chloroform); $\nu_{max}^{KBr}$ 3270 (NH), 1650 and 1560 (NHCO), 1740 (OAc), and 1710 cm ($CF_3CO$).

*Anal.* Calc. for $C_{19}H_{28}F_3NO_9$ (471.43): C, 48.41; H, 5.99; N, 2.97. Found: C, 48.51; H, 6.09; N, 2.63.

In addition to the desired disaccharide, two by-products were eluted from the chromatograph. The first was identified as 3,4-di-*O*-acetyl-L-fucal (yield 49 mg), m.p. and mixed m.p. 49–50°; lit.[4] m.p. 48–50°; $R_F$ 0.81 (3:7 ethyl acetate–hexane).

The other by-product was identified as 3,4-di-*O*-acetyl-2,6-dideoxy-α(or β)-L-*lyxo*-hexopyranosyl 3,4-di-*O*-acetyl-2,6-dideoxy-α(or β)-L-*lyxo*-hexopyranoside (**5**), yield 56 mg, m.p. 181°; $R_F$ 0.58 (3:4 ethyl acetate–hexane). Unlike the mass spectrum of compound **3**, which showed peaks originating from both the daunosamine and the 2-deoxy-L-fucopyranosyl moieties, the mass spectrum of compound **5** showed only the *m/z* 215 and 155 peaks, which originated from the 2-deoxy-L-fucosyl groups.

## REFERENCES

1 H. Brockmann and H. Greve, *Tetrahedron Lett.*, (1975) 831–834.
2 L. Ettlinger, E. Garrmann, R. Hutter, W. Keller-Schlierlein, F. Kradolter, L. Neipp, V. Prelog, P. Reusser, and H. Zahner, *Chem. Ber.*, 92 (1959) 1867–1879; W. Richle, E. K. Winkler, D. M. Hawley, M. Dobler, and W. Keller-Schlierlein, *Helv. Chim. Acta*, 55 (1972) 467–480.
3 H. S. El Khadem and A. Liav, *Carbohydr. Res.*, 74 (1979) 199–205.
4 H. S. El Khadem, D. L. Swartz, J. K. Nelson, and L. A. Berry, *Carbohydr. Res.*, 58 (1977) 230–234.
5 A. Vigevani, B. Gioia, and G. Cassinelli, *Carbohydr. Res.*, 32 (1974) 321–330; D. Horton and W. Weckerle, *ibid.*, 44 (1975) 227–240.