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The Synthesis of 8-(S)-Fluoro-N-Trifluoroacetylidarubicin

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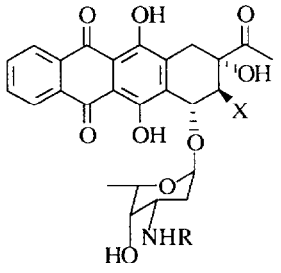
abstract: (+,-)4-Demethoxy-8-fluoro-(7,8-trans)-daunomycinone is obtained by total synthesis and coupled with daunosamine to give 8-(S)-fluoroidarubicin-N-trifluoroacetate, the first anthracycline substituted with a fluorine atom on ring A.

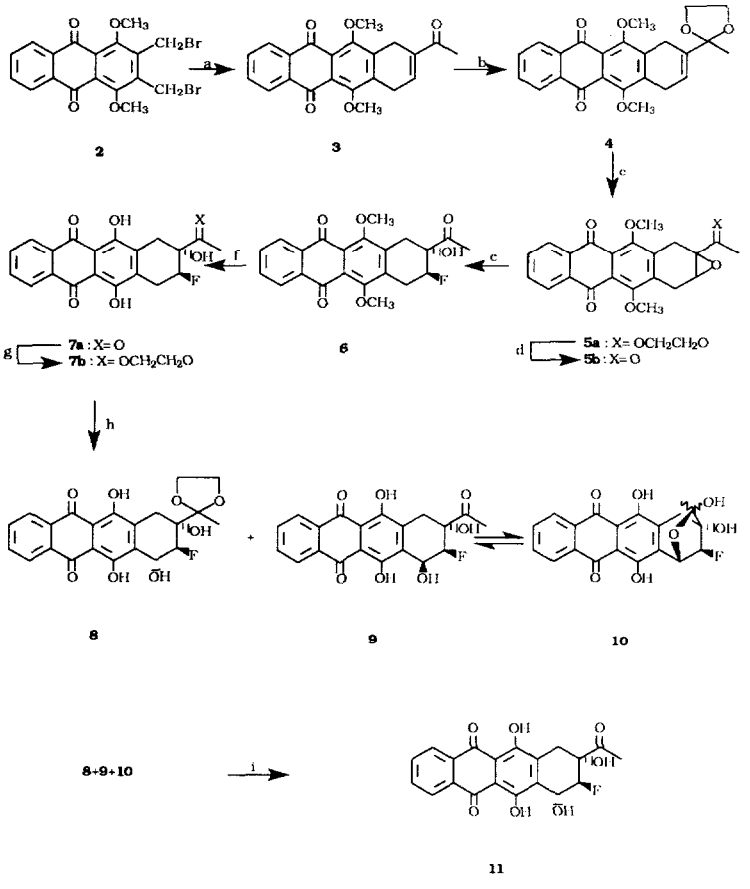
The introduction of fluorine into biologically active compounds is of growing interest because of the particular effects that fluorine can exert on the properties of the parent compound without altering its steric bulk.[1] Here, we wish to report the total synthesis of 8-(S)-fluoroidarubicin-N-trifluoroacetate (**1a**), the first ring A-fluorinated anthracycline,[2] the parent compound idarubicin, **1b**, (4-demethoxydaunorubicin), being a recently marketed powerful antitumor agent.[3] This new chemical modification of antitumor anthracyclines stems from the observations 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.[4]



1a: X=F; R=$COCF_3$
1b: X=H; R=H

Recent studies[5] have shown that the 9-OH group contributes to the stabilization of the complexes between daunorubicin and oligonucleotides through hydrogen bond interactions with N-3 and N-4 of a guanine. Thus, it was thought that the introduction of a fluorine atom at position 8 could reinforce the strength of such interactions at the intercalation site because of the electron withdrawing effects of the fluorine substituent.

Scheme 1



a) 3-butyn-2-one, NaI, DMA, 65°C; b) Collidinium tosylate cat., E.G., C_6H_6 refl.; c) mCPBA, $CHCl_3$, r.t.; d) TFA/H_2O, r.t.; e) HF/py; 70%; f) BCl_3, CH_2Cl_2, -78°C, then MeOH; g) pTSA cat., E.G., C_6H_6, refl.; h) PVPHP, AIBN, CCl_4 refl., then FCC; i) TFA r.t., then MeOH.

Racemic aglycon **11** (scheme 1) was synthetized following an adaptation of Cava's route to anthracylinones.[6] α,β-Unsaturated ketone **3** (m.p.=195-198°C) was obtained (80%) by trapping the orthoquinodimethane generated *in situ* from 1,4-dimethoxy-2,3-bis(bromomethyl)anthraquinone **2**[7] with an excess of 3-butyn-2-one. Conversion of **3** into the corresponding epoxyketone **5b** (m.p.=240-244°C) required the protection as the diethylene ketal (ethylene glycol, catalytic collidinium p-toluene sulfonate[8] in a Dean Stark apparatus) before the epoxidation of the double bond (m-CPBA, $CHCl_3$, r.t.). The action of 90% aqueous trifluoroacetic acid (r.t., 1h) allowed to restore the ketone function (65% overall yield from **3**).[9]

The introduction of fluorine was accomplished by means of Olah's reagent[10] (r.t., 8 h). NMR spectral data[11] of the only fluorinated compound isolated (60% yield) are in agreement with the expected structure **6**: δ_H 4.76 (app. dt, 1H, J = 49.6, 2.9; H-8), δ_C 87.99 (d, $J_{C-8,F}$ = 177.2).[12] Bromination of **7b** (m.p.= 239-241°C dec., 85% yield from **6**) was firstly attempted following the reported procedure for the non fluorinated compound,[13] but many difficulties were encountered in monitoring the reaction and complex mixtures of products were obtained. Fortunately, bromination with polymer supported pyridinium hydrobromide perbromide (PVPHP)[14] resulted easier to handle and to monitor by ^{1}H-NMR. So, on the base of this approach, we realized that the bromination step was less regioselective than it was reported in the case of the non fluorinated compound,[15] 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 at 50-60% conversion. Direct flash column cromathography[16] of the crude reaction mixture on silica gel allowed recovery of starting material (30%), the hydrolysis of the brominated products and the purification of derivatives **8** δ_H 5.18 (1H, ddd; J = 2.3, 9.6, 13.7; H-7), 5.18 (1H, dd, J = 2.4, 45.7; H-8), 4.07-4.19 (4H, m; -OCH_2CH_2O-), 3.70 (1H, d, J = 9.6; OH-7) and **9** δ_H 5.45 (1H, broad dt, ; J = 3.0, 26.8; H-8), 4.82 (1H, dd, J = 3.1, 51.4; H-8), 2.56 (3H, d, J = 2.8; $CO\underline{CH_3}$), which, in $CDCl_3$ solution, exists in equilibrium with **10** δ_H 5.70, (1H, d, J = 11.1; H-7); 4.98 (1H, d, J = 54.8; H-8); 1.36 (3H, s, CH_3-14).[17] For preparative purposes the mixture of **8**,**9**, and **10** was almost quantitatively converted to **11** (20-25% from **7b**) by trifluoroacetic acid treatment and methanolic work up. The latter compound was glycosidated with 3-N-trifluoroacetyl-1,4-bis(O-p-nitrobenzoyl)-L-daunosamine and TMSOTf as condensing agent;[18] the diastereomeric glycosides were separated by flash column cromatography and the OH-4' was deprotected (NaOH/ MeOH, O°C, 10 min.). Finally, the desired diasteroisomer **1a** (27% from **11**)[19] was selected on the base of the similarity of the CD curve to that of natural daunomycin.

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References and Notes

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19. M.p.: 283.4 °C (DSC). MS (Thermo spray in the negative ion mode injection): m/z = 611 (M^+). UV/VIS: λ_{max} ($CHCl_3$) = 236, 252, 286, 486, 520. $[\alpha]_D^{20}$ = +115° ($CHCl_3$, C = 0.021) ^{1}H-NMR: δ_H 1.30 (3H, d, J = 6.6; CH_3-5'), 1.76-2.16 (2H, m; CH_2-2'), 2.45 (3H, d, J = 1.2; -CO<u>CH_3</u>), 3.21 (1H, J = 1.8, 19.0) and 3.34 (1H, J = 2.8, 19.0); AB counterpart of an apparent ABX spectrum where AB = CH_2-10 and X = Fluorine. 3.66 (1H, broad s; H-4'), 4.27 (2H, broad q, J = 6.5; H-5' and H-3'), 4.95 (1H, dd, J = 2.6, 45.3; H-8), 5.14 (1H, dd, J = 2.6, 13.5; H-7), 5.53 (1H, d, J =3.6; H-1'), 6.63 (1H, broad d, J = 8.4; N<u>H</u>$COCF_3$), 7.82-7.90 (2H, m, aromatic protons), 8.33-8.42 (2H, m, aromatic protons), 13.37 (1H, s, phenolic proton), 13.60 (1H, s, phenolic proton).

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