A 5′-(Trifluoromethyl)anthracycline Glycoside: Synthesis of Antitumor-Active 7-*O*-(2,6-Dideoxy-6,6,6-trifluoro-α-L-*lyxo*-hexopyranosyl)adriamycinone

Yasushi Takagi,[†] Ken Nakai,[†] Tsutomu Tsuchiya,*[,†] and Tomio Takeuchi[‡]

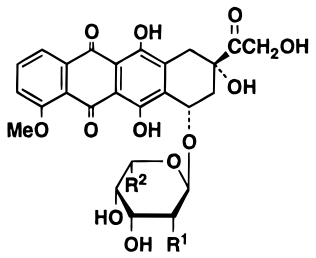
Institute of Bioorganic Chemistry, 1614 Ida, Nakahara-ku, Kawasaki, 211, Japan, and Institute of Microbial Chemistry, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141, Japan

Received March 4, 1996[⊗]

7-*O*-(2,6-Dideoxy-6,6,6-trifluoro-α-L-*lyxo*-hexopyranosyl)adriamycinone (**3**), whose substituent at C-5′ is a lipophilic trifluoromethyl group, has been prepared by coupling of 3,4-di-*O*-acetyl-2,6-dideoxy-6,6,6-trifluoro-α-L-*lyxo*-hexopyranosyl bromide (**20**) with 14-*O*-(*tert*-butyldimethylsilyl)adriamycinone under the Koenigs−Knorr conditions. The key step in this synthesis was the *C*-trifluoromethylation of 5-*O*-acetyl-2,3-di-*O*-benzyl-4-deoxy-*aldehydo*-L-*erythro*-pentose (**10**), derived from D-lyxose in 10 steps, with (trifluoromethyl)trimethylsilane in the presence of tetrabutylammonium fluoride, whereupon 1,1,1-trifluoro-L-*arabino*-hexitol (**11**) was obtained along with its 2-epimer. The synthetic product **3** showed remarkable antitumor activity *in vivo* in a low dose range compared to the analogs including doxorubicin. The fact may be ascribed to the presence of a trifluoromethyl group at C-5′, suggesting the importance of the group in view of biological activity.

Introduction

Recently several promising anticancer drugs such as calicheamicins,[1] camptothecin analogs,[2] dynemicins,[3] esperamicins,[4] etoposide,[5] and taxol[6] have been developed; however, doxorubicin (DOX), an anthracycline glycosidic antibiotic, is still one of the most important anticancer drugs in chemotherapy. Its clinical use, however, is limited due to drug-cumulative cardiotoxicity, myelosuppression, and other undesirable side effects as well as occurrence of natural and acquired resistance to this drug in tumor cells. To overcome these drawbacks, a number of chemical and biosynthetical modifications have been undertaken on both the aglycon and sugar portions for over two decades.[7−22] Among the studies, Horton and co-workers synthesized, in 1984, 3′-deamino-3′-hydroxydoxorubicin[23] (**1**) which had fairy good antitumor activity with less toxicity, albeit it has no amino group. This indicates that the C-3′ amino group is not essential in its activity. On the 2′-position, most of the DOX analogs including **1** have no substituent, and this will be the reason why these antibiotics are unstable in acidic conditions, giving inactive aglycons. This problem, however, was solved by introducing a strongly electron-withdrawing fluorine at C-2′, as illustrated by 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)adriamycinone[24,25] (**2**), which was stable against acid[26] and exhibited stronger antitumor activity with less toxicity in comparison to those for DOX. Additionally, **2** was found to be absorbed[27] more rapidly and accumulated more readily into tumor cells than DOX. 4′-*O*-Glycosylated derivatives of **2** were also prepared.[28] Although the precise relationships between the chemical stability and antitumor activity *in vivo* in DOX analogs is not clear, the above result of **2** encouraged us to search for another type of stable compounds. We considered that introduction of an electron-withdrawing group at C-5′ may also strengthen the glycosidic bond by decreasing the electron density of the glycosidic oxygen as experienced for F-2′, and a trifluoromethyl group was chosen as the candidate. Another reason for this selection is in its high lipophilicity[29] compared to a methyl group; the CF_3 at C-5′ was expected to enhance the cellular uptake of the drugs bearing the group and facilitate effective transportation into organs or tumor cells when administered *in vivo*. We report here on the preparation and antitumor activity of 7-*O*-(2,6-dideoxy-6,6,6-trifluoro-α-L-*lyxo*-hexopyranosyl)adriamycinone (**3**).



1 $R^1 = H$, $R^2 = CH_3$
2 $R^1 = F$, $R^2 = CH_3$
3 $R^1 = H$, $R^2 = CF_3$

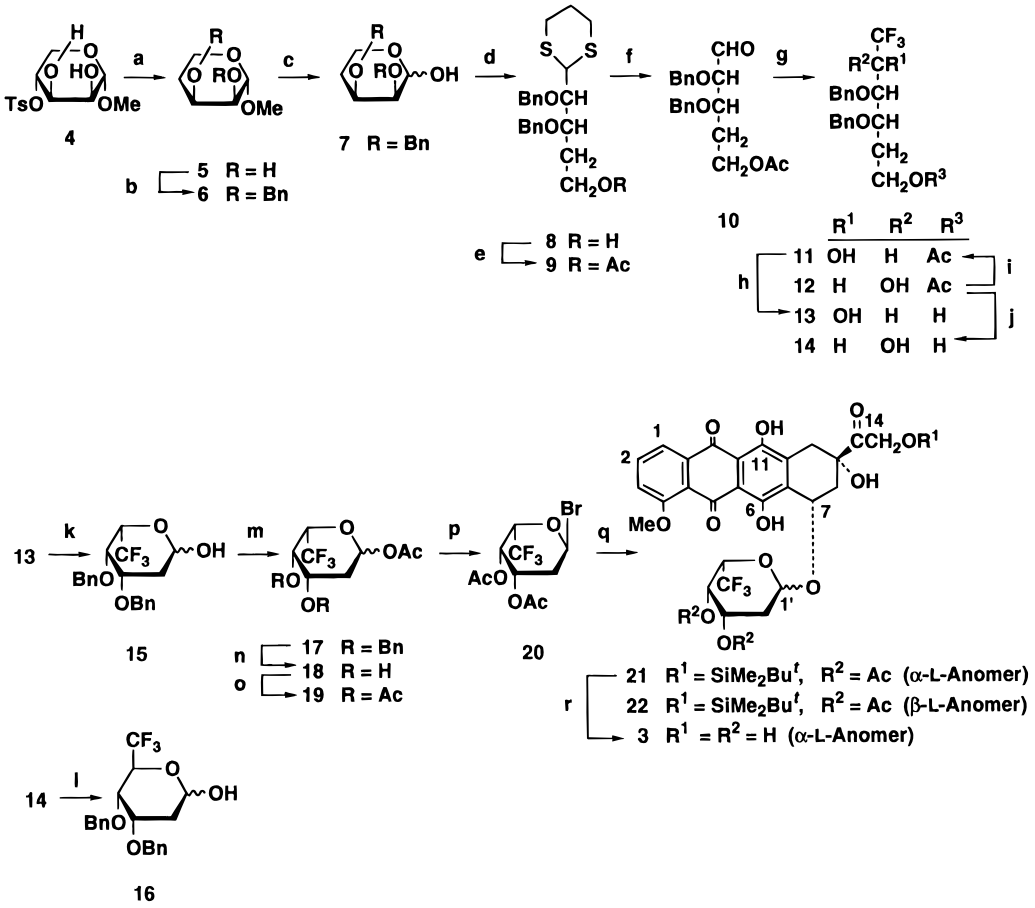
Results and Discussion

The synthesis was accomplished by coupling a 2,6-dideoxy-6,6,6-trifluoro sugar with a protected adriamycinone derivative (Scheme 1). During the past 6 years, several 6-deoxy-6,6,6-trifluoro sugars have been synthesized from simple sugars[30,31] or nonsugar building blocks.[32−36] In this study, we adopted D-lyxose as a starting material for preparation of 2,6-dideoxy-6,6,6-trifluoro-L-*lyxo*-hexopyranose. Methyl 4-*O*-(*p*-tolylsulfonyl)-α-D-lyxopyranoside[37,38] (**4**), prepared from D-lyxose in four steps, was treated with $LiAlH_4$ to give the 4-deoxy derivative **5**.[39] After protection of the hydroxyl groups with benzyl ethers (BnBr, NaH in DMF), the resulting compound **6** was hydrolyzed (0.4 M HCl in aqueous 80% AcOH, 80 °C) to give the free sugar **7**. Treatment of **7** with 1,3-propanedithiol in the presence

* Author to whom correspondence should be sent.
[†] Institute of Bioorganic Chemistry.
[‡] Institute of Microbial Chemistry.
[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1996.

0022-2623/96/1839-1582$12.00/0

Scheme 1[a]



[a] (a) $LiAlH_4$, THF, reflux (65%); (b) BnBr, NaH, DMF (81%); (c) 1:4 aqueous 2 M HCl/AcOH, 80 °C (82%); (d) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, $Cl(CH_2)_2Cl$, 60 °C (64%); (e) Ac_2O, Py (97%); (f) $Hg(ClO_4)_2{\cdot}3H_2O$, $CaCO_3$, aqueous THF (99%); (g) (i) $TMSCF_3$, $Bu_4NF{\cdot}3H_2O$, THF; (ii) aqueous 80% AcOH, 50 °C (37% of **11**, 37% of **12**); (h) MeONa, MeOH (99%); (i) (i) $(CF_3SO_2)_2O$, Py, CH_2Cl_2, 0 °C; (ii) $NaNO_2$, DMF, 95 °C (43%); (j) MeONa, MeOH (quantitative); (k) (i) TMSCl, DMAP, Py; (ii) CrO_3, Py, CH_2Cl_2, 0 °C; (iii) 1:10 aqueous 1.1 M HCl/1,4-dioxane (98%); (l) The same with (k) (92%); (m) Ac_2O, Py (88%); (n) H_2, Pd black, 10:1 aqueous 90% 1,4-dioxane/AcOH (98%); (o) Ac_2O, Py (quantitative); (p) 30% HBr in AcOH (90%); (q) 14-*O*-(*tert*-butyldimethylsilyl)adriamycinone, $HgBr_2$, HgO(yellow), molecular sieves 3A, $Cl(CH_2)_2Cl$ (26% of **21**, 25% of **22**); (r) (i) MeONa, MeOH; (ii) aqueous 80% AcOH, 80 °C (69%).

of $BF_3{\cdot}Et_2O$ in $Cl(CH_2)_2Cl$ gave the dithioacetal **8**, which was then acetylated to give the 5-acetate **9**. After removal of the dithioacetal group with $Hg(ClO_4)_2-CaCO_3$ in aqueous THF, the resulting aldehyde **10** was trifluoromethylated according to the procedure reported by Prakash *et al.*:[40] treatment of **10** with $CF_3Si(CH_3)_3$ in the presence of a catalytic amount of Bu_4NF in THF, followed by deprotection of the resulting trimethylsilyl group (aqueous 80% AcOH, 50 °C), gave, after chromatography, the desired 1,1,1-trifluoro-L-*arabino*-hexitol derivative (**11**) together with its 2-epimer (the 6,6,6-trifluoro-D-*ribo*-hexitol derivative **12**) in a ratio of 1:1 in 74% overall yield. Compound **12** was able to be converted into **11** by treatment of the triflate of **12** with $NaNO_2$[41] in 43% yield. After deacetylation (MeONa–MeOH) of **11**, the primary hydroxyl group of **13** was selectively oxidized according to the procedure of Mahrwald *et al.*[42] To do that, compound **13**, after trimethylsilylation (TMSCl, DMAP in pyridine), was oxidized (Collins oxidation), and the resulting aldehyde was desilylated (0.1 M HCl in aqueous 1,4-dioxane) to give an anomeric mixture of 3,4-di-*O*-benzyl-2,6-dideoxy-6,6,6-trifluoro-L-*lyxo*-hexopyranose (**15**; 98% overall yield based on **13**). The structure (and the $^1C_4$(L) conformation) was confirmed by a large coupling constant $J_{2ax,3}$ (12 Hz) in its ^1H NMR spectrum as well as the existence of NOE between H-3 and H-5 (saturation of H-3 showed 8.2% H-5 signal increase). Compound **12** was similarly converted to the D-*ribo*-hexopyranose derivative **16** through **14**, and the structure was confirmed by the NMR study (see the Experimental Section). Acetylation of **15** gave the 1-acetate **17** and successive catalytic hydrogenolysis (to give **18**) and reacetylation gave the triacetate **19**. Several attempts to couple **19** or other 1-esters or 1-halides with 14-*O*-(*tert*-butyldimethylsilyl)-adriamycinone[23] in the presence of an appropriate catalyst, however, did not proceed well, as demonstrated by lack of coupling of **19** with the aglycon in the presence of trimethylsilyl triflate. This may be the reason why no couplings of 5-CF_3 sugars to anthracyclinones have ever been reported. Further attempts to couple using either the protected phenylthioglycoside (in the presence of *N*-bromosuccinimide[43] or *N*-iodosuccinimide–CF_3SO_3H[44]) or the glycosyl fluoride (in the presence of $Cp_2ZrCl_2-AgClO_4$[45]) failed to give the condensation product. However, the most classical coupling using the glycosyl bromide **20** (prepared from **19** with 30% HBr–AcOH) and 14-*O*-(*tert*-butyldimethylsilyl)adriamycinone under the Koenigs–Knorr conditions [HgO(yellow), $HgBr_2$, molecular sieves 3A in $Cl(CH_2)_2Cl$] gave, after chromatography, the desired α-L-glycoside **21** ($J_{1',2'ax}$ 3.5 Hz) along with the β-L-glycoside **22** ($J_{1',2'ax}$ 10 Hz) in 26% and 25% yield, respectively. Deacetylation (MeONa–MeOH) followed by desilylation (aqueous 80% AcOH,

Table 1. Growth Inhibitory Effect of **3** and DOX against Various Cell Lines *in Vitro*[a]

	IC_{50} (μg/mL)							
compound	K562	HMV-1	KB	MKN-1	PC-14	T24	P388	P388/ADR
3	0.049	0.14	0.045	0.21	0.21	0.060	<0.0098	0.17
DOX·HCl	0.045	0.063	0.033	0.076	0.19	0.061	0.017	0.51

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

Table 2. Antitumor Activities (T/C, %; 60 Day Survivor Numbers/Treated Numbers of Mice) of **3** and DOX against L1210[a]

		dose (mg/kg/day)							
compound		5	2.5	1.25	0.6	0.3	0.15	0.08	0.04
3	T/C	135[c]	194[c]	203	>406	>606	>612	148	114
	survivor	0/4	0/4	0/4	1/4	3/4	3/4	0/4	0/4
DOX·HCl[b]	T/C	177[c]	273[c]	330	208	132	140		
	survivor	0/4	0/4	0/4	0/4	0/4	0/4		

[a] Leukemia L1210 cells (10^5) were inoculated into CDF_1 mice intraperitoneally. Drugs were administered daily, starting 24 h after inoculation, from day 1 to 9, intraperitoneally. [b] See ref 46. [c] Toxic.

80 °C) gave the trifluoromethyl analog **3** as a red powder. The compound was fairly stable against acid; in monitoring by TLC, DOX was completely hydrolyzed within 3.5 h in 0.5 M HCl in 1:1 DMSO/H_2O at 60 °C, whereas **3** was only partially hydrolyzed even after 7 h in the same conditions.

Antitumor activity of **3** was examined by growth inhibition assay against human and murine tumor cell lines. As shown in Table 1, **3** exhibited comparative or slightly-weaker activity than DOX against six human cell lines [K562 (human leukemia), HMV-1 (human melanoma), KB (human nasopharyngeal carcinoma), MKN-1 (human gastric adenocarcinoma), PC-14 (human lung carcinoma), and T24 (human bladder carcinoma)] although 3-fold stronger activity than DOX against P388/ADR (DOX-resistant P388 murine leukemia). Compound **3**, however, displayed significant antitumor activity against L1210 murine leukemia *in vivo* in comparison to DOX (Table 2). It is noteworthy that, in a low dose range (0.6−0.15 mg/kg/day), seven mice out of twelve survived 60 days, whereas no survivors were observed in DOX. 3′-Deamino-3′-hydroxydoxorubicin **1**, whose substituent at C-5′ is a methyl, was reported[23] to show the highest T/C value (462%) at 25 mg/kg (P388 murine leukemia by single ip injection on the first day; no long-term survivors were reported). In the case of **2**, 60-day survivors were observed in a relatively high dose range (2.5−5 mg/kg/day).[24] Comparison of these results indicates that **3** has a remarkably high potency *in vivo*. The higher activity of **3** versus **1** or **2** may be reasonably ascribed to the presence of a trifluoromethyl group at C-5′, whose contribution to its stability as well as high lipophilicity may enhance the cellular uptake of this analog, facilitating the transportation into organs as well.

In summary, we have been able to prepare a novel anthracycline glycoside having a CF_3 group at C-5′ with significant antitumor activity *in vivo*. Short syntheses of the sugar and further biological evaluations of **3** (together with the related analogs) are now under study.

Experimental Section

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. ^{1}H NMR (at 250 MHz) and ^{19}F NMR (at 235.3 MHz) spectra were recorded with a Bruker AC 250P spectrometer, unless otherwise stated. ^{1}H NMR (at 500 MHz) and ^{13}C NMR (at 125.8 MHz) spectra were recorded with a Bruker AMX 500 spectrometer. Chemical shifts (δ) for ^{1}H, ^{13}C, and ^{19}F were measured, respectively, downfield from internal Me_4Si, Me_4Si, and $CFCl_3$. Mass spectra were recorded with a JEOL SX-102 spectrometer. TLC was performed on Kieselgel 60 F_{254} (Merck) and column chromatography, on Kieselgel 60 (230−400 mesh, Merck).

Methyl 4-Deoxy-β-L-*erythro*-pentopyranoside (5). To a cold (0 °C) suspension of $LiAlH_4$ (1.03 g, 27 mmol) in dry tetrahydrofuran (THF, 4 mL, freshly distilled from sodium benzophenone ketyl) was added slowly a solution of methyl 4-*O*-(*p*-tolylsulfonyl)-α-D-lyxopyranoside[37] (**4**, 2.14 g, 6.7 mmol) in THF (11 mL), and the mixture was refluxed for 1.5 h. After cooling to 0 °C, aqueous 10% NH_4Cl (11 mL) and EtOAc (25 mL) were added, the mixture was stirred for 1 h at room temperature and filtered through a pad of Celite, and the filtrate was concentrated to give a residue that was chromatographed (10:1 $CHCl_3$/MeOH) to give **5** as a syrup (0.64 g, 65%), together with methyl α-D-lyxopyranoside (0.13 g, 12%). Compound **5** had $[\alpha]^{24}_D$ +101° (*c* 0.2, H_2O) [lit.[37] $[\alpha]^{21}_D$ +39.2° (*c* 0.2, H_2O); this value is incorrect]; ^{1}H NMR (CD_3OD) δ 1.60 (ddt, J = 13, 4.5, 4.5, and 3 Hz, 1H, H-4eq), 1.90 (dddd, J = 13, 10, 8.5, and 5.5 Hz, 1H, H-4ax), 3.36 (s, 3H, OMe), 3.55 (apparently t, J = 3.5 and 3 Hz, 1H, H-2), 3.61−3.77 (m, 2H, H-5ax,5eq), 3.90 (ddd, J = 10, 4.5, and 3 Hz, 1H, H-3), 4.57 (d, J = 3.5 Hz, 1H, H-1). Anal. ($C_6H_{12}O_4$) C, H.

Methyl 2,3-Di-*O*-benzyl-4-deoxy-β-L-*erythro*-pentopyranoside (6). A mixture of **5** (2.75 g, 18.6 mmol) and NaH (60% in mineral oil, 3.74 g, 94 mmol) in dry *N*,*N*-dimethylformamide (DMF, 19 mL) was stirred for 1 h at room temperature. The mixture was cooled (0° C), benzyl bromide (6.6 mL, 56 mmol) was added, and the mixture was stirred for 1 h at room temperature. After addition of aqueous 5% AcOH (160 mL), the mixture was extracted with $CHCl_3$. The extract was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated. Column chromatography (30:1 toluene/Me_2CO) of the residue gave **6** as a pale yellow syrup (4.93 g, 81%): $[\alpha]^{23}_D$ +35° (*c* 1.9, $CHCl_3$); TLC R_f 0.55 (12:1 toluene/Me_2CO); ^{1}H NMR ($CDCl_3$) δ 1.69 (br ddt, J = 13, 4.5, 3, and 3 Hz, 1H, H-4eq), 2.14 (dddd, J = 13, 10.5, 10, and 5 Hz, 1H, H-4ax), 3.35 (s, 3H, OMe), 3.61 (ddd, J = 3, 2.5, and 1 Hz, 1H, H-2), 3.63−3.79 (m, 2H, H-5a,5b), 3.83 (ddd, J = 10.5, 4.5, and 2.5 Hz, 1H, H-3), 4.56 (s, 2H, PhCH_2), 4.71 (d, J = 3 Hz, 1H, H-1), 4.73 and 4.78 (each d of 1H, J = 12 Hz, PhCH_2), 7.20−7.45 (m, 10H, Ph). Anal. ($C_{20}H_{24}O_4$) C, H.

2,3-Di-*O*-benzyl-4-deoxy-L-*erythro*-pentopyranose (7). A solution of **6** (4.81 g, 14.7 mmol) in 1:4 aqueous 2 M HCl/AcOH (48 mL) was heated for 30 min at 80 °C and then poured into aqueous $NaHCO_3$ (saturated, 400 mL). Extraction of the product with $CHCl_3$ gave a syrup that was purified by column chromatography (12:1 toluene/Me_2CO) to give **7** as a syrup (3.78 g, 82%): $[\alpha]^{25}_D$ +24.5° (*c* 1.1, $CHCl_3$, 24 h after dissolution); TLC R_f 0.20 (12:1 toluene/Me_2CO). Anal. ($C_{19}H_{22}O_4$) C, H.

2,3-Di-*O*-benzyl-4-deoxy-L-*erythro*-pentose Trimethylene Dithioacetal (8). A mixture of **7** (10.3 g, 32.7 mmol), 1,3-propanedithiol (5.9 mL, 59 mmol), and BF_3·Et_2O (1.2 mL,

9.8 mmol) in dry $Cl(CH_2)_2Cl$ (60 mL) was heated for 3.5 h at 60 °C. Chloroform (300 mL) was added, and the solution was washed with aqueous 5% NaOH and water, dried (Na_2SO_4), and concentrated. The residue was chromatographed (12:1 toluene/Me_2CO) to give **8** as a colorless syrup (8.50 g, 64%): $[\alpha]^{25}_D$ −39° (*c* 1.1, $CHCl_3$); TLC R_f 0.27 (12:1 toluene/Me_2CO); ^{1}H NMR ($CDCl_3$) δ 1.81−1.99 (m, 3H, H-4a and SCH_2CH_2-CH_2S), 2.05−2.17 (m, 2H, H-4b and OH), 2.72−2.92 (m, 4H, $SCH_2CH_2CH_2S$), 3.72 (q, collapsed to t in addition of D_2O, J = 5.5 Hz, 2H, H-5a,5b), 3.83 (dd, J = 5.5 and 4.5 Hz, 1H, H-2), 3.98 (dt, J = 5.5, 5.5 and 4.5 Hz, 1H, H-3), 4.36 (d, J = 5.5 Hz, 1H, H-1), 4.57 and 4.65 (each d of 1H, J = 11.5 Hz, $PhCH_2$), 4.75 and 4.90 (each d of 1H, J = 11 Hz, $PhCH_2$), 7.21−7.49 (m, 10H, Ph). Anal. ($C_{22}H_{28}O_3S_2$) C, H, S.

5-*O*-Acetyl-2,3-di-*O*-benzyl-4-deoxy-L-*erythro*-pentose Trimethylene Dithioacetal (9). A solution of **8** (1.03 g, 2.5 mmol) and Ac_2O (0.4 mL, 4.2 mmol) in pyridine (8 mL) was treated conventionally to give **9** as a colorless syrup (1.09 g, 97%): $[\alpha]^{21}_D$ −37.5° (*c* 0.7, $CHCl_3$); TLC R_f 0.62 (12:1 toluene/Me_2CO); ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 3H, Ac), 1.81−2.17 (m, 4H, H-4a,4b and $SCH_2CH_2CH_2S$), 2.71−2.92 (m, 4H, SCH_2-CH_2CH_2S), 3.77 (apparently t, J = ∼5 Hz, 1H, H-2), 3.87 (ddd, J = 7.5, 5, and 4 Hz, 1H, H-3), 4.13−4.23 (m, 2H, H-5a,5b), 4.36 (d, J = 5.5 Hz, 1H, H-1), 4.53, 4.63, 4.74, and 4.90 (each d of 1H, $2PhCH_2$), 7.22−7.49 (m, 10H, Ph). Anal. ($C_{24}H_{30}O_4S_2$) C, H, S.

5-*O*-Acetyl-2,3-di-*O*-benzyl-4-deoxy-*aldehydo*-L-*erythro*-pentose (10). To a mixture of **9** (1.09 g, 2.45 mmol) and $CaCO_3$ (4.70 g) in 3:1 THF/H_2O (15 mL) was added $Hg(ClO_4)_2 \cdot 3H_2O$ (2.90 g, 6 mmol) in THF (9 mL), and the mixture was stirred for 1 h at room temperature. After addition of CH_2Cl_2 (50 mL), the mixture was shaken with aqueous $NaHCO_3$ (saturated, 20 mL) and filtered through a pad of Celite, and the filtrate was washed with aqueous 10% KI and water, dried (Na_2SO_4), and concentrated to give **10** as a syrup (0.87 g, 99%) that was used without purification to the next step: $[\alpha]^{20}_D$ −71° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.82 (ddt, J = 15, 7.5, 7.5, and 3.5 Hz, 1H, H-4a), 1.96 (s, 3H, Ac), 1.97−2.11 (m, 1H, H-4b), 3.89 (dt, J = 9, 3.5, and 3.5 Hz, 1H, H-3), 3.95 (dd, J = 3.5 and 1.5 Hz, 1H, H-2), 4.08−4.18 (m, 2H, H-5a,5b), 4.52, 4.64, 4.64, and 4.72 (each d of 1H, J = 11.5 Hz, $2PhCH_2$), 7.22−7.49 (m, 10H, Ph), 9.71 (d, J = 1.5 Hz, 1H, H-1); FAB-MS *m*/*e* 357 $(M + H)^+$.

6-*O*-Acetyl-3,4-di-*O*-benzyl-1,5-dideoxy-1,1,1-trifluoro-L-*arabino*-hexitol (11) and 1-*O*-acetyl-3,4-di-*O*-benzyl-2,6-dideoxy-6,6,6-trifluoro-D-*ribo*-hexitol (12). To a cold (0 °C) solution of **10** (0.81 g, 2.28 mmol) and CF_3SiMe_3 (0.5 mL, 3.4 mmol) in THF (8 mL) was added $Bu_4NF \cdot 3H_2O$ (71 mg, 0.23 mmol) in THF (2 mL), and the solution was kept for 1.5 h at room temperature. TLC (25:1 toluene/EtOAc) of the solution showed three spots at R_f 0.08 (**12**), 0.17 (**11**), and 0.38 (*O*-trimethylsilyl derivatives of **11** and **12**). After concentration, the residue was extracted with $CHCl_3$, and the solution was washed with water, dried (Na_2SO_4), and concentrated. The resulting syrup was dissolved in aqueous 80% AcOH (4 mL) and kept for 1.5 h at 50 °C. In TLC, the spot at R_f 0.38 disappeared. Evaporation of solvents by codistillation with toluene gave a residue that was chromatographed (25:1 toluene/EtOAc) to give **11** (0.36 g, 37%) and **12** (0.36 g, 37%) as syrups.

Compound **11** had $[\alpha]^{24}_D$ −24° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3H, Ac), 1.84−2.12 (m, 2H, H-5a,5b), 3.28 (d, J = 9.5 Hz, 1H, OH, disappeared on deuteration), 3.67 (ddd, J = 7, 6, and 4 Hz, 1H, H-4), 3.83 (dd, J = 6 and 1.5 Hz, 1H, H-3), 4.08 (ddq, $J_{2,F}$ = 7.5, $J_{2,OH}$ = 9.5, and $J_{2,3}$ = 1.5 Hz, which collapsed to dq on deuteration 1H, H-2), 4.12−4.26 (m, 2H, H-6a,6b), 4.56 and 4.62 (each d of 1H, $PhCH_2$), 4.66 and 4.72 (each d of 1H, $PhCH_2$), 7.23−7.42 (m, 10H, Ph); ^{19}F NMR ($CDCl_3$) δ −77.6 (d, J = 7.5 Hz, CF_3). Anal. ($C_{21}H_{25}F_3O_5$) C, H, F.

Compound **12** had $[\alpha]^{23}_D$ −31° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3H, Ac), 1.88−2.14 (m, 2H, H-2a,2b), 3.20 (br, 1H, OH), 3.85−3.94 and 4.04−4.24 (each m of 2H and 3H, respectively, H-1a,1b,3,4,5), 4.56 and 4.67 (each d of 1H, $PhCH_2$), 4.62 and 4.74 (each d of 1H, $PhCH_2$), 7.23−7.41 (m, 10H, Ph); ^{19}F NMR ($CDCl_3$) δ −76.1 (d, J = 7 Hz, CF_3). Anal. ($C_{21}H_{25}F_3O_5$) C, H, F.

Preparation of 11 from 12. To a cold (0 °C) solution of **12** (42 mg, 0.1 mmol) in CH_2Cl_2 (0.4 mL) were added $(CF_3SO_2)_2O$ (25 μL, 0.15 mmol) and pyridine (0.05 mL), and the solution was kept for 1.5 h at 0 °C. MeOH (0.06 mL) was added, and after dilution with CH_2Cl_2, the solution was washed successively with cold aqueous 20% $KHSO_4$, aqueous $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated to give the 5-triflate of **12** as a chromatographically homogeneous syrup (51 mg, 93%): TLC R_f 0.5 (25:1 toluene/EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.35 (dq, 1H, J = 6, 6, 6, and 3.5 Hz, H-5); ^{19}F NMR ($CDCl_3$) δ −74.3 (q, 3F, $J_{CF3SO3,F\text{-}6}$ = 3.5 Hz CF_3SO_3), −72.1 (dq, 3F, J = 6, 3.5, 3.5, and 3.5 Hz, F-6). A mixture of the syrup (46 mg, 0.08 mmol) and $NaNO_2$ (73 mg, 1.1 mmol) in DMF (0.45 mL) was stirred for 2.5 h at 95 °C. Evaporation of the solvent after addition of water and xylene gave a residue that was chromatographed (25:1 toluene/EtOAc) to give **11** (16 mg, 43% based on **12**), which was identical with the specimen obtained from **10**.

3,4-Di-*O*-benzyl-1,5-dideoxy-1,1,1-trifluoro-L-*arabino*-hexitol (13). A solution of **11** (296 mg, 0.70 mmol) in methanolic 0.025 M MeONa (5 mL, 0.13 mmol) was kept for 1 h at room temperature. Neutralization with Dowex 50W X-2 resin (H^+ form) followed by filtration and concentration gave **13** as a syrup (266 mg, 99%): $[\alpha]^{21}_D$ −17° (*c* 0.7, $CHCl_3$); TLC R_f 0.2 (10:1 toluene/Me_2CO). Anal. ($C_{20}H_{23}F_3O_4$) C, H, F.

3,4-Di-*O*-benzyl-2,6-dideoxy-6,6,6-trifluoro-D-*ribo*-hexitol (14). Compound **12** (273 mg) was treated similarly as described for **13** to give **14** as a syrup (246 mg, quantitative): $[\alpha]^{24}_D$ −31° (*c* 0.5, $CHCl_3$). Anal. ($C_{20}H_{23}F_3O_4$) C, H, F.

3,4-Di-*O*-benzyl-2,6-dideoxy-6,6,6-trifluoro-L-*lyxo*-hexopyranose (15). A mixture of **13** (1.46 g, 3.8 mmol), Me_3SiCl (1.74 mL, 13.7 mmol), and 4-dimethylaminopyridine (183 mg, 1.5 mmol) in pyridine (15 mL) was stirred for 15 h at room temperature. The mixture showed, in TLC (10:1 toluene/Me_2CO), a spot at R_f 0.9 (the 2,6-di-*O*-TMS derivative). After concentration, the residue dissolved in EtOAc was washed with water, dried (Na_2SO_4), and concentrated to give a pale yellow syrup (2.07 g). The syrup dissolved in CH_2Cl_2 (3.5 mL) was added to a mixture of dry CrO_3 (1.82 g, 18.2 mmol) and pyridine (3.0 mL, 37 mmol) in CH_2Cl_2 (25 mL), which was previously stirred for 30 min at room temperature and cooled (0 °C), and stirred for 40 min at the temperature. TLC (10:1 toluene/Me_2CO) showed two spots at R_f 0.35 (**15**) and 0.75 (the 5-*O*-TMS derivative). After filtration through a pad of silica gel with aid of EtOAc, the mixture was concentrated. The residue dissolved in EtOAc was again treated as above to eliminate insoluble matters. The resulting brown syrup (1.83 g) dissolved in a mixture of 1:10 aqueous 1.1 M HCl/1,4-dioxane (18 mL) was kept for 1 h at room temperature. TLC (10:1 toluene/Me_2CO) showed a single spot (**15**) with disappearance of the one of R_f 0.75. After neutralization (aqueous $NaHCO_3$), the product was extracted with CH_2Cl_2 to give, after usual purification, **15** (1.42 g, 98%) as a syrup of an anomeric mixture (α:β ∼14:1), which solidified after 1 month: mp 71.5−72 °C; $[\alpha]^{24}_D$ −72° (*c* 0.4, $CHCl_3$, 24 h after dissolution); ^{1}H NMR ($CDCl_3$, only for α-L-anomer) δ 2.02 (ddt, J = 13, 4.5, ∼1.5, and ∼1.5 Hz, 1H, H-2eq), 2.30 (ddd, J = 13, 12, and 3.5 Hz, 1H, H-2ax), ∼2.8 (br, 1H, OH), 3.96 (ddd, J = 12, 4.5, and 2.5 Hz, 1H, H-3), 4.11 (br s, 1H, H-4), 4.28 (br q, J = 7 Hz, 1H, H-5), 4.60 (s, 2H, $PhCH_2$), 4.71 and 4.91 (each d of 1H, J = 11 Hz, $PhCH_2$), 5.54 (br d, J = 3.5 Hz, 1H, H-1), 7.28−7.42 (m, 10H, Ph); ^{19}F NMR ($CDCl_3$) δ −74.0 (d, J = 7 Hz, ∼2.8F, CF_3 of α-L-anomer), −73.6 (d, J = 6.5 Hz, ∼0.2F, CF_3 of β-L-anomer). Anal. ($C_{20}H_{21}F_3O_4$) C, H, F.

3,4-Di-*O*-benzyl-2,6-dideoxy-6,6,6-trifluoro-D-*ribo*-hexopyranose (16). Compound **14** (192 mg) was treated similarly as described for **15** to give **16** as a syrup (175 mg, 92%). An analytical sample was prepared by column chromatography (25:1 toluene/EtOAc) followed by recrystallization (EtOAc/hexane) as needles: mp 74.5−75.5 °C; $[\alpha]^{24}_D$ +51° (*c* 0.5, $CHCl_3$, 24 h after dissolution); TLC R_f 0.2 (25:1 toluene/EtOAc; *cf.* **15**, R_f 0.1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 [ddd, J = 13.5, 9.5, and 2.5 Hz, 0.2H, H-2ax(β-L-anomer)], 1.79 [ddd, J = 14.5, 3.5, and 2.5 Hz, 0.8H, H-2ax(α-L-anomer)], 2.13 [ddd,

J = 14.5, 4, and ~1 Hz, 0.8H, H-2eq(α)], 2.24 [ddd, J = 13.5, 4, and 2 Hz, 0.2H, H-2eq(*β*)], ~3.1 [br, 0.2H, HO-1(*β*)], 3.65 [dd, J = 9.5 and 2.5 Hz, 1H, H-4(α and *β*)], 3.98 [m, 0.2H, H-3(*β*)], 4.09 [m, 0.8H, H-3(α)], 4.39 [dq, J = 9.5, 6.5, 6.5, and 6.5 Hz, 0.2H, H-5(*β*)], 4.56 [dq, J = 9.5, 6.5, 6.5, and 6.5 Hz, 0.8H, H-5(α)], 4.69 [d, J = 11.5 Hz, 0.2H, PhCH_2(*β*)], 4.55, 4.62, 4.64, and 4.85 [each d of 0.8H, J = 11.5 Hz, PhCH_2(α)], 5.21 [br dd, J = 11 and 3.5 Hz, 0.8H, H-1(α)], 5.26 [dd after deuteration; J = 9.5 and 2 Hz, 0.2H, H-1(*β*)], 5.27 [d, J = 11 Hz, 0.8H, HO-1(α)], 7.25−7.40 (m, 10H, Ph); saturation of H-2ax(α) showed 5.2% signal increase of H-4; ^{19}F NMR ($CDCl_3$) δ −74.6 [d, J = 6.5 Hz, 0.6F, CF_3(*β*)], −74.2 [d, J = 6.5 Hz, 2.4F, CF_3(α)]. Anal. ($C_{20}H_{21}F_3O_4$) C, H, F.

1-*O*-Acetyl-3,4-di-*O*-benzyl-2,6-dideoxy-6,6,6-trifluoro-L-*lyxo*-hexopyranose (17). A solution of **15** (1.34 g, 3.5 mmol) in pyridine (11 mL) was treated with Ac_2O (0.5 mL, 5.3 mmol) conventionally to give **17** as a syrup (1.31 g, α-L:*β*-L 7:3, 88%); ^{1}H NMR ($CDCl_3$) δ (selected signals only) 1.96−2.13 [m, 1H, H-2eq (α- and *β*-L-anomer)], 2.07 [s, 2.1H, Ac(α)], 2.11 [s, 0.9H, Ac(*β*)], 2.31 [dt, J = 12, 12, and 10.5 Hz, 0.3H, H-2ax-(*β*)], 2.45 [ddd, J = 13.5, 12, and 3.5 Hz, 0.7H, H-2ax(α)], 5.71 [dd, J = 10.5 and 2.5 Hz, 0.3H, H-1(*β*)], 6.38 [br d, J = 3.5 Hz, 0.7H, H-1(α)]; ^{19}F NMR ($CDCl_3$) δ −74.1 [d, J = 6.5 Hz, 2.1F, CF_3(α)], −73.5 [d, J = 6.5 Hz, 0.9F, CF_3(*β*)]. Anal. ($C_{22}H_{23}F_3O_5$) C, H, F.

1-*O*-Acetyl-2,6-dideoxy-6,6,6-trifluoro-L-*lyxo*-hexopyranose (18). A solution of **17** (1.31 g) in 10:1 aqueous 90% 1,4-dioxane/AcOH (25 mL) was hydrogenated in the presence of Pd black under gentle bubbling of H_2 for 5 h at room temperature. Filtration followed by evaporation of the solvents with toluene gave **18** as a syrup (736 mg, 98%), which was precipitated from the EtOAc solution by addition of hexane to give a solid: ^{1}H NMR (CD_3OD) δ 1.99 [s, 2.1H, Ac(α-L)], 2.00 [s, 0.9H, Ac(*β*-L)], 1.66−2.12 [m, 2H, H-2ax(α),2eq(α),2ax(*β*), 2eq(*β*)], 3.72 [ddd, J = 11.5, 5.5, and 3 Hz, 0.3H, H-3(*β*)], 3.82−4.00 [m, 1.7H, H-3(α),4(α),4(*β*)], 4.19 (br d, J = 7 Hz, 1H, H-5), 5.66 [dd, J = 10 and 3 Hz, 0.3H, H-1(*β*)], 6.15 [br d, J = 3.5 Hz, 0.7H, H-1(α)]; ^{19}F NMR (CD_3OD) δ −73.9 [d, J = 7 Hz, 2.1F, CF_3(α)], −73.4 [d, J = 7 Hz, 0.9F, CF_3(*β*)]. Anal. ($C_8H_{11}F_3O_5$) C, H, F.

1,3,4-Tri-*O*-acetyl-2,6-dideoxy-6,6,6-trifluoro-L-*lyxo*-hexopyranose (19). A solution of **18** (0.74 g, 3.0 mmol) and Ac_2O (0.7 mL, 7.4 mmol) in pyridine (6 mL) was kept for 15 h at room temperature. Conventional processing gave **19** as a syrup (0.99 g, quantitative); TLC (CH_2Cl_2): R_f 0.35(α) and 0.2-(*β*). Analytical samples were obtained by chromatographic separation using CH_2Cl_2.

α-L-Anomer (solid): mp 91.5−92.5 °C; $[\alpha]^{19}_D$ −100° (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.94 (ddt, J = 13.5, 5, 1.5, and 1.5 Hz, 1H, H-2eq), 2.02, 2.14, and 2.15 (each s of 3H, Ac), 2.32 (ddd, J = 13.5, 12.5, and 3.5 Hz, 1H, H-2ax), 4.36 (br q, J = 6 Hz, 1H, H-5), 5.28 (ddd, J = 12.5, 5, and 3 Hz, 1H, H-3), 5.66 (m, 1H, H-4), 6.44 (br d, J = 3.5 Hz, 1H, H-1); ^{19}F NMR ($CDCl_3$) δ −75.0 (d, J = 6 Hz, CF_3). Anal. ($C_{12}H_{15}F_3O_7$) C, H, F.

β-L-Anomer (syrup): $[\alpha]^{22}_D$ −26° (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H, Ac), 2.16 (s, 6H, 2Ac), 1.99−2.25 (m, 2H, H-2ax,2eq), 4.05 (dq, J = 6 and ~1 Hz, 1H, H-5), 5.06 (ddd, J = 12.5, 5, and 3 Hz, 1H, H-3), 5.58 (br d, J = 5 Hz, 1H, H-4), 5.85 (dd, J = 10 and 2.5 Hz, 1H, H-1); ^{19}F NMR ($CDCl_3$) δ −74.4 (d, J = 6 Hz, CF_3).

3,4-Di-*O*-acetyl-2,6-dideoxy-6,6,6-trifluoro-α-L-*lyxo*-hexopyranosyl Bromide (20). A solution of **19** (89 mg, 0.27 mmol) in 30% HBr in AcOH (0.9 mL) was kept for 5 h at room temperature. $CHCl_3$ (15 mL) was added, and the solution was washed with aqueous $NaHCO_3$ (saturated) and water, dried ($MgSO_4$), and concentrated to give **20** as a pale yellow syrup (85 mg, 90%), which was used without purification: TLC R_f 0.6 (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.02 and 2.14 (each s of 3H, Ac), 2.30 (ddt, J = 13.5, 5, 1, and 1 Hz, 1H, H-2eq), 2.64 (ddd, J = 13.5, 12, and 4 Hz, 1H, H-2ax), 4.56 (br q, J = 6.5 Hz, 1H, H-5), 5.47 (ddd, J = 12, 5, and 3 Hz, 1H, H-3), 5.72 (m, 1H, H-4), 6.72 (br d, J = 4 Hz, 1H, H-1); ^{19}F NMR ($CDCl_3$) δ −74.3 (d, J = 6.5 Hz, CF_3).

14-*O*-(*tert*-Butyldimethylsilyl)-7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-6,6,6-trifluoro-α- and -*β*-L-*lyxo*-hexopyranosyl)-adriamycinone (21 and 22). A mixture of **20** (85 mg, 0.24 mmol) and 14-*O*-(*tert*-butyldimethylsilyl)adriamycinone[23] (142 mg, 0.27 mmol) in dry $Cl(CH_2)_2Cl$ (4 mL, freshly distilled from CaH_2) was stirred in the dark in the presence of yellow HgO (498 mg, 2.3 mmol), $HgBr_2$ (174 mg, 0.48 mmol), and molecular sieves 3A (700 mg) for 15 h at room temperature. After addition of $CHCl_3$, the mixture was filtered through a pad of Celite, which was thoroughly washed with $CHCl_3$, and the filtrates combined were washed successively with aqueous 30% KI, aqueous $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. TLC (10:1 toluene/Me_2CO) of the residue showed three spots at R_f 0.17 (an adriamycinone derivative), 0.25 (**22**), and 0.28 (**21**). Separation of the products by twice column chromatography (10:1 toluene/Me_2CO → 30:1 $CHCl_3$/Me_2CO) gave **21** (50 mg, 26%) and **22** (49 mg, 25%) as red solids. Analytical samples of each compound were obtained by reprecipitation from $CHCl_3$/hexane.

Compound **21**: $[\alpha]^{22}_D$ +202° (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.13 and 0.15 (each s of 3H, $SiMe_2$), 0.96 (s, 9H, ^{t}Bu), 1.93 (br dd, J = 12.5 and 5 Hz, 1H, H-2′eq), 1.95 and 2.15 (each s of 3H, 2Ac), 2.20 (dt, J = 12.5, 12.5, and 3.5 Hz, 1H, H-2′ax), 2.22 (dd, J = 15 and 4.5 Hz, 1H, H-8ax), 2.41 (ddd, J = 15, 2.5, and 1.5 Hz, 1H, H-8eq), 3.02 (d, J = 19 Hz, 1H, H-10ax), 3.22 (dd, J = 19 and 1.5 Hz, 1H, H-10eq), 3.84 (s, 1H, HO-9), 4.09 (s, 3H, OMe), 4.55 (br q, J = 6.5 Hz, 1H, H-5′), 4.79 and 4.87 (each d of 1H, J = 19.5 Hz, H-14a,14b), 5.06 (ddd, J = 12.5, 5, and 3 Hz, 1H, H-3′), 5.26 (dd, J = 4.5 and 2.5 Hz, 1H, H-7), 5.65 (br d, J = 3 Hz, 1H, H-4′), 5.73 (br d, J = 3.5 Hz, 1H, H-1′), 7.40 (dd, J = 8.5 and ~1 Hz, 1H, H-3), 7.79 (apparently t, J = 8.5 and 7.5 Hz, 1H, H-2), 8.03 (dd, J = 7.5 and ~1 Hz, 1H, H-1), 13.20 and 13.98 (each s of 1H, HO-6,11); ^{19}F NMR ($CDCl_3$) δ −74.6 (d, J = 6.5 Hz, CF_3). Anal. ($C_{37}H_{43}F_3O_{14}Si\cdot0.5H_2O$) C, H, F.

Compound **22**: $[\alpha]^{23}_D$ +247° (*c* 0.1, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 0.16 and 0.18 (each s of 3H, $SiMe_2$), 1.06 (s, 9H, ^{t}Bu), 1.52 and 1.67 (each s of 3H, 2Ac), 1.68 (m, 1H, H-2′eq), 1.91 (dd, J = 15 and 3.5 Hz, 1H, H-8ax), 1.93 (dt, J = 12.5, 12.5, and 10 Hz, 1H, H-2′ax), 2.25 (br d, J = 15 Hz, 1H, H-8eq), 3.04 (dq, J = 6, 6, 6, and ~1 Hz, 1H, H-5′), 3.25 (d, J = 19.5 Hz, 1H, H-10ax), 3.32 (s, 3H, OMe), 3.33 (br d, J = 19.5 Hz, 1H, H-10eq), 4.60 (s, 1H, HO-9), 4.62 (dd, J = 10 and 2.5 Hz, 1H, H-1′), 4.69 (ddd, J = 12.5, 5, and 3 Hz, 1H, H-3′), 4.96 and 5.11 (each d of 1H, J = 20 Hz, H-14a,14b), 5.24 (dd, J = 3.5 and 2.5 Hz, 1H, H-7), 5.45 (br d, J = 3 Hz, 1H, H-4′), 6.50 (dd, J = 8.5 and ~1 Hz, 1H, H-3), 7.02 (apparently t, J = 8.5 and 8 Hz, 1H, H-2), 7.94 (dd, J = 8 and ~1 Hz, 1H, H-1), 13.51 and 14.68 (each s of 1H, HO-6,11); ^{19}F NMR (C_6D_6) δ −73.8 (d, J = 6 Hz, CF_3). Anal. ($C_{37}H_{43}F_3O_{14}Si\cdot0.5H_2O$) C, H, F.

7-*O*-(2,6-Dideoxy-6,6,6-trifluoro-α-L-*lyxo*-hexopyranosyl)adriamycinone (3). To a suspension of **21** (40 mg, 50 *μ*mol) in dry MeOH (3.6 mL) was added methanolic 0.25 M MeONa (0.13 mL, 32 *μ*mol), and the mixture was stirred for 2.5 h at room temperature. After a piece of dry ice was added, and the mixture was concentrated. The residue was extracted with $CHCl_3$, and the product [TLC (1:1 toluene/Me_2CO) R_f 0.55] dissolved in aqueous 80% AcOH (1 mL) was kept for 40 min at 80 °C. Concentration together with toluene gave a residue, which was washed alternately with water and toluene and dried to give **3** as a dark red solid (21 mg, 69%): $[\alpha]^{21}_D$ +188° (*c* 0.02, pyridine); TLC R_f 0.35 (1:1 toluene/Me_2CO); ^{1}H NMR (500 MHz, pyridine-d_5) δ 2.40 (br dd, J = 12 and 4.5 Hz, 1H, H-2′eq), 2.50 (dd, J = 14.5 and 5 Hz, 1H, H-8ax), 2.72 (dt, J = 12, 12, and 3.5 Hz, 1H, H-2′ax), 2.99 (apparently dt, J = 14.5, 2.5, and 1.5 Hz, 1H, H-8eq), 3.44 (d, J = 19 Hz, 1H, H-10ax), 3.55 (dd, J = 19 and 1.5 Hz, 1H, H-10eq), 3.96 (s, 3H, OMe), 4.51 (br dt, J = 12, ~4, and ~4 Hz, 1H, H-3′), 4.53 (br s, 1H, H-4′), 5.25 (br q, J = 7 Hz, 1H, H-5′), 5.37 and 5.42 (each d of 1H, J = 20 Hz, H-14a,14b), 5.42 (dd, J = 5 and 2.5 Hz, 1H, H-7), 5.95 (br d, J = 3.5 Hz, 1H, H-1′), 6.55 (br s, 2H, 2OH), ~7.1 (v br, 1H, OH), 7.41 (br d, J = 8 Hz, 1H, H-3), 7.71 (t, J = 8 Hz, 1H, H-2), 8.06 (br d, J = 8 Hz, 1H, H-1), 13.53 and 14.58 (each s of 1H, HO-6,11); ^{19}F NMR (pyridine-d_5) δ −72.2 (d, J = 7 Hz, CF_3); ^{13}C NMR (pyridine-d_5) δ 33.5 (C-10), 34.3 (C-2′), 37.2 (C-8), 56.6 (OCH_3), 65.3 (C-3′), 65.7 (C-14), 67.3 (C-4′), 71.0 (q, J = 30 Hz, C-5′), 71.9 (C-7), 76.3 (C-9), 103.2 (C-1′), 111.5 and 111.8 (C-5a,11a), 119.5 (C-3), 119.6 (C-1), 121.2 (C-4a), 125.6 (q, J = 281 Hz, C-6′), 134.7, 135.6, and

135.8 (C-6a,10a,12a), 136.0 (C-2), 155.6 and 157.1 (C-6,11), 161.5 (C-4), 187.1 (C-5,12), 215.2 (C-13). Anal. ($C_{27}H_{25}F_3O_{12}$) C, H, F.

Cell Growth Inhibitory Measurements *in Vitro*. K 562 human leukemia, HMV-1 human melanoma, KB human nasopharyngeal carcinoma, MKN-1 human gastric adenocarcinoma, PC-14 human lung carcinoma, T24 human bladder carcinoma, and P388 murine leukemia cells were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum, and DOX-resistant P388 cells (P388/ADR) were cultured in a medium containing 2-hydroxyethyl disulfide additionally added. Compound **3** (1 mg) and DOX·HCl (1 mg) were dissolved respectively in DMSO (1 mL) and water (1 mL), and each solution was diluted with RPMI 1640 medium to a concentration of 5−0.0098 μg/mL. The cultured cells, after addition of each of the above solutions, were allowed to proliferate in an incubator under the atmosphere of 5% CO_2 and 95% air in 100% relative humidity at 37 °C for 72 h, and the cell densities were measured using a MTT colorimetric method[47] to give the drug concentration inhibiting 50% cellular growth (IC_{50}, μg/mL).

Antitumor Activity *in Vivo*. L1210 murine leukemia cells (10^5) were innoculated into female CDF_1 mice (5 weeks old, 20 ± 1 g) intraperitoneally, and then compound **3**, which was previously suspended in 5% DMSO in physiological saline and diluted with the same saline, or DOX·HCl in saline was administered intraperitoneally to each experimental group containing four mice, daily, starting 24 h after inoculation, for 9 consecutive days. Mortality was checked daily for 60 days. The control group with four mice was treated similarly by replacing the drug solution with the neat saline. Antitumor activity (T/C, %) was determined by the ratio of the median survival time of the treated (T) and control (C) mice.

Acknowledgment. We are grateful to Pharmaceutical Research Center of Meiji Seika Co., Ltd. for carrying out the bioassay for Table 1. We also express deep thanks to Ms. Chisato Nosaka of IMC for antitumor assay *in vivo*.

References

(1) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. Calichemicins, a Novel Family of Antitumor Antibiotics. 1. Chemistry and Partial Structure of Calichemicin γ_1^I. *J. Am. Chem. Soc.* **1987**, *109*, 3464−3466.

(2) Wall, M. E.; Wani, M. C. Antitumor and Topoisomerase I Inhibition Activity of Camptothecin and Its Analogs. In *Economic and Medicinal Plant Research, Vol. 5*; Wagner, H., Farnsworth, N. R., Eds.; Academic Press: London, 1991; pp 111−127.

(3) (a) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. Dynemicin A, a Novel Antibiotic with the Anthraquinone and 1,5-Diyn-3-ene Subunit. *J. Antibiot.* **1989**, *42*, 1449−1452. (b) Shiomi, K.; Iinuma, H.; Naganawa, H.; Hamada, M.; Hattori, S.; Nakamura, H.; Takeuchi, T.; Iitaka, Y. New Antibiotic Produced by *Micromonospora globosa*. *J. Antibiot.* **1990**, *43*, 1000−1005.

(4) Konishi, M.; Ohkuma, H.; Saitoh, K.; Kawaguchi, H.; Golik, J.; Dubay, G.; Groenewold, G.; Krishnan, B.; Doyle, T. W. Esperamicins, a Novel Class of Potent Antitumor Antibiotics I. Physico-Chemical Data and Partial Structure. *J. Antibiot.* **1985**, *38*, 1605−1609.

(5) Doyle, T. W. The Chemistry of Etoposide. In *Etoposide (VP-16), Current Status and New Developments;* Issel B. F., Muggia, F. M., Carter S. K., Eds.; Academic Press: Orlando, 1984; pp 15−32.

(6) Rowinsky, E. K.; Wright, M.; Monsarrat, B.; Lesser, G. J.; Donehower, R. C. Taxol: Pharmacology, Metabolism and Clinical Implications. In *Cancer Surveys Volume 17: Pharmacokinetics and Cancer Chemotherapy*; Workman, P., Graham, M. A., Eds.; Cold Spring Harbor Laboratory Press: New York, 1993; pp 283−304.

(7) Arcamone, F. *Doxorubicin Anticancer Antibiotics*; Academic Press: New York, 1981; pp 163−299.

(8) Naff, M. B.; Plowman, J.; Narayanan, V. L. Anthracyclines in the National Cancer Institute Program. In *Anthracycline Antibiotics*; El Khadem, H. S., Ed.; Academic Press: New York, 1982; pp 1−57.

(9) Arcamone, F.; Cassinelli, G.; Penco, S. Recent Developments in the Chemistry of Doxorubicin-Related Anthracycline Glycosides. In *Anthracycline Antibiotics*; El Khadem, H. S., Ed.; Academic Press: New York, 1982; pp 59−73.

(10) Acton, E. M.; Mosher, C. W.; Gruber, J. M. Approaches to More Effective Anthracyclines by Analog Synthesis and Evaluation. In *Anthracycline Antibiotics*; El Khadem, H. S., Ed.; Academic Press: New York, 1982; pp 119−139.

(11) Horton, D.; Priebe, W. Glycon- and C-14-Modified, Antitumor Doxorubicin Analogs. In *Anthracycline Antibiotics*; El Khadem, H. S., Ed.; Academic Press: New York, 1982; pp 197−224.

(12) Arcamone, F.; Penco, S. Synthesis of New Doxorubicin Analogs. In *Anthracycline and Anthracenedione-Based Anticancer Agents*; Lown, J. W., Ed.; Elsevier: Amsterdam, 1988; pp 1−53.

(13) Acton, E. M.; Wasserman, K.; Newman, R. Morpholinyl Anthracyclines. In *Anthracycline and Anthracendione-Based anticancer Agents*; Lown, J. W., Ed.; Elsevier: Amsterdam, 1988; pp 55−101.

(14) Tone, H.; Takeuchi, T. Aclarubicin and Pirarubicin: Basic Research. In *Antitumor Natural Products*; Takeuchi, T., Nitta, K., Tanaka, N., Eds.; Japan Scientific Societies Press: Tokyo, 1989; pp 95−108.

(15) Suarato, A.; Angelucci, F.; Bargiotti, A. Antitumor Anthracyclines. *Chimicaoggi* **1990**, *8*, 9−19.

(16) Acton, E. M. Unresolved Structure-Activity Relationships in Anthracycline Analogue Development. In *Anthracycline Antibiotics: New Analogues, Methods of Delivery, and Mechanisms of Action*; Priebe, W., Ed.; American Chemical Society: Washington, DC, 1995; pp 1−13.

(17) Priebe, W.; Skibicki, P.; Varela, O., Neamati, N.; Sznaidman. M.; Dziewiszek, K.; Grinkiewicz, G.; Horton, D.; Zou, Y.; Ling, Y.-H.; Perez-Solar, R. Non-Cross-Resistant Anthracyclines with Reduced Basicity and Increased Stability of the Glycosidic Bond. In *Anthracycline Antibiotics: New Analogues, Methods of Delivery, and Mechanisms of Action*; Priebe, W., Ed.; American Chemical Society: Washington, DC, 1995; pp 14−46.

(18) Guidi, A.; Canfarini, F.; Giolitti, A.; Pasqui, F.; Pestellini, V.; Arcamone, F. Fluorinated Anthracyclinones and Their Glycosylated Products. In *Anthracycline Antibiotics: New Analogues, Methods of Delivery, and Mechanisms of Action*; Priebe, W., Ed.; American Chemical Society: Washington, DC, 1995; pp 47−58.

(19) Kolar, C.; Bosslet, K.; Czech, J.; Gerken, M.; Hermentin, P.; Hoffmann, D., Sedlacek, H.-H. Semisynthetic Rhodomycins and Anthracycline Prodrugs. In *Anthracycline Antibiotics: New Analogues, Methods of Delivery, and Mechanisms of Action*; Priebe, W., Ed.; American Chemical Society: Washington, DC, 1995; pp 59−77.

(20) Monneret, C.; Florent J.-C.; Gesson J.-P.; Jacquesy J.-C.; Tillequin, F.; Koch, M. Synthetic Options for Reversal of Anthracycline Resistance and Cardiotoxicity. In *Anthracycline Antibiotics: New Analogues, Methods of Delivery, and Mechanisms of Action*; Priebe, W., Ed.; American Chemical Society: Washington, DC, 1995; pp 78−99.

(21) Tsuchiya, T.; Takagi, Y. Synthesis and Biological Activities of Fluorinated Daunorubicin and Doxorubicin Analogues. In *Anthracycline Antibiotics: New Analogues, Methods of Delivery, and Mechanisms of Action*; Priebe, W., Ed.; American Chemical Society: Washington, DC, 1995; pp 100−114.

(22) Suarato, A.; Angelucci, F.; Bargiotti, A.; Caruso, M.; Faiardi, D.; Capolongo, L.; Geroni, C.; Ripamonti, M.; Grandi, M. Synthesis and Study of Structure−Activity Relationships of New Classes of Anthracyclines. In *Anthracycline Antibiotics: New Analogues, Methods of Delivery, and Mechanisms of Action*; Priebe, W., Ed.; American Chemical Society: Washington, DC, 1995; pp 142−155.

(23) Horton, D.; Priebe, W.; Varela, O. Synthesis and Antitumor Activity of 3′-Deamino-3′-hydroxydoxorubicin. A Facile Procedure for the Preparation of Doxorubicin Analogs. *J. Antibiot.* **1984**, *37*, 853−858.

(24) Tsuchiya, T.; Takagi, Y.; Ok, K.-D.; Umezawa, S.; Takeuchi, T.; Wako, N.; Umezawa, H. Synthesis and Antitumor Activities of 7-*O*-(2,6-Dideoxy-2-fluoro-α-L-talopyranosyl)-daunomycinone and -adriamycinone. *J. Antibiot.* **1986**, *39*, 731−733.

(25) Ok, K.-D.; Takagi, Y.; Tsuchiya, T.; Umezawa, S.; Umezawa, H. Synthesis of Antitumor-active 7-*O*-(2,6-Dideoxy-2-fluoro-α-L-talopyranosyl)-daunomycinone and -adriamycinone. *Carbohydr. Res.* **1987**, *169*, 69−81.

(26) During our synthesis, Horton *et al.* reported studies, substantially on the same lines as ours, on the preparation of daunorubicin and doxorubicin analogs having a halogen atom (X = I, Br, and Cl) at C-2′, which exhibited antitumor activity. (a) Horton, D.; Priebe, W.; Varela, O. Synthesis of Antitumor-active (7*S*,9*S*)-4-Demethoxy-7-*O*-(2,6-dideoxy-2-iodo-α-L-mannopyranosyl)adriamycinone: Preparative Resolution of a Racemic Anthracyclinone by Alkoxyhalogenation of a Glycal. *Carbohydr. Res.* **1984**, *130*, C1−C3. (b) Horton, D.; Priebe, W. Oxyhalogenation of Glycals for the Synthesis of Antitumor-active 2′-Halo

Daunorubicin Analogs. *Carbohydr. Res.* **1985**, *136*, 391−396. (c) Horton, D.; Priebe, W.; Varela, O. Synthesis and Antitumor Activity of 2′-Bromo- and 2′-Chloro-3′-acetoxy-3′-deaminodaunorubicin Analogs. *Carbohydr. Res.* **1985**, *144*, 305−315.

(27) Kunimoto, S.; Komuro, K.; Nosaka, C.; Tsuchiya, T.; Fukatsu, S.; Takeuchi, T. Biological Activities of New Anthracyclines Containing Fluorine, FAD104 and its Metabolites. *J. Antibiot.* **1990**, *43*, 556−565.

(28) Takagi, Y.; Sohtome, H.; Tsuchiya, T.; Umezawa, S.; Takeuchi, T. Synthesis of 7-*O*-[2,6-Dideoxy-2-fluoro-4-*O*-(3-fluorotetrahydropyran-2-yl)-α-L-talopyranosyl]daunomycinone. *J. Antibiot.* **1992**, *45*, 355−362.

(29) Filler, R. Fluoromedicinal Chemistry - An Overview of Recent Developments. In *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications.* Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993; pp 1−22.

(30) Hanzawa, Y.; Uda, J.; Kobayashi, Y.; Ishido, Y.; Taguchi, T.; Shiro, M. Trifluoromethylation of Chiral Aldehyde and Synthesis of 6-Deoxy-6,6,6-trifluorohexoses. *Chem. Pharm. Bull.* **1991**, *39*, 2459−2461.

(31) Bansal, R. C.; Dean, B.; Hakomori, S.; Toyokuni, T. Synthesis of Trifluoromethyl Analogue of L-Fucose and 6-Deoxy-D-altrose. *J. Chem. Soc., Chem. Commun.* **1991**, 796−798.

(32) Differding, E.; Frick, W.; Lang, R. W.; Martin, P.; Schmit, C.; Veenstra, S.; Greuter, H. Fluorinated Heterocycles: Targets in the Search for Bioactive Compounds and Tools for Their Preparation. *Bull. Soc. Chim. Belg.* **1990**, *99*, 647−671.

(33) Yamazaki, T.; Mizutani, K.; Takeda, M.; Kitazume, T. Chiral Trifluoromethylated 2-Butenolides for the Construction of 6-Deoxy-6,6,6-trifluorosugars. *J. Chem. Soc., Chem. Commun.* **1992**, 55−57.

(34) Yamazaki, T.; Mizutani, K.; Kitazume, T. Preparation of 6-Deoxy-6,6,6-trifluoro-D-mannose and D-Allose from Enzymatically Resolved 2-Butenolides. *Tetrahedoron: Asymmetry* **1993**, *4*, 1059−1062.

(35) Yamazaki, T.; Mizutani, K.; Kitazume, T. Development of a Novel Pathway To Access 6-Deoxy-6,6,6-trifluorosugars via 1,2-Migration of a *tert*-Butyldimethylsilyl Group. *J. Org. Chem.* **1993**, *58*, 4346−4359.

(36) Mizutani, K.; Yamazaki, T.; Kitazume, T. Novel Stereoselective Syntheses of Chiral 2,6-Dideoxy-6,6,6-trifluoro Sugars *via* Enzymatic Resolution of Trifluoromethylated Propynylic Alcohol. *J. Chem. Soc., Chem. Commun.* **1995**, 51−52.

(37) Kent, P. W.; Ward, P. F. V. Synthesis of 4-Deoxy-L-ribose from D-Lyxose. *J. Chem. Soc.* **1953**, 416−418. The optical rotational value of methyl 4-*O*-(*p*-tolylsulfonyl)-α-D-lyxopyranoside (**4**) reported in this reference is incorrect. See ref 38.

(38) Verheijden, J. P.; Stoffyn, P. J. Synthesis of 2,3-Di-*O*-methyl-D-lyxose. *Tetrahedron* **1957**, *1*, 253−258.

(39) The optical rotation value of **5** in ref 37 is incorrect. See the Experimental Section.

(40) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. Fluoride-Induced Trifluoromethylation of Carbonyl Compounds with Trifluoromethyltrimethylsilane (TMS-CF_3). A Trifluoromethide Equivalent. *J. Am. Chem. Soc.* **1989**, *111*, 393−395.

(41) Albert, R.; Dax, K.; Link, R. W.; Stütz, A. E. Carbohydrate Triflates: Reaction with Nitrite, Leading Directly to Epi-hydroxy Compounds. *Carbohydr. Res.* **1983**, *118*, C5−C6.

(42) Mahrwald, R.; Theil, F.; Schick, H.; Schwarz, S.; Palme, H.-J.; Weber, G. The Oxidation of Primary Trimethylsilyl Ethers to Aldehydes−a Selective Conversion of a Primary Hydroxy Group into an Aldehyde Group in the Presence of a Secondary Hydroxy Group. *J. Prakt. Chem.* **1986**, *328*, 777−783.

(43) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. A Mild and General Method for the Synthesis of *O*-Glycosides. *J. Am. Chem. Soc.* **1983**, *105*, 2430−2434.

(44) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. Iodonium Promoted Reactions of Disarmed Thioglycosides. *Tetrahedron Lett.* **1990**, *31*, 4313−4316.

(45) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. New Glycosidation Reaction 1. Combinational Use of Cp_2ZrCl_2−$AgClO_4$ for Activation of Glycosyl Fluorides and Application to Highly β-Selective Glycosidation of D-Mycinose. *Tetrahedron Lett.* **1988**, *29*, 3567−3570.

(46) Takagi, Y.; Park H.; Tsuchiya, T.; Umezawa, S. Syntheses and Antitumor Activities of 7-*O*-(3-Amino-2,3,6-trideoxy-2-fluoro-α-L-talopyranosyl)-daunomycinone and -adriamycinone. *J. Antibiot.* **1989**, *42*, 1315−1317.

(47) Alley, M. C.; Scudiero, D. A.; Monks, A.; Hursey, M. L.; Czerwinski, M. J.; Fine, D. L.; Abbott, B. J.; Mayo, J. G.; Shoemaker, R. M.; Boyd, M. R. Feasibility of Drug Screening with Panels of Human Tumor Cell Lines Using a Microculture Tetrazolium Assay. *Cancer Res.* **1988**, *48*, 589−601.

JM960177X