SYNTHESIS OF 7-*O*-[2,6-DIDEOXY-2-FLUORO-4-*O*-(3-FLUOROTETRAHYDROPYRAN-2-YL)-α-L-TALOPYRANOSYL]DAUNOMYCINONE

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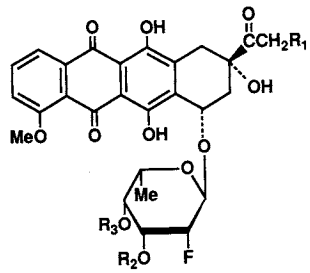
7-*O*-[2,6-Dideoxy-2-fluoro-4-*O*-(3-fluorotetrahydropyran-2-yl)-α-L-talopyranosyl]daunomycinones (**7a**~**7c**) have been prepared by condensation of 3'-*O*-benzoyl derivative of 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone with 2,3-difluorotetrahydropyran as the key reaction. Antitumor activities of these compounds are described.

Recently we reported the synthesis and antitumor activities of 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone (**1**) and -adriamycinone[1,2] (**2**) together with their analogs.[3~5] Most of them showed higher antitumor activities than doxorubicin and daunorubicin, and showed much lower toxicity. Characteristic features of these compounds in terms of chemical structure are that some of them have no amino group at C-3',[1~3,5] which has been believed to be essential for activity, and most of the compounds have a C-2' fluorine,[1~4] no functional group being attached here in the usual anthracycline antitumor antibiotics. On the other hand, structurally related aclacinomycins[6,7] and (2"*R*)-4'-*O*-tetrahydropyranyladriamycin,[8,9] have a 4'-*O*-glycosyl moiety and exhibit lower toxicity with higher antitumor activity[10,11] than doxorubicin. Further, the last compound was reported[12] to be readily taken up by tumor cells. With all of these facts in mind, we have undertaken to prepare several 4'-*O*-glycosyl derivatives of **1** and **2**. This paper describes the synthesis and antitumor activity of 4'-*O*-(3-fluorotetrahydropyran-2-yl) derivatives (**7**) of **1**. As these compounds **7** have a tetrahydropyranyl moiety bearing a fluorine at the vicinal position to the glycosyl bond, the moiety would be expected to resist acid-catalyzed hydrolysis due to the strong electron-withdrawing property of the vicinal fluorine; in the cases of aclacinomycins and 4'-*O*-tetrahydropyranyl derivatives, the 4'-*O*-glycosyl group is readily cleaved chemically. We undertook the preparation of **7** to test whether the enhanced chemical stability would also be retained in *in vivo* experiments.

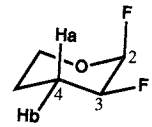
Treatment of **1** with benzoyl chloride in dichloromethane-pyridine gave selectively the 3'-*O*-benzoyl derivative (**3**) with the axial 4'-OH remained free. Next, in order to introduce 3-fluorotetrahydropyran-2-yl group at the 4'-OH, 2,3-difluorotetrahydropyran was first prepared. Introduction of fluorine gas into 3,4-dihydro-2*H*-pyran in cold (−78°C) dichloromethane readily gave the difluoro derivatives (**4** and **5**); however, these products were markedly unstable in an acidic medium (in this case, HF was formed inevitably), and decomposed on concentration, so that they could not be isolated in a pure state. Therefore, the above reaction mixture was immediately coupled with **3** in the presence of $AgClO_4$, $SnCl_2$, and molecular

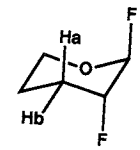
Fig. 1. Structures of **1**~**3** and 4′-*O*-(3-fluorotetrahydropyranyl) derivatives of **1**.



	R_1	R_2	R_3
1	H	H	H
2	OH	H	H
3	H	C_6H_5CO	H
6	H	C_6H_5CO	
7a	H	H	
7b	H	H	
7c	H	H	

Table 1. Coupling constants (Hz) of the ^{19}F NMR spectra for **4** and **5** in CD_2Cl_2.





	4	**5**
$J_{2,2\text{-F}}$	55	50
$J_{3,2\text{-F}}$	24	≤2
$J_{2,3\text{-F}}$	≤2	~4
$J_{3,3\text{-F}}$	47	47
$J_{4a,3\text{-F}}$	4~5	58
$J_{4b,3\text{-F}}$	4~5	~4
$J_{2\text{-F},3\text{-F}}$	19.5	15
One wing of the signal range of 3-F	50	80

sieves in dichloromethane to give a mixture of 4′-*O*-(3-fluorotetrahydropyran-2-yl) derivatives (**6**) in good yield. The structures of the 2,3-difluorotetrahydropyran, however, could be proved by the ^1H and ^{19}F NMR spectra on the sample prepared as follows: After treatment of 3,4-dihydro-2*H*-pyran with F_2 in argon in cold (−78°C) dichloromethane-d_2, the solution was washed thoroughly with cold aqueous sodium thiosulfate, and, without delay, the ^1H and ^{19}F NMR spectra were measured; the ^{19}F spectrum showed clear signals (Table 1) for *cis* (**4**) and *trans* 2,3-difluoroterahydropyran (**5**) in a 7.5:2.5 ratio. The coupling constants indicate (based on the reported coupling constants[13]) for 2-fluoroglycopyranosyl fluorides) that both **4** and **5** have a chair conformation, respectively, having 2-axial-3-equatorial (for **4**) and 2,3-diaxial fluorines (for **5**). It was surprising that these fundamental substances **4** and **5** have not been reported previously.

Debenzoylation of **6** with methanolic sodium hydroxide gave the three final products (**7a**, **7b**, and **7c**). Separation of them was, however, tedious and performed only by repeated column chromatography and HPLC to give pure products in 31.4 (**7a**), 6.4 (**7b**), and 20.1% (**7c**), respectively. The structures of the products were determined from their NMR spectra (^1H, ^{19}F, and ^{13}C (Table 2)) to be the expected 4′-*O*-(3-fluorotetrahydropyran-2-yl) derivatives of **1**, but the absolute configurations at C-2″ and C-3″ remained undetermined. However, judging from the ^1H and ^{19}F NMR data as shown in Table 3 (in some signal-regions assignments are difficult due to bad signal dissolution or overlapping), the structures could partly be clarified. First, compound **7b** is determined to be a 2″,3″-*cis* product (the large $J_{3'',4''_a}$ value, and narrow signal-range of one wing of the broad 3″-F doublet suggest the equatorial 3″-F, and the small $J_{2'',3''}$ value suggests the axial 2″-OR) with a chair conformation of $^{2''}C_{5''}$ (3″*S*) (C) or $^{5''}C_{2''}$ (3″*R*) (C′) (see Fig. 2). Compound **7a** was concluded to have a 2″,3″-*trans* structure with 3″*S* or 3″*R* as a mixture of two chair conformations (A and B, or D and E) (judged from relatively large $J_{2'',3''}$ value (6 Hz) and relatively large signal-range of one wing of the broad 3″-F doublet (Table 3)). It should be stressed here

Table 2. ^{13}C NMR data of compounds **7a**, **7b**, and **7c** (in $CDCl_3$).

C	7a	7b	7c
1	119.7	119.9	119.8
2	135.7	135.8	135.7
3	118.5	118.6	118.5
4	161.1	161.2	161.1
4a	120.8	121.0	120.8
5	186.8[a]	187.1[a]	186.9[a]
5a	111.5[b]	111.65[b]	111.5[b]
6	156.2[c]	156.3[c]	156.3[c]
6a	134.2[d]	134.3[d]	134.2[d]
7	70.9	70.8	70.8
8	35.1	35.2	35.1
9	76.5	[g]	76.5
10	33.1	33.3	33.2
10a	135.4[d]	135.6[d]	135.4[d]
11	155.5[c]	155.7[c]	155.5[c]
11a	111.4[b]	111.59[b]	111.4[b]
12	186.7[a]	186.9[a]	186.7[a]
12a	133.3[d]	133.4[d]	133.3[d]
13	211.3	211.4	211.3
14	24.6	24.6	24.6
OMe	56.6	56.7	56.7
1′	100.9 and 101.5, d	101.2 and 101.8, d	101.3 and 101.8, d
2′	85.8 and 88.6, d	86.3 and 89.1, d	86.1 and 89.0[e], d
3′	66.5 and 66.7, d	66.3 and 66.5, d	65.7 and 66.0, d
4′	78.5	82.3	82.3
5′	67.0	67.7	67.4
6′	16.9	16.5	16.4
2″	102.7 and 103.1, d	99.4 and 99.8, d	102.7 and 103.1, d
3″	87.3 and 90.1, d	86.5 and 89.4, d	86.3 and 89.2[e], d
4″	27.4 and 27.7, d	24.0 and 24.3, d	26.6 and 26.9, d
5″	23.0 and 23.1, d	23.6 and 23.8, d	22.1 and 22.2, d
6″	64.2	60.8 and 60.9, d	64.2
J (Hz)			
$J_{1'\text{-C},2'\text{-F}}$	32.4	32.3	32.3
$J_{2'\text{-C},2'\text{-F}}$	177.9	179.3	180.3[f]
$J_{3'\text{-C},2'\text{-F}}$	16.9	17.2	16.9
$J_{2''\text{-C},3''\text{-F}}$	25.0	22.4	27.3
$J_{3''\text{-C},3''\text{-F}}$	175.9	184.0	177.5[f]
$J_{4''\text{-C},3''\text{-F}}$	19.0	18.9	19.4
$J_{5''\text{-C},3''\text{-F}}$	7.0	8.4	6.2
$J_{6''\text{-C},3''\text{-F}}$		7.0	

[a,b,c,d,e,f] Figures in the same column may be interconvertible.
[g] Overlapped with the signal of $CDCl_3$.

that the observed coupling ($J=6$ Hz) between 3′-O*H* and 3″-F is considered to be a through-space coupling. This indicates that both atoms come close to each other, suggesting the contribution of the A conformation of **7a** (see later in detail). Compound **7c** will be a 2″,3″-*trans* product, judging from the similarity of the signal pattern with that for **7a** and therefore, it will be an enantiomer of **7a** in terms of its 3-fluorotetrahydropyranyl portion, and the conformation will be a mixture of D and E, or A and B. ^1H-Shifts of 2″-H for **7a**, **7b**, and **7c** also support the above conclusions, that is, 2″-H of **7b** is the most deshielded (Table 3), whereas the 2″-H's of **7a** and **7c** are comparatively shielded suggesting the involvement of the axial 2″-H.

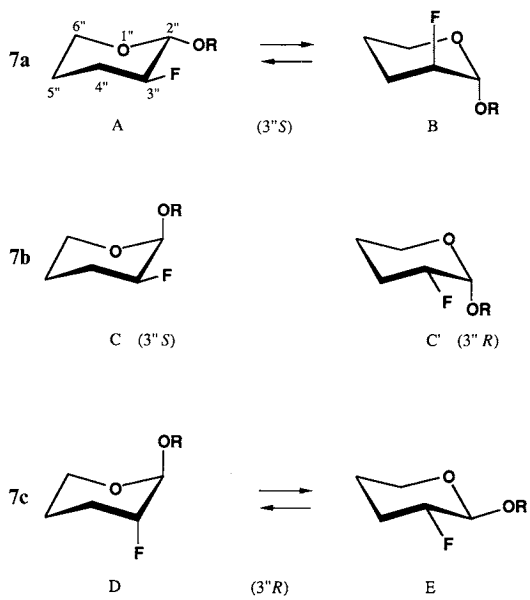
Table 3. ^{1}H and ^{19}F NMR data relating to the 3″-F and optical rotations of **7a**, **7b**, and **7c**.

	7a	**7b**	**7c**
2″-H (δ)	4.66 (dd)	4.83 (t)	4.45 (t)
3″-H (δ)	4.45	4.56	4.44
Signal range for 3″-H (Hz)	20	23	20
3″-F (δ)	−186.2 (br d)	−186.0 (br d)	−187.3 (dddd)[a]
Signal range of one wing of 3″-F (Hz)	47	33	50
$J_{2'',3''}$ (Hz)	6	3.5	5
$J_{3'',4''a}$		~11	
$J_{3'',4''b}$		~5	
$J_{2'',F}$	5	3	5
$J_{3'',F}$	~50	~50	50
$J_{4''a,F}$			~21
$J_{4''b,F}$			~12
$[\alpha]_D$ (*c* 0.1, $CHCl_3$)	+148°	+55°	+101°

[a] Slightly deformed dddd.

Although, as described above, absolute configurations of the 3-flurotetrahydropyranyl portion at C-2″ and C-3″ of **7a**, **7b**, and **7c** remained undetermined, the large difference in optical rotations among them (Table 3) suggests their configurations. In simple alkyl glycohexopyranosides with an equatorial C-5 substituent (the configuration at C-5 determines D and L), four types of chair conformations (I, II, III, and IV; see Fig. 3) exist and their optical rotations are ganerally determined by the types (α-D > β-L > β-D > α-L). This phenomenon originates from the difference in electron-density around the anomeric center. If such an experimental rule is applied to our cases (although the C-6″ substituents of **7a**~**7c** are two hydrogens, there will be little difference from the alkyl substituent in I~IV in terms of the contribution to the rotations), the following assignments will be made. As the contribution of the 3-flurotetrahydropyranyl portion of **7b** to its rotation is expected to be highly negative, structure C (resembles IV), rather than C′ is assigned. Compound **7a** has the highest rotational value, and therefore it should be a mixture of A and B (resembles II and I) rather than that of D and E (resembles IV and III) and **7c**, *vice versa*. In conclusion, we decided that the structures of **7a**, **7b**, and **7c** are as shown in Fig. 1.

Fig. 2. Conformations of **7a**, **7b**, and **7c**.



R = [7-*O*-(2,6-Dideoxy-2-fluoro-α-L-talopyranosyl)-daunomycinone]-4′-yl

Antitumor activities of **7a**, **7b**, and **7c** were measured (Tables 4 and 5) and it was concluded that the three compounds and **1** have similar activity. However, as the three compounds were non-toxic in the amount of 100 μg/mouse/day (Table 5), this derivation will give less toxic derivatives compared to the parent

anthracycline antibiotics. Other biological characteristics will be reported in the future with other related compounds.

Experimental

Optical rotations were measured with a Perkin-Elmer 241 polarimeter. TLC was carried out on precoated Kieselgel 60 F_{254} (Merck). Column chromatography was performed on Wakogel C-200. HPLC was performed with a SSC-6200 instrument (Senshu Scientific Co.) with a UV detector (SSC 3000A-II) set at 290 nm. NMR spectra (^1H at 250 MHz, ^{19}F at 235.3 MHz, and ^{13}C at 62.9 MHz) were recorded with a Bruker WM 250 spectrometer. Chemical shifts (δ) are reported downfield from internal tetramethylsilane or Freon 11 ($CFCl_3$; for ^{19}F).

7-*O*-(3-*O*-Benzoyl-2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone (**3**)

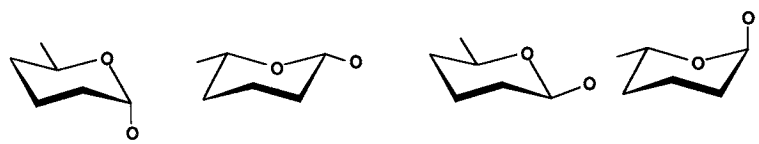
To a suspension of **1** (72.6 mg, 0.13 mmol) in pyridine-dichloromethane (1:8, 1.4 ml) was added a solution of benzoyl chloride (16.2 μl, 0.14 mmol) in dichloromethane (0.32 ml), and the mixture was stirred at room temperature for 2 hours. The resulting solution showed, on TLC with C_6H_6-Me_2CO (4:1), spots at Rf 0.4 (**3**, major) and 0.7 (trace). Methanol (10 μl) and then $CHCl_3$ (20 ml) were added and the solution was washed successively with 20% aq $KHSO_4$, saturated aq $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. The residue was separated by silica gel column chromatography with $CHCl_3$-Me_2CO (12:1) to give **3** as a reddish-orange solid, 78 mg (90%). An analytical sample was obtained by reprecipitation from $CHCl_3$-hexane: $[\alpha]_D^{25}$ +168° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.41 (3H, d, $J_{5',6'}=6.5$ Hz,

Table 4. Growth inhibitory effect of **7a**, **7b**, and **7c** in comparison with **1** and doxorubicin on P388/S and P388/ADM cells *in vitro*.[a]

Compound	IC_{50} (ng/ml)		RF[b]
	P388/S	P388/ADM	
7a	13	210	16
7b	33	210	6.4
7c	22	160	7.3
1	33	150	4.5
Doxorubicin	19	920	48

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

Fig. 3. Relationship between optical rotations and glycohexopyranoside structures with an equatorial C-5 substituent.



	I	II	III	IV
	α-D	β-L	β-D	α-L
Optical rotation	+ +	+ or ~0	− or ~0	− −

Table 5. Antitumor activities (T/C, %) of **7a**, **7b**, and **7c** on L1210.

Compound	Dose (μg/mouse/day)					
	100	50	25	12.5	6.25	3.13
7a	176	113	110	101	104	101
7b	236	143	107	104	99	101
7c	236	131	113	104	104	104
Daunorubicin[4)]	117*	151*	193	166	133	130

Leukemia L1210 cells (10^5) were inoculated into CDF_1 mice (20±1 g) intraperitoneally. Drugs were administered daily, starting 24 hours after inoculation, from day-1 to -9, intraperitoneally.
* Toxic.

5'-Me), 2.21 (1H, dd, $J_{7,8ax}=4.5$, $J_{8ax,8eq}=15$ Hz, 8-H_{ax}), 2.33 (1H, t, $J_{OH,4'}=10.5$, $J_{OH,F}=\sim 10$ Hz, 4'-OH), 2.40 (1H, br d, 8-H_{eq}), 2.42 (3H, s, 13-Me), 2.84 (1H, d, $J_{10ax,10eq}=19$ Hz, 10-H_{ax}), 3.17 (1H, dd, $J_{8eq,10eq}=\sim 1.5$ Hz, 10-H_{eq}), 3.90 (1H, s, 9-OH), 3.94 (1H, br d, 4'-H), 4.04 (3H, s, OMe), 4.31 (1H, br q, 5'-H), 4.84 (1H, br d, $J_{2',F}=50$ Hz, 2'-H), 5.10 (1H, dt, $J_{2',3'}=J_{3',4'}=\sim 3$, $J_{3',F}=33.5$ Hz, 3'-H), 5.29 (1H, br d, 7-H), 5.67 (1H, dd, $J_{1',2'}=\sim 1.5$, $J_{1',F}=10$ Hz, 1'-H), 7.35 (1H, br d, $J_{2,3}=\sim 8.5$ Hz, 3-H), 7.41 (2H, m, Bz), 7.54 (1H, m, Bz), 7.74 (1H, t, 2-H), 7.95 (1H, br d, $J_{1,2}=\sim 7.5$ Hz, 1-H), 8.04 (2H, m, Bz), 13.12 and 13.96 (each 1H, s, 6, 11-OH); ^{19}F NMR ($CDCl_3$) δ −198.3 (ddt, $J=50$, 33.5, 10, and 10 Hz).

Anal Calcd for $C_{34}H_{31}FO_{12}\cdot H_2O$: C 61.08, H 4.97, F 2.84.
Found: C 61.18, H 4.74, F 2.70.

Preparation of DL-2,3-*cis*-2,3-Difluorotetrahydropyran (**4**) and DL-2,3-*trans*-2,3-Difluorotetrahydropyran (**5**) in CD_2Cl_2

To a cold (−78°C) solution of 3,4-dihydro-2*H*-pyran (50 mg) in CD_2Cl_2 (2 ml, dried over molecular sieves 4A) was introduced fluorine (600 ml of 5% F_2 in argon) by gentle bubbling for 30 minutes. Nitrogen was then bubbled for a while at the temperature to remove a part of excess fluorine remained. The resulting solution, which is strongly acidic when examined by pH-test paper, was thoroughly washed with ice-cold aqueous $Na_2S_2O_3$ (5 ml × 6; washing should be done until the clear aqueous layer was resulted, the turbidity being caused by the sulfur liberated by the reaction between F_2 and this reagent; insufficient washing caused decomposition of the products during storage), aqueous saturated $NaHCO_3$, aqueous saturated NaCl, and finally with D_2O, and dried over $MgSO_4$. The solution was directly measured by NMR spectroscopy.

^{1}H NMR δ 1.4~2.3 (4H, m, 4-H_a, H_b, 5-H_a, H_b), 3.5~4.0 (2H, m, 6-H_a, H_b), 4.3~4.7 (1H, m, 3-H), 5.50 (~0.3H, br d, $J_{2,2\text{-}F}=50$ Hz, 2-H of **5**), 5.61 (~0.7H, br d, $J_{2,2\text{-}F}=55$ Hz, 2-H of **4**); ^{19}F NMR δ −194.5 (~0.26 F, slightly unresolved ddddd, 3-F of **5**), −189.7 (~0.74 F, unresolved dddd, 3-F of **4**), −155.9 (~0.73 F, clear-cut ddd, 2-F of **4**), and −142.5 (~0.27 F, dd, 2-F of **5**).

7-*O*-[3-*O*-Benzoyl-2,6-dideoxy-2-fluoro-4-*O*-(3-fluorotetrahydropyran-2-yl)-α-L-talopyranosyl]daunomycinone (**6**)

A stream of 5% F_2 in argon (1.6 liters) was introduced into a solution of 3,4-dihydro-2*H*-pyran (0.2 g) in dry dichloromethane (4 ml) by gentle bubbling at −78°C for 1 hour. A portion of the resulting solution (2.2 ml) was added immediately to an ice-cold suspension of **3** (166 mg), $AgClO_4$ (116 mg), $SnCl_2$ (97 mg), and powdered molecular sieves 4A (830 mg) in dry dichloromethane (3.3 ml), and the mixture was stirred vigorously at 0°C for 4 hours. The supernatant layer showed, on TLC with $CHCl_3$-Me_2CO (30:1), spots at Rf 0.3 (slight), 0.23 (major, **6**), 0.17 (slight), and 0.1 (minor, **3**). The reaction mixture was filtered with aid of Celite and the mass was washed thoroughly with $CHCl_3$. The combined filtrates were washed successively with saturated aq $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated. The residue was chromatographed on a column of silica gel with $CHCl_3$-Me_2CO (30:1) to give a red solid of **6** as a mixture of three diastereomers (1:2.6:3.1, judged by ^{19}F NMR), 152 mg (79%). An analytical sample was prepared by reprecipitation from $CHCl_3$-hexane. ^{1}H NMR ($CDCl_3$) δ 1.36, 1.42, and 1.47 (3H in total, each d, $J_{5',6'}=6.5$ Hz, 5'-Me), 2.43 (3H, s, 13-Me), 4.07 and 4.08 (3H in toral, each s, OMe), 13.26 and 13.27 (1H in total, each s, 11- or 6-OH), 14.01, 14.03, and 14.04 (1H in total, each s, 6- or 11-OH); ^{19}F NMR ($CDCl_3$) δ −201.8 (0.45 F, ddd, $J_{1'\text{-}H,2'\text{-}F}=10$, $J_{2'\text{-}H,2'\text{-}F}=49.5$, $J_{3'\text{-}H,2'\text{-}F}=32$ Hz, 2'-F), −200.83 (0.15 F, ddd, $J=49.5$, 33, and 10 Hz, 2'-F), −200.82 (0.4 F, ddd, $J=49.5$, 33, and 10 Hz, 2'-F), −189.9 (0.45 F, m, 3''-F), −188.9 (0.4 F, br dddd, $J=\sim 49$, ~37, ~12, and ~6.5 Hz, 3''-F), −183.2 (0.15 F, br d, $J=\sim 49$ Hz, 3''-F).

Anal Calcd for $C_{39}H_{38}F_2O_{13}$: C 62.23, H 5.09, F 5.05.
Found: C 62.08, H 5.10, F 4.98.

7-*O*-[2,6-Dideoxy-2-fluoro-4-*O*-(3-fluorotetrahydropyran-2-yl)-α-L-talopyranosyl]daunomycinone (**7a**, **7b**, and **7c**)

To an ice-cold solution of **6** (196 mg) in oxolane-MeOH (1:1, 20 ml) was added 0.4 M methanolic NaOH (10 ml) and the mixture was stirred at 0°C for 1 hour. The resulting deep-purple solution showed, on TLC with $CHCl_3$-Me_2CO (15:1), spots at Rf 0.13 (**7a**) and 0.19 (**7b** and **7c**). After gradual neutralization

with cold aq 0.2 M HCl, the mixture was extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed on a column of silica gel with $CHCl_3$-Me_2CO (15:1) to give a red solid of **7a**, 36.7 mg, a mixture of **7b** and **7c**, 51.4 mg, and a mixture of **7a**, **7b**, and **7c**, 80 mg. Repeated chromatography of the last mixture with the same solvent system as above afforded an additional crop of **7a**, 16.4 mg, a mixture of **7b** and **7c**, 13 mg, and a mixture of the three, 26.7 mg. Total yield of **7a** was 53.1 mg (31.4%). The combined mixtures of **7b** and **7c** (64.4 mg) were separated by HPLC on a column (30 mm × 25 cm) of Senshu Pak. SSC-Silica-842, with toluene-MeOH (20:1), at a flow rate of 10 ml/minute, and a pressure of 150 kg/cm^2, to give a red solid of **7b** (Rt 18.6 minutes), 10.8 mg (6.4%), and **7c** (Rt 20.2 minutes), 34 mg (20.1%). Analytical samples were prepared by reprecipitation from $CHCl_3$-hexane.

7a: ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, d, $J_{5',6'}=6.5$ Hz, 5'-Me), 1.58~1.83 (3H, m, 4''-H_a, 5''-H_a, H_b), 2.17 (1H, dd, $J_{7,8ax}=4.5$, $J_{8ax,8eq}=15$ Hz, 8-H_{ax}), ~2.2 (1H, m, 4''-H_b), 2.38 (1H, br d, 8-H_{eq}), 2.40 (3H, s, 13-Me), 2.95 (1H, d, $J_{10ax,10eq}=19$ Hz, 10-H_{ax}), 3.01 (1H, dd, $J_{3',3'\text{-OH}}=11.5$, $J_{3'\text{-OH},3''\text{-F}}=6$ Hz, 3'-OH), 3.21 (1H, dd, $J_{8eq,10eq}=\sim 2$ Hz, 10-H_{eq}), 3.44 (1H, ddd, $J=12$, 9, and 2.5 Hz, 6''-H_a), 3.74 (1H, m, 3'-H; collapsed to dt on deuteration, $J_{2',3'}=J_{3',4'}=\sim 3$ Hz), 3.79 (1H, m, 4'-H), 3.94 (1H, m, 6''-H_b), 4.07 (1H, s, 9-OH), 4.09 (3H, s, OMe), 4.17 (1H, br q, 5'-H), 4.50 (1H, br d, $J_{2',2'\text{-F}}=\sim 50$ Hz, 2'-H), 5.31 (1H, dd, $J_{7,8eq}=\sim 1.5$ Hz, 7-H), 5.64 (1H, dd, $J_{1',2'\text{-F}}=10$, $J_{1',2'}=1.5$ Hz, 1'-H), 7.40 (1H, dd, $J_{2,3}=8.5$, $J_{1,3}=\sim 1$ Hz, 3-H), 7.78 (1H, t, 2-H), 8.03 (1H, dd, $J_{1,2}=7.5$ Hz, 1-H), 13.25 and 14.00 (each 1H, s, 6, 11-OH); ^{19}F NMR ($CDCl_3$) δ −204.8 (1F, ddd, $J=49$, 31 ($=J_{3',2'\text{-F}}$), and 10 Hz, 2'-F).

Anal Calcd for $C_{32}H_{34}F_2O_{12}$: C 59.26, H 5.28, F 5.86.
Found: C 59.34, H 5.41, F 5.70.

7b: ^{1}H NMR ($CDCl_3$) δ 1.41 (1H, d, $J_{5',6'}=6.5$ Hz, 5'-Me), 1.63~1.84 (2H, m, 5''-H_a, H_b), ~1.94 (1H, m, 4''-H_a), ~2.1 (1H, m, 4''-H_b), 2.17 (1H, dd, $J_{7,8ax}=4.5$, $J_{8ax,8eq}=15$ Hz, 8-H_{ax}), 2.37 (1H, dt, $J_{7,8eq}=J_{8eq,10eq}=\sim 2$ Hz, 8-H_{eq}), 2.40 (3H, s, 13-Me), 2.97 (1H, d, $J_{10ax,10eq}=19$ Hz, 10-H_{ax}), 3.24 (1H, dd, 10-H_{eq}), 3.52~3.81 (3H, m, 3', 4'-H, 6''-H_a; 3'-H at δ 3.63 collapsed to dt on deuteration, $J_{3',2'\text{-F}}=33.5$, $J_{2',3'}=J_{3',4'}=\sim 3$ Hz), 4.04 (1H, dd, $J=11.5$ and 4 Hz, 6''-H_b), 4.08 (1H, s, 9-OH), 4.09 (3H, s, OMe), 4.22 (1H, br q, 5'-H), 4.46 (1H, d, $J_{3',3'\text{-OH}}=11$ Hz, 3'-OH), 4.51 (1H, br d, $J_{2',2'\text{-F}}=\sim 50$ Hz, 2'-H), 5.33 (1H, dd, 7-H), 5.67 (1H, br d, $J_{1',2'\text{-F}}=10$ Hz, 1'-H), 7.41 (1H, dd, $J_{2,3}=8.5$, $J_{1,3}=\sim 1$ Hz, 3-H), 7.79 (1H, t, 2-H), 8.04 (1H, dd, $J_{1,2}=7.5$ Hz, 1-H), 13.27 and 14.02 (each 1H, s, 6, 11-OH); ^{19}F NMR ($CDCl_3$) δ −203.0 (1F, ddd, $J=49$, 33.5, and 10 Hz, 2'-F).

Anal Calcd for $C_{32}H_{34}F_2O_{12}\cdot\frac{1}{2}H_2O$: C 58.44, H 5.36, F 5.78.
Found: C 58.70, H 5.39, F 5.64.

7c: ^{1}H NMR ($CDCl_3$) δ 1.38 (1H, d, $J_{5',6'}=6.5$ Hz, 5'-Me), 1.53~1.91 (3H, m, 4''-H_a, 5''-H_a, H_b), ~2.15 (1H, m, 4''-H_b), 2.17 (1H, dd, $J_{7,8ax}=4.5$, $J_{8ax,8eq}=15$ Hz, 8-H_{ax}), 2.36 (1H, dt, $J_{7,8eq}=J_{8eq,10eq}=\sim 2$ Hz, 8-H_{eq}), 2.40 (3H, s, 13-Me), 2.95 (1H, d, $J_{10ax,10eq}=19$ Hz, 10-H_{ax}), 3.23 (1H, dd, 10-H_{eq}), 3.57 (1H, ddd, $J=\sim 11$, ~8, and ~3 Hz, 6''-H_a), 3.63 (1H, ddt, $J_{2',3'}=J_{3',4'}=\sim 3$, $J_{3'OH}=11$, $J_{3',2'\text{-F}}=33$ Hz, 3'-H; collapsed to dt on deuteration), 3.68 (1H, m, 4'-H), ~4.05 (1H, m, 6''-H_b), 4.07 (1H, s, 9-OH), 4.09 (3H, s, OMe), 4.21 (1H, br q, 5'-H), 4.46 (1H, d, 3'-OH), 4.49 (1H, br d, $J_{2',2'\text{-F}}=\sim 50$ Hz, 2'-H), 5.33 (1H, dd, 7-H), 5.65 (1H, dd, $J_{1',2'}=\sim 1.5$, $J_{1',2'\text{-F}}=10$ Hz, 1'-H), 7.40 (1H, dd, $J_{1,3}=\sim 1$, $J_{2,3}=8.5$ Hz, 3-H), 7.78 (1H, t, 2-H), 8.03 (1H, dd, $J_{1,2}=7.5$ Hz, 1-H), 13.26 and 14.00 (each 1H, s, 6, 11-OH); ^{19}F NMR ($CDCl_3$) δ −203.3 (1F, ddd, $J=49$, 33.5, and 10 Hz, 2'-F).

Anal Calcd for $C_{32}H_{34}F_2O_{12}$: C 59.26, H 5.28, F 5.86.
Found: C 59.06, H 5.30, F 5.87.

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