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Semisynthesis of a Highly Functionalized Daunorubicin Derivative

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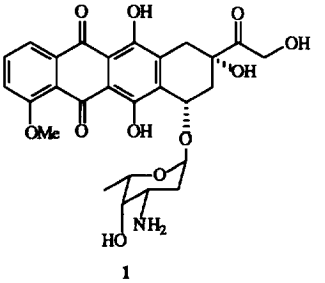
Abstract: (8R, 9S, 10S)-9-deoxy-8,9-epoxy-10-hydroxydaunorubicin (**5**) was obtained from daunorubicin in 4 synthetic steps. The key reaction was a highly regio- and stereoselective allylic bromination onto the aglycone moiety of 9,10-anhydro-N-trifluoroacetyldaunorubicin.

Since the discovery of doxorubicin (14-hydroxydaunorubicin, **1**) and the disclosure of its outstanding clinically useful antitumour activity,[1] many efforts have been made to provide a congener showing improved pharmacological and curative properties. More than 2000 doxorubicin analogs are estimated to have been synthesized and tested for antitumor activity in the last 20 years and although a certain scepticism begins to pervade the medical community,[2] anthracycline chemistry remains an area of broad interest and study.[3] As a part of a program directed to the extensive chemical modification of the ring A of doxorubicin skeleton, we studied the non deglycosidative manipulation of daunorubicin aimed at novel synthetic tools for a facile and fast entry to new functionalized derivatives. In fact, modifications of ring A in anthracyclines have never been much investigated from the semisynthetic point of view, probably because of the difficulties which one could expect to face when manipulating molecules carrying different reactive groups and a labile glycosidic linkage.

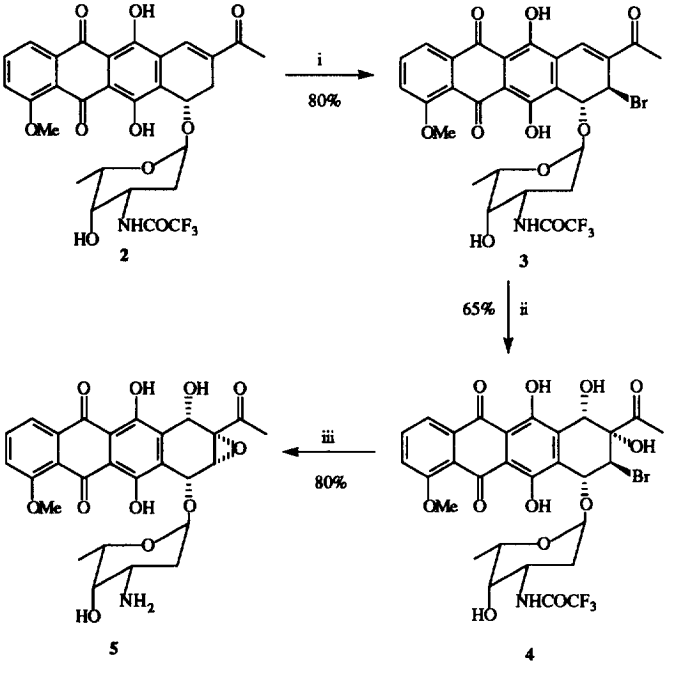


1

Compound **2**[4] was straightforwardly brominated (scheme 1) under radical conditions. Interestingly, the reaction resulted highly regio and stereo selective, as shown by TLC and 200 MHz PMR analysis of the crude product.[5] As for the stereochemistry, the PMR spectrum of compound **3** indicated a vicinal coupling, J_{H7H8} = 1.9 Hertz and a virtually zero allylic coupling (H-10 resonates at 8.07 ppm as sharp singlet). Accordingly to

literature for a mechanistic interpretation[6] and our own previous experience in the field of 9,10-anhydro daunorubicinones,[7] this datum agrees with a trans dipseudoaxial relationship between the substituents at C_7 and C_8. Compound **3**, as a crude, was osmylated under stoichiometric conditions,[8] and compound **5** was finally obtained upon basic aqueous treatment and isolated by preparative TLC.[9]

Scheme 1



(i) NBS, AIBN, sim-collidine, refluxing CCl_4; (ii) OsO_4, pyridine, then aqueous $NaHSO_3$; (iii) 0.1 M NaOH.

References and Notes

1. Arcamone, F. *Doxorubicin Anticancer Antibiotics*, Academic Press, New York, 1981.
2. Weiss, R. B. *Seminars in Oncology* **1992**, 19, 670.
3. *Anthracyclines Antibiotics*, W. Priebe Ed., ACS Symposium Series 574, Washington, DC, 1995.
4. Cassinelli, G.; Arcamone, F. *British Patent Specification* 53456/76 (22th Dec., 1976).
5. Compound **3** appears as a cherry colored spot by TLC analysis on silica. The evidence of a high selectivity is nevetherless clear when analysing the phenolic proton resonances in the ^{1}H-NMR spectrum: phenolic signals belonging to residual starting material and to bisanhydro aglycones integrate <15% of the total.
6. Nerinckx, W.; De Clercq, P. J. *Tetrahedron* **1991**, 47, 9419.
7. Guidi, A.; Canfarini, F.; Pasqui, F; Pestellini, V.; Triolo, A.; Arcamone, F. *An. Quím.* **1995**, 91, 236.
8. Baran, J. S. *J. Am. Chem. Soc.* **1960**, 82, 257. Compound **3** has to be added portionwise to the stirred solution of OsO_4 in pyridine. The inversion of addition order causes poorer yields.
9. ^{1}H-NMR of the hydrochloride (200 MHz, CD_3OD), inter alia: δ_H 1.36 (d, 3H, J = 6.2); 2.21 (s, 3H); 4.05 (s, 3H); 4.12 (d, 1H, J = 4.0); 5.16 (d, 1H, J = 4.0); 5.50 (broad, 1H); 6.01 (s, 1H). MS (thermo spray in the positive ione mode injection): m/z = 542 ($M+1^+$).

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