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Synthesis and antitumor activity of 5′-demethyl-5′-trifluoromethyl-daunorubicin and -doxorubicin

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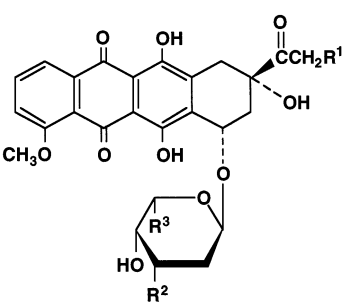
Abstract

The title compounds were prepared by coupling phenyl 4-*O*-acetyl-2,3,6-trideoxy-6,6,6-trifluoro-1-thio-3-trifluoroacetamido-α-L- and β-L-*lyxo*-hexopyranoside with daunomycinone. The key step of this synthesis is the *C*-trifluoromethylation of a 1-protected 2,3-dideoxy-3-azido-D-*erythro*-pentodialdose, prepared from 2-deoxy-D-*erythro*-pentose, to give a 6,6,6-trifluoro-L-*lyxo*-hexose derivative. The synthetic products showed higher cytotoxicity than doxorubicin against most of the human tumor cell lines tested in vitro, possibly by the effect of the CF_3 group at C-5′.

Keywords: Anthracycline glycoside; Antitumor activity; Trifluoromethyl; 5′-demethyl-5′-trifluoromethyldoxorubicin

1. Introduction

In the course of our study to develop novel anthracycline glycosides [1] having higher antitumor activity with lower toxicity than the clinically used anthracycline antibiotics, such as daunorubicin and doxorubicin (DOX), we have recently reported 7-*O*-(2,6-dideoxy-6,6,6-trifluoro - α - L - *lyxo* - hexopyranosyl)adriamycinone (**1**), which showed stronger antitumor activity than DOX against murine leukemia L1210 in vivo in a low dose range [2].



	R^1	R^2	R^3
DOX	OH	NH_2	CH_3
1	OH	OH	CF_3
2	H	NH_2	CF_3
3	OH	NH_2	CF_3

A characteristic chemical feature of **1** is that it has the strongly electron-withdrawing CF_3 group at C-5′ instead of the CH_3 group present in normal anthracycline antibiotics; this replacement stabilizes the glycosidic bond against acidic hydrolysis by decreasing the

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electron density at the glycosidic oxygen, and thus restricting protonation. The high activity of **1** may be attributed to this stabilization and is also because of the high lipophilicity of the CF_3 group, which may enhance cellular uptake of the compound. In pursuing our research, we are interested in introducing a 3′-NH_2 group instead of the 3′-OH group in **1** because the protonated 3′-NH_2 group could form a hydrogen bond with O-2 of thymidine or with the O-4′ atom (ring O) of deoxycytidine in DNA, respectively, at the d(CGATCG) site of the substrate–DNA complex [3], or could form a multiple water bridge with a backbone phosphate oxygen of DNA, stabilizing the complex, as reported on the DOX–DNA complex [3]. Furthermore, the presence of the 3′-NH_2 group is expected to promote the formation of ion-pair bonding with DNA, which is acidic in nature, owing to the initial adhesion mechanism [4] (which occurs before the final complexing), facilitating the approach of **2** (or **3**) to DNA. We report here the preparation and antitumor activity of 7-*O*-(3-amino-2,3,6-trideoxy-6,6,6-trifluoro-α-L-*lyxo*-hexopyranosyl)-daunomycinone (**2**) and -adriamycinone (**3**), that is, 5′-demethyl-5′-trifluoromethyl-daunorubicin and -doxorubicin, respectively.

2. Results and discussion

Synthesis.—We designed the synthesis of compounds **2** and **3** by the coupling of a suitably protected 5-demethyl-5-trifluoromethyldaunosamine with daunomycinone. Synthesis of such 5-CF_3 sugars has been rarely reported, and although 3-(*N*-benzyltrifluoroacetamido)-2,3,6-trideoxy-6,6,6-trifluoro-4-*O*-methoxymethyl-1-*O*-*p*-nitrobenzoyl-L-*lyxo*-hexopyranose was prepared [5] from D-glyceraldehyde in 14 steps, the coupling of this synthetic sugar with daunomycinone has not been described.

We chose methyl 3-azido-5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-α-D-*erythro*-pentofuranoside (**4**) [6,7] as the starting material, prepared from 2-deoxy-D-*erythro*-pentose. Treatment of **4** with 1,3-propanedithiol in the presence of $BF_3{\cdot}OEt_2$ in $Cl(CH_2)_2Cl$ gave the dithioacetal **5**. Benzylation of **5** (to give **6**) with subsequent desilylation gave an acyclic, 5-hydroxyl sugar **7**. Swern oxidation of **7** gave an unstable aldehyde **8**, which was trifluoromethylated by treatment with Me_3SiCF_3 in the presence of a catalytic amount of Bu_4NF (oxolane, −40 °C) according to the procedure of Prakash et al. [8]. Desilylation of the resulting products gave a mixture of the desired 3-azido-4-*O*-benzyl-2,3,6-trideoxy-6,6,6-trifluoro-L-*lyxo*-hexose propane-1,3-diyl dithioacetal **9** (31%) and its epimer, 3-azido-4-*O*-benzyl-2,3,6-trideoxy-6,6,6-trifluoro-D-*ribo*-hexose propane-1,3-diyl dithioacetal **10** (40%) in approximately equal amounts. The configurations of the newly introduced asymmetric center at C-5 were determined after converting the products into the corresponding pyranoses. The undesired isomer **10** could be converted into **9** by treating the triflate of **10** with $NaNO_2$ in DMF [9], although the yield was low. Deprotection of the dithioacetal group [$Hg(ClO_4)_2{\cdot}3H_2O$ and $CaCO_3$] of **9** gave the unstable cyclic sugar **11**, which was isolated as its 1-acetate **12** as an anomeric mixture. The L-*lyxo* structure with the $^1C_4$(L) conformation of **12** was supported by the large $J_{2ax,3}$ (13 Hz) and small coupling constants $J_{4,5}$ (<2 Hz) in its ^{1}H NMR spectrum as well as the presence of NOEs between H-3 and H-5 (for the α- and β-L anomers) and between H-1 and H-5 (for the β-L anomer). Similarly, **10** was converted into the 1-acetate **14** via **13**. Its structure was determined to be β-D-*ribo* with the $^4C_1$(D) conformation from the large coupling constants of $J_{1,2ax}$ (7.5 Hz) and $J_{4,5}$ (7.5 Hz) and the existence of NOEs between H-1 and H-5, and between H-2*ax* and H-4. Reduction of **12** with Raney nickel gave an amino sugar **15**, which was successively hydrogenolyzed over $Pd(OH)_2$ catalyst on carbon with cyclohexene (catalytic hydrogen-transfer hydrogenolysis of benzyl groups [10]) to give **16**. Compound **16**, after 3-trifluoroacetylation (to give **17**), was acetylated to give a mixture of 1,4-diacetates **18** (α-L) and **19** (β-L). The structures of the compounds were confirmed by their ^{1}H and ^{19}F NMR spectra (Table 1).

Coupling of the 1-bromo (or 1-iodo) derivative of **18** and **19** with daunomycinone under Koenigs–Knorr conditions [HgO (yellow),

Table 1
Selected ^{1}H and ^{19}F NMR data for compounds **5**–**12** and **14**–**21** in $CDCl_3$

Compound	Chemical shifts in ppm (J in Hz)									
	H-1	H-2a (or 2*ax*)	H-2b (or 2*eq*)	H-3	H-4	H-5	SCH_2	PhCH_2	Ac	CF_3
5	4.17 dd $J_{1,2a}$ 10.5 $J_{1,2b}$ 4.5	2.08 ddd $Je_{2a,2b}$ 14.5 $J_{2a,3}$ 3	1.83 ddd $J_{2b,3}$ 10.5	3.88 ddd $J_{3,4}$ 5.5	3.67 ddt $J_{4,5a}$ 6 $J_{4,5b}$ 4 $J_{4,OH}$ 5	3.78 (5a) dd $J_{5a,5b}$ 10.5 3.74 (5b) dd	2.77–2.98 m			
6	4.17 dd $J_{1,2a}$ 10 $J_{1,2b}$ 5	←2.20–1.80→		4.06 dt $J_{2a,3}$ 10 $J_{2b,3}$ 4 $J_{3,4}$ 4	3.54 dt $J_{4,5a}$ 5 $J_{4,5b}$ 5	3.80 (5a) dd $J_{5a,5b}$ 11 3.75 (5b) dd	2.77–2.98 m	4.55 d 4.49 d J_{gem} 12		
7	4.18 dd $J_{1,2a}$ 10 $J_{1,2b}$ 4.5	2.10 ddd $J_{2a,2b}$ 14.5 $J_{2a,3}$ 3.5	1.85 ddd $J_{2b,3}$ 10	4.03 ddd $J_{3,4}$ 5	3.53 appar. q $J_{4,5a}$ ~4.5 $J_{4,5b}$ ~4.5	3.75 (5a,5b) br	2.79–2.99 m	4.70 d 4.63 d J_{gem} 11.5		
8	4.12 dd $J_{1,2a}$ 10 $J_{1,2b}$ 5	←2.19–1.81→		4.10 dt $J_{2a,3}$ 10 $J_{2b,3}$ 3.5 $J_{3,4}$ 3.5	3.87 dd $J_{4,5}$ 2	9.68 d	2.79–2.97 m	4.74 d 4.70 d J_{gem} 12		
9	4.16 dd $J_{1,2a}$ 10.5 $J_{1,2b}$ 4.5	2.11 ddd $J_{2a,2b}$ 14.5 $J_{2a,3}$ 3	1.87 ddd $J_{2b,3}$ 10.5	3.94 ddd $J_{3,4}$ 6	3.71 dd $J_{4,5}$ 1	4.04 ddq $J_{5,OH}$ 10.5 J_{5,CF_3} 7.5	2.75–3.04 m	4.68 s		−77.9 d
10	[a]	←2.21–1.80→		[a]	3.86 dd *J* 7.5 *J* 2.5	[a]	2.79–3.00 m	4.75 d 4.63 d J_{gem} 11		−76.1 d J_{5,CF_3} 7
11[b]	5.56 br s	2.34 ddt $J_{1,2ax}$ 3.5 $J_{2ax,2eq}$ 12.5 $J_{2ax,3}$ 12.5 $J_{2ax,OH}$ 2	1.98 ddt $J_{1,2eq}$ ~1 $J_{2eq,3}$ 4.5 $J_{2eq,4}$ ~1	3.76 ddd $J_{3,4}$ 2.5	4.00 br s	4.33 dq $J_{4,5}$ ~1 J_{5,CF_3} 6.5		4.77 d 4.70 d J_{gem} 10.5		−73.6 (β-L) d (0.4 F) J_{5,CF_3} 6.5 −74.0 (α-L) d (2.6 F)
12[b]	6.40 br d $J_{1,2ax}$ 3.5	2.48 dt $J_{2ax,2eq}$ 13 $J_{2ax,3}$ 13	1.97 ddt $J_{1,2eq}$ ~1 $J_{2eq,3}$ 4.5 $J_{2eq,4}$ ~1	3.68 ddd $J_{3,4}$ 2.5	4.04 br s	4.16 br q J_{5,CF_3} 6.5		4.77 d 4.71 d J_{gem} 10.5	2.11 s	−73.5 (β-L) d (0.8 F) J_{5,CF_3} 6 −74.0 (α-L) d (2.2 F)
14	6.02 dd $J_{1,2ax}$ 7.5 $J_{1,2eq}$ 2.5	1.83 ddd $J_{2ax,2eq}$ 13.5 $J_{2ax,3}$ 3.5	2.14 ddd $J_{2eq,3}$ 5.5	4.00 dt $J_{3,4}$ 3.5	3.83 dd $J_{4,5}$ 7.5	4.33 dq J_{5,CF_3} 7		4.68 d 4.63 d J_{gem} 11.5	2.08 s	−74.4 d

Table 1 (Continued)

Compound	Chemical shifts in ppm (J in Hz)									
	H-1	H-2a (or 2*ax*)	H-2b (or 2*eq*)	H-3	H-4	H-5	SCH_2	$PhCH_2$	Ac	CF_3
15 [b]	6.31 br d $J_{1,2ax}$ ~3.5	2.02 ddd $J_{2ax,2eq}$ 13.5 $J_{2ax,3}$ 12.5	1.75 ddt $J_{1,2eq}$ ~1 $J_{2eq,3}$ 4.5 $J_{2eq,4}$ ~1	3.14 ddd $J_{3,4}$ 2.5	3.87 br s	4.19 br q J_{5,CF_3} 7		4.86 d 4.54 d J_{gem} 11	2.09 s	−73.7 (β-L) d (1 F) J_{5,CF_3} 6.5 −74.2 (α-L) d (2 F)
16 [b]	6.32 br d $J_{1,2ax}$ ~3.5	2.00 ddd $J_{2ax,2eq}$ 14 $J_{2ax,3}$ 12	1.76 ddt $J_{1,2eq}$ ~1 $J_{2eq,3}$ 4.5 $J_{2eq,4}$ ~1	3.31 ddd $J_{3,4}$ 3	3.95 br s	4.17 br q J_{5,CF_3} 6.5			2.11 s	−74.1 (β-L) d (0.6 F) J_{5,CF_3} 6.5 −74.6 (α-L) d (2.4 F)
17 [b]	6.36 br d $J_{1,2ax}$ ~3.5	2.23 ddd $J_{2ax,2eq}$ 14 $J_{2ax,3}$ 13	1.95 br dd $J_{2eq,3}$ 5	4.48 dddd $J_{3,4}$ 2.5 $J_{3,NH}$ 8.5	4.21 br d	4.28 br q J_{5,CF_3} 6.5			2.15 s	−74.1 (β-L) d (0.7 F) J_{5,CF_3} 6 −74.6 (α-L) d (2.3 F) −76.35 s (β-L, $COCF_3$) −76.36 s (α-L, $COCF_3$)
18	6.43 br d $J_{1,2ax}$ 3.5	2.18 ddd $J_{2ax,2eq}$ 13.5 $J_{2ax,3}$ 12.5	2.06 dddd $J_{1,2eq}$ 1.5 $J_{2eq,3}$ 5 $J_{2eq,4}$ ~1	4.58 dddd $J_{3,4}$ 2.5 $J_{3,NH}$ 8	5.60 br s	4.39 dq $J_{4,5}$ ~1 J_{5,CF_3} 6			2.18 s 2.16 s	−75.2 d −76.43 s ($COCF_3$)
19	5.89 dd $J_{1,2ax}$ 9.5 $J_{1,2eq}$ 2.5	2.02 dt $J_{2ax,2eq}$ 12.5 $J_{2ax,3}$ 12.5	2.18 dddd $J_{2eq,3}$ 4.5 $J_{2eq,4}$ ~1	4.34 dddd $J_{3,4}$ 3 $J_{3,NH}$ 7.5	5.51 br d	4.10 dq $J_{4,5}$ 1 J_{5,CF_3} 6			2.20 s 2.16 s	−74.6 d −76.40 s ($COCF_3$)
20	5.80 br d $J_{1,2ax}$ 5.5	2.44 dt $J_{2ax,2eq}$ 13 $J_{2ax,3}$ 13	2.26 ddt $J_{1,2eq}$ ~1 $J_{2eq,3}$ 4.5 $J_{2eq,4}$ ~1	4.52 dddd $J_{3,4}$ 2.5 $J_{3,NH}$ 7	5.60 br d	4.91 dq $J_{4,5}$ ~1 J_{5,CF_3} 6.5			2.17 s	−74.4 d −76.38 s ($COCF_3$)
21	4.90 dd $J_{1,2ax}$ 11.5 $J_{1,2eq}$ 2.5	1.98 appar. q $J_{2ax,2eq}$ 12.5 $J_{2ax,3}$ 12.5	2.26 dddd $J_{2eq,3}$ 4.5 $J_{2eq,4}$ ~1	4.28 dddd $J_{3,4}$ 3 $J_{3,NH}$ 7	5.48 br d	3.98 dq $J_{4,5}$ 1 J_{5,CF_3} 6			2.16 s	−74.9 d −76.40 s ($COCF_3$)

[a] δ 4.22–4.11.
[b] ^1H NMR data for the α-L anomer.

$HgBr_2$ or HgI_2, molecular sieves 3 Å] was first expected to be easy, since an analogous synthesis of **1** with the corresponding 3,4-di-*O*-acetyl-5-trifluoromethyl glycosyl bromide was successful [2]; however, this mode of coupling gave no product. The reason is not clear, however it may be the formation of a $(F_3CCO)N^-(HgX)^+$ salt (X: Br or I) at N-3 of the sugar halides; the HgX_2 catalyst is not expected to approach Br(or I)-1 of the glycosyl halides because of positive charge repulsion between Hg and Hg. A similar coupling using 4-*O*-acetyl-2,3,6-trideoxy-2-fluoro-3-trifluoroacetamido-L-talopyranosyl bromide with daunomycinone also gave the condensation product in only poor yield [11]. Coupling of a mixture of **18** and **19** with daunomycinone in the presence of $Me_3SiOSO_2CF_3$ [12] also failed. However, coupling of daunomycinone with phenyl thioglycosides **20** (α-L) and **21** (β-L), prepared from a mixture of **18** and **19** with Me_3SiSPh and $Me_3SiOSO_2CF_3$, in the presence of *N*-iodosuccinimide and CF_3SO_3H [13], gave the α-L-glycoside **22** ($J_{1',2'ax} < 3$ Hz) in moderate yield. Alkaline deblocking of **22** gave desired 5′-demethyl-5′-trifluoromethyldaunorubicin **2**. Compound **2** was next transformed into the doxorubicin-type compound **3** according to, basically, the procedure of Arcamone et al. [14]. Bromination of **2** with Br_2 in the presence of $HC(OMe)_3$ gave the 14-bromo-13-dimethyl acetal, the dimethyl acetal being removed subsequently by treatment with acetone to give the 14-bromo derivative. Treatment of the derivative with HCO_2Na in aqueous acetone gave the desired 5′-demethyl-5′-trifluoromethyldoxorubicin **3** (49%). The structures of **2** and **3** were confirmed by their ^1H, ^{19}F, and ^{13}C NMR spectra (Table 2).

Antitumor activity.—The DOX-type compound **3** showed antitumor activity comparable with that of DOX against murine leukemia L1210 in vivo, although it is slightly more toxic in a high dose range (Table 3). Compound **2** was less active. However, both **2** and **3** (especially **3**) showed stronger growth inhibitory activity than DOX against various human tumor cell lines in vitro (Table 4). It should be stressed that these compounds displayed 60–70 fold stronger activity against human epithelioid carcinoma (HeLa) and human leukemia (HL60), suggesting that the 5′-CF_3 group plays a notable role in eliciting the antitumor activity in comparison with the 5′-CH_3 group.

Table 2
^{13}C NMR chemical shifts (δ, ppm) and coupling constants ($J_{C,F}$, Hz in parentheses) of compounds **2** and **3** (both as hydrochlorides) in D_2O

C	**2**	**3** [a]
1	120.4 [b]	120.5 [b]
2	137.5	137.5
3	120.3 [b]	120.3 [b]
4	161.2	161.3
4a	119.6	119.6
5	186.5 [c]	186.6 [c]
5a	111.38 [d]	111.50 [d]
6	154.9 [e]	154.8 [e]
6a	134.4 [f]	134.1 [f]
7	70.8	70.5
8	36.0	36.1
9	76.6	76.1
10	32.3	32.7
10a	134.4 [f]	134.47 [f]
11	156.5 [e]	156.3 [e]
11a	111.44 [d]	111.54 [d]
12	186.8 [c]	186.8 [c]
12a	135.1 [f]	134.53 [f]
13	216.0	215.1
14	25.0	65.0
OMe	57.2	57.3
1′	100.6	100.4
2′	28.8	28.6
3′	46.8	46.8
4′	62.6	62.4
5′	69.9 q (30.5)	69.9 q (30)
6′	124.3 q (279.5)	124.3 q (280)

[a] Measured at 45 °C.
[b,c,d,e,f] Figs. in the same column may be interconvertible.

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. TLC was performed on Kieselgel 60 F_{254} (E. Merck), column chromatography on Kieselgel 60, and flash column chromatography on Wakogel C-300. Solvent A for TLC is a solution of 20:3.8:0.45 $CHCl_3$–MeOH–aq 17% NH_4OH.

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

Compound [c]	Dose (mg kg^{-1} day^{-1})					
	5	2.5	1.25	0.6	0.3	0.15
2	92 [d]	129 [d]	169 [d]	227	146	132
	0/4	0/4	0/4	0/4	0/4	0/4
3	132 [d]	176 [d]	>481 [d]	>559	>302	329
	0/4	0/4	1/4	2/4	1/4	0/4
DOX	190 [d]	>603	>529	>451	>519	>312
	0/4	2/4	2/4	1/4	2/4	1/4

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

*3-Azido-5-*O*-tert-butyldiphenylsilyl-2,3-dideoxy-*D*-erythro-pentose propane-1,3-diyl dithioacetal* (**5**).—A solution of **4** (18.96 g, 46 mmol), 1,3-propanedithiol (6.8 mL, 68 mmol), and $BF_3 \cdot OEt_2$ (1.7 mL, 14 mmol) in dry $Cl(CH_2)_2Cl$ (150 mL) was kept for 70 min at 50 °C. After dilution with $CHCl_3$, the solution was washed with aq 5% NaOH and water, dried ($MgSO_4$), and concentrated. The residue was chromatographed (toluene → 25:1 toluene–EtOAc) to give **5** as a colorless syrup, 19.62 g (87%), TLC (toluene): R_f 0.2 (cf **4**: R_f 0.35), $[\alpha]_D^{20}$ −22° (*c* 1, $CHCl_3$); IR (liquid film): *v* 2100 cm^{-1} (N_3). Anal. Calcd for $C_{24}H_{33}N_3O_2S_2Si$: C, 59.10; H, 6.82; N, 8.62. Found: C, 59.44; H, 6.93; N, 8.20 (Scheme 1).

*3-Azido-4-*O*-benzyl-5-*O*-tert-butyldiphenylsilyl-2,3-dideoxy-*D*-erythro-pentose propane-1,3-diyl dithioacetal* (**6**).—To a cold (−40 °C) suspension of NaH (1.72 g, 60% NaH in mineral oil, 43 mmol) in dry DMF (70 mL) was added a solution of **5** (19.52 g, 40 mmol) and $PhCH_2Br$ (5.0 mL, 42 mmol) in DMF (80 mL) over 5 min, and the mixture was stirred for 4 h at 0 °C. After addition of AcOH (2.5 mL) followed by water (1 L), the mixture was extracted with $CHCl_3$. The extracts were washed with aq $NaHCO_3$ (saturated) and water, dried (Na_2SO_4), and concentrated. The residue was chromatographed (1:2 hexane–toluene) to give **6** as a colorless syrup, 17.69 g (77%), $[\alpha]_D^{21}$ −15° (*c* 1, $CHCl_3$); IR (liquid film): *v* 2100 cm^{-1} (N_3). Anal Calcd for $C_{31}H_{39}N_3O_2S_2Si$: C, 64.43; H, 6.80; N, 7.27. Found: C, 64.68; H, 6.92; N, 7.34.

*3-Azido-4-*O*-benzyl-2,3-dideoxy-*D*-erythro-pentose propane-1,3-diyl dithioacetal* (**7**).—To a solution of **6** (17.69 g, 30.6 mmol) in oxolane (120 mL) was added $Bu_4NF \cdot 3H_2O$ (10.10 g, 32 mmol) and the solution was kept for 1.5 h at room temperature (rt). After concentration of the solution, the residue was chromatographed (toluene → 12:1 toluene–EtOAc) to give **7** as a colorless syrup, 8.86 g (85%), $[\alpha]_D^{19}$ +23° (*c* 1.5, $CHCl_3$); IR (liquid film): *v* 2110 cm^{-1} (N_3). Anal. Calcd for $C_{15}H_{21}N_3O_2S_2$: C, 53.07; H, 6.23; N, 12.38; S, 18.89. Found: C, 53.19; H, 6.31; N, 12.12; S, 18.64.

*3-Azido-4-*O*-benzyl-2,3,6-trideoxy-6,6,6-trifluoro-*L*-lyxo-hexose propane-1,3-diyl dithioacetal* (**9**) *and 3-azido-4-*O*-benzyl-2,3,6-trideoxy-6,6,6-trifluoro-*D*-ribo-hexose propane-1,3-diyl dithioacetal* (**10**).—To a cold (−78 °C) solution of $(COCl)_2$ (1.55 mL, 18 mmol) in dry CH_2Cl_2 (24 mL) was added $(CH_3)_2SO$ (1.9 mL, 27 mmol) and **7** (3.02 g, 8.9 mmol) in CH_2Cl_2 (42 mL), and the mixture was stirred for 40 min at the same temperature under the atmosphere of Ar. Ethyldiisopropylamine (7.8 mL, 45 mmol) was added, and the mixture was stirred for 30 min, then for 1.5 h at 0 °C. Ice-cooled aq NH_4Cl (saturated) was added, and the mixture was extracted with CH_2Cl_2. The extracts were washed with cold water, dried ($MgSO_4$), and concentrated to give crude aldehyde **8** as a yellowish brown syrup, 3.08 g, which was positive to the Tollens reaction; TLC: R_f 0.2 (100:1 toluene–EtOAc). To a cold (−40 °C) mixture of the syrup

(3.08 g) and Me_3SiCF_3 (2.4 mL, 16 mmol) in oxolane (30 mL) was added a 0.6 M solution of $Bu_4NF{\cdot}3H_2O$ in oxolane (1.5 mL) and the solution was kept for 10 min at the same temperature. TLC (100:1 toluene–EtOAc) showed two major spots at R_f 0.7 and 0.8 (trimethylsilyl ethers of **9** and **10**). After addition of a 0.6 M solution of $Bu_4NF{\cdot}3H_2O$ in oxolane (15 mL) the mixture was kept for 10 min at 0 °C. Concentration gave a residue, to which water (100 mL) was added, and the mixture was extracted with $CHCl_3$. The extracts were dried ($MgSO_4$), and concentrated. Flash chromatography (100:1 toluene–EtOAc) of the residue gave **9** as a colorless syrup (chromatographically homogeneous), 0.26 g (7%), along with crude **9** (1.05 g), and **10** as a colorless syrup, 1.45 g (40%), the last being crystallized from EtOAc–hexane to afford plates. Flash chromatography (2:1 hexane–$^i Pr_2O$) of crude **9** afforded 0.88 g (24%) of pure material. The total yield of **9** was 1.14 g (31%). Compound **9**, TLC: R_f 0.2 (100:1 toluene–EtOAc), $[\alpha]_D^{19}$ +9° (*c* 1, $CHCl_3$); IR (liquid film): *v* 2125 cm^{-1} (N_3). Anal. Calcd for $C_{16}H_{20}F_3N_3O_2S_2$: C, 47.16; H, 4.95; N, 10.31. Found: C, 47.42; H, 5.02; N, 10.39. Compound **10**, TLC: R_f 0.15 (100:1 toluene–EtOAc), mp 90–91 °C, $[\alpha]_D^{22}$ −3° (*c* 1, $CHCl_3$); IR (KBr): *v* 2120 cm^{-1} (N_3). Anal. Calcd for $C_{16}H_{20}F_3N_3O_2S_2$: C, 47.16; H, 4.95; N, 10.31. Found. C, 47.17; H, 5.00; N, 10.38.

Preparation of **9** *from* **10**.—A mixture of **10** (416 mg, 1.02 mmol), $(CF_3SO_2)_2O$ (0.22 mL, 1.3 mmol), and pyridine (0.41 mL, 5.1 mmol) in dry CH_2Cl_2 (6 mL) was kept for 1 h at 0 °C. MeOH 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 5-triflate as a chromatographically homogeneous syrup, 593 mg; ^{19}F NMR ($CDCl_3$): δ −72.0 (br dq, $J_{5,F\text{-}6}$ ~6, $J_{F\text{-}6,SO_2CF(F',F'')}$ 3 Hz, CF_3-5), −74.1 (q, CF_3SO_2). A mixture of the syrup, $NaNO_2$ (315 mg, 4.6 mmol), and 15-crown-5 (0.40 mL, 2.0 mmol) in DMF (5.6 mL) was stirred for 4 h at rt. After dilution with water, the mixture was extracted with $CHCl_3$. The extracts were washed with water, dried (Na_2SO_4), and concentrated. Chromatography (100:1 toluene–EtOAc) of the residue gave **9**, 158 mg (38%), which was identical with the specimen obtained from **8**.

*1-O-Acetyl-3-azido-4-O-benzyl-2,3,6-trideoxy-6,6,6-trifluoro-*L*-lyxo-hexopyranose* (**12**).—To a mixture of **9** (1.83 g, 4.5 mmol) and $CaCO_3$ (2.74 g, 27 mmol) in aq oxolane (1:3.8, 26 mL) was added $Hg(ClO_4)_2{\cdot}3H_2O$ (10.86 g, 22.5 mmol) in oxolane (16 mL) and the mixture was stirred for 1 h at rt. After addition of aq $NaHCO_3$ (saturated, 30 mL) followed by CH_2Cl_2, the mixture was filtered through a Celite bed, which was repeatedly washed with CH_2Cl_2. The filtrate and washings combined were washed with aq $NaHCO_3$ (saturated), aq 10% KI, and water, dried ($MgSO_4$), and concentrated to give **11** as a pale yellowish–green syrup, 1.51 g, which was positive to the Tollens reagent; TLC: R_f 0.05 (toluene). A solution of the syrup and Ac_2O (0.70 mL, 7.4 mmol) in pyridine (9.5 mL) was kept for 15 h at rt. Water was added, the solution was concentrated with the aid of toluene, and the residue was subjected to flash chromatography (toluene) to give an anomeric

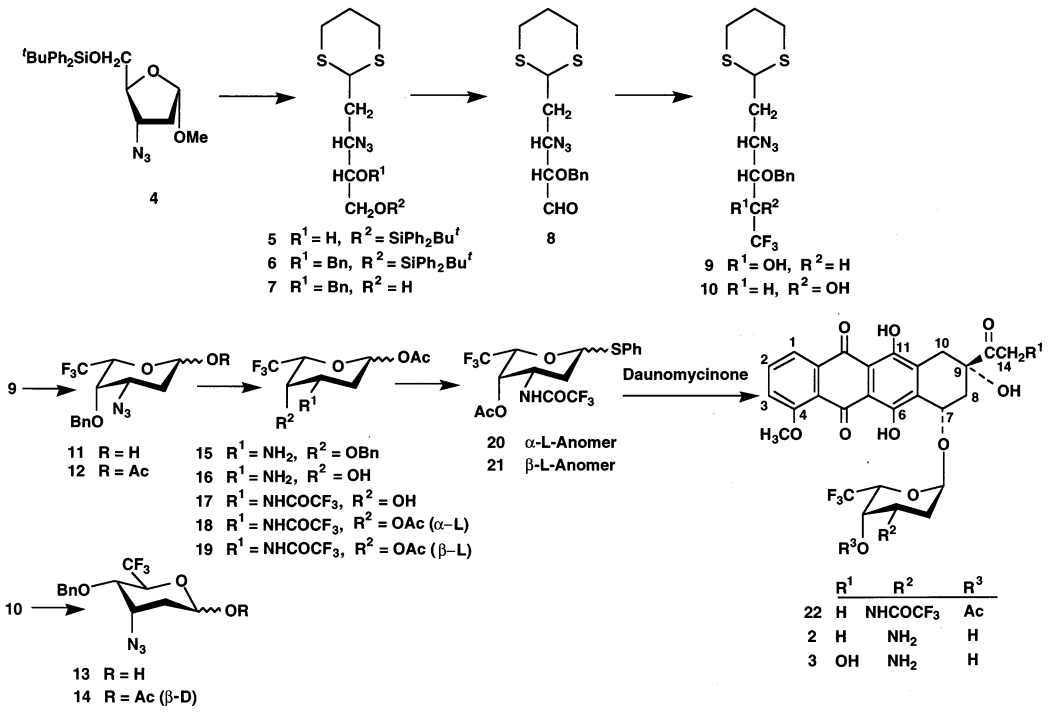
Table 4
Growth-inhibitory effect of **2** and **3** in comparison with DOX against various human cell lines [a] in vitro

Compound [b]	IC_{50} [c] (μg mL^{-1})							
	HeLa	HL60	PC3	A431	PC6	MCF7	TT	DLD-1
2	0.47	0.025	0.79	0.49	0.48	0.32	0.56	0.83
3	0.18	0.032	1.52	0.086	0.11	0.11	0.23	0.26
DOX	12.2	1.54	10.3	0.73	0.78	0.47	0.46	0.77

[a] HeLa, human epithelioid carcinoma; HL60, human leukemia; PC3, human prostatic adenocarcinoma; A431, human epidermoid carcinoma; PC6, human lung carcinoma; MCF7, human breast adenocarcinoma; TT, human esophageal carcinoma; DLD-1, human colon carcinoma.

[b] Hydrochloride.

[c] IC_{50} values (50% inhibition concentration) were determined by MTT assay [15] on day-3 culture.



Scheme 1.

mixture of **12** as a colorless syrup, 1.09 g (68%). From other fractions, crude **12** (pale-yellow syrup, 310 mg) and the 5-acetate of **9** [colorless syrup, 71 mg (3.5%)] were obtained. Flash chromatography (toluene) of crude **12** afforded 160 mg (10%) of pure material and the 5-acetate of **9**, 80 mg (4.4%). Total yield of **12** was 1.25 g (78%). Compound **12**, TLC: R_f 0.2 (toluene); IR (liquid film): ν 2110 (N_3), 1770 cm^{-1} (C=O). Anal. Calcd for $C_{15}H_{16}F_3N_3O_4$: C, 50.14; H, 4.49; F, 15.86; N, 11.70. Found: C, 50.29; H, 4.31; F, 16.21; N, 11.73.

*1-O-Acetyl-3-azido-4-O-benzyl-2,3,6-trideoxy-6,6,6-trifluoro-β-*D-ribo-*hexopyranose* (**14**).—To a mixture of **10** (100 mg, 0.25 mmol) and $CaCO_3$ (149 mg, 1.5 mmol) in aq oxolane (1:4, 1.5 mL) was added $Hg(ClO_4)_2 \cdot 3H_2O$ (607 mg, 1.3 mmol) in oxolane (0.8 mL) and the mixture was stirred for 30 min at rt. Successive processing as described for **11** gave **13** as a pale yellowish–green syrup, 80 mg, which was unstable and positive to the Tollens reaction; TLC: R_f 0.1 (30:1 toluene–EtOAc). A solution of the syrup and Ac_2O (0.05 mL, 0.5 mmol) in pyridine (0.5 mL) was kept for 2 h at rt. After addition of water, the solution was concentrated. The residue, after dissolution in $CHCl_3$, was washed with aq 20% $KHSO_4$, aq $NaHCO_3$ (saturated), and water, dried ($MgSO_4$), and concentrated to give **14** as a colorless syrup, 85 mg (96%), which was crystallized from $CHCl_3$–hexane to give prisms, TLC: R_f 0.4 (30:1 toluene–EtOAc), mp 90–90.5 °C, $[\alpha]_D^{23}$ +21° (*c* 1, $CHCl_3$); IR (KBr): ν 2090 (N_3), 1760 cm^{-1} (C=O). Anal. Calcd for $C_{15}H_{16}F_3N_3O_4$: C, 50.14; H, 4.49; N, 11.70, Found: C, 50.06; H, 4.54; N, 11.65.

*1-O-Acetyl-3-amino-2,3,6-trideoxy-6,6,6-trifluoro-*L-lyxo-*hexopyranose* (**16**).—To a solution of **12** (498 mg, 1.4 mmol) in 1,4-dioxane (6 mL) was added Raney Ni (thick suspension in water, ~4 mL) portionwise over 1 h, whereupon the spot of **12** (R_f 0.9) in TLC (10:1 $CHCl_3$–MeOH) disappeared. After dilution with EtOAc, the mixture was filtered through a Celite bed and washed thoroughly with EtOAc. The filtrate and washings combined were washed with brine, dried (Na_2SO_4), and concentrated to give crude **15** as a syrup, 386 mg, which contained ~10% of **16**. A mixture of the syrup, cyclohexene (4.7 mL, 46 mmol), and 20% $Pd(OH)_2$ on carbon (Pearlman's catalyst, 103 mg) in EtOH (9.6 mL) was stirred for 15 h at 75 °C. Additional cyclohexene (twice; each 1.2 mL, 12 mmol) was added

halfway. The mixture was filtered through a Celite bed and washed thoroughly with 1:2 cyclohexene–EtOH. The filtrate and washings were concentrated and the turbid solution of the residue in EtOAc containing the catalyst particles accompanied was filtered through a Celite bed with successive washing with EtOAc, then the solution was concentrated. This procedure was repeated twice to obtain an anomeric mixture of **16** as yellow–green foam, 251 mg (75%). An analytical sample was prepared by flash chromatography (solvent A) to give a colorless solid, TLC: R_f 0.1 (10:1 $CHCl_3$–MeOH). Anal. Calcd for $C_8H_{12}F_3NO_4$: C, 39.51; H, 4.97; N, 5.76. Found: C, 39.83; H, 5.14; N, 5.89.

*1,4-Di-*O*-acetyl-2,3,6-trideoxy-6,6,6-trifluoro-3-trifluoroacetamido-α-*L*-* ***(18)*** *and β-*L*-lyxo-hexopyranose* (**19**).—To an ice-cold solution of **16** (1.02 g, 4.2 mmol) and pyridine (1.9 mL, 23.6 mmol) in dry CH_2Cl_2 (18.5 mL) was added $(CF_3CO)_2O$ (1.2 mL, 8.5 mmol) and the solution was kept for 1 h at 0 °C. TLC (10:1 $CHCl_3$–MeOH) showed two spots corresponding to **17** (R_f 0.5, major) and to the 4-*O*-trifluoroacetyl derivative of **17** (R_f 0.9). After addition of MeOH (1 mL) followed by EtOAc (60 mL), the solution was poured into 20% NaCl in aq $NaHCO_3$ (saturated, 120 mL) and the mixture was stirred vigorously for 30 min at rt, whereupon the spot at R_f 0.9 disappeared. The aqueous layer separated was repeatedly extracted with EtOAc. The extracts and the original organic layer combined were washed with brine, dried (Na_2SO_4), and concentrated to give **17** as a yellow–brown foam, 1.45 g. A solution of this and Ac_2O (0.8 mL, 8.5 mmol) in pyridine (13 mL) was kept for 15 h at rt, concentrated, and the residue was subjected to flash chromatography (12:1 toluene–acetone) to give a mixture of **18** and **19** as a solid, 1.13 g (71%). Analytical samples were prepared by further flash chromatography (12:1 toluene–acetone) of the solid followed by crystallization ($CHCl_3$–hexane) of the separated products to give **18** as needles and **19** as an amorphous solid, respectively. Compound **18**, TLC: R_f 0.18 (12:1 toluene–acetone), mp 138.5–141 °C, $[\alpha]_D^{20}$ −107° (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{12}H_{13}F_6NO_6$: C, 37.81; H, 3.44; N, 3.67. Found: C, 37.67; H, 3.38; N, 3.53. Compound **19**, TLC: R_f 0.21 (12:1 toluene–acetone), $[\alpha]_D^{19}$ −34° (*c* 0.6, $CHCl_3$). Anal. Calcd for $C_{12}H_{13}F_6NO_6$: C, 37.81; H, 3.44; N, 3.67. Found: C, 38.14; H, 3.39; N, 3.60.

*Phenyl 4-*O*-acetyl-2,3,6-trideoxy-6,6,6-trifluoro-1-thio-3-trifluoroacetamido-α-*L*-* (**20**) *and -β-*L*-lyxo-hexopyranoside* (**21**).—To a solution of a mixture of **18** and **19** (596 mg, 1.56 mmol) in dry CH_2Cl_2 (12 mL) were added Me_3SiSPh (1.2 mL, 6.2 mmol) and $Me_3SiOSO_2CF_3$ (0.34 mL, 1.9 mmol) and the solution was refluxed for 15 h. After dilution with EtOAc, the solution was washed with cold aq 5% NaOH and cold brine, dried (Na_2SO_4), and concentrated. Flash chromatography (50:1 CH_2Cl_2–EtOAc) of the residue gave an anomeric mixture of **20** and **21**, in a 54:46 ratio, as a solid (488 mg, 72%). The anomers were resolved by flash chromatography (25:1 toluene–acetone). Crystallization of each anomer from EtOAc–hexane afforded **20** as needles and **21** as an amorphous solid. Compound **20** sublimes at ~170 °C, TLC: R_f 0.15 (25:1 toluene–acetone), $[\alpha]_D^{21}$ −184° (*c* 0.85, $CHCl_3$). Anal. Calcd for $C_{16}H_{15}F_6NO_4S$: C, 44.55; H, 3.50; N, 3.25. Found: C, 44.65; H, 3.48; N, 3.21. Compound **21**, TLC: R_f 0.25 (25:1 toluene–acetone), $[\alpha]_D^{21}$ +34° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{16}H_{15}F_6NO_4S$: C, 44.55; H, 3.50; N, 3.25. Found: C, 44.67; H, 3.66; N, 3.27.

*7-*O*-(4-*O*-Acetyl-2,3,6-trideoxy-6,6,6-trifluoro-3-trifluoroacetamido-α-*L*-lyxo-hexopyranosyl)daunomycinone* (**22**).—To an ice-cold suspension of an anomeric mixture of **20** and **21** (368 mg, 0.85 mmol), daunomycinone (548 mg, 1.38 mmol), and powdered 4 Å molecular sieves (594 mg, activated at 350 °C under a stream of N_2) in dry $Cl(CH_2)_2Cl$ (60 mL) were added *N*-iodosuccinimide (200 mg, 0.89 mmol) and a 0.09 M solution of CF_3SO_3H in $Cl(CH_2)_2Cl$ (0.3 mL), and the mixture was stirred at 0 °C. After 20 min, additional CF_3SO_3H solution (0.5 mL) was poured, and the stirring was continued for 30 min at the temperature. Triethylamine (0.04 mL) was added, and the mixture was filtered through Celite together with $CHCl_3$. The organic solution was washed with aq $NaHCO_3$ (saturated), aq 10% $Na_2S_2O_3$, and water, dried (Na_2SO_4),

and concentrated. Flash chromatography (6:1 CH_2Cl_2–EtOAc) of the residue followed by precipitation from EtOAc–hexane gave **22** as a red solid, 245 mg (40%), TLC: R_f 0.3 (6:1 CH_2Cl_2–EtOAc), $[\alpha]_D^{23}$ +225° (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 14.00, 13.25 (each 1 H s, OH–6,11), 8.04 (dd, 1 H, $J_{1,2}$ 7.5, $J_{1,3} \sim 1$ Hz, H-1), 7.79 (dd, 1 H, $J_{1,2}$ 7.5, $J_{2,3}$ 8.5 Hz, H-2), 7.40 (dd, 1 H, H-3), 6.29 (br d, 1 H, $J_{3',NH} \sim 7$ Hz, NH), 5.71 (br s, 1 H, H-1′), 5.60 (br d, 1 H, $J_{3',4'}$ 2.5 Hz, H-4′), 5.28 (dd, 1 H, $J_{7,8ax}$ 4.5, $J_{7,8eq}$ 2 Hz, H-7), 4.69 (br q, 1 H, $J_{5',F}$ 6.5 Hz, H-5′), 4.44–4.31 (m, 1 H, H-3′), 4.08 (s, 3 H, OMe-4), 3.79 (s, 1 H, OH-9), 3.19 (dd, 1 H, $J_{10ax,10eq}$ 19, $J_{10eq,8eq}$ 1.5 Hz, H-10*eq*), 3.01 (d, 1 H, H-10*ax*), 2.39 (s, 3 H, H-14), 2.17 (s, 3 H, OAc), 2.47–2.37 and 2.23–2.03 (each m of 1 H and 3 H, respectively, H-2′*ax*, 2′*eq*, 8*ax*, 8*eq*). ^{19}F NMR ($CDCl_3$): δ −74.9 (d, 3 F, $J_{5',F}$ 6.5 Hz, CF_3-5′), −76.5 (s, 3 F, $COCF_3$). Anal. Calcd for $C_{31}H_{27}F_6NO_{12}\cdot 1.5\ H_2O$: C, 49.87; H, 4.05; N, 1.88. Found: C, 49.93; H, 3.92; N, 1.90.

7-O-*(3-Amino-2,3,6-trideoxy-6,6,6-trifluoro-α*-L-lyxo-*hexopyranosyl)daunomycinone* (**2**).— A suspension of **22** (45 mg, 0.063 mmol) in aq 0.2 M NaOH (4.6 mL) was stirred for 2.5 h at 0 °C. After addition of water (2 mL), the deep-purple solution was neutralized with aq 0.1 M HCl (10.7 mL) and the aq solution was washed with $CHCl_3$. Aqueous $NaHCO_3$ (saturated, 2 mL) was added, and the aqueous solution was repeatedly extracted with $CHCl_3$. The organic solution was dried (Na_2SO_4), and concentrated. To a solution of the residue in $CHCl_3$ (0.15 mL)–MeOH (0.15 mL)–0.3 M methanolic HCl (0.25 mL) was added diisopropyl ether, and the resulting precipitate was collected (centrifugation) and thoroughly washed with diisopropyl ether. A red solid of **2** (hydrochloride) was obtained, 31 mg (79%), TLC: R_f 0.45 (solvent A), $[\alpha]_D^{22}$ +240° (*c* 0.1, MeOH); ^{1}H NMR (D_2O): δ 7.58 (apparently t, 1 H, $J_{1,2} = J_{2,3} \sim 8$ Hz, H-2), 7.35–7.29 (m, 2 H, H-1, 3), 5.63 (br d, 1 H, $J_{1',2'ax}$ 4 Hz, H-1′), 4.76 (br, 1 H, H-7), 4.69 (br q, 1 H, $J_{5',F}$ 6.5 Hz, H-5′), 4.36 (br s, 1 H, H-4′), 3.86 (s, 3 H, OMe), 3.75 (ddd, 1 H, $J_{2'ax,3'}$ 13, $J_{2'eq,3'}$ 4.5, $J_{3',4'}$ 3 Hz, H-3′), 2.85 (br d, 1 H, $J_{10a,10b}$ 18 Hz, H-10a), 2.67 (br d, 1 H, H-10b), 2.43 (s, 3 H, H-14), 2.22 (br d, 1 H, $J_{8a,8b}$ 14.5 Hz, H-8a), 2.15 (apparently dt, 1 H, $J_{1',2'ax}$ 4, $J_{2'ax,2'eq}$ 13.5, $J_{2'ax,3'}$ 13 Hz, H-2′*ax*), ~2.08 (1 H, overlapped with the signals of H-2′*eq*, H-8b), 2.06 (br dd, 1 H, H-2′*eq*). ^{19}F NMR (D_2O): δ −74.9 (d, $J_{5',F}$ 6.5 Hz, CF_3). Anal. Calcd for $C_{27}H_{26}F_3NO_{10}\cdot HCl\cdot 1.5\ H_2O$: C, 50.28; H, 4.69; N, 2.17. Found: C, 50.29; H, 4.79; N, 2.18.

7-O-*(3-Amino-2,3,6-trideoxy-6,6,6-trifluoro-α*-L-lyxo-*hexopyranosyl)adriamycinone* (**3**).— To a suspension of **2** (hydrochloride, 31 mg, 50 μmol) in dry 1,4-dioxane (1.1 mL) was added a 5% solution of $HC(OMe)_3$ in dry MeOH (0.76 mL), and the solution was kept for 45 min at rt. After cooling (ice bath), 2.1% Br_2 in dry CH_2Cl_2 (0.17 mL; Br_2, 66 μmol) was added, and the solution was kept for 30 min at 0 °C, and then 2 h at rt. TLC (solvent A) of the solution showed a main spot at R_f 0.53 (the 14-bromo-13-dimethyl acetal, *cf* **2**: R_f 0.48). The solution was poured into diisopropyl ether (4 mL) with subsequent addition of hexane (10 mL) to give a red precipitate, which was collected (centrifugation) and washed with hexane. A solution of the solid in acetone (1.8 mL) was kept for 1 h at rt, whereupon a spot at R_f 0.48 (solvent A) (13-dedimethyl acetal) became a major one. After concentration, a mixture of the residue and HCO_2Na (65 mg, 0.96 mmol) in 1:1.5 aq acetone (3 mL) was stirred vigorously for 15 h at rt. An additional amount of HCO_2Na (18 mg, 0.26 mmol) was added and stirring was continued further 5 h. TLC (solvent A) of the mixture showed a main spot at R_f 0.35 (**3**). Concentration gave a residue, which was diluted with water and the mixture was washed with $CHCl_3$. To the aqueous solution was added $NaHCO_3$ (920 mg) and the product was extracted with $CHCl_3$. The organic solution was dried (Na_2SO_4) and concentrated. To the residue dissolved in 0.24 M methanolic HCl (0.27 mL) was added toluene, and the resulting precipitate was collected (centrifugation) and washed thoroughly with toluene to give a red solid of **3** as the hydrochloride, 16 mg (49%), $[\alpha]_D^{22}$ +243° (*c* 0.1, MeOH); ^{1}H NMR (D_2O, 45 °C): δ 7.62 (br t, 1 H, $J_{1,2} = J_{2,3}$ 8 Hz, H-2), 7.39–7.34 (m, 2 H, H-1,3), 5.68 (br d, 1 H, $J_{1',2'ax}$ 4 Hz, H-1′), 4.80 (s, 2 H, H-14), 4.78 (br, 1 H, H-7), 4.69 (br q, 1 H, $J_{5',F}$ 6.5 Hz, H-5′), 4.38 (br s, 1 H, H-4′), 3.90 (s, 3 H,

OMe), 3.77 (ddd, 1 H, $J_{2'ax,3'}$ 13, $J_{2'eq,3'}$ 5, $J_{3',4'}$ 2.5 Hz, H-3′), 2.93 (d, 1 H, $J_{10a,10b}$ 18 Hz, H-10a), 2.65 (d, 1 H, H-10b), 2.28 (br d, 1 H, $J_{8a,8b}$ 15 Hz, H-8a), 2.18 (apparently dt, 1 H, $J_{1',2'ax}$ 4, $J_{2'ax,2'eq}$ 13.5, $J_{2'ax,3'}$ 13 Hz, H-2′*ax*), 2.08 (dd, 1 H, H-2′*eq*), 2.04 (dd, 1 H, $J_{8a,8b}$ 15, $J_{7,8b}$ 5 Hz, H-8b). ^{19}F NMR (D_2O): δ −74.9 (d, $J_{5',F}$ 6.5 Hz, CF_3). Anal. Calcd for $C_{27}H_{26}F_3NO_{11}\cdot HCl\cdot H_2O$: C, 49.74; H, 4.48; N, 2.15. Found: C, 50.10; H, 4.70; N, 2.03.

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