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CARBOHYDRATE COMPONENTS FOR MODIFIED ANTHRACYCLINES: SYNTHESIS OF DERIVATIVES OF 3-AMINO-3,4,6-TRIDEOXY-L-*lyxo*- AND -L-*xylo*-HEXOSE, AND ATTEMPTS AT FLUORINATION OF C-2

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ABSTRACT

Two new trideoxyglycosides, methyl 3,4,6-trideoxy-3-nitro-α-L-*lyxo*-hexopyranoside (**7**) and its α-L-*arabino* isomer, as well as the known α-L-*xylo* isomer (**15**), were synthesized from methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside (**1**) by methods involving elimination and reduction processes in mesylates prepared from **1**. Catalytic hydrogenation of **7** and **15** gave the new and the known aminodeoxyglycosides, respectively, both of which were *N*-(trifluoroacetyl)ated and subsubsequently *O*-(trifluoromethylsulfonyl)ated. Various attempts to effect displacement by fluoride ion in the *N*-protected 2-triflates so obtained, and also in a related 3-azido-2-triflate, were unsuccessful as far as fluorination at C-2 was concerned. Among other products, two new 2-enopyranosides resulting from elimination of triflic acid were obtained.

INTRODUCTION

Following recent reports[1,2] on a synthesis of (*S*)-2′-fluorodaunorubicin and on its biological activity, we now describe further studies undertaken as part of a project of preparing new, modified anthracyclines that may show promise as antitumor agents. In the quest for anticancer drugs having improved therapeutic properties, a large number of different sugars have been combined with the aglycons of daunorubicin and doxorubicin, replacing the natural component L-daunosamine that is present[3] in these antibiotics. Among those sugars were several 3-amino-2,3,6-trideoxyhexoses, *i.e.*, stereoisomers of daunosamine, but, apparently, no regioisomers of the 3-amino-3,4,6-trideoxy type. The presence of a hydroxyl group on C-4 of the amino sugar is evidently not a prerequisite for antitumor activity, as synthetic 4′-deoxydaunorubicin is highly active[4]. It should therefore be interesting also to examine the effect of a transposition of the hydroxyl group from C-4′ to C-2′, which may include both axial and equatorial placement at that carbon atom. Of the two sugars envisaged as constituents of such modified anthracyclines, namely, the 3-amino-3,4,6-trideoxy-L-*xylo*- and -L-*lyxo*-hexoses, the former is available[5] in the form of its methyl α-pyranoside **16**, whereas the

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latter is unknown, and some glycosidic derivatives (**9–12**) became the target of the present work, to be used in future syntheses of modified antibiotics.

In our earlier articles[1,2], a rationale was given for introduction of fluorine into the sugar moiety of anthracyclines, and these considerations have received forceful support from recent, related work[6] in the laboratories of the Umezawas. The hitherto unknown 2-deoxy-2-fluoro derivatives of the aminotrideoxy sugars just mentioned are therefore considered to be logical candidates for inclusion in the project. Unfortunately, several attempts to produce such derivatives from the available precursors were unsuccessful.

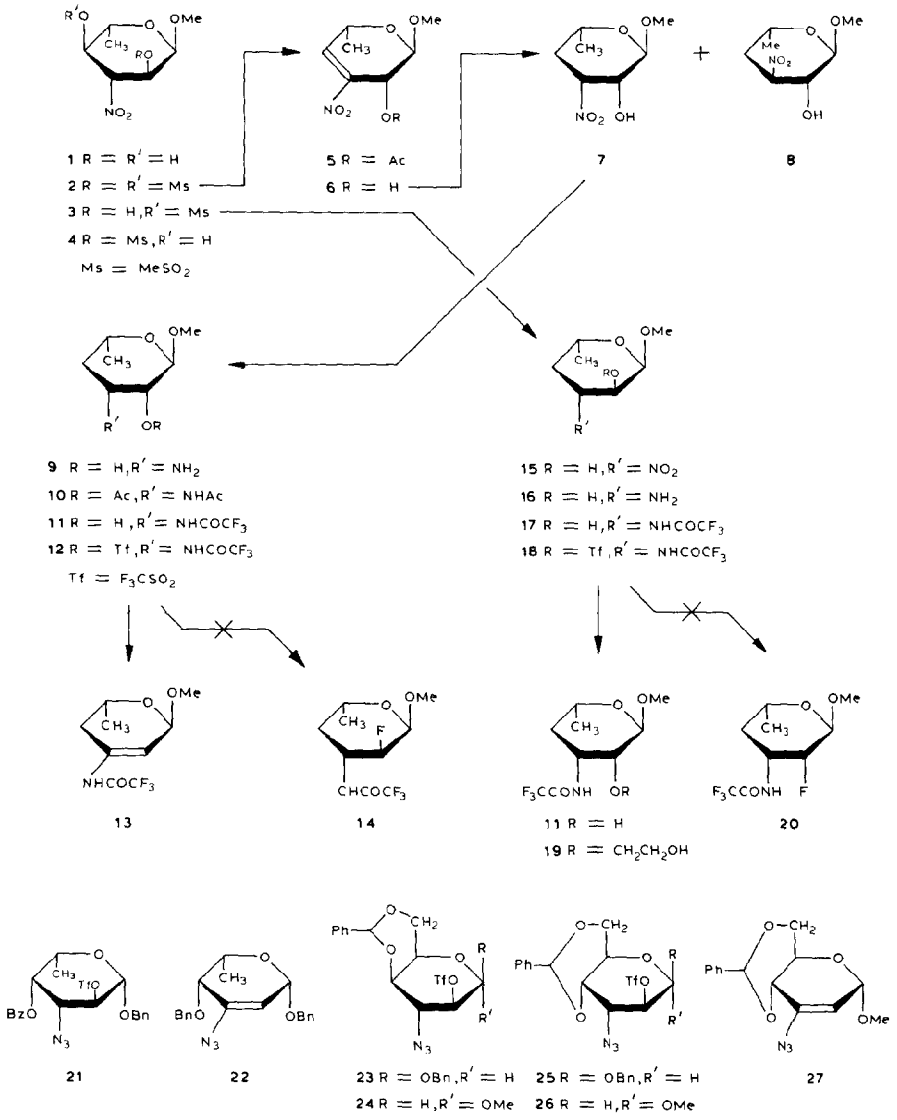
RESULTS AND DISCUSSION

The starting point for the present study was known[7] methyl 3,6-dideoxy-3-nitro-α-L-glucopyranoside (**1**), which is readily prepared[8] from methyl α-L-rhamnopyranoside and had previously been converted by high-yielding reactions into its dimesylate **2** and thence into the[8] 2-*O*-acetyl-3-enoside **5**, from which the corresponding alcohol **6** had been obtained[9]. Treatment of **6** with sodium borohydride now gave methyl 3,4,6-trideoxy-3-nitro-α-L-*lyxo*-hexopyranoside (**7**), together with a small proportion of the axial-nitro, L-*arabino* isomer **8**, separable by chromatograph*. Configurational assignments for **7** and **8** based on their well-resolved ^{1}H-n.m.r. spectra were straightforward; neither compound had been described previously, although a synthesis, but no physical or spectral data, of DL-**7** had been reported[12]. Catalytic hydrogenation of **7** over platinum in the presence of hydrochloric acid furnished syrupy methyl 3-amino-3,4,6-trideoxy-α-L-*lyxo*-hexopyranoside hydrochloride (**9**), characterized as the crystalline *N*-acetyl-*O*-acetyl derivative **10**.

For an attempt to replace its 2-hydroxyl group by fluorine, compound **9** was sequentially *N*-(trifluoroacetyl)ated and *O*-(trifluoromethylsulfonyl)ated, affording the crystalline derivatives **11** and **12**. Treatment of **12** with tetrabutylammonium fluoride in acetonitrile led to elimination, giving the enoside **13**, and the desired 2-fluoroglycoside **14** was not obtained.

An approach to the 2-epimeric, 2-deoxy-2-fluoroglycoside **20** was undertaken as follows. By procedures previously detailed[13] for the corresponding D enantiomers, compound **1** was partially mesylated, and the resulting 4-monomesylate **3** was reductively de(hydromethylsulfonyloxyl)ated with sodium borohydride, to give the known[5] methyl 3,4,6-trideoxy-3-nitro-α-L-*xylo*- hexopyranoside (**15**). The amine **16** obtainable[5] therefrom was then sequentially *N*-(trifluoroacetyl)ated and *O*-(trifluoromethylsulfonyl)ated, affording the crystalline

*Protonation of 3-deoxyhexopyranoside 3-nitronates (and of deoxynitroinositol salts) generally leads exclusively[10] to the thermodynamically more-stable, equatorial-nitro compound. However, absence of one or both of the vicinal hydroxyl groups appears to render the axial-nitro epimer, which may arise as a kinetic product of protonation, sufficiently stable for isolation. Cases in point were encountered in the preparation[8] of the 2,3,4,6-tetradeoxy analogs of **7** and **8**, and in certain deoxynitrocyclitols[11].



derivatives **17** and **18** in high yields. It was considered that **18** might be amenable to nucleophilic displacement by fluoride ion at C-2, although a possible intervention of neighboring-group participation by the amide function could not be precluded. Whereas oxygen participation should be strongly discouraged by the inductive effect of the trifluoromethyl group, nitrogen participation seemed a possibility, and it would give a 2,3-epimine which, if it could subsequently be opened by fluoride attack, would presumably do so diaxially (by the Fürst–Plattner rule), to produce a 2-amino-3-fluoro sugar. However, the targeted 2-deoxy-2-fluoroglycoside **20** could

not be prepared from **18** by any of the displacement reactions studied. Tetrabutylammonium fluoride in acetonitrile gave the alcohol **11**, even though the usual efforts had been made to exclude water from the reaction medium. With potassium hydrogenfluoride in ethylene glycol[14], displacement by solvent instead of by fluoride ion occurred, affording the hydroxyethyl ether **19**. Reaction with cesium fluoride in *N,N*-dimethylformamide (DMF) led to unidentified products.

Similar difficulties were in some instances encountered by Lukacs and his collaborators[15,16] during their extensive studies on the synthesis of aminofluoro sugars. Thus, reaction of fluorine-containing nucleophilic reagents with the triflate **21** invariably led[15] to the elimination product **22**. Whereas the D-*ido* triflates **23** (ref. 15) and **24** (ref. 16) underwent the desired displacement with cesium and tetrabutylammonium fluoride, respectively (both in DMF solution), the same treatments applied to the D-*altro* isomers **25** (ref. 15) and **26** (ref. 16) were unsuccessful. Compound **25** was reported to remain unchanged under the conditions used, and the fate of **26** was not disclosed. When we treated **26** with cesium fluoride in a mixture of Me_2SO and hexamethylphosphoric triamide (HMPT) at 80°, we obtained the crystalline enoside **27** in 60% yield, and detected no displacement product.

EXPERIMENTAL

General. — Column chromatography was performed on silica gel Merck 7734 (100–200 mesh) at ordinary pressure, and thin-layer chromatography, on precoated silica gel plates. Unless stated otherwise, the following solvent combinations (v/v) were used: ether–hexane in the ratios (*A*) 3:1, (*B*) 2:1, (*C*) 1:1, (*D*) 1:2, and (*E*) 1:3, and ethyl acetate–hexane (*F*) 2:1, (*G*) 1:1, and (*H*) 1:4. Optical rotations were determined at ~25° for solutions in chloroform unless otherwise noted. Mass-spectral data (*m/z*) were obtained by the chemical ionization method using ether. The ^{1}H-n.m.r. data (see Table I) were recorded at 300 MHz, and the ^{13}C-n.m.r. data (Table II) at 75.43 MHz, both for $CDCl_3$ solutions unless otherwise specified. Infrared data (ν_{max}) were obtained for Nujol mulls for solids, and for thin films for syrups.

*Methyl 3,6-dideoxy-3-nitro-α-*L*-glucopyranoside 2,4-di(methanesulfonate)* (**2**), *4-methanesulfonate* (**3**), *and 2-methanesulfonate* (**4**). — The nitroglucoside **1** and its dimesylate **2** were prepared as described[8]. For the preparation of the 4-mesylate **3**, the procedure detailed[13] for its D enantiomer was essentially followed. The mixture of partially mesylated products obtained from **1** (5.0 g) was chromatographed by use of chloroform as the eluant, whereby fast-moving **2** and slow-moving, unconsumed **1** were separated from a mixture of monomesylates (**3** and **4**) which had intermediate mobility and were subsequently separated by chromatography using solvent *D*. There was obtained, in order of decreasing mobility, 2,4-dimesylate **2** (1.15 g, 13%), 2-mesylate **4** (0.25 g, 3.6%), 4-mesylate **3** (2.67 g, 39%), and unreacted **1** (1.7 g, 34%) usable for recycling.

TABLE I

^{1}H-NUCLEAR MAGNETIC RESONANCE DATA (300 MHz) FOR GLYCOSIDES IN $CDCl_3$ SOLUTION

Compound	*Chemical shifts (δ)*									
	H-1	*H-2*	*H-3*	*H-4e*	*H-4a*	*H-5*	*C-CH₃*	*O-CH₃*	*OH*	*NH*
3	4.79d	4.12m	~4.80m[a]		~4.80m[a]	3.85m	1.40d	3.47s[b]	2.31d	
4	5.01d	4.90m (2 H)[a]			3.75m (2 H)[a]		1.34d	3.46s[b]	2.56d	
7	4.75d	4.38dt	4.69ddd	2.11m (2 H)		3.88m	1.30d	3.38s	2.27s	
8	4.59d	4.31sp	4.53dt	2.37ddd	1.91sp	4.21qdd	1.26d	3.34s	2.30d	
10	4.68d	4.73t	4.50m	1.76dt	1.44q	3.94m	1.19d	3.34s[c]		5.47bs
11	4.66d	3.64dt	4.34m	1.85ddd	1.39q	3.93qdd	1.20d	3.37s	1.93d	6.7bs
12	4.87s (2 H)		4.63m	1.77ddd	1.61sx	4.02qdd	1.26d	3.41s		6.25bs
13	5.02d	6.21t		2.13dd	2.31ddt	4.12m	1.29d	3.41s		7.03bs
17	4.75d	3.43m[d]	4.14m	2.17ddd	1.29q	3.94qdd	1.19d	3.43s	1.97d	6.24bs
18	4.90d	4.70dd	4.64m	2.16ddd	1.58sx	4.04qdd	1.21d	3.45s		6.27bs
26	4.73~s	4.85~d	4.24~t		4.08dd	4.36–4.26[e]		3.46s		
27	4.99~dd	5.30dd			4.28dt[f]	4.40ddd		3.42s		

Compound	*Coupling constants (Hz)*								
	$J_{1,2}$	$J_{2,3}$	$J_{2,OH}$	$J_{3,4a}$	$J_{3,4e}$	$J_{4a,5}$	$J_{4e,5}$	$-J_{4a,4e}$	$J_{5,Me}$
3	4.5	10	11.5	[g]		9			6.3
4	3.4		5.6						5.8
7	1.5	2.5	7.3	11	5.5	10	3.5		6.2
8	2.7	4.8	7.7	4.7	4.7	10	3.3	14.8	6.4
10	1.5	1.6		~12	~4.5	~11.5	~4.5	~12.5	6.3
11	1.7	2.8	9.2	12	4.9	11.7	2.4	13	6.3
12	~0	<1		12.5	4.8	11.3	2.5	13	6.4
13	3.4[h]	−2.2 ($J_{2,4}$)				10.7[i]	3.5	16.7	6.3
17	3.5	10	12	11.7	4.3	11.7	2.2	13	6.3
18	3.2	10.6		11.5	4.5	11.5	2.4	13	6.3
26	~0	2.7		3.6		9.4			
27	3[j]	−2.1 ($J_{2,4}$)				9[i]			

[a]AB part of ABX or ABM system. [b]The CH_3SO_3 signal (s, 3 H) occurred at δ 2.94 and 2.99 in the spectra of **3** and **4**, respectively. [c]The signals (s, 3 H) for O-Ac and NH-Ac ocurred at δ 2.14 and 1.95, respectively. [d]The signal was a td or ddd, with the center part obscured by the O-Me signal; it was narrowed by 12 Hz on D_2O exchange. [e]A two-proton multiplet for H-5 and H-6*e*; H-6*a* gave a distorted triplet at δ 3.80. [f]Partially overlapped by doublet of doublets for H-6*e* at δ 4.32; H-6*a* gave a triplet (*J* 10.3 Hz) at δ 3.83. [g]Not determined. [h]Lines broadened by small coupling with H-4. [i]Lines of the H-4*a* doublet split into narrow multiplets (W ~3.6 Hz) due to allylic and homoallylic couplings. [j]Lines of the H-1 doublet split into narrow multiplets (W ~2 Hz) due to long-range couplings.

TABLE II

^{13}C-CHEMICAL SHIFTS (p.p.m.) FOR GLYCOSIDES IN $CDCl_3$ SOLUTION

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*OCH_3*	*CF_3*
7	100.6	66.5	80.5	30.6	63.4	21.0	55.0	
8	99.9	67.4	80.8	30.2	61.5	20.5	55.3	
10	98.0	69.9	43.6	34.4	64.1	[a]	54.8	
11[b]	98.0	66.8	45.9	33.2	63.5	21.0	54.9	117.5
12[b]	97.5	80.4	44.7	32.5	64.0	20.7	55.3	116.8, 120.1
13[b]	95.9	112.0	133.3	34.3	62.1	20.7	55.3	117.1
15	98.9	69.7	85.2	37.0	63.0	20.5	55.4	
17[b,c]	100.6	71.3	49.8	38.9	64.1	21.0	55.1	118.6
18[b]	96.7	83.4	46.1	38.6	63.6	20.2	55.6	116.4, 120.1

[a]Signals at 21.0, 21.2 and 23.5 p.p.m. for C-6 and two $CO\text{-}CH_3$ groups; the carbonyl carbon atoms of the latter resonated at 170.4 and 169.0 p.p.m. [b]Resonance for the carbonyl carbon atom of the trifluoroacetyl group was not discernible with certainty. [c]In acetone-d_6–$CDCl_3$.

Compound **3** crystallized as needles that sintered at 93–94° and melted at 102–103°, $[\alpha]_D$ −128° (*c* 0.7); lit.[13] for D enantiomer: m.p. 93–93.5°, $[\alpha]_D$ +96.6°.

Compound **4** (needles) had m.p. 112–113° and $[\alpha]_D$ −152° (*c* 1); lit.[17] for D enantiomer, m.p. 106–107°, $[\alpha]_D$ +148°.

The ^{1}H-n.m.r. spectra of **3** and of **4** (see Table I), which show distinctive chemical-shift differences, revealed absolutely no contamination of the one with the other.

*Methyl 3,4,6-trideoxy-3-nitro-α-*L-threo-*hex-3-enopyranoside* (**6**). — Dimesylate **2** was converted into methyl 2-*O*-acetyl-3,4,6-trideoxy-3-nitro-α-L-*threo*-hex-3-enopyranoside (**5**) as described[8]. A solution of **5** (3.30 g) in 3% methanolic hydrogen chloride (30 mL) was kept for 42 h at room temperature and then evaporated *in vacuo*, to give a pale-yellow syrup. Chromatography on a short column with solvent *H* gave, in the forefractions, a minor, syrupy by-product (350 mg, 12%) that had not been noticed in an earlier, small-scale experiment[9]. Its i.r. and ^{1}H-n.m.r. spectra were superposable on those of the *2-O-methyl derivative* of **6** previously obtained in other ways[9,18]. The main fractions from the column furnished syrupy **6** (1.06 g, 70%) whose ^{1}H-n.m.r. data were identical with those recorded[9].

*Methyl 3,4,6-trideoxy-α-*L-lyxo-*hexopyranoside* (**7**) *and α-*L-arabino *isomer* **8**. — A solution of **6** (1.06 g) in 99% ethanol (80 mL) was stirred at 0° with $NaBH_4$ (0.43 g, added gradually during 3 min). After 25 min, some methanol was added, and the solution was stirred with Amberlite IR-120 (H^+) resin until neutral, the suspension filtered, and the filtrate evaporated to dryness. Multiple portions of methanol were added to and evaporated from the residue for removal of boric acid. In t.l.c. (solvent *B*), a strong spot for **7** (R_F 0.5) was seen, together with a weak spot (R_F 0.4) that represented **8**, although it was difficult to differentiate it from starting **6** (R_F 0.43). Chromatography on a column with solvent *E* afforded homogeneous **7**

(782 mg, 73%) followed by **8** (100 mg, 9.5%), both crystallizing from ether–hexane.

Compound **7** had m.p. 65°, $[\alpha]_D$ −30.4° (*c* 1); ν_{max}^{KBr} 3430 (OH), 1546 and 1389 cm^{-1} (NO_2); *m/z* 192 (0.9%, M^+ +1), 160 (100%, $M^+ + 1 - CH_3OH$), and 113 (42%, $M^+ + 1 - CH_3OH - HNO_2$).

Anal. Calc. for $C_7H_{13}NO_5$ (191.2): C, 43.97; H, 6.85; N, 7.32. Found: C, 43.98; H, 6.86; N, 7.29.

Compound **8** had m.p. 103–104°, $[\alpha]_D$ −42.4° (*c* 0.5); ν_{max}^{KBr} 3392 (OH), 1548 and 3 bands near 1365 cm^{-1} (NO_2); *m/z* 160 (9%, $M^+ + 1 - CH_3OH$) and 113 (100%, $M^+ + 1 - CH_3OH - HNO_2$).

Anal. Calc., as for **7**; Found: C, 44.04; H, 6.86; N, 7.33.

*Methyl 3-amino-3,4,6-trideoxy-α-*L*-lyxo-hexopyranoside* (**9**) *and its* N,O-*diacetyl derivative* **10**. — Nitro glycoside **7** (823 mg) dissolved in ethanol (10 mL) and water (20 mL) containing M HCl (4.5 mL) was hydrogenated during 24 h over Adams' catalyst (500 mg of PtO_2, prehydrogenated), at ambient temperature and pressure. The catalyst was removed and washed well with water, and the filtrate and washings combined and evaporated, to give, quantitatively, the syrupy hydrochloride of **9**. The product was de-ionized in aqueous methanol by treatment with Dowex-1 X8 resin (carbonate form), to give **9** as a syrupy carbonate (740 mg, 90%). For characterization, a 100-mg sample was acetylated overnight with acetic anhydride (5 mL) and pyridine (2 mL). Customary processing gave **10**, which, after passage through a column of silica gel by means of ether, was obtained crystalline, and was recrystallized from ether–hexane; yield, 66 mg; m.p. 162–164°, $[\alpha]_D$ −26° (*c* 1); ν_{max} 3280 (NH), 1740 (ester CO), 1660 and 1540 cm^{-1} (amide I and II); *m/z* 246 (67%, $M^+ + 1$) and 214 (100%, $M^+ + 1 - CH_3OH$).

Anal. Calc. for $C_{11}H_{19}NO_5$ (245.3): C, 53.86; H, 7.81; N, 5.11. Found: C, 54.04; H, 7.55; N, 5.46.

*Methyl 3,4,6-trideoxy-3-(trifluoroacetamido)-α-*L*-lyxo-hexopyranoside* (**11**). — Compound **9** (as carbonate; 573 mg) was treated with trifluoroacetic anhydride (2.5 mL) in dry ether (10 mL) at 0°. The mixture was stirred for 3.5 h, and then evaporated with repeated additions of fresh ether. The *N,O*-diacylated product was *O*-deacylated by dissolution in methanol (15 mL) and storage overnight at room temperature. Removal of the solvent, and passage of the syrupy product through a column of silica gel with solvent *C*, furnished **11**, which crystallized as fine needles (618 mg, 80%); m.p. 139–140°, $[\alpha]_D$ −91.5° (*c* 1); ν_{max} 3470 and 3335 (sharp, OH, NH), 1710 and 1560 cm^{-1} (amide); *m/z* 258 (13%, $M^+ + 1$) and 226 (100%, $M^+ + 1 - CH_3OH$).

Anal. Calc. for $C_9H_{14}F_3NO_4$ (257.2): C, 42.03; H, 5.49; F, 22.16. Found: C, 41.86; H, 5.43; F, 22.41.

*Methyl 3,4,6-trideoxy-3-(trifluoroacetamido)-2-*O*-(trifluoromethylsulfonyl)-α-*L*-lyxo-hexopyranoside* (**12**). — Trifluoromethanesulfonic anhydride (0.11 mL) was added at −10° to dry 1,2-dichloroethane (10 mL) containing pyridine (0.06 mL). After 10 min, a solution of **11** (80 mg) in dry 1,2-dichloroethane (3 mL) was added dropwise. Cooling was discontinued, and, after standing for 1 h at ambient

temperature, the mixture was diluted with dichloromethane (25 mL), washed successively with saturated $NaHCO_3$ solution (2 × 50 mL) and water (50 mL), dried ($MgSO_4$), and evaporated, to give crude **12** (103 mg, 85%). Purification on a small column of silica gel (solvent *E*) afforded crystalline **12** (90 mg, 74.3%); m.p. 127–133°, $[\alpha]_D$ +15.3° (*c* 1); ν_{max} 3350 (NH), 1710 and 1540 (amide I and II); *m/z* 390 (22%, $M^+ + 1$) and 358 (100%, $M^+ + 1 - CH_3OH$).

Anal. Calc. for $C_{10}H_{13}F_6NO_6S$ (389.3): C, 30.85; H, 3.36; S, 8.24. Found: C, 31.14; H, 3.52; S, 8.31.

*Methyl 2,3,4,6-tetradeoxy-3-(trifluoroacetamido)-α-*L*-glycero-hex-2-enopyranoside* (**13**). — A solution of scrupulously dried **1** and anhydrous tetrabutylammonium fluoride (450 mg) in dry acetonitrile (5 mL; freshly distilled from P_2O_5) was added at −20° to a solution of **12** (118 mg) in acetonitrile (5 mL). The mixture was kept for 1 h at −20° and then for 1 h at room temperature, and evaporated, and the residue was chromatographed on silica gel by use of solvent *G* followed by solvent *F*. (Monitoring by t.l.c., with solvent *F*, necessitated inspection of the plates under u.v. light, as spraying with H_2SO_4 was ineffective.) There was obtained crystalline **13** (60 mg, 83%). Recrystallization from hexane gave **13** (23 mg) containing a small proportion of an unidentified impurity revealed by the n.m.r. spectrum; m.p. 108–109°, $[\alpha]_D$ −6°, $[\alpha]_{436}$ −31° (*c* 1); ν_{max} 3300, 1730 (weak), 1710 (strong), 1680 (weak), and 1570 (medium strong) cm^{-1}; *m/z* 240 (3%, $M^+ + 1$) and 208 (100%, $M^+ + 1 - CH_3OH$).

Anal. Calc. for $C_9H_{12}F_3NO_3$ (239.2): C, 45.19; H, 5.06. Found: C, 44.58; H, 4.73.

*Methyl 3,4,6-trideoxy-3-(trifluoroacetamido)-α-*L*-xylo-hexopyranoside* (**17**). — Reductive de(hydromethylsulfonyloxyl)ation of 4-monomesylate **3** with $NaBH_4$ in ethanol as described[13] for the D enantiomer gave the known[5] methyl 3,4,6-trideoxy-3-nitro-α-L-*xylo*-hexopyranoside (**15**) in 60% yield. Catalytic hydrogenation of **15** furnished a 96% yield of aminoglycoside[5] **16**. Trifluoroacetylation of **16** as described for the preparation of **11** afforded a 93% yield of crystalline **17**; m.p. 233–234°. $[\alpha]_D$ −143° (*c* 1, methanol); ν_{max} 3440, 3290 (OH, NH), 1700 and 1565 cm^{-1} (amide I and II); *m/z* 258 (10%, $M^+ + 1$) and 226 (100%, $M^+ + 1 - CH_3OH$).

Anal. Calc. for $C_9H_{14}F_3NO_4$ (257.2): C, 42.03; H, 5.49; F, 22.16. Found: C, 42.19; H, 5.31; F, 22.09.

*Methyl 3,4,6-trideoxy-3-(trifluoroacetamido)-2-*O*-(trifluoromethylsulfonyl)-α-*L*-xylo-hexopyranoside* (**18**). — Compound **17** was triflated as described for **11**, furnishing, after chromatography, a 76% yield of **18** (recrystallized from ether–hexane); m.p. 141–142°, $[\alpha]_D$ −76° (*c* 1); ν_{max} 3300 (NH), 1710 and 1565 cm^{-1} (amide I and II); *m/z* 390 (44%, $M^+ + 1$), 358 (29%, $M^+ + 1 - CH_3OH$), 245 (100%, $M^+ - CH_3OH - CF_3CONH$), and 240 (26%, $M^+ - CF_3SO_3$).

Anal. Calc. for $C_{10}H_{13}F_6NO_6S$ (389.3): C, 30.85; H, 3.36; S, 8.24. Found: C, 31.14; H, 3.40; S, 8.25.

Reactions of triflate **18** *with fluoride ion. — (a) With tetrabutylammonium*

fluoride. To a solution of **18** (139 mg) in dry acetonitrile (10 mL), cooled to 0°, was added a cooled solution of anhydrous tetrabutylammonium fluoride (750 mg) in dry acetonitrile (4 mL). After 1 h, all of the **18** (R_F 0.25) had been consumed, and product spots having R_F 0.5 and 0.0 were seen in t.l.c. (solvent *C*). The solvent was evaporated, and the residue chromatographed with solvent *A*. It appeared that the fast-moving product decomposed on the column during the operation, as only traces, insufficient for characterization, were eluted. The column was then eluted with methanol, the eluate evaporated, and the residue chromatographed with solvent *G*. There was obtained 29 mg (31%) of crystalline alcohol **11**, identified by comparison of its mass spectrum and ^{1}H- and ^{13}C-n.m.r. spectra with those of authentic **11**.

(b) With potassium hydrogendifluoride. A solution of **18** (30 mg) in ethylene glycol (2 mL, dried by refluxing overnight over magnesium turnings) was mixed with KHF_2 (100 mg, oven-dried at 160°), and the mixture was heated for 90 min at ~120° under a N_2 atmosphere; all of the **18** (R_F 0.25) had then been converted into more-polar material (R_F 0.0 with solvent *C*; with ether as the t.l.c. solvent, a major and a minor product, having R_F 0.3 and 0.6, respectively, were seen). The mixture was diluted with water (5 mL) and extracted with chloroform (3 × 15 mL). The extracts were combined, dried (Na_2SO_4), and evaporated, to give an amorphous solid (25 mg) which was chromatographed on a small column by use of solvent *B*. The faster-moving product was isolated as a syrup (a few milligrams only); *m/z* 270 (47%), 208 (19%), 157 (11%), and 149 (100%), similar to the main product. The less-mobile product was obtained as a crystalline solid (18 mg) that had m.p. 102–104°, and was assigned the structure of methyl 3,4,6-trideoxy-2-*O*-(2-hydroxyethyl)-3-(trifluoroacetamido)-α-L-*lyxo*-hexopyranoside (**19**) on the basis of spectral evidence; ν_{max} 3500–3400 (OH), 3300 (NH), 1710 and 1570 cm^{-1} (amide I and II); *m/z* 270 (63%, $M^+ + 1 - CH_3OH$), 240 [69%, $M^+ + 1 - C_2H_4(OH)_2$]; 208 [32%, $M^+ + 1 - CH_3OH - C_2H_4(OH)_2$], 157 (10%), and 149 (100%); ^{1}H-n.m.r.: δ 6.5 (br, exchangeable, NH), 4.55–4.35 (m, 2 H, H-1,3), 4.22 (m, *W* 34 Hz, *J* ≈ 4, 6, and 12 Hz, H-5), 3.85 and 3.65 (2 m, 2 and 3 H, H-2, O-CH_2CH_2-O), 3.43 (s, 3 H, OMe), 3.05 (t, exchangeable, OH), 2.64 (septet, *W* 25 Hz, J_{gem} 12 Hz, H-4e), 1.53 (dt, $J_{3,4a}$ 9, $J_{4a,5} = J_{gem}$ = 12 Hz, H-4a), and 1.31 (d, *J* 6.1 Hz, C-CH_3).

*Methyl 3-azido-4,6-O-benzylidene-3-deoxy-2-O-(trifluoromethylsulfonyl)-α-*D-*altropyranoside* (**26**). — Although compound **26** had been prepared before[16], we record our mode of preparation because of some discrepancy in physical constants found for the product. Trifluoromethanesulfonic anhydride (0.77 mL, 4.55 mmol) was added to dry dichloromethane (30 mL) containing dry pyridine (1.3 mL), with stirring under N_2 at −15°. After 10 min, a solution of methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside (1.0 g; m.p. 135–136° as reported[19]) in dichloromethane (6 mL) and pyridine (1.3 mL) was added dropwise but rapidly, and stirring was continued for 10 min at −15° and 40 min at 0°. A clean conversion of the starting glycoside (R_F 0.17) into **26** (R_F 0.65) was indicated by t.l.c. (1:3 ethyl acetate–hexane). The mixture was diluted with dichloromethane, and washed

successively with ice-cold $NaHCO_3$ solution (2 × 100 mL) and water twice, dried (Na_2SO_4), and evaporated, with several additions of toluene, to give a yellow residue from which, on trituration with ethyl acetate, several crops of crystalline, almost colorless **26** could be isolated (895 mg total); m.p. 145–147° (dec.). The yellow material of the mother liquor was chromatographed with 1:9 ethyl acetate–hexane as the eluant, to furnish a further 415 mg of pure **26**, for a total yield of 91.6%. Recrystallized from chloroform–petroleum ether, **26** had m.p. 146–147° (dec.), $[\alpha]_D$ +8.2° (*c* 1.5); lit.[16] m.p. 131–133°, $[\alpha]_D$ +45°; ν_{max} 2110 cm^{-1} (N_3); *m/z* 440 (100%, $M^+ + 1$), 412 (25%, $M^+ + 1 - N_2$), and 262 (19%, $M^+ + 1 - N_2 - CF_3SO_3H$).

Anal. Calc. for $C_{15}H_{16}F_3N_3O_7S$ (439.4): C, 41.00; H, 3.67; N, 9.56. Found: C, 41.04; H, 3.72; N, 9.43.

*Methyl 3-azido-4,6-O-benzylidene-2,3-dideoxy-α-*D-erythro-*hex-2-enopyranoside* (**27**). — A solution of **26** (100 mg) in 1:1 dimethyl sulfoxide–hexamethylphosphoric triamide (5 mL) was stirred in a stoppered flask at 80° with a mixture of anhydrous CsF and CaF_2 (200 mg of each, dried at 120°). The conversion of **26** (R_F 0.6) into **27** appeared complete after 1.5 h (t.l.c. with solvent *G*). The suspension was filtered through a plug of cotton, and the filtrate was introduced into ice-cold water (~25 mL), to give a milky suspension which soon turned into a voluminous precipitate of felt-like needles of **27**. Collected after some cooling, washed with cold water, and air-dried, it weighed 40 mg (60%); m.p. 121–123° (dec., with evolution of gas), $[\alpha]_D$ +27° (*c* 0.9); ν_{max} 2110 (N_3) and 1655 cm^{-1} (alkene); *m/z* 290 (2.4%, $M^+ + 1$), 262 (18%, $M^+ + 1 - N_2$), 258 (8%, $M^+ + 1 - CH_3OH$), 230 (38%, $M^+ + 1 - N_2 - CH_3OH$), 179 (93%), 149 (100%), and 121 (89%).

Anal. Calc. for $C_{14}H_{15}N_3O_4$ (289.3): C, 58.12; H, 5.23. Found: C, 58.26; H, 5.41.

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