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Synthesis and antitumor activity of 7-*O*-[2,6-dideoxy-2-fluoro-5-*C*-(trifluoromethyl)-α-L-talopyranosyl]-daunomycinone and -adriamycinone

Ken Nakai, Yasushi Takagi *, Tsutomu Tsuchiya

Institute of Bioorganic Chemistry, 3-34-17 Ida, Nakahara-ku, Kawasaki 211-0035, Japan

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Abstract

7-*O*-[2,6-Dideoxy-2-fluoro-5-*C*-(trifluoromethyl)-α-L-talopyranosyl]-daunomycinone and -adriamycinone have been prepared by the coupling of 3,4-di-*O*-acetyl-2,6-dideoxy-2-fluoro-5-*C*-(trifluoromethyl)-α-L-talopyranosyl iodide with daunomycinone. The key steps in this synthesis are the regioselective fluorination of methyl α-D-lyxopyranoside to give the 4-deoxy-4-fluoro-β-L-ribopyranoside and the *C*-trifluoromethylation of the *aldehydo*-L-ribose derivative to give the 1,1,1-trifluoro-5-monofluoro-L-altritol derivative. Antitumor activities of the synthetic products were compared with those for the 2′-deoxy-2′-fluoro and 2′,6′-dideoxy-5′-*C*-trifluoromethyl analogs.

Keywords: Carbohydrates; Deoxyfluoro sugars; Anthracycline glycoside; Antitumor activity; 7-*O*-[2,6-Dideoxy-2-fluoro-5-*C*-(trifluoromethyl)-α-L-talopyranosyl]adriamycinone

1. Introduction

Anthracycline glycosides, such as daunorubicin and doxorubicin (DOX), are a group of the most important antitumor agents used during the past two decades. Their use is, however, restricted by cardiotoxicity and other undesirable side-effects, as well as the occurrence of resistant tumor cells. In preceding papers [1–9] we reported several fluorine-containing analogs of daunorubicin and doxorubicin, and some of them proved to have strong antitumor activities. For example, 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)-adriamycinone (**1**) [1] showed stronger antitumor activity than DOX against murine leukemia L1210, with lower toxicity in vivo. Chemically, compound **1** has the strongly electron-withdrawing fluorine atom at C-2′, stabilizing the glycosidic bond against acidic hydrolysis due to a decrease of the electron density at the glycosidic oxygen, thus restricting protonation, and the 3′-amino group in DOX is replaced by a hydroxyl group; this replacement was first reported by Horton and co-workers [10], suggesting that the 3′-amino group in DOX is not necessarily essential. Another example is 7-*O*-[2,6-dideoxy-5-*C*-(trifluoromethyl)-α-L-*lyxo*-hexopyranosyl]-adriamycinone (**2**) [8]. This compound also showed stronger antitumor activity than DOX against murine leukemia L1210 in vivo in a low dose range, as indicated by the survival of seven out of 12 mice tested (ip injection) [8]. Compound **2** also has a strongly electron-withdrawing trifluoromethyl group at C-5′; the

* Corresponding author. Fax: +81-44-755-3099.

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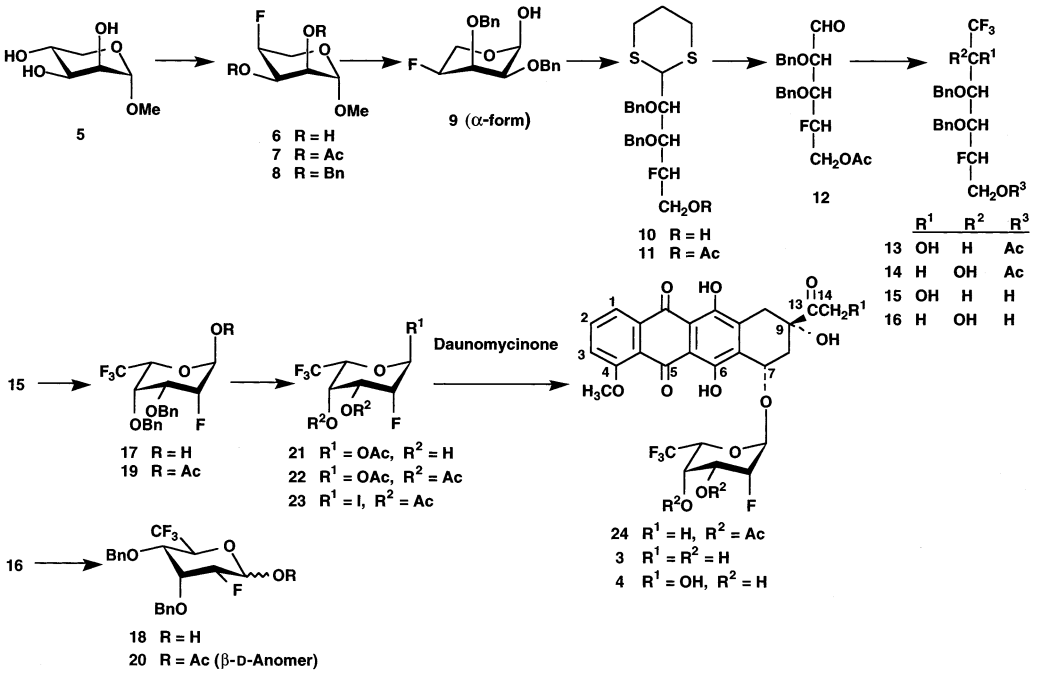
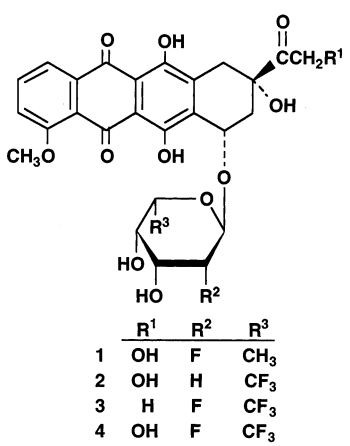


Scheme 1.

CF_3 group, as against a CH_3 group, is also expected to strengthen the glycosidic bond. The higher lipophilicity of the CF_3 group as compared with the CH_3 group would also be a factor raising activity, enhancing the cellular uptake and facilitating the transportation of the compound into organs. Based on these results, we have undertaken to introduce a fluorine atom at C-2′ and a CF_3 group at C-5′, hoping that the new compound would show much stronger antitumor activity. We report here the preparation and antitumor activity of 7-*O*-[2,6-dideoxy-2-fluoro-5-*C*-(trifluoromethyl)-α-L-talopyranosyl]-daunomycinone (**3**) and -adriamycinone (**4**).



2. Results and discussion

Synthesis.—We prepared the fluorine-containing sugar by introducing a CF_3 group at C-1 of a precursor sugar derivative. As this approach necessarily requires head-to-tail inversion, the fluorine atom at C-2 of the final sugar, 2,6-dideoxy-2-fluoro-5-*C*-(trifluoromethyl)-L-talopyranose, must be brought in by attachment of a fluorine atom at C-4 of the starting sugar. For this reason, we chose methyl α-D-lyxopyranoside (**5**) as the precursor (see Scheme 1).

Treatment of **5** with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 gave selectively the 4-deoxy-4-fluoro-β-L-ribopyranoside (**6**) in high yield; the facile reaction may be attributed to the formation of a 2,3,4-tris[diethylamino(difluorosulfoxy)] intermediate; one of the S*F* atoms of the 2-OSF_2NEt_2 group may attack C-4 from the upper side, as reported in the synthesis of methyl 4,6-dideoxy-4,6-difluoro-α-D-talopyranoside from methyl α-D-mannopyranoside [11]. The large coupling constants $J_{4,F}$ (49 Hz), $J_{3,F}$ (29.5 Hz) and $J_{5ax,F}$ (38 Hz) in the ^1H and ^{19}F NMR spectra indicate that the fluorine atom is introduced axially at C-4 of **5**. An interspace coupling (7.5 Hz) between F and O*H*-2 also supports the structure. The structure was further confi-

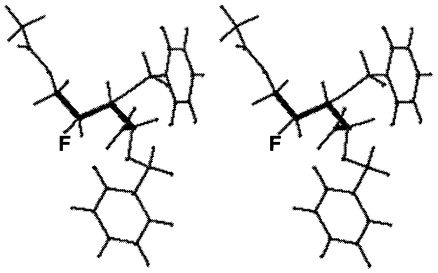


Fig. 1. A stereoview of **12** in one of the lowest energy conformations (the H-1–F-4 distance is 2.98 Å).

rmed by preparing the 2,3-diacetate **7**. Benzylation of **6** (to give **8**) with subsequent acid hydrolysis gave the free sugar **9**. This compound showed a complicated ^{1}H NMR spectrum, but its ^{19}F NMR spectrum showed distinct two-region signals, suggesting that **9** is an anomeric mixture with α:β ratios of 1:2 (initially dissolved in $CDCl_3$) and 4:1 (after 180 h). The α anomer was confirmed to have the $^1C_4$(L) structure by the large $J_{4,5ax}$ (10.5 Hz) coupling constant, an NOE between H-2 and H-4 (upon H-2 irradiation, a 4.1% signal increase was observed), and a long-range coupling ($^5J \sim 4$ Hz) between H-1 and F-4.

Compound **9** was converted into the dithioacetal **10** by treating it with 1,3-propanedithiol in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2, and the product was acetylated to give the 5-acetate **11**. Removal of the dithioacetal group [$Hg(ClO_4)_2{\cdot}3H_2O$ and $CaCO_3$] gave the aldehydo sugar **12**. This compound showed in its ^{1}H and ^{19}F spectra a $J_{1,F}$ coupling (3.5 Hz) (see Section 3). This coupling was first considered to be derived from a long-range coupling (^5J) between the H-1 and F-4, however, if the C-1, -2, -3, -4 and F-4 atoms adopt a periplanar zigzag conformation (typical conditions to give a long-range coupling; in **9**, $^5J_{H\text{-}1,F\text{-}4}$ coupling was observed due to its periplanar conformation), the structure does not satisfy the $J_{H,H}$ and $J_{H,F}$ coupling values observed. Thus, a through-space coupling between the slightly acidic C*H*O and the basic F-4 atoms was considered instead. An energy-minimal conformation (Fig. 1) obtained by MOPAC calculation (in $CHCl_3$) was consistent with the data.

Trifluoromethylation of **12** by treatment with Me_3SiCF_3 in the presence of catalytic amounts of Bu_4NF (in oxolane) according to the procedure of Prakash and co-workers [12], followed by acid hydrolysis, gave the desired 1,5-dideoxy-1,1,1,5-tetrafluoro-L-altritol **13** (29%), together with its epimer 1,5-dideoxy-1,1,1,5-tetrafluoro-L-allitol (2,6-dideoxy-2,6,-6,6-tetrafluoro-D-allitol) **14** (39%). The configurations of the newly introduced asymmetric center at the C-2 of **13** and **14** were determined by transforming the alditols into the corresponding pyranoses (vide infra). The undesired compound **14** could be converted back into **13** by treatment of the triflate of **14** with $NaNO_2$ in DMF [13] in 42% yield. After Zemplén deacetylation of **13**, the primary hydroxyl group of **15** was oxidized selectively. Mizutani and co-workers reported that the hydroxyl group closest to a trifluoromethyl group is unusually resistant to oxidation [14]. Thus, Swern oxidation of **15** gave a cyclic sugar **17**, which was isolated as its 1-acetate **19**. The α-L-*talo* structure of **19** with the $^1C_4$(L) conformation was supported by a large $J_{F\text{-}2,3}$ (31 Hz) coupling constant, couplings of $J_{4,5}$ (1.5 Hz) and $J_{1,F\text{-}2}$ (8.5 Hz) in its ^{1}H NMR spectrum, and the presence of NOE between H-3 and H-5. Similarly, **14** was converted into the 1-acetate **20** through **16** and **18**, whose structure was determined to be β-D-*allo* with the $^4C_1$(D) conformation from the large coupling constants $J_{1,2}$ (8 Hz) and $J_{4,5}$ (9.5 Hz) and the existence of the NOE between H-2 and H-4.

Catalytic hydrogenolysis of **19** followed by acetylation of the resulting **21** gave the triacetate **22**. Activation of the anomeric center of **22** was somewhat difficult, possibly because of the electron-withdrawing F-2 and CF_3-5. Conventional bromination (30% HBr in AcOH or $TiBr_4$ in CH_2Cl_2–EtOAc) failed, giving rise only to starting material. An attempt to prepare the ethyl thioglycoside (using EtSH, $BF_3{\cdot}OEt_2$ in CH_2Cl_2) also gave only **22**. However, phenyl thioglycosidation [$PhSSiMe_3$, Bu_4NI, ZnI_2 in $Cl(CH_2)_2Cl$] [15] gave a mixture of the phenyl thioglycoside and the glycosyl iodide **23**. Compound **22**, therefore, was treated with Me_3SiI (in toluene at 80 °C), whereupon **23** was produced successfully, although the yield was not high (57%). The

Table 1
^{1}H and ^{19}F NMR data (chemical shifts in ppm (δ) and coupling constants (J) in Hz) for compounds **24**, **3**, and **4**

	Multiplicity	H-1 d ($J_{1,2}$)	H-2 t ($J_{2,3}$)	H-3 d	H-7 dd ($J_{7,8ax}$) ($J_{7,8eq}$)	H-8*ax* dd ($J_{8ax,8eq}$)	H-8*eq* br d	H-10*ax* d ($J_{10ax,10eq}$)	H-10*eq* dd ($J_{8eq,10eq}$)	H-14 s	OH-9 s	OH-6, 11 (each s)
24[a]		8.09 (7.5)	7.80 (8.5)	7.40	5.28 (4.5) (~1.5)	2.22 (15.5)	2.47	2.96 (19)	3.15 (~1.5)	2.39	3.60	13.23, 14.02
3[b]		8.06 (7)	7.72 (8)	7.41	5.50 (5.5) (2.5)	2.49 (15)	2.92	3.41 (18)	3.50 (~1)	2.58	[c]	13.55, 14.59
4[b]		8.05 (7.5)	7.72 (8.5)	7.42	5.48 (5) (2)	2.55 (15)	2.97	3.42 (18.5)	3.56[d]	5.40[e]	[c]	13.48, 14.55
	Multiplicity	OCH_3 s	H-1′ br d ($J_{1',F-2'}$)	H-2′ br d ($J_{2',F-2'}$)	H-3′ dt ($J_{2',3'}$) ($J_{3',4'}$) ($J_{3',F-2'}$)	H-4′ br s	H-5′ br q ($J_{5',F-6'}$)	OAc s	F-2 ddd	F-6 d		
24[a]		4.12	5.75 (9)	4.61 (49.5)	5.01 (3) (3) (32)	5.62	4.78 (6.5)	2.15, 2.03	−201.7	−74.1		
3[b]		3.98	6.18 (9)	5.22 (49.5)	4.31 (3) (3) (34)	4.55	5.33 (7)		−200.3	−71.9		
4[b]		3.98	6.14 (9)	5.20 (49)	4.28 (~3) (~3) (34)	4.55	5.34 (7)		−200.3	−71.9		

[a] In $CDCl_3$.
[b] In pyridine-d_5.
[c] Not detected.
[d] br d.
[e] ABq, J_{gem} 20 Hz.

anomeric structure of **23** could not be determined from the $J_{1,F-2}$ value (13.5 Hz) because it is intermediate between the usual α-L (~ 8 Hz) and β-L (~ 20 Hz) values [16]. However, the presence of NOEs between F-2 and H-1, and H-5 and H-3, and the absence of NOE between H-5 and H-1 all indicate that **23** should be mainly the α-L anomer. The glycosyl iodide **23** was relatively stable and could be stored for at least 3 days at − 30 °C without decomposition.

Coupling of **23** with daunomycinone under Koenigs–Knorr conditions [yellow HgO and HgI_2, in $Cl(CH_2)_2Cl$ at 80 °C] gave the α-L-glycoside **24** ($J_{1',F-2'}$ 9 Hz) in 67% yield. Judging from the fact that, in the preparation of **2** [8], the α-L- and β-L-glycosides were produced almost in equal amounts, the selective α-L-glycosidation might be attributable to the axial F-2 in **23**. Alkaline deacetylation of **24** gave the desired 7-*O*-[2,6-dideoxy-2-fluoro-5-*C*-(trifluoromethyl)-α-L-talopyranosyl]daunomycinone (**3**). Compound **3** thus prepared was then transformed into the doxorubicin-type compound **4** according to the general procedure of Arcamone and co-workers [17], and the specific procedure for the preparation of **1** [2]. Bromination of **3** with Br_2 in the presence of $HC(OMe)_3$ gave the 14-bromo-13-dimethyl acetal, which on treatment with acetone afforded the 14-bromo derivative together with the small amount of the 14-bromo-3′,4′-isopropylidene acetal. Treatment of the mixture with HCO_2Na (aq acetone–oxolane) gave a mixture of four products, namely **4**, the 14-formyloxy derivative of **4**, the 14-hydroxy-3′,4′-isopropylidene acetal, and the 14-formyloxy-3′,4′-isopropylidene acetal. After the formyloxy and isopropylidene groups had been hydrolyzed off (aq NH_3 in MeOH–oxolane and aq 80% AcOH at 80 °C, respectively), the desired 7-*O*-[2,6-dideoxy-2-fluoro-5-*C*-(trifluoromethyl)-α-L-talopyranosyl]-adriamycinone (**4**) could be obtained in 70% yield. The structures of **3** and **4** were confirmed by the ^1H, ^{19}F (Table 1) and ^{13}C NMR spectra (Table 2).

Antitumor activity.—Antitumor activities of the synthetic products (**3** and **4**) were compared with those for the 2′-fluoro (**1**) and 5′-trifluoromethyl analogs (**2**) against L1210 murine leukemia in vivo (Table 3). The doxorubicin-type analog **4** showed a slightly higher antitumor activity than **1**, although **4** did not attain the level exhibited by **2**. However, as the efficacy of antitumor drugs is determined after a variety of biological tests, a final evaluation of **4** remains to be established. It is noteworthy, however, that the daunorubicin-type analog **3** showed only low activity, which suggests that the 14-hydroxyl group is important in exhibiting antitumor activity in these compounds.

Table 2
^{13}C NMR chemical shifts (δ, ppm) and coupling constants ($J_{C,F}$, Hz in parentheses) for compounds **3** and **4** in pyridine-d_5

C	**3**	**4**
1	119.6	119.62
2	135.6	136.1
3	119.5	119.55
4	161.5	161.5
4a	121.1	121.2
5	187.0[a]	187.1[a]
5a	111.6[b]	111.7[b]
6	155.5[c]	155.5[c]
6a	[e]	134.5[d]
7	73.4	73.2
8	36.9	37.3
9	76.1	76.0
10	32.8	33.3
10a	[e]	134.8[d]
11	157.0[c]	156.9[c]
11a	111.9[b]	112.0[b]
12	187.2[a]	187.2[a]
12a	[e]	135.6
13	212.5	215.2
14	24.5	65.6
OMe	56.7	56.7
1′	103.0 d (32.5)	103.0 d (31.7)
2′	90.0 d (180.7)	89.9 d (180.1)
3′	66.2 d (16.4)	66.2 d (16.6)
4′	67.4	67.3
5′	70.9 q (30.4)	70.9 q (30.0)
6′	125.3 q (279.6)	125.2[f] q[g]

[a,b,c,d] Figures in the same column may be interconvertible.
[e] Not assigned due to overlapping of the signals with those for pyridine-d_5.
[f] Judged from the F-6′-decoupled ^{13}C NMR.
[g] Judged by the HMBC method.

Table 3
Antitumor activities[a] (T/C[b] (%) and 60-day survivor numbers/treated numbers of mice) of **3** and **4** in comparison with **1** and **2** against the murine L1210 cell line

Compound	Dose (mg kg^{-1} day^{-1})					
	5	2.5	1.25	0.6	0.3	0.15
3	158[c]	210[c]	294	132	119	106
	0/4	0/4	0/4	0/4	0/4	0/4
4	128[c]	233[c]	>348	>459	>407	144
	0/4	0/4	1/4	1/4	1/4	0/4
1	>482[c]	>656	>416	>348	193	164
	2/4	3/4	1/4	1/4	0/4	0/4
2[d]	135[c]	194[c]	203	>406	>606	>612
	0/4	0/4	0/4	1/4	3/4	3/4

[a] Leukemia L1210 cells (10^5) were inoculated into CDF_1 mice (20 ± 1 g) intraperitoneally. Drugs were administered daily, starting 24 h after inoculation, from day 1 to 9 intraperitoneally.
[b] (Mean survival days of treated mice/mean survival days of control mice) × 100.
[c] More than 10% weight decrease in the treated mice was observed.
[d] See ref. [8].

3. Experimental

General methods.—Melting points were determined on a Kofler block, and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. NMR spectra (^1H at 250 and 500 MHz, ^{13}C at 125.8 MHz, and ^{19}F at 235.3 MHz) were recorded with Bruker AC-250P and AMX-500 spectrometers, using Me_4Si and $CFCl_3$ (for ^{19}F) as the internal standards. Mass spectra were measured by the fast-atom bombardment method with a Jeol SX-102 spectrometer. TLC was performed on Kieselgel 60 F_{254} (E. Merck), column chromatography on Wakogel C-200, and flash column chromatography on Wakogel C-300.

Computation.—Calculation for the stereoview of **12** (Fig. 1) was performed on a Macintosh 9500 computer with CAChe Version 4.0 (Sony Tektronix) software using MM2, refined by MOPAC6/PM3 by setting the dielectric constant as 4.80 ($CHCl_3$).

Methyl 4-deoxy-4-fluoro-β-L-ribopyranoside (**6**).—To a cold (−40 °C) suspension of **5** [18] (8.27 g, 50.4 mmol) in dry CH_2Cl_2 (170 mL), DAST (26.8 mL, 203 mmol) was added over 5 min and the mixture was stirred for 70 min at room temperature (rt). After addition of MeOH (170 mL) to the recooled solution (−20 °C), the solution was kept for 15 h at rt. Sodium hydrogencarbonate (105 g) was added, and the mixture was filtered through a Celite bed with successive washing with CH_2Cl_2. The combined filtrate and washings were concentrated to give a brown syrup, which was chromatographed (7:1 $CHCl_3$–acetone) to give **6** as a syrup: 7.54 g (90%), TLC (7:1 $CHCl_3$–acetone): R_f 0.15 (cf **5**: R_f 0.02), $[\alpha]_D^{23}$ +146° (*c* 0.7, $CHCl_3$); *m/z* 167.12 ($M^+ + 1$), calcd for $C_6H_{11}FO_4$: *m/z* 166.11; ^1H NMR ($CDCl_3$): δ 4.79 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 4.74 (br d, 1 H, $J_{4,F}$ 49 Hz, H-4), 4.0–3.7 (m, 4 H, H-2,3,5*ax*, 5*eq*), 3.42 (s, 3 H, OMe), 3.08 (d, 1 H, $J_{3,OH\text{-}3}$ 10.5 Hz, OH-3), 2.34 (dd, 1 H, $J_{2,OH\text{-}2}$ 11.5, $J_{F,OH\text{-}2}$ 7.5 Hz, OH-2). ^{19}F NMR ($CDCl_3$): δ −203.0 (ddddd, $J_{3,F}$ 29.5, $J_{4,F}$ 49, $J_{5ax,F}$ 38, $J_{5eq,F}$ 15.5, $J_{OH\text{-}2,F}$ 7.5 Hz).

Methyl 2,3-di-O-acetyl-4-deoxy-4-fluoro-β-L-ribopyranoside (**7**).—A solution of **6** (50 mg, 0.30 mmol) and Ac_2O (0.17 mL, 1.81 mmol) in pyridine (1 mL) was kept for 2 h at rt. TLC (12:1 $CHCl_3$–acetone) of the solution showed a single spot at R_f 0.55. Conventional work up gave **7** as a syrup: 68 mg (91%), $[\alpha]_D^{24}$ +98° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.24 (dt, 1 H, $J_{2,3} \approx J_{3,4}$ 3.5, $J_{3,F}$ 29 Hz, H-3), 5.11 (ddd, 1 H, $J_{1,2}$ 2, $J_{2,3}$ 3.5, $J_{2,4}$ ~1 Hz, H-2), 4.75 (d, 1 H, H-1), 4.73 (br d, 1 H, $J_{4,F}$ 50 Hz, H-4), 4.04–3.83 (m, 2 H, H-5*ax*, 5*eq*), 3.43 (s, 3 H, OMe), 2.15 and 2.11 (each 3 H s, Ac). ^{19}F NMR ($CDCl_3$): δ −202.9 (m). Anal. Calcd for $C_{10}H_{15}FO_6$: C, 48.00; H, 6.04. Found: C, 47.95; H, 6.07.

*Methyl 2,3-di-*O*-benzyl-4-deoxy-4-fluoro-β-*L*-ribopyranoside* (**8**).—To a suspension of NaH (9.36 g, 60% NaH in mineral oil, 234 mmol) in dry DMF (35 mL), a solution of **6** (7.44 g, 44.8 mmol) in DMF (35 mL) was added over 10 min, and the mixture was stirred until hydrogen evolution had ceased (~1 h). $PhCH_2Br$ (16.0 mL, 135 mmol) was added at 0 °C and the stirring was continued for 2 h at rt. TLC (12:1 $CHCl_3$–acetone) of the solution showed a spot at R_f 0.65. The mixture was poured into aq 2.6% AcOH (500 mL) and the whole mixture was extracted with $CHCl_3$. The extracts were washed with aq $NaHCO_3$ (saturated), dried (Na_2SO_4), and concentrated together with xylene. Chromatography (30:1 toluene–EtOAc) of the residue gave **8** as a syrup: 12.62 g (81%), $[\alpha]_D^{23}$ +63° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$; only important signals): δ 4.74 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.66 (ddt, 1 H, $J_{3,4} = J_{4,5ax}$ 3, $J_{4,5eq}$ 5, $J_{4,F}$ 48.5 Hz, H-4), 3.98 (ddd, 1 H, $J_{5eq,4}$ 5, $J_{5eq,5ax}$ 12, $J_{5eq,F}$ 9.5 Hz, H-5*eq*), 3.85 (dt, 1 H, $J_{2,3} = J_{3,4}$ 3, $J_{3,F}$ 23.5 Hz, H-3), 3.79 (ddd, 1 H, $J_{5ax,5eq}$ 12, $J_{5ax,4}$ 3, $J_{5ax,F}$ 24 Hz, H-5*ax*), 3.52 (dd, 1 H, H-2), 3.40 (s, 3 H, OMe). ^{19}F NMR ($CDCl_3$): δ −202.3 (dddd, $J_{3,F}$ 23.5, $J_{4,F}$ 48.5, $J_{5ax,F}$ 24, $J_{5eq,F}$ 9.5 Hz). Anal. Calcd for $C_{20}H_{23}FO_4$: C, 69.35; H, 6.69; F, 5.48. Found: C, 69.20; H, 6.92; F, 5.63.

*2,3-Di-*O*-benzyl-4-deoxy-4-fluoro-*L*-ribopyranose* (**9**).—A solution of **8** (3.06 g, 8.83 mmol) in 0.4 M HCl in aq 80% AcOH (30 mL) was kept for 3.5 h at 80 °C. TLC (5:2 hexane–EtOAc) of the solution showed spots at R_f 0.15 (**9**) and 0.4 (slight, **8**). After cooling to rt, the solution was poured into an aq suspension (200 mL) containing $NaHCO_3$ (38 g), and the whole mixture was extracted with $CHCl_3$. The extracts were washed with brine, dried (Na_2SO_4), and concentrated to give a dark brown syrup, which was chromatographed (5:2 hexane–EtOAc) to give a pale-yellow syrup of **9** (an anomeric mixture): 2.58 g (88%) with **8** recovered, 0.29 g (9.4%). Compound **9**, $[\alpha]_D^{22}$ +45° (*c* 0.75, $CHCl_3$, after 180 h); ^{1}H NMR ($CDCl_3$) (only signals for the major α anomer were described): δ 7.45–7.20 (m, Ph), 5.25 (d, $J_{1,OH}$ 10.5 Hz, OH), 5.11 (br dt, $J_{1,2}$ 3.5, $J_{1,F}$ ~4, $J_{1,OH}$ 10.5 Hz, H-1), 4.83 and 4.77 (ABq, J_{gem} 11.5 Hz, $PhCH_2$), 4.67 and 4.58 (ABq, J_{gem} 12 Hz, $PhCH_2$), 4.54 (dddd, $J_{3,4}$ 2.5, $J_{4,5eq}$ 5.5, $J_{4,5ax}$ 10.5, $J_{4,F}$ 46.5 Hz, H-4), 4.31 (br dd, $J_{3,4}$ 2.5, $J_{3,F}$ 10 Hz, H-3), 4.11 (apparent dt, $J_{4,5ax}$ 10.5, $J_{5ax,5eq}$ 11, $J_{5ax,F}$ 3 Hz, H-5*ax*), 3.72 (dddd, $J_{4,5eq}$ 5.5, $J_{5eq,5ax}$ 11, $J_{5eq,F}$ 1.5, $J_{5eq,3}$ ~1 Hz, H-5*eq*), 3.40 (narrow-range m, H-2). ^{19}F NMR ($CDCl_3$): δ −199.2 (br dd, 0.8 F, $J_{3,F}$ 10, $J_{4,F}$ 47 Hz, α anomer), −202.5 (dddd, 0.2 F, *J* 48, 19, 15.5, 8.5 Hz, the minor product). Anal. Calcd for $C_{19}H_{21}FO_4$: C, 68.66; H, 6.37; F, 5.72. Found: C, 68.65; H, 6.50; F, 5.72.

*2,3-Di-*O*-benzyl-4-deoxy-4-fluoro-*L*-ribose propane-1,3-diyl dithioacetal* (**10**).—A mixture of **9** (4.13 g, 12.4 mmol), 1,3-propanedithiol (2.1 mL, 21 mmol), and $BF_3{\cdot}OEt_2$ (0.53 mL, 4.3 mmol) in dry CH_2Cl_2 (75 mL) was stirred for 2 h at rt. TLC (12:1 toluene–EtOAc) of the mixture showed three spots at R_f 0.4, (slight) 0.25 (**10**, major), and 0.15 (**9**, slight). After dilution with $CHCl_3$, the solution was washed with aq 5% NaOH and water, dried (Na_2SO_4), and concentrated. The residue was chromatographed (12:1 toluene–EtOAc) to give **10** as a colorless syrup: 3.92 g (75%) with **9** recovered 143 mg (3.5%). Compound **10**, $[\alpha]_D^{24}$ −21° (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.45–7.20 (m, 10 H, Ph × 2), 4.95 and 4.67 (ABq, J_{gem} 11 Hz, $PhCH_2$), 4.87 (ddt, 1 H, $J_{3,4} = J_{4,5a}$ 3.5, $J_{4,5b}$ 5, $J_{4,F}$ 46.5 Hz, H-4), 4.78 and 4.67 (ABq, J_{gem} 11 Hz, $PhCH_2$), 4.42 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1), 4.19 (ddd, 1 H, $J_{2,3}$ 6, $J_{3,4}$ 3.5, $J_{3,F}$ 14 Hz, H-3), 3.84 (dddd, 1 H, $J_{4,5b}$ 5, $J_{5a,5b}$ 13, $J_{5b,OH}$ 6, $J_{5b,F}$ 24 Hz, H-5b), 3.78 (dd, 1 H, H-2), 3.74 (dddd, $J_{4,5a}$ 3.5, $J_{5a,5b}$ 13, $J_{5a,OH}$ 7, $J_{5a,F}$ 24.5 Hz, H-5a), 2.90–2.50 (m, 4 H, SCH_2 × 2), 2.09 (dd, 1 H, OH), 2.15–2.02 and 2.00–1.80 (each 1 H m, $CH_2CH_2CH_2$). ^{19}F NMR ($CDCl_3$): δ −195.6 (ddt, $J_{3,F}$ 14, $J_{4,F}$ 46.5, $J_{5a,F} = J_{5b,F}$ 24 Hz). Anal. Calcd for $C_{22}H_{27}FO_3S_2$: C, 62.53; H, 6.44; S, 15.17. Found: C, 62.68; H, 6.31; S, 15.33.

*5-*O*-Acetyl-2,3-di-*O*-benzyl-4-deoxy-4-fluoro-*L*-ribose propane-1,3-diyl dithioacetal* (**11**).—A solution of **10** (2.40 g, 5.67 mmol) and Ac_2O (2.7 mL, 28.4 mmol) in pyridine (24 mL) was kept for 4 h at rt. TLC (12:1 toluene–EtOAc) of the solution showed a single spot at R_f 0.5. Conventional work up gave **11**, 2.64 g (quant), as a colorless syrup, $[\alpha]_D^{24}$ −26° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$; only

important signals): δ 5.01 (ddt, 1 H, H-4), 4.44 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.40–4.17 (m, 2 H, H-5a, 5b), 4.14 (ddd, 1 H, H-3), 3.74 (dd, 1 H, H-2), 2.05 (s, 3 H, OAc). ^{19}F NMR ($CDCl_3$): δ −193.0 (dddd, $J_{3,F}$ 15, $J_{4,F}$ 48, $J_{5a,F}$ 32, $J_{5b,F}$ 21 Hz). Anal. Calcd for $C_{24}H_{29}FO_4S_2$: C, 62.04; H, 6.29. Found: C, 62.00; H, 6.15.

5-O-Acetyl-2,3-di-O-benzyl-4-deoxy-4-fluoro-aldehydo-L-*ribose* (**12**).—To a solution of **11** (2.58 g, 5.55 mmol) in 10:3 oxolane–water (35 mL), $CaCO_3$ (10.24 g, 102 mmol) and $Hg(ClO_4)_2{\cdot}3H_2O$ [6.01 g (12.5 mmol) in 20 mL oxolane] were added, and the mixture was stirred for 2 h at rt. More $Hg(ClO_4)_2{\cdot}3H_2O$ (0.57 g in 6 mL oxolane) was added, and the stirring was continued for a further 30 min. The mixture was filtered through a Celite bed with successive washing with CH_2Cl_2. The combined filtrate and washings were washed with aq $NaHCO_3$ (saturated) and the resultant precipitate was filtered off. The organic solution was washed with aq 10% KI and water, dried (Na_2SO_4), and concentrated to give **12** as a syrup: 1.92 g (92%). An analytical sample was prepared by flash column chromatography (30:1 toluene–EtOAc). TLC: R_f 0.4 (12:1 toluene–EtOAc), $[\alpha]_D^{23}$ −62° (*c* 1, $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ 9.65 (dd, 1 H, $J_{1,2}$ 1.5, $J_{1,F}$ 3.5 Hz, H-1), 7.50–7.20 (m, 10 H, Ph × 2), 4.93 (dddd, $J_{3,4}$ 7.5, $J_{4,5a}$ 5, $J_{4,5b}$ 2, $J_{4,F}$ 46 Hz, H-4), 4.77 and 4.70 (ABq, J_{gem} 12 Hz, PhCH_2), 4.62 and 4.52 (ABq, J_{gem} 11.5 Hz, PhCH_2), 4.41 (ddd, 1 H, $J_{4,5b}$ 2, $J_{5a,5b}$ 13, $J_{5b,F}$ 26 Hz, H-5b), 4.23 (ddd, 1 H, H-5a), 4.09 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 3 Hz, H-2), 4.00 (ddd, 1 H, H-3), 2.01 (s, 3 H, OAc). ^{19}F NMR ($CDCl_3$): δ −194.7 (ddddd, $J_{1,F}$ 3.5, $J_{3,F}$ 5.5, $J_{4,F}$ 46, $J_{5a,F}$ 29, $J_{5b,F}$ 26 Hz). Anal. Calcd for $C_{21}H_{23}FO_5$: C, 67.37; H, 6.19. Found: C, 67.02; H, 6.04.

6-O-Acetyl-3,4-di-O-benzyl-1,5-dideoxy-1,1,1,5-tetrafluoro-L-*altritol* (**13**) *and 6-O-acetyl-3,4-di-O-benzyl-1,5-dideoxy-1,1,1,5-tetrafluoro*-L-*allitol* (**14**).—To an ice-cold solution of **12** (1.87 g, 5.0 mmol) and Me_3SiCF_3 (1.18 mL, 8.0 mmol) in oxolane (15 mL), $Bu_4NF{\cdot}3H_2O$ [158 mg (0.5 mmol) in 3.6 mL oxolane] was added and the solution was kept for 1 h at rt. After concentration, the residue dissolved in $CHCl_3$ was washed with water, dried (Na_2SO_4), and concentrated to give a brown syrup; the TLC (30:1 toluene–EtOAc) of the syrup showed three spots at R_f 0.45 (trimethylsilyl ethers of **13** and **14**), 0.25 (**13**) and 0.15 (**14**). The syrup dissolved in aq 80% AcOH (20 mL) was kept for 3 h at 50 °C, whereupon the spot at R_f 0.45 disappeared. Concentration of the solution together with toluene gave a residue, which was chromatographed (30:1 toluene–EtOAc) to give **13**, 649 mg (29%) and **14**, 873 mg (39%) as colorless syrups, respectively. Compound **13**, $[\alpha]_D^{19}$ −20° (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 10 H, Ph × 2), 4.92 (ddt, 1 H, $J_{4,5} = J_{5,6b}$ 3, $J_{5,6a}$ 7, $J_{5,F\text{-}5}$ 48 Hz, H-5), 4.74 and 4.64 (ABq, J_{gem} 11 Hz, PhCH_2), 4.67 (s, 2 H, PhCH_2), 4.38 (ddd, 1 H, $J_{5,6b}$ 3, $J_{6a,6b}$ 13, $J_{6b,F\text{-}5}$ 30 Hz, H-6b), 4.30 (ddd, 1 H, $J_{5,6a}$ 7, $J_{6a,6b}$ 13, $J_{6a,F\text{-}5}$ 21.5 Hz, H-6a), 4.17 (br dq, 1 H, $J_{2,OH}$ 10, $J_{2,F\text{-}1(1',1'')}$ 7.5 Hz, H-2), 3.99–3.87 (m, 2 H, H-3,4), 3.11 (d, 1 H, OH), 2.08 (s, 3 H, OAc). ^{19}F NMR ($CDCl_3$): δ −77.0 (d, 3 F, $J_{2,F\text{-}1}$ 7.5 Hz, CF_3), −193.3 (m, 1 F, F-5). Anal. Calcd for $C_{22}H_{24}F_4O_5$: C, 59.46; F, 17.10; H, 5.44. Found: C, 59.62; H, 5.57; F, 17.16. Compound **14**, $[\alpha]_D^{21}$ −33° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.41–7.22 (m 10 H, Ph × 2), 5.02 (dddd, 1 H, $J_{4,5}$ 7, $J_{5,6a}$ 6, $J_{5,6b}$ 2, $J_{5,F\text{-}5}$ 47 Hz, H-5), 4.73 and 4.64 (ABq, J_{gem} 11 Hz, PhCH_2), 4.71 and 4.63 (ABq, J_{gem} 11.5 Hz, PhCH_2), 4.44 (ddd, 1 H, $J_{5,6b}$ 2, $J_{6a,6b}$ 13, $J_{6b,F\text{-}5}$ 28 Hz, H-6b), 4.35–4.21 (m, 1 H, H-2), 4.27 (ddd, 1 H, $J_{5,6a}$ 6, $J_{6a,6b}$ 13, $J_{6a,F\text{-}5}$ 27.5 Hz, H-6a), 4.08 (ddd, 1 H, $J_{3,4}$ 2.5, $J_{4,5}$ 7, $J_{4,F\text{-}5}$ 9.5 Hz, H-4), 4.01 (dd, $J_{2,3}$ 7.5, $J_{3,4}$ 2.5 Hz, H-3), 2.83 (d, 1 H, $J_{2,OH}$ 5 Hz, OH), 2.04 (s, 3 H, OAc). ^{19}F NMR ($CDCl_3$): δ −76.2 (d, 3 F, $J_{2,F\text{-}1}$ 7 Hz, CF_3), −194.9 (apparent ddt, 1 F, $J_{4,F\text{-}5}$ 9.5, $J_{5,F\text{-}5}$ 47, $J_{6a,F\text{-}5} \approx J_{6b,F\text{-}5}$ 28 Hz, F-5). Anal. Calcd for $C_{22}H_{24}F_4O_5$: C, 59.46; H, 5.44; F, 17.10. Found: C, 59.15; H, 5.34; F, 17.35.

Preparation of **13** *from* **14**.—A solution of **14** (768 mg, 1.73 mmol), $(CF_3SO_2)_2O$ (0.52 mL, 3.1 mmol) and pyridine (0.85 mL, 10.5 mmol) in dry CH_2Cl_2 (8 mL) was kept for 1.5 h at 0 °C. MeOH (0.63 mL) was added, and the solution, after dilution with CH_2Cl_2, was washed with aq $NaHCO_3$ (saturated), aq 20% $KHSO_4$, and water, dried (Na_2SO_4) and concentrated to give the 2-triflate of **14** as a

chromatographically homogeneous syrup: 1.00 g (quant); ^{19}F NMR ($CDCl_3$): δ −72.4 (br dq, 3 F, $J_{2,F-1}$ ~6, $J_{F-1,SO_2CF(F',F'')}$ 3.5 Hz, CF_3-2), −74.2 (q, 3 F, CF_3SO_2), −194.9 (ddt, 1 F, $J_{4,F-5}$ 13, $J_{5,F-5}$ 47, $J_{6a,F-5} = J_{6b,F-5}$ 26 Hz, F-5). A mixture of the syrup and $NaNO_2$ (964 mg, 14 mmol) in DMF (6 mL) was stirred for 1.5 h at 80 °C. After concentration together with xylene, water was added, and the mixture was extracted with toluene. The organic solution was washed with water, dried (Na_2SO_4), and concentrated. Duplicate chromatographies (30:1 toluene–EtOAc) of the residue gave **13**, 324 mg (42% based on **14**), which was identical to the specimen obtained from **12**.

3,4-Di-O-*benzyl*-*1,5-dideoxy*-*1,1,1,5-tetrafluoro*-L-*altritol* (**15**).—A solution of **13** (618 mg, 1.39 mmol) in methanolic 0.023 M NaOMe (17 mL) was kept for 20 min at rt. TLC (6:1 toluene–EtOAc) of the solution showed a single spot at R_f 0.25. Neutralization with Dowex 50WX2 (H^+ form) followed by concentration gave a pale-yellow syrup, which was crystallized from $CHCl_3$–hexane to give **15** as needles, 521 mg, (97%); mp 64.5–65 °C, $[\alpha]_D^{23}$ −3° (*c* 0.9, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}F_4O_4$: C, 59.70; H, 5.51. Found: C, 59.79; H, 5.63.

3,4-Di-O-*benzyl*-*1,5-dideoxy*-*1,1,1,5-tetrafluoro*-L-*allitol* (**16**).—Compound **14** (175 mg, 0.39 mmol) was deacetylated as described for **15** to give **16** as a pale-yellow syrup, 158 mg (quant), $[\alpha]_D^{22}$ −25° (*c* 0.7, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}F_4O_4$: C, 59.70; H, 5.51. Found: C, 59.30; H, 5.50.

1-O-*Acetyl*-*3,4-di*-O-*benzyl*-*2,6-dideoxy*-*2-fluoro*-*5*-C-*(trifluoromethyl)*-α-L-*talopyranose* (**19**).—To a cold (−78 °C) solution of $(COCl)_2$ (0.27 mL, 3.15 mmol) in dry CH_2Cl_2 (8 mL), $(CH_3)_2SO$ [0.36 mL (5.0 mmol) in CH_2Cl_2 (3.5 mL)] and **15** [1.02 g (2.54 mmol) in CH_2Cl_2 (8.6 mL)] were added, and the mixture was stirred for 40 min at the same temperature. Ethyldiisopropylamine (2.15 mL, 12.3 mmol) was added, and the mixture was stirred for 30 min, then for 1 h at 0 °C. After addition of ice-cooled aq NH_4Cl (saturated, 50 mL), the mixture was extracted with CH_2Cl_2 and the extracts were washed with water, dried ($MgSO_4$), and concentrated to give a pale-yellow syrup of crude **17**: 1.07 g. ^{19}F NMR ($CDCl_3$): δ −73.5 (d, ~3 F, $J_{5,F-6}$ 6.5 Hz, CF_3), −203.5 (m, ~1 F; sharp ddd on deuteration, $J_{1,F-2}$ 9, $J_{2,F}$ 49.5, $J_{3,F-2}$ 32 Hz, F-2). A solution of the syrup and Ac_2O (0.38 mL, 4.0 mmol) in pyridine (9 mL) was kept for 15 h at rt, water (0.2 mL) was added, and the mixture was concentrated to a small volume. After dilution with $CHCl_3$, the solution was washed with aq 20% $KHSO_4$, aq $NaHCO_3$ (saturated), and water, dried (Na_2SO_4), and concentrated. Flash chromatography (30:1 toluene–EtOAc) of the residue gave a syrup of **19**, which was crystallized (EtOAc–hexane) to give needles: 878 mg (78%), mp 80.5–81 °C, $[\alpha]_D^{22}$ −57° (*c* 0.85, $CHCl_3$). ^{1}H NMR (C_6D_6; benzyl signals are not described): δ 6.49 (dd, 1 H, $J_{1,2}$ 1.5, $J_{1,F-2}$ 8.5 Hz, H-1), 4.28 (ddt, 1 H, $J_{1,2} = J_{2,4}$ 1.5, $J_{2,3}$ 3, $J_{2,F-2}$ 48.5 Hz, H-2), 3.83 (br, 1 H, H-4), 3.76 (dq, 1 H, $J_{4,5}$ 1.5, $J_{5,F-6(6',6'')}$ 6.5 Hz, H-5), 3.17 (dt, 1 H, $J_{2,3} = J_{3,4}$ 3, $J_{3,F-2}$ 31 Hz, H-3), 1.43 (s, 3 H, OAc); irradiation of H-3 showed a 8.3% signal increase of H-5. ^{19}F NMR (C_6D_6): δ −72.9 (d, 3 F, $J_{5,F-6}$ 6.5 Hz, CF_3), −202.1 (ddd, 1 F, $J_{1,F-2}$ 8.5, $J_{2,F-2}$ 48.5, $J_{3,F-2}$ 31 Hz, F-2). Anal. Calcd for $C_{22}H_{22}F_4O_5$: C, 59.73; H, 5.01. Found: C, 59.87; H, 4.98.

1-O-*Acetyl*-*3,4-di*-O-*benzyl*-*2,6-dideoxy*-*2-fluoro*-*5*-C-*(trifluoromethyl)*-β-D-*allopyranose* (**20**).—Compound **16** (100 mg, 0.25 mmol) was treated with $(COCl)_2$ (28 μL, 0.33 mmol) and $(CH_3)_2SO$ [35 μL (0.49 mmol) in 2.2 ml CH_2Cl_2] and subsequently with $^iPr_2NEt$ (0.23 mL, 1.3 mmol) as described for **17** to give a pale-yellow syrup of **18** (104 mg). Acetylation of the syrup in a usual manner followed by flash chromatography (toluene) gave a syrup, which was recrystallized from EtOAc–hexane to give **20** as needles: 77 mg (74%), mp 79.5–80 °C, $[\alpha]_D^{23}$ +48° (*c* 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$; benzyl signals are not described): δ 6.16 (dd, 1 H, $J_{1,2}$ 8, $J_{1,F-2}$ ~2 Hz, H-1), 4.44 (dq, 1 H, $J_{4,5}$ 9.5, $J_{5,F-6(6',6'')}$ 6 Hz, H-5), 4.32 (ddd, 1 H, $J_{1,2}$ 8, $J_{2,3}$ 2.5, $J_{2,F-2}$ 48 Hz, H-2), 4.25 (dt, 1 H, $J_{2,3}$ 2.5, $J_{3,4}$ ~2, $J_{3,F-2}$ ~9 Hz, H-3), 3.65 (dt, 1 H, H-4; $J_{4,F-2}$ ~2 Hz), 2.15 (s, 3 H, OAc); irradiation of H-4 showed a 5.2% signal increase of H-2. ^{19}F NMR ($CDCl_3$): δ −74.5 (d, 3 F, $J_{5,F-6}$ 6 Hz, CF_3), −202.1 (br dd, 1 F, $J_{2,F-2}$ ~48, $J_{3,F-2}$ ~9 Hz,

F-2). Anal. Calcd for $C_{22}H_{22}F_4O_5$: C, 59.73; H, 5.01. Found: C, 59.84; H, 4.98.

1-O-Acetyl-2,6-dideoxy-2-fluoro-5-C-(trifluoromethyl)-α-L-talopyranose (**21**).—A solution of **19** (598 mg, 1.35 mmol) in 1,4-dioxane–H_2O–AcOH (10:1:1, 18 mL) was hydrogenolyzed in the presence of Pd black under gentle bubbling of H_2 for 7 h at rt. After filtration, the filtrate was concentrated with toluene to give a residue that was recrystallized from EtOAc–hexane to give **21** as needles: 332 mg (94%). TLC (1:1 $CHCl_3$–EtOAc): R_f 0.2, mp 117–119.5 °C, $[\alpha]_D^{27}$ −90° (*c* 1, MeOH). ^{1}H NMR (CD_3OD): δ 6.21 (dd, 1 H, $J_{1,2}$ 1.5, $J_{1,F\text{-}2}$ 8.5 Hz, H-1), 4.50 (dddd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 3, $J_{2,4}$ ~1, $J_{2,F\text{-}2}$ 48.5 Hz, H-2), 4.32 (dq, 1 H, $J_{4,5}$ ~1, $J_{5,F\text{-}6(6',6'')}$ 7 Hz, H-5), 4.04 (br d, 1 H, $J_{3,4}$ 3.5 Hz, H-4), 3.79 (apparent dt, 1 H, $J_{2,3}$ 3, $J_{3,4}$ 3.5, $J_{3,F\text{-}2}$ 32.5 Hz, H-3), 2.03 (s, 3 H, OAc). ^{19}F NMR (CD_3OD): δ −73.6 (d, 3 F, $J_{5,F\text{-}6}$ 7 Hz, CF_3), −202.8 (dddd, 1 F, $J_{1,F\text{-}2}$ 8.5, $J_{2,F\text{-}2}$ 48.5, $J_{3,F\text{-}2}$ 32.5, $J_{4(?),F\text{-}2}$ ~1 Hz, F-2). Anal. Calcd for $C_8H_{10}F_4O_5$: C, 36.65; H, 3.85. Found: C, 36.75; H, 4.07.

1,3,4-Tri-O-acetyl-2,6-dideoxy-2-fluoro-5-C-(trifluoromethyl)-α-L-talopyranose (**22**).—A solution of **21** (271 mg, 1.0 mmol) and Ac_2O (0.98 mL, 10.3 mmol) in pyridine (5.5 mL) was kept for 21 h at rt. Working up as described for **19** gave **22** as a colorless syrup: 318 mg (89%), which crystallized on standing for a day. Recrystallization from EtOAc–hexane gave needles, mp 86–87 °C, $[\alpha]_D^{23}$ −72° (*c* 1, $CHCl_3$). ^{19}F NMR ($CDCl_3$): δ −74.5 (d, 3 F, $J_{5,F\text{-}6}$ 6 Hz, CF_3), −202.3 (ddd, 1 F, $J_{1,F\text{-}2}$ 8, $J_{2,F\text{-}2}$ 48, $J_{3,F\text{-}2}$ 30.5 Hz, F-2). Anal. Calcd for $C_{12}H_{14}F_4O_7$: C, 41.63; H, 4.08. Found: C, 41.65; H, 4.05.

3,4-Di-O-acetyl-2,6-dideoxy-2-fluoro-5-C-(trifluoromethyl)-α-L-talopyranosyl iodide (**23**).—A solution of **22** (195 mg, 0.56 mmol) and Me_3SiI (0.53 mL, 3.7 mmol) in dry toluene (3.8 mL) was kept for 15 h at 80 °C in the dark. After dilution with toluene, the solution was washed successively with aq 10% $Na_2S_2O_3$, aq $NaHCO_3$ (saturated), and water, dried (Na_2SO_4) and concentrated. The residue was subjected to flash chromatography (6:1 hexane–EtOAc) to give **23** as a pale-brown syrup: 132 mg (57%), which was used without further purification; TLC (6:1 hexane–EtOAc): R_f 0.2, positive Beilstein test. ^{1}H NMR ($CDCl_3$): δ 7.01 (br d, 1 H, $J_{1,F\text{-}2}$ 13.5 Hz, H-1), 5.75 (slightly deformed dd, 1 H, $J_{3,4}$ ~3, $J_{4,5}$ 1.5 Hz, H-4), 5.60 (dt, 1 H, $J_{2,3} = J_{3,4}$ ~3, $J_{3,F\text{-}2}$ 28.5 Hz, H-3), 4.92 (br d, 1 H, $J_{2,F\text{-}2}$ 49.5 Hz, H-2), 4.36 (br q, 1 H, $J_{5,F\text{-}6(6',6'')}$ 6 Hz, H-5), 2.14 and 2.11 (each 3 H s, OAc); irradiation of F-2 showed a 32% signal increase of H-1 based on a 100% signal increase of H-2. ^{19}F NMR ($CDCl_3$): δ −73.8 (d, 3 F, $J_{5,F\text{-}6}$ 6 Hz, CF_3), −173.6 (ddd, 1 F, $J_{1,F\text{-}2}$ 13.5, $J_{2,F\text{-}2}$ 49.5, $J_{3,F\text{-}2}$ 28.5 Hz, F-2).

7-O-(3,4-Di-O-acetyl-2,6-dideoxy-2-fluoro-5-C-(trifluoromethyl)-α-L-talopyranosyl)daunomycinone (**24**).—A mixture of **23** (130 mg, 0.32 mmol), daunomycinone (178 mg, 0.45 mmol), yellow HgO (617 mg, 2.85 mmol), HgI_2 (298 mg, 0.66 mmol), and powdered 3 Å molecular sieves (694 mg, activated at 350 °C under a stream of N_2) in dry $Cl(CH_2)_2Cl$ (8.5 mL) was stirred for 9.5 h at 80 °C in a dark place. The mixture was filtered through a Celite bed, which was repeatedly washed with $CHCl_3$. The filtrate and washings combined were washed with aq 30% KI, aq $NaHCO_3$ (saturated), and water, dried (Na_2SO_4), and concentrated. The residue was chromatographed (7:1 $CHCl_3$–EtOAc) to give **24** as a red solid: 145 mg (67%). An analytical sample was prepared by reprecipitation from $CHCl_3$–hexane, $[\alpha]_D^{24}$ +202° (*c* 0.7, $CHCl_3$). Anal. Calcd for $C_{31}H_{28}F_4O_{13}$: C, 54.39; H, 4.12. Found: C, 54.14; H, 4.10.

7-O-(2,6-Dideoxy-2-fluoro-5-C-(trifluoromethyl)-α-L-talopyranosyl)daunomycinone (**3**).—A suspension of **24** (28 mg, 0.041 mmol) in aq 0.2 M NaOH (2.8 mL) was stirred for 3.5 h at 0 °C under the atmosphere of N_2. After neutralization of the resulting deep purple solution with aq 1 M HCl (0.56 mL), followed by addition of NaCl (1.1 g), the mixture was extracted with $CHCl_3$. The extracts were washed with brine, dried (Na_2SO_4), and concentrated to give **3** as a red solid: 23 mg (94%). An analytical sample was prepared by reprecipitation from oxolane–hexane. TLC (2:1 toluene–acetone): R_f 0.3, $[\alpha]_D^{24}$ +138° (*c* 0.56, oxolane). Anal. Calcd for $C_{27}H_{24}F_4O_{11}$: C, 54.01; H, 4.03. Found: C, 54.24; H, 4.10.

7-O-(2,6-Dideoxy-2-fluoro-5-C-(trifluoromethyl)-α-L-talopyranosyl)adriamycinone (**4**). —A solution of **3** (42 mg, 0.07 mmol) and $HC(OMe)_3$ (59 μL, 0.54 mmol) in 3:5 dry MeOH–1,4-dioxane (2.5 mL) was kept for 30 min at rt, then Br_2 [16 mg (0.1 mmol) in 0.2 mL dry CH_2Cl_2] was added at 0 °C, and the solution was kept for 20 min at that temperature, and 2.5 h at rt. TLC (20:3.8:0.45 $CHCl_3$–MeOH–aq 17% NH_4OH) of the solution showed a main spot at R_f 0.52 (the 14-bromo-13-dimethyl acetal; cf **3**: R_f 0.48). After concentration to a half volume, the solution was poured into hexane (20 mL), and the resulting precipitate was collected by centrifugation and washed with hexane. The solid was suspended in acetone (4.5 mL) and the mixture was stirred for 3 h at rt. TLC (2:1 toluene–acetone) showed two spots at R_f 0.3 (major; the 14-bromo-13-oxo derivative) and 0.75 (minor, the 14-bromo-3′,4′-*O*-isopropylidene derivative). After concentration, a mixture of the residue and HCO_2Na [83 mg in 2:1 acetone–oxolane (4 mL)] was stirred vigorously for 15 h at rt; the mixture showed, in TLC (2:1 toluene–acetone), four spots at R_f 0.15 (**4**), 0.25 (the 14-*O*-formyl derivative of **4**), 0.6 (minor, the 14-hydroxy-3′,4′-*O*-isopropylidene derivative), and 0.7 (minor, the 14-*O*-formyl-3′,4′-*O*-isopropylidene derivative). After evaporation of the solvent, cold water was added, and the insoluble matter was collected by centrifugation (to give a red solid, 43 mg). A suspension of the solid in 18:6:1 oxolane–MeOH–aq 1 M NH_4OH (3.5 mL) was stirred for 45 min at 0 °C, whereupon the spots at R_f 0.25 and 0.7 had disappeared. Concentration of the solution gave a residue, which was dissolved in aq 80% AcOH (2 mL) and the solution was kept for 3 h at 80 °C. Concentration with aid of toluene gave a residue, which was suspended in water and collected by centrifugation. The solid obtained was reprecipitated from oxolane–diisopropyl ether to give **4** as a dark red solid, 30 mg (70%). An analytical sample was prepared by reprecipitation from oxolane–toluene, $[\alpha]_D^{24}$ + 154° (*c* 0.07, oxolane). Anal. Calcd for $C_{27}H_{24}F_4O_{12}$: C, 52.60; H, 3.92. Found: C, 52.55; H, 3.61.

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