Synthesis of 14,14-Difluoro-4-demethoxydaunorubicin[1)]

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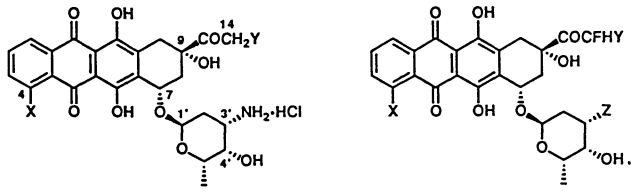
The title compound, (+)-14,14-difluoro-4-demethoxydaunorubicin hydrochloride (**9**), was prepared starting from the readily available (−)-hydroxy ester (**10**). This synthesis featured the efficient synthetic route to (−)-14,14-difluoro-4-demethoxy-7-deoxydaunomycinone (**20**) employing the Reformatsky reaction of ethyl bromodifluoroacetate with the (−)-siloxy aldehyde (**14**) and previously developed glycosylation method in which trimethylsilyl trifluoromethanesulfonate was used as an activator. In P388 *in vitro* test, **9** was found to be fifty times more active than adriamycin (**1**). Prominent antitumor activity was also observed for **9** in P388 *in vivo* test.

The anthracyclines, represented by adriamycin (**1**) and daunorubicin (**2**), are important anticancer agents exhibiting clinical effectiveness against leukemia and solid tumors.[2,3)] However, their utility for cancer chemotherapy is seriously restricted by various undesired side effects, the most notable of which is dose-related cardiotoxicity. Thus, numerous attempts have been made to prepare various structural types of congeners by chemical synthesis with an aim to overcome these disadvantages. Among synthetically elaborated analogues of **1** and **2**, unnatural 4-demethoxyadriamycin (**3**) and 4-demethoxydaunorubicin (**4**) have been reported to show better therapeutic indices than natural **1** and **2**.[2−4)]

On the other hand, a large number of the fluorinated biologically active compounds have been synthesized in the last decade to improve therapeutic property of the parent compounds or to explore novel pharmacological activity.[5)] In the field of anthracyclines, some derivatives possessing fluorinated sugar[6)] or D-ring[7)] have been synthesized. In conjunction with our program directed toward the development of novel synthetic anthracycline congeners as anticancer agents, we achieved the first synthesis of the 14-fluoroanthracyclines (**5**—**8**) which had a fluoroacetyl group as their C-9 side chain. Furthermore, these novel anthracyclines showed potent antitumor activity against P388 murine leukemia *in vitro* and *in vivo*.[8)] Thus, taking into account of these results, we are interested in evaluating the antitumor activity of 14,14-difluoro-4-demethoxydaunorubicin (**9**), the most representative member of 14,14-difluoroanthracyclines. Recently, the first synthesis of **9** has been accomplished by employing the Reformatsky reaction of ethyl bromodifluoroacetate as a key step. Moreover, **9** was found to exhibit prominent *in vitro* cytotoxicity and *in vivo* antitumor activity against P388 murine leukemia.[1)] This report deals with full details of the synthesis and antitumor activity of the novel 14,14-difluoroanthracycline (**9**).



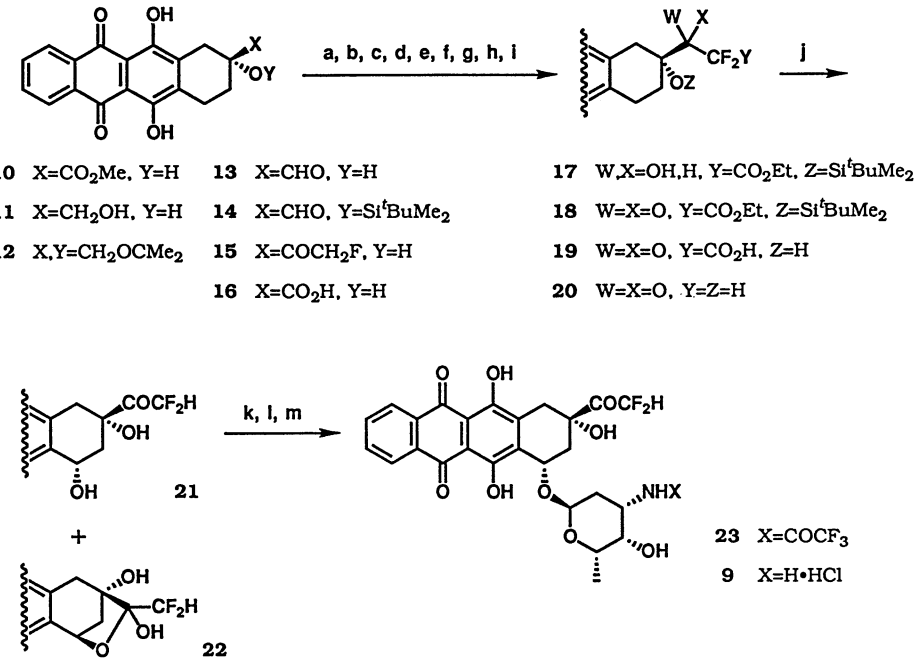
1 X=OMe, Y=OH
2 X=OMe, Y=H
3 X=H, Y=OH
4 X=Y=H

5 X=OMe, Y=H, Z=NH_2·HCl
6 X=Y=H, Z=NH_2·HCl
7 X=OMe, Y=H, Z=OH
8 X=Y=H, Z=OH
9 X=H, Y=F, Z=NH_2·HCl

Fig. 1.

Results and Discussion

Preparation of 14,14-Difluoro-4-demethoxydaunomycinone. Numerous preliminary experimentations were carried out using racemic anthracyclinone derivatives to construct a difluoroacetyl side chain at the C-9 position. At the outset of this work, introduction of fluorine atom into the C-14 position of racemic 14-fluoro-4-demethoxy-7-deoxydaunomycinone (*dl*-**15**) was examined according to the fluorination method previously explored for 7-deoxydaunomycinones.[8)] However, attempted bromination of *dl*-**15** always produced complex mixtures of reaction products. Accordingly, the Reformatsky reaction of ethyl bromodifluoroacetate[9)] was next studied, which had been frequently used to introduce a difluorinated carbon chain.[10)] Although the Reformatsky reaction with the hydroxy aldehyde (*dl*-**13**) or the acylimidazole derivative generated from the hydroxy acid (*dl*-**16**)[11)] resulted in decomposition or recovery of the starting material respectively, it was finally uncovered that the reaction with the siloxy aldehyde (*dl*-**14**) successfully produced the addition product, β-hydroxy ester (*dl*-**17**). In contrast, *dl*-**17** could not be obtained from *dl*-**14** when methyl difluoroiodoacetate[12)] was employed instead of ethyl bromodifluoroacetate probably due to instability of the zinc enolate generated *in situ*. The racemic aldehydes (*dl*-**13** and *dl*-**14**) could be prepared from the hydroxy ester (*dl*-**10**)[11)] according to the same procedures as described for optically active compounds (vide infra). On the basis of these results, an efficient synthetic method of 14,14-difluoro-4-demethoxy-7-deoxydaunomycinone (**20**) as described below was eventu-



10 X=CO_2Me, Y=H
11 X=CH_2OH, Y=H
12 X,Y=CH_2OCMe_2
13 X=CHO, Y=H
14 X=CHO, Y=Si^tBuMe_2
15 X=$COCH_2F$, Y=H
16 X=CO_2H, Y=H
17 W,X=OH,H, Y=CO_2Et, Z=Si^tBuMe_2
18 W=X=O, Y=CO_2Et, Z=Si^tBuMe_2
19 W=X=O, Y=CO_2H, Z=H
20 W=X=O, Y=Z=H
21
22
23 X=$COCF_3$
9 X=H•HCl

Scheme 1. a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, $CHCl_3$–MeOH, 0 °C→rt, 3 h b) CSA, $Me_2C(OMe)_2$–acetone–THF, rt, 4 h, 78% (2 steps) c) 12 mol dm^{-3} HCl, THF, 0 °C, 4 h, 90% d) $SO_3 \cdot$ Py, Et_3N, DMSO, rt, 10 min, 79% e) TBDMSOTf, 2,6-Lu, CH_2Cl_2, 0 °C→rt, 5.5 h, 86% f) $BrCF_2CO_2Et$, Zn, THF, reflux, 30 min, 42% g) Dess–Martin reagent, CH_2Cl_2, 0 °C→rt, 20 min, 45% h) 0.5 mol dm^{-3} KOH, THF–MeOH, 0 °C, 30 min, then 1 mol dm^{-3} HCl i) DMF, 60 °C, 35 min, 73% (2 steps) j) 1) Br_2, $h\nu$, CCl_4–$CHCl_3$–H_2O, rt, 2.5 h, 2) 2.5 mol dm^{-3} NaOH, 0 °C, 15 min, then 1 mol dm^{-3} HCl, 26% (**21**), 31% (**22**) k) L-Daunosamine derivative, TMSOTf, 4A-MS, CH_2Cl_2–Et_2O–THF, −10 °C, 5.5 h l) 0.1 mol dm^{-3} NaOH, MeOH, rt, 20 min, then 2 mol dm^{-3} AcOH, 89% (2 steps) m) 1) 0.05 mol dm^{-3} NaOH, THF, rt, 50 min, then 1 mol dm^{-3} HCl 2) 0.25 mol dm^{-3} HCl, MeOH, 40% (2 steps).

ally explored employing the Reformatsky reaction of ethyl bromodifluoroacetate with **14** as a key step.

The synthesis of optically pure **14** was carried out by utilizing the readily available optically pure (−)-hydroxy ester (**10**),[11] mp 214—215 °C, $[\alpha]_D^{20}$ −63.6° (*c* 0.110, $CHCl_3$), as the starting material. Reduction of **10** with sodium borohydride in the presence of cerium(III) chloride heptahydrate yielded the (−)-diol (**11**). The reduction product (**11**) was purified by silica-gel chromatography in a form of the corresponding (−)-acetonide (**12**), mp 220—223 °C, $[\alpha]_D^{20}$ −51.0° (*c* 0.050, $CHCl_3$), because of its sparing solubility in usual organic solvents. According to this procedure, **12** could be obtained in a higher yield (78% from **10**) than that previously reported for the reduction of **10** with lithium tri-*t*-butoxyaluminum hydride (55% from **10**).[11] Acidic hydrolysis of **12** yielded a pure sample of **11**, mp 260—263 °C, $[\alpha]_D^{20}$ −50.0° (*c* 0.060, dioxane). The (−)-siloxy aldehyde (**14**), mp 251—252 °C, $[\alpha]_D^{20}$ −76.9° (*c* 0.104, $CHCl_3$), was derived from **11** by sequential oxidation and silylation of the resulting (−)-hydroxy aldehyde (**13**), mp 248—249 °C, $[\alpha]_D^{20}$ −54.5° (*c* 0.110, dioxane).

The Reformatsky reaction of ethyl bromodifluoroacetate with **14** took place cleanly under the usual conditions,[9] giving rise to the β-hydroxy ester (**17**) as an epimeric mixture. The ratio of two epimers estimated by the ^1H NMR spectra of the mixture was 2 : 1. Without separation of the epimers, **17** was oxidized to the (−)-β-keto ester (**18**), mp 119—121 °C, $[\alpha]_D^{20}$ −91.8° (*c* 0.098, $CHCl_3$), using the Dess–Martin periodinane[13] as an oxidizing reagent. The oxidation of **17** appeared to be exceptionally difficult. Oxidants other than the Dess–Martin reagent resulted in complete recovery of **17**.[14] Sequential hydrolysis of the ethyl ester and decarboxylation of the formed β-keto acid (**19**) afforded (−)-14,14-difluoro-4-demethoxy-7-deoxydaunomycinone (**20**),[16] mp 225—228 °C, $[\alpha]_D^{20}$ −26.1° (*c* 0.153, dioxane).

Next, preparation of 14,14-difluoro-4-demethoxydaunomycinone (**21**) from **20** was examined. Since all the attempts to protect the ketonic function of **20** in a form of acetal met with failure probably due to the adjacent two fluorine atoms, direct introduction of the C_7-hydroxyl group was studied. Bromination of **20** with bromine under irradiation followed by immediate treatment of the resulting unstable C_7-bromide with aqueous alkali gave (+)-14,14-difluoro-4-demethoxydaunomycinone (**21**),[16] mp 210—213 °C, $[\alpha]_D^{20}$ +44.2° (*c*

0.113, dioxane), along with its $C_{7\beta}$-epimer in a form of the (−)-hemiacetal (**22**), mp 253—255 °C, $[\alpha]_D^{20}$ −153° (*c* 0.157 dioxane). The mixture of **21** and **22** could be separated by preparative TLC on silica gel. The stereochemistry of the C_7-position of **21** was established by the ^{1}H NMR spectrum ($CDCl_3$) which showed a W_H value of 8.0 Hz for the signal of the $C_{7\beta}$-H [δ=5.36—5.45 (m)]. On the other hand, in the ^{1}H NMR spectrum ($CDCl_3$) of **22**, a single triplet assignable to the C_{14}-methine proton appeared at δ=5.58 (J=54 Hz). Thus, it becomes apparent that **22** consists of a single hemiacetal whose stereostructure at the hemiacetal carbon could not be determined. All the attempts to epimerize **22** under acidic conditions[17] resulted in simple recovery of the starting material. Additionally, 14,14-difluoro-7-deoxydaunomycinone (**20**) could be obtained only in low yield (32%) by hydrogenolysis of **22** following the reported procedure (H_2, Pd–$BaSO_4$, MeOH, rt, 2 h).[18] These phenomena might originate from the electron-withdrawing effect accumulated by the two fluorine atoms making the hemiacetal form highly stable.

Preparation of 14,14-Difluoro-4-demethoxydaunorubicin. With **21** in hand, glycosylation was attempted using the L-daunosamine derivative according to the procedure previously reported by us.[19] Thus, **21** was allowed to react with 3-*N*-trifluoroacetyl-1,4-bis-*O*-(*p*-nitrobenzoyl)-L-daunosamine[19] in the presence of trimethylsllyl trifluoromethanesulfonate. The formed glycoside was treated with dilute alkali to effect hydrolysis of the 4′-*O*-*p*-nitrobenzoyl group, affording (+)-3′-*N*-trifluoroacetyl-14,14-difluoro-4-demethoxydaunorubicin (**23**),[16] $[\alpha]_D^{20}$ +117° (*c* 0.163, dioxane), as a sole product. The α-glycoside structure of **23** could be readily confirmed by the coupling pattern of the $C_{1'}$-H [δ=5.53 (d, J=4.2 Hz)] in the ^{1}H NMR spectrum ($CDCl_3$) of **23**. The assigned structure was further supported by comparison of the ^{1}H NMR spectrum with that of 3′-*N*-trifluoroacetyl-4-demethoxydaunorubicin.[19] Further alkaline hydrolysis of the 3′-*N*-trifluoroacetyl group followed by salt formation furnished (+)-14,14-difluoro-4-demethoxydaunorubicin hydrochloride (**9**), mp 168—171 °C, $[\alpha]_D^{20}$ +111° (*c* 0.090, MeOH). The ^{1}H NMR and ^{19}F NMR spectra (DMSO-d_6+D_2O) of **9** proved that this compound was composed of a mixture of the ketonic and the hydrate forms (3:1 by ^{1}H NMR).[16] Representative NMR spectral data are as follows; **9**: ^{1}H NMR δ=6.04 (t, J=55.8 Hz, CHF_2, hydrate), 6.85 (t, J=52.9 Hz, CHF_2, ketone); ^{19}F NMR δ=−128.0 (d, J=52.9 Hz, ketone), −131.2 (d, J=55.8 Hz, hydrate).

Antitumor Activity of 14,14-Difluoro-4-demethoxydaunorubicin. 14,14-Difluoro-4-demethoxydaunorubicin (**9**) was subjected to P388 murine leukemia *in vitro* assay along with its 3′-*N*-trifluoroacetyl derivative (**23**). While **23** showed comparable cytotoxicity (IC_{50}=1.1×10^{-3} μg ml^{-1})[20] to that of adriamycin (**1**) (IC_{50}=2.5×10^{-3} μg ml^{-1}), **9** was found to be at least fifty-fold more active (IC_{50}=4.6×10^{-5} μg ml^{-1}) than **1**. Since cytotoxicity of 14-fluoro-4-demethoxydaunorubicin (**6**) has already been disclosed to be compared well with that of **1**,[8] it appeared that **9** was obviously more cytotoxic than **6**. Furthermore, in P388 *in vivo* test,[21] it turned out that **9** exhibited potent inhibitory activity [T/C=161% (1.0 mg kg^{-1})].[22]

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

Experimental

General. All melting points were determined with a Yamato MP-21 melting point apparatus and are uncorrected. Measurements of optical rotations were carried out by using a Horiba SEPA-200 automatic digital polarimeter. IR spectral measurements were performed with a JASCO A-202 IR spectrometer. ^{1}H NMR spectra were measured with a Hitachi R-90H spectrometer (90 MHz) and a Bruker AM-400 spectrometer (400 MHz). Measurement of ^{19}F NMR spectra were carried out with a Varian XL-100 spectrometer (94 MHz). All ^{1}H and ^{19}F-signals were expressed as ppm downfield from tetramethylsilane ($SiMe_4$) and trichlorofluoromethane ($CFCl_3$), respectively, used as an internal standard (δ-value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Assignments of peaks are indicated according to the numbering of IUPAC nomenclature. Mass spectra (MS) were taken with a Hitachi RMU-6MG mass spectrometer (EI-MS) and a Hitachi M-80A mass spectrometer (SI-MS). Wako Gel C-200 and Merck Silica Gel 60F_{254} were used for column chromatography and preparative thin-layer chromatography (TLC), respectively. All reactions were performed by using anhydrous solvents. In particular, tetrahydrofuran and ether freshly distilled from sodium benzophenone ketyl, and commercially available dichloromethane stabilized with 2-methyl-2-butene were used. The following abbreviations are used for solvents; acetic acid (AcOH), carbon tetrachloride (CCl_4), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), ethyl acetate (AcOEt), methanol (MeOH), tetrahydrofuran (THF), toluene (PhMe).

(*R*)-6,8,11-Trihydroxy-8-hydroxymethyl-7,8,9,10-tetrahydro-5,12-naphthacenedione (11). $NaBH_4$ (8.11 g, 214 mmol) was added in small portions to a stirred solution of (*R*)-6,8,11-trihydroxy-8-methoxycarbonyl-7,8,9,10-tetrahydro-5,12-naphthacenedione (**10**),[11] mp 214—215 °C, $[\alpha]_D^{20}$ −63.6° (*c* 0.110, $CHCl_3$), (7.89 g, 21.4 mmol) and $CeCl_3\cdot7H_2O$ (40.0 g, 107 mmol) in a mixture of $CHCl_3$ (400 ml) and MeOH (160 ml) cooled at 0 °C. The reaction mixture was allowed to warm up to ambient temperature and stirring was continued at the same temperature for 3 h. After further amounts of $CeCl_3\cdot7H_2O$ (40.0 g, 107 mmol) and $NaBH_4$ (8.11 g, 214 mmol) were successively added at room temperature, the reaction mixture was further stirred at the same temperature for 4 h. The mixture was poured into 1 mol dm^{-3} HCl, and extracted with a mixture of AcOEt and THF. The combined organic extracts were washed with H_2O, and dried over anhydrous $MgSO_4$. Filtration and concentration in vacuo gave crude **11**, which was dissolved in a mixture of THF (420 ml) and acetone (210 ml). After 2,2-dimethoxypropane (830 ml) and *d*-10-camphorsulfonic acid (800 mg, 3.44 mmol) were successively added to the solution at ambient temperature, the mixture was stirred at the same temperature for 4 h, poured

into saturated $NaHCO_3$, and extracted with $CHCl_3$. The organic layers were combined, washed successively with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. The residue was purified by column chromatography (SiO_2, PhMe–AcOEt 200 : 1) to give (*R*)-5′,12′-dihyroxy-2,2-dimethyl-3′,4′-dihydrospiro[1,3-dioxolane-4,2′(1′*H*)-naphthacene]-6′,11′-dione (**12**) as a red solid (6.37 g, 78%), mp 220—223 °C, $[\alpha]_D^{20}$ −51.0° (*c* 0.050, $CHCl_3$) [lit,[11] mp 222—223 °C, $[\alpha]_D^{20}$ −52.0° (*c* 0.050, $CHCl_3$)]. Spectral and chromatographic comparison showed that **12** was identical with an authentic sample.[11]

Twelve mol dm^{-3} hydrochloric acid (160 ml) was added to a suspension of **12** (6.37 g, 16.9 mmol) in THF (640 ml) at room temperature. After stirring at the same temperature for 4 h, the mixture was poured into ice-water, and extracted with a mixture of AcOEt and THF. The combined extracts were washed successively with H_2O and saturated $NaHCO_3$. dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo. Trituration of the residue with ether gave pure **11** as a dark orange solid (5.12 g, 90%), mp 260—263 °C, $[\alpha]_D^{20}$ −50.0° (*c* 0.060, dioxane) [lit,[11] mp 265—267 °C, $[\alpha]_D^{20}$ −52.0° (*c* 0.050, dioxane)]. The spectra and chromatographic behaviors of this sample were identical with those of an authentic sample.[11]

(*R*)-8-Formyl-6,8,11-trihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (13). A suspension of sulfur trioxide pyridine complex (467 mg, 2.93 mmol) in DMSO (1.0 ml) was added with stirring under an Ar atmosphere to a solution of **11** (49.8 mg, 0.146 mmol) and triethylamine (0.61 ml, 4.38 mmol) in DMSO (3.0 ml) at ambient temperature. After stirring at the same temperature for 10 min, the mixture was poured into 1 mol dm^{-3} HCl, and extracted with AcOEt. The combined organic layers were washed successively with H_2O and brine, and dried over anhydrous Na_2SO_4. Filtration and concentration in vacuo gave the crude product, which was purified by column chromatography (SiO_2, PhMe–AcOEt 20 : 1→10 : 1), affording pure **13** as a red powder (39.0 mg, 79%). This was recrystallized from PhMe, giving an analytical sample of **13** as red crystals, mp 248—249 °C, $[\alpha]_D^{20}$ −54.5° (*c* 0.110, dioxane). IR (KBr) 3500, 1730, 1620, 1580 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=1.80—2.00 (2H, m, C_9–H_2), 2.50 (1H, s, C_8–OH), 2.97—3.20 (4H, m, C_7–H_2, C_{10}–H_2), 7.77—7.93, 8.30—8.50 (each 2H, m, ArH×4), 9.75 (1H, s, CHO), 13.50 (2H, s, ArOH×2). EI-MS *m*/*z* 338 (M^+), 309 (M^+ −CHO), 291. Anal. Calcd for $C_{19}H_{14}O_6$: C, 67.45; H, 4.17%. Found: C, 67.18; H, 4.22%. The racemic hydroxy aldehyde (*dl*-**13**) prepared by the same procedure as described above, showed mp 251—253 °C. The ^{1}H NMR spectrum ($CDCl_3$) of *dl*-**13** was identical with that of the optically active compound.

(*R*)-8-*t*-Butyldimethylsilyloxy-8-formyl-6,11-dihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (14). 2,6-Lutidine (25.2 ml, 216 mmol) and *t*-butyldimethylsilyl trifluoromethanesulfonate (50.5 ml, 220 mmol) was successively added under an Ar atmosphere to a stirred suspension of **13** (3.69 g, 10.9 mmol) in CH_2Cl_2 (80 ml) at 0 °C. After stirring was continued at the same temperature for 30 min, the reaction mixture was allowed to warm up to room temperature, then stirred at the same temperature for 5 h. The mixture was poured into saturated $NaHCO_3$, and extracted with $CHCl_3$. The extracts were combined, washed successively with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo. Recrystallization of the residue from PhMe gave pure **14** as orange crystals (4.23 g, 86%), mp 251—252 °C, $[\alpha]_D^{20}$ −76.9° (*c* 0.104, $CHCl_3$). IR (KBr) 3450, 2880, 1730, 1620, 1590 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=−0.10, 0.15 (each 3H, s, $SiMe_2$), 0.83 (9H, s, ^{t}Bu), 1.63—2.20 (2H, m, C_9–H_2), 2.83—3.20 (4H, m, C_7–H_2, C_{10}–H_2), 7.70—7.90, 8.23—8.47 (each 2H, m, ArH×4), 9.30 (1H, s, CHO), 12.95, 12.98 (each 1H, s, ArOH×2). EI-MS *m*/*z* 452 (M^+), 437 (M^+ −Me) 395 (M^+ −^{t}Bu). Anal. Calcd for $C_{25}H_{28}O_6Si$: C, 66.35; H, 6.24%. Found: 66.57; H, 6.25%. The racemic siloxy aldehyde (*dl*-**14**) prepared by the same procedure as described above, showed mp 255—257 °C. The ^{1}H NMR spectrum ($CDCl_3$) of *dl*-**14** was identical with that of the optically active compound.

(*R*)-8-*t*-Butyldimethylsilyloxy-8-(2-ethoxycarbonyl-2,2-difluoro-1-hydroxyethyl)-6,11-dihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (17). A mixture of Zn (1.28 g, 19.5 mmol) and ethyl bromodifluoroacetate[9] (4.22 g, 20.8 mmol) in THF (60 ml) was heated at reflux under an Ar atmosphere for 1 min. After a solution of **14** (588 mg, 1.30 mmol) in THF (60 ml) was added under reflux to the reaction mixture, stirring was continued under reflux for 30 min. After cooling, the mixture was poured into 1 mol dm^{-3} $KHSO_4$ cooled in an ice bath, and extracted with AcOEt. The combined extracts were washed with brine, and dried over anhydrous Na_2SO_4. Filtration and concentration in vacuo gave the crude product, which was chromatographed (SiO_2, PhMe–AcOEt 50 : 1→30 : 1) to give pure **17** (a 2 : 1 mixture of the diastereomers by ^{1}H NMR) as a red amorphous powder (313 mg, 42%). IR (KBr) 3500, 1760, 1620, 1580 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=0.00, 0.20 (each 3H, s, $SiMe_2$), 0.90, 0.92 (total 9H, each s, ^{t}Bu), 1.33 (3H, t, *J*=6.0 Hz, CH_2*Me*), 1.80—2.50 (2H, m, C_9–H_2), 2.60—3.67 (4H, m, C_7–H_2, C_{10}–H_2), 3.70—4.20 (1H, m, $C_{1'}$–H), 4.35 (2H, q, *J*=6.0 Hz, CH_2Me), 7.60—7.93, 8.20—8.40 (each 2H, m, ArH×4), 13.40, 13.46, 13.44 (total 2H, each s, ArOH×2). ^{19}F NMR ($CDCl_3$) δ=−106.4 (d, *J*=260.0 Hz), −106.7 (d, *J*=257.0 Hz), −124.3 (dd, *J*=260.0, 20.0 Hz), −125.9 (dd, *J*=257.0, 22.5 Hz). EI-MS *m*/*z* 577 (M^+ +H), 519 (M^+ −^{t}Bu).

(*R*)-8-*t*-Butyldimethylsilyloxy-8-ethoxycarbonyldifluoroacetyl-6,11-dihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (18). Dess–Martin reagent (428 mg, 1.01 mmol) was added under an Ar atmosphere to a stirred solution of **17** (116 mg, 0.202 mmol) in CH_2Cl_2 (20 ml) at 0 °C. The reaction mixture was allowed to warm up to room temperature, stirred at the same temperature for 20 min, poured into saturated $NaHCO_3$ containing excess $Na_2S_2O_3$, and extracted with ether. The organic layers were combined, washed successively with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo. The residue was purified by column chromatography (SiO_2, PhMe–AcOEt 30 ; 1), giving pure **18** as an orange solid (52.0 mg, 45%). This was recrystallized from hexane–PhMe to afford an analytical sample of **18** as orange crystals, mp 119—121 °C, $[\alpha]_D^{20}$ −91.8° (*c* 0.098, $CHCl_3$). IR (KBr) 3450, 1790, 1740, 1620, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=0.01, 0.19 (each 3H, s, $SiMe_2$), 0.85 (9H, s, ^{t}Bu), 1.36 (3H, t, *J*=7.2 Hz, CH_2*Me*), 2.19 (1H, dt, *J*=13.2, 6.2 Hz, $C_{9\text{-ax}}$–H), 2.33 (1H, dt, *J*=13.2, 6.2 Hz, $C_{9\text{-eq}}$–H), 2.88 (1H, ddd, *J*=19.2, 7.4, 6.2 Hz, $C_{10\text{-ax}}$–H), 3.00 (1H, d, *J*=18.6 Hz, $C_{7\text{-aq}}$–H), 3.09 (1H, dt, *J*=19.2, 6.2 Hz, $C_{10\text{-eq}}$–H), 3.44 (1H, d, *J*=18.6 Hz, $C_{7\text{-eq}}$–H), 4.38 (2H, q, *J*=7.2 Hz, CH_2Me), 7.80—7.85, 8.34—8.38 (each 2H, m, ArH×4), 13.44, 13.50 (each 1H, s, ArOH×2). ^{19}F NMR ($CDCl_3$) δ=−109.1 (s). EI-MS *m*/*z* 575 (M^+ +H), 559 (M^+ −Me), 517 (M^+ −^{t}Bu). Anal. Calcd for $C_{29}H_{32}O_8F_2Si$: C, 60.61; H, 5.61%. Found: C, 60.57; H, 5.69%.

(*R*)-8-Difluoroacetyl-6,8,11-trihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione(14,14-difluoro-4-demethoxy-7-deoxydaunomycinone) (20). A 0.53 mol dm^{-3} solution of KOH (0.74 ml, 0.392 mmol) was added to a solution of **18** (102 mg, 0.177 mmol) in a mixture of THF (5.0 ml) and MeOH (5.0 ml) cooled in an ice bath. After stirring at 0 °C for 30 min, the mixture was neutralized with 1 mol dm^{-3} HCl (pH 7), diluted with brine, and extracted with AcOEt. The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4. Filtration and concentration in vacuo gave crude (*R*)-8-carboxydifluoroacetyl-6,8,11-trihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (**19**), which was dissolved in DMF (10 ml). The solution was heated at 60 °C for 35 min, poured into brine, extracted with AcOEt. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo. The residue was purified by preparative TLC (SiO_2, PhMe–AcOEt 1 : 1) and successive azeotropic removal of H_2O using PhMe[16] to afford pure **20** as a red powder (50.5 mg, 73%). Recrystalllzation from PhMe gave an analytical sample of **20** as red crystals, mp 225—228 °C, $[\alpha]_D^{20}$ −26.1° (*c* 0.153, dioxane). IR (KBr) 3500, 1750, 1620, 1590 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.00—2.30 (2H, m, C_9–H_2), 2.72 (1H, s, C_8–OH), 2.57—3.55 (4H, m, C_7–H_2, C_{10}–H_2), 6.40 (1H, t, *J*=4.3 Hz, CHF_2), 7.67—8.06, 8.20—8.57 (each 2H, m, ArH×4), 13.41 (2H, s, ArOH×2). ^{19}F NMR ($CDCl_3$) δ=−127.1 (d, *J*=54.3 Hz). EI-MS *m/z* 388 (M^+), 309,291. Anal. Calcd for $C_{20}H_{14}O_6F_2$: C, 61.86; H, 3.63%. Found: C, 61.67; H, 3.54%.

(8*S*,10*S*)-8-Difluoroacetyl-6,8,10,11-tetrahydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (14,14-Difluoro-4-demethoxydaunomycinone) (21) and (1*R*,3*S*)-13—Difluoromethyl-3,5,12,13-tetrahydroxy-1,2,3,4-tetrahydro-1,3-(epoxymethano)-6,11-naphthacenedione (22). A 0.083 mol dm^{-3} solution of Br_2 in CCl_4 (0.57 ml) was added with stirring to a mixture of **20** (30.5 mg, 0.0785 mmol) in a two-layer mixture of CCl_4 (3.1 ml), $CHCl_3$ (6.1 ml), and H_2O (4.6 ml) at ambient temperature, then the reaction mixture was stirred under irradiation with a 60 W tungsten lamp at the same temperature for 2.5 h. Further amounts of 0.083 mol dm^{-3} solution of Br_2 in CCl_4 (0.19 ml×7, total 1.90 ml, 0.158 mmol) were added after 15, 20, 25, 30, 35, 40, and 45 min. After cooling in an ice bath, 2.5 mol dm^{-3} NaOH (0.19 ml, 0.475 mmol) was added, and stirring was continued at 0 °C for 15 min. The mixture was neutralized with 1 mol dm^{-3} HCl (pH 7), and extracted with AcOEt. The combined organic layers were washed successively with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo. The residue was separated by preparative TLC (SiO_2, $CHCl_3$–MeOH 10 : 1), affording pure **21** (containing a small amount of the hydrate form by ^{1}H NMR)[16] as a red powder (8.3 mg, 26%) and pure **22** as a red powder (9.8 mg, 31%). Recrystallizations of these from PhMe gave analytical samples of **21** and **22** as red crystals, respectively.

21: Mp 210—213 °C, $[\alpha]_D^{20}$ +44.2° (*c* 0.113, dioxane). IR (KBr) 3450, 1750, 1620, 1590 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.18 (1H, dd, *J*=14.8, 4.8 Hz, $C_{9\text{-aq}}$–H), 2.60 (1H, d, *J*=14.8 Hz, $C_{9\text{-eq}}$–H), 3.03 (1H, d, *J*=18.8 Hz, $C_{7\text{-ax}}$–H), 3.34 (1H, brs, C_{10}–OH), 3.40 (1H, dd, *J*=18.8, 2.3 Hz, $C_{7\text{-eq}}$–H), 4.76 (1H, s, C_8–OH), 5.36—5.45 (1H, m, C_{10}–H), 6.60 (1H, t, *J*=53.1 Hz, CHF_2), 7.79—7.94, 8.30—8.43 (each 2H, m, ArH×4), 13.27, 13.58 (each 1H, s, ArOH×2). ^{19}F NMR ($CDCl_3$) δ=−129.5, −130.0 (each dd, *J*=315.0, 53.1 Hz). EI-MS *m/z* 404 (M^+), 386, 368, 317, 307, 289. High-resolution MS, Found: *m/z* 404.0706. Calcd for $C_{20}H_{14}O_7F_2$: M, 404.0706.

22: Mp 253—255 °C, $[\alpha]_D^{20}$ −153° (*c* 0.157, dioxane). IR (KBr) 3500, 1625, 1590 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.04 (1H, dd, *J*=11.2, 1.8 Hz, $C_{2\text{-ax}}$–H), 2.78 (1H, ddd, *J*=11.2, 5.7, 1.8 Hz, $C_{2\text{-eq}}$–H), 3.24 (1H, d, *J*=19.5 Hz, $C_{4\text{-ax}}$–H), 3.40 (1H, d, *J*=19.5 Hz, $C_{4\text{-eq}}$–H), 5.58 (1H, t, *J*=54.5 Hz, CHF_2), 5.74 (1H, dd, *J*=5.7, 1.0 Hz, C_1–H), 7.82—7.88, 8.32—8.39 (each 2H, m, ArH×4), 13.15, 13.23 (each 1H, s, ArOH×2). ^{19}F NMR ($CDCl_3$) δ=−1287, −136.3 (each dd, *J*=347.0, 54.5 Hz). EI-MS *m/z* 404 (M^+), 368, 308, 290. High-resolution MS, Found: *m/z* 404.0703. Calcd for $C_{20}H_{14}O_7F_2$: M, 404.0706.

Preparation off 20 from 22. A mixture of **22** (9.8 mg, 0.0243 mmol) and 10% Pd–$BaSO_4$ (11.2 mg) in MeOH (2.5 ml) was stirred under a H_2 atmosphere at room temperature for 2 h. The catalyst was filtered off and washed with MeOH. The combined filtrates were concentrated in vacuo. Purification of the residue by preparative TLC (SiO_2, PhMe–AcOEt, 1 : 1) afforded pure **20** as a red powder (3.0 mg, 32%). Spectral and chromatographic comparisons revealed that this was identical with an authentic sample synthesized as described above.

(8*S*,10*S*)-10-*O*-(2,3,6-Trideoxy-3-trifluoroacetoamido-α-L-*lyxo*-hexopyranosyl)-8-difluoroscetyl-6,8,11-trihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (3′-*N*-Trifluoroacetyl-14,14-difluoro-4-demethoxydaunorubicin) (23). A 1.0 mol dm^{-3} solution of trimethylsilyl trifluoromethanesulfonate in CH_2Cl_2 (0.17 ml, 0.170 mmol) was added under an Ar atmosphere to a mixture of 1,4-bis-*O*-(*p*-nitrobenzoyl)-3-*N*-trifluoroacetyl-L-daunosamine[19] (46.0 mg, 0.0850 mmol) and molecular sieves 4A (257 mg) in a mixture of ether (3.7 ml) and CH_2Cl_2 (4.6 ml) at −40 °C. The mixture was stirred at 0 °C for 40 min, then cooled to −20 °C. After a solution of **21** (9.2 mg, 0.0228 mmol) in THF (4.0 ml) was added to the reaction mixture, stirring was continued at −10 °C for 5.5 h. The mixture was poured into a two-layer mixture of AcOEt and saturated $NaHCO_3$, and extracted with AcOEt. The combined extracts were washed successively with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in MeOH (20 ml), and 0.1 mol dm^{-3} NaOH (0.2 ml) was added to the solution cooled in an ice bath. After stirring at the same temperature for 20 min, the mixture was neutralized with 2 mol dm^{-3} AcOH, diluted with H_2O, and extracted with AcOEt. The organic layers were combined, washed successively with H_2O and brine, dried over Na_2SO_4, filtered, then concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, $CHCl_3$→$CHCl_3$–acetone 10 : 1) followed by trituration with ether and azeotropic removal of H_2O using PhMe,[16] giving pure **23** as a red amorphous powder (12.8 mg, 89%), $[\alpha]_D^{20}$ +117° (*c* 0.163, dioxane). IR (KBr) 3450, 1750, 1720, 1625, 1590 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=1.31 (3H, d, *J*=6.6 Hz, $C_{5'}$–Me), 1.86 (1H, dt, *J*=13.2, 4.2 Hz, $C_{2'\text{-ax}}$–H), 1.93—1.98 (1H, m, $C_{4'}$–OH), 2.03 (1H, dd, *J*=13.2, 5.3 Hz, $C_{2'\text{-eq}}$–H), 2.12 (1H, dd, *J*=14.7, 4.0 Hz, $C_{9\text{-ax}}$–H), 2.63 (1H, d, *J*=14.7 Hz, $C_{9\text{-eq}}$–H), 3.16 (1H, d, *J*=19.1 Hz, $C_{7\text{-ax}}$–H), 3.40 (1H, dd, *J*=19.1, 1.9 Hz, $C_{7\text{-eq}}$–H), 3.65—3.72 (1H, m, $C_{4'}$–H), 4.16—4.26 (1H, m, $C_{3'}$–H), 4.25 (1H, q, *J*=6.6 Hz, $C_{5'}$–H), 4.67 (1H, s, C_8–OH), 5.28 (1H, dd, *J*=4.0, 1.9 Hz, C_{10}–H), 5.53 (1H, d, *J*=4.2 Hz, $C_{1'}$–H), 6.60 (1H, t, *J*=54.6 Hz, CHF_2), 6.67 (1H, brd, *J*=8.5 Hz, NH), 7.80—7.90, 8.32—8.41 (each 2H, m, ArH×4), 13.32, 13.59 (each 1H, s, ArOH×2). EI-MS *m/z* 629 (M^+), 404, 386, 368, 317, 307. High-resolution MS, Found: *m/z* 629.1334. Calcd for $C_{28}H_{24}NO_{10}F_5$: M, 629.1318.

(8*S*,10*S*)-10-*O*-(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-8-difluoracetyl-6,8,11-trihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione Hydrochloride and (8*S*,10*S*)-10-*O*-(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)-8-(2,2-difluoro-1,1-dihydroxyethyl)-6,8,11-trihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione Hydrochloride [14,14-Difluoro-4-demethoxydaunorubicin Hydrochloride] (9). A 0.05 mol dm^{-3} solution of NaOH (4.3 ml) was added to a solution of **23** (22.5 mg, 0.0357 mmol) in THF (0.9 ml) at ambient temperature. After stirring was continued at the same temperature for 50 min, the mixture was neutralized (pH 9) with 1 mol dm^{-3} HCl, and extracted with $CHCl_3$. The combined extracts were washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to ca. 0.5 ml in volume. When 0.25 mol dm^{-3} HCl in MeOH (0.7 ml) and ether (ca. 20 ml) was successively added to the concentrated solution, a red powder separated. This was collected by decantation and triturated with ether. The upper ethereal layer was removed, and the precipitation was dried over KOH in vacuo, giving pure **9** (a 3 : 1 mixture of ketonic and hydrate forms by ^{1}H NMR) as a red powder (8.1 mg, 40%), mp 168—171 °C, $[\alpha]_D^{20}$ +111° (*c* 0.090, MeOH). IR (KBr) 3450, 1620, 1590 cm^{-1}. ^{1}H NMR (DMSO-d_6+D_2O) δ=1.15 (3H, d, *J*=6.6 Hz, $C_{5'}$-Me), 1.62—2.24 (3H, m, $C_{2'}$-H_2, C_{9-ax}-H), 2.36 (0.75H, d, *J*=14.9 Hz, C_{9-eq}-H, ketone), 2.43 (0.25H, d, *J*=14.9 Hz, C_{9-eq}-H, hydrate), 2.86 (0.25H, d, *J*=18.8 Hz, C_{7-ax}-H, hydrate), 3.05 (0.75H, d, *J*=18.8 Hz, C_{7-ax}-H, ketone), 4.11—4.23 (1H, m, $C_{5'}$-H), 4.96—5.04 (1H, m, C_{10}-H), 5.29—5.35 (1H, m, $C_{1'}$-H), 6.04 (0.25H, t, *J*=55.8 Hz, CHF_2, hydrate), 6.85 (0.75H, t, *J*=52.9 Hz, CHF_2, ketone), 7.96—8.04, 8.26—8.35 (each 2H, m, ArH×4). ^{19}F NMR (DMSO-d_6 +D_2O) δ=−128.0 (d, *J*=52.9 Hz, ketone), −131.2, (d, *J*=55.8 Hz, hydrate). SI-MS *m*/*z* 552 (M^+ +H−HCl+H_2O), 534 (M^+ +H−HCl), 495, 405, 387, 369, 308.

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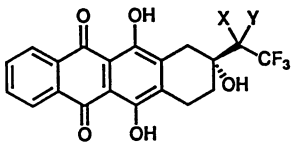
14) Synthesis of 14,14,14-trifluoro-4-demethoxy-7-deoxydaunomycinone (**i**) according to the same synthetic strategy was also examined. Thus, fluoride-induced trifluoromethylation of *dl*-**13** with trifluoromethyltrimethylsilane using tetrabutylammonium fluoride as a fluoride source[15] [CF_3SiMe_3, Bu_4NF, THF, rt, then 1 mol dm^{-3} HCl, 35%] afforded 14,14,14-trifluorodaunomycinol (*dl*-**ii**) (a 1 : 1 epimeric mixture by ^{1}H NMR) as a red powder, ^{1}H NMR ($CDCl_3$) δ=1.62—2.54 (4H, m, C_8-H_2, OH×2), 2.80—3.20 (4H, m, C_7-H_2, C_{10}-H_2), 3.75—4.25 (1H, m, $CHCF_3$), 7.62—8.01, 8.12—8.50 (each 2H, m, ArH×4), 13.44, 13.47 (each 1H, s, ArOH×2). ^{19}F NMR ($CDCl_3$) δ=−72.66, −72.73 (each d, *J*=7 Hz). EI-MS *m*/*z* 408 (M^+), 388, 309. However, attempted oxidation of *dl*-**ii** with various oxidizing reagents including the Dess-Martin periodinane resulted in simple recovery of the starting material.



i X,Y=O

ii X,Y=H,OH

Fig. 2.

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16) Measurements of the ^{1}H- and ^{19}F NMR spectra ($CDCl_3$) with the samples of **20**, **21**, and **23** purified by silica-gel chromatography made it clear that these compounds consisted of a mixture of the ketonic and the hydrate forms in which the former predominated (ca. 10 : 1). After azeotropic removal of water using toluene, signals corresponding to the hydrate form disappeared. Formation of the hydrate form may be rationalized by considering electron-withdrawing property of the two fluorine atoms. Representative NMR spectral data are as follows; **20**: ^{1}H NMR δ=6.01 (t, J=52.7 Hz, CHF_2, hydrate), 6.40 (t, J=54.3 Hz, CHF_2, ketone); ^{19}F NMR δ=127.1 (d, J=54.3 Hz, ketone). **21:** ^{1}H NMR δ=5.97 (t, J=55.2 Hz, CHF_2, hydrate), 6.60 (t, J=53.1 Hz, CHF_2, ketone); ^{19}F NMR δ=−129.5, −130.0 (each, dd, J=315.0, 53.1 Hz, ketone), −133.2 (d, J=55.2 Hz, hydrate). **23:** ^{1}H NMR δ=6.00 (t, J=55.3 Hz, CHF_2, hydrate), 6.60 (t, J=54.6 Hz, CHF_2, ketone).

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20) Concentration ($\mu g\,ml^{-1}$) necessary to inhibit cell growth (initial cell density: 5×10^4 cells ml^{-1}) by 50% after incubation for 48 h at 37 °C.

21) Evaluated by the same method as employed at the Drug Evaluation Branch, National Cancer Institute (NCI), NIH, U.S.A. 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 5.

22) Median survival time of test animals×100/median survival time of control animals.