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Note

Preparation of 4-*O*-acetyl-1,5-anhydro-2,3,6-trideoxy-3-trifluoroacetamido-L-*lyxo*-hex-1-enitol, a key intermediate in synthesis of daunosamine glycosides*

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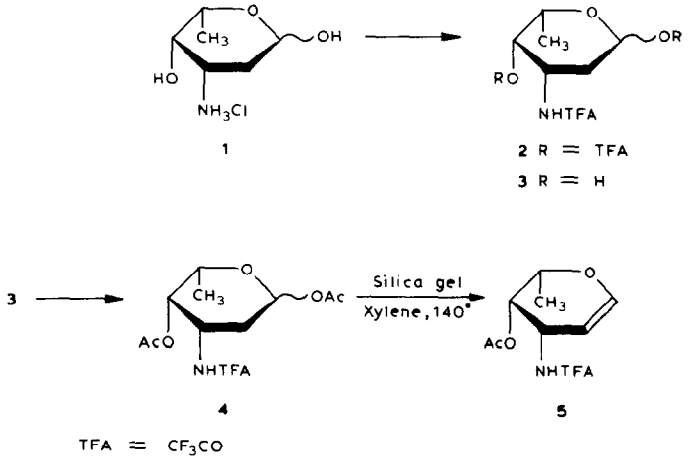
The title glycal[1] **5** is a particularly convenient daunosamine derivative for high-yielding preparation of anthracycline glycosides incorporating daunosamine with the desired α-L anomeric specificity and having a readily removable *N*-protecting group. As part of a general program[1–5] concerned with the synthesis of anthracycline glycosides and 2′-halo analogs, this article describes a high-yield preparation of glycal **5** from daunosamine (**1**). Coupling of various glycals with anthracyclinone aglycons has been documented in detail in previous work from our laboratory[3–6]. The synthesis of daunosamine in high net yield from D-mannose[7] remains perhaps the most practical of the numerous routes that have been proposed for this important amino sugar.



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Daunosamine hydrochloride (**1**) was trifluoroacetylated under the general conditions of Arcamone *et al.*[8]. Without purification, the intermediate **2** was selectively *O*-deacylated with methanolic sodium methoxide to afford *N*-trifluoroacetyldaunosamine (**3**) as an anomeric mixture (~1:1 based on ^{1}H-n.m.r.). Acetylation of **3** afforded the 1,4-di-*O*-acetyl derivative **4**, again as a mixture of anomers. This product was treated with silica gel in boiling xylene[3,6] to effect elimination of acetic acid at the anomeric center and afford the glycal **5**, isolated crystalline in overall 53% net yield from **1**.

Detailed 500-MHz n.m.r.-spectral data for the products are given in the Experimental section.

EXPERIMENTAL

General methods. — Melting points were determined in open glass capillaries with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter. ^{1}H-N.m.r. spectra were recorded at 500 MHz by Dr. C. A. Cottrell with a Bruker AM-500 spectrometer. The samples were dissolved in $CDCl_3$ and the chemical shifts (δ) refer to an internal standard of Me_4Si (δ 0.00). T.l.c. was performed on precoated aluminum sheets (0.2 mm) and glass plates (0.25 mm) coated with Silica Gel 60F-254 (E. Merck, Darmstadt, GFR); components were detected by spraying the plates with 0.1M $CeSO_4$ in 2M H_2SO_4 acid, with subsequent heating. Column chromatography was performed with Silica gel 60 (230–400 mesh, E. Merck, Darmstadt, GFR). Solvents were dried and redistilled just prior to use. Elemental analyses were determined by Atlantic Microlab, Inc., Atlanta, Georgia.

*2,3,5-Trideoxy-3-trifluoroacetamido-α,β-*L*-lyxo-hexopyranose (N-trifluoroacetyl-α,β-daunosamine)* (**3**). — A suspension of 3.86 g (21 mmol) of L-daunosamine hydrochloride[7] (**1**) in dry ether (100 mL) was cooled to 0° and then 29.0 mL (208 mmol) of trifluoroacetic anhydride was added dropwise with vigorous magnetic stirring under an inert atmosphere. After 1 h at 0°, the solid had completely dissolved. Stirring was continued for 3 h at room temperature. The solution was then evaporated, and ether was evaporated several times from the residue to remove the remaining trifluoroacetic acid. The brown solid **2** thus obtained was used in the next step without further purification.

The solid was dissolved in dry methanol (100 mL) at ~25° and then M sodium methoxide in methanol was added until the pH reached 8. The reaction was monitored by t.l.c. (1:1 hexane–ethyl acetate) until the starting material had disappeared (0.5 h). Only one component (R_F 0.1) was detected. The reaction was terminated by adding water (50 mL) and Dowex 50W ion-exchange resin until the pH was brought to 7. The mixture was then filtered and the filtrate evaporated to afford 4.85 g (95%) of **3**; m.p. 145–147° (ethyl acetate); lit.[9], m.p. 146–147° (ethyl acetate).

*1,4-Di-O-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α,β-*L*-lyxo-hexopyranose*

(1,4-di-O-acetyl-N-trifluoroacetyl-α,β-daunosamine) (**4**). — To a solution of **3** (1.5 g, 6.1 mmol) in dry pyridine (50 mL) at 0° was added acetic anhydride (25 mL) and the mixture was kept overnight at room temperature. The mixture was poured into ice–water (150 mL) and extracted with dichloromethane (3 × 100 mL). The organic layer was washed with 5% HCl (2 × 100 mL), water (2 × 100 mL), aq. $NaHCO_3$ (2 × 100 mL), and finally with water (2 × 100 mL). The solution was dried (Na_2SO_4) and evaporated to afford a solid (yield 1.85 g, 92%) which, by t.l.c. (1:1 hexane–ethyl acetate), showed two spots (R_F 0.60 and 0.55) corresponding to the α and β anomers of **4** in 1:1 ratio according to ^{1}H-n.m.r. spectral data; ^{1}H-n.m.r. (anomeric mixture): δ 6.57 and 6.51 (bs each, 2 H, NH α and β), 6.26 (s, 1 H, H-1α), 5.78 (dd, 1 H, $J_{1\beta,2a\beta}$ 9.9, $J_{1\beta,2e\beta}$ 2.3 Hz, H-1β), 5.14 (s, 1 H, H-4α), 5.05 (d, 1 H, $J_{3\beta,4\beta}$ 2.6 Hz, H-4β), 4.55 (dd, 1 H, $J_{2a\alpha,3\alpha}$ 7.8, $J_{2e\alpha,3\alpha}$ 5.0 Hz, H-3α), 4.30 (ddd, 1 H, $J_{2a\beta,3\beta}$ 8.0, $J_{2e\beta,3\beta}$ 4.9 Hz, H-3β), 4.17 (q, 1 H, $J_{5\alpha,6\alpha}$ 6.3 Hz, H-5α), 3.85 (q, 1 H, $J_{5\beta,6\beta}$ 6.3 Hz, H-5β), 2.18, 2.17, 2.11, 2.10 (4 s, 3 H each, OAc α and β), 1.20 (d, 3 H, H_3-6β), and 1.13 (d, 3 H, H_3-6α); ^{13}C-n.m.r.: δ 92.0 (C-1β), 91.2 (C-1α), 71.58 (C-5β), 70.0 (C-4α), 69.1 (C-4β), 67.9 (C-5α), 48.5 (C-3β), 45.5 (C-3α), 30.6 and 29.1 (C-2α and β), 2.17 and 21.1 (OAc α and β), 17.2 and 17.1 (C-6α and β).

Anal. Calc. for $C_{12}H_{16}F_3NO_6$: C, 44.04; H, 4.93; N, 4.28. Found: C, 44.16; H, 4.95; N, 4.28.

*4-O-Acetyl-1,5-anhydro-2,3,6-trideoxy-3-trifluoroacetamido-*L-lyxo-*hex-1-enitol* (**5**). — Silica gel 60 (230–400 mesh, E. Merck, Darmstadt, GFR, 10 g) was suspended in dry xylene (150 mL) and the slurry was then evaporated under diminished pressure to one-half the volume at ~50°. The anomeric mixture **4** (1.0 g, 3.1 mmol) was added to this suspension, which was then boiled under reflux for 45 min. The cooled suspension was then filtered, the silica gel was washed with dichloromethane (250 mL) and acetone (150 mL), and the filtrates and washings were evaporated at ~50° to a syrup that was purified by column chromatography (4:1 hexane–ethyl acetate, 50 g of silica gel) to give a solid that was crystallized from acetone–hexane yielding pure **5** (0.49 g, 60%), m.p. 118–119°, $[\alpha]_D^{25}$ −98° (*c* 1.0, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 6.50 (dd, 1 H, $J_{1,2}$ 6.2, $J_{1,3}$ 2.1 Hz, H-1), 6.32 (bs, 1 H, NH), 5.30 (d, 1 H, $J_{3,4}$ 4.7 Hz, H-4), 4.90 (m, 1 H, $J_{1,3} + J_{2,3} + J_{3,4}$ = 9 Hz, H-3), 4.51 (dt, 1 H, $J_{2,3}$ 1.8, $J_{2,4}$ 1.8 Hz, H-2), 4.18 (q, 1 H, $J_{5,6}$ 6.6 Hz, H-5), 2.13 (s, 3 H, OAc), and 1.22 (d, 3 H, H_3-6); ^{13}C-n.m.r. ($CDCl_3$): 147.31 (C-1), 97.83 (C-2), 72.40 (C-5), 66.98 (C-4), 45.11 (C-3), 21.00 (OAc), and 17.20 (C-6).

Anal. Calc. for $C_{10}H_{12}F_3NO_4$: C, 44.95; H, 4.53; N, 5.24. Found: C, 44.94; H, 4.57; N, 5.20.

REFERENCES

1 D. Horton and W. Priebe, U.S. Patent 4 562 177, Dec. 31, 1985.
2 E. F. Fuchs, D. Horton, W. Weckerle, and E. Winter-Mihaly, *J. Med. Chem.*, 22 (1979) 406–411.
3 D. Horton, R. G. Nickol, W. Weckerle, and E. Winter- Mihaly, *Carbohydr. Res.*, 76 (1979) 269–276.

4 D. HORTON, W. PRIEBE, AND O. VARELA, *Carbohydr. Res.*, 130 (1984) c1–c3.
5 D. HORTON, W. PRIEBE, AND O. VARELA, *Carbohydr. Res.*, 144 (1985) 305–315.
6 E. F. FUCHS, D. HORTON, W. WECKERLE, AND B. WINTER, *J. Antibiot.*, 32 (1979) 229–238.
7 D. HORTON AND W. WECKERLE, *Carbohydr. Res.*, 44 (1975) 227–240.
8 F. ARCAMONE, S. PENCO, A. VIGEVANI, S. REDAELLI, G. FRANCHI, A. DIMARCO, A. M. CASAZZA, T. DASDIA, F. FORMELLI, A. NECCO, AND C. SORANZO, *J. Med. Chem.*, 18 (1975) 703–707.
9 T. H. SMITH, A. N. FUJIWARA, W. W. LEE, H. Y. WU, AND D. W. HENRY, *J. Org. Chem.*, 42 (1977) 3653–3660.