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EFFICIENT SYNTHESIS AND ANTITUMOR ACTIVITY OF NOVEL 14-FLUOROANTHRACYCLINES

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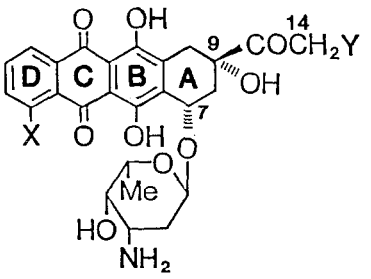
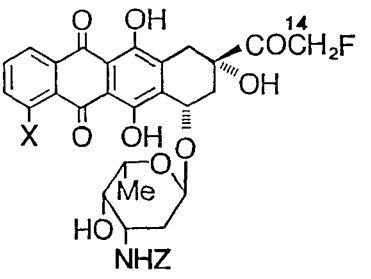
Abstract: The title compounds, (+)-14-fluoro-4-demethoxy- and (+)-14-fluorodaunorubicin, were synthesized from (-)-7-deoxy-4-demethoxy- and (-)-7-deoxydaunomycinone, respectively, by featuring the novel fluorination reaction in which tetrabuthylammonium fluoride is employed in the presence of a half equiv of p-toluenesulfonic acid as a key step. These novel anthracyclines were found to exhibit significant inhibitory activity against P388 murine leukemia *in vitro* and *in vivo*.

The anthracyclines, adriamycin (**1**) and daunorubicin (**2**), are of great current interest because of their activity against many types of human cancers.[1,2] However, their uses for cancer chemotherapy are seriously hampered by their side effects, especially by dose-related cardiotoxicity. Thus, numerous synthetic efforts have been devoted to overcome these disadvantages culminating in the development of unnatural 4-demethoxyadriamycin (**3**) and 4-demethoxydaunorubicin (**4**), which could show better therapeutic indices than natural **1** and **2**.[1-3]

In the last decade, a great number of the fluorinated biologically active compounds have been prepared to improve therapeutic property of the parent compounds or to explore novel pharmacological activity.[4] In the field of anthracyclines, some derivatives possessing fluorinated sugers or D-ring have been synthesized recently.[5,6] However, synthesis of the anthracyclines carrying a fluorinated C-9 side chain, the most interesting and promising congeners in light of the structure-activity relationships, have not been reported due to the



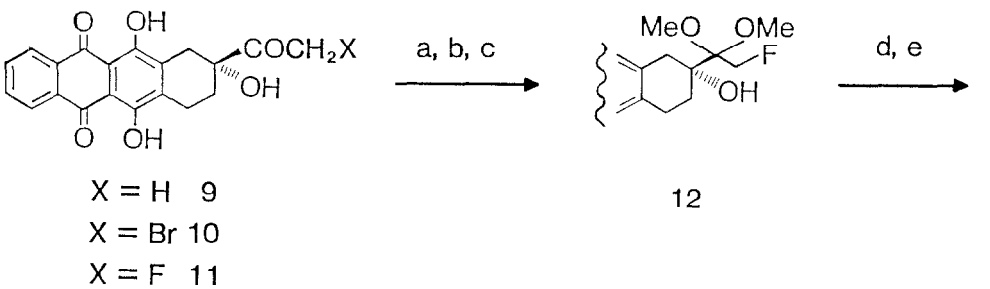
	X	Y
1	OMe	OH
2	OMe	H
3	H	OH
4	H	H



	X	Z
5	H	H
6	H	$COCF_3$
7	OMe	H
8	OMe	$COCF_3$

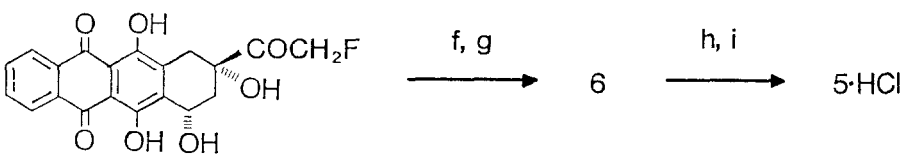
difficulty which may be encountered to introduce a fluorine atom into the C-9 side chain. In conjunction with our program directed toward the development of novel synthetic anthracycline congeners as anticancer agents, we achieved the first synthesis of the 14-fluoroanthracyclines, (+)-14-fluoro-4-demethoxy- and (+)-14-fluorodaunorubicin (**5** and **7**), and their 3'-N-trifluoroacetates (**6** and **8**). These compounds were found to show significant inhibitory activity against P388 murine leukemia *in vitro* and *in vivo*.

The preliminary experiments for fluorinating the C-14 position were performed by employing the C-14 bromide (**10**), derived by selective bromination of the readily available racemic 7-deoxy-4-demethoxydaunomycinone (**9**)[7] with pyridinium hydrobromide perbromide,[8] as a model compound. These investigation revealed that displacement reaction cleanly occurred by the treatment with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) in the presence of a half equiv of pyridinium p-toluenesulfonate (PPTS) to TBAF. The best result was obtained by carrying out the reaction with 6 equiv of TBAF and 3 equiv of PPTS to **9**, giving racemic 14-fluoro-7-deoxy-4-demethoxydaunomycinone (**11**) in 54% overall yield from **9**. Interestingly, the treatment of **10** with TBAF in the absence of PPTS or in the presence of 1 equiv of PPTS to TBAF resulted in complete decomposition of the starting material (**10**) or recovery of **10**, respectively. Further improvement was achieved by using p-toluenesulfonic acid in place of PPTS under the same conditions to afford **11** in 61% overall yield from **9**.[9]



X = H 9
X = Br 10
X = F 11

12



13

a) Py•HBr•Br_2, THF, rt, 1.5 h b) Bu_4N•F, TsOH, THF, reflux, 2 h c) $CH(OMe)_3$, TMSOTf, CH_2Cl_2, rt, 2 h d) 1) Br_2, hν, $CHCl_3$-CCl_4-H_2O, reflux, 2 h 2) 10% NaOH, rt, 25 min e) 12M HCl, THF, rt, 16.5 h f) Daunosamine derivative, TMSOTf, 4A-MS, CH_2Cl_2-Et_2O-THF, -10 °C, 5.5 h g) 0.1M NaOH, MeOH, 0 °C, 20 min h) 0.05M NaOH, THF, rt, 40 min i) 0.25M HCl-MeOH, 0 °C

Since application of this newly developed method to direct fluorination of 4-demethoxydaunorubicin hydrochloride (**4-HCl**) and 4-demethoxydaunomycinone gave unsatisfactory results,[10] we selected optically pure (+)-**9**[11] as a starting material for the synthesis of **5**. After further detailed studies on this displacement reaction by employing optically pure **10** prepared from (+)-**9**, 14-fluoro-7-deoxy-4-demethoxydaunomycinone (**11**), mp 251-255 °C, $[\alpha]_D^{20}$ -34.8° (dioxane), was ultimately obtained in 81% overall yield from (+)-**9** by careful dropwise addition of TBAF to a THF-solution of **10** and p-toluenesulfonic acid.

The 14-fluorodeoxyaglycone (**11**) thus obtained was converted into (+)-14-fluoro-4-demethoxydaunomycinone (**13**) at the next stage of the synthesis. Acetalization of **11** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a catalyst produced the corresponding dimethylacetal (**12**) in 88% yield. Bromination of **12** with bromine under irradiation followed by treatment of the resulting unstable C-7 bromide with aqueous alkali to introduce the 7α hydroxyl group stereoselectively, gave rise to **13** in 61% overall yield from **12** after acidic removal of the acetal group.[12] The optically pure aglycone (**13**), mp 129.5-132 °C, $[\alpha]_D^{20}$ +162° (dioxane), was obtained by recrystallization from benzene.

Glycosidation of **13** with the daunosamine derivative was next attempted according to the reported procedure.[13] Thus, **13** was reacted with 3-N-trifluoroacetyl-1,4-bis(O-p-nitrobenzoyl)-L-daunosamine[14] in the presence of TMSOTf, followed by immediate treatment with dilute alkali to effect hydrolysis of the 4'-O-p-nitrobenzoyl group, producing 3'-N-trifluoroacetyl-14-fluoro-4-demethoxydaunorubicin (**6**), mp 161-163.5 °C, $[\alpha]_D^{20}$ +173° (dioxane), as a sole product in 91% overall yield from **13**. Further alkaline hydrolysis of the 3'-N-trifluoroacetyl group and salt formation afforded 14-fluoro-4-demethoxydaunorubicin hydrochloride (**5-HCl**), mp 231-235 °C, $[\alpha]_D^{20}$ +122° (MeOH), in 55% yield.

Following the same synthetic scheme as that described above, 14-fluorodaunorubicin hydrochloride (**7-HCl**), mp 209 °C (decomp.), $[\alpha]_D^{20}$ +176° (MeOH), was synthesized from (-)-7-deoxydaunomycinone,[15] by way of 3'-N-trifluoroacetyl-14-fluorodaunorubicin (**8**), mp 161.5-164 °C, $[\alpha]_D^{20}$ +185° (dioxane).

These 14-fluoroanthracyclines (**5-HCl**, **7-HCl**, **6**, and **8**) were subjected to P388 murine leukemia *in vitro* assay. Although fairly weak cytotoxity was only observed for the 3'-N-trifluoroacetyl derivatives (**6** and **8**) (**6**; IC_{50} = 1.2 x 10^{-3} μg/ml; **8**; IC_{50} = 1.9 x 10^{-3} μg/ml), **5-HCl** and **7-HCl** exhibited prominent cytotoxicity (**5-HCl**; IC_{50} = 1.3 x 10^{-4} μg/ml; **7-HCl**; IC_{50} = 1.5 x 10^{-4} μg/ml) being well compared with that of **1-HCl** (IC_{50} = 2.3 x 10^{-4} μg/ml). Furthermore, in P388 *in vivo* test, **5-HCl** and **7-HCl** were found to show significant inhibitory activity [**5-HCl**; T/C = 169% (0.62 mg/kg); **7-HCl**; T/C = 183% (2.5 mg/kg)]. Further studies aimed at characterizing antitumor activity of **5-HCl** and **7-HCl** are in progress and will be reported shortly.

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9) Treatment of **10** with TBAF in the presence of benzoic acid instead of PPTS afforded 14-benzoyloxy-7-deoxy-4-demethoxydaunomycinone. Considering these results and possibility of strong hydrogen bonding between proton and fluoride anion, it was anticipated that tetrabutylammonium hydrogendifluoride might be generated *in situ* as an active species.

10) The same reaction examined with the C-14 bromide prepared from 4-demethoxydaunorubicin hydrochloride (**4-HCl**) resulted in aromatization of the A-ring. On the other hand, the 14-fluoroaglycone (**13**) was obtained from 4-demethoxydaunomycinone according to the same procedure only in a low yield.

11) Preparation of **9**, mp 219-221 °C, $[\alpha]_D^{20}$ -84.9° ($CHCl_3$) [lit.,[7a] mp 218-219 °C, $[\alpha]_D^{20}$ -90.3° ($CHCl_3$)] was carried out according to the reported method.[7a]

12) Complete absence of the 7β epimer was ascertained by the ^{1}H-NMR spectrum of the crude product.

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15) Following the known procedure,[16] 7-deoxydaunomycinone, mp 228-230 °C, $[\alpha]_D^{20}$ -84.7° ($CHCl_3$) [lit.,[16] mp 229-231 °C, $[\alpha]_D^{20}$ -91° ($CHCl_3$)], was prepared by hydrogenation of daunorubicin hydrochloride (**2-HCl**).

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