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Synthesis and antitumor activity of the 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone derivatives modified at C-3′ or C-4′

Yasushi Takagi, Naoki Kobayashi, Min Sun Chang, Geun-Jho Lim, Tsutomu Tsuchiya *

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

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Abstract

As a part of a study to exploit anthracycline glycosides effective against resistant tumor cells, the 3′-*O*-methyl (**3**), 4′-*O*-methyl (**4**), 3′-deoxy (**6**), 3′-deoxy-3′-fluoro (**7**), and 3′-deoxy-3′-iodo (**8**) derivatives of 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone have been prepared by coupling suitably protected glycosyl bromides with daunomycinone. The doxorubicin-type analog (**5**) of **4** was also prepared. Among the compounds prepared, **5** showed the highest antitumor activity. Relationships between chemical structures of the synthetic products and antitumor activities, together with the degree of resistance were discussed.

Keywords: Anthracycline glycoside; Antitumor activity; Multidrug resistance; 7-*O*-(2,6-Dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone

1. Introduction

Anthracycline antibiotics as exemplified by daunorubicin (DNR) and doxorubicin (DOX) are antitumor agents widely used in cancer chemotherapy. Their clinical use is, however, limited by undesirable side-effects such as drug-cumulative cardiotoxicity and myelosuppression, as well as the appearance of multidrug resistance (MDR) in tumor cells. To circumvent these drawbacks, many chemical and biosynthetic modifications have been undertaken [1,2]. In previous papers [3,4], we reported the synthesis of 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)-daunomycinone (**1**) and -adriamycinone (**2**), both of which showed higher antitumor activities than DNR and DOX in murine leukemia L1210 *in vivo*; moreover they showed stronger cytotoxicity against P388 and its DOX-resistant cell lines (P388/DOX) than DNR and DOX (this paper; Table 6). Another notable fact was that they had lower toxicity than DNR and DOX. From the standpoint of chemical structure, **1** and **2** have a fluorine atom at C-2′ and a hydroxyl group at C-3′ instead of the 3′-amino or 3′-alkylamino group present in conventional anthracycline glycosides; this replacement by a hydroxyl group, first reported by Horton and co-workers [5], is

* Corresponding author.

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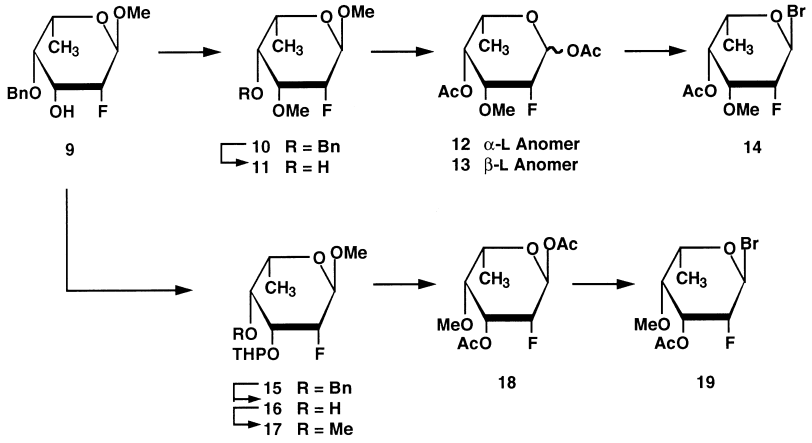
important in view of altering the resistance factor [6]. We further synthesized the 14-hemipimelate [7] of **2** to make **2** soluble in water, and found that this compound exhibited stronger antitumor activity than the parent compound **2** against sensitive P388, but showed slightly lower activity against the P388/DOX cell line ([8] and unpublished data). These results stimulated us to exploit further derivatization of **1** or **2** in the hope of obtaining compounds more effective against MDR cells.

Studies on the mechanism of MDR have shown considerable recent advances. A large proportion of MDR cells has been shown to over-express P-glycoprotein, an ATP-dependent drug-transport protein [9,10], in the plasma membrane, which causes such lipophilic drugs as doxorubicin to remain outside the cells, resulting in low intracellular drug-accumulation. Another interesting feature of MDR cells is their high Ca^{2+} content inside the cells as compared to the normal cells [11]. It has been reported that coadministration of verapamil, a calcium channel blocker, or its analogs [12], or calmodulin inhibitors, with DOX reversed the MDR activity [13]. Other types of MDR and the circumvention of resistance have been reviewed [14].

In spite of these findings, however, the relationship between drug structure and MDR is still obscure, except for the lipophilicity of the drug molecules [15]. For this reason, determination of the direction required for improving the biological properties of the drugs (in terms of antitumor activity, MDR, and side effects) is not easy. In this paper, we describe the activity-changes brought about by altering the functional groups at C-3′ or 4′ in **1** and **2** with several other groups, in the hope of finding a clue to this MDR problem in anthracycline glycosides [16].

2. Results and discussion

Synthesis.—At first, the 3′-*O*- (**3**) and 4′-*O*-methyl derivatives (**4**) of **1** were prepared. Conventional methylation (MeI, NaH in DMF) of methyl 4-*O*-benzyl-2,6-dideoxy-2-fluoro-α-L-talopyranoside **9** [4] (to give **10**) with subsequent catalytic debenzylation gave the 4-ol **11** (Scheme 1). Its ^{19}F NMR spectrum showed a through-space coupling (~5 Hz) between O*H*-4 and F-2, supporting the $^{1}C_4$(L) conformation of **11** (the conformation is not necessarily distinct if judged only from the $J_{H,H}$ values) (Tables 1 and 2). Acetylation of **11** with Ac_2O in $MeNO_2$ in the presence of a catalytic amount of H_2SO_4 gave a mixture (~11:1) of 1,4-di-*O*-acetyl-α-L (**12**) and -β-L anomers **13**. Their anomeric configurations were assigned based on the small ($J_{H\text{-}1,F\text{-}2}$ 8.5 Hz for **12**) and large ($J_{H\text{-}1,F\text{-}2}$ 20 Hz for **13**) coupling constants. The mixture was converted into the α-L-talopyranosyl bromide **14** by treatment with $TiBr_4$, and **14** was used for the next coupling. The corresponding 4-*O*-methyl-α-L-talopyranosyl bromide **19** was prepared also from **9**. A first attempt at applying a sequence of reactions involving 3-*O*-acetylation, catalytic debenzylation, and methylation (MeI, Ag_2O in DMF) failed, giving a mixture of 3-*O*- and 4-*O*-methyl derivatives, possibly by acetyl migration in the final step. The hydroxyl group of **9** was therefore first protected with 3,4-dihydro-2*H*-pyran and the 3-*O*-tetrahydropyranyl derivative **15** was hydrogenolyzed, and the resulting 4-ol **16** was



Scheme 1.

Table 1
^1H and ^{19}F chemical shifts (δ (ppm)) and multiplicity of fluoro sugar derivatives in $CDCl_3$

Multiplicity	H-1 dd[a]	H-2 ddt[a]	H-3 dt[a]	H-4	H-5 dq[a]	H_3C-5 d[a]	CH_3O s	Ac s	^{19}F ddd[a]
10	4.94	4.68	3.46	3.61 dt	3.83	1.24	3.37		−204.0
11	4.90 br d	4.68 br d	3.46	3.81 br s	3.86	1.36	3.40 3.50		[b]
12	6.33	4.59	3.56	5.37 dt	4.10	1.22	3.48	2.13 2.18	−202.9
13	5.65	4.78	3.41 ddd	5.33 dt	3.80	1.29	3.47	2.18 2.19	−220.0
14	6.57	4.86	3.97 ddd	5.43 dt	4.24	1.27	3.49	2.17	−180.9
15	4.90	4.62	3.93	3.57	3.87	1.23	3.36		−204.0
	4.92	4.69	4.02	dt 3.61 dt	3.90	1.27	3.37		(0.44 F) −202.7 (0.56 F)
16	4.89 4.90	4.63 4.69 br d		←3.75–4.0→		1.35	3.40		−201.8 ddt −200.4 ddt
17	4.90	4.57 (0.38H)	3.97	~3.36	~3.91	1.32	3.37(3 H) 3.58		−204.1 (0.38 F)
	4.87	4.63 (0.62H)	3.92				3.64		−202.9 (0.62 F)
18	6.29	4.56	5.12	3.45 dt	4.09	1.34	3.56	2.11 2.20	−202.2
19	6.54 br d	4.84	5.44	~3.55	4.22	1.38	3.57	2.20	−180.2
21	4.73	4.41 ddd	5.06	3.61 dd	4.15	1.27	3.45		−194.7 dddq
22	4.83	4.46 br ddd	4.58	3.52 m	4.08	1.25	3.39		−185.1
23	4.79 br d	4.43 dddt	1.85 ddt 2.39 dddt	3.29 m	3.94	1.28	3.40		−187.0 dddd
25	4.86 br d	4.49 dddt	2.22 ddt 2.40 dddt	5.06 m	4.15	1.26	3.46		−186.5 ddt
26	6.29 br d	4.52 br d	2.26 ddt 2.52 dddd	5.12 br s	4.26	1.27		2.15	−185.1 ddt
27	5.79	4.71 br dt	2.14 dddd 2.65 ddt	5.12 m	4.08	1.34		2.23	−202.2 dddd
28	6.61 br d	4.81 br d	2.66 ddt 2.48 dddd	5.19 m	4.37	1.32			−163.2 dddd
29	4.94 ddd	4.72 dddt	4.74 ddt	3.71 ddt	3.86 tq	1.26 dd	3.37		−205.5(F-2) dddd −2.02.9(F-3) br ddq
31	6.34 ddd	4.69 ddddd	4.84 br ddt	5.41 br ddt	4.14 tq	1.24 dd		2.13 2.19	−204.6(F-2) dddd −206.2(F-3) br ddq
32	5.67 br dd	4.87 dddt	4.68 dddd	5.38 ddt	3.83 tq	1.31 br d		2.19 2.20	−220.7(F-2) dddd −202.6(F-3) br dddd
33	6.53 br dd	4.97 dddt	5.21 dddd	5.49 ddt	4.28 br q	1.29 dd		2.18	−182.8(F-2) dddd

(continued)

Table 1—*contd*

Multiplicity	H-1 dd[a]	H-2 ddt[a]	H-3 dt[a]	H-4	H-5 dq[a]	H_3C-5 d[a]	CH_3O s	Ac s	^{19}F ddd[a]
									−207.4(F-3) br ddq
35	4.78 br d	4.44 dddd	5.07 ddt	~3.45 m	4.20	1.30	3.43	2.10	−191.9 dddd
40	4.91	4.53 dddd	4.74 ddd	5.37 ddd	4.29	1.22	3.46		−185.6
41	6.32	4.53 br d	4.75	5.44 m	4.39	1.22		2.18	−183.7
42	6.58	4.81	5.13	5.49 m	4.51	1.28			−163.0

[a] Unless otherwise stated.
[b] See Experimental section.

Table 2
^1H-^1H and ^1H-^{19}F coupling constants (J, Hz) of fluoro sugar derivatives in $CDCl_3$

	$J_{1,2}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,5}$	$J_{5,CH_{3\text{-}5}}$	$J_{1,F}$	$J_{2,F}$	$J_{3,F}$
10	1.5	3	1.5	3	1.5	6.5	9.5	49.5	33
11		3		3	~1.5	6.5	9	50	32.5
12	2	3	~1	3.5	1.5	6.5	8.5	48.5	31.5
13	≤1	2.5	~1	3.5	1.5	6.5	20	51	30.5
14	~1	3	1.5	3.5	~1.5	6.5	11.5	49.5	30
15	1.5	3	1.5	3	1.5	6.5	9	49.5	33
16	1.5	3	1.5			6.5	~7	49.5	33
17	1.5	3	1.5	3		6.5	9.5	49.5	33.5
18	2	3	~1.5	3	~1.5	6.5	8.5	49	31.5
19	1.5	3	1.5	3	~1.5	6.5	11.5	50.5	30.5
21	4.5	6.5	~0	6.5	4.5	6.5	9	48	12
22	1.5	3		3	~1.5	6.5	8.5	46.5	37.5
23[a,b]	2	3.5 ($J_{2,3ax}$)	~1	3.5 ($J_{3ax,4}$)	2	6.5	10	47	45 ($J_{3ax,F}$)
		3 ($J_{2,3eq}$)		3 ($J_{3eq,4}$)					13 ($J_{3eq,F}$)
25[a,c]	~1	3.5 ($J_{2,3ax}$)	~1	3.5 ($J_{3ax,4}$)	1.5	6.5	9.5	46.5	45.5 ($J_{3ax,F}$)
		2.5 ($J_{2,3eq}$)		2.5 ($J_{3eq,4}$)					14.5 ($J_{3eq,F}$)
26[d]		3.5 ($J_{2,3ax}$)		3.5 ($J_{3ax,4}$)	1.5	6.5	8.5	45.5	45 ($J_{3ax,F}$)
		3.5 ($J_{2,3eq}$)		2.5 ($J_{3eq,4}$)					13.5 ($J_{3eq,F}$)
27[d]	1	3 ($J_{2,3ax}$)		4 ($J_{3ax,4}$)	2	6.5	21	48.5	43.5 ($J_{3ax,F}$)
		~3 ($J_{2,3eq}$)		~3 ($J_{3eq,4}$)					11.5 ($J_{3eq,F}$)
28[d]		~3 ($J_{2,3ax}$)		~3 ($J_{3ax,4}$)	1.5	6.5	11	47	43.5 ($J_{3ax,F}$)
		2.5 ($J_{2,3eq}$)		4.5 ($J_{3eq,4}$)					14 ($J_{3eq,F}$)
29[e,f,g,h]	1.5	3	1.5	3	1.5	6.5	9 (F-2) 7 (F-3)	49.5 (F-2) 7 (F-3)	31.5 (F-2) 44 (F-3)
31[i,f,j,k]	2	3	1.5	4	1.5	6.5	8 (F-2) 6 (F-3)	49 (F-2) 6.5 (F-3)	30 (F-2) 43 (F-3)
32[l,f,m]	1	3	1	4	1.5	6.5	19 (F-2) 2 (F-3)	52 (F-2) 7 (F-3)	28 (F-2) 42.5 (F-3)
33[e,n,h]	1.5	3	1.5	4	1.5	6.5	11.5 (F-2) 6.5 (F-3)	50 (F-2) 5 (F-3)	28 (F-2) 42.5 (F-3)
35[o]	2	3.5	1	3.5	2	6.5	13	45	11
40	1.5	2.5	1	3.5	1.5	6.5	7.5	46.5	36.5
41	1.5	3		3	1.5	6.5	7.5	46	35.5
42	1	3	1	3.5	~1.5	6.5	10	46.5	34

[a] $J_{1,3eq}$ 1.5 Hz. [b] $J_{3ax,3eq}$ 15.5 Hz. [c] $J_{3ax,3eq}$ 16 Hz. [d] $J_{3ax,3eq}$ 16.5 Hz. [e] $J_{4,F\text{-}3}$ 6 Hz. [f] $J_{5,F\text{-}3}$ 1.5 Hz. [g] $J_{6,F\text{-}3}$ 0.8 Hz. [h] $J_{F\text{-}2,F\text{-}3}$ 14 Hz. [i] $J_{4,F\text{-}3}$ 5.5 Hz. [j] $J_{6,F\text{-}3}$ 1 Hz. [k] $J_{F\text{-}2,F\text{-}3}$ 13.5 Hz. [l] $J_{4,F\text{-}3}$ 5 Hz. [m] $J_{F\text{-}2,F\text{-}3}$ 13 Hz. [n] $J_{6,F\text{-}3}$ 0.7 Hz. [o] $J_{1,3}$ 1 Hz.

methylated to give the 4-*O*-methyl derivative **17**. Compound **17** was then acetolyzed (Ac_2O, AcOH, cat. H_2SO_4) and the resulting 1,3-di-*O*-acetyl-α-L-talopyranose (**18**) was brominated with $TiBr_4$ to give the α-1-bromide **19** in high yield.

Coupling of **12** with daunomycinone was first attempted according to the procedure reported [17] ($CF_3SO_3SiMe_3$ and molecular sieves 4A in CH_2Cl_2–Et_2O), but the desired product was not obtained. Coupling of the bromide **14** with daunomycinone under Koenigs–Knorr conditions, however, gave the α-L- (**43**) and β-L-glycosides **44** in 38 and 8% yields, respectively. The anomeric configurations of **43** and **44** were again determined by their $J_{H\text{-}1',F\text{-}2'}$ coupling constants (9.5 Hz for **43** and 19 Hz for **44**). Previously, we reported [4] that the coupling of 3,4-di-*O*-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranosyl bromide (an analog of **14**) with daunomycinone gave the 3′,4′-di-*O*-acetyl derivative of **1** in high yield (82%) without accompaniment of the undesirable β-L anomer; the present poor yield of **43** (confirmed by repeated experiments), therefore, must be ascribed to the difference in substituent at C-3 in **14**. Alkaline treatment of **43** gave the desired 7-*O*-(2,6-dideoxy-2-fluoro-3-*O*-methyl-α-L-talopyranosyl)daunomycinone (**3**). The structure was confirmed by the ^1H (Table 3), ^{19}F, and ^{13}C NMR spectra (Table 4). In its ^{19}F NMR spectrum, through-space coupling $J_{OH\text{-}4',F\text{-}2'}$ (9 Hz) was observed.

Next, 4-*O*-methyl-α-L-talopyranosyl bromide **19** was coupled with daunomycinone as described for **43**, giving the α-L-glycoside **45** in 50% yield. Alkaline hydrolysis of **45** gave 7-*O*-(2,6-dideoxy-2-fluoro-4-*O*-methyl-α-L-talopyranosyl)daunomycinone **4** in good yield. The daunomycin-type structure of **4** was then transformed into a doxorubicin-type structure by applying, basically, a sequence of reactions reported by Arcamone et al. [18]; bromination of **4** with Br_2 in the presence of $HC(OMe)_3$ gave the 14-bromo-13-dimethylacetal, the acetal portion being then deblocked by treatment with

Table 3
Selected ^1H NMR chemical shifts (δ (ppm)) and coupling constants (*J*, Hz) of **3**–**8** and **43**–**51** in $CDCl_3$

Compound	H-7	OMe-4	H-14	H-1′	H-2′	H-3′*ax*	H-4′	OMe-3′ or 4′	$J_{7,8ax}$	$J_{7,8eq}$	$J_{1',2'}$	$J_{2',3'ax}$	$J_{3'ax,4'}$	$J_{1',F\text{-}2'}$	$J_{2',F\text{-}2'}$	$J_{3'ax,F\text{-}2'}$ ($J_{3'eq,F\text{-}2'}$)
3	5.27 dd	4.03 s	2.41 s	5.61 dd	4.73 br d	3.32 dt	3.84 br d	3.44 s	4.5	1.5	~1	3	3	10	~50	32.5
4	5.26 dd	4.07 s	2.40 s	5.58 br d	4.50 br d	3.69 ddt[a]	3.33 br d	3.60 s	4	~2	*	~4	4	10	49.5	31.5
5	5.34 dd	4.09 s	4.74 br s	5.62 dd	4.47 br d	3.65 ddt[a]	3.34 br d	3.61 s	4	2	1.5	~3	~4	10	49	31
6	5.35 dd	4.08 s	2.41 s	5.50 br d	4.56 br d	1.92 ddt[b]	3.55 br d[c]		4	2	*	3	3	10	47	49 (13)
7	5.28 dd	4.09 s	2.40 s	5.65 ddd	4.83 dddt[d]	4.57 ddt	3.92 m		4.5	2	2	3	3	9.5	50.5	31.5
8	5.30 dd	4.09 s	2.41 s	5.53 dd	4.56 br d	4.42 dt	3.59 br d[e]		4.5	1.5	1.5	3	3	8.5	46.5	38
43	5.30 dd	4.09 s	2.41 s	5.63 dd	4.62 br d	3.38 dt	5.34 m	3.39 s	4.5	2	1.5	~3	~3	9.5	49	32.5
44	5.57 br t	4.09 s	2.43 s	4.95 d	4.79 br dd	3.31 ddd	5.18 br dd	3.45 s	3.5	~2.5	~0	2.5	4	19	51	30.5
45	5.26 dd	4.07 s	2.41 s	5.59 dd	4.59 br d	4.90 dt	3.47 m	3.55 s	4	~2	1.5	3	3	10	50	32.5
46	5.39 dd	4.09 s	2.43 s	5.60 br d	4.52 br d	2.08 ddt[b]	5.10 br s		4	1.5	*	~3	~3	10	46	46 (13)
47	5.63 dd	4.09 s	2.45 s	5.11 br d	4.68 br d	2.05 ddt[b]	4.96 br s		3.5	3	*	~4	~4	20	48.5	43.5 (12)
48	5.28 dd	4.09 s	2.40 s	5.66 ddd	4.73 br d	4.67 ddt	5.39 m		4.5	2	1.5	3.5	3.5	9.5	50	30
49	5.59 t	4.09 s	2.44 s	5.00 dd	4.85 ddd	4.58 dddd	5.23 br dd		3.5	~3	~0	2.5	4	18	52	28.5
50	5.32 dd	4.10 s	2.42 s	5.62 br d	4.57 br d	4.61 dt	5.39 br s		4	1.5	*	~3	~3	8	45.5	37
51	5.62 br t	4.09 s	2.46 s	5.21 br d	4.73 br dd	4.48 dt	5.23 br s		3.5	~2.5	*	3	3	19.5	48	34.5

[a] $J_{3',OH\text{-}3'}$ 11.5 Hz. [b] $J_{3'ax,3'eq}$ 16 Hz. [c] $J_{4',OH\text{-}4'}$ 11 Hz. [d] $J_{2',4'}$ 2 Hz. [e] $J_{4',OH\text{-}4'}$ 10 Hz.
* Not detected by broadening.

Table 4
^{13}C NMR chemical shifts (δ (ppm)) and coupling constants ($J_{C,F}$, Hz, in parentheses) for compounds **3**–**8** in $CDCl_3$

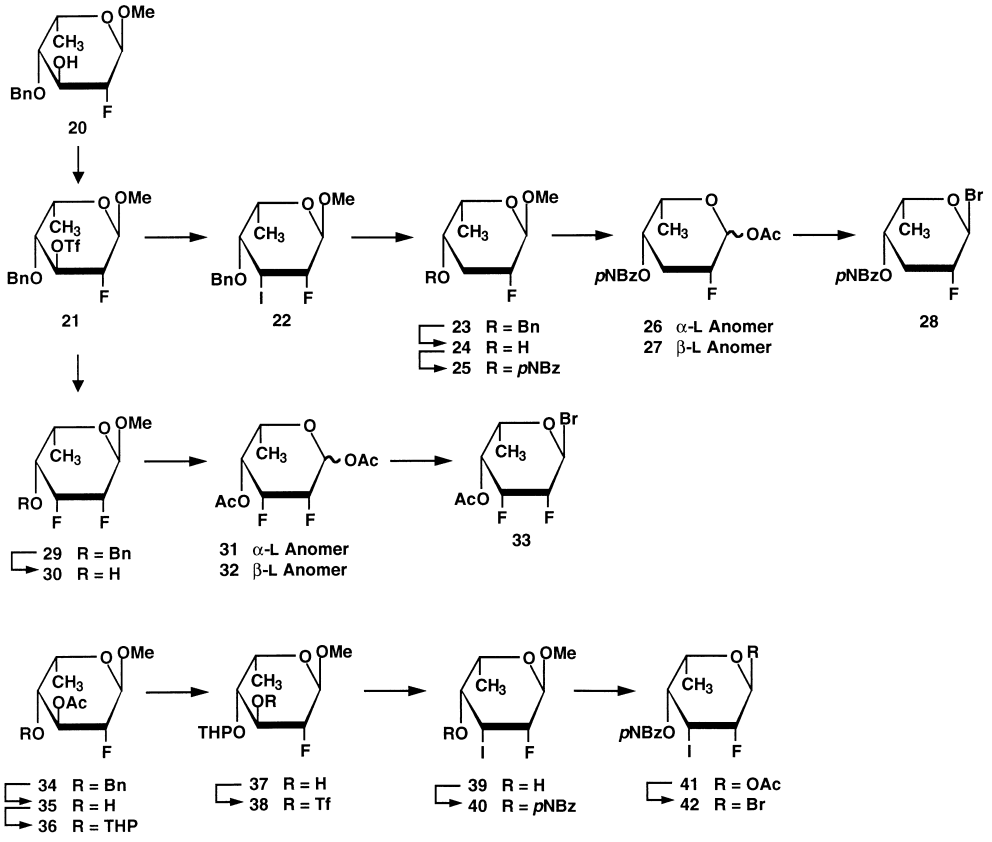
C	3	4	5	6	7[a]	8
1	119.9	119.7	119.9	119.8	119.9	119.9
2	135.8	135.7	135.8	135.4	135.9	135.9
3	118.6	118.5	118.6	118.5	118.6	118.6
4	161.2	161.1	161.2	161.1	161.2	161.2
4a	120.9	120.8	120.9	120.8	120.9	120.9
5	187.0[b]	186.8[b]	187.0[b]	186.9[b]	187.1	187.1[b]
5a	111.6[c]	111.54[c]	111.7	111.4	111.7	111.7[c]
6	156.3[d]	155.7[d]	156.0[c]	156.6[c]	156.2	156.2[d]
6a	133.2[e]	133.1[e]	132.7[d]	133.4[d]	132.9	133.0[e]
7	71.4	71.0	70.8	70.9	71.4	71.4
8	35.2	35.0	35.6	35.1	35.3	35.4
9	76.5	76.4	76.6	76.6	76.3	76.3
10	33.1	33.1	33.9	33.2	33.1	33.1
10a	134.3[e]	134.0[e]	133.4[d]	134.4[d]	134.1	134.1[e]
11	155.6[d]	155.1[d]	155.4[c]	155.3[c]	155.5	155.6[d]
11a	111.5[c]	111.48[c]	111.7	111.4	111.6	111.6[c]
12	186.7[b]	186.6[b]	186.8[b]	186.7[b]	186.9	186.8[b]
12a	135.5[e]	135.4[e]	135.5[d]	135.8[d]	135.5	135.5[e]
13	211.1	211.3	213.4	211.5	211.0	211.0
14	24.6	24.6	65.4	24.7	24.5	24.5
OMe-4	56.7	56.6	56.7	56.7	56.7	56.7
OMe-3′	55.9					
OMe-4′		62.9	63.0			
1′	101.4 d (31.5)	101.3 d (32.2)	101.1 d (32.2)	100.3 d (34.0)	101.3 dd (30.5, 6.8)	100.5 d (34.4)
2′	86.3 d (176.9)	87.3 d (177.0)	87.1 d (177.6)	86.5 d (166.7)	87.0 dd (178.2, 17.1)	89.9 d (176.9)
3′	74.5 d (14.8)	66.0 d (17.1)	66.0 d (16.9)	30.8 d (17.6)	85.7 dd (192.3, 14.7)	25.8 d (16.9)
4′	68.7	81.0	80.9	66.5	70.4 d (17.4)	72.3
5′	68.0	67.5	67.8	67.9	67.8 d (5.9)	68.2
6′	16.5	16.7	16.8	16.9	16.1 d (2.1)	17.4

[a] Measured at 125.8 MHz and confirmed by the HMQC followed by HMBC method.
[b, c, d, e] Figures in the same column may be interconvertible.

acetone. The resulting 14-bromo-13-oxo derivative was hydrolyzed with sodium formate in aq acetone giving a mixture of **5** and its 14-*O*-formyl derivative; thorough deblocking of the mixture with NH_4OH in $CHCl_3$–MeOH gave the doxorubicin-type derivative **5**.

Next, the 3′-deoxy (**6**), 3′-deoxy-3′-fluoro (**7**), and 3′-deoxy-3′-iodo derivatives (**8**) of **1** were prepared. The synthetic routes for the glycosyl bromides are shown in Scheme 2. Treatment of methyl 4-*O*-benzyl-2,6-dideoxy-2-fluoro-α-L-idopyranoside **20** [4] with $(CF_3SO_2)_2O$ gave the unstable 3-triflate **21**, whose ^{19}F NMR spectrum showed interspace coupling (6 Hz) between F-2 and CF_3. It is worth mentioning that **21** showed somewhat different $J_{H,H}$ values from those for similar α-L-*ido* derivatives (**20** [4], **34** [4], **35**), suggesting the presence of some influence of the CF_3SO_2-3 group on its conformation. Iodination (NaI in DMF, 90 °C) of **21** gave the 3-deoxy-3-iodo derivative **22**. The L-*talo* structure was confirmed by the large coupling constant ($J_{H\text{-}3,F\text{-}2}$ 37.5 Hz); if L-*ido* had been the structure, the $J_{H\text{-}3,F\text{-}2}$ value should be small, irrespective of the conformations. Its ^{13}C NMR spectrum showed a doublet ($J_{C\text{-}3,F\text{-}2}$ 15.7 Hz) at high field (δ 24.2), indicating the presence of I-3. Radical deiodination of **22** with Bu_3SnH gave the 3-deoxy derivative **23** quantitatively. Hydrogenolysis of **23** (to give **24**) followed by *p*-nitrobenzoylation afforded the 4-*p*-nitrobenzoate **25**. Acetylation of **25** in the manner described for **12** gave a mixture of 1-*O*-acetyl-α-L (**26**) and -β-L anomers **27**, the ratio being 6:1. Compound **26** was then converted into the α-L-*lyxo*-hexopyranosyl bromide **28** by treatment with HBr in AcOH.

Preparation of 3-deoxy-3-fluoro-α-L-talopyranosyl bromide **33** was attempted initially by treatment of **20** with Et_2NSF_3 (DAST), but it failed, giving only a complex mixture. Then the 3-triflate **21** was treated with $(Me_2N)_3S^+$ $(Me_3SiF_2)^-$ (TASF) [19] and the resulting 2,3,6-trideoxy-2,3-difluoro-α-L-talopyranoside **29** was hydrogenolysed (to give **30**) and acetolyzed as described for **18** to give a mixture of 1,3-di-*O*-acetyl-α-L (**31**)

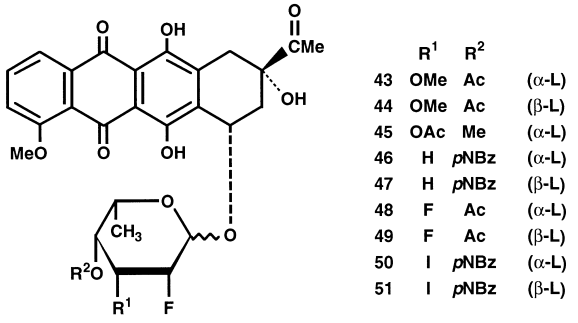


Scheme 2.

and -β-L anomers **32**, the ratio being 2.5:1. Bromination of **31** as described for **28** gave the crystalline α-L-talopyranosyl bromide **33**.

The 3-deoxy-3-iodo-α-L-talopyranosyl bromide **42** was prepared from methyl 3-*O*-acetyl-4-*O*-benzyl-2,6-dideoxy-2-fluoro-α-L-idopyranoside **34** [4]. Successive debenzylation of **34** (to give **35**), protection of the OH-4 group with a tetrahydropyranyl group (to give **36**), deacetylation of **36** (to give **37**), and triflation gave the unstable 3-triflate **38**. Iodination of **38** with NaI in DMF gave the 3-deoxy-3-iodo-α-L-talopyranoside **39**, the tetrahydropyranyl group in **38** being removed during the reaction. After *p*-nitrobenzoylation, the resulting ester **40** was acetolyzed (to give the 1-acetate **41**), and brominated to give the α-L-talopyranosyl bromide **42**.

Characteristic features of the 1-bromides prepared in the ^{19}F NMR spectra are that the shift-values for F-2 always appear downfield by $\sim$20 ppm compared to those for the parent methyl α-L-glycosides or α-L-glycosyl acetates (compare **11** (or **12**) and **14**; **17** (or **18**) and **19**; **25** (or **26**) and **28**; **29** (or **31**) and **33**; and **40** (or **41**) and **42**; Table 1).



Coupling of the respective glycosyl bromides **28**, **33**, and **42** with daunomycinone was performed in the manner described for **43** to give the corresponding coupling products: α-L (**46**, 43%) and β-L anomers (**47**, 41%) from **28**; α-L (**48**, 28%) and β-L anomers (**49**, 16%) from **33**; α-L (**50**, 22%) and β-L anomers (**51**, 62%) from **42**, the ratios of α-L: β-L anomers being $\sim$1:1, 1.8:1, and 1:2.8, in the foregoing order. In these coupling reactions, the α-selectivity observed [4] in **1** was completely lost and the undesirable β-L anomers were sometimes major products. The anomeric configurations of the products were determined by their $J_{H\text{-}1',F\text{-}2'}$ values in the ^{1}H and ^{19}F NMR spectra. Alkaline treatment

Table 5
Antitumor activities[a] (T/C[b] (%)) of **1**–**8** against the murine L1210 cell line

Compound	Dose ($mg\,kg^{-1}\,day^{-1}$)							C_{150}[c]	E[c]
	10	5	2.5	1.25	0.6	0.3	0.15		
1		184	217	171	125	105	105	0.9	5.7
2		> 740	> 352	275	185	182	127	0.2	6.0
3	174	109	112	100	91	94	—	8.2	12.3
4		> 314[d]	260	146	124	117	111	1.25	5.1
5	102[d]	124[d]	> 761[d]	> 501	279	152	—	0.3	6.0
6		121	113	113	96	110	107	> 5	> 12.5
7		148	135	114	117	108	105	5	18
8		116	97	106	103	97	97	> 5	> 16

[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. Survival studies were continued up to 60 days; a part of the data were reported [3,16].
[b] Mean survival days of treated mice/mean survival days of control mice $\times 100$.
[c] See text portion.
[d] More than 10% weight decrease in the treated mice was observed.

of **46**, **48**, and **50** gave the respective desired products **6**, **7**, and **8** in good yields.

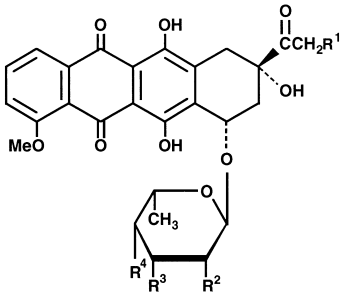
Antitumor activity.—Antitumor activities of **3**–**8** against L1210 murine leukemia *in vivo* (Table 5) showed that only **4** and **5** exhibited strong antitumor activity (**5** was much stronger). This result suggests, together with the activities [3] of the parent compounds **1** and **2**, that those modifications that remove the exchangeable hydrogen from the HO-3 group (as in **3**, **6**–**8**) cause total loss or great decreases in the activity inherent in the parent anthracycline antibiotics. However, in view of drug resistance against P388/DOX (Table 6), there was a considerable difference between **4** and **5** (**4** showed partial drug-resistance against P388/DOX). Judging from the resistant factor (RF)-values (Table 6), it appears that HO-14 (in **2**, **5**, and DOX) induced resistance (possibly by MDR), and absence of the HO-3′ (or H_2N-3′) group reversed the resistance. However, these hydroxyl groups, especially HO-3′, seem to be the groups essential for manifesting antitumor activity in these anthracycline glycosides. It appears, therefore, that the more active compounds suffer the stronger resistance. In this context, a 3′,4′-di-*O*-methyl analog of DNR, SO-075R1 [20] was expected to show only weak antitumor activity. However, we set a parameter (E) as a measure for estimating the antitumor activity and resistance (to P388/DOX) concurrently, by multiplying the RF-value in Table 6 and the dose (C_{150}) needed to attain the value of T/C 150% in Table 5 (for example, in **4**: $4.1 \times 1.25 = 5.1$; the values are shown in the last column in Table 5). Based on this parameter, the antitumor activities of **4** and **5** (as well as **1** and **2**) are estimated as being almost equal, and superior to those of the other derivatives. Since the Ca^{2+} ion is considered to play an important role in MDR, the pursuit of the relationship between Ca-chelating ability of our synthetic products and RF (or E) value will be an interesting problem in future.

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. ^1H NMR (at 250 MHz) and ^{19}F NMR (at 235.7 MHz) spectra were recorded with a Bruker WM 250 spectrometer. ^{13}C NMR (at 62.9 or 125.8 MHz) spectra were recorded with a Bruker WM 250 or Bruker AMX 500 spectrometer. Chemical shifts (δ) for ^1H, ^{13}C, and ^{19}F spectra were measured, downfield from internal Me_4Si, downfield from Me_4Si with aid of internal 1,4-dioxane ($\delta = \delta_{1,4\text{-dioxane}} + 67.4$), and downfield from internal Freon 11 ($CFCl_3$), respectively. TLC was performed on Kieselgel 60 F_{254} (Merck), and column chromatography on Wakogel C-200.

Methyl 4-O-benzyl-2,6-dideoxy-2-fluoro-3-O-methyl-α-L-talopyranoside (**10**).—A mixture of NaH (170 mg, 60% NaH in mineral oil, 4.3 mmol) and **9** [4] (460 mg, 1.7 mmol) in dry DMF (4.6 ml) was stirred under an atmosphere of N_2. After hydrogen evolution had ceased, MeI (1 mL, 10.8 mmol) was added, and the stirring was continued for 1 h at room temperature. After addition

Table 6
Growth inhibitory effect of **1**–**8**, DNR, and DOX against P388 and P388/DOX cell lines *in vitro* [a]



Compound	Substituent				IC_{50} ($\mu g\,mL^{-1}$)		RF[b]
	R^1	R^2	R^3	R^4	P388	P388/DOX	
1	H	F	OH	OH	0.008	0.05	6.3
2	OH	F	OH	OH	0.003	0.09	30
3	H	F	OMe	OH	0.066	0.10	1.5
4	H	F	OH	OMe	0.032	0.13	4.1
5	OH	F	OH	OMe	0.004	0.08	20
6	H	F	H	OH	0.150	0.37	2.5
7	H	F	F	OH	0.073	0.26	3.6
8	H	F	I	OH	0.130	0.42	3.2
DNR	H	H	NH_2	OH	0.020	0.34	17
DOX	OH	H	NH_2	OH	0.014	>0.50	>36

[a] IC_{50} values (50% inhibition concentration) were determined on day-3 culture.
[b] Resistant factor (RF): IC_{50} for resistant subline/IC_{50} for sensitive subline.

of AcOH (0.2 mL) followed by $CHCl_3$, the solution was washed with aq NaCl (saturated), dried (Na_2SO_4), and concentrated with occasional addition of xylene. The residue was chromatographed (9:1 toluene–EtOAc) to give **10** as a syrup, 409 mg (84%), TLC (10:1 toluene–EtOAc): R_f 0.27 (*cf* **9**: R_f 0.17), $[\alpha]_D^{24}$ −38° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{15}H_{21}FO_4$: C, 63.36; H, 7.44; F, 6.68. Found: C, 63.37; H, 7.41; F, 6.73.

1,4-Di-O-*acetyl-2,6-dideoxy-2-fluoro-3*-O-*methyl*-α- (**12**) *and* -β-L-*talopyranose* (**13**).—To a solution of **10** (379 mg, 1.3 mmol) and AcOH (1.9 mL) in 1,4-dioxane—H_2O (8:1, 21 mL) was gently introduced H_2 in the presence of palladium black for 1 h at room temperature. Filtration followed by concentration with aid of toluene gave **11** as a syrup, which was chromatographically homogeneous, 260 mg (quant), R_f 0.2 (TLC, 30:1 $CHCl_3$–acetone); ^{19}F NMR ($CDCl_3$) δ −201.6 (br dddd, which collapsed to sharp ddd in addition of D_2O; $J_{OH-4,F}$ ~5 Hz; Table 2). To an ice-cold solution of the syrup in dry $MeNO_2$ (8 mL) were added Ac_2O (1.3 mL, 13.8 mmol) and H_2SO_4 (8 μL), and the solution was kept for 2.5 h at room temperature. TLC (30:1 $CHCl_3$–acetone) showed two spots at R_f 0.3 (**12**, major) and 0.2 (**13**, minor). After pouring into $NaHCO_3$ (4.7 g) suspended in water (13.7 mL), and stirring for 1 h, the mixture was extracted with $CHCl_3$. The solution was washed with aq 10% NaCl, dried (Na_2SO_4), and concentrated. Chromatography (30:1 $CHCl_3$–acetone) of the residue gave **12** as crystals, 236 mg (67%), and a mixture of **12** and **13** (74 mg). Rechromatography of the latter with the same solvent system gave an additional crop of **12**, 38 mg (11%), and **13** as a syrup, 25 mg (7.2%). Compound **12**, mp 139–140 °C (prisms from $CHCl_3$–diisopropyl ether); $[\alpha]_D^{21}$ −159° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{11}H_{17}FO_6$: C, 50.00; H, 6.48; F, 7.19. Found: C, 49.90; H, 6.72; F, 6.93. Compound **13** had $[\alpha]_D^{23}$ −28° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{11}H_{17}FO_6$: C, 50.00; H, 6.48. Found: C, 50.20; H, 6.51.

4-O-*Acetyl-2,6-dideoxy-2-fluoro-3*-O-*methyl*-α-L-*talopyranosyl bromide* (**14**).—A mixture of **12** (329 mg, 1.2 mmol) and $TiBr_4$ (1.14 g, 3.8 mmol) in dry CH_2Cl_2–EtOAc (9:1, 7.3 mL) was stirred for 16 h at room temperature. TLC (3:1 hexane–acetone) of the deep-brown mixture showed a single

spot at R_f 0.35. After dilution with dry MeCN (13 mL), anhydrous NaOAc (2.88 g) was added at 0 °C and the mixture was stirred until the color faded to pale yellow. The mixture was filtered through Celite with aid of toluene, and the organic solution was concentrated. Extraction of the residue with toluene followed by concentration gave **14** as a pale-yellow syrup (314 mg, 88%), which was used without further purification.

*Methyl 4-*O*-benzyl-2,6-dideoxy-2-fluoro-3-*O*-tetrahydropyran-2-yl-*α*-*L*-talopyranoside* (**15**).—A mixture of **9** (536 mg, 2.0 mmol), 3,4-dihydro-2*H*-pyran (0.53 mL, 6 mmol), and pyridinium *p*-toluenesulfonate (57 mg, 0.23 mmol) in dry CH_2Cl_2 (8 mL) was kept for 5 h at room temperature. The solution, after pouring into aq $NaHCO_3$ (saturated), was extracted with $CHCl_3$ and the extract was concentrated. Chromatography (20:1 toluene–acetone) of the residue gave a diastereoisomeric mixture (1:0.8 by ^{19}F NMR) of **15** as a syrup, 571 mg (81%), TLC (20:1 toluene–acetone): R_f 0.25, $[\alpha]_D^{22}$ −47° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) (signals not listed in Table 1): δ 7.2–7.5 (5 H, m, Ph), 4.81–4.87 (1 H, H-2′), 4.71, 4.75, 4.91, 5.01 (each d, 2 H in total, *J* 12 Hz, PhC*H*$_2$), ~3.9 (1 H, H-6′b), 3.48-3.55 (1 H, H-6′a), 1.5–2.0 (6 H, H-3′a,b, 4′a,b, 5′a,b of THP), Anal. Calcd for $C_{19}H_{27}FO_5$: C, 64.39; H, 7.68; F, 5.36. Found: C, 64.31; H, 7.66; F, 5.11.

*Methyl 2,6-dideoxy-2-fluoro-3-*O*-tetrahydropyran-2-yl-*α*-*L*-talopyranoside* (**16**).—Compound **15** (666 mg, 1.9 mmol) was hydrogenolyzed in 1,4-dioxane–H_2O (16:1, 34 mL) for 2 h as described for **11**, and the products were chromatographed (10:1 $CHCl_3$–EtOAc) to give **16** as a diastereoisomeric mixture of semi-crystalline syrup, 411 mg (83%). ^1H NMR ($CDCl_3$) (signals not listed in Table 1): δ 4.85–4.94 (1 H, H-2′), 3.75–4.0 (4 H, H-3, 4, 5, 6′b), 3.54 (m, 1 H, H-6′a), 2.39 (t, 0.86 H, $J_{4,OH\text{-}4} = J_{OH\text{-}4,F}$ 7 Hz, OH-4 of the major isomer), 2.28 (t, 0.14 H, $J_{4,OH\text{-}4} = J_{OH\text{-}4,F}$ 8.5 Hz, OH-4 of the minor isomer), 1.5–2.0 (6 H, H-3′a,b, 4′a,b, 5′a,b). Anal. Calcd for $C_{12}H_{21}FO_5$: C, 54.53; H, 8.01; F, 7.19. Found: C, 54.62; H, 8.01; F, 6.88.

*Methyl 2,6-dideoxy-2-fluoro-4-*O*-methyl-3-*O*-tetrahydropyran-2-yl-*α*-*L*-talopyranoside* (**17**).—Compound **16** (434 mg, 1.6 mmol) in DMF (4.3 mL) was treated with NaH (188 mg, 60% in mineral oil, 4.7 mmol) and MeI (0.4 mL, 6.4 mmol; 2 h) as described for **10**. Column chromatography (10:1 $CHCl_3$–EtOAc) of the products gave a diastereoisomeric mixture (1:0.6 by ^{19}F NMR) of **17** as a syrup, 338 mg (74%), TLC (10:1 $CHCl_3$–EtOAc): R_f 0.3, $[\alpha]_D^{25}$ −103° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) (signals not listed in Table 1): δ 4.78–4.90 (1 H, H-2′), 3.86–3.96 (2 H, H-5, 6′b), 3.3–3.6 (2 H, H-4, 6′a), 1.5–2.0 (6 H, H-3′a,b, 4′a,b, 5′a,b). Anal. Calcd for $C_{13}H_{23}FO_5$: C, 56.10; H, 8.33; F, 6.83. Found: C, 55.94; H, 8.27; F, 6.96.

*1,3-Di-*O*-acetyl-2,6-dideoxy-2-fluoro-4-*O*-methyl-α-L-talopyranose* (**18**).—A mixture of **17** (425 mg, 1.5 mmol), Ac_2O (4.2 mL), AcOH (4.2 mL), and H_2SO_4 (85 μL, 1.6 μmol) was kept for 1 h at 0 °C, then for 1.5 h at room temperature. The dark-brown solution resulted was poured into ice-cold aq NaHCO3 (saturated, 40 mL) and the mixture was stirred for 1.5 h. Extraction of the product with $CHCl_3$ and concentration gave a residue, which was chromatographed (30:1 $CHCl_3$–EtOAc) to give **18** as crystals, 260 mg (64%), mp 92–93 °C (prisms from EtOAc–hexane), $[\alpha]_D^{22}$ −97° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{11}H_{17}FO_6$: C, 50.00; H, 6.48; F, 7.19. Found: C, 50.12; H, 6.48; F, 7.20.

*3-*O*-Acetyl-2,6-dideoxy-2-fluoro-4-*O*-methyl-α-L-talopyranosyl bromide* (**19**).—A mixture of **18** (230 mg, 0.87 mmol) and $TiBr_4$ (800 mg, 2.2 mmol) in dry CH_2Cl_2–EtOAc (10:1, 5 mL) was stirred for 16 h at room temperature. The deep-brown mixture was treated as described for **14** to give **19** as a pale-yellow syrup, 246 mg (quant), which was used without further purification.

*Methyl 4-*O*-benzyl-2,6-dideoxy-2-fluoro-3-*O*-trifluoromethylsulfonyl-α-L-idopyranoside* (**21**).—To a cold (−20 °C) solution of **20** [4] (2.00 g, 7.4 mmol) in pyridine (3.6 mL)–CH_2Cl_2 (20 mL) was added $(CF_3SO_2)_2O$ (1.9 mL, 11 mmol) and the solution was kept for 1 h at 0 °C. After addition of MeOH (10 mL) followed by dilution with $CHCl_3$, the solution was washed successively with aq 20% $KHSO_4$, aq $NaHCO_3$ (saturated), and water, dried (Na_2SO_4), and concentrated to give **21** as a pale-yellow syrup, 2.83 g (95%) which was used without further purification; ^{19}F NMR ($CDCl_3$): δ −194.7 (dddq, 1 F, F-2; collapsed to ddd by irradiation at δ −75.1), −75.1 (d, 3 F, $J_{CF_3,F\text{-}2}$ 6 Hz, CF_3).

*Methyl 4-*O*-benzyl-2,3,6-trideoxy-2-fluoro-3-iodo-α-L-talopyranoside* (**22**).—A mixture of **21** (2.83 g, 7.0 mmol) and NaI (5.28 g, 32 mmol) in DMF (29 mL) was stirred the dark place for 3 h at 90 °C. Dilution of the solution with $CHCl_3$ gave a precipitate, which was filtered and washed with $CHCl_3$. The filtrates combined were washed with aq 20% $Na_2S_2O_3$ and water, dried (Na_2SO_4), and concentrated with aid of xylene. Chromatography

(50:1 toluene–EtOAc) of the residue gave **22** as an amorphous solid, 2.01 g (75%), $[\alpha]_D^{23}$ −74° (*c* 1, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 127.7, 128.1, 128.3, 137.4 (Ph), 98.3 (d, $J_{C\text{-}1,F}$ 31.3 Hz, C-1), 87.9 (d, $J_{C\text{-}2,F}$ 188.4 Hz, C-2), 78.9 (C-4), 76.3 (PhCH_2), 67.3 (C-5), 55.2 (OCH_3), 24.2 (d, $J_{C\text{-}3,F}$ 15.7 Hz, C-3). Anal. Calcd for $C_{14}H_{18}FIO_3$; C, 44.23; H, 4.77; F, 5.00; I, 33.38. Found: C, 44.56; H, 4.93; F, 4.84; I, 33.56.

Methyl 4-O-*benzyl-2,3,6-trideoxy-2-fluoro*-α-L-*lyxo-hexopyranoside* (**23**).—A mixture of **22** (1.99 g, 5.2 mmol), Bu_3SnH (8.4 mL, 31.3 mmol), and 2,2′-azobisisobutyronitrile (43 mg, 0.26 mmol) in dry 1,4-dioxane was stirred for 1 h at 80 °C under the atmosphere of N_2. After concentration, the residue was chromatographed (1:1 toluene–hexane→$CHCl_3$) to give **23** as a syrup, 1.32 g (quant), TLC (50:1 toluene–EtOAc) R_f 0.25 (*cf* **22** : R_f 0.35), $[\alpha]_D^{23}$ −31° (*c* 2, $CHCl_3$). Anal. Calcd for $C_{14}H_{19}FO_3$: C, 66.12; H, 7.53; F, 7.47. Found: C, 65.85; H, 7.64; F, 7.61.

Methyl 2,3,6-trideoxy-2-fluoro-4-O-p-*nitrobenzoyl*-α-L-*lyxo-hexopyranoside* (**25**).—A solution of **23** (50 mg, 0.20 mmol) in 1,4-dioxane–H_2O–AcOH (10:1:1, 1 mL) was hydrogenated in the presence of Pd black under gentle bubbling of H_2 for 2 h at room temperature. In TLC (3:1 hexane–acetone), the solution showed a single spot at R_f 0.4 of **24** (*cf* **23**: R_f 0.5). After filtration followed by dilution with CH_2Cl_2, the organic solution was washed with aq $NaHCO_3$ (saturated), dried ($MgSO_4$), and concentrated. To the residue in CH_2Cl_2 (1.5 mL) *p*-nitrobenzoyl chloride (110 mg, 0.59 mmol) and pyridine (0.7 mL) were added, and the mixture was stirred for 11 h at room temperature. Water (0.05 mL) was added, and stirring was continued for 1 h. After addition of large amount of $CHCl_3$, the organic solution was washed successively with aq 20% $KHSO_4$, aq $NaHCO_3$ (saturated), and water, dried (Na_2SO_4), and concentrated to give **25** as needles (58 mg, 94% based on **23**), mp 107–108 °C, $[\alpha]_D^{23}$ −56° (*c* 1, $CHCl_3$), IR (KBr): 1720 (C=O), 1530 cm^{-1} (NO_2). Anal. Calcd for $C_{14}H_{16}FNO_6$: C, 53.68; H, 5.15; F, 6.06; N, 4.47. Found: C, 53.97; H, 5.12; F, 6.09; N, 4.44.

1-O-*Acetyl-2,3,6-trideoxy-2-fluoro-4*-O-p-*nitrobenzoyl*-α- (**26**) *and* -β-L-lyxo-*hexopyranose* (**27**).—A solution of **25** (420 mg, 1.3 mmol), Ac_2O (1.0 mL, 10.8 mmol), and H_2SO_4 (7.2 μL) in dry $MeNO_2$ (9 mL) was kept for 1 h at room temperature. After pouring into cold water (13 mL) containing $NaHCO_3$ (3.6 g), the mixture was stirred for 1 h, and the products were extracted with $CHCl_3$. The solution was washed with water, dried (Na_2SO_4), and concentrated. Chromatography (50:1 $CHCl_3$–EtOAc) of the residue gave **26** as crystals, 356 mg (78%), TLC: R_f 0.35 (3:1 hexane–acetone) and **27** as crystals, 58 mg (13%), R_f 0.25. Compound **26**, mp 126–127.5 °C, $[\alpha]_D^{23}$ −62° (*c*, 1.5, $CHCl_3$). Anal. Calcd for $C_{15}H_{16}FNO_7$: C, 52.79; H, 4.73; F, 5.57; N, 4.10. Found: C, 52.96; H, 4.65; F, 5.30; N, 4.04. Compound **27**, mp 189.5–190.5 °C, $[\alpha]_D^{23}$ −5° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{15}H_{16}FNO_7$: C, 52.79; H, 4.73; F, 5.57; N, 4.10. Found: C, 52.59; H, 4.63; F, 5.40; N,3.83.

2,3,6-Trideoxy-2-fluoro-4-O-p-*nitrobenzoyl*-α-L-lyxo-*hexopyranosyl bromide* (**28**).—A solution of **26** (329 mg, 0.97 mmol) in 30% HBr in AcOH (3.3 mL) was kept for 1.5 h at room temperature. $CHCl_3$ (60 mL) was added, and the solution was washed with cold aq $NaHCO_3$ (saturated) and water, dried ($MgSO_4$), and concentrated to give **28** as a pale-yellow syrup, 349 mg (quant), which was used without purification; TLC (3:1 hexane–acetone) R_f 0.45.

Methyl 4-O-*benzyl-2,3,6-trideoxy-2,3-difluoro*-α-L-*talopyranoside* (**29**).—A mixture of **21** (2.70 g, 6.7 mmol) and tris(dimethylamino)sulfonium difluorotrimethylsilicate [19] (6.67 g, 24.2 mmol) in dry CH_2Cl_2 (54 mL) was stirred for 15 h under an atmosphere of N_2 at room temperature. After dilution with $CHCl_3$, the solution was washed with aq $NaHCO_3$ (saturated) and water, dried (Na_2SO_4), and concentrated. The residue was chromatographed (30:1 toluene–EtOAc) to give **29** as a solid, 1.20 g (66%). Recrystallization from $CHCl_3$–hexane gave prisms, mp 51.5–52.5 °C, $[\alpha]_D^{25}$ −41° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{14}H_{18}F_2O_3$: C, 61.75; H, 6.66; F, 13.95. Found: C, 61.84; H, 6.85; F, 13.75.

1,4-Di-O-*acetyl-2,3,6-trideoxy-2,3-difluoro*-α- (**31**) *and* -β-L-*talopyranose* (**32**).—A solution of **29** (1.09 g, 4.0 mmol) in 1,4-dioxane–H_2O–AcOH (10:1:1, 22 mL) was hydrogenated in the presence of Pd black under gentle bubbling of H_2 for 3.5 h at room temperature. After filtration, the filtrate diluted with CH_2Cl_2 was washed with aq $NaHCO_3$ (saturated) and water, dried ($MgSO_4$), and concentrated to give **30** as a syrup, 0.63 g (86%), TLC (30:1 $CHCl_3$–EtOAc) R_f 0.3 (*cf* **29**: R_f 0.6). To an ice-cold solution of **30** (0.62 g, 3.4 mmol) in AcOH (6.2 mL) were added Ac_2O (9.3 mL) and H_2SO_4 (0.06 mL), and the solution was kept for 4 h at room temperature. Processing as described for **12** followed by chromatography (30:1 $CHCl_3$–EtOAc) gave the

α-L anomer **31** as prisms, 0.44 g (52%) and the β-L anomer **32** as plates, 0.17 g (20%). Compound **31**, TLC (30:1 $CHCl_3$–EtOAc) R_f 0.3, mp 143.5-144.5 °C, $[\alpha]_D^{25}$ −120° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{10}H_{14}F_2O_5$: C, 47.62; H, 5.60; F, 15.07. Found: C, 47.76; H,5.80; F, 14.79. Compound **32**, TLC (30:1 $CHCl_3$–EtOAc) R_f 0.2, mp 108–109 °C, $[\alpha]_D^{23}$ −20° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{10}H_{14}F_2O_5$: C, 47.62; H, 5.60; F, 15.07. Found: C, 47.43; H, 5.73; F, 14.83.

4-O-Acetyl-2,3,6-trideoxy-2,3-difluoro-α-L-talopyranosyl bromide (**33**).—A solution of **31** (320 mg, 1.3 mmol) in 30% HBr in AcOH (3.2 mL) was kept for 2 h at room temperature. Working up as described for **28** gave **33** as crystals, 346 mg (quant). Analytical samples were prepared by recrystallization ($CHCl_3$–hexane) as prisms, mp 57.5–59 °C, $[\alpha]_D^{19}$ −260° (*c* 1, $CHCl_3$). Anal. Calcd for $C_8H_{11}BrF_2O_3$: C, 35.19; H, 4.06; Br, 29.26; F, 13.91. Found: C, 35.46; H, 4.30; Br, 28.99; F, 13.99.

Methyl 3-O-acetyl-2,6-dideoxy-2-fluoro-α-L-idopyranoside (**35**).—A solution of **34** [4] (108 mg, 0.35 mmol) in 1,4-dioxane–H_2O–AcOH (10:1:1, 2.5 mL) was hydrogenated as described for **11** to give **35** as a pale yellow syrup, 77 mg (quant), $[\alpha]_D^{23}$ −104° (*c* 1.8, $CHCl_3$). Anal. Calcd for $C_9H_{15}FO_5$: C, 48.65; H, 6.80; F, 8.55. Found: C, 48.69; H, 6.86; F, 8.85.

Methyl 3-O-acetyl-2,6-dideoxy-2-fluoro-4-O-tetrahydropyran-2-yl-α-L-idopyranoside (**36**).—A solution of **35** (71 mg, 0.32 mmol), 3,4-dihydro-2*H*-pyran (88 μL, 0.96 mmol), and pyridinium *p*-toluenesulfonate (8 mg, 0.03 mmol) in dry CH_2Cl_2 (1.5 mL) was kept overnight at room temperature. After working up as described for **15**, the products were chromatographed (10:1 toluene–EtOAc) to give a diastereoisomeric mixture (1:2 by ^{19}F NMR) of **36** as a syrup, 95 mg (97%), $[\alpha]_D^{23}$ −92° (*c* 3, $CHCl_3$); ^1H NMR ($CDCl_3$) (only selected signals): δ 5.33 and 5.24 (each dt, 2:1 in strength, 1 H in total, H-3), 4.35 (ddd, 0.67 H, H-2), 3.444 and 3.436 (each s, 3 H in total, OMe), 2.10 (s, 3 H, Ac), 1.38 and 1.28 (each d, 1:2 in strength, 3 H in total, Me-5); $J_{1,2}$ 3.5, $J_{2,3} = J_{3,4}$ 5.5 Hz. ^{19}F NMR ($CDCl_3$): δ −194.8 (ddd, 0.33 F, $J_{1,F}$ 10.5, $J_{2,F}$ 46.5, $J_{3,F}$ 12.5 Hz), −195.9 (dt, 0.67 F, $J_{1,F} = J_{3,F}$ 11.5, $J_{2,F}$ 47 Hz). Anal. Calcd for $C_{14}H_{23}FO_6$: C, 54.89; H, 7.57; F, 6.20. Found: C, 55.25; H, 7.69; F, 6.19.

Methyl 2,6-dideoxy-2-fluoro-4-O-tetrahydropyran-2-yl-α-L-idopyranoside (**37**).—Zemplén deacetylation of **36** (122 mg, 0.40 mmol) in MeOH (0.1 mL) gave, after conventional post-treatment, **37** as a pale-yellow syrup, 103 mg (98%), $[\alpha]_D^{23}$ −89° (*c* 3, $CHCl_3$); ^1H NMR ($CDCl_3$) (only selected signals): δ 3.47 and 3.46 (each s, 3 H in total, OMe), 1.37 and 1.28 (each d, 1:2 in strength, 3 H in total, $J_{5,6}$ 6.5 Hz, Me-5). ^{19}F NMR ($CDCl_3$): δ −196.2 (br dt, 0.33 F, $J_{1,F} = J_{3,F}$ ~10, $J_{2,F}$ 47 Hz), −197.9 (ddd, 0.67 F, $J_{1,F}$ 9.5, $J_{2,F}$ 49.5, $J_{3,F}$ 13 Hz). Anal. Calcd for $C_{12}H_{21}FO_5$: C, 54.53; H, 8.01; F, 7.19. Found: C, 54.36; H, 7.96; F, 7.47.

Methyl 2,3,6-trideoxy-2-fluoro-3-iodo-4-O-p-nitrobenzoyl-α-L-talopyranoside (**40**).—To an ice-cold solution of **37** (315 mg, 1.2 mmol) in pyridine (0.6 mL, 7.3 mmol)–CH_2Cl_2 (4.4 mL) was added $(CF_3SO_2)_2O$ (0.3 mL, 2.1 mmol) and the solution was kept for 1 h in the cold. MeOH (0.4 mL) was added, and after dilution with $CHCl_3$, the solution was washed successively with cold aq 20% $KHSO_4$, aq $NaHCO_3$ (saturated), and water, dried (Na_2SO_4), and concentrated to give **38** (442 mg, 94%) as an unstable syrup, TLC (4:1 toluene–EtOAc) R_f 0.65. A mixture of the syrup (430 mg, 1.1 mmol) and NaI (820 mg, 5.5 mmol) in dry DMF (4.5 mL) was stirred for 3 h at 90 °C. In TLC (4:1 toluene–EtOAc), the mixture showed a main spot at R_f 0.5 (**39**). After cooling to room temperature, *p*-nitrobenzoyl chloride (610 mg, 3.3 mmol) and 4-dimethylaminopyridine (400 mg, 3.3 mmol) were added, and the mixture was stirred for 2.5 h at room temperature. Water (0.2 mL) was added, and after dilution with $CHCl_3$, the organic solution was washed successively with aq 20% $Na_2S_2O_3$, aq 20% $KHSO_4$, aq $NaHCO_3$ (saturated), and water, dried (Na_2SO_4), and concentrated. Chromatography (toluene) of the residue gave **40** as an amorphous solid, 276 mg (58% based on **38**), TLC (4:1 toluene–EtOAc) R_f 0.7, $[\alpha]_D^{22}$ −117° (*c* 1.8, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 164.2 (C=O), 150.9, 134.8, 131.5, 123.7 (Ph), 98.1 (d, $J_{C\text{-}1,F}$ 32.8 Hz, C-1), 87.7 (d, $J_{C\text{-}2,F}$ 183.2 Hz, C-2), 72.8 (C-4), 65.8 (C-5), 55.5 (OCH_3), 21.1 (d, $J_{C\text{-}3,F}$ 18.6 Hz, C-3), 17.3 (Me-5). Anal. Calcd for $C_{14}H_{15}FINO_6$: C, 38.29; H, 3.44; F, 4.33; I, 28.89; N, 3.19. Found: C, 38.44; H, 3.54; F, 4.40; I, 28.95; N, 3.16.

1-O-Acetyl-2,3,6-trideoxy-2-fluoro-3-iodo-4-O-p-nitrobenzoyl-α-L-talopyranose (**41**).—A solution of **40** (170 mg, 0.39 mmol), Ac_2O (0.29 mL, 3.1 mmol), and H_2SO_4 (7 μL) in dry $MeNO_2$ (3.8 mL) was kept for 2 h at room temperature. Working up as described for **26** gave a solid, which was chromatographed (20:1 toluene–EtOAc) to give **41** as an amorphous solid, 130 mg (72%), $[\alpha]_D^{22}$ −147° (*c*

2.7, $CHCl_3$). Anal. Calcd for $C_{15}H_{15}FINO_7$: C, 38.56; H, 3.24; F, 4.07; I, 27.16; N, 2.30. Found: C, 38.64; H, 3.49; F, 3.67; I, 27.33; N, 2.52.

*2,3,6-Trideoxy-2-fluoro-3-iodo-4-*O-p-*nitrobenzoyl-*α-L-*talopyranosyl bromide* (**42**).—A solution of **41** (200 mg, 0.43 mmol) in 30% HBr in AcOH (2 mL) was kept for 2 h at room temperature. Working up as described for **28** gave **42** as an amorphous solid, 209 mg (99%), TLC (20:1 toluene–EtOAc) R_f 0.7 (*cf* **41**: R_f 0.3), $[\alpha]_D^{22}$ −223° (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{13}H_{12}BrFINO_5$: C, 31.99; H, 2.48; F, 3.89; N, 2.87. Found: C, 31.77; H, 2.64; F, 3.59; N, 2.58.

*7-*O-*(4-*O-*Acetyl-2,6-dideoxy-2-fluoro-3-*O-*methyl-*α- (**43**) *and* -β-L-*talopyranosyl)daunomycinone* (**44**).—A mixture of daunomycinone (349 mg, 0.88 mmol), yellow HgO (1.26 g, 5.8 mmol), $HgBr_2$ (360 mg, 1.0 mmol), and powdered molecular sieves 3A (3.34 g, activated at 350 °C under a stream of N_2) in dry CH_2Cl_2 (58 mL) was stirred for 30 min at room temperature. After **14** (304 mg, 1.1 mmol) in dry CH_2Cl_2 (2.4 mL) was added, the mixture was refluxed for 17 h in a dark place. In TLC (10:1 $CHCl_3$–acetone), the mixture showed spots at R_f 0.33 (**43**, major), 0.22 (daunomycinone, slight), and 0.14 (**44**, minor) along with several minor spots. The mixture was filtered through a Celite bed, the bed being washed repeatedly 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. Triplicate chromatographies (10:1 $CHCl_3$–acetone →1:1 $CHCl_3$–EtOAc →1:1 toluene–EtOAc) of the residue gave **43**, 206 mg (38%) and **44**, 42 mg (8%) as reddish-orange solids. Analytical samples were prepared by reprecipitation from $CHCl_3$–hexane. Compound **43**, $[\alpha]_D^{24}$ +175° (*c* 0.02, $CHCl_3$); ^{19}F NMR ($CDCl_3$): δ −202.2 (ddd). Anal. Calcd for $C_{30}H_{31}FO_{12}\cdot 0.5\ H_2O$: C, 58.92; H, 5.27; F, 3.11. Found: C, 59.19; H, 5.07; F, 2.70. Compound **44**, $[\alpha]_D^{26}$ +426° (*c* 0.02, $CHCl_3$); ^{19}F NMR ($CDCl_3$): δ −220.9 (ddd). Anal. Calcd for $C_{30}H_{31}FO_{12}\cdot 0.5\ H_2O$: C, 58.92; H, 5.27; F, 3.11. Found: C, 58.62; H, 5.10; F, 2.98.

*7-*O-*(2,6-Dideoxy-2-fluoro-3-*O-*methyl-*α-L-*talopyranosyl)daunomycinone* (**3**).—To an ice-cold solution of **43** (53 mg, 0.09 mmol) in 2:1 $CHCl_3$–MeOH (6.3 mL) was added 0.3 M methanolic NaOH (2.1 mL), and the mixture was stirred for 4 h at 0 °C under the atmosphere of N_2. After neutralization of the deep-purple mixture with aq 0.5 M HCl, the mixture was extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and concentrated. Chromatography of the residue (6:1 $CHCl_3$–acetone) gave **3** as a reddish-orange solid, 34 mg (69%), TLC (6:1 $CHCl_3$–acetone) R_f 0.3, $[\alpha]_D^{24}$ +176° (*c* 0.02, $CHCl_3$); ^{19}F NMR ($CDCl_3$): δ −199.6 (ddt; $J_{OH\text{-}4',F}$ ~9 Hz; the signals collapsed to ddd on addition of D_2O). Anal. Calcd for $C_{28}H_{29}FO_{11}\cdot 0.5\ H_2O$: C, 59.05; H, 5.31; F,3.34. Found: C, 59.29; H, 5.23; F, 3.39.

*7-*O-*(3-*O-*Acetyl-2,6-dideoxy-2-fluoro-4-*O-*methyl-*α-L-*talopyranosyl)daunomycinone* (**45**).—A mixture of daunomycinone (292 mg, 0.73 mmol), yellow HgO (713 mg, 3.3 mmol), $HgBr_2$ (212 mg, 0.59 mmol), and powdered molecular sieves 3A (2.84 g) in dry CH_2Cl_2 (48 mL) was stirred for 30 min at room temperature. A solution of **19** (254 mg, 0.89 mmol) in dry CH_2Cl_2 (1.9 mL) was added, and the mixture was refluxed for 19 h in the dark place. In TLC (15:1 $CHCl_3$–acetone), the mixture showed spots at R_f 0.26 (**45**, major), 0.18 (trace), 0.13 (slight), and 0.09 (slight). Working up as described for **43** gave a solid, which was doubly chromatographed (15:1 $CHCl_3$–acetone) to give **45** as a reddish-orange solid, 220 mg (50%). An analytical sample was prepared by reprecipitation from $CHCl_3$–Et_2O–hexane, $[\alpha]_D^{22}$ +251° (*c*, 0.02, $CHCl_3$); ^{19}F NMR ($CDCl_3$): δ −201.3 (ddd). Anal. Calcd for $C_{30}H_{31}FO_{12}$: C, 59.80; H, 5.19; F, 3.15. Found: C, 59.89; H, 5.13; F, 2.98.

*7-*O-*(2,6-Dideoxy-2-fluoro-4-*O-*methyl-*α-L-*talopyranosyl)daunomycinone* (**4**).—To an ice-cold solution of **45** (115 mg, 0.19 mmol) in oxolane (7.3 mL) was added aq 1 M NaOH (1.7 mL), and the mixture was stirred for 1 h in the cold. The resultant deep-purple solution was neutralized with aq 1 M HCl, concentrated to a small volume, and after addition of $CHCl_3$, the solution was washed with aq 20% NaCl, dried (Na_2SO_4), and concentrated. The residue was passed through a short column of silica gel with 5:1 $CHCl_3$–acetone giving **4** as a reddish-orange solid, 103 mg (96%). An analytical sample was prepared by reprecipitation from $CHCl_3$–Et_2O–hexane, TLC (5:1 $CHCl_3$–acetone): R_f 0.6, $[\alpha]_D^{22}$ +159° (*c*, 0.02, $CHCl_3$); ^{19}F NMR ($CDCl_3$): δ −204.2 (slightly br ddd, which sharpened on addition of D_2O). Anal. Calcd for $C_{28}H_{29}FO_{11}\cdot 0.5\ H_2O$: C, 59.05; H, 5.31; F, 3.34. Found: C, 58.96; H, 5.19; F, 3.35.

*7-*O-*(2,6-Dideoxy-2-fluoro-4-*O-*methyl-*α-L-*talopyranosyl)adriamycinone* (**5**).—To a solution of **4** (83 mg, 0.15 mmol) and $HC(OMe)_3$ (0.11 mL, 1.0 mmol) in dry 2:3 MeOH–1,4-dioxane (5 mL) was added Br_2 (35 mg, 0.22 mmol) in CH_2Cl_2

(0.35 mL), and the solution was kept for 0.5 h at 0 °C, and then for 3 h at room temperature. TLC (2:1 benzene–acetone) of the solution showed a main spot at R_f 0.35. Addition of diisopropyl ether followed by hexane gave a precipitate, which was collected and washed with hexane to give a red solid (mainly the 14-bromo-13-dimethylacetal derivative). A suspension of the solid in acetone (15 mL) was shaken for 1.5 h at room temperature, and concentrated to give a dark-red solid (mainly the deacetalated 14-bromo derivative). A mixture of the solid and HCO_2Na (169 mg, 2.5 mmol) in 4:1 acetone–H_2O (10 mL) was stirred vigorously for 15 h at room temperature, whereupon, in TLC (2:1 benzene–acetone), two spots of R_f 0.28 (the 14-*O*-formyl derivative of **5**) and 0.15 (**5**) appeared. After concentration to a small volume followed by addition of water, the products were extracted with $CHCl_3$. The organic solution was washed with water, dried (Na_2SO_4), and concentrated. A suspension of the dark-red solid (83 mg) in 4:4:1 $CHCl_3$–MeOH–aq 1 M NH_3 (9 mL) was shaken for 45 min at 0 °C, when a substance with R_f 0.28 disappeared and **5** became the major one. After dilution with water, products were extracted with $CHCl_3$, and the solution was washed with aq 0.05 M HCl and aq 20% NaCl, dried (Na_2SO_4), and concentrated. The residue was chromatographed on a short column with 3:2 $CHCl_3$–acetone to give **5** as a red solid, 64 mg (75%). An analytical sample was prepared by reprecipitation from $CHCl_3$–MeOH–Et_2O–hexane, $[\alpha]_D^{23}$ +155° (*c* 0.02, $CHCl_3$); ^{19}F NMR ($CDCl_3$): δ −204.0 (ddd). Anal. Calcd for $C_{28}H_{29}FO_{12}\cdot 0.25\ H_2O$: C, 57.88; H, 5.12; F, 3.27. Found: C, 57.91; H, 5.19; F, 2.93.

7-O-*(2,3,6-Trideoxy-2-fluoro-4*-O-p-*nitrobenzoyl*-α- (**46**) *and* -β-L-*lyxo-hexopyranosyl)daunomycinone* (**47**). A mixture of **28** (349 mg, 0.97 mmol), daunomycinone (298 mg, 0.73 mmol), yellow HgO (729 mg, 3.37 mmol), $HgBr_2$ (216 mg, 0.60 mmol), and powdered molecular sieves 3A (1.2 g) in dry CH_2Cl_2 (65 mL) was refluxed under stirring for 17 h in a dark place. Post-treatment as described for **43** gave a residue, which showed, in TLC (30:1 $CHCl_3$–acetone), three spots at R_f 0.03 (daunomycinone), 0.15 (**47**), and 0.2 (**46**). Chromatography (10:1 $CHCl_3$–EtOAc) of the residue gave **46**, 217 mg (43%) and **47**, 207 mg (41%) as red solids. Compound **46**, $[\alpha]_D^{23}$ −119° (*c* 0.1, $CHCl_3$). ^{19}F NMR ($CDCl_3$): δ −184.3 (ddt). Anal. Calcd for $C_{34}H_{30}FNO_{13}\cdot H_2O$: C, 58.54; H, 4.62; F, 2.72; N, 2.01. Found: C, 58.33; H, 4.43; F, 3.05; N, 1.76. Compound **47**, $[\alpha]_D^{23}$ +601° (*c* 0.1, $CHCl_3$). ^{19}F NMR ($CDCl_3$): δ −205.4 (dddd). Anal. Calcd for $C_{34}H_{30}FNO_{13}\cdot H_2O$: C, 58.54; H, 4.62; F, 2.72; N, 2.01. Found: C, 58.84; H, 4.49; F, 2.92; N, 1.87.

7-O-*(2,3,6-Trideoxy-2-fluoro*-α-L-*lyxo-hexopyranosyl)daunomycinone* (**6**).—A mixture of **46** (15 mg, 0.022 mmol) in 0.2 M NaOH in oxolane–H_2O (4:1, 1.9 mL) was stirred for 15 h at 0 °C. Conventional work-up as described for **3** gave a solid, which was chromatographed (15:1 $CHCl_3$–acetone) and purified by reprecipitation from $CHCl_3$–Et_2O–hexane gave **6** as a red solid, 10.1 mg (76%), $[\alpha]_D^{23}$ +72° (*c* 0.06, $CHCl_3$). ^{19}F NMR ($CDCl_3$): δ −180.8 (ddddd; $J_{OH\text{-}4',F}$ 11 Hz). Anal. Calcd for $C_{27}H_{27}FO_{10}\cdot 0.5\ H_2O$: C, 60.11; H, 5.23; F, 3.52. Found: C, 60.23; H, 5.18; F, 3.21.

7-O-*(4*-O-*Acetyl-2,3,6-trideoxy-2,3-difluoro*-α- (**48**) *and* -β-L-*talopyranosyl)daunomycinone* (**49**).—A mixture of **33** (296 mg, 1.1 mmol), daunomycinone (424 mg, 1.1 mmol), yellow HgO (693 mg, 3.2 mmol), $HgBr_2$ (194 mg, 0.54 mmol), and powdered molecular sieves 3A (2.31 g) in dry CH_2Cl_2 (71 mL) was refluxed under stirring for 19 h in a dark place. Additional yellow HgO (700 mg, 3.2 mmol), $HgBr_2$ (145 mg, 0.40 mmol), and powdered molecular sieves 3A (567 mg) were added and the refluxing was continued for further 21 h. Post-treatment as described for **43** gave a red solid, which showed, in TLC (6:1 toluene–acetone), three spots at R_f 0.15 (daunomycinone), 0.25 (**49**), and 0.4 (**48**). Chromatography (6:1 toluene–acetone) of the solid gave **48**, 175 mg (28%) and **49**, 99 mg (16%). An analytical sample of **48** was prepared by recrystallization from $CHCl_3$–acetone–Et_2O as red needles, and the sample of **49** by reprecipitation from $CHCl_3$–Et_2O as a red solid. Compound **48**, mp 222.5–225 °C, $[\alpha]_D^{24}$ +85° (*c* 0.02, $CHCl_3$). ^{19}F NMR ($CDCl_3$): δ −206.1 (br ddq, 1 F, $J_{1',F\text{-}3'} = J_{2',F\text{-}3'} = J_{4',F\text{-}3'} \sim 6$, $J_{3',F\text{-}3'}$ 43, $J_{F\text{-}2',F\text{-}3'}$ 14 Hz F-3′), −203.9 (dddd, 1 F, F-2′). Anal. Calcd for $C_{29}H_{28}F_2O_{11}\cdot 0.5\ H_2O$: C, 58.10; H, 4.88; F, 6.34. Found: C, 58.16; H, 4.71; F, 6.24. Compound **49**, $[\alpha]_D^{22}$ +431° (*c* 0.02, $CHCl_3$), ^{19}F NMR ($CDCl_3$): δ −221.4 (br dddd, 1 F; $J_{F\text{-}2',F\text{-}3'}$ 13 Hz, F-2′), −202.4 (br dddd, 1 F, $J_{2',F\text{-}3'}$ 7.5, $J_{3',F\text{-}3'}$ 43, $J_{4',F\text{-}3'}$ 5, $J_{F\text{-}2',F\text{-}3'}$ 13 Hz, F-3′). Anal. Calcd for $C_{29}H_{28}F_2O_{11}\cdot 0.5\ H_2O$: C, 58.10; H, 4.88; F, 6.34. Found: C, 58.28; H, 5.03; F, 6.42.

7-O-*(2,3,6-Trideoxy-2,3-difluoro*-α-L-*talopyranosyl)daunomycinone* (**7**).—To a cold solution of **48** (30 mg, 0.05 mmol) in 3:2 $CHCl_3$–MeOH (1.2 mL) was added 0.3 M NaOH in MeOH (1.5 mL) and the mixture was stirred for 3 h at −5 °C under an

atmosphere of N_2. Working up as described for **3** gave a red solid, which was chromatographed (7:1 $CHCl_3$–acetone) to give **7**, 22 mg (78%), $[\alpha]_D^{24}$ +111° (*c* 0.02, $CHCl_3$). ^{19}F NMR ($CDCl_3$): δ −205.2 (br ddq, 1 F, $J_{1',F\text{-}3'} = J_{2',F\text{-}3'} = J_{4',F\text{-}3'}$ 6, $J_{3',F\text{-}3'}$ 43.5, $J_{F\text{-}2',F\text{-}3'}$ 16 Hz, F-3′), −200.8 (br dddt, 1 F, $J_{OH\text{-}4',F\text{-}2'}$ 9.5, $J_{F\text{-}2',F\text{-}3'}$ 16 Hz, F-2′). Anal. Calcd for $C_{27}H_{26}F_2O_{10}\cdot 0.25\ H_2O$: C, 58.64; H, 4.83; F, 6.87. Found: C, 58.72; H, 4.82; F, 7.16.

7-O-*(2,3,6-Trideoxy-2-fluoro-3-iodo-4*-O-p-*nitrobenzoyl*-α- (**50**) *and* -β-L-*talopyranosyl)daunomycinone* (**51**).—A mixture of **42** (209 mg, 0.43 mmol), daunomycinone (142 mg, 0.36 mmol), yellow HgO (348 mg, 1.6 mmol), $HgBr_2$ (103 mg, 0.29 mmol), and powdered molecular sieves 3A (568 mg) in dry CH_2Cl_2 (29 mL) was refluxed for 14 h in the dark place. Additional yellow HgO (348 mg, 1.6 mmol) and $HgBr_2$ (103 mg, 0.29 mmol) were added and the refluxing was continued for further 24 h. Working up as described for **43** gave a red solid, which was chromatographed (30:1 $CHCl_3$–acetone) to give **50**, 63 mg (22%), R_f 0.35 in TLC (30:1 $CHCl_3$–acetone), and **51**, 178 mg (62%), R_f 0.25. Compound **50**, $[\alpha]_D^{22}$ +20° (*c* 0.1, $CHCl_3$). ^{19}F NMR ($CDCl_3$): δ −183.4 (ddd). Anal. Calcd for $C_{34}H_{29}FINO_{13}\cdot H_2O$: C, 49.59; H, 3.79; F, 2.31; I, 15.41; N, 1.70. Found: C, 49.75; H, 3.73; F, 2.66; I, 15.63; N, 1.78. Compound **51**, $[\alpha]_D^{22}$ +427° (*c* 0.1, $CHCl_3$). ^{19}F NMR ($CDCl_3$): δ −203.7 (ddd). Anal. Calcd for $C_{34}H_{29}FINO_{13}\cdot 1.5\ H_2O$: C, 49.05; H, 3.87; F, 2.28; I, 15.24; N, 1.68. Found: C, 48.96; H, 3.62; F, 2.54; I, 15.18; N, 1.82.

7-O-*(2,3,6-Trideoxy-2-fluoro-3-iodo*-α-L-*talopyranosyl)daunomycinone* (**8**).—A mixture of **50** (33 mg, 0.04 mmol) in 0.1 M NaOH in oxolane–H_2O (1:1, 3.3 mL) was stirred for 19 h at 0 °C. Working up as described for **3** gave a red solid, which was chromatographed (20:1 $CHCl_3$–acetone) and reprecipitated from $CHCl_3$–Et_2O–hexane to give **8**, 18 mg (68%), $[\alpha]_D^{23}$ +203° (*c* 0.1, $CHCl_3$). ^{19}F NMR ($CDCl_3$): δ −180.6 (apparently ddt; $J_{OH\text{-}4',F}$ 9 Hz). Anal. Calcd for $C_{27}H_{26}FIO_{10}\cdot H_2O$: C, 48.09; H, 4.18; F, 2.82; I, 18.82. Found: C, 48.05; H, 4.21; F. 3.18; I, 18.49.

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