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Preliminary communication

Synthesis of derivatives of 3-amino-2,3,4,6-tetradeoxy-L-*threo*-hexose (4-deoxydaunosamine) and its L-*erythro* isomer*

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The anthracycline antibiotics daunorubicin (daunomycin) and doxorubicin (adriamycin), which are clinically used as anticancer agents, contain as the sugar component, daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose)[1]. Among intensive research efforts to develop semisynthetic, modified analogs[2–4] of these drugs that might show improved therapeutic properties was a four-step conversion[3] of methyl 2,3,6-trideoxy-3-(trifluoroacetamido)-α-L-*lyxo*-hexopyranoside (methyl *N*-trifluoroacetyldaunosaminide) into 2,3,4,6-tetradeoxy-3-(trifluoroacetamido-L-*threo*-hexose (**10**), to be combined with the aglycon daunomycinone. The 4′-deoxy analogs of daunorubicin and adriamycin, thus obtained after short sequences of reactions, displayed equal or improved biological activities, as compared to the parent antibiotics[3]. Although a multistep, achiral synthesis of 4-deoxy-DL-daunosamine has been reported[5], an application of the conversion just cited[3] to synthetic L-daunosamine (which can be prepared, on a practical scale, from D-mannose[6]) appears at present to be the only economical avenue to the required L-enantiomer or its *N*-trifluoroacetyl derivative **10**. We now report an alternative, and significantly shorter, approach to derivatives of 4-deoxydaunosamine (including **10**), as well as to the corresponding, hitherto unknown, L-*erythro* isomers. This work is based on a further elaboration of the route[7,8] from nitro sugars to nitrogenous, polydeoxy sugars.

Methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside (**1**), obtainable crystalline in 35–45% yield from methyl α-L-rhamnopyranoside by the nitromethane cyclization method (with[9] or without[8b] the use of column chromatography), was methanesulfonylated as already detailed[8a] for the D-enantiomer, to give an 80% yield of the dimesylate **2**, m.p. 132–133° (lit.[8a] for D-**2**, m.p. 132–132.5°). Treatment[8c] of **2** with sodium acetate and acetic acid in refluxing acetone (60 min) yielded (70%) known[7a] methyl 2-*O*-acetyl-3,4,6-trideoxy-3-nitro-α-L-*threo*-hex-3-enopyranoside (**3**), m.p. 81–82° (lit.[7a] m.p. 81–81.5° and, for[8c] D-**3**, 81–82°). Reduction of **3** with sodium borohydride in ethanol at ~25°, followed by neutralization with acetic acid, gave within a few minutes a 2:3 mixture of methyl 2,3,4,6-tetradeoxy-3-nitro-α-L-*threo*-hexopyranoside (**4**) and its α-L-*erythro* isomer (**5**). The product ratio did not seem greatly affected by lowering the reaction temperature. A similar mixture of **4** and **5** was obtained, more conveniently, by

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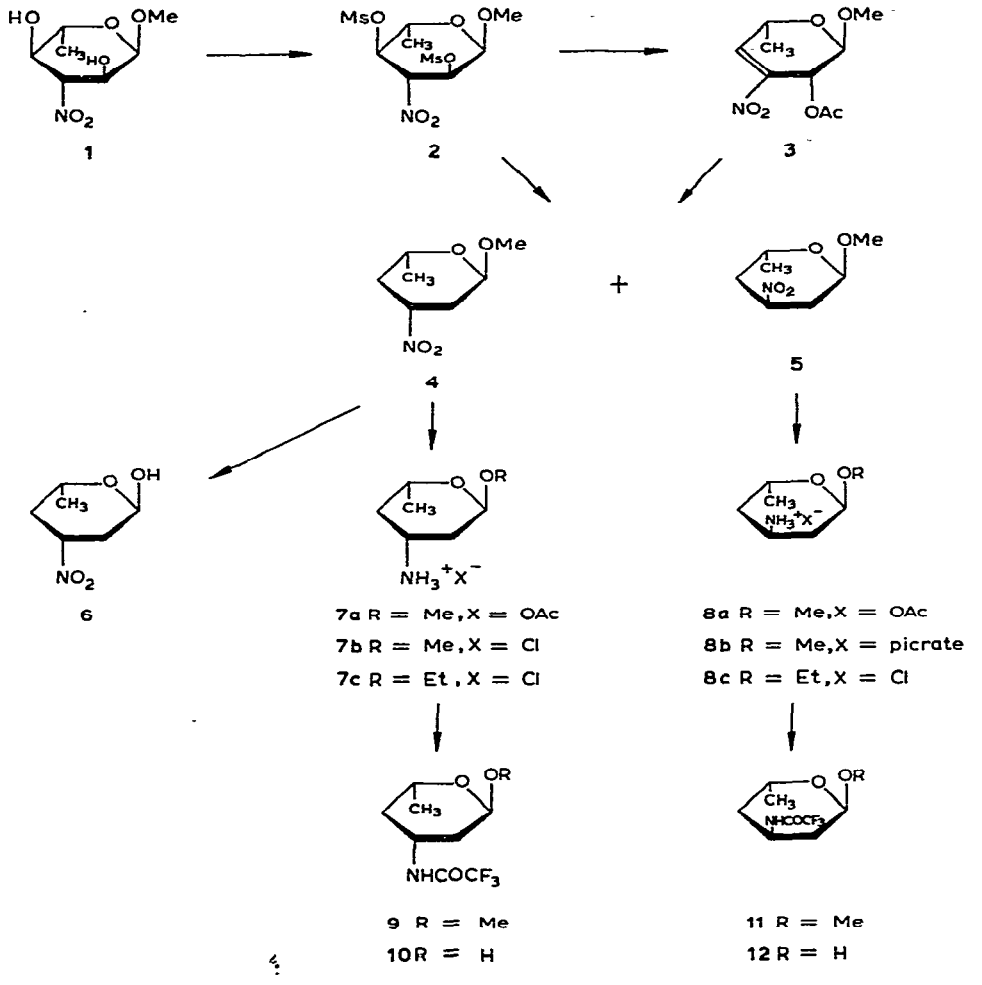
treatment of the dimesylate **2**, directly, with sodium borohydride in ethanol–dichloromethane (~25°, 1 h). The isomers **4** and **5** (R_F 0.42 and 0.28, respectively; t.l.c. in 4:1 petroleum ether–ethyl acetate) were isolated in 27 and 53% yields by column chromatography on silica gel that had been pretreated with acetic acid; the eluant was 8:2:1 petroleum ether–benzene–ethyl acetate to which 2.2% of acetic acid was added. Omission of the acid caused **5** to be partially epimerized, and prevented its isolation in pure form. Such an epimerization, induced by traces of alkali, may be utilized to enhance the yield of **4** which, having an equatorial nitro group, is evidently the thermodynamically favored epimer. The twofold, reductive elimination **2**→(**4**+**5**) constitutes a logical extension of previously reported, single dehydromethylsulfonyloxylations[8b,c] and dehydroacetoxylations[9] by sodium borohydride.

The glycoside **4** was a mobile oil, $[\alpha]_D^{25}$ −139° (*c* 1.3, chloroform), ν_{max}^{neat} 1550 cm^{-1}; n.m.r. ($CDCl_3$): δ 4.83 (tt, $J_{2e,3} = J_{3,4e} = 4.5$, $J_{2a,3} = J_{3,4a} = 12.5$ Hz, H-3). It was hydrolyzed by 0.5M sulfuric acid (1 h, 98°), to give crystalline 2,3,4,6-tetradeoxy-3-nitro-α-L-*threo*-hexose (**6**), m.p. 117–118°, $[\alpha]_D^{25}$ −96 (3 min) → −76.3° (21 h, final; *c* 1, chloroform) and −39.8 (8 min) → −36.0° (20 and 120 min; *c* 1, water); n.m.r. ($CDCl_3$): δ 4.92 (tt, *J* 4.5 and 12.2 Hz, H-3). Hydrogenation of **4** in the presence of Adams' catalyst readily furnished methyl 3-amino-2,3,4,6-tetradeoxy-α-L-*threo*-hexopyranoside, which was isolated as the crystalline acetate **7a**, m.p. 108°, or hydrochloride **7b**, m.p. 182–183° (dec.), $[\alpha]_D^{25}$ −108.3° (*c* 1, water). By dissolution in chloroform that contained small proportions of ethanol and hydrogen chloride, **7a** was rapidly converted into the ethyl glycoside hydrochloride **7c**, m.p. 190–192° (dec.), $[\alpha]_D^{25}$ −94° (*c* 0.7, water). Reaction of **7a** (or **7b**) with trifluoroacetic anhydride–triethylamine in chloroform solution at −20° gave the *N*-trifluoroacetyl glycoside **9** as long needles (from ethyl acetate–petroleum ether), m.p. 123–123.5° $[\alpha]_D^{25}$ −128.8° (*c* 0.7, chloroform). Hydrolysis of **9** with 3.5M acetic acid (3 h, 90°) produced 4-deoxy-*N*-(trifluoroacetyl)daunosamine (**10**), m.p. 166°; *m/e* 227 (M^+), 210 (weak, M^+–OH) and 209 (strong, M^+–H_2O); $[\alpha]_D^{25}$ −85 (initial, extrapolated) → −80 (5 min) → −74 (15 min) → −57 (80 min) → −48 (4 h) → −47° (20 h; *c* 0.18, chloroform), and −26.4 (4 min) → 24.6° (2 h, final; *c* 0.5, water); lit.[3] m.p. 159°–160°, $[\alpha]_D$ −80° (*c* 0.1, chloroform; no mutarotation recorded). The n.m.r. spectrum in dimethylsulfoxide-d_6 was in accord with the reported[3] data.

The glycoside **5** was crystalline, m.p. 43°, $[\alpha]_D^{25}$ −145° (*c* 1.1, chloroform); n.m.r. ($CDCl_3$): δ 4.47 (complex multiplet containing small splittings only; total width, 17 Hz, eq. H-3). The following products were obtained from **5** by reactions performed in full analogy to those starting from **4**. Catalytic hydrogenation gave methyl 3-amino-2,3,4,6-tetradeoxy-α-L-*erythro*-hexopyranoside, which was obtained as a rather volatile, liquid acetate (**8a**) and was characterized as the picrate **8b**, m.p. 163–165° (dec.), $[\alpha]_D^{25}$ −59.2° (*c* 1.4, methanol). The ethyl glycoside hydrochloride **8c** showed m.p. 141–142° (dec.), and $[\alpha]_D^{25}$ −84.6° (*c* 0.7, water). *N*-(Trifluoroacetyl)ation of **8a** gave the *N*-trifluoroacetyl derivative **11** as a volatile syrup that was hydrolyzed, without further characterization, to produce 2,3,4,6-tetradeoxy-3-(trifluoroacetamido)-L-*erythro*-hexose (**12**), m.p. 112–113°; (*m/e* 227 (M^+), 210 (weak, M^+ –OH), and 209 (strong, M^+ –H_2O); $[\alpha]_D^{25}$ + 28.9° (*c* 1.5, chloroform) and +10° (*c* 1.3, water). Although mutarotation was not observed, the small splittings present in the H-1 signal of the n.m.r. spectrum (in $CDCl_3$) indicated the α-anomeric configuration: δ 8.3 (broad, 1 H, removed by D_2O exchange, NH), 5.43 (dd, W_H



~6 Hz, H-1), 4.45–4.05 (complex m, 2 H, H-3,5), 3.84 (t, 1 H, W_H 6 Hz, removed by D_2O exchange, OH), 2.0–1.35 (m, 4 H, H-2,4,2′,4′), and 1.20 (d, 3 H, J 6 Hz, C-Me).

The microanalytical data for all of the crystalline, new compounds, as well as their remaining n.m.r. parameters, were in agreement with the structures assigned.

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