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Preliminary communication

Synthesis of a configurational analog of daunorubicin

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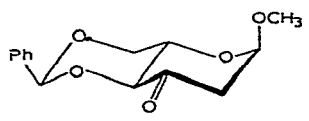
Daunorubicin and adriamycin[1], glycosides belonging to the anthracycline family of antibiotics, are clinically useful as cancer chemotherapeutic agents. In order to obtain information about the structure–activity relationships, and eventually new drugs having greater efficacy, a broader spectrum of activity, and possibly decreased toxicity, we have synthesized new analogs of daunorubicin and adriamycin in which the amino sugar residue is configurationally different with respect to the parent antibiotics. It has been shown that new analogs, in which the sugar moiety is changed from the L-*lyxo* to the L-*arabino* configuration, display high activity in experimental tumors in mice[2,3]. Another class of semisynthetic analog would be that in which daunosamine is replaced by 3-amino-2,3,6-trideoxy-L-*ribo*-hexose. This amino sugar, named ristosamine, is present in the antibiotic ristomycin[4]. The determination of structure[5,6] and syntheses of ristosamine[7] and *N*-benzoylristosamine[8] have been recently described.

We now describe a facile synthesis of methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-L-*ribo*-hexopyranoside (4), a key intermediate in the synthesis of new, antitumor, anthracycline analogs possessing the L-*ribo* configuration in the sugar moiety, and a suitable, alternate precursor of ristosamine.

Treatment of oxime 2, m.p. 211–213°, $[\alpha]_D^{25}$ –201.5° (*c* 0.5, chloroform), derived from methyl 4,6-*O*-benzylidene-2-deoxy-α-L-*erythro*-hexopyranosid-3-ulose[9] (1), with lithium aluminum hydride, followed by hydrolysis of the acetal function and *N*-trifluoroacetylation, gave methyl 2,3-dideoxy-3-trifluoroacetamido-α-L-*ribo*-hexopyranoside (3) as a syrup, $[\alpha]_D^{25}$ –71.5° (*c* 0.7, chloroform)*; *m/e* 242 ($M^+ - 31$); p.m.r. data ($CDCl_3$, p.p.m.): 1.9–2.2 (m, 2H, H-2), 3.47 (s, CH_3O), 3.5 (m, H-3), 3.8–4.0 (m, 2H, H-6), 4.85 (dd, $J \sim 2$ Hz, H-1), and 8.05 (very broad s, NH).

Treatment of 3 with triphenylphosphine and *N*-bromosuccinimide in *N*,*N*-dimethylformamide[10] gave the 6-bromo derivative, m.p. 123–125°; p.m.r. data ($CDCl_3$, p.p.m.): 1.95–2.2 (m, 2H, H-2), 3.48 (s, CH_3O), 3.5 (m, H-3), 3.6–3.95 (m, 2H, H-6), 4.87 (dd,

*All new compounds gave correct elemental analyses.



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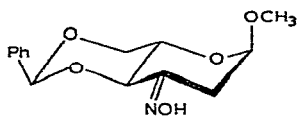

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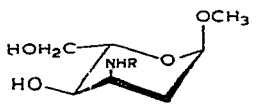
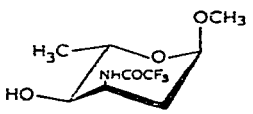


3 R = $COCF_3$



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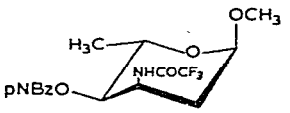

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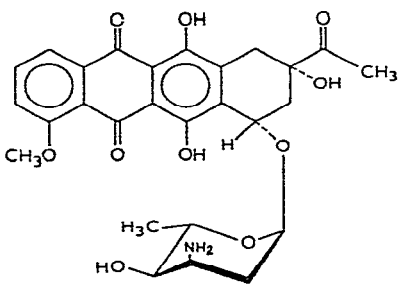

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J ~2 Hz, H-1), and 8.10 (very broad s, NH). Catalytic reduction of the 6-bromo derivative gave the desired intermediate **4** as a syrup, $[\alpha]_D^{25}$ −61.9° (*c* 0.5, benzene); p.m.r. data ($CDCl_3$, p.p.m.): 1.28 (d, 3H, H-6), 1.9 (m, 2H, H-2), 3.42 (s, CH_3O), 3.50 (m, H-3), 4.78 (dd, J ~2Hz, H-1), and 8.10 (very broad s, NH). *p*-Nitrobenzoylation of **4**, in the usual manner, gave the crystalline 4-*p*-nitrobenzoate **5**, m.p. 174–176°, $[\alpha]_D^{25}$ −124.2° (*c* 1, chloroform). Acid hydrolysis, essentially as previously described[3], followed by *p*-nitrobenzoylation of the resulting free sugar, and subsequent treatment with dry hydrogen chloride in anhydrous dichloromethane, gave the glycosyl chloride **6** as an amorphous solid. Compound **6** is a suitable intermediate for the preparation of novel anthracycline glycosides. For example, it is a precursor of the daunorubicin analog **7**, m.p. 180–181° (dec.), $[\alpha]_D^{25}$ +243.5° (*c* 0.05, methanol), which displays significant antitumor activity in experimental animals[11].

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