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14-Fluoroanthracyclines. Novel Syntheses and Antitumor Activity[1)]

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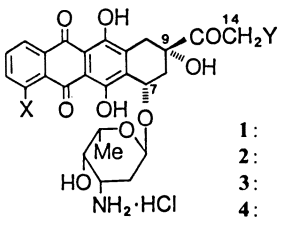
The 14-fluoroanthracyclines (**5**—**10**) carrying L-daunosamine, D-2-deoxyribose, or L-2-deoxyfucose as their glycosidic sugar moieties, were synthesized starting from (−)-7-deoxy-4-demethoxydaunomycinone ((*R*)-**11a**) or (−)-7-deoxydaunomycinone ((*R*)-**11b**). As key steps, the synthetic route features a novel fluorination reaction in which tetrabutylammonium fluoride is employed in the presence of a half equivalent of *p*-toluenesulfonic acid, and the previously explored glycosidation reaction in which trimethylsilyl trifluoromethanesulfonate is utilized as an activating reagent. In P388 *in vitro* tests, **5**, **6**, **9**, and **10** exhibited prominent cytotoxicity comparable with that of adriamycin (**1**). Notable antitumor activity was also observed for **6** and **9** in P388 *in vivo* tests.

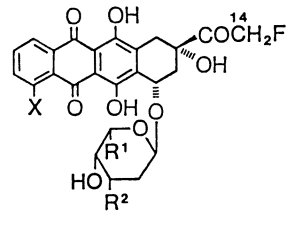
Keywords——14-fluoroanthracycline; 14-fluoroanthracyclinone; 7-deoxy-4-demethoxydaunomycinone; 7-deoxydaunomycinone; fluorination; tetrabutylammonium fluoride; *p*-toluenesulfonic acid; glycosidation; *in vitro* cytotoxicity; *in vivo* antitumor activity

The anthracycline antibiotics, adriamycin (**1**) and daunorubicin (**2**), are important anticancer agents which are widely used in the clinic for treating leukemia and solid tumors.[2)] However, their utility for cancer chemotherapy is seriously restricted by various undesirable side effects, the most well-known and serious of which is dose-related cardiotoxicity.[2)] Thus, extensive studies on the structure–activity relationships have been carried out to overcome these disadvantages, culminating in the syntheses of various notable congeners of **1** and **2**, some of which show superior anticancer activity in the P388 *in vivo* murine leukemia test system.[2,3)] Among these congeners of **1** and **2**, 4-demethoxyadriamycin (**3**) and 4-demethoxydaunorubicin (**4**) are well recognized to exhibit better therapeutic indices than natural **1** and **2**.[2−5)]

With the aims of improving the therapeutic properties of pharmacologically active compounds, and moreover, of finding novel pharmacological activities different from those of the parent compounds, a great number of fluorinated derivatives of biologically active compounds have been prepared in the last decade.[6,7)] In the field of anthracyclines, some derivatives involving fluorinated sugars[8)] or D-rings[9)] have recently been synthesized. However, syntheses of anthracycline congeners carrying fluorinated C_9-side chains have not been reported, probably due to the difficulty which may be encountered in introducing



	X	Y
1:	OMe	OH
2:	OMe	H
3:	H	OH
4:	H	H



	X	R^1	R^2
5:	H	Me	$NH_2 \cdot HCl$
6:	OMe	Me	$NH_2 \cdot HCl$
7:	H	H	OH
8:	OMe	H	OH
9:	H	Me	OH
10:	OMe	Me	OH

fluorine atom(s) into the side chain of anthracyclinone. Taking into account the notable difference of anticancer activity spectrum between **1** and **2**,[2] these fluorinated anthracyclines are anticipated to be the most interesting and promising congeners in terms of the structure–activity relationships.

In conjunction with our program directed toward exploration of novel anthracycline congeners as candidate anticancer agents,[5,10] we recently succeeded in the first total syntheses of 14-fluoroanthracyclines (**5**—**10**) which have L-daunosamine, D-2-deoxyribose, or L-2-deoxyfucose as their glycosidic sugars,[1] by employing a novel fluorination reaction and an efficient glycosidation method. This report deals with the syntheses and preliminary evaluation of the anticancer activity of **5**—**10**.[1]

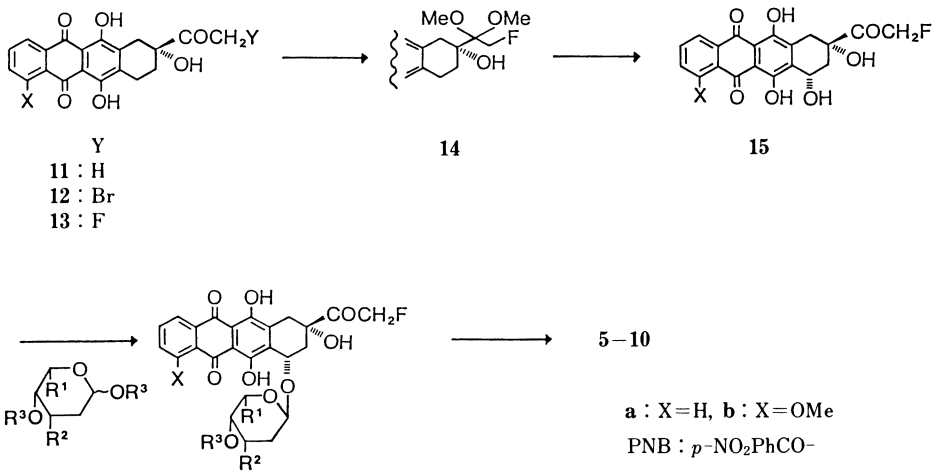
Results and Discussion

Preparation of (+)-14-Fluoro-4-demethoxydaunomycinone ((+)-15a) and (+)-14-Fluorodaunomycinone ((+)-15b)

At the outset of this work, it was expected that introduction of a fluorine atom into the C_{14}-position of the anthracycline skeleton could be achieved at the stage of 7-deoxyanthracyclinone, anthracyclinone, or anthracycline. In order to develop a novel fluorination method usable for this purpose, preliminary experiments were carried out employing *dl*-7-deoxy-4-demethoxydaunomycinone (*dl*-**11a**),[11] which is readily available in large quantities, as a model compound. According to the reported procedure,[11a,c] the racemic C_{14}-bromide (*dl*-**12a**) could be produced by selective bromination of *dl*-**11a** with pyridinium bromide perbromide. Without isolation by aqueous work-up, *dl*-**12a** was directly treated with 3.0 equivalents (eq) of tetrabutylammonium fluoride (TBAF) in the bromination reaction mixture, affording *dl*-7-deoxy-14-fluoro-4-demethoxydaunomycinone (*dl*-**13a**) in 24% yield (Table I, run 1). In order to improve the chemical yield of *dl*-**13a**, the same fluorination was next examined by employing *dl*-**12a** separated by usual extractive isolation. However, contrary to our expectation, the attempted fluorination was found to produce merely a complex mixture of polar compounds as main reaction products,[12] although formation of a trace amount of *dl*-**13a** could be detected by thin layer chromatography (TLC) (Table I, run 2). Comparing these experimental results and considering possible strong hydrogen bonding between proton and fluoride anion, pyridinium bromide present in the reaction medium may behave as a proton source instead of *dl*-**12a** to produce tetrabutylammonium hydrogendifluoride from TBAF as an active species.[13,14] Accordingly, *dl*-**12a** may have a stable diphenolic structure during the fluorination in the presence of pyridinium bromide to afford *dl*-**13a**. This assumption agrees well with the observation that the former fluorination in the presence of pyridinium bromide maintains the characteristic red color of the diphenolic form of *dl*-**12a** throughout the reaction. On the other hand, the dark violet color characterizing the diphenolate form of *dl*-**12a** immediately appears on addition of TBAF to a tetrahydrofuran (THF) solution of *dl*-**12a**.

Based on these preliminary results, fluorination of *dl*-**12a** was examined using 3.0 eq of TBAF in the presence of 2.0 eq of pyridinium *p*-toluenesulfonate (PPTS). As expected, *dl*-**13a** could be prepared in 48% yield (Table I, run 3). The best yield of *dl*-**13a** was realized using 6.0 eq of TBAF and 3.0 eq of PPTS (Table I, run 4). When PPTS was replaced with *p*-toluenesulfonic acid (TsOH), which is more acidic than PPTS, the yield of *dl*-**13a** could be further improved to 79% (Table I, run 6).

With the method for fluorinating the C_{14}-position of the anthracycline skeleton secured, we attempted to produce 14-fluoro-4-demethoxydaunorubicin (**5**) and 14-fluoro-4-demethoxydaunomycinone (**15a**) directly from **4** and 4-demethoxydaunomycinone, respectively, since it had been established that bromination of **4** and 4-demethoxydaunomycinone could readily give rise to the corresponding C_{14}-bromides.[11] However, the same fluorination



	R^1	R^2	R^3		R^1	R^2	R^3
16 :	Me	$NHCOCF_3$	PNB	**19** :	Me	$NHCOCF_3$	H
17 :	H	OAc	Ac	**20** :	H	OAc	Ac
18 :	Me	OAc	Ac	**21** :	Me	OAc	Ac

Chart 1

TABLE I. Syntheses of 7-Deoxy-14-fluoro-4-demethoxydaunomycinone (**13a**) by Treating 14-Bromo-7-deoxy-4-demethoxydaunomycinone (**12a**) with Tetrabutylammonium Fluoride under Various Conditions[a)]

Run	$Bu_4N \cdot F$[b)] (eq)	Additive[c)] (eq)	Conditions Temp. (°C)	Conditions Time (h)	Yield of **13a** (%)
1[d)]	3.0	—	r.t.	0.5	24
			67[e)]	3.0	
2[f)]	3.0	—	r.t.	0.5	0[g)]
			67[e)]	1.0	
3[f)]	3.0	PPTS (2.0)	r.t.	0.5	48
			67[e)]	3.0	
4[f)]	6.0	PPTS (3.0)	r.t.	0.5	54
			67[e)]	2.0	
5[f)]	8.0	PPTS (4.0)	r.t.	0.5	40
			67[e)]	1.0	
6[f)]	6.0	TsOH (3.0)	r.t.	0.5	79
			67[e)]	3.0	
7[h)]	6.0	TsOH (3.0)	r.t.	0.5	81
			67[e)]	3.0	

a) All reactions were carried out in THF by using *dl*-**12a** except for run 7. *b*) A 1.0 M solution in THF was used. *c*) PPTS = pyridinium *p*-toluenesulfonate, TsOH = *p*-toluenesulfonic acid. *d*) A THF solution of tetrabutylammonium fluoride was directly added to the bromination reaction mixture without isolating *dl*-**12a** by aqueous work-up. *e*) Boiling point of THF. *f*) The racemic bromide (*dl*-**12a**) isolated by aqueous work-up was subjected to the fluorination. *g*) A complex mixture of polar compounds was produced. Formation of a trace amount of *dl*-**13a** was detected by TLC analysis of the reaction mixture. *h*) The optically active bromide ((*R*)-**12a**) isolated by aqueous work-up was used. r.t.: room temperature.

of the C_{14}-bromide derived from **4** as that developed with *dl*-**12a** was found to simply effect aromatization of the A ring. Only a low yield of (+)-14-fluoro-4-demethoxydaunomycinone ((+)-**15a**) was obtained when the C_{14}-bromide prepared from 4-demethoxydaunomycinone[11)] was subjected to fluorination in the same manner as described for *dl*-**12a**.

Taking into account these results, it was concluded that fluorination of the C_{14}-bromide should be performed at the stage of 7-deoxyanthracyclinone. Thus, sequential treatments of (*R*)-**11a**[3,15] in the same manner as described for *dl*-**11a** produced (*R*)-**13a** in 81% overall yield (Table I, run 7).

At the next stage of synthesis, preparation of optically active (+)-**15a** from (*R*)-**13a** was attempted. Acetalization of (*R*)-**13a** with trimethoxymethane in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave an 88% yield of the corresponding dimethylacetal ((*R*)-**14a**). Bromination of (*R*)-**14a** with bromine under irradiation, followed by treating the resulting unstable C_7-bromide with aqueous alkali to introduce the $C_{7\alpha}$-hydroxyl group stereoselectively, gave rise to (+)-**15a** in 61% overall yield from (*R*)-**14a** after acidic removal of the acetal group. The stereochemistry of the C_7-position could be readily established by the nuclear magnetic resonance (NMR) spectrum, which showed a W_h value of 8.0 Hz for the signal of the $C_{7\beta}$-proton.[11]

Since **5** derived from (+)-**15a** was found to exhibit prominent *in vitro* cytotoxicity against P388 murine leukemia (*vide infra*), evaluation of the cytotoxicity of 14-fluorodaunorubicin (**6**) was required. Accordingly, preparation of optically active (+)-14-fluorodaunomycinone ((+)-**15b**) was examined following the same synthetic scheme as that explored for (+)-**15a**. Thus, sequential bromination of (*R*)-**11b** prepared by hydrogenolysis of commercially available **2** according to the reported method,[16] and fluorination of the produced C_{14}-bromide ((*R*)-**12b**) under the same conditions as those employed for (*R*)-**12a**, afforded optically active 7-deoxy-14-fluorodaunomycinone ((*R*)-**13b**) in 68% overall yield from (*R*)-**11b**. Similarly to (*R*)-**13a**, (*R*)-**13b** was readily transformed into (+)-**15b**. The yield of acetalization and that of introduction of the $C_{7\alpha}$-hydroxyl group followed by deprotection, were 92% and 52%, respectively. With two sorts of 14-fluoroanthracyclinones ((+)-**15a, b**) in hand, their glycosidations were next examined.

Preparation of Various 14-Fluoroanthracyclines (5—10)

Glycosidation of (+)-**15a** was first attempted using the daunosamine derivative according to the reported procedure.[5] Thus, (+)-**15a** was reacted with (−)-1,4-bis(*O*-*p*-nitrobenzoyl)-3-*N*-trifluoroacetyl-L-daunosamine (**16**)[17] in the presence of TMSOTf in a mixture of ether and dichloromethane. The formed glycoside was immediately treated with dilute aqueous alkali to effect hydrolysis of the 4′-*O*-*p*-nitrobenzoyl group, producing 3′-*N*-trifluoroacetyl-14-fluoro-4-demethoxydaunorubicin (**19a**) in 91% yield. The α-glycoside structure of **19a** could be readily determined from the NMR spectrum, which showed a W_h value of 7.0 Hz for the signal of the $C_{1'}$-proton. Comparison of the NMR spectrum of **19a** with that of 3′-*N*-trifluoroacetyl-4-demethoxydaunorubicin further supported the assigned structure of **19a**. Further, alkaline hydrolysis of the 3′-*N*-trifluoroacetyl group followed by salt formation gave **5**, mp 231—235 °C and $[\alpha]_D^{20}$ +122° (methanol), in 55% yield.

Following the same synthetic scheme as described above, **6**, mp 209 °C (dec.) and $[\alpha]_D^{20}$ +176° (methanol), could be produced from (+)-**15b** by way of 3′-*N*-trifluoroacetyl-14-fluorodaunorubicin (**19b**). The yield of **19b** from (+)-**15b** and that of **6** from **19b** were 91% and 53%, respectively.

Excellent *in vitro* cytotoxicity and *in vivo* antitumor activity against P388 murine leukemia observed for **5** and **6** (*vide infra*), prompted us to synthesize their congeners (**7**—**10**) in which the L-daunosamine residue was replaced with D-2-deoxyribose and L-2-deoxyfucose. Some congeners of **1** carrying the L-2-deoxyfucose derivatives in place of L-daunosamine, have been reported to exhibit prominent antitumor activity equal to or better than that of **1**, with low acute toxicity.[18] It has also been reported that substitution of L-daunosamine with D-2-deoxyribose is a promising method for producing anthracycline congeners which may show prominent anticancer activity.[19]

Glycosidation of (+)-**15a, b** with (−)-1,3,4-tri-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranose (**17**), obtainable from D-2-deoxyribose according to the reported procedure,[20] was found to proceed in a highly stereoselective fashion in the presence of TMSOTf in a similar manner to that observed with **16**, giving the 3′,4′-di-*O*-acetyl-β-glycosides (**20a, b**) in 66% and 62% yields, respectively. Formation of the desired β-glycosides (**20a, b**) as sole products was definitely ascertained by observing the W_h values of 8.0 Hz for the signals of the $C_{1'}$-protons in their NMR spectra. Transesterification of **20a, b** in methanol in the presence of potassium carbonate produced the 7-*O*-(2-deoxy-β-D-ribopyranosyl)-14-fluoroanthracyclinones (**7** and **8**), mp 225—227 °C, $[\alpha]_D^{20}$ +76.2° (methanol–chloroform, 1 : 1) and mp 230 °C (dec.), $[\alpha]_D^{20}$ +120° (methanol–chloroform, 1 : 1), in 72% and 40% yields, respectively.

By employing (−)-1,3,4-tri-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranose (**18**), accessible from L-fucose according to the reported method,[21] in place of **17**, the 7-*O*-(2-deoxy-α-L-fucopyranosyl)-14-fluoroanthracyclinones (**9** and **10**), mp 222—224 °C, $[\alpha]_D^{20}$ +150° (methanol–chloroform, 1 : 1) and mp 230 °C (dec.), $[\alpha]_D^{20}$ +196° (methanol–chloroform, 1 : 1), could be obtained from (+)-**15a, b** by way of the 3′,4′-di-*O*-acetyl-α-glycosides (**21a, b**). The yields of the glycosidation and transesterification steps were 78% (for **21a**) and 86% (for **21b**), and 62% (for **9**) and 58% (for **10**), respectively. The α-glycoside structures of **21a, b** were established in the same manner as described for **19a, b** and **20a, b**.

As mentioned above, the syntheses of various 14-fluoroanthracyclines (**5**—**10**) from (+)-**15a, b** were accomplished by employing the previously explored glycosidation method in which TMSOTf can be utilized as an activating reagent. The successful preparations of these novel 14-fluoroanthracyclines clearly show that the glycosidation reaction previously developed by us holds promise as a reliable method for producing anthracyclines from the corresponding anthracyclinones.

Antitumor Activity of 14-Fluoroanthracyclines

Various 14-fluoroanthracyclines (**5**—**10**) were first subjected to *in vitro* cytotoxicity assay against P388 murine leukemia cells along with their 3′-*N*-trifluoroacetyl and 3′,4′-di-*O*-acetyl derivatives (**19a, b**—**21a, b**). The results are summarized in Table II. Four of the 14-fluoroanthracyclines (**5**, **6**, **9**, and **10**) exhibit prominent cytotoxicity, comparable to that of **1** (IC_{50} 5.5×10^{-3}—1.3×10^{-4} μg/ml), and the cytotoxicity of the deprotected glycosides (**5**—**10**) is consistently higher than that of their protected forms (**19a, b**—**21a, b**). Accordingly, evaluation of *in vivo* antitumor activity against P388 murine leukemia was carried out using **5**, **6**, **9**, and **10**.

As shown in Table III, the 14-fluoroanthracyclines (**5**, **6**, **9**, and **10**) were found to exhibit highly effective *T/C* values at the optimal doses: **5**, *T/C* 169 (0.62 mg/kg); **6**, *T/C* 183 (2.5 mg/kg); **9**, *T/C* 329 (10 mg/kg); **10**, *T/C* 213 (25 mg/kg). The antitumor activity of **6** and **9**

Table II. *In Vitro* Cytotoxicity of 14-Fluoroanthracyclines (**5**—**10** and **19a, b**—**21a, b**) against P388 Murine Leukemia Cells

Compound	IC_{50} (μg/ml)[a]	Compound	IC_{50} (μg/ml)[a]
5	1.3×10^{-4}	**19a**	1.2×10^{-3}
6	1.5×10^{-4}	**19b**	1.9×10^{-3}
7	9.0×10^{-3}	**20a**	2.0×10^{-2}
8	1.1×10^{-2}	**20b**	9.9×10^{-2}
9	2.2×10^{-3}	**21a**	1.9×10^{-2}
10	5.5×10^{-3}	**21b**	8.2×10^{-2}

a) Concentration (μg/ml) necessary to inhibit cell growth (initial cell density: 5×10^4 cells/ml) by 50% after incubation for 48 h at 37 °C.

TABLE III. *In Vivo* Antitumor Activity of 14-Fluoroanthracyclines (**5**, **6**, **9**, and **10**) against P388 Murine Leukemia Cells[a]

Compd.	T/C (%)[b]							
	Dose (mg/kg)[c]							
	40	20 (25)	10 (12.5)	5 (6.25)	2.5	1.25	0.62	0.31
5	—	—	73	95	117	124	169	151
6	—	—	164	135	183	158	124	126
9	74 (1/6)[d]	293 (1/6)[d]	329 (4/6)[d]	265 (1/6)[d]	184	148	—	—
10	—	(213)[e]	(155)[e]	(153)[e]	—	—	—	—

a) Evaluated by the same method as that employed at the Drug Evaluation Branch, National Cancer Institute (NCI), NIH, U.S.A. *b*) Median survival time of test animals × 100/median survival time of control animals. *c*) P388 murine leukemia cells (10^6) were inoculated into CDF_1 mice (6 mice/group) intraperitoneally. Drugs were administered intraperitoneally, starting 24 h after inoculation, at day 1 and day 5. *d*) Number of cured mice/number of tested mice. *e*) T/C (%) value at the dose level (mg/kg) indicated in parenthesis.

is noteworthy since **1** was reported to show a T/C value of *ca.* 200 (2.5—3.0 mg/kg) in the same assay system. It is also noteworthy that **9** cured four among six mice at the optimal dose (10 mg/kg) and that **6** and **9** showed effective T/C values over a wide range of dose levels (0.31—10 mg/kg for **6** and 1.25—20 mg/kg for **9**).

Further studies aimed at characterizing the antitumor activity of **6** and **9** are in progress and will be reported shortly.

Experimental[22]

***dl*- and (*R*)-(−)-2-Acetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione (*dl*- and (−)-7-Deoxy-4-demethoxydaunomycinone) (*dl*- and (*R*)-11a)**——Prepared according to the reported methods.[11] *dl*-**11a**, mp 216—218 °C (lit.,[11b] mp 213—216 °C; lit.,[11c] mp 217—218 °C). (*R*)-**11a**, mp 219—221 °C and $[\alpha]_D^{20}$ −84.9° (*c* = 0.106, $CHCl_3$) (lit.,[11a] mp 218—219.5 °C and $[\alpha]_D^{20}$ −90.0° (*c* = 0.106, $CHCl_3$); lit.,[11b] mp 214—216 °C and $[\alpha]_D^{20}$ −90.6° (*c* = 0.106, $CHCl_3$)).

***dl*- and (*R*)-(−)-2-Fluoroacetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione (*dl*- and (*R*)-(−)-7-Deoxy-14-fluoro-4-demethoxydaunomycinone) (*dl*- and (*R*)-13a)**——a) Preparation of *dl*-**13a** from *dl*-**11a** by Way of *dl*-**12a** (Table I, run 6): A mixture of *dl*-**11a** (51.7 mg, 0.15 mmol) and pyridinium bromide perbromide (56.3 mg, 0.18 mmol) in THF (5 ml) was stirred at room temperature under an argon atmosphere for 2 h,[11a] and then poured into 50% saturated NaCl. The aqueous mixture was extracted with EtOAc. The combined organic extracts were washed with saturated NaCl and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* gave crude *dl*-**12a** as an orange solid, which, without purification, was dissolved in THF (10 ml) containing anhydrous TsOH (prepared from TsOH monohydrate (89.1 mg, 0.47 mmol)). A 1.0 M THF solution of TBAF (0.75 ml, 0.75 mmol) was added to a mixture of *dl*-**12a** and TsOH in THF with stirring under an argon atmosphere. The mixture was stirred at room temperature for 0.5 h, then under reflux for 1 h. After further 1.0 M THF solution of TBAF (0.15 ml, 0.15 mmol, total 0.90 mmol) had been added, the stirring under reflux was continued for 2 h. After cooling, the mixture was poured into 50% saturated NaCl and extracted with EtOAc. The combined organic extracts were washed successively with H_2O and saturated NaCl, and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* gave a red solid, which was purified by column chromatography (SiO_2, PhH–EtOAc, 20 : 1) to give *dl*-**13a** as a red solid (43.0 mg, 79%). Recrystallization of this sample from PhMe gave an analytical sample of *dl*-**13a** as red crystals, mp 248—250 °C. IR (KBr): 3450, 1730, 1620, 1585 cm^{-1}. The NMR spectrum and MS of *dl*-**13a** were identical with those of (*R*)-**13a** described in b). *Anal.* Calcd for $C_{20}H_{15}FO_6$: C, 64.87; H, 4.08. Found: C, 64.68; H, 4.06.

b) Preparation of (*R*)-**13a** from (*R*)-**11a** by Way of (*R*)-**12a** (Table I, run 7): Bromination of (*R*)-**11a** (153 mg, 0.43 mmol) with pyridinium bromide perbromide (222 mg, 0.70 mmol) by the same procedure as described in a)[11a] gave crude (*R*)-**12a** as an orange solid after concentration of the organic extracts *in vacuo*. This was dissolved in THF (30 ml) containing anhydrous TsOH (prepared from TsOH monohydrate (250 mg, 1.31 mmol)). A 1.0 M THF solution of TBAF (2.17 ml, 2.17 mmol) was added to the mixture of (*R*)-**12a** and TsOH in THF obtained above, and the whole was stirred at room temperature for 0.5 h, then under reflux for 1 h. Further amounts of a 1.0 M THF

solution of TBAF (0.43 ml, 0.43 mmol, and 0.10 ml, 0.10 mmol, total 2.70 mmol) were added to the reaction mixture after 1 h and 2 h, respectively, and the heating under reflux was continued for a total of 3 h. After cooling, the mixture was worked up by the same procedure as described in a), giving (*R*)-**13a** as a red solid (130 mg, 81%) after purification by column chromatography. Recrystallization of this sample from PhMe gave an analytical sample of (*R*)-**13a** as red needles, mp 251—255 °C and $[\alpha]_D^{20}$ −34.8° (*c*=0.058, dioxane). IR (KBr): 3510, 1735, 1625, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.98—2.22 (2H, m, C_3-H_2), 2.80 (1H, s, C_2-OH), 2.85—3.28 (4H, m, C_1-H_2 and C_4-H_2), 5.44 (2H, d, *J*= 47 Hz, CH_2F), 7.73—7.96 (2H, m, aromatic protons), 8.26—8.52 (2H, m, aromatic protons), 13.50 (2H, s, phenolic OH × 2). MS *m/z*: 370 (M^+), 352, 309. *Anal.* Calcd for $C_{20}H_{15}FO_6$: C, 64.87; H, 4.08. Found: C, 64.78; H, 4.17.

(*R*)-2-(2-Fluoro-1,1-dimethoxyethyl)-2,5,12-trihydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((*R*)-14a)——$CH(OMe)_3$ (2.0 ml, 18 mmol) and a 1.0 M C_6H_{14} solution of TMSOTf (0.18 ml, 0.18 mmol) were added to a suspension of (*R*)-**13a** (337 mg, 0.91 mmol) in CH_2Cl_2 (67 ml), and the mixture was stirred in an ice bath for 0.5 h, then at room temperature for 4 h. The mixture was poured into saturated $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were washed successively with H_2O and saturated NaCl, and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* gave a red solid, which was purified by column chromatography (SiO_2, PhH–EtOAc, 100 : 1) to afford (*R*)-**14a** as a red powder (331 mg, 88%), mp 206.5—209.5 °C. IR (KBr): 3600, 3470, 1620, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.62—2.37 (2H, m, C_3-H_2), 2.53 (1H, s, C_2-OH), 2.60—3.32 (4H, m, C_1-H_2 and C_4-H_2), 3.56, 3.59 (6H, two s, OMe × 2), 4.62 (2H, d, *J*=47 Hz, CH_2F), 7.72—7.95 (2H, m, aromatic protons), 8.22—8.57 (2H, m, aromatic protons), 13.53, 13.58 (2H, two s, phenolic OH × 2). MS *m/z*: 416 (M^+), 107. This sample was directly used for the next step.

(2*S*,4*S*)-(+)-2-Fluoroacetyl-2,4,5,11-tetrahydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((+)-14-Fluoro-4-demethoxydaunomycinone) ((+)-15a)——A 0.067 M solution of Br_2 in CCl_4 (5.8 ml, 0.39 mmol) was added to a mixture of (*R*)-**14a** (301 mg, 0.72 mmol) in a two-layer mixture of $CHCl_3$ (30 ml), CCl_4 (15 ml), and H_2O (22.5 ml), and the reaction mixture was stirred at 60 °C under irradiation with a 60 W tungsten lamp for 2 h. Further amounts of a 0.067 M solution of Br_2 in CCl_4 (1.7 ml × 5, total 14.3 ml, 0.95 mmol) were added after 15, 20, 25, 30, and 35 min. After cooling of the reaction mixture, 10% NaOH (1.5 ml, 3.8 mmol) was added, and stirring was continued at 0 °C for 10 min, then at room temperature for 25 min. The mixture was neutralized with 1 M HCl (3.8 ml), and extracted with $CHCl_3$. The combined extracts were washed successively with H_2O and saturated NaCl, and dried over anhydrous Na_2SO_4. Filtration and concentration *in vacuo* gave a red solid, which was dissolved in THF (30 ml). Concentrated HCl (6 ml) was added to the THF solution, and the mixture was stirred at room temperature for 16.5 h, then diluted with H_2O and $CHCl_3$. The chloroform layer was separated, and the aqueous phase was further extracted with $CHCl_3$. The combined organic extracts were washed successively with H_2O and saturated NaCl, dried over anhydrous Na_2SO_4, filtered, then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, PhH–EtOAc, 20 : 1→10 : 1), giving (+)-**15a** as a red powder (171 mg, 61% from (*R*)-**14a**). This was recrystallized successively from PhH and a mixture of PhH and C_6H_{14}, giving an analytical sample of (+)-**15a** as a red powder, mp 129.5—132 °C and $[\alpha]_D^{20}$ +162° (*c*=0.111, dioxane). IR (KBr): 3440, 1735, 1620, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (1H, dd, *J*=14, 5 Hz, C_{3ax}-H), 2.42 (1H, dt, *J*=14, 2 Hz, C_{3eq}-H), 3.04 (1H, d, *J*=19 Hz, C_{1ax}-H), 3.27 (1H, dd, *J*=19, 2 Hz, C_{1eq}-H), 3.36 (1H, t, *J*=3 Hz, C_4-OH), 4.63 (1H, s, C_2-OH), 5.33—5.48 (1H, m, W_h=8 Hz, C_4-H), 5.57 (2H, d, *J*=48 Hz, CH_2F), 7.75—8.02 (2H, m, aromatic protons), 8.25—8.53 (2H, m, aromatic protons), 13.25, 13.57 (2H, two s, phenolic OH × 2). ^{19}F-NMR ($CDCl_3$) δ: −236 (t, *J*=48.1 Hz). MS *m/z*: 386 (M^+), 368, 350, 307. *Anal.* Calcd for $C_{20}H_{15}FO_7$: C, 62.18; H, 3.91. Found: C, 62.18; H, 3.92.

(*R*)-(−)-2-Acetyl-2,5,12-trihydroxy-7-methoxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((−)-7-Deoxydaunomycinone) ((*R*)-11b)——Prepared in 100% yield by subjecting commercially available **2** to hydrogenation over 5% Pd on $BaSO_4$ according to the reported method.[16] A sample recrystallized from PhH showed mp 228—230 °C and $[\alpha]_D^{20}$ −93.8° (*c*=0.096, $CHCl_3$) (lit.,[16] mp 229—231 °C and $[\alpha]_D^{20}$ −91° (*c*=0.11, $CHCl_3$)).

(*R*)-(−)-2-Fluoroacetyl-2,5,12-trihydroxy-7-methoxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((*R*)-(−)-7-Deoxy-14-fluorodaunomycinone) ((*R*)-13b)——Treatment of (*R*)-**11b** (101 mg, 0.26 mmol) as described for (*R*)-**11a** gave (*R*)-**13b** as a red powder (72.3 mg, 68%) by way of (*R*)-**12b**. Recrystallization from PhMe gave an analytical sample as red needles, mp 253—257 °C and $[\alpha]_D^{20}$ −19.2° (*c*=0.052, dioxane). IR (KBr): 3490, 1735, 1610, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.20 (2H, m, C_3-H_2), 2.92 (1H, s, C_2-OH), 2.85—3.40 (4H, m, C_1-H_2 and C_4-H_2), 4.12 (3H, s, C_7-OMe), 5.46 (2H, d, *J*=47 Hz, CH_2F), 7.43 (1H, dd, *J*=8, 1 Hz, C_8-H), 7.79 (1H, t, *J*=8 Hz, C_9-H), 8.05 (1H, dd, *J*=8, 1 Hz, C_{10}-H), 13.37, 13.79 (2H, two s, phenolic OH × 2). MS *m/z*: 400 (M^+), 382, 339. *Anal.* Calcd for $C_{21}H_{17}FO_7$: C, 63.00; H, 4.28. Found: C, 62.70; H, 4.27.

(*R*)-2-(2-Fluoro-1,1-dimethoxyethyl)-2,5,12-trihydroxy-7-methoxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((*R*)-14b)——Treatment of (*R*)-**13b** (71.5 mg, 0.18 mmol) in the same manner as described for (*R*)-**13a** gave (*R*)-**14b** as a red powder (73.6 mg, 92%) after purification by column chromatography (SiO_2, PhH–EtOAc, 20 : 1). The sample showed mp 242.5—244 °C. IR (KBr): 3450, 1615, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.57—2.32 (2H, m, C_3-H_2), 2.52 (1H, s, C_2-OH), 2.67—3.34 (4H, m, C_1-H_2 and C_4-H_2), 3.55, 3.58 (6H, two s, OMe × 2), 4.10 (3H, s, C_7-OMe), 4.62 (2H, d, *J*=47 Hz, CH_2F), 7.39 (1H, dd, *J*=8, 1 Hz, C_8-H), 7.77 (1H, t, *J*=8 Hz, C_9-H), 8.04 (1H, dd, *J*=8, 1 Hz, C_{10}-H), 13.54, 13.88 (2H, two s, phenolic OH × 2). MS *m/z*: 446 (M^+), 107. This sample was directly used for the next step in a similar manner to (*R*)-**14a**.

(2*S*,4*S*)-(+)-2-Fluoroacetyl-2,4,5,11-tetrahydroxy-7-methoxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((+)-14-Fluorodaunomycinone) ((+)-15b)——Treatment of (*R*)-**14b** (33.3 mg, 0.075 mmol) in the same manner as described for (*R*)-**14a** gave (+)-**15b** as a red powder (16.1 mg, 52%) after purification by column chromatography (SiO_2, PhH–EtOAc, 10:1→5:1). An analytical sample of (+)-**15b** prepared by successive recrystallizations from PhH and a mixture of PhH and C_6H_{14}, showed mp 213—218 °C and $[\alpha]_D^{20}$ +179° (*c*=0.106, dioxane). IR (KBr): 3450, 1740, 1615, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.22 (1H, dd, *J*=15, 5 Hz, C_{3ax}-H), 2.44 (1H, dd, *J*=15, 2 Hz, C_{3eq}-H), 3.05 (1H, d, *J*=19 Hz, C_{1ax}-H), 3.27 (1H, dd, *J*=19, 2 Hz, C_{1eq}-H), 3.29—3.49 (1H, m, C_4-OH), 4.13 (3H, s, C_7-OMe), 4.66 (1H, s, C_2-OH), 5.34—5.51 (1H, m, W_h=8 Hz, C_4-H), 5.59 (2H, d, *J*=48 Hz, CH_2F), 7.46 (1H, dd, *J*=8, 1 Hz, C_8-H), 7.83 (1H, t, *J*=8 Hz, C_9-H), 8.09 (1H, dd, *J*=8, 1 Hz, C_{10}-H), 13.25, 14.01 (2H, two s, phenolic OH×2). ^{19}F-NMR ($CDCl_3$) δ: −236 (t, *J*=48.2 Hz). MS *m/z*: 416 (M^+), 398, 380, 337. *Anal.* Calcd for $C_{21}H_{17}FO_8 \cdot 0.5H_2O$: C, 59.30; H, 4.27. Found: C, 59.12; H, 3.98.

(2*S*,4*S*)-(+)-4-*O*-(2,3,6-Trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-2-fluoroacetyl-2,4,5,12-tetrahydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((+)-3′-*N*-Trifluoroacetyl-14-fluoro-4-demethoxydaunorubicin) (19a)[11b]——TMSOTf (0.08 ml, 0.41 mmol) was added to a mixture of **16**[17] (108 mg, 0.20 mmol) and MS-4A (803 mg) in a mixture of CH_2Cl_2 (10 ml) and Et_2O (8 ml) at −40 °C under an argon atmosphere. The mixture was stirred in an ice bath for 40 min, then cooled at −20 °C. A solution of (+)-**15a** (43.3 mg, 0.11 mmol) in THF (6 ml) was added to the cooled mixture. The whole mixture was stirred at −10—−15 °C for 5.5 h, and poured into a two-layer mixture of saturated $NaHCO_3$ and EtOAc. The upper ethyl acetate layer was separated and the lower aqueous phase was extracted with EtOAc. The combined organic extracts were washed successively with H_2O and saturated NaCl, dried over anhydrous Na_2SO_4, filtered, then concentrated *in vacuo*. The red residue was dissolved in MeOH (100 ml), and 0.1 M NaOH (2.0 ml) was added to the methanolic solution cooled in an ice bath. After being stirred in an ice bath for 20 min, the mixture was neutralized with 10% AcOH, diluted with H_2O, then extracted with EtOAc. The combined ethyl acetate extracts were washed successively with H_2O and saturated NaCl, dried over anhydrous Na_2SO_4, filtered, then concentrated *in vacuo*, to give crude **19a** as a red solid. This was purified by column chromatography (SiO_2, $CHCl_3$, then $CHCl_3$–Me_2CO, 30:1) to afford pure **19a** as an orange powder (62.6 mg, 91% from (+)-**15a**), mp 161—163.5 °C and $[\alpha]_D^{20}$ +173° (*c*=0.133, dioxane). IR (KBr): 3450, 1740, 1720, 1625, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, *J*=6.6 Hz, $C_{5'}$-Me), 1.85 (1H, dt, *J*=13.2, 4.1 Hz, $C_{2'ax}$-H), 1.94 (1H, d, *J*=8.0 Hz, $C_{4'}$-OH), 2.00 (1H, dd, *J*=13.2, 5.2 Hz, $C_{2'eq}$-H), 2.24 (1H, dd, *J*=14.9, 4.0 Hz, C_{3ax}-H), 2.38 (1H, dt, *J*=14.9, 1.8 Hz, C_{3eq}-H), 3.09 (1H, d, *J*=19.0 Hz, C_{1ax}-H), 3.35 (1H, dd, *J*=19.0, 1.8 Hz, C_{1eq}-H), 3.69 (1H, dd, *J*=8.0, 2.3 Hz, $C_{4'}$-H), 4.15—4.25 (1H, m, $C_{3'}$-H), 4.19 (1H, q, *J*=6.6 Hz, $C_{5'}$-H), 4.42 (1H, s, C_2-OH), 5.32 (1H, dd, *J*=4.0, 1.8 Hz, C_4-H), 5.52 (2H, d, *J*=47.8 Hz, CH_2F), 5.53 (1H, d, *J*=4.1 Hz, W_h=7.0 Hz, $C_{1'}$-H), 6.66 (1H, br d, *J*=8.2 Hz, NH), 7.83—7.89 (2H, m, aromatic protons), 8.34—8.41 (2H, m, aromatic protons), 13.33, 13.63 (2H, two s, phenolic OH×2). MS *m/z*: 611 (M^+), 386, 368, 350, 307. *Anal.* Calcd for $C_{28}H_{25}F_4NO_{10} \cdot 0.75H_2O$: C, 53.81; H, 4.27; N, 2.24. Found: C, 53.78; H, 4.18; N, 2.36.

(2*S*,4*S*)-(+)-4-*O*-(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-2-fluoroacetyl-2,4,5,12-tetrahydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione Hydrochloride ((+)-14-Fluoro-4-demethoxydaunorubicin Hydrochloride) (5)——A 0.05 M NaOH solution (5.2 ml) was added to a suspension of **19a** (31.9 mg, 0.052 mmol) in THF (1.25 ml) with stirring in an ice bath. Stirring was continued at 0 °C for 15 min and at room temperature for 30 min, then the mixture was neutralized (pH 9) with 1 M HCl and extracted with $CHCl_3$. The combined chloroform extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered, then concentrated *in vacuo* to *ca.* 2 ml in volume. When 0.25 M HCl in MeOH (1.05 ml) and Et_2O (*ca.* 30 ml) were successively added to the concentrated chloroform solution, an orange powder separated. This was collected by decantation and triturated with Et_2O. The upper ethereal layer was removed, and the precipitated orange powder was dried over KOH *in vacuo*, giving **5** (15.8 mg, 55%), mp 231—235 °C and $[\alpha]_D^{20}$ +122° (*c*=0.082, MeOH). IR (KBr): 3450, 1740, 1625, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.17 (3H, d, *J*=6.5 Hz, $C_{5'}$-Me), 1.69 (1H, dd, *J*=12.5, 4.2 Hz, $C_{2'eq}$-H), 1.89 (1H, dt, *J*=12.5, 3.5 Hz, $C_{2'ax}$-H), 2.16 (1H, dd, *J*=14.5, 5.7 Hz, C_{3ax}-H), 2.23 (1H, d, *J*=14.5 Hz, C_{3eq}-H), 2.95 (1H, d, *J*=18.4 Hz, C_{1ax}-H), 3.12 (1H, d, *J*=18.4 Hz, C_{1eq}-H), 3.56 (1H, br d, *J*=6.1 Hz, $C_{4'}$-H), 4.18 (1H, q, *J*=6.5 Hz, $C_{5'}$-H), 4.99 (1H, dd, *J*=5.7, 3.0 Hz, C_4-H), 5.32 (1H, br d, *J*=3.5 Hz, W_h=7.0 Hz, $C_{1'}$-H), 5.48 (1H, d, *J*=6.1 Hz, $C_{4'}$-OH), 5.56, 5.64 (2H, two dd, *J*=each 47.2, 17.5 Hz, CH_2F), 5.65 (1H, s, C_2-OH), 7.85 (3H, br s, NH_3^+), 7.97—8.04 (2H, m, aromatic protons), 8.27—8.34 (2H, m, aromatic protons), 13.33, 13.55 (2H, two br s, phenolic OH×2). ^{19}F-NMR (DMSO-d_6) δ: −234 (t, *J*=48.0 Hz). MS (SIMS) *m/z*: 516 [(MH−HCl)$^+$], 351, 291. *Anal.* Calcd for $C_{26}H_{27}ClFNO_9 \cdot 0.75HCl$: C, 53.91; H, 4.83; N, 2.42. Found: C, 53.73; H, 4.78; N, 2.24.

(2*S*,4*S*)-(+)-4-*O*-(2,3,6-Trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranosyl)-2-fluoroacetyl-2,4,5,12-tetrahydroxy-7-methoxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((+)-3′-*N*-Trifluoroacetyl-14-fluorodaunorubicin) (19b)[11b]——Glycosidation of (+)-**15b** (19.5 mg, 0.047 mmol) with **16**[17] (40.7 mg, 0.075 mmol), followed by alkaline hydrolysis of the 4′-*O*-*p*-nitrobenzoyl group of the formed glycoside in the same manner as described for the preparation of **19a**, gave **19b** as a red powder (27.2 mg, 91%), after purification by column chromatography (SiO_2, $CHCl_3$, then $CHCl_3$–Me_2CO, 30:1). The sample showed mp 161.5—164 °C and $[\alpha]_D^{20}$ +185° (*c*=0.108, dioxane). IR (KBr): 3500, 3440, 1740, 1720, 1615, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, *J*=6.6 Hz, $C_{5'}$-Me), 1.83 (1H, dt, *J*=13.2, 4.1 Hz, $C_{2'ax}$-H), 1.95 (1H, dd, *J*=13.2, 5.2 Hz, $C_{2'eq}$-H), 2.00 (1H, d, *J*=8.1 Hz, $C_{4'}$-OH), 2.23 (1H, dd, *J*=

14.8, 4.0 Hz, C_{3ax}-H), 2.36 (1H, dt, J=14.8, 1.7 Hz, C_{3eq}-H), 3.00 (1H, d, J=18.9 Hz, C_{1ax}-H), 3.30 (1H, dd, J=18.9, 1.7 Hz, C_{1eq}-H), 3.67 (1H, dd, J=8.1, 2.2 Hz, $C_{4'}$-H), 4.09 (3H, s, C_7-OMe), 4.14—4.22 (1H, m, $C_{3'}$-H), 4.17 (1H, q, J=6.6 Hz, $C_{5'}$-H), 4.40 (1H, s, C_2-OH), 5.32 (1H, dd, J=4.0, 1.7 Hz, C_4-H), 5.52 (2H, d, J=47.7 Hz, CH_2F), 5.54 (1H, d, J=4.1 Hz, W_h=7.0 Hz, $C_{1'}$-H), 6.66 (1H, br d, J=8.6 Hz, NH), 7.41 (1H, dd, J=8.0, 0.9 Hz, C_8-H), 7.80 (1H, t, J=8.0 Hz, C_9-H), 8.05 (1H, dd, J=8.0, 0.9 Hz, C_{10}-H), 13.25, 14.01 (2H, two s, phenolic OH × 2). MS m/z: 641 (M^+), 416, 398, 380, 337. *Anal.* Calcd for $C_{29}H_{27}F_4NO_{11}$: C, 54.30; H, 4.24; N, 2.18. Found: C, 54.21; H, 4.45; N, 1.98.

(2*S*,4*S*)-(+)-4-*O*-(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-2-fluoroacetyl-2,4,5,12-tetrahydroxy-7-methoxy-1,2,3,4-tetrahydro-6,11-naphthacenedione Hydrochloride ((+)-14-Fluorodaunorubicin Hydrochloride) (6)——Treatment of **19b** (19.9 mg, 0.031 mmol) as described for **19a** gave **6** as a red powder (9.6 mg, 53%) after trituration with Et_2O and drying over KOH *in vacuo*. The sample showed mp 209 °C (dec.) and $[\alpha]_D^{20}$ +176° (c=0.091, MeOH). IR (KBr): 3450, 1735, 1615, 1590 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.16 (3H, d, J=6.5 Hz, $C_{5'}$-Me), 1.68 (1H, dd, J=12.5, 3.6 Hz, $C_{2'eq}$-H), 1.88 (1H, dt, J=12.5, 3.2 Hz, $C_{2'ax}$-H), 2.14 (1H, dd, J=14.1, 5.3 Hz, C_{3ax}-H), 2.21 (1H, d, J=14.1 Hz, C_{3eq}-H), 2.89 (1H, d, J=18.3 Hz, C_{1ax}-H), 3.09 (1H, d, J=18.3 Hz, C_{1eq}-H), 3.57 (1H, br d, J=6.1 Hz, $C_{4'}$-H), 4.00 (3H, s, C_7-OMe), 4.17 (1H, q, J=6.5 Hz, $C_{5'}$-H), 4.98 (1H, dd, J=5.3, 2.9 Hz, C_4-H), 5.31 (1H, d, J=3.2 Hz, W_h=7.0 Hz, $C_{1'}$-H), 5.47 (1H, d, J=6.1 Hz, $C_{4'}$-OH), 5.57, 5.64 (2H, two dd, J=each 47.2, 17.6 Hz, CH_2F), 5.63 (1H, s, C_2-OH), 7.64—7.70 (1H, m, aromatic protons), 7.86 (3H, br s, NH_3^+), 7.90—7.97 (2H, m, aromatic protons), 13.26, 14.05 (2H, two s, phenolic OH × 2). ^{19}F-NMR (DMSO-d_6) δ: −234 (t, J=46.7 Hz). MS (SIMS) m/z: 546 [(MH − HCl)$^+$], 381, 321. *Anal.* Calcd for $C_{27}H_{29}ClFNO_{10}\cdot 1.75H_2O$: C, 52.86; H, 5.34; N, 2.28. Found: C, 52.77; H, 5.13; N, 2.25.

(−)-1,3,4-Tri-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranose (17)——Prepared from 2-deoxy-D-ribose according to the reported method.[20] The sample recrystallized from a mixture of $CHCl_3$ and C_6H_{12} showed mp 97—98 °C and $[\alpha]_D^{23}$ −160° (c=0.57, $CHCl_3$) (lit.,[20] mp 98 °C and $[\alpha]_D^{23}$ −171.8° (c=0.56, $CHCl_3$)).

(2*S*,4*S*)-(+)-4-*O*-(3,4-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranosyl)-2-fluoroacetyl-2,4,5,12-tetrahydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((7*S*,9*S*)-(+)-7-*O*-(3,4-Di-*O*-acetyl-2-deoxy-β-D-ribopyranosyl)-14-fluoro-4-demethoxydaunomycinone) (20a)——A 1.0 M solution of TMSOTf in CH_2Cl_2 (0.08 ml, 0.08 mmol) was added to a mixture of (+)-**15a** (20.6 mg, 0.053 mmol), **17** (20.8 mg, 0.080 mmol), and MS-4A (200 mg) in a mixture of THF (2.0 ml), CH_2Cl_2 (2.0 ml), and Et_2O (2.0 ml) cooled at −20 °C under an argon atmosphere. The mixture was stirred at −15—−5 °C for 1.5 h, and poured into a two-layer mixture of H_2O and EtOAc cooled in an ice bath. The upper organic layer was separated, and the lower aqueous phase was further extracted with EtOAc. The combined organic extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered, then concentrated *in vacuo*. The residue was purified by preparative TLC (SiO_2, $CHCl_3$–Me_2CO, 20 : 1) to give crude **20a** as a red solid. Trituration of crude **20a** with Et_2O gave pure **20a** as a red powder (21.1 mg, 67%), mp 198—201 °C and $[\alpha]_D^{20}$ +113° (c=0.106, $CHCl_3$). IR (KBr): 3500, 1740, 1620, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.88 (1H, dt, J=12.4, 3.6 Hz, $C_{2'ax}$-H), 2.03, 2.13 (6H, two s, COMe × 2), 2.15—2.23 (1H, m, $C_{2'eq}$-H), 2.19 (1H, dd, J=14.9, 4.1 Hz, C_{3ax}-H), 2.51 (1H, dt, J=14.9, 1.8 Hz, C_{3eq}-H), 3.08 (1H, d, J=19.1 Hz, C_{1ax}-H), 3.32 (1H, dd, J=19.1, 1.8 Hz, C_{1eq}-H), 3.90 (1H, dd, J=12.6, 4.2 Hz, $C_{5'ax}$-H), 4.04 (1H, dd, J=12.6, 2.1 Hz, $C_{5'eq}$-H), 4.50 (1H, s, C_2-OH), 5.10—5.19 (2H, m, $C_{3'}$-H and $C_{4'}$-H), 5.33 (1H, dd, J=4.1, 1.8 Hz, C_4-H), 5.52, 5.59 (2H, two dd, J=each 47.8, 18.1 Hz, CH_2F), 5.54 (1H, t, J=3.6 Hz, W_h=8.0 Hz, $C_{1'}$-H), 7.84—7.88 (2H, m, aromatic protons), 8.35—8.38 (2H, m, aromatic protons), 13.30, 13.63 (2H, two s, phenolic OH × 2). MS m/z: 587 [(M + 1)$^+$], 586 (M^+), 386. *Anal.* Calcd for $C_{29}H_{27}FO_{12}\cdot 0.33H_2O$: C, 58.79; H, 4.71. Found: C, 58.73; H, 4.66.

(2*S*,4*S*)-(+)-4-*O*-(2-Deoxy-β-D-*erythro*-pentopyranosyl)-2-fluoroacetyl-2,4,5,12-tetrahydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((7*S*,9*S*)-(+)-7-*O*-(2-Deoxy-β-D-ribopyranosyl)-14-fluoro-4-demethoxydaunomycinone) (7)——A 0.05 M solution of K_2CO_3 in MeOH (3.4 ml, 0.17 mmol) was added to a solution of **20a** (40.6 mg, 0.069 mmol) in $CHCl_3$ (5 ml) cooled in an ice bath, and the mixture was stirred at the same temperature for 1 h. The reaction was quenched by adding 5% HCl, and the mixture was extracted with $CHCl_3$. The chloroform extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered, then concentrated *in vacuo*. The concentrated residue was triturated with a small amount of Et_2O, and the upper ethereal layer was removed. The residual ethereal suspension was diluted with $CHCl_3$ to give **7** as a red powder (25.0 mg, 72%), mp 225—227 °C and $[\alpha]_D^{20}$ +76.2° (c=0.105, $CHCl_3$–MeOH, 1 : 1). IR (KBr): 3450, 1740, 1620, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.81 (1H, dt, J=13.6, 4.3 Hz, $C_{2'ax}$-H), 2.05 (1H, dd, J=13.6, 3.6 Hz, $C_{2'eq}$-H), 2.01, 2.11 (2H, two d, J=each 5.3 Hz, $C_{3'}$-OH and $C_{4'}$-OH or $C_{4'}$-OH and $C_{3'}$-OH), 2.17 (1H, dd, J=14.9, 4.2 Hz, C_{3ax}-H), 2.55 (1H, dt, J=14.9, 1.9 Hz, C_{3eq}-H), 3.09 (1H, d, J=19.1 Hz, C_{1ax}-H), 3.32 (1H, dd, J=19.1, 1.9 Hz, C_{1eq}-H), 3.85—4.01 (4H, m, $C_{3'}$-H, $C_{4'}$-H and $C_{5'}$-H_2), 4.69 (1H, s, C_2-OH), 5.34 (1H, dd, J=4.2, 1.9 Hz, C_4-H), 5.50, 5.58 (2H, two dd, J=each 47.2, 18.0 Hz, CH_2F), 5.49 (1H, t, J=4.3 Hz, W_h=8.0 Hz, $C_{1'}$-H), 7.85—7.87 (2H, m, aromatic protons), 8.36—8.39 (2H, m, aromatic protons), 13.33, 13.61 (2H, two s, phenolic OH × 2). MS m/z: 502 (M^+), 386. *Anal.* Calcd for $C_{25}H_{23}FO_{10}\cdot H_2O$: C, 57.69; H, 4.84. Found: C, 57.51; H, 4.47.

(2*S*,4*S*)-(+)-4-*O*-(3,4-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranosyl)-2-fluoroacetyl-2,4,5,12-tetrahydroxy-7-methoxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((7*S*,9*S*)-(+)-7-*O*-(3,4-Di-*O*-acetyl-2-deoxy-β-D-ribopyranosyl)-14-fluorodaunomycinone) (20b)——Glycosidation of (+)-**15b** (10.2 mg, 0.025 mmol) with **17** (13.6 mg, 0.052 mmol) by the same method as described for the preparation of **20a**, followed by purification by preparative TLC (SiO_2, $CHCl_3$–

Me_2CO, 10:1) and trituration with Et_2O, gave **20b** as a red powder (10.0 mg, 66%), mp 117—119 °C and $[\alpha]_D^{20}$ +97.3° (c=0.113, $CHCl_3$). IR (KBr): 3450, 1740, 1620, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (1H, dt, J=12.6, 3.6 Hz, $C_{2'ax}$-H), 1.95—2.23 (1H, m, $C_{2'eq}$-H), 2.03, 2.14 (6H, two s, COMe × 2), 2.20 (1H, dd, J=14.9, 4.0 Hz, C_{3ax}-H), 2.50 (1H, dt, J=14.9, 1.9 Hz, C_{3eq}-H), 3.03 (1H, d, J=18.9 Hz, C_{1ax}-H), 3.29 (1H, dd, J=18.9, 1.9 Hz, C_{1eq}-H), 3.89 (1H, dd, J=12.5, 4.4 Hz, $C_{5'ax}$-H), 4.02 (1H, dd, J=12.5, 2.2 Hz, $C_{5'eq}$-H), 4.10 (3H, s, C_7-OMe), 4.49 (1H, s, C_2-OH), 5.12—5.18 (2H, m, $C_{3'}$-H and $C_{4'}$-H), 5.33 (1H, dd, J=4.0, 1.9 Hz, C_4-H), 5.54 (1H, t, J=3.6 Hz, W_h=8.0 Hz, $C_{1'}$-H), 5.51, 5.59 (2H, two dd, J=each 47.8, 18.1 Hz, CH_2F), 7.42 (1H, dd, J=7.8, 0.8 Hz, C_8-H), 7.81 (1H, t, J=7.8 Hz, C_9-H), 8.06 (1H, dd, J=7.8, 0.8 Hz, C_{10}-H), 13.30, 14.40 (2H, two s, phenolic OH × 2). MS m/z: 616 (M^+), 416.

(2*S*,4*S*)-(+)-4-*O*-(2-Deoxy-β-D-*erythro*-pentopyranosyl)-2-fluoroacetyl-2,4,5,12-tetrahydroxy-7-methoxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((7*S*,9*S*)-(+)-7-*O*-(2-Deoxy-β-D-ribopyranosyl)-14-fluorodaunomycinone) (8)——Treatment of **20b** (47.9 mg, 0.078 mmol) in the same manner as described for **20a** gave crude **8** as a red solid (16.6 mg, 40%) after concentration of the combined chloroform extracts. Recrystallization from $CHCl_3$ afforded an analytical sample of **8** as a red powder, mp 230 °C (dec.) and $[\alpha]_D^{20}$ +120° (c=0.117, $CHCl_3$–MeOH, 1:1). IR (KBr): 3450, 1740, 1620, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.80 (1H, dt, J=13.7, 4.0 Hz, $C_{2'ax}$-H), 2.00 (1H, ddd, J=13.7, 9.2, 3.5 Hz, $C_{2'eq}$-H), 2.02, 2.17 (2H, two d, J=5.6, 5.1 Hz, $C_{3'}$-OH and $C_{4'}$-OH or $C_{4'}$-OH and $C_{3'}$-OH), 2.16 (1H, dd, J=14.8, 4.0 Hz, C_{3ax}-H), 2.52 (1H, dt, J=14.8, 1.9 Hz, C_{3eq}-H), 3.06 (1H, d, J=19.0 Hz, C_{1ax}-H), 3.29 (1H, dd, J=19.0, 1.9 Hz, C_{1eq}-H), 3.87 (1H, dd, J=13.5, 4.8 Hz, $C_{5'ax}$-H), 3.95 (1H, dd, J=13.5, 4.5 Hz, $C_{5'eq}$-H), 3.86—3.97 (2H, m, $C_{3'}$-H and $C_{4'}$-H), 4.10 (3H, s, C_7-OMe), 4.69 (1H, s, C_2-OH), 5.34 (1H, dd, J=4.0, 1.9 Hz, C_4-H), 5.50, 5.55 (2H, two dd, J=each 47.8, 18.0 Hz, CH_2F), 5.49 (1H, t, J=4.0 Hz, W_h=8.0 Hz, $C_{1'}$-H), 7.41 (1H, dd, J=7.8, 0.9 Hz, C_8-H), 7.80 (1H, t, J=7.8 Hz, C_9-H), 8.05 (1H, dd, J=7.8, 0.9 Hz, C_{10}-H), 13.28, 14.00 (2H, two s, phenolic OH × 2). MS m/z: 532 (M^+), 416. *Anal.* Calcd for $C_{26}H_{25}FO_{11}\cdot 2H_2O$: C, 54.93; H, 5.14. Found: C, 54.43; H, 4.65.

(−)-1,3,4-Tri-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranose (18)——Preparation of this sample was carried out starting from L-fucose according to the reported method.[21] The sample recrystallized from Me_2CHOH showed mp 111—112 °C and $[\alpha]_D^{20}$ −137° (c=0.707, $CHCl_3$) (lit.,[21c] mp 112 °C and $[\alpha]_D^{20}$ −137° (c=0.7, $CHCl_3$)).

(2*S*,4*S*)-(+)-4-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)-2-fluoroacetyl-2,4,5,12-tetrahydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((7*S*,9*S*)-(+)-7-*O*-(3,4-Di-*O*-acetyl-2-deoxy-α-L-fucopyranosyl)-14-fluoro-4-demethoxydaunomycinone) (21a)——A 1.0 M solution of TMSOTf in CH_2Cl_2 (0.14 ml, 0.14 mmol) was added to a mixture of (+)-**15a** (36.0 mg, 0.093 mmol), **18** (38.3 mg, 0.14 mmol), and MS-4A (280 mg) in a mixture of CH_2Cl_2 (3.8 ml), Et_2O (3.8 ml), and THF (7.0 ml) cooled at −30 °C under an argon atmosphere. The mixture was stirred at −15——5 °C for 1 h, and poured into a two-layer mixture of EtOAc and H_2O cooled in an ice bath. The upper organic layer was separated and the lower aqueous phase was further extracted with EtOAc. The combined organic extracts were washed successively with H_2O and saturated NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC (SiO_2, $CHCl_3$–Me_2CO, 9:1) to give **21a** as a red powder (43.4 mg, 78%), mp 235—237 °C and $[\alpha]_D^{20}$ +160° (c=0.100, $CHCl_3$). IR (KBr): 3450, 1740, 1620, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=6.4 Hz, $C_{6'}$-H_3), 1.90 (1H, dd, J=13.1, 5.1 Hz, $C_{2'ax}$-H), 1.96, 2.18 (6H, two s, COMe × 2), 2.11 (1H, dd, J=13.1, 4.1 Hz, $C_{2'eq}$-H), 2.22 (1H, dd, J=14.8, 4.0 Hz, C_{3ax}-H), 2.38 (1H, dt, J=14.8, 1.9 Hz, C_{3eq}-H), 3.08 (1H, d, J=19.0 Hz, C_{1ax}-H), 3.33 (1H, dd, J=19.0, 1.9 Hz, C_{1eq}-H), 4.20 (1H, br q, J=6.4 Hz, $C_{5'}$-H), 4.49 (1H, s, C_2-OH), 5.05 (1H, ddd, J=12.7, 5.1, 3.0 Hz, $C_{3'}$-H), 5.22—5.25 (1H, m, $C_{4'}$-H), 5.34 (1H, dd, J=4.0, 1.9 Hz, C_4-H), 5.54 (2H, d, J=47.8 Hz, CH_2F), 5.62 (1H, d, J=3.6 Hz, W_h=8.0 Hz, $C_{1'}$-H), 7.84—7.89 (2H, m, aromatic protons), 8.34—8.39 (2H, m, aromatic protons), 13.31, 13.62 (2H, two s, phenolic OH × 2). MS m/z: 600 (M^+), 386, 350. *Anal.* Calcd for $C_{30}H_{29}FO_{12}\cdot 0.25H_2O$: C, 59.55; H, 4.91. Found: C, 59.61; H, 5.00.

(2*S*,4*S*)-(+)-4-*O*-(2,6-Dideoxy-α-L-*lyxo*-hexopyranosyl)-2-fluoroacetyl-2,4,5,12-tetrahydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((7*S*,9*S*)-(+)-7-*O*-(2-Deoxy-α-L-fucopyranosyl)-14-fluoro-4-demethoxydaunomycinone) (9)——A 0.05 M solution of K_2CO_3 in MeOH (11.8 ml, 0.59 mmol) was added to a solution of **21a** (140 mg, 0.23 mmol) in $CHCl_3$ (14 ml) cooled in an ice bath, and the mixture was stirred at the same temperature for 3 h. The reaction was quenched by adding 5% HCl. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed successively with H_2O and saturated NaCl, dried over anhydrous Na_2SO_4, filtered, then concentrated *in vacuo*, to give crude **9** as a red solid. Recrystallization of this sample from $CHCl_3$ gave **9** as a red powder (74.6 mg, 62%), mp 222—224 °C and $[\alpha]_D^{20}$ +150° (c=0.100, $CHCl_3$–MeOH, 1:1). IR (KBr): 3450, 1740, 1620, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, d, J=6.6 Hz, $C_{6'}$-H_3), 1.85—1.93 (2H, m, $C_{2'}$-H_2), 1.96, 1.98 (2H, two d, J=7.9, 5.7 Hz, $C_{3'}$-OH and $C_{4'}$-OH or $C_{4'}$-OH and $C_{3'}$-OH), 2.19 (1H, dd, J=14.8, 4.0 Hz, C_{3ax}-H), 2.38 (1H, dt, J=14.8, 1.9 Hz, C_{3eq}-H), 3.11 (1H, d, J=19.1 Hz, C_{1ax}-H), 3.33 (1H, dd, J=19.1, 1.9 Hz, C_{1eq}-H), 3.70—3.73 (1H, m, $C_{4'}$-H), 3.84 (1H, ddd, J=14.1, 6.5, 3.0 Hz, $C_{3'}$-H), 4.05 (1H, br q, J=6.6 Hz, $C_{5'}$-H), 4.69 (1H, s, C_2-OH), 5.34 (1H, dd, J=4.0, 1.9 Hz, C_4-H), 5.51 (2H, d, J=47.8 Hz, CH_2F), 5.55 (1H, d, J=2.6 Hz, W_h=8.0 Hz, $C_{1'}$-H), 7.84—7.89 (2H, m, aromatic protons), 8.35—8.40 (2H, m, aromatic protons), 13.33, 13.62 (2H, two s, phenolic OH × 2). MS m/z: 386, 350. *Anal.* Calcd for $C_{26}H_{25}FO_{10}\cdot H_2O$: C, 58.42; H, 5.09. Found: C, 58.57; H, 4.83.

(2*S*,4*S*)-(+)-4-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)-2-fluoroacetyl-2,4,5,12-tetrahydroxy-7-methoxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((7*S*,9*S*)-(+)-7-*O*-(3,4-Di-*O*-acetyl-2-deoxy-α-L-fucopyranosyl)-14-fluorodaunomycinone) (21b)——Glycosidation of (+)-**15b** (31.1 mg, 0.075 mmol) with **18** (30.7 mg, 0.11 mmol) in

the same manner as described for the preparation of **21a**, followed by purification by preparative TLC (SiO_2, $CHCl_3$–Me_2CO, 9 : 1), gave **21b** as a red powder (40.7 mg, 86%), mp 147—148 °C and $[\alpha]_D^{20}$ +194° (c=0.103, $CHCl_3$). IR (KBr): 3450, 1740, 1620, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, J=6.5 Hz, $C_{6'}$-H_3), 1.86 (1H, dd, J=12.9, 5.1 Hz, $C_{2'ax}$-H), 1.95, 2.18 (6H, two s, COMe × 2), 1.99—2.13 (1H, m, $C_{2'eq}$-H), 2.22 (1H, dd, J=14.8, 3.9 Hz, C_{3ax}-H), 2.36 (1H, d, J=14.8 Hz, C_{3eq}-H), 3.05 (1H, d, J=18.9 Hz, C_{1ax}-H), 3.31 (1H, dd, J=18.9, 1.8 Hz, C_{1eq}-H), 4.10 (3H, s, C_7-OMe), 4.18 (1H, br q, J=6.5 Hz, $C_{5'}$-H), 4.47 (1H, s, C_2-OH), 5.03 (1H, ddd, J=14.9, 5.0, 3.0 Hz, $C_{3'}$-H), 5.21—5.24 (1H, m, $C_{4'}$-H), 5.33 (1H, dd, J=3.9, 1.8 Hz, C_4-H), 5.53 (2H, d, J=47.7 Hz, CH_2F), 5.63 (1H, d, J=3.7 Hz, W_h=8.0 Hz, $C_{1'}$-H), 7.36 (1H, dd, J=7.8, 1.0 Hz, C_8-H), 7.80 (1H, t, J=7.8 Hz, C_9-H), 8.06 (1H, dd, J=7.8, 1.0 Hz, C_{10}-H), 13.27, 14.02 (2H, two s, phenolic OH × 2). MS m/z: 630 (M^+), 416, 380. *Anal.* Calcd for $C_{31}H_{31}FO_{13}\cdot 0.5H_2O$: C, 58.22; H, 5.04. Found: C, 58.27; H, 5.07.

(2*S*,4*S*)-(+)-4-*O*-(2,6-Dideoxy-α-L-*lyxo*-hexopyranosyl)-2-fluoroacetyl-2,4,5,12-tetrahydroxy-7-methoxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((7*S*,9*S*)-(+)-7-*O*-(2-Deoxy-α-L-fucopyranosyl)-14-fluorodaunomycinone) (10) ——Treatment of **21b** (109 mg, 0.17 mmol) in the same manner as described for **21a**, followed by recrystallization from $CHCl_3$, gave **10** as a red powder (55.0 mg, 58%), mp 230 °C (dec.) and $[\alpha]_D^{20}$ +196° (c=0.051, $CHCl_3$–MeOH, 1 : 1). IR (KBr): 3450, 1740, 1620, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, d, J=6.6 Hz, $C_{6'}$-H_3), 1.85—1.89 (2H, m, $C_{2'}$-H_2), 1.94, 1.96 (2H, two d, J=7.8, 5.8 Hz, $C_{3'}$-OH and $C_{4'}$-OH or $C_{4'}$-OH and $C_{3'}$-OH), 2.19 (1H, dd, J=14.9, 4.0 Hz, C_{3ax}-H), 2.36 (1H, dt, J=14.9, 1.8 Hz, C_{3eq}-H), 3.08 (1H, d, J=18.9 Hz, C_{1ax}-H), 3.30 (1H, dd, J=18.9, 1.8 Hz, C_{1eq}-H), 3.68—3.77 (1H, m, $C_{4'}$-H), 3.78—3.87 (1H, m, $C_{3'}$-H), 4.04 (1H, br q, J=6.6 Hz, $C_{5'}$-H), 4.10 (3H, s, C_7-OMe), 4.68 (1H, s, C_2-OH), 5.34 (1H, dd, J=4.0, 1.8 Hz, C_4-H), 5.51 (2H, d, J=47.8 Hz, CH_2F), 5.55—5.57 (1H, m, W_h=8.0 Hz, $C_{1'}$-H), 7.41 (1H, dd, J=7.8, 1.0 Hz, C_8-H), 7.80 (1H, t, J=7.8 Hz, C_9-H), 8.06 (1H, dd, J=7.8, 1.0 Hz, C_{10}-H), 13.28, 14.02 (2H, two s, phenolic OH × 2). MS m/z: 546 (M^+), 416, 380. *Anal.* Calcd for $C_{27}H_{27}FO_{11}\cdot 0.75H_2O$: C, 57.91; H, 5.13. Found: C, 57.96; H, 5.20.

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References and Notes

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presence of 6.0 eq of PPTS, complete recovery of *dl*-**12a** was observed. These results may further support the *in situ* generation of tetrabutylammonium hydrogendifluoride[14] as an active species.

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22) All melting points were determined with a Yamato MP-21 melting point apparatus and are not corrected. IR spectral measurements were performed using a JASCO A-202 diffraction grating infrared spectrometer. ^{1}H-NMR spectra were measured with a Hitachi R-90H spectrometer (90 MHz) and a Bruker AM-400 spectrometer (400 MHz). All ^{1}H-signals were expressed as ppm downfield from tetramethylsilane (TMS) used as an internal standard (δ-value). Measurements of ^{19}F-NMR spectra were carried out with a Varian XL-100 spectrometer (94 MHz). All ^{19}F-signals were expressed as ppm downfield from fluorotrichloromethane ($CFCl_3$) used as an internal standard. Mass spectra (MS) were taken with a Hitachi RMU-6MG mass spectrometer and a Hitachi M-80A mass spectrometer [Secondary Ion Mass Spectrometry (SIMS)]. Measurements of optical rotations were carried out with a Horiba SEPA-200 automatic digital polarimeter. Wakogel C-200 was used as an adsorbent for column chromatography. All reactions were performed using anhydrous solvents. In particular, tetrahydrofuran, ether, and dioxane freshly distilled from sodium benzophenone ketyl, and commercially available dichloromethane stabilized with amylene were used. Trimethylsilyl trifluoromethanesulfonate and tetrabutylammonium fluoride purchased from Petrarch System Inc. (Chisso) and Aldrich Chemical Co., respectively, were used without further purification. The following abbreviations are used for solvents and reagents; acetic acid (AcOH), acetone (Me_2CO), benzene (PhH), bromine (Br_2), carbon tetrachloride (CCl_4), chloroform ($CHCl_3$), cyclohexane (C_6H_{12}), dichloromethane (CH_2Cl_2), ether (Et_2O), ethyl acetate (EtOAc), hexane (C_6H_{14}), methanol (MeOH), molecular sieves-4A (MS-4A), 2-propanol (Me_2CHOH), toluene (PhMe), trimethoxymethane ($CH(OMe)_3$).