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Synthesis of Ring A Fluorinated Anthracyclines[1]

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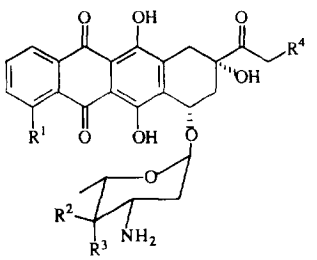
Abstract: The synthesis of different anthracyclines of the daunorubicin family, fluorinated at position 8 or 10 is described. The 8-fluoroderivatives (**2a-c**) were obtained by glycosylation of the corresponding fluorinated aglycones. The 10-fluoroderivatives (**2d-g**) were synthesized directly from daunorubicin (**1a**) and idarubicin (**1c**) following a non deglycosidative approach. 8-(*S*)-Fluorodoxorubicin was obtained from 8-(*S*)-fluorodaunorubicin, although in very low yield.

The anthracyclines of the daunorubicin family (Figure 1) are important, clinically useful anticancer chemotherapeutic agents.[2] Daunorubicin (**1a**)[3] and doxorubicin (**1b**)[4] are natural glycosides whose antitumor activity was demonstrated in the 1960's. Idarubicin (**1c**)[5] and epirubicin (**1d**)[6] are semisynthetic[7,8] analogs endowed with a different pharmacological and toxicological profile. In particular, **1c** is a potent antileukemic agent and shows activity in various tumor types also when given orally, whereas **1d** is replacing its epimer **1b** in a great number of polichemiotherapy regimens because of its reduced cardiotoxicity.[9] However, haematologic and cardiac toxicity, the appearence of resistance phenomena and, more significantly, the lack of efficacy in important human tumors including colon cancer, melanoma and chronic leukemia, limit the clinical utilization of the said anthracyclines; hence, the search for less toxic and non cross resistant congeners endowed with broader spectrum of antitumor activity, has never been abandoned.

In this paper we wish to describe the synthesis of analogs **2a-g** (Figure 2) of antitumor anthracyclines **1a-d**, characterized by the replacement of a hydrogen atom at position 8 or 10 with a fluorine.[10] This idea stemmed from the observation that intranuclear DNA bound drug accumulation is responsible for cytotoxicity and that all anthracyclines having reached the clinical stage belong to the group showing the highest affinity for DNA.[11] In addition, SAR[2] and crystallographic data of complexes between antitumor anthracyclines and oligonucleotides[12] indicate that the 9-OH group, a strict requirement for bioactivity, is involved in hydrogen

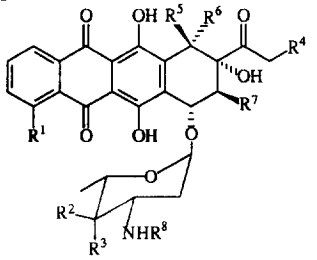
Figure 1



1a: R^1 = OMe, R^2 = R^4 = H, R^3 = OH
1b: R^1 = OMe, R^2 = H, R^3 = R^4 = OH
1c: R^1 = R^2 = R^4 = H, R^3 = OH
1d: R^1 = OMe, R^2 = R^4 = OH, R^3 = H

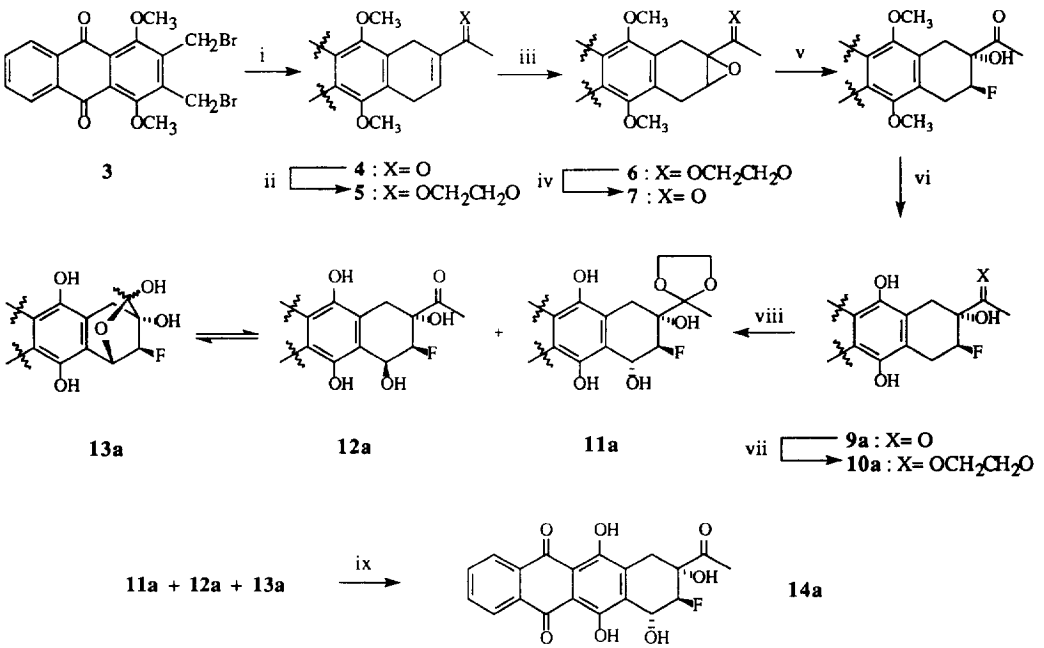
bond interactions with N-3 and N-4 of a guanine. Thus, we thought that the introduction of a fluorine atom, a strong electronwithdrawing, poor steric demanding substituent,[13] close to this important structural determinant might enhance the binding of the drug to the receptor site.

Figure 2



2a: $R^1 = R^2 = R^4 = R^5 = R^6 = H, R^7 = F, R^8 = COCF_3, R^3 = OH$
2b: $R^1 = OMe, R^2 = R^4 = R^5 = R^6 = R^8 = H, R^7 = F, R^3 = OH$
2c: $R^1 = OMe, R^2 = R^5 = R^6 = R^8 = H, R^7 = F, R^3 = R^4 = OH$
2d: $R^1 = OMe, R^3 = R^4 = R^6 = R^7 = R^8 = H, R^5 = F, R^2 = OH$
2e: $R^1 = OMe, R^3 = R^4 = R^5 = R^7 = R^8 = H, R^6 = F, R^2 = OH$
2f: $R^1 = R^3 = R^4 = R^6 = R^7 = R^8 = H, R^5 = F, R^2 = OH$
2g: $R^1 = R^3 = R^4 = R^5 = R^7 = R^8 = H, R^6 = F, R^2 = OH$

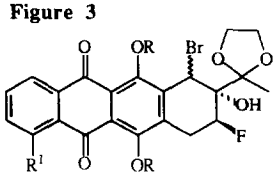
Two different synthetic strategies were pursued in order to obtain compounds **2a-g**. Following a classical approach,[14] the aglycones of anthracyclines **2a-b** were synthesized and condensed with protected daunosamine according to standard procedures; 8-(S)-Fluorodoxorubicin **2c** was eventually obtained, though in very low yield, from **2b** *via* the corresponding 14-bromo derivative. Compounds **2d** and **2e** were instead obtained from daunorubicin with preservation of the glycosidic linkage, and the same sequence of reactions was subsequently carried out to give **2f** and **2g**, starting from preformed idarubicin.



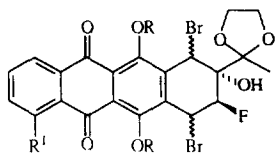
Scheme 1: (i) 3-butyn-2-one, NaI, DMA, 65°C; (ii) Collidinium tosylate cat., ethylene glycol (E.G.), C_6H_6 refl.; (iii) *m*CPBA, $CHCl_3$, r.t.; (iv) TFA/H_2O, r.t.; (v) HF/py; 70%; (vi) BCl_3, CH_2Cl_2, -78°C, then MeOH; (vii) *p*TSA cat., E.G., C_6H_6, refl.; (viii) PVPHP, AIBN, CCl_4 refl., then FCC; (ix) TFA r.t., then MeOH.

Racemic aglycone **14a** was synthesized (Scheme 1) by an adaptation of Cava's route to anthracylinones.[15] α,β-Unsaturated ketone **4** was obtained by trapping the orthoquinodimethane generated *in situ* from 1,4-dimethoxy-2,3-bis(bromomethyl)anthraquinone **3**[16] with an excess of 3-butyn-2-one. Conversion of **4** into the corresponding epoxy ketone **7** required the protection as ethylene ketal under mild conditions[17] before the epoxidation of the double bond. The action of 90% aqueous trifluoroacetic acid allowed to restore the ketone function. The introduction of fluorine was accomplished by means of Olah's reagent.[18] NMR spectral data of the only fluorinated compound isolated are in agreement with the expected structure **9a**. Bromination of **10a** was first attempted following the reported procedure for the non fluorinated compound,[19] but difficulties were encountered in monitoring the reaction and complex mixtures of products were obtained.

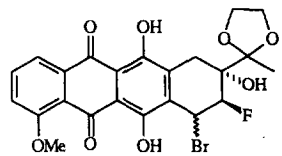
Figure 3



15a: R^1 = H, R = Me
15b: R^1 = OMe, R =H



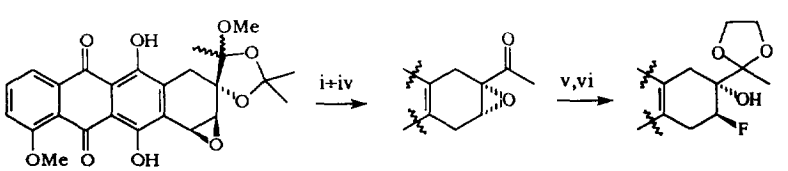
16a: R^1 = H, R = Me
16b: R^1 = OMe, R =H



21b

An important observation was that compounds with assigned structures (only one diasstereomer) **15a** and **16a** were formed and separated by preparative TLC when 6,11-dimethyl ether derivative of **10a** was brominated applying original literature conditions.[20] On the other hand, bromination with polymer supported pyridinium hydrobromide perbromide (PVPHP)[21] resulted easier to be handled and monitored by ^{1}H-NMR, filtration and removal of CCl_4 under reduced pressure being the only work up operation. At this time we realized that the bromination step was more stereoselective than regioselective and that at least one 7,10-dibrominated product was formed before the complete consumption of starting material. The latter observation obliged us to stop the bromination of **10a** at 50-60% conversion. The recovery of starting material, the hydrolysis of the brominated products and the purification of derivatives **12a**, which, in $CDCl_3$ solution, exists in mixture with **13a** were simply performed through direct flash column chromatography of the crude reaction mixture on silica gel. For preparative purposes the mixture of **11a**, **12a**, and **13a** was directly converted to **14a** by trifluoroacetic acid treatment and methanolic work up.

The ^{1}H-NMR spectrum of **13a** confirmed the validity of the indicated configuration at C-8. Indeed, the coupling pattern shows that $J_{H\text{-}7,H\text{-}8} < 0.5$ Hz, and this is more consistent with the given stereochemistry (ϕ HC_7-HC_8 close to 90°), referred to the locked structure attributed here to **13a**, rather than in the case of the other configuration. Subsequently, the same conclusion was reached on the basis of NOE experiments.[22]



17 **17b** **10b**

Scheme 2 (i) H_2, 1 eq., Kipp apparatus, 10% Pd/C, pyridine; (ii) MsCl, pyridine, 0°C; (iii) TFA, acetone/CH_2Cl_2 6:1, reflux; (iv) MeONa/MeOH, $CHCl_3$, 0°C; (v) liquid HF; (vi) *p*TSA cat., E.G., C_7H_8, reflux.

The known epimeric mixture of epoxides **17**, (22% yield; two steps from daunorubicinone)[23] was chosen as precursor of 8-(*S*)-fluorodaunorubicinone, and converted into the 7-deoxy aglycone **10b** as reported in Scheme 2. Noteworthly, both steps of the hydrogenation in pyridine with a stoichiometric amount of hydrogen and the introduction of fluorine with liquid HF, gave the desired products nearly quantitatively, thus permitting to perform the whole sequence without the isolation of any intermediate (overall yield 52%). Finally, compound **10b** was converted into **14b** under the same conditions used for **14a**.

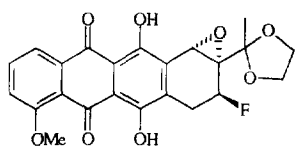
At this stage we were able to define the outcome of the bromination at position 7 more clearly; indeed, the dispersion of phenolic proton chemical shifts[24] allowed ^{1}H-NMR integration better than in the case of idarubicinone derivative **10a**. Our interst resided also in the fact that the hydroxylation at position 7 through the corresponding brominated intermediate is pivotal in anthracyclinone chemistry and moving from Wong's experience,[20] it has been considered to be sterically driven. Thus the finding that a fluorine at position 8 could significantly affect the regioselectivity of the bromination step was somewhat a surprise. On the other hand, if it is likely that the electronegativity of fluorine may render position 7 less prone to be oxidated,[25] the same argument, that is the electronwithdrawing character of the geminal substitution at position 9, could be claimed to explain the regioselectivity of the bromination of the non fluorinated compound, at least in concurrence with steric factors.

In Table 1 compound **10b** and the three major compounds of the bromination are considered. Their relative amount is measured by ^{1}H-NMR integration of the phenol signals, while the reaction is in progress.

Table 1. Relative amounts of the components in the reaction mixture of **10b** bromination.

	65'	130'	160'	175'
10b	67.8	47.9	38.8	37.2
21b	16.3	28.6	30.1	30.9
15b	10.5	12.6	13.0	13.2
16b	3.4	10.8	18.1	19.8

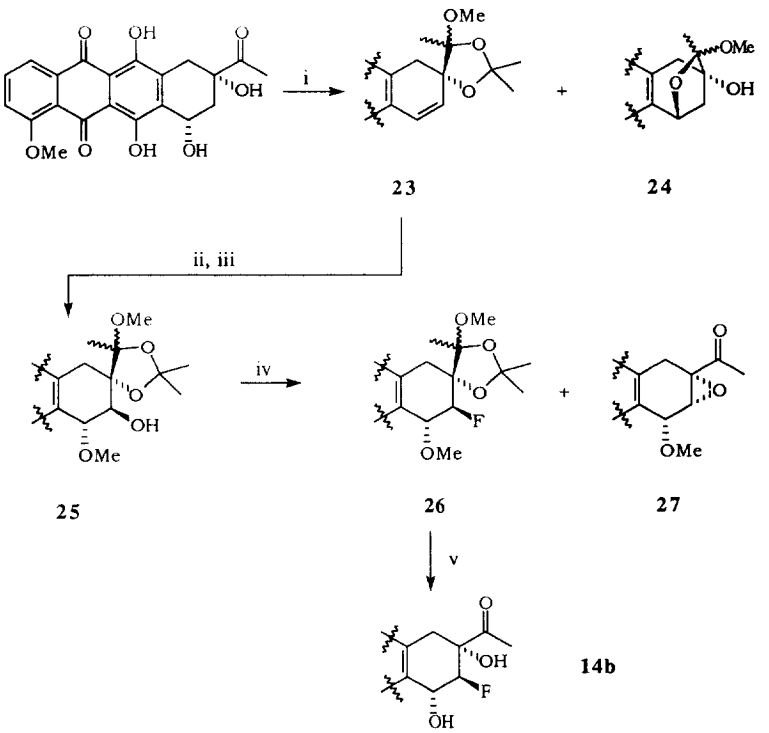
The analysis of the corresponding spectral regions between 4.5 and 6.3 ppm and the comparison with the spectra of compounds **15a** and **16a** show that the major products of the bromination step are **15b** (phenols: δ_H 13.61, 13.66), **16b** (phenols: δ_H 13.41, 13.87) and **21b** (phenols: δ_H 13.32, 14.14). Although the stereochemistry of these intermediates has not been assigned and two other minor products may be inferred to be formed by ^{1}H-NMR analysis, it appears clearly that only one isomer is preferentially formed in each case. Operatively, the reaction suffers of reproducibility problems in respect to its initiation and mantaining but the herratic behaviour never affected the selectivity. Compound **22** is a co-product which was isolated by FCC, before the methanolysis of the intermediate trifluoroacetates. Since it does not seem to be present in the crude product of the bromination step, it is likely that its precursor is **15b**.



22

While the latter synthesis was carried out, attempts were made to reduce the number of steps and maximize the overall yield. We therefore reinvestigated steps (i), (ii), (iii) of the known sequence reported in Scheme 3,[23] and considered the direct fluorination of epimeric alcohols **25** in order to avoid the troublesome

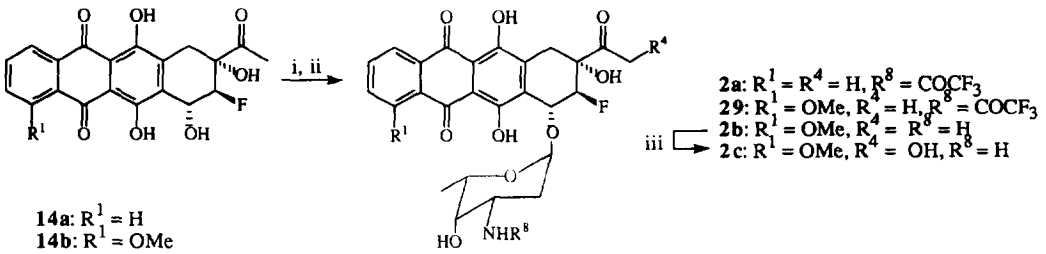
bromination at position 7. In the first step, methoxytetrahydrofuran **24**,[26] as single epimer at C-13, was the major reaction product, aside from ring-A bisanhydro derivatives, but it could not be converted into the methoxydioxolane **23** under the adopted reaction conditions. In the third step, best results were obtained when the heterogeneous reaction mixture was sonicated.



Scheme 3: (i) dimethoxypropane, *p*TSA, $CHCl_3$, reflux; (ii) *m*CPBA, $CHCl_3$, RT; (iii) anhydrous MeOH, anhydrous *p*TSA cat., sonication, 20-35 °C; (iv) DAST, 10 molar equivalents, anhydrous THF, 40-45 °C, 2 hours; (v) 95% TFA, reflux, then aqueous Na_2CO_3/MeOH, RT.

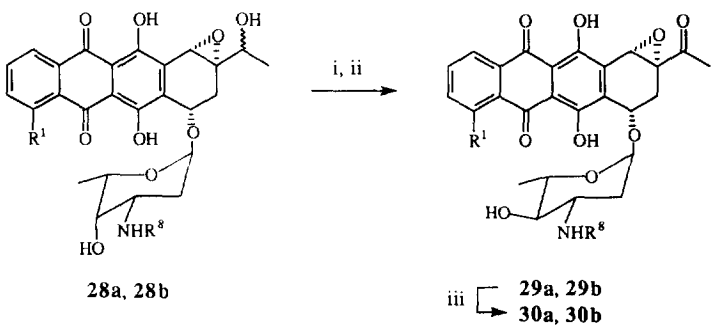
Eventually, steps (iv) and (v) were studied. As for the introduction of fluorine, the epimeric alcoholic mixture **25** gave 34% of fluorides **26**, together with 20% of epoxide **27**,[27] when allowed to react with DAST [(diethylamino)sulfur trifluoride][28] in anhydrous THF at 40 °C. Other solvent and reaction conditions were unsuccesfully tested to improve the yield and the selectivity; on the other hands, 8-(*R*)-fluorides were never recognized either in the crude of these experiments, or in the isolated products. As regards the reaction mechanism, we think that the origin of the retention of configuration can be related to the neighbouring group partecipation from the oxygen in position 9, but the influence of a stabilization of the incoming carbocation from the phenolic ring-B cannot be discarded.[29] The mixture of epimeric fluorides **26** was separated by FCC, fully deprotected in trifluoroacetic acid and, after the mild basic hydrolysis of the intermediate 7-*O*-trifluoroacetyl esters, the desired aglycone **14b** was obtained in 62% yield from **26**.

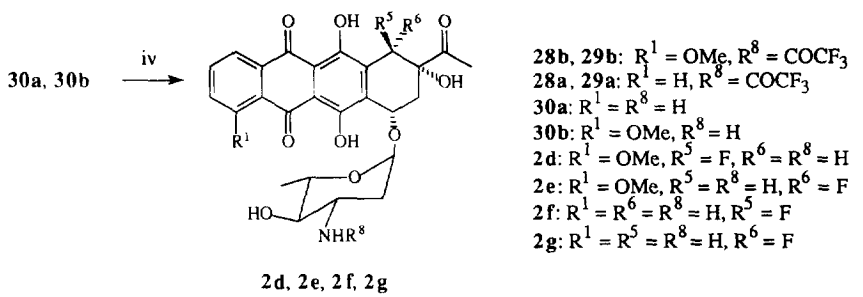
The condensation of aglycones **14a**, and **14b** with daunosamine was performed referring to Terashima[30] (Scheme 4) and, in the case of racemic **14a**, the desired isomer **2a** was selected on the basis of the similarity



Scheme 4: (i) 3-*N*-trifluoroacetyl-1,4-bis(*O*-*p*-nitrobenzoyl)-L-daunosamine, TMSOTf, CH_2Cl_2/Et_2O; (ii) NaOH/MeOH, 0 °C, 10 min.or, for 14b, 0.1 M aqueous NaOH, 0 °C, 1h; (iii) Br_2, dioxane/MeOH/H_2O, then aqueous HBr pH = 0.8-1.0, then HCOONa at pH = 4.5.

of the circular dichroic curve with that of natural **1a**. Attempts were made to convert 8-(*S*)-fluorodaunorubicin **2b** into 8-(*S*)-fluorodoxorubicin **2c** under usual conditions;[31] but, unexpectedly, the bromination step did not take place at 0 °C and even when the temperature was raised to about 20 °C, the reaction resulted very slow; furtherly, massive deglycosidation could not be avoided and the final compound **2c** was obtained in very low





Scheme 5: (i) TFAA, DMSO, CH_2Cl_2, -78 °C, then DBU; (ii) $NaBH_4$, MeOH/CH_2Cl_2, -30 °C; (iii) For compound **28a**: NaOH, H_2O/MeOH. For compound **28b**: NaOH, $MgSO_4$, H_2O/MeOH; (iv) TEA·3HF, 50 °C.

yield (5%) as the hydrochloride. We are not able to infer the reason of the observed inertness to bromination; on the other hand, this experimental observation was confirmed by the results obtained in another laboratory. Indeed it has been noted that also **14a** is brominated at position 14 more slowly than idarubicinone.[32]

The synthesis of 10-fluoroderivatives **2d** and **2e** was achieved starting from the known epimeric mixture of epoxyalcohols **28b**.[33] Oxidation with activated DMSO followed by regio and stereoselective reduction with $NABH_4$ at low temperature gave epoxyketone **29b** (Scheme 5);[34] the latter compound was detrifluoroacetylated in hydroalcoholic base and hydrofluorinated with the complex TEA·3HF[35] (the use of Olah's reagent caused complete deglycosidation). Equal amount of compounds **2d** and **2e** were formed, as observed monitoring the reaction by HPLC. After the removal of aglycons by extractive work up, an estimate of the residue by ^{1}H-NMR and HPLC indicated about 30% cumulative yield, one of the two products showing a small long range $J_{H\text{-}H}$ coupling involving H-10. In daunorubicin, only H_{10eq} shows a "W" coupling with H_{8eq}, so the product showing the long range coupling was considered to be 10-(*R*) isomer **2d**, under the hypothesis that the conformation of daunorubicin were conserved in **2d**. The desired compounds were separated by preparative HPLC and lyophilized as the hydrochloride. Interestingly, the yield of the detrifluoroacetylation reaction was greatly improved by performing the reaction in the presence of $MgSO_4$. Compounds **2f** and **2g** were obtained similarly from preformed idarubicin **1c**.

As for the biological behavior of compounds **2a-2g**, data expressing their affinity for DNA are not yet available; however these new anthracyclines mantain high cytotoxicity levels when compared with parent compounds. Furtherly, the free amine obtained from **2a** on detrifluoroacetylation, exhibited antitumor activity in animal models comparable to that shown by doxorubicin.[36]

In Table 2, the antiproliferative activity of 10-fluoroanthracyclines **2d, 2f, 2g** in different subpanels of tumor cell lines in vitro is reported (screening data from National Cancer Institute Developmental Therapeutic Program). Although less potent, 10-fluoroanthracyclines **2d, 2f, 2g** show a value of resistance index lower than that of doxorubicin (ratio of GI_{50} in entry 10 over that in entry 9) and both epimers **2f** and **2g** are nearly equally cytostatic.

Table 2. Antiproliferative activity of anthracyclines in different subpanels of tumor cell lines in vitro (a).

	TUMOR	**1b**	**2d**	**2g**	**2f**
1	Leukemia	0.031 (3)	0.14 (5)	<0.060 (6)	0.060 (5)
2	NSC-Lung Ca.	0.050 (8)	1.5 (7)	0.35 (9)	1.0 (9)
3	Colon Ca.	0.12 (7)	2.4 (7)	0.93 (7)	0.95 (7)
4	CNS Cancer	0.035 (6)	2.3 (5)	0.87 (5)	1.1 (5)
5	Melanoma	0.066 (7)	2.4 (6)	0.74 (8)	1.8 (8)
6	Ovarian Ca.	0.19 (6)	2.6 (5)	0.74 (6)	2.6 (6)
7	Renal Ca.	0.11 (7)	2.7 (7)	0.60 (6)	1.6 (6)
8	Prostate Ca.	0.095 (2)	3.9 (2)	0.60 (5)	0.45 (2)
9	Breast Ca.	0.050 (7)	1.6 (5)	1.1 (6)	1.5 (6)
10	Breast Ca. (b)	>25 (1)	9.8 (1)	6.9 (1)	7.4

(a) Data expressed as GI_{50} (mM) (N). GI_{50} = concentration inhibiting 50% of growth after 48 h exposure to the drug (mean value); N = Number of cell lines tested. (b) Doxorubicin resistant cell line.

In conclusion, fluorine substitution on ring A of antitumor anthracyclines has been studied. Three out of four possible monosubstitution topologies at position 8 and 10 have been synthesized and the new fluoroanthracyclines retain bioactivity. From the synthetic point of view, we have noted that fluorine substitution may affect negatively the reactivity in two pivotal reactions of anthracyline chemistry such as the brominations at position 7 and 14.

Experimental

General. Flash column chromatography was performed using Merck Kieselgel 60 (230–400 mesh). Preparative HPLC separations were performed on a Shimadzu LC-10A liquid chromatograph using a μBondapack C_{18} 125Å 10 μm column (19 mm i. d. X 300 mm), eluting at a flow rate of 50 mL/min with

water, pH = 2 by phosphoric acid/acetonitrile 95:5 v/v (UV monitoring at 254 nm). Analytical HPLC analyses were performed with a Perkin Elmer Analyst liquid chromatograph equipped with a Perkin Elmer 235 diode array detector and a LCI-100 integrator. HPLC assay of final compounds **2a-g** was performed with a μBondapack C_{18} 125Å 10 μm column (3.9 mm i. d. X 150 mm), eluting at a flow rate of 4 mL/min with water, pH = 2 by phosphoric acid/acetonitrile 3:1 v/v (UV monitoring at 254 nm). NMR spectra were obtained using a Varian Gemini 200 spectrometer at 200 MHz and 50 MHz for ^1H and ^{13}C spectra respectively. ^{13}C spectra were recorded with complete proton decoupling; multiplicity was assigned on the base of the attached proton test and ^{13}C-^{19}F coupling, the observed value of the latter is reported in parenthesis. All coupling constants are given in Hertz. Unless otherwise noted, all spectra were recorded in $CDCl_3$. Low resolution EI and TS mass spectra were recorded on a HP 5988A. EI-MS are reported as m/z (relative intensity at 15 eV). TS-MS were recorded either in the negative, or in the positive ion modes injection. High resolution mass spectra were recorded on a VG 70-70 spectrometer. Optical rotations were measured with a Perkin Elmer 241 polarimeter. FT-IR spectra were recorded on a Perkin Elmer 1170 spectrometer. Unless otherwise noted, melting points were determined in capillary tubes and are uncorrected.

Enone (**4**). NaI (29.0 g) and 3-butyn-2-one (6.6 g, 97 mmoles) are dissolved in a mixture of dimethylacetamide (50 ml) and 1,4-dioxane (10 ml). The mixture is gently warmed at 65 °C and a solution of **3**, 5.0 g (11 mmoles), in dimethylacetammide (100 ml) is added dropwise over a hour, through a dropping funnel. After further stirring for a hour at 70 °C and cooling, the mixture is poured into water (600 ml); the solid is filtered off, washed with water and dried under vacuum over P_2O_5. 3.85 g of crude **4** are obtained which are purified by preparative LC on silica (Waters Prep. LC/System 500A. Column: 2 x PrepPAK-500. Eluent $CHCl_3$, butan-2-one, 70/1 v/v). 2.70 g of **4** are obtained (67%). M.P. (toluene) 209-213°C (dec.). ^1H-NMR δ 2.40 (s, 3H, CH_3-14); 3.61-3.80 (m, 4H, CH_2-7 and CH_2-10); 3.91 (s, 3H, OCH_3); 3.92 (s, 3H, OCH_3); 7.00-7.08 (m, 1H, H-8); 7.66-7.76 (m, 2H, H-2 and H-3); 8.10-8.21 (m, 2H, H-1 and H-4). ^{13}C-NMR δ 23.49 (t); 25.44 (q); 26.78 (t); 61.80 (q); 61.86 (q); 125.15 (s); 125.53 (s); 127.00 (d); 127.09 (d); 134.01 (d); 134.07 (d); 134.56 (s); 134.66 (s); 135.96 (d); 136.71 (s); 136.81 (s); 139.02 (s); 155.11 (s); 155.73 (s); 183.36 (s); 183.43 (s); 198.32 (s). MS m/z (%) 362 ($M^{+\cdot}$, 100); 360 (91); 347 (27); 344 (14); 331 (49); 320 (30); 319 (60). IR (nujol) cm^{-1} 1667; 1592; 1556; 1342; 1310; 1261; 1237. Anal. Calcd for $C_{22}H_{18}O_5$: C, 72.92; H, 5.01. Found C: 73.00; H: 4.98%.

Dioxolane (**5**). Enone **4** [5.1 g, containing 12% of the corresponding 5,12-naphthacenequinone ("bisanhydroderivative"), 12.4 mmoles] dissolved in a mixture of benzene (400 ml) and ethylene glycol (60 ml) in a Dean-Stark apparatus in the presence of collidinium paratoluensulfonate (1.0 g). Water is azeotropically removed while benzene is rinsed over 4.5 hours. The organic phase is washed with water repeatedly and dried over anhydrous Na_2SO_4. After removal of the solvent 4.8 g of compound **5** are obtained in 7/2 mixture with the corresponding bisanhydro derivatives (≈72%). ^1H-NMR δ 1.57 (s, 3H, CH_3-14); 3.40 - 3.60 (m, 4H, CH_2-7 and CH_2-10); 3.93 (s, 3H, OCH_3); 3.94 (s, 3H, OCH_3); 3.80 - 4.10 (m, 4H, OCH_2-CH_2O); 6.10 - 6.15 (m, 1H, H-8); 7.70 - 7.80 (m, 2H, H-2 and H-3); 8.15 - 8.25 (m, 2H, H-1 and H-4).

Epoxyketone (**7**). Compound **5** (6.0 g, containing 30% of "bisanhydroderivative", 10.2 mmoles) and 3-chloroperbenzoic acid (5.3 g, 5.1 mmoles) are dissolved in $CHCl_3$ (400 ml) and the solution is stirred overnight at room temperature. The excess oxidant is destroyed with aqueous pH 6 $NaHSO_3$/$NaHCO_3$ and the organic phase is washed with sat. $NaHCO_3$, water, and dried over anhydrous Na_2SO_4. Afer removal of the solvent, 6.0 g of crude epoxide **6** (containing 30% of "bisanhydroderivative") are obtained which can be used in the following step without further purification. Crude epoxy ketal **6** (6.0 g) is dissolved in TFA (200 ml, 90% strenght). The solution is stirred at room temperature for 60' and then poured into water. The red solid is filtered, washed with water and dried in a oven at 80°C. The crude epoxy ketone **7** is suspended in boiling butan-2-one and most of "bisanhydroderivative" is filtered off. 3.4 g of **7** from the solution (85% purity, yield ≈ 75% from **5**). The repetition of the purification procedure affords an analitycally pure sample. Mp 240 - 244 °C. ^1H-NMR δ 2.16 (s, 3H, CH_3-14); 3.05 (dd, J = 18.0, 1.0, 1H, H-7); 3.58 (s, 2H, CH_2-10); 3.71 (s, 1H, H-8); 3.83 (d, 1H, J = 19, H-7), 3.88 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 7.65 - 7.75 (m, 2H, H-2 and H-3); 8.10 - 8.20 (m, 2H, H-1 and H-4). ^{13}C-NMR δ 22.91(t); 23.52 (q); 24.81(t); 56.15 (d); 61.94 (q) (2xOMe); 62.83 (s); 125.44 (s); 125.60 (s); 127.02 (d); 127.08 (d); 134.07 (d); 134.10 (d); 134.53 (s); 134.58 (s); 135.19(s); 136.86 (s); 155.62 (s); 155.80 (s); 183.33 (s); 207.30 (s). MS m/z (%) 378 ($M^{+\cdot}$, 70); 347 (26); 346 (41); 335 (61); 331 (25); 317 (35).

Fluoroalcohol (**8**). Compound **7** (1.10 g, 85% purity, 2.6 mmoles) is treated with Olah's reagent (70 ml) in a poliethylene vessel over one day at room temperature and then poured into ice. The mixture is extracted with CH_2Cl_2 and the organic phase is washed repeatedly with water, then with sat. $NaHCO_3$, again with water and dried over anhydrous Na_2SO_4. After the removal of CH_2Cl_2, the residue is suspended in boiling acetone and the "bisanhydroderivatives" are filtered off. The crude fluoroalcohol, recovered from the solution,

is chromatographated on silica (FCC, eluent: n-hexane/ethyl acetate 50% v/v). Pure **8** is obtained (0.63g, 61%) M.P. 241 - 245 °C (dec.). ^{1}H-NMR δ 2.49 (d, *J* = 2.6, 3H, CH_3-14); 2.95 - 3.45 (m, 4H, CH_2-7 and CH_2-10); 3.90 (s, 3H, OCH_3); 3.92 (s, 3H, OCH_3); 4.24 (s, 1H, OH); 4.77 (br dt, *J* = 46.9, H-8); 7.69 - 7.76 (m, 2H, H-2 and H-3); 8.10 - 8.21 (m, 2H, H-1 and H-4). ^{13}C-NMR δ 26.20 (dq, *J* = 6.5); 27.89 (dt, *J* = 21.7); 29.05 (t); 61.77 (q); 61.91 (q); 75.88 (d, *J* = 25.0); 87.98 (dd, *J* = 177.2); 125.44 (s); 125.60 (s); 127.06 (d); 134.08 (d); 134.57 (s); 136.65 (s); 136.96 (s); 155.62 (s); 155.80 (s); 183.38 (s); 211.30 (s). MS m/z (%) 398 ($M^{+\cdot}$, 100); 380 (12); 355 (36); 335 (30).

Fluoroalcohol (9a). Fluoroalcohol **8** (402 mg, 1.01 mmoles) is dissolved in anhydrous CH_2Cl_2 (60 ml) and the solution is cooled at -65 °C. Boron trichloride (12 ml of a 1M solution in CH_2Cl_2, 12 mmoles) is added dropwise to the stirred solution through a syringe and the reaction mixture is left 30' under stirring before the addition of methanol (15 ml, dropwise). The cooling bath is removed and the solvent distilled off (rotary evaporator) to give 356 mg of pure, very insoluble **9a** (95%). Mp 247- 253 °C (dec.). ^{1}H-NMR δ (DMSO-d_6) 2.35 (s, 3H, CH_3-14); 2.85 - 3.25 (m, 4H, CH_2-7 and CH_2-10); 5.26 (br d, *J* = 47.7, 1H, H-8) 6.34 (br s, 1H, OH); 7.90 - 8.00 (m, 2H, H-2 and H-3); 8.20 - 8.25 (m, 2H, H-1 and H-4) 13.23 (s, 1H, OH); 13.28 (s, 1H, OH). MS m/z (%) 370 ($M^{+\cdot}$, 24); 352 (55); 332 (62); 307 (100).

Fluoroalcohol (10a). Compound **9a** (320 mg, 0.86 mmoles) is dissolved in a mixture of benzene (75 ml) and ethylene glycol (7 ml) in a Dean-Stark apparatus, and *p*TSA (25 mg) is added. Water is azeotropically removed over 8 hours. Most of solvent is distilled off, then heating is removed and an orange solid is left to separate. After filtration, washing with benzene, ethanol, water, sat. $NaHCO_3$, water, the solid is dried at 80 °C under reduced pressure to give 283 mg of **10a** (79%). Mp 237- 240 °C. ^{1}H-NMR δ 1.50 (d, *J* = 2.4, 3H, CH_3-14); 2.43 (d, *J* = 2.2, 1H, OH); 2.90- 3.45 (m, 4H, CH_2-7 and CH_2-10); 4.05 - 4.20 (m, 4H, OCH_2-CH_2O); 5.13 (dt, *J* = 48.9, 2.0, 1H, CH-8); 7.70 - 7.85 (m, 2H, H-2 and H-3); 8.25 - 8.35 (m, 2H, H-1 and H-4); 13.40 (s, 1H, OH); 13.44 (s, 1H, OH). ^{13}C-NMR δ 20.67 (dq, *J* = 5.4); 27.52 (t); 22.31 (dt, J = 22.1); 65.70 (t); 66.15 (t); 73.93 (d, *J* = 23.2); 87.04 (dd, *J* = 173.3); 110.14 (s); 110.23 (s); 111.35 (s); 127.34 (d); 134.23 (s); 134.59 (d); 135.96 (s); 157.30 (s); 157.44 (s); 187.19 (s); 187.25 (s). MS m/z (%) 414 ($M^{+\cdot}$, 2); 376 (1); 361 (3); 308 (17); 87 (100).

Bromination of 10a. Compound **10a** (400 mg, 0.97 mmoles) is dissolved in boiling CCl_4 (100 ml). AIBN (135 mg, 0.82 mmoles) and PVPHP (880 mg, ≈ 2.1 mmoles) are added. The solvent is refluxed for 135 min. After cooling, the polymer is removed by filtration, the solution is concentrated and the residue chromatographated (FCC, eluition with a gradient mixture of CCl_4/Ethyl acetate from 3/1 to 1/1 by vol.). The fractions containing **11a** and the mixture **12a**, **13a**, are evaporated and treated with 99% trifluoroacetic acid overnight at room temperature. The mixture is diluted with water and extracted with CH_2Cl_2. The essiccated solution (anhydrous Na_2SO_4) is evaporated and the intermediate trifluoroacetate ester is transesterified by evaporating its methanolic solution repeatedly. Eventually, compound **14a** (71 mg, 19%) is obtained after FCC ($CHCl_3$/acetone 15:1 v/v). **Fluoroalcohol (11a).** ^{1}H-NMR δ 1.53 (d, *J* = 2.2, 3H, CH_3-14); 2.95 (d, *J* = 2.2, 1H, OH-9); 2.99 (*J* = 18.7, 2.4, 1H); 3.25 (*J* = 18.4, 2.3, 0.5, 1H), the latter two protons resonate as AB counterpart of an ABX spectrum where AB = CH_2-10 , X = F. In addition, one of AB components is furtherly doubled; 3.70 (d, *J* = 9.6, 1H, OH-7); 4.07-4.19 (m, 4H, OCH_2-CH_2O); 5.18 (dd, *J* = 45.7, 2.4, 1H, H-8); 5.18 (ddd, *J* = 13.7, 9.6, 2.3, 1H, H-7); 7.75-7.90 (m, 2H, H-2 and H-3); 8.30-8.40 (m, 2H, H-1 and H-4); 13.41 (s, 1H, OH); 13.63 (s, 1H, OH). ^{13}C-NMR δ 20.16 (dq, *J* = 5.1); 27.57 (t); 65.48 (dd, *J* = 31.1); 65.50 (t); 65.97 (t); 74.82 (d, *J* = 22.9); 87.69 (dd *J* = 178.1); 110.92 (s); 110.97 (s); 111.61 (s) 127.20 (d); 133.78 (s); 133.92 (s); 134.53 (d); 134.65 (d); 135.68 (d); 156.51 (s); 157.62 (s); 187.16 (s); 187.31 (s). **Mixture 12a + 13a.** ^{1}H-NMR δ Signals of **12a**: 2.56 (d, 2.8, 3H, CH_3-14); 2.95 (*J* = 17.7, 4.4, 1H); 3.37 (*J* = 17.3, 3.1, 1H), the latter two protons resonate as AB counterpart of an ABX spectrum where AB = CH_2-10 , X = F; 4.30 (s, 1H, OH-9); 4.47 (br d, *J* = 2.6, 1H, OH-7); 4.82 (dd, *J* = 51.4, 3.1, 1H, H-8); 5.45 (br dt, *J* = 26.8, 3.0, 1H, H-7); 7.75-7.90 (m, 2H, H-2 and H-3); 8.25-8.40 (m, 2H, H-1 and H-4); 13.28 (s, 1H, OH); 14.00 (s, 1H, OH). Signals of **13a**: 1.36 (s, 3H, CH_3); 3.20 and 3.36 (AB spectrum, *J* = 18.5, 2H, CH_2-10); 3.48 (s, broad, 1H, OH); 4.98 (d, *J* = 54.8, 1H, H-8); 5.70 (d, *J* = 11.1, 1H, H-7); 7.75-7.90 (m, 2H, H-2 and H-3); 8.25-8.40 (m, 2H, H-1 and H-4); 13.09 (s, 1H, OH); 13.20 (s, 1H, OH). MS m/z (%) 386 ($M^{+\cdot}$, 8); 348 (13); 326 (22); 325 (11); 307 (23); 306 (100).

(7*RS*,8*SR*,9*RS*) 8-fluoro-idaunorubicinone (14a). ^{1}H-NMR δ 2.48 (d, *J* = 2.4, 3H, CH_3-14); 3.15 (*J* = 18.4, 2.7, 1H); 3.24 (*J* = 18.6, 3.2, 1H), the latter two protons resonate as AB counterpart of an ABX spectrum where AB = CH_2-10 , X = F; 3.80-3.90 (br s, 1H, OH-7); 4.60-4.75 (br s, 1H, OH-9); 4.87 (dd, *J* = 46.2, 2.4, 1H, H-8); 5.18 (br d, *J* = 13.7, 1H, H-7); 7.75-7.90 (m, 2H, H-2 and H-3); 8.25-8.35 (m, 2H, H-1 and H-4); 13.25 (s, 1H, OH); 13.50 (s, 1H, OH). ^{13}C-NMR δ 25.51 (dq, J = 5.2); 29.08 (t); 65.10 (dd *J* = 29.7); C-9 signal obscured by the solvent; 88.71 (dd, *J* = 183.0); 111.66 (s); 112.27(s); 127.75 (d);

134.11 (s); 134.25 (s); 134.31 (s); 134.44 (s); 134.90 (d); 135.27 (d); 156.41 (s); 157.87 (s); 187.46 (s); 187.80 (s); 208.97 (s). MS m/z (%) 386 ($M^{+\cdot}$, 78); 348 (21); 326 (12); 325 (24); 323 (100).

Fluoroalcohol (10b). The crude epimeric mixture of epoxide **17** (4.98 g, maximum 10.6 mmoles), dissolved in anhydrous pyridine (155ml), is hydrogenated (240 ml, ≈10.7 mmoles) on Pd/C 10% (2.5 g), in a Kipp apparatus, and then filtered through a short pad of silica gel. The filter is washed with ethyl acetate and the solution concentrated under reduced pressure, before diluting with methylene chloride. Remaining pyridine is extracted with 2% aqueous hydrochloric acid and the organic phase is washed with water and dried over anhydrous Na_2SO_4, before removal of methylene chloride. A red residue (4.98 g) is obtained and used without further purification in the next step. TLC: ($CHCl_3$, acetone: 15/1 v/v) Rf = 0.27 and 0.40. ^{1}H-NMR δ (among the others) 3.34 (s, 3H, OCH_3-13); 3.41 (s, 3H, OCH_3-13); 4.08 (s, 6H, 2 x OCH_3-4); 4.20 - 4.30 (br, 1H, H-7); 4.52 - 4.62 (br q, 1H, H-7); 13.34 (s, 1H, OH); 13.50 (s, 1H, OH); 13.75 (s, 1H, OH); 13.78 (s, 1H, OH). Methanesulfonyl chloride (3.55 ml, ≈45.9 mmoles) is added dropwise through a syringe in 15 min to the cold (-15 °C), stirred solution of crude alcohols, obtained as above (3.59 g, 7.63 mmoles) in anhydrous pyridine (80 ml). The solution is kept at 0-5 °C overnight without stirring before quenching with cold water (50 ml, dropwise, T: < 20 °C), and diluting with chloroform. Pyridine is extracted with 10% HCl, the organic phase is washed with water, brine, and dried over anhydrous Na_2SO_4 to give 4.60 g of crude epimeric mixture of methanesulfonates [TLC: ($CHCl_3$, acetone: 15/1 v/v) single spot at Rf = 0.59] after distillation of the solvent in vacuo. This material is dissolved in a mixture of acetone (60 ml) and CH_2Cl_2 (10 ml), then trifluoroacetic acid (10 ml) is added and the solvent is refluxed for 3 hours. The reaction mixture is left at room temperature overnight. The solvent is refluxed for additional 6 hours. The precipitate material is filtered and washed with diethyl ether. A second crop is obtained after concentration of the mother liquors. Altogether, 3.08 g of crude deprotected methanesulfonate ester are obtained [TLC: ($CHCl_3$, acetone: 8/1 v/v) Rf = 0.71. ^{1}H-NMR δ, among the others, 2.46 (s, 3H, CH_3-14); 3.03 (s, 3H, $SO_2C\underline{H}_3$); 5.01 (t, J = 4.0, H-7).] and suspended in anhydrous $CHCl_3$ (150 ml). A solution of NaOMe (1.16 g, 36.3 mmoles) in anhydrous methanol (125 ml) is added dropwise in 20 min through a dropping funnel, to the well stirred suspension kept at -10°C. Stirring is continued for further 90 min at the same temperature. Glacial acetic acid is added dropwise until the colour of the solution changes to orange. The reaction mixture is diluted with ether (200 ml) and the solid material is filtered. After washings with ether and water, and drying at 60 °C under vacuum, 1.96 g of crude epoxide **17b** are obtained [TLC: ($CHCl_3$, acetone: 40/1 v/v) Rf = 0.26. ^{1}H-NMR corresponding to that of compound **7**. MS m/z (%) 380 ($M^{+\cdot}$, 100); 365 (11); 363 (11); 362 (39); 344 (11); 338 (23); 337 (69); 322 (16). $[\alpha]^{20}_{589}$ = +185° (nitrobenzene, c = 0.025).] and hydrofluorinated with anhydrous HF (Applied Biosystems apparatus; 30 minutes at -78 °C, 60 minutes at 0 °C before evacuation of HF) to give 2.06 g of crude fluoroalcohol as single spot at TLC analysis ($CHCl_3$, acetone: 15/1 v/v, Rf = 0.41). M. P. 242 °C (dec); $[\alpha]^{20}_{589}$ = +26.8 (c = 0.10, dioxane). The latter compound (2.06 g) is ketalized in a Dean Stark apparatus (600 ml toluene, 30 ml of ethylene glycol, 400 mg of *p*TSA, 3 hours) before concentration to 100 ml and removal of precipitate by filtration. The reddish very insoluble crude ketal is throughly washed with ether and then with water and finally dried under vacuum at 50 °C giving 1.95 g of pure **10b** (52% on **17**). TLC ($CHCl_3$, acetone: 15/1 v/v) Rf = 0.24. Mp 272 °C (dec.). ^{1}H-NMR δ (DMSO-d_6) 1.38 (d, J = 2.0, 3H, CH_3-14); 2.75 - 2.20 (m, 4H, CH_2-7 and CH_2-10); 3.80 - 4.20 (m, 4H, OCH_2-CH_2O); 3.98 (s, 3H, OCH_3); 5.13 (dt, J = 48.8, 2.9, 1H, H-8); 5.24 (br s, 1H, OH); 13.32 (s, 1H, OH); 13.82 (s, 1H, OH). ^{13}C-NMR δ (DMSO-d_6) 20.74 (dq, J = 4.9); 26.49 (t); 27.85 (dt, J = 22.5); 56.37 (q); 64.74 (t); 65.20 (t); 72.28 (d, J = 21.13); 86.38 (dd, J = 172.0); 109.26 (s); 109.98 (s); 110.67 (s); 118.69 (d); 119.42 (d); 133.89 (s); 133.95 (s); 135.78 (d); 154.87 (s); 154.94 (s); 160.60 (s); 186.02 (s); 186.06 (s). MS m/z (%) 444 ($M^{+\cdot}$, 11); 338 (23); 87 (100).

(8*S*) 8-Fluorodaunorubicinone (14b). Compound **10b** (880 mg, 1.98 mmoles) is dissolved in boiling $CHCl_3$ (200 ml, stabilized with amylene). AIBN (400 mg, 2.43 mmoles) and PVPHP (1040 mg, ≈ 2.5 mmoles) are added. The solvent is refluxed for 70 min. Further PVPHP (1040 mg, ≈ 2.5 mmoles) is added and refluxing is mantained for 105 min. After cooling, the polymer is removed by filtration, the solution is concentrated and the residue chromatographated (FCC, Ø = 5 cm, conditioning by CH_2Cl_2, eluition with a gradient mixture of $CHCl_3$/ acetone from 40/1 to 10/1 by vol.). Compound **22** (105 mg, 12%), a minimal amount of deketalized starting material, starting material (226 mg, 26%) and **14b**, as ethylene ketal (95 mg), are recovered. Elution of the latter compound is completed with the mixture dichlorometane, MeOH, water, 60/10/1 by vol. The red eluate is washed repeatedly with water and the organic phase essiccated over anhydrous Na_2SO_4. After removing the solvent in vacuo, 240 mg of **14b**, as ethylene ketal, are obtained. The latter compound (335 mg) is deprotected in wet TFA (50 ml, one night). The mixture is diluted with water and extracted with CH_2Cl_2. The desiccated solution (anhydrous Na_2SO_4) is evaporated and the intermediate trifluoroacetate ester is transesterified by evaporating its methanolic solution repeatedly to give 265 mg of pure **14b** (32%). $[\alpha]^{20}_{589}$ = +131° (c = 0.10 in $CHCl_3$). Mp 190-193 °C (dec.). ^{1}H-NMR δ 2.51 (d, J = 2.3, 3H,

CH_3-14); 3.14 (J = 18.2, 2.3, 1H); 3. 24 (J = 18.4, 3.1, 1H), the latter two protons resonate as AB counterpart of an ABX spectrum where AB = CH_2-10 , X = F; 3.80-3.90 (br s, 1H, OH-7); 4.09 (s, 3H, OCH_3); 4.61 (br s, 1H, OH-9); 4.87 (dd, J = 46.0, 2.3, 1H, H-8); 5.10 - 5.30 (br d, 1H, H-7); 7.39 (dd, J = 8.4, 1.0, 1H, H-3); 7.78 (t, J = 8.4, 1H, H-2); 8.01 (dd, J = 8.4, 1.0, 1H, H-1); 13.28 (s, 1H, OH); 13.93 (s, 1H, OH). ^{13}C-NMR δ 26.22 (dq J = 5.4); 29.15 (t); 57.42 (q); 65.22 (dd, J = 29.6); C-9 signal obscured by the solvent; 88.62 (dd J = 182.8); 112.08 (s); 112.53 (s); 119.22 (d); 120.45 (d); 121.56 (s); 132.84 (s); 134.65 (s); 136.10 (s); 136.41 (d); 155.75 (s); 157.48 (s); 161.79 (s); 187.55 (s); 187.64 (s); 209.05 (s). MS m/z (%) 416 ($M^{+\cdot}$, 100); 378 (25); 355 (18); 354 (18); 353 (76). **Fluoroepoxide (22).** ^{1}H-NMR δ 1.60 (d, J = 3.3, 3H, CH_3-14); 2.74 (ddd, J = 47.3, 17.9, 3.5, 1H, H-7); 3.66 (ddd, J = 17.8, 15.2; 2.5, 1H, H-7); 4.08 (s, overlapped on a multiplet, 7H, OCH_3 and OCH_2-CH_2O), 4.75 (s, 1H, CH-10); 5.67 (dt, J = 48.7, 3.0, 1H, H-8); 7.39 (d, J = 8.4, 1H, H-3); 7.77 (t, J = 8.4, 1H, H-2); 8.05 (d, J = 8.4, 1H, H-1); 13.18 (s, 1H, OH); 13.41 (s, 1H, OH). ^{13}C-NMR δ 23.25 (dq, J = 5.8); 26.92 (dt, J = 22.2); 49.04 (d); 56.69 (q); 64.67 (d, J = 28.5); 65.75 (t); 66.56 (t); 85.54 (dd, J = 170.1); 107.25 (d, J = 2.6); 111.17 (s); 113.18 (s); 118.42 (d); 119.69 (d); 121.12 (s); 130.39 (s); 134.96 (s); 135.53 (d); 135.63 (s) 155.20 (s); 156.08 (s); 161.20 (s); 186.66 (s); 187.08 (s). MS (Thermo spray in the positive ion mode injection) m/z 443 ($M+H^{+\cdot}$); 363; 377; 87.

Fluoro derivative (26). Epimeric alcohols **25** (170 mg, 0.34 mmoles) are dissolved in anhydrous THF (15 ml). A solution of DAST (420 µl, ca. 3.20 mmoles) in anhydrous THF (8 ml) is added dropwise, through a dropping funnel over 10min. The reaction mixture is stirred at 40-45 °C over two 2 hours and, after cooling, concentrated under reduced pressure. The crude is directly chromatographated (FCC; $CHCl_3$, acetone: 100/1 v/v) to give 58 mg of **26** (34%), 22 mg of **27**,[27] and 11 mg of the mixture **26** + **27**. **26**: ^{1}H-NMR δ 2.78 (dd, J = 17.8, 3.4, 1H, H-10); 2.81 (dd, J = 19.2, 3.8, 1H, H-10); 3.31 (dd, J = 17.9, 3.4, 1H, H-10); 3.35 (s, 3H, OCH_3); 3.42 (s, 3H, OCH_3); 3.44 (dd, J = 18.9, 4.0, 1H, H-10); 3.72 (s, 6H, 2 x OCH_3); 4.07 (s, 6H, 2 x OCH_3); 4.60 (dd, J = 15.4, 1.9, 1H, H-7); 4.66 (dd, J = 15.2, 2.3, 1H, H-7); 4.96 (dd, J = 44.8, 2.3, 1H, H-8); 5.39 (d, J = 44.2, 1H, H-8); 7.34 (d, J = 8.5, 2H, 2 x H-3); 7.74 (t, J = 8.5, 2H, 2 x H-2); 8.01 (dd, J = 8.5, 2H, 2 x H-1); 13.42 (s, 2H, 2 x OH); 13.9 (s, 1H, OH); 13.94 (s, 1H, OH). MS m/z (%) 502 ($M^{+\cdot}$, 42); 470 (87); 438 (17); 394 (63); 392 (100).

Deprotection of 26. Compound **26** (120 mg, 0.23 mmoles) is dissolved in TFA (10 ml) and the solvent is refluxed for 5 hours. The reaction mixture is diluted with dichloromethane, washed with sat. $NaHCO_3$ and essiccated. Upon removal of the solvent, 129 mg of crude 7-O -trifluoroacetate ester of **14b** [^{1}H-NMR δ 2.49 (d, 3H, J = 2.2, CH_3-14); 3.21 (J = 18.3, 1.8, 1H); 3.29 (J = 18.3, 3.3, 1H), the latter two protons resonate as AB counterpart of an ABX spectrum where AB = CH_2-10 , X = F; 4.06 (s, 3H, OCH_3); 4.78 (dd, J = 45.1, 2.7, 1H, H-8); 6.52 (dd, J = 16.6, 2.7, 1H, H-7); 7.39 (d, J = 8.4, 1H, H-3); 7.78 (t, J = 8.4, 1H, H-2); 7.96 (d, J = 8.2, 1H, H-1); 13.15 (s, 1H, OH); 13.69 (s, 1H, OH)] are obtained. This product (129 mg) is dissolved in MeOH (60 ml) and detrifluoroacetilated with Na_2CO_3 0.2 M (3 ml). The reaction mixture is diluted with $CHCl_3$, washed with 10% aq HCl, essiccated and concentrated under reduced pressure. Compound **14b** is eventually obtained (61 mg, 62%) by FCC (deactivated silica, $CHCl_3$/EtOH 100/1). A mixture (33 mg) containing (8*S*) 7'-epi-8-fluorodaunorubicinone and (8S) 8-fluorodaunorubicinone-7-*O*-methyl ether is also obtained.

(8*S*)-8-Fluorodaunorubicin (2b). Aglycone **14b** (735 mg, 1.78 mmoles) and 3-*N*-trifluoroacetyl-1,4-bis(O-p-nitrobenzoyl)-L-daunosamine (1040 mg, 2.03 mmoles) are dissolved in a mixture of anhydrous CH_2Cl_2 (146 ml) and anhydrous diethyl ether (124 ml) in the presence of activated 4 Å granular molecular sieves. The mixture is cooled at -20 °C and 750 µl of TMSOTf are added though a syringe. The mixture is magnetically stirred at -20 °C until the disappearance of starting material (4 hours). The reaction is quenched by adding sat. $NaHCO_3$ and the organic phase is washed with water and dried before the removal of the solvent (rotary evaporator). 4-Nitrobenzoylester group is removed by treating the residue, dissolved in CH_2Cl_2 (20 ml) and MeOH (800 ml), with aqueous NaOH (0.1N, 18.5 ml) over 10 min at 0 °C. The solution is neutralized by adding 20% acetic acid, and extracted with CH_2Cl_2. The organic phase is washed with water and dried over Na_2SO_4. After concentration (rotary evaporator), the residue is recrystallized from CH_2Cl_2 (30 ml), CCl_4 (200 ml) and petroleum ether (80 ml) to give 900 mg of crude (8*S*) *N*-Trifluoroacetyl-8-fluoro-daunorubicin. A second crop (72 mg) is obtained from the mother liquors and purified by FCC. On the whole, 954 mg of (8*S*) *N*-trifluoroacetyl-8-fluorodaunorubicin are obtained [^{1}H-NMR δ 1.27 (d, J = 6.6, 3H, CH_3-5'); 1.73-2.12 (m, 2H, CH_2-2'); 2.42 (d, J = 1.4, 3H, CH_3-14); 3.15 (J = 18.5, 1.9, 1H); 3.28 (J = 18.5, 3.3, 1H), the latter two protons resonate as AB counterpart of an ABX spectrum where AB = CH_2-10 , X = F; 3.64 (br d, J = 7.2, 1H, H-4'); 3.96 (s, 1H, OH); 4.05 (s, 3H, OCH_3), 4.23 (q, J = 6.8, overlapped on a multiplet, 2H, CH-5' and CH-3'); 4.89 (dd, J = 45.4, 2.9, 1H, H-8), 5.12 (dd, J = 16.4, 2.9, 1H, H-7); 5.45 (d, J = 3.6, 1H, H-1'); 6.33 (d, J = 8.2, 1H, NH); 7.36 (dd, J = 8.4, 1.0, 1H, H-3); 7.75 (t, J = 7.9, 1H, H-2); 7.99 (dd, J = 7.7, 1.1, 1H, H-1). MS (Thermo spray in the negative ion mode

injection) m/z 676 (M^{-} + NH_4OH); 641 ($M^{-\cdot}$)]. *N*-trifluoroacetyl-8-fluorodaunorubicin (440 mg, ≈ 0.69 mmoles), obtained as above, is dissolved in precooled aqueous NaOH (0.1N, 200 ml). After 2 hours the detrifluoroacetylation is complete and the solution is acidified to pH 3 by adding 0.3 N HCl, dropwise. The acidic aqueous phase is extracted with $CHCl_3$, then the pH is adjusted at 8-8.5 and the aminoglycoside is extracted with the mixture $CHCl_3$/MeOH, 6:1 by vol.. After washing the organic phase with 1% $NaHCO_3$, drying and removal of the solvent under reduced pressure, 290 mg of **2b** are obtained (78%). Its hydrochloride M.P. (DSC) 185.9 °C (dec). ^{1}H-NMR (CD_3OD) δ 1.32 (d, *J* = 6.6, 3H, H-5'); 1.85-2.20 (m, 2H, CH_2-2'); 2.40 (s, 3H, CH_3-14); 3.03 (*J* = 18.8, 1H); 3.29 (*J* = 18.8, 3.9, 1H), the latter two protons resonate as AB counterpart of an ABX spectrum where AB = CH_2-10 , X = F; 3.50-3.85 (m, 4H, H-3' and H-4'); 3.99 (s, 3H,); 4.30 (q, *J* = 6.6, 1H, H-5'); 5.09 (dd, *J* = 46.2, 3.1, 1H, H-8), 5.09 (dd, *J* = 16.3, 3.1, 1H, H-7); 5.54 (br d, *J* = 2.6, 1H, H-1'); 7.43 (d, *J* = 8.0, 1.0, 1H, H-3); 7.65-7.85 (m, 2H, H-2 and H-1). MS (Thermo spray in the positive ion mode injection) m/z 546 ($M+1^+$); 417 (aglycone+$1^{+\cdot}$).] is dissolved in water and freeze-dried. Purity >95%. HRMS (caesium ion bombardment) calcd for $C_{27}H_{28}FNO_{10}$, 545.1697; found, 545.1722. CD spectrum corresponding to that of natural daunorubicin.

(8*S*) 8-Fluoro-*N*-trifluoroacetylidarubicin (2a). The glycosidation is performed under the same conditions as in the case of **2b**. Two products are visible by TLC analysis. At the end of the reaction they are separated by FCC (CCl_4/acetone 6:1) and separately de 4-nitrobenzoylated as described above. Only the compound derived from the fast moving (CCl_4/acetone 6:1) 4-nitrobenzoylester shows a dichroic curve corresponding to that of natural daunorubicin. **2a** (13 mg from 30 mg of **14a**, 27%). $[\alpha]_{589}^{20}$ = +115° ($CHCl_3$, c = 0.021). M. P. (DSC) 283.4 °C. Rf = 0.40 ($CHCl_3$/acetone 3:1). ^{1}H-NMR δ 1.30 (d, *J* = 6.6, 3H, CH_3-5'); 1.76-2.16 (m, 2H, CH_2-2'); 2.45 (d, *J* = 1.2, 3H, CH_3-14); 3.21 (1H, *J* = 19.0, 1.8) and 3.34 (1H, *J* = 19.0, 2.8); AB counterparts of an apparent ABX spectrum where AB = CH_2-10 and X = F; 3.66 (br s, 1H, H-4'); 4.27 (q, overlapped on a multiplet, *J* = 6.5, 2H, H-5' and H-3'); 4.95 (dd, *J* = 45.3, 2.6, 1H, H-8); 5.14 (dd, *J* = 13.5, 2.6, 1H, H-7); 5.53 (d, *J* =3.6, 1H, H-1'); 6.63 (d, *J* = 8.4, 1H, NH); 7.82-7.90 (m, 2H, H-2 and H-3); 8.33-8.42 (m, 2H, H-1 and H-4); 13.37 (s, 1H, OH); 13.60 (s, 1H, OH). MS (Thermo spray in the negative ion mode injection) m/z 611 ($M^{-\cdot}$). **7*S*,8*R*,9*S* isomer** (8 mg from 30 mg of **14a**, 17%) ^{1}H-NMR δ 1.31 (d, *J* = 6.6, 3H, CH_3-5'); 1.85-2.05 (m, 3H, CH_2-2' and OH); 2.38 (d, *J* = 1.3, 3H, CH_3-14); 3.20 (1H, *J* = 19.6) and 3.44 (1H, *J* = 18.8, 2.4); AB counterparts of an apparent ABX spectrum where AB = CH_2-10 and X = F; 3.64 (br d, *J* = 5.7, 1H, H-4'); 4.23 (s, 1H, OH); 4.35 (dq, *J* = 8.3, 1.9, 1H, H-3'); 4.48 (q, *J* = 6.8, 1H, H-5'); 5.10 (dd, *J* = 45.3, 2.7, 1H, H-8); 5.41 (br s, 1H, H-1'); 5.51 (dd, *J* = 10.2, 2.8, 1H, H-7); 6.70 (d, *J* = 8.4, 1H, NH); 7.82-7.90 (m, 2H, H-2 and H-3), 8.33-8.42 (m, 2H, H-1 and H-4); 13.35 (s, 1H, OH); 13.72 (s, 1H, OH). MS (Thermo spray in the negative ion mode injection) m/z 611 ($M^{-\cdot}$).

(8*S*) 8-Fluorodoxorubicin (2c). This compound was obtained following the reported procedure,[31] except for the bromination step that was carried out at room temperature. The yield was only 13 mg of free base from 270 mg of **2b**. For the freeze-dried hydrochloride: purity >90% (HPLC). MS (Thermo spray in the positive ion mode injection) m/z 562 ($M+1^+$). HRMS (caesium ion bombardment) calcd for $C_{27}H_{28}FNO_{11}$, 561.1646; found, 561.1603.

Epoxyketone 29b. A solution of anhydrous DMSO (13 ml, 183 mmoles) in anhydrous CH_2Cl_2 (75 ml) is cooled at -78 °C. Trifluoroacetic anhydride (10 ml) in anhydrous CH_2Cl_2 (50 ml) is added dropwise (T<-70°C). The solution is stirred for 30 min, then **28b** (6.92 g, 10.1 mmoles), dissolved in anhydrous CH_2Cl_2 (90 ml) is added through a dropping funnel in 90min. Stirring is continued for 30 min, then DBU (25 ml, 166 mmoles) is added through a syringe. The solution is stirred at -70 °C for 30 min, then the reaction mixture is quenched with acetic acid (20% in CH_2Cl_2) until the colour of the solution changes from purple to greenish . The cooling bath is removed and the reaction mixture is washed with water (200 ml), HCl 0.3 N (200 ml), $NaHCO_3$ sat., brine, and dried. The crude is dissolved in CH_2Cl_2 (150 ml), cooled at -70 °C and diluted with MeOH (400 ml). Solid $NaBH_4$ (60 mg, 1.58 mmoles) is added portionwise. After 10 min, acetone is added and the cooling bath removed. The reaction mixture is diluted with CH_2Cl_2, washed with water and dried. After concentration under reduced pressure, the residue is chromatographated (FCC, silica; conditioning with $CHCl_3$, eluition with $CHCl_3$/acetone from 10/1 to 4/1 by vol.) to give 2.50 g (39.8%) of pure **29b**. M.P. 204-208 °C (isopropyl alcohol, dec.). $[\alpha]_{589}^{20}$ = +80.5°, ($CHCl_3$, c = 0.12). ^{1}H-NMR δ 1.34 (d, *J* = 6.2, 3H, CH_3-5'); 1.76 (dt, *J* = 12.7, 3.8, 1H, H-2'); 2.10 (dd, *J* = 12.9, 4.7, 1H, H-2'); 2.27 (s, 3H, CH_3-14); 2.52 (dd, *J* = 16.7, 5.1, 1H, H-8); 2.70 (d, *J* = 16.5, 1H, H-8); 3.21 (t, *J* = 9.5, 1H, H-4'); 3.80-4.00 (m, 1H, H-5'); 4.08 (s, 3H, OCH_3); 4.10 - 4.25 (m, 1H, H-3'); 4.78 (s, 1H, H-10); 5.32 - 5.40 (doublet overlapping on a broad singlet, 2H,); 6.38 (d, *J* = 7.3, 1H, NH); 7.40 (d, *J* = 8.4, 1H, H-3); 7.78 (t, *J* = 8.4, 1H, H-2); 8.02 (d, *J* = 8.2, 1H, H-1); 13.33 (s, 1H); 13.72 (s, 1H). ^{13}C-NMR δ 17.51 (q); 23.40 (q); 27.06 (t); 35.44 (t); 48.88 (d); 50.23 (d); 56.61 (q); 64.88 (s); 65.76 (d); 69.12 (d); 75.84 (d); 97.96 (d); 112.03 (s); 113.69 (s); 115.00 (q, *J* = 287.5); 118.62 (d); 119.74 (d); 120.45 (s); 130.59 (s); 135.00 (s);

135.75 (s); 135.96 (d); 155.10 (s); 156.13 (s); 158.53 (q, J = 36.3); 161.02 (s); 186.66 (s); 186.93 (s); 205.91 (s). MS (Thermo spray in the negative ion mode injection) m/z 621 ($M^{-\cdot}$); 378; 227. IR (KBr) cm^{-1} 3421; 2927; 1709; 1620.

Epoxyketone (30b), procedure I. Compound **29b** (118 mg, 190 μmoles), is stirred in aqueous methanol (100 ml, 1/4) at 0°C. Precooled 0.1 N NaOH (15 ml) is added and stirring is mantained over 2.5 hours. The solution is acidified (10% HCl) to pH = 2.5, the the reaction mixture is extracted with $CHCl_3$; the pH of aqueous phase is adjusted to 7.5 with solid $NaHCO_3$ and the solution is extracted with with the mixture MeOH/$CHCl_3$, 1:4, v/v. The organic phase is rinsed with $CHCl_3$ and evaporated under reduced pressure (rotary evaporator, temp. < 35°C). The residue (55 mg, maximum 55%) is used without further purification in the following step. ^{1}H-NMR δ 1.29 (d, J = 6.2, 3H, CH_3-5'); 1.40 - 1.60 (m, 1H, H-2'); 1.80 (m, 1H, H-2'); 2.22 (s, 3H, CH_3-14); 2.48 (J = 16.3, 5.0, 1H); 2.66 (J = 16.3, 1H) the latter two protons (CH_2-8) resonate as an ABX whose X component resonates at 5.36 ppm; 2.90-3.10 (m, 2H, H-3' and H-4'); 3.81 (m, 1H, H-5'); 4.04 (s, 3H, OCH_3); 4.70 (s, 1H, H-10); 5.36 (d, J = 3.7, 2H, H-1' and H-7); 7.36 (d, J = 8.4, 1H, H-3); 7.58 (t, J = 8.1, 1H, H-2); 7.98 (d, J = 7.7, 1H, H-1). MS (Thermo spray in the negative ion mode injection) m/z 525 ($M^{-\cdot}$); 509 ($M^{-\cdot}$ - 16).

Epoxyketone (30b), procedure II. Compound **29b** (505 mg, 826 μmoles), is suspended in $MgSO_4$ eptahydrate 0.1% solution (400 ml). The suspension is cooled at 0-5 °C. NaOH (0.1 M, 180 ml) is added dropwise and the reaction mixture is stirred at 0-5 °C over 2.5 hours. The solution is acidified to pH = 6.8 by HCl 10%, then extracted with a mixture $CHCl_3$/MeOH 3:1 v/v (7x150 ml). The organic phase is washed (3x200 ml) with Titriplex III (0.1 M, Merck) and concentrated to a small volume (rotary evaporator, temp. < 35°C) and chromatographated on silica gel (Silica gel 60, 70-230 mesh, Merck, Ø = 3 cm, h = 15 cm; Conditioning with $CHCl_3$; eluition with 20% acetone in $CHCl_3$, followed by the mixture $CHCl_3$/MeOH/H_2O 125:60:2 by vol.. The fractions containing the desired compound are diluted with $CHCl_3$, the solvent is removed under reduced pressure and the residue dried under vacuum to give 374 mg of **30b** (87%).

(10*R*) 10-Fluoro-4'-epi-daunorubicin (2d) and (10*S*) isomer (2e). Compound **30b** (200 mg) is suspended in TEA·3HF and the mixture is heated at 58 °C in a thermostat over 118 hours in the dark. The reaction mixture is poured into a stirred two phase system ($CHCl_3$, 200 ml/$NaHCO_3$ sat., 200 ml). The organic phase is separated and the aqueous phase is repeatedly washed with $CHCl_3$. The organic phases are collected and extracted with 0.01 M HCl. The pH of the aqueous phase is adjusted to pH 6.4, then extractedwith the mixture $CHCl_3$/MeOH 3:1 by vol. The residue obtained by evaporation of the solvent and drying under vacuum (115 mg) is analyzed by ^{1}H-NMR, TLC and HPLC. The analysis indicates 91.5% conversion and 1.2/1 ratio of two fluoro derivatives; only one of the fluorine containing compounds shows a long range $J_{H\text{-}H}$ =1.1 Hz at C-H_{10}, thus suggesting the absolute configuration 10(*R*). The crude is separated by preparative HPLC to give **2d**, 34 mg as the hydrochloride (15%), >97% purity (HPLC) after freeze-drying [^{1}H-NMR (free base) δ 1.31 (d, J = 6.0, 3H, CH_3-5'); 1.50-1.67 (m, 1H, H-2'); 1.95-2.05 (m, 1H, H-2'); 2.35 (br d, J = 15.4, 1H, H-8); 2.46 (s, 3H, CH_3-14); 2.51 (dd, J = 14.9, 4.0, 1H, H-8); 2.72-2.87 (m, 1H, H-3'); 2.96 (t, J = 9.4, 1H, H-4'); 3.60-3.85 (m, 1H, H-5'); 4.09 (s, 3H, OCH_3); 5.34 (s, broad, 1H, H-7); 5.48 (d, J = 3.7, 1H, H-1'); 5.89 (d, J = 47.1, 1H, H-10); 7.39 (d, J = 8.4, 1H, H-3); 7.80 (t, J = 8.1, 1H, H-2); 8.03 (d, J = 7.7, 1H, H-1). MS (FAB) m/z 546 ($M+H^{+\cdot}$), 399; 363; 336; 148; HRMS (caesium ion bombardment) calcd for $C_{27}H_{28}FNO_{10}$, 545.1697; found, 545.1704] and **2e**, 19 mg as the hydrochloride (8%), >99% purity (HPLC) after freeze-drying, [^{1}H-NMR (free base) δ 1.29 (s, J = 6.2, 3H, CH_3-5'); 1.53-1.70 (m, 1H, H-2'); 1.95-2.10 (m, 1H, H-2'); 2.33 (s, overlapped on a multiplet, 5H, CH_3-14, and CH_2-8); 2.70-3.10 (m, 2H, H-3' and H-4'); 3.70-3.90 (m, 1H, H-5'); 4.03 (s, 3H, OCH_3); 5.01-5.08 (m, 1H, H-7); 5.38 (d, J = 3.3, H-1'); 5.96 (d, J = 47.3, 1H, H-10); 7.36 (d, J = 8.4, 1H, H-3); 7.76 (t, J = 8.1, 1H, H-2); 7.95 (d, J = 7.7, 1H, H-1); MS (FAB) m/z 546 ($M+H^{+\cdot}$), 416, 398; 380; 338; 148; HRMS (caesium ion bombardment) calcd for $C_{27}H_{28}FNO_{10}$, 545.1697; found, 545.1703].

Compounds **28a**, **29a**, **30a**, **2f** and **2g** are obtained following the same sequence of reactions described for the corresponding compounds in the 4-methoxy series, starting from preformed idarubicin **1c**. In the case of **29a** detrifluoroacetylation, only procedure I was carried out. The spectral data of **28a**, **29a**, **30a**, **2f** and **2g** correspond to those reported for **28b**, **29b**, **30b**, **2d** and **2e**, respectively. In addition, for **2f**, as the freeze-dried hydrochloride, >97% purity (HPLC): HRMS (caesium ion bombardment) calcd for $C_{26}H_{26}FNO_9$, 515.1591; found, 515.1628. For **2g**, as the freeze-dried hydrochloride, >98% purity (HPLC): HRMS (caesium ion bombardment) calcd for $C_{26}H_{26}FNO_9$, 515.1591; found, 515.1606.

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References and Notes

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