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SYNTHESIS OF ANTITUMOR-ACTIVE 7-*O*-(2,6-DIDEOXY-2-FLUORO-α-L-TALOPYRANOSYL)-DAUNOMYCINONE AND -ADRIAMYCINONE*†

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ABSTRACT

The title compounds (**17** and **23**) were prepared by coupling 3,4-di-*O*-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranosyl bromide (**15**) with daunomycinone. The key step in the preparation of **15** was the epoxide-ring opening of methyl 2,3-anhydro-4-*O*-benzyl-6-deoxy-α-L-gulopyranoside with KHF_2 in ethylene glycol, whereupon 2-fluoro-α-L-idopyranoside was obtained. Compounds **17** and **23** showed strong antitumor activity.

INTRODUCTION

The anthracycline glycosides exemplified by adriamycin are clinically important antitumor antibiotics. However, their use is restricted by their cardiotoxic character and other undesirable side-toxicities, as well as by the occurrence of resistance in the tumor cells after repeated medication. Asbell *et al.*[2,3] reported that the glycoside linkages of daunorubicin and adriamycin are cleaved anaerobically by rat-liver and -kidney homogenates to afford 7-deoxyanthracyclinones. If this process occurs during clinical use, the antitumor antibiotics would be inactivated, giving the undesirable and possibly cardiotoxic[4] 7-deoxyanthracyclinones. Derivatives resistant to such a biological transformation are thus of interest.

Introduction of an electron-attracting group at C-2′ of the antibiotics is expected to strengthen the glycosidic bond chemically. However, if the mechanism proposed[5] for the foregoing glycoside cleavage[2,3], beginning with one-electron donation to the carbonyl group at C-12, is correct, such a modifiation would result

*Dedicated to Dr. R. Stuart Tipson. The early stage of manufacture of Dibekacin, the first commercially successful, chemically modified aminoglycoside antibiotic, active against resistant bacteria, was achieved by use of the Tipson–Cohen method [*Carbohydr. Res.*, 1 (1965) 338] developed by Horton *et al.* [*Carbohydr. Res.*, 2 (1966) 349] for deoxygenation of a *trans*-diequatorial diol in a pyranoside ring, to effect the 3′,4′-unsaturation of kanamycin B, the key step for the prepration.

†For a preliminary report, see ref. 1.

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in a reverse effect by accelerating the cleavage because of the electron-withdrawing property of the 2′-functional group.

To clarify this question, we undertook the introduction of fluorine at C-2′ of adriamycin. Fluorine is the most electronegative of all atoms (thus offering the most clear conclusion to the question on the effect of an electron-attracting group), and has a small van der Waals radius; the latter property permits preparation of an adriamycin analogue the least-changed around C-2′ in terms of stereochemistry.

Horton *et al.*[6–10] reported that replacement of the 3′-amino group of daunorubicin and adriamycin by a hydroxyl group gave fairly good antitumor derivatives having weak toxicity. This finding indicates that the 3′-amino group is not essential for antitumor activity. El Khadem *et al.*[11] prepared a similar 3′-hydroxy compound, 2,6-dideoxy-α-L-*lyxo*-hexopyranosyl-ε-rhodomycinone, but reported it to be inactive. We thus changed our synthetic target to 3′-deamino-2′-fluoro-3′-hydroxyadriamycin from 2′-fluoroadriamycin. During our synthesis, Horton *et al.*[12] reported a stimulating study, substantially on the same line as ours, in preparing 4-demethoxy-7-*O*-(2,6-dideoxy-2-iodo-α-L-mannopyranosyl)adriamycinone having antitumor activity, and found[12–14] that all derivatives having C(2′*R*)-halo and C(2′*S*)-halo (X = Cl, Br, and I) substituents are active and inactive, respectively. This result indicates that the orientation of the substituent at C-2′ is an important factor.

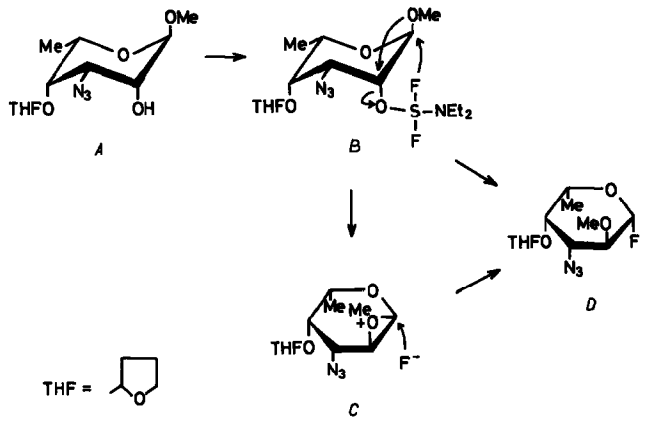
Considering these results, we set out to prepare, for the first candidate, 3′-deamino-2′-(*R*)-fluoro-3′-hydroxyadriamycin, that is, 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)adriamycinone (**23**), from L-fucose and daunomycinone.

RESULTS AND DISCUSSION

Chemical synthesis. — (2*S*)-Fluorodaunosamine and its derivatives have been prepared[15–18] by several groups, but the corresponding (2*R*)-fluoro isomer has not been reported. Butchard and Kent[19] prepared a (2*R*)-fluoro compound, 2-deoxy-2-fluoro-L-rhamnose, from di-*O*-acetyl-L-rhamnal by treatment with CF_3OF, and recently Baptistella *et al.*[20] reported the synthesis of methyl 3-acetamido-4-*O*-benzoyl-2,3,6-trideoxy-2-fluoro-β-L-mannopyranoside.

Before commencing our present study, we carried out an experiment[21] to introduce fluorine at C-2 of methyl 3-azido-3,6-dideoxy-4-*O*-tetrahydrofuranyl-α-L-talopyranoside (*A*) with diethylaminosulfur trifluoride (DAST) in dichloromethane, but the desired 2-fluoro-L-*galacto* compound was not obtained; instead a compound presumed to be the 1-fluoro-2-*O*-methyl derivative (*D*) was produced, possibly via *B* or the 1,2-anhydrooxonium intermediate[22] (*C*). This indicated that introduction of fluorine at C-2 by an SN2 reaction would not be easy as compared with the introduction of the other halogens. Thus we decided to introduce (2*R*)-fluorine through 2,3-epoxide-ring opening.

Methyl 3,4-*O*-isopropylidene-α-L-fucopyranoside[23] (**1**) was prepared from an anomeric mixture of methyl L-fucosides by treatment with 2,2-dimethoxypropane;



1 was readily separated chromatographically from the accompanying methyl 3,4-*O*-isopropylidene-β-L-fucopyranoside[24] (**2**). After acetylation[25] (to give **3**) and subsequent deacetonation[25], the 3,4-diol[25] (**4**) was tosylated to give the 3-sulfonate **5** in high yield. The selective tosylation at the equatorial HO-3 of **4** was proved by the chemical shift of H-3 (δ 4.94), which is ~1 p.p.m. lower than that of **4**. Alkaline treatment of **5** to form a 2,3-epoxide gave a mixture, possibly by equilibrium of the first-produced L-*gulo*-2,3-epoxide with the L-*galacto*-3,4-epoxide formed by epoxide migration. Therefore, HO-4 of **5** was protected by benzylation. Benzylation with α-bromotoluene and silver oxide (or NaH) gave a complex mixture, but the reaction performed with benzyl trichloroacetimidate[26] under slightly acidic conditions successfully gave **6**. Treatment of the 4-*O*-benzyl derivative **6** with sodium methoxide in methanol gave the L-*gulo*-2,3-epoxide (**7**) *via* the deacetyl intermediate. The ^{1}H-n.m.r. spectrum established the structure of **7** by the shifts of H-2 and H-3 (δ 3.3–3.4), and by the small-coupling constants ($J_{1,2}$, $J_{2,3}$, and $J_{3,4}$) relating them, typical for 2,3-epoxypyranosides.

Fluorination of **7** with epoxide-ring opening was only successful when potassium hydrogenfluoride (KHF_2) in ethylene glycol was used. A rather high reaction-temperature (180°, 3 h) was also necessary. The 2-fluoro-L-idopyranoside **8** was obtained in moderate yield (44%). Use of such other fluorinating agents as tetrabutylammonium fluoride and such solvents as *N,N*-dimethylformamide (DMF) and hexamethylphosphoric triamide gave **8** in poor yield or not at all. The structure of **8** was proved by its ^{1}H-n.m.r. spectrum. As the H-1 and H-2 signals appeared as a double doublet ($J_{H\text{-}1,H\text{-}2}$ 3 and $J_{H\text{-}1,F\text{-}2}$ 9 Hz) and a multiplet ($J_{H\text{-}2,F\text{-}2}$ 47.5, $J_{H\text{-}2,H\text{-}3}$ 5, and $J_{H\text{-}2,H\text{-}4}$ 0.5 Hz), respectively, it was concluded that fluorine had been introduced at C-2 to give the 2-fluoro-L-idoside (**8**). Had the fluorine been introduced at C-3 to give the 3-fluoro-L-galactoside having the $^1C_4$(L) conformation, the $J_{H\text{-}2a,H\text{-}3a}$ coupling should have been large and long-range coupling ($^4J_{H\text{-}2,H\text{-}4}$) would not have been observed. The structure of **8** was further confirmed by data for its 3-*O*-acetyl derivative (**9**).

Inversion of HO-3 in **8** was firstly performed by an oxidation–reduction sequence with the Pfitzner–Moffatt reagent[27] (to give the glycos-3-ulose, **10**) and sodium borohydride. However, in using the latter reagent, the resulting L-talopyranoside (**11**) was contaminated by a small amount of **8**, and these could not be separated by recrystallization (both are syrups) or by column chromatography (they have the same mobility). Use of lithium aluminum hydride, however, gave pure **11**; the ^{1}H-n.m.r. spectrum showed almost no signals attributable to **8**. This difference in behavior between the reagents could not be explained, but if the aluminum ion liberated during the reaction is assumed to form a chelate complex between F-2 and $C_6H_5CH_2O$-4, the approach of the hydride reagent from the α-side would be hindered and give **11**. The structure of **11** was confirmed by its ^{19}F- and ^{1}H-n.m.r. spectra[28]; a large coupling-constant of $J_{F\text{-}2,H\text{-}3}$ (31.5 Hz; compare that for **8**:11 Hz) and a small one for $J_{H\text{-}3,H\text{-}4}$ (4 Hz) indicate that both F-2 and H-3 are axially disposed, and H-4 is equatorial.

Compound **11** was then converted into the protected glycosyl bromide. Catalytic debenzylation of **11** (to give **12**) followed by acetylation with acetic anhydride in the presence of a catalytic amount of sulfuric acid in nitromethane gave an anomeric mixture of 1,3,4-tri-*O*-acetyl derivatives (**13** and **14**), which was separated by column chromatography. Structure assignments for the major **13** (α-L anomer) and minor **14** (β-L anomer) components were made from the $J_{H\text{-}1,F\text{-}2}$ coupling-constants[28] in their ^{1}H-n.m.r. spectra: **14** gave a large value (20 Hz) indicating the antiperiplanar relationship (*trans*-diaxial) between H-1 and F-2, whereas for **13**, a small value (8 Hz) indicates the gauche relationship. The major acetate (**13**) was converted in high yield into the corresponding α-L-bromide (**15**) by treatment with titanium tetrabromide in 1:10 ethyl acetate–dichloromethane.

Coupling of **15** with daunomycinone was performed by a Koenigs–Knorr type of reaction [yellow mercury(II) oxide, mercury(II) bromide, and molecular sieves in dichloromethane] to give the α-L-glycoside (**16**) in 82% yield. Formation of the β-L anomer was negligible. The anomeric configuration of **16** was established by the $J_{H\text{-}1',F\text{-}2'}$ coupling-constant (9.5 Hz), which is much smaller than that expected for the β-L anomer (~20 Hz). The position of coupling of the aglycon to the sugar was determined by comparison of the ^{13}C spectrum of **16** with that of daunorubicin, especially at C-7 (~70 p.p.m.). Alkaline treatment of **16** gave the desired deacetylated product, 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone (**17**), as a red solid.

Transformation of **17** into the corresponding final 14-hydroxy compound (**23**) was performed substantially according to Arcamone *et al.*[29]. Bromination of **17** at C-14 by using bromine in the presence of methyl orthoformate gave the 14-bromo-13-dimethyl acetal (**18**), which, on treatment with acetone, afforded the 14-bromo-3′,4′-isopropylidene acetal (**19**) accompanied by the corresponding 14-bromo-3′,4′-diol (**20**). Treatment of the product-mixture with sodium formate in aqueous acetone hydrolyzed the 14-bromide to give a mixture composed mainly of the 14-formyloxy-3′,4′-isopropylidene acetal (**21**) and the 14-hydroxy-3′,4′-isopropylidene

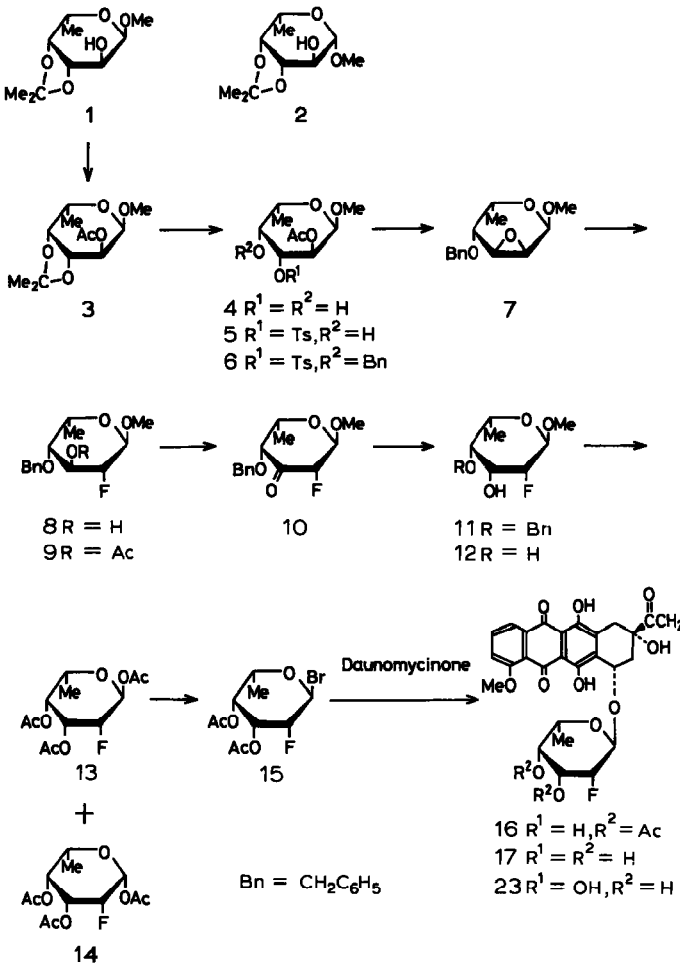

1
2
3
4 R1 = R2 = H
5 R1 = Ts, R2 = H
6 R1 = Ts, R2 = Bn
7
8 R = H
9 R = Ac
10
11 R = Bn
12 R = H
13
14
15
Daunomycinone
Bn = CH2C6H5
16 R1 = H, R2 = Ac
17 R1 = R2 = H
23 R1 = OH, R2 = H
17
18
19 R1 = Br, R2 = CMe2
20 R1 = Br, R2 = H, H
21 R1 = OCHO, R2 = CMe2
22 R1 = OH, R2 = CMe2
23

TABLE I

^{13}C-N.M.R. DATA[a] FOR COMPOUNDS **16**, **17**, AND **23**

C	16	17	23
1	119.9	119.6[b]	119.5
2	135.7	135.9[c]	135.9
3	118.8	119.5[b]	119.4
4	161.2	161.5	161.4
4a	119.9	121.2	120.9
5	186.8[b]	187.0[d]	186.9[b]
5a	111.56[c]	111.6[e]	111.4[c]
6	156.3[d]	*157.0*[f]	157.0[d]
6a	134.4[e]	135.6[c]	135.0[e]
7	69.0	72.1	72.01[f]
8	35.5	37.1	37.5
9	76.4	76.4	76.2
10	33.2	33.0	33.3
10a	135.5[e]	135.9[c]	135.4[e]
11	155.5[d]	155.6[f]	155.4[d]
11a	111.63[c]	111.8[e]	111.7[c]
12	186.6[b]	186.8[d]	186.8[b]
12a	133.2[e]	135.2[c]	134.7[e]
13	211.2	211.8	214.8
14	24.5	24.4	65.6
OMe	56.7	56.6	56.6
1′	101.3, 101.8	102.0, 102.5	102.1, 102.6
2′	83.7, 86.6	88.8, 91.6	88.8, 91.6
3′	66.7, 66.9	67.1, 67.4	67.1, 67.4
4′	71.6	72.1	71.96[f]
5′	66.2	68.3	68.3
6′	16.2	16.9	16.9
OCO*Me*	20.6, 20.7		
O*C*OMe	169.6, 170.9		
J (Hz)			
$J_{C\text{-}1',F}$	d, 31.5	d, 31.6	d, 31.5
$J_{C\text{-}2',F}$	d, 184.5	d, 176.2	d, 176.7
$J_{C\text{-}3',F}$	d, 15.4	d, 16.0	d, 16.1

[a]For solutions in $CDCl_3$ (**16**) and C_5D_5N (**17** and **23**). [b,c,d,e,f]Figures in the same column may be interconvertible.

acetal (**22**), with other minor products. Dissolving the mixture in a solvent containing aqueous ammonia readily hydrolyzed the 14-formate group to give mainly compound **22**. Subsequent deacetonation with aqueous acetic acid gave the final product (**23**) as a red solid in moderate (56%) yield from **17**. The structure of **23** was confirmed from its ^{19}F-, ^{1}H-, and ^{13}C-n.m.r. spectra. Compounds **17** and **23** were fairly stable in acidic media.

Throughout these studies, the structures of the fluorine-containing compounds were readily determined unambiguously[30] by the $J_{H,F}$ and $J_{C,F}$ values from their n.m.r. spectra (Table I), because they were larger and more stereosensitive than the $J_{H,H}$ coupling-constants.

Biological activity. — Compounds **17** and **23** showed strong antitumor activity[1] against leukemia L-1210 cells [T/C* for **17**: 217 and 184 at 2.5 and 5 mg/kg, respectively; for **23**: >352 and >740; for adriamycin: 228 and 191 (toxic)] and low toxicity in comparison to adriamycin.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler block, and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. N.m.r. spectra (^1H at 250 MHz, ^{13}C at 62.9 MHz, and ^{19}F at 235.3 MHz) were recorded in the F.t. mode with a Bruker WM 250 spectrometer. Chemical shifts (δ) are reported downfield from internal Me_4Si or Freon 11 ($CFCl_3$; for ^{19}F) and coupling constants (J by Hz) are first-order. T.l.c. was performed on Kieselgel 60 F_{254} (Merck), and column chromatography on Wakogel C-200.

Methyl 3,4-O-isopropylidene-α- and -β-L-fucopyranosides (**1** *and* **2**). — A solution of L-fucose (2.90 g) in methanolic 1% HCl (40 mL) was boiled under reflux for 8 h. After cooling, basic lead carbonate was added with vigorous stirring until the solution became neutral. Filtration followed by evaporation of the filtrate gave a residue that was thoroughly dried (3.04 g). A mixture of the residue, 2,2-dimethoxypropane (6.6 mL), and *p*-toluenesulfonic acid (870 mg of the monohydrate was dried *in vacuo* for 2 h at 100°) dissolved in DMF (40 mL, dried over 4Å molecular sieves) was kept for 2 h at room temperature. T.l.c. (2:1 hexane–Me_2CO) of the solution showed major (R_F 0.3) and minor spots (R_F 0.25) with additional faint spots. After most of the DMF had been evaporated *in vacuo,* the residue was dissolved in $CHCl_3$ and the solution was washed with aq. saturated $NaHCO_3$ dried ($MgSO_4$), and evaporated. The residual syrup was chromatographed over silica gel (250 g) with 2:1 hexane–Me_2CO to give **1** as a syrup, which crystallized on refrigeration (it showed no clear m.p. and melted below 30°); yield 2.28 g (59%), and **2** as a solid; yield 841 mg (22%).

Compound **1** had $[\alpha]_D^{26}$ −154° (*c* 1, $CHCl_3$) [lit.[23] $[\alpha]_D^{15}$ −160° (water)]; ^1H-n.m.r. ($CDCl_3$): δ 1.33 (d, 3 H, Me-5), 1.36 and 1.52 (each s, 3 H, CMe_2), 2.27 (d, 1 H, OH), 3.44 (s, 3 H, OMe), 3.79 (dt, 1 H, H-2), 4.05 (dd, 1 H, H-4), 4.10 (dq, 1 H, H-5), 4.19 (t, 1 H, H-3), and 4.72 (d, 1 H, H-1); $J_{1,2}$ 3.5, $J_{2,3}$ 6.5, $J_{2,OH}$ 6.5, $J_{3,4}$ 6, $J_{4,5}$ 2, and $J_{5,6}$ 6.5 Hz.

Compound **2** had m.p. 64–65° (needles from Et_2O–hexane), lit.[24] m.p. 58–62° (monohydrate), $[\alpha]_D^{26}$ −23° (*c* 1, $CHCl_3$) [lit.[24] $[\alpha]_D^{20}$ −21.7° ($CHCl_3$)]; ^1H-n.m.r. (C_6D_6): δ 1.35 (d, 3 H, Me-5), 1.27 and 1.48 (each s, 3 H, CMe_2), 3.00 (d, 1 H, OH), 3.32 (dq, 1 H, H-5), 3.34 (s, 3 H, OMe), 3.55 (dd, 1 H, H-4), 3.73 (ddd, 1

*Leukemia L-1210 cells (10^5) were inoculated into CDF_1 mice (20 ±1 g) intraperitoneally. Drugs were administered daily, starting 24 h after inoculation, from day 1 to 9, intraperitoneally. Survival studies were continued up to 60 days[1].

H, H-2), 3.88 (d, 1 H, H-1), and 4.00 (dd, 1 H, H-3); $J_{1,2}$ 8, $J_{2,3}$ 7, $J_{2,OH}$ 2.5, $J_{3,4}$ 5.5, and $J_{4,5}$ 2 Hz.

Methyl 2-O-acetyl-3,4-O-isopropylidene-α-L-fucopyranoside (**3**). — This compound had m.p. 101–102° (needles from Et_2O–hexane) [lit.[25] m.p. 100–101° (petroleum ether)], $[\alpha]_D^{26}$ −176° (*c* 1, $CHCl_3$) [lit.[25] $[\alpha]_D^{25}$ −230° (C_6H_6)].

Methyl 2-O-acetyl-α-L-fucopyranoside (**4**). — A solution of **3** (13.8 g) in aq. 80% AcOH (140 mL) was heated for 1 h at 80°. Evaporation gave a residue that was chromatographed over silica gel (300 g) with 1:2 hexane–Me_2CO to give **4** as a solid; yield 11.17 g (96%) (lit.[25], 63%), m.p. 77–78° (Et_2O–hexane) [lit.[25] 82–83° (C_6H_6–petroleum ether)], $[\alpha]_D^{26}$ −182° (*c* 2, $CHCl_3$) [lit.[25] $[\alpha]_D^{23}$ −196° ($CHCl_3$)].

Methyl 2-O-acetyl-3-O-p-tolylsulfonyl-α-L-fucopyranoside (**5**). — To a cold (−20°) solution of **4** (11.0 g) in C_5H_5N (200 mL) was added TsCl (13.3 g) and the solution was kept overnight with gradual raising of the temperature to ambient. T.l.c. (1:1 hexane–Me_2CO) of the solution showed a single major spot (R_F 0.5) with a slight spot (R_F 0.27) for **4**. After conventional processing, the crude product was purified by column chromatography on silica gel with 1:1 hexane–Me_2CO to give **5** as a solid; yield 16.25 g (87%), m.p. 118–120° (needles from Et_2O–hexane), $[\alpha]_D^{26}$ −136° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.30 (d, 3 H, Me-5), 1.79 (s, 3 H, Ac), 2.34 (dd, 1 H, *J* 4 and ~0.5 Hz, OH), 2.45 [s, 3 H, Ts(Me)], 3.34 (s, 3 H, OMe), 4.00 (br q, 1 H, H-5), 4.06 (br d, 1 H, H-4), 4.87 (d, 1 H, H-1), 4.94 (dd, 1 H, H-3), and 5.16 (dd, 1 H, H-2); $J_{1,2}$ 3.5, $J_{2,3}$ 10.5, and $J_{3,4}$ 3 Hz.

Anal. Calc. for $C_{16}H_{22}O_8S$: C, 51.33; H, 5.92; S, 8.56. Found: C, 51.41; H, 6.06; S, 8.65.

Methyl 2-O-acetyl-4-O-benzyl-3-O-p-tolylsulfonyl-α-L-fucopyranoside (**6**). — To a solution of **5** (159 mg) in 2:1 cyclohexane–CH_2Cl_2 (3.2 mL) were added benzyl trichloroacetimidate (214 mg, 2 molar equiv. for **5**) and trifluoromethanesulfonic acid (15 μL), and the mixture was stirred for 2 h at room temperature. T.l.c. (3:1 hexane–Me_2CO) of the mixture showed a major spot at R_F 0.35. $CHCl_3$ (50 mL) was added, and the solution was washed with aq. saturated $NaHCO_3$ dried ($MgSO_4$), and evaporated. Column chromatography (6:1 PhMe–EtOAc) of the residue gave **6** as a syrup; yield 164 mg (83%), $[\alpha]_D^{26}$ −101° (*c* 1.5, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.74 (s, 3 H, Ac), 2.44 [s, 3 H, Ts(Me)], 3.30 (s, 3 H, OMe), 4.61 and 4.93 (each d, 1 H, *J* 11 Hz, PhCH_2O).

Anal. Calc. for $C_{23}H_{28}O_8S$: C, 59.47; H, 6.08; S, 6.90. Found: C, 59.13; H, 6.10; S, 7.00.

Methyl 2,3-anhydro-4-O-benzyl-6-deoxy-α-L-gulopyranoside (**7**). — To a suspension of **6** (19.72 g) in MeOH (400 mL) was added methanolic 28% NaOMe (123 mL) and the mixture was stirred at room temperature. After 1 h the mixture showed (t.l.c., 3:1 hexane–Me_2CO) two spots having R_F 0.23 (deacetyl derivative) and 0.42 (**7**, compare **6**: R_F 0.35); after 4.5 h, only the spot of higher mobility was observed. After introduction of an excess of CO_2, the mixture was evaporated, and the residue was extracted with $CHCl_3$. The resultant crude product was then chromatographed on a column of silica gel with 3:1 hexane–Me_2CO to give **7** as a

syrup; yield 6.62 g (62%), $[\alpha]_D^{26}$ −25° (*c* 3, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.20 (d, 3 H, Me-5), 3.32 (dd, 1 H, H-3), 3.36 (t, 1 H, H-2), 3.58 (t, 1 H, H-4), 3.94 (dq, 1 H, H-5), 4.71 (s, 2 H, PhCH_2O), 4.95 (d, 1 H, H-1), and 7.25–7.45 (m, 5 H, Ph); $J_{1,2}$ 3, $J_{2,3}$ 3.5, $J_{3,4}$ 2, and $J_{4,5}$ 1.5 Hz.

Anal. Calc. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.91; H, 7.16.

Methyl 4-O-benzyl-2,6-dideoxy-2-fluoro-α-L-idopyranoside (**8**). — A mixture of **7** (140 mg), KHF_2 (877 mg, dried *in vacuo* for 2 h at 100°), and ethylene glycol (2.8 mL, dried over molecular sieves 4Å, and then distilled *in vacuo*) was stirred for 3 h at 180°. Chloroform (50 mL) was added and the organic solution was washed with aq. $NaHCO_3$ and dried ($MgSO_4$). T.l.c. (3:1 hexane–Me_2CO) of the solution showed a major spot (**8**, R_F 0.25) and several minor ones. Evaporation gave a residue that was chromatographed on a column of silica gel with 3:1 hexane–Me_2CO to give **8** as a syrup; yield 67 mg (44%), $[\alpha]_D^{26}$ −62° (*c* 2, $CHCl_3$); ^{19}F-n.m.r. ($CDCl_3$): δ −196.0 (dt); ^{1}H-n.m.r. ($CDCl_3$): δ 1.27 (d, 3 H, Me-5), 2.7–2.95 (1 H, OH), 3.35 (dd, 1 H, H-4), 3.44 (s, 3 H, OMe), 4.08 (dt, 1 H, H-3), 4.16 (dq, 1 H, H-5), 4.32 (dddd, 1 H, H-2), 4.57 and 4.71 (each d, 1 H, *J* 12 Hz, PhCH_2O), and 4.79 (dd, 1 H, H-1); $J_{1,2}$ 3, $J_{2,3}$ 5, $J_{3,4}$ 5, $J_{2,4}$ ~0.5, $J_{4,5}$ 3, $J_{5,6}$ 6.5, $J_{1,F}$ 9, $J_{2,F}$ 47.5, and $J_{3,F}$ 11 Hz.

Anal. Calc. for $C_{14}H_{19}FO_4$: C, 62.21; H, 7.08; F, 7.03. Found: C, 61.98; H, 7.17; F, 7.01.

Methyl 3-O-acetyl-4-O-benzyl-2,6-dideoxy-2-fluoro-α-L-idopyranoside (**9**). — A solution of **8** (17.8 mg) and Ac_2O (60 μL) in C_5H_5N (0.35 mL) was treated conventionally to give **9** as a syrup; yield 17.7 mg (86%), $[\alpha]_D^{26}$ −26° (*c* 1.3, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 2.08 (s, 3 H, Ac), 3.42 (s, 3 H, OMe), 4.32 (dddd, 1 H, H-2), 4.79 (dd, 1 H, H-1), and 5.32 (dt, 1 H, H-3); $J_{1,2}$ 3, $J_{2,3} = J_{3,4}$ 4.5, $J_{2,4}$ ~0.5, $J_{4,5}$ 3, $J_{1,F}$ 11, $J_{2,F}$ 46, and $J_{3,F}$ 13 Hz.

Anal. Calc. for $C_{16}H_{21}FO_5$: C, 61.53; H, 6.78. Found: C, 61.95; H, 6.58.

Methyl 4-O-benzyl-2,6-dideoxy-2-fluoro-α-L-lyxo-hexopyranosid-3-ulose (**10**). — To a solution of **8** (139 mg) in C_6H_6 (1 mL) were added Me_2SO (140 μL), *N,N'*-dicyclohexylcarbodiimide (155 mg), and pyridinium trifluoroacetate (23 mg, Aldrich Chem. Co.), and the mixture was stirred for 3 h at room temperature. After gradual addition of oxalic acid (142 mg) in MeOH (1.5 mL) and the evolution of gas had ceased, C_6H_6 (30 mL) was added, and insoluble material was filtered off. The organic layer was washed with aq. saturated $NaHCO_3$, aqueous 10% $KHSO_4$, and water, and dried ($MgSO_4$). Removal of the solvents yielded a residue that was subjected to column chromatography with 3:1 hexane–Me_2CO to give needles of **10**; yield 110 mg (79%), m.p. 63–64°, $[\alpha]_D^{26}$ −7° (*c* 1, $CHCl_3$); ν_{max}^{KBr} 1745 cm^{-1} (CO); ^{19}F-n.m.r. ($CDCl_3$): δ −204.7 (dd, *J* 7.5 and 48.5 Hz), ^{1}H-n.m.r. ($CDCl_3$): δ 1.27 (d, 3 H, Me-5), 3.52 (s, 3 H, OMe), 4.12 (dd, 1 H, H-4), 4.42 (dq, 1 H, H-5), 4.66 (ddd, 1 H, H-2), 4.80 (dd, 1 H, H-1), 4.51 and 4.86 (each d, 1 H, *J* 12 Hz, PhCH_2O), and 7.35 (s, 5 H, Ph): $J_{1,2}$ 6, $J_{2,4}$ 1, $J_{4,5}$ 5.5, $J_{1,F}$ 7.5, and $J_{2,F}$ 48.5 Hz.

Anal. Calc. for $C_{14}H_{17}FO_4$: C, 62.68; H, 6.39; F, 7.08. Found: C, 62.76; H, 6.37; F, 6.83.

Methyl 4-O-benzyl-2,6-dideoxy-2-fluoro-α-L-talopyranoside (**11**). — A cold (−30°) mixture of **10** (698 mg) and $LiAlH_4$ (198 mg) in dry oxolane (16 mL) was stirred for 1 h at −30°, for 2 h at −10°, and then for 30 min at 0°. After gradual addition of aq. saturated NH_4Cl to decompose the excess of $LiAlH_4$, $CHCl_3$ (50 mL) was added, and the insoluble material was filtered off. The organic layer was washed with aq. saturated NaCl, dried ($MgSO_4$), and evaporated. The syrup was purified by passing it through a short column of silica gel with 3:1 hexane–Me_2CO to give **11** as a thick syrup; yield 576 mg (82%), $[\alpha]_D^{26}$ −98° (*c* 3.5, $CHCl_3$); ^{19}F-n.m.r. ($CDCl_3$): δ −206.0 (ddd, *J* 9, 31.5, and 49.5 Hz); ^{1}H-n.m.r. ($CDCl_3$): δ 1.32 (d, 3 H, Me-5), 2.68 (dd, 1 H, OH), 3.37 (s, 3 H, OMe), 3.55 (br d, 1 H, H-4), 3.79 (ddt, 1 H, H-3), 3.90 (dq, 1 H, H-5), 4.45 (dddd, 1 H, H-2), 4.60 and 4.84 (each d, 1 H, PhCH_2O), 4.90 (dd, 1 H, H-1), and 7.25–7.45 (m, 5 H, Ph); $J_{1,2}$ 1.5, $J_{2,3}$ 3, $J_{2,4}$ ~0.5, $J_{3,4}$ 4, $J_{1,F}$ 9, $J_{2,F}$ 49.5, $J_{3,F}$ 31.5, $J_{3,OH}$ 11.5, and $J_{F,OH}$ ~1 Hz.

Anal. Calc. for $C_{14}H_{19}FO_4$: C, 62.21; H, 7.08; F, 7.03. Found: C, 62.40; H, 7.04; F, 7.18.

1,3,4-Tri-O-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranose (**13**). — Hydrogen was introduced into a mixture of **11** (345 mg), AcOH (720 μL), and Pd black in 1,4-dioxane (7.2 mL) by gentle bubbling for 4 h at room temperature. Filtration followed by evaporation gave **12** as a chromatographically homogeneous solid; yield 230 mg (quant.), R_F 0.3 (t.l.c. with 1:1 hexane–Me_2CO). To a solution of the solid in CH_3NO_2 (7.6 mL) were added Ac_2O (1.3 mL) and H_2SO_4 (36.5 μL), and the solution was kept for 4 h at room temperature. Neutralization with aq. saturated $NaHCO_3$ was followed by extraction with $CHCl_3$. The organic solution was washed with water, dried ($MgSO_4$), and evaporated. T.l.c. (3:1 hexane–Me_2CO) of the residue showed two spots having R_F 0.17 (minor, **14**) and 0.24 (**13**). Separation by column chromatography with 3:1 hexane–Me_2CO gave **13** (313 mg, 84% based on **11**) and **14** (14 mg, 4%) as solids.

Compound **13** had m.p. 102–103° (cubes from Et_2O–hexane), $[\alpha]_D^{26}$ −111° (*c* 1, $CHCl_3$); ^{19}F-n.m.r. ($CDCl_3$): δ −202.1 (ddd, *J* 8, 32, and 49 Hz); ^{1}H-n.m.r. ($CDCl_3$): δ 1.23 (d, 1 H, Me-5), 2.10, 2.14, and 2.18 (each s, 3 H, Ac × 3), 4.23 (dq, 1 H, H-5), 4.55 (dddd, 1 H, H-2), 5.21 (dt, 1 H, H-3), 5.25 (m, 1 H, H-4), and 6.33 (dd, 1 H, H-1); $J_{1,2}$ 2, $J_{2,3}$ 3, $J_{2,4}$ ~1, $J_{3,4}$ 3.5, $J_{4,5}$ ~1, $J_{1,F}$ 8, $J_{2,F}$ 48.5, and $J_{3,F}$ 32 Hz.

Anal. Calc. for $C_{12}H_{17}FO_7$: C, 49.32; H, 5.86; F, 6.50. Found: C, 49.19; H, 6.00; F, 6.39.

Compound **14** had ^{1}H-n.m.r. ($CDCl_3$): δ 2.11, 2.18, and 2.20 (each s, 3 H, Ac × 3), 4.72 (ddt, 1 H, H-2), 5.02 (ddd, 1 H, H-3), 5.20 (dt, 1 H, H-4), and 5.72 (dd, 1 H, H-1); $J_{1,2}$ ~0.5, $J_{2,3}$ 2.5, $J_{2,4}$ ~1, $J_{3,4}$ 3.5, $J_{4,5}$ 1.5, $J_{1,F}$ 20, $J_{2,F}$ 51.5, and $J_{3,F}$ 30.5 Hz.

3,4-Di-O-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranosyl bromide (**15**). — A mixture of **13** (327 mg) and $TiBr_4$ (534 mg) in 1:10 EtOAc–CH_2Cl_2 (7 mL) was stirred for 22 h at room temperature. T.l.c. (3:1 hexane–Me_2CO) of the deep-brown mixture showed a single spot at R_F 0.35 (compare **13**: R_F 0.17). After addi-

tion of CH_3CN (11 mL), anhydrous NaOAc (1.67 g) was added and the mixture was stirred until the color faded to pale yellow. Toluene (21 mL) was added and, after filtration, the organic solution was evaporated. The residue was extracted with PhMe (21 mL) and, after filtration, the extract was evaporated to give **15** as a pale-yellow syrup; yield 331 mg (95%), which was used for the next step without further purification; ^{1}H-n.m.r. ($CDCl_3$): δ 2.10 and 2.17 (each s, 3 H, Ac × 2), 4.81 (ddt, 1 H, H-2), 5.31 (m, 1 H, H-4), 5.56 (ddd, 1 H, H-3), and 6.55 (br d, 1 H, H-1); $J_{1,2} = J_{2,4}$ ~1.5, $J_{2,3}$ 3, $J_{3,4}$ 3.5, $J_{4,5}$ ~1, $J_{1,F}$ 11, $J_{2,F}$ 49.5, and $J_{3,F}$ 30.5 Hz.

7-O-(3,4-Di-O-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone (**16**). — A mixture of daunomycinone (290 mg), yellow HgO (940 mg), $HgBr_2$ (270 mg), and 3Å molecular sieves (4.5 g, freshly activated) in dry CH_2Cl_2 (36 mL) was stirred for 30 min at room temperature. The 1-bromide (**15**; 331 mg, 1.45 molar equiv. for daunomycinone) in CH_2Cl_2 (9 mL) was added, and the mixture was stirred for 20 h in the dark. After filtration with the aid of $CHCl_3$, the organic solution was washed with aq. 30% KI, aq. saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated. T.l.c. (4:1 C_6H_6–Me_2CO) of the residue showed a major spot at R_F 0.38 (compare daunomycinone: R_F 0.28). Purification of the product by column chromatography on silica gel with 4:1 C_6H_6–Me_2CO gave **16** as a red solid; yield 379 mg (82%), m.p. 144–146° (reprecipitated from $CHCl_3$–hexane), $[\alpha]_D^{26}$ +211° (*c* 0.036, $CHCl_3$); ^{19}F-n.m.r. ($CDCl_3$): δ −201.0 (ddd, *J* 9.5, 32.5, and 49.5 Hz); ^{1}H-n.m.r. ($CDCl_3$): δ 1.26 (d, 3 H, Me-5′), 2.03 and 2.18 (each s, 3 H, Ac × 2), 2.20 (dd, 1 H, H-8*ax*), 2.36 (br d, 1 H, H-8*e*), 2.41 (s, 3 H, Me-13), 2.87 (d, 1 H, H-10*ax*), 3.18 (dd, 1 H, H-10*e*), 3.85 (s, 1 H, HO-9), 4.08 (s, 3 H, OMe), 4.36 (dq, 1 H, H-5′), 4.58 (br d, 1 H, H-2′), 4.99 (dt, 1 H, H-3′), 5.22 (m, 1 H, H-4′), 5.27 (dd, 1 H, H-7), 5.64 (dd, 1 H, H-1′), 7.39 (dd, 1 H, H-3), 7.78 (t, 1 H, H-2), 8.00 (dd, 1 H, H-1), and 13.17 and 13.98 (each s, 1 H, HO-6,11); $J_{1,2}$ 7.5, $J_{1,3}$ ~1, $J_{2,3}$ 8.5, $J_{7,8ax}$ 4.5, $J_{7,8e}$ 1.5, $J_{8ax,8e}$ 15, $J_{8e,10e}$ 1.5, $J_{10ax,10e}$ 19, $J_{1',2'}$ 1.5, $J_{2',3'} = J_{3',4'}$ 3, $J_{4',5'}$ ~1, $J_{5',6'}$ 6.5, $J_{1',F}$ 9.5, $J_{2',F}$ 49.5, and $J_{3',F}$ 32.5 Hz.

Anal. Calc. for $C_{31}H_{31}FO_{13}\cdot H_2O$: C, 57.41; H, 5.13; F, 2.93. Found: C, 57.77; H, 5.28; F, 3.21.

7-O-(2,6-Dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone (**17**). — A solution of **16** (100 mg) in aqueous 0.2M NaOH was kept for 5 h at 0°. After gradual neutralization of the deep-purple solution with cold aqueous M hydrochloric acid, the mixture was extracted with $CHCl_3$. The organic solution was washed with aq. saturated NaCl, dried ($MgSO_4$), and evaporated. Reprecipitation of the residue from the $CHCl_3$ solution by adding hexane gave **17** as a red solid; yield 62.2 mg (72%), $[\alpha]_D^{25}$ +197° (*c* 0.02, 1:1 $CHCl_3$–MeOH); ^{19}F-n.m.r. (C_5D_5N): δ −199.1 (ddd, *J* 10, 34.5, and 50 Hz); ^{1}H-n.m.r. (C_5D_5N): δ 1.59 (d, 3 H, Me-5′), 2.57 (s, 3 H, Me-13), 2.49 (dd, 1 H, H-8*ax*), 2.81 (br dd, 1 H, H-8*e*), 3.41 (d, 1 H, H-10*ax*), 3.50 (sl. br d, 1 H, H-10*e*), 3.98 (s, 3 H, OMe), 3.97 (1 H, H-4′), 4.26 (dt, 1 H, H-3′), 4.75 (dq, 1 H, H-5′), 5.16 (br d, 1 H, H-2′), 5.47 (dd, 1 H, H-7), 6.02 (br d, 1 H, H-1′), 6.93 (br s, 1 H, one of OHs), 7.40 (dd, 1 H, H-3), 7.70 (t, 1 H, H-2), 8.05 (dd, 1 H, H-1), and 13.59 and 14.59 (each s, 1 H, HO-6,11); $J_{7,8ax}$ 5.5, $J_{7,8e}$ 2.5,

$J_{8ax,8e}$ 14.5, $J_{1',2'}$ ~1.5, $J_{2',3'} = J_{3',4'}$ ~3, $J_{4',5'}$ ~1, $J_{1',F}$ 10, $J_{2',F}$ 50, and $J_{3',F}$ 34.5 Hz.

Anal. Calc. for $C_{27}H_{27}FO_{11} \cdot 2\ H_2O$: C, 55.67; H, 5.36; F, 3.26. Found: C, 55.53; H, 5.36; F, 3.64.

7-O-(2,6-Dideoxy-2-fluoro-α-L-talopyranosyl)adriamycinone (**23**). — To a mixture of **17** (37.8 mg) and trimethoxymethane (0.052 mL) in dry MeOH (0.9 mL) and 1,4-dioxane (1.4 mL) was added a solution of Br_2 (15 mg) in CH_2Cl_2 (0.15 mL), and the suspension was stirred for 1 h at 0°, then for 1.5 h at room temperature. T.l.c. (1:1 C_6H_6–Me_2CO) of the resulting clear solution showed a major spot at R_F 0.58 (compare **17**: R_F 0.45). Addition of diisopropyl ether gave a precipitate that was collected by centrifugation and washed with diisopropyl ether to give a pasty mass composed mainly of **18**. A suspension of the mass in Me_2CO (3 mL) was stirred for 40 min at room temperature. The resulting clear solution showed, on t.l.c. with 1:1 C_6H_6–Me_2CO, two spots of R_F 0.6 (major, **19**) and 0.05 (**20**). Addition of a mixture of diisopropyl ether (5 mL) and hexane (20 mL) gave a red solid (35 mg). A mixture of the solid and sodium formate (65 mg) in Me_2CO–H_2O (4:1, 4 mL) was stirred vigorously for 17 h at room temperature. T.l.c. (4:1 C_6H_6–Me_2CO) of the solution showed two spots at R_F 0.49 (**21**) and 0.28 (**22**) with two trace spots at R_F 0.04 (14-formyloxy-3′,4′-diol) and 0 (**23**). Evaporation gave a residue that was washed with water to give a red solid (29 mg); ^{1}H-n.m.r. ($CDCl_3$): δ 1.31 and 1.34 (each d, ~3 H, in total, *J* 6.5 Hz, Me-5′), 1.39 and 1.57 (each s, ~3 H, CMe_2), and 8.21 (s, ~0.4 H, OCHO of **21**).

A solution of the solid in 1:1 $CHCl_3$–MeOH (3 mL) containing aqueous M NH_4OH (0.37 mL) was kept for 40 min at 0°, whereupon **21** disappeared and **22** became the major product. Evaporation gave a residue that was dissolved in aq. 80% AcOH (1.4 mL), and the solution was kept for 1.5 h at 80°. T.l.c. (1:1 C_6H_6–Me_2CO) showed a major spot (R_F 0.32). Evaporation gave a syrup that was thoroughly washed with water to give a solid. Reprecipitation of the solid from the $CHCl_3$–MeOH solution by addition of diisopropyl ether gave **23** as a red solid; yield 16.7 mg (43%). The combined aqueous washings were charged onto a column of Diaion HP-50 (3 mL, Mitsubishi Chemical Industries). The column was washed with water and then developed with aq. 80–90% MeOH to give additional solid **23** (5 mg). The combined yield of **23** was 56%, based on **17**. An analytical sample was obtained by passing the product through a column of silica gel with 12:1 $CHCl_3$–MeOH; $[\alpha]_D^{25}$ +194° (*c* 0.01, 1:1 $CHCl_3$–MeOH); ^{19}F-n.m.r. (C_5D_5N): δ −199.3 (ddd, *J* 10, 34, and 49 Hz); ^{1}H-n.m.r. (C_5D_5N): δ 1.53 (d, 3 H, Me-5′), 2.50 (dd, 1 H, H-8*ax*), 2.82 (br d, 1 H, H-8*e*), 3.41 (d, 1 H, H-10*ax*), 3.53 (br d, 1 H, H-10*e*), 3.96 (s, 3 H, OMe), 3.96 (1 H, H-4′), 4.20 (dt, 1 H, H-3′), 4.71 (br q, 1 H, H-5′), 5.09 (br d, 1 H, H-2′), 5.33 (s, 2 H, H-14a,b), 5.43 (br dd, 1 H, H-7), 5.95 (br d, 1 H, H-1′), 6.90 (br s, 1 H, one of the OH groups), 7.39 (br d, 1 H, H-3), 7.70 (t, 1 H, H-2), 8.03 (br d, 1 H, H-1), and 13.54 and 14.57 (each s, 1 H, HO-6, 11); $J_{7,8ax}$ 5.5, $J_{7,8e}$ ~2, $J_{8ax,8e}$ 14.5, $J_{8e,10e}$ ~2, $J_{10ax,10e}$ 17.5, $J_{1',2'}$ ~1, $J_{2',3'} = J_{3',4'}$ 3, $J_{4',5'}$ ~1, $J_{1',F}$ 10, $J_{2',F}$ 49, and $J_{3',F}$ 34.5 Hz.

Anal. Calc. for $C_{27}H_{27}FO_{12} \cdot 0.5\ H_2O$: C, 56.74; H, 4.94; F, 3.32. Found: C, 56.57; H, 5.11; F, 3.12.

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