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Synthesis of 14-fluorodoxorubicin

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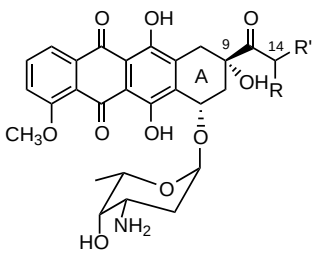
Abstract—Synthesis of the novel anthracycline 14-fluorodoxorubicin is described. A key step in the synthesis is the hydrolysis of 14-bromo,14-fluoro derivative **14** with $AgBF_4$ and DMSO, to give the geminal fluorohydrin system.

Anthracycline antibiotics are well known antitumor agents. Doxorubicin **1** (Fig. 1), widely used in clinical therapy since the early 1970s, is still a major drug in the treatment of solid tumors.[1] Advances in the knowledge of the mechanism of action of anthracyclines highlight the enzyme DNA topoisomerase II as the primary cellular target for these molecules.[2] According to this mechanism, formation of a stable DNA–enzyme–drug complex hinders the relegation of the DNA strands and results in irreversible DNA breaks, eventually leading to apoptosis and cell death.[3,4] The molecular interactions of the drug in the ternary complex are still unclear and structural requirements for optimal activity remain to be elucidated. However, recent studies indicate the crucial role of the sugar moiety and of the cyclohexene ring (ring A) of the anthracyclines[5–7] and a study concerning their structural and stereochemical requirements has been reported.[8]

The 14 hydroxyl group is held responsible for the higher in vivo activity of **1** as compared with daunorubicin **2** against solid tumors.[1] Even if the reason of this notable difference in antitumor efficacy is still unknown, it was reasonable to conclude that selected modifications in the C-9 side chain and particularly at position 14 of the tetracyclic quinone chromophore might favorably influence the biological activity of the new derivatives. Introduction of the strongly electron-withdrawing and poorly steric-demanding fluorine atom at C-14 to give interesting derivative (**3**) is presently reported.



1) R=H, R'=OH, Doxorubicin
2) R=H, R'=H, Daunorubicin
3) R=F, R'=OH

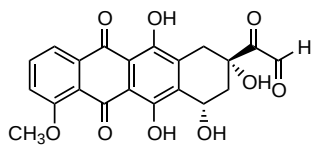


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Figure 1.

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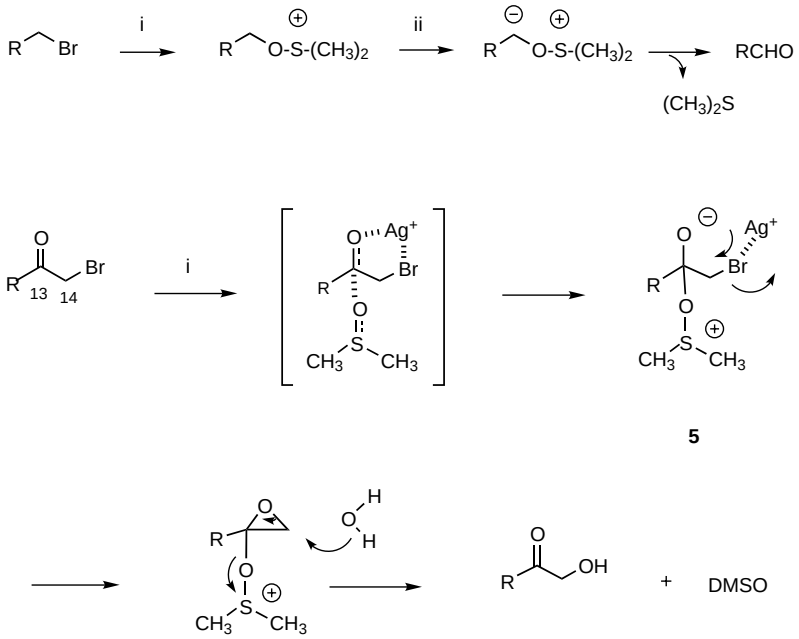
Anthracyclines derivatives carrying a fluorinated C-9 side chain have been synthesized,[9,10] but the fluorine atom and the hydroxyl group were never simultaneously present on the same carbon atom. Besides, only very few examples of biologically active compounds carrying the geminal fluorohydrin system can be found in the literature.[11,12] In the study of Guest et al.[12] the geminal fluorohydrin was obtained in the reaction of diethylaminosulphur trifluoride (DAST) with aldehydes, a reaction known to give difluoroderivatives.[13] Model experiments aimed at the preparation of a 14-fluorohydrin were thus carried out in the first instance in the aglycon series and the synthesis of ketoaldehyde **4** from daunomycinone **7** via the known[14] 14-bromo derivative **8** was attempted. Daunomycinone is obtained upon acid hydrolysis of **2**, a readily available biosynthetic product. In case of success with such model compounds we could have either coupled the sugar moiety with the functionalized aglycone, or transferred the methodology to derivatives of a preformed anthracycline glycoside. Unfortunately, treatment of **8** with different oxidative systems (Na_2CO_3, KI, DMSO, 120°C;[15] DMSO, Sym Collidine, rt;[16] $AgBF_4$, DMSO, Et_3N, rt[17]) did not give the desired **4**, but during the reaction of compound **8** with $AgBF_4$ and DMSO, a mild method for the preparation of aldehydes from alkyl halides by a mechanism similar to the Moffat/Swern oxidation,[17] we obtained 14-hydroxydaunomycinone (adriamycinone, **9**). In the reported oxidation of alkyl bromides, $AgBF_4$ facilitates the displacement of bromine by DMSO affording an oxysulfonium salt which generates the aldehyde in presence of base (Scheme 1). Formation of **9** on the contrary, may be explained by admitting a nucleophilic attack of DMSO to the C-13 carbonyl instead of the C-14 to form intermediate **5**; this latter may undergo nucleophilic displacement with neighboring-group participation to **6**. Hydrolysis of the oxysulfonium provides the observed α-hydroxyketo derivative (Scheme 1).

Even compound **9**, under typical oxidation conditions (CrO_3, pyridine, CH_2Cl_2, rt; ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, –40°C), did not afford desired **4**.

However, these results allowed the exploration of a different synthetic strategy based on the preparation of 14-bromo,14-fluoro derivative **11**. In fact mild substitution of the bromine with a hydroxyl group by reaction with $AgBF_4$ and DMSO as previously observed would have afforded the desired fluorohydrin.

The necessary intermediate 14-fluorodaunomycinone **10** has already been synthesized upon reacting 14-bromo derivative with tetrabutyl ammonium fluoride; but this reaction did not work on compound **8** albeit only on its 7-deoxy derivative.[9,18] It had thus been necessary to reintroduce the 7 hydroxyl group on the 7-deoxy-14-fluoro derivative in order to perform the coupling with the sugar residue. Our different methodology, allowing the substitution of bromine with a fluorine atom directly on compound **8** provided a more practical synthetic pathway to the final glycoside.

A first sample of 14-fluorodaunomycinone was obtained upon refluxing **8** and $[n\text{-}Bu_4N]^+$ $[Ph_3SnF_2]^-$ in a 2:1 (by vol.) mixture of acetonitrile and tetrahydrofuran.[19] However, the prolonged reaction time (40 h) and low reaction yield (35%) prompted us to further investigate this step.



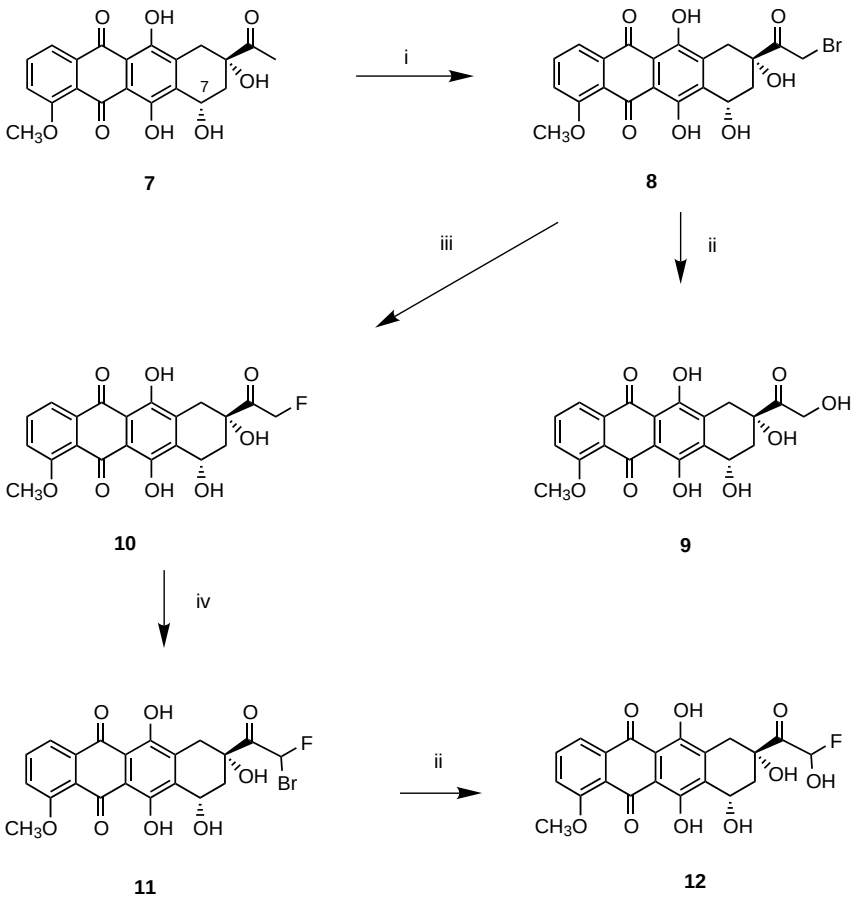
Scheme 1. (i) $AgBF_4$, DMSO; (ii) base.

Better results were obtained using $3HF{\cdot}Et_3N$ complex as fluorinating agent. Heating compound **8** and neat $3HF{\cdot}Et_3N$ complex to 100°C for 4 h gave, after flash chromatography purification, 14-fluoro derivative **10** in a 73% yield. Addition of different solvents (toluene, dioxane, acetonitrile, dimethoxyethane, triethylamine) did not increase the yield.

The standard bromination procedure already used for the preparation of **8**[14] appeared not to be applicable to **10**. However, 14-bromo,14-fluorodaunomycinone **11** was obtained in a 61% yield using a large excess of pyridinium bromide perbromide (6 equiv. every 3 h five times) and refluxing for 20 h in tetrahydrofuran. Compound **11** was then dissolved in DMSO and added to a solution of $AgBF_4$ in DMSO. After a few minutes stirring at room temperature water was added and the mixture extracted with dichloromethane to give 14-fluoro,14-hydroxy daunomycinone **12**, as a mixture of diastereoisomers in a 95% yield (Scheme 2).

Having achieved the synthesis of the geminal fluorohydrin system, our attention focused on compound **3**. With regard to the coupling reaction of the sugar moiety with the aglycone, some considerations must be made. If 14-fluoro,14-hydroxy daunomycinone **12** is used in the condensation reaction, the 14-hydroxyl group should be selectively protected. Moreover, observations made during the preparation of **12** showed that the geminal fluorohydrin rapidly decomposes in even mild basic conditions. On the other hand, a strong acidic medium could not be tolerated by the newly formed glycosidic linkage. Taking account of the acceptable yield of the glycosidation reaction (over 50%) and of that of the hydroxylation (practically quantitative) the condensation reaction was performed on **11**, using a suitably protected sugar derivative. The selected glycosylating residue was 1-*O*-*p*-nitrobenzoyl-3-*N*,4-*O*-di-allyloxycarbonyl-L-daunosamine **13**, obtained in a three-step sequence from commercially available **2**.[†] Both amino and hydroxyl functionalities were protected with an allyloxycarbonyl group, because it is easily removable under neutral conditions.[20]

Compounds **11** and **13** were allowed to react in the presence of TMSOTf as activating agent in a mixture of diethyl ether and dichloromethane according to a well known procedure[21] and the crude reaction mixture purified by flash chromatography to give **14** with a 54%



Scheme 2. (i) Pyridinium bromide perbromide (PBP), THF, rt, 70%; (ii) $AgBF_4$, DMSO, rt, 95%; (iii) $Et_3N{\cdot}3HF$, CH_3CN, reflux, 73%; (iv) PBP, THF, reflux, 61%.

[†] Daunorubicin **2** was treated with allylchloroformiate in dichloromethane and pyridine and then submitted to hydrolysis in dioxane/6N HCl at 60°C to give daunomycinone **7** and 3-*N*,4-*O*-diallyloxy carbonyl-L-daunosamine which was activated at the anomeric position by treatment with *p*-nitro benzoylchloride in pyridine to give **13**.

yield. The obtained glycoside was then dissolved in DMSO and added to a solution of $AgBF_4$ in DMSO. After 5 min stirring at room temperature the mixture was added with water and extracted with dichloromethane to give **15** with a 95% yield. The final deprotection step was performed in dichloromethane in the presence of tetrakis (triphenylphosphine) palladium(0), trimethylsilyl acetate and *N*,*N*-dimethyl, trimethylsilylamine[20] affording **3** in a 94% yield (Scheme 3).

In conclusion, we have described the synthesis of the novel anthracycline 14-fluorodoxorubicin. Its cytotoxic activity against A2780 and GLC-4 cell lines turned out to be about ten-fold lower than that of doxorubicin **1** (internal report), while antitumor efficacy against human tumor cell lines grown in athymic nude mice, is currently under investigation. We have also described a useful method to introduce both fluorine atom and hydroxyl group in the C_9-side chain of anthracyclines and we believe that this approach should also prove convenient for the synthesis of geminal fluorohydrins α to a carbonyl group.

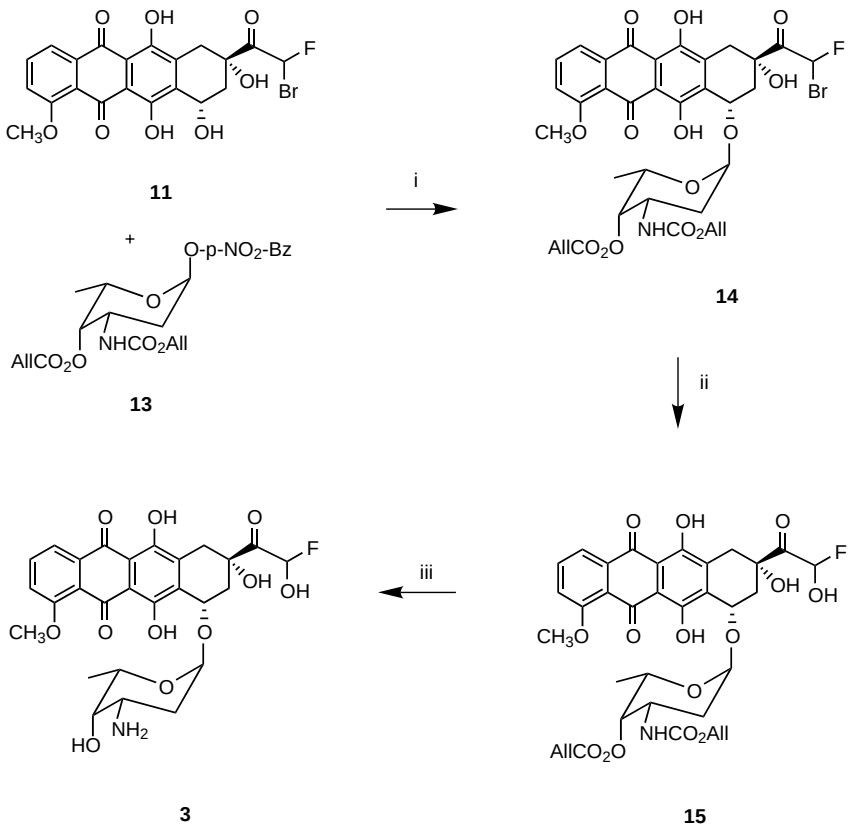
Selected experimental data

Compound **11** (mixture of two diastereoisomers)
^{1}H NMR ($CDCl_3$): δ 13.2 (2H, d, Ph-OH), 8.05 (1H, d, H-1), 7.8 (1H, t, H-2), 7.46 (0.5H, d, H-14, $J=52$ Hz), 7.42 (1H, d, H-3), 7.40 (0.5H, d, H-14, $J=52$ Hz), 5.4 (1H, m, H-7), 4.8 (1H, d, 7-OH), 4.15 (3H, s, OCH_3), 3.6–3.3 (2H, m, H-10), 3.4 (1H, s, 9-OH), 3.15–2.8 (1H, m, H-10), 2.5–2.2 (2H, m, H-8). ESMS m/z calcd for $C_{21}H_{16}BrFO_8$ $(M+H)^+$ 496.26, found 496.41.

Compound **12** (mixture of two diastereoisomers)
^{1}H NMR ($CDCl_3$): δ 13.2 (2H, d, Ph-OH), 8.05 (1H, d, H-1), 7.8 (1H, t, H-2), 7.4 (1H, d, H-3), 7.2 (0.5H, d, H-14, $J=52$ Hz), 7.05 (0.5H, d, H-14, $J=52$ Hz), 5.4 (1H, m, H-7), 4.75 (1H, d, 7-OH), 4.1 (3H, s, OCH_3), 3.4 (1H, s, 9-OH), 3.3 (1H, dd, H-10), 3.05 (1H, dd, H-10), 2.75–2.3 (2H, m, H-8). ESMS m/z calcd for $C_{21}H_{17}FO_9$ $(M+H)^+$ 433.37, found 433.55.

Compound **14** (mixture of two diastereoisomers)
^{1}H NMR ($CDCl_3$): δ 13.2 (2H, d, Ph-OH), 8.0 (1H, d, H-1), 7.8 (1H, t, H-2), 7.44 (1H, d, H-14, $J=52$ Hz), 7.4 (1H, d, H-3), 6.0–5.8 (2H, m, CH=CH_2), 5.55 (1H, s, H-1′), 5.4–5.15 (5H, m, CH=CH_2, H-7), 5.0 (1H, s, H-4′), 4.75–4.5 (5H, m, OCH_2-CH, H-3′), 4.2 (3H, s, OCH3), 4.2–4.1 (1H, m, H-5′), 3.55 (1H, d, H-10), 3.2 (1H, d, H-10), 2.4–2.25 (2H, m, H-8), 1.85 (2H, m, H-2′), 1.2 (3H, d, H-6). ESMS m/z calcd for $C_{35}H_{35}BrFNO_{14}$ $(M+H)^+$ 793.57, found 793.70.

Compound **15** (mixture of two diastereoisomers)
^{1}H NMR ($CDCl_3$): δ 13.2 (2H, d, Ph-OH), 8.0 (1H, d, H-1), 7.8 (1H, t, H-2), 7.4 (1H, d, H-3), 7.15 (0.5H, d, H-14, $J=52$ Hz), 7.1 (0.5H, d, H-14, $J=52$ Hz), 6.0–5.8 (2H, m, CH=CH_2), 5.55 (1H, s, H-1′), 5.4–5.1 (5H, m,



Scheme 3. (i) TMSOTf, CH_2Cl_2/Et_2O, −20°C, m.s., 54%; (ii) $AgBF_4$, DMSO, rt, 95%; (iii) $[(Ph_3P)_4]Pd$, $(CH_3)_2NTMS$, AcOTMS, CH_2Cl_2, rt, dark, 94%.

$CH{=}CH_2$, H-7), 5.0 (1H, s, H-4′), 4.8 (1H, m, H-3′), 4.6–4.5 (4H, m, OCH_2-CH), 4.3–4.15 (1H, m, H-5′), 4.05 (3H, s, OCH_3), 3.4–2.65 (2H, m, H-10), 2.4–2.25 (2H, m, H-8), 2.0 (1H, d, 14-OH), 1.9 (2H, m, H-2′), 1.25 (3H, d, H-6). ESMS m/z calcd for $C_{35}H_{36}FNO_{15}$ $(M+H)^+$ 730.67, found 730.78.

Compound **3** (mixture of two diastereoisomers) ^{1}H NMR ($CDCl_3$): δ 13.2 (2H, d, Ph-OH), 8.0 (1H, d, H-1), 7.8 (1H, t, H-2), 7.4 (1H, d, H-3), 7.1 (0.5H, d, H-14, $J=52$ Hz), 7.05 (0.5H, d, H-14, $J=52$ Hz), 5.55 (1H, s, H-1′), 5.35 (1H, s, H-7), 4.1 (3H, s, OCH_3), 4.0 (1H, m, H-5′), 3.5–3.4 (2H, m, H-10, H-4′), 3.2–3.05 (2H, m, H-10, H-3′), 2.75–2.2 (2H, m, H-8), 1.85–1.6 (2H, m, H-2′), 1.25 (3H, d, H-6).). ESMS m/z calcd for $C_{27}H_{29}ClFNO_{11}$ $(M+H)^+$ 598.98, found 599.13.

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