A Novel Synthesis of (+)-4-Demethoxydaunomycinone

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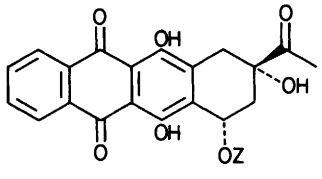
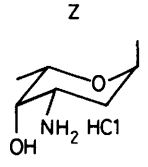
(+)4-Demethoxydaunomycinone (**2**) was obtained in five steps through the selective formation of the trifluoromethanesulphonate (**4**) and its palladium-catalysed reduction.

The clinical efficacy of the antitumour agents daunorubicin and doxorubicin has stimulated the search for new anthracyclines with improved pharmacological profiles. The synthetic analogue 4-demethoxydaunorubicin (idarubicin) (**1**) is a potent inducer of remission in relapsed or refractory adult and pediatric leukemias and is active against other tumour types also when given orally.[1] Several total syntheses of the aglycone



(**1**) :



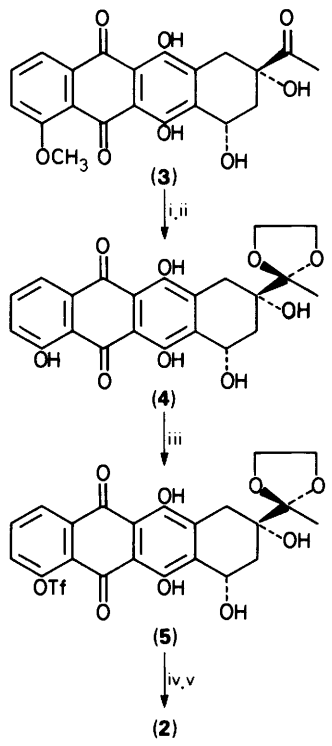
(**2**) : H

4-demethoxydaunomycinone (**2**) have been described.[2] We now report a basically new, simple, and efficient synthesis of (**2**), using the natural daunomycinone (**3**)[3] as starting material.

Our synthetic strategy centres on the selective formation of the 4-trifluoromethanesulphonate (**5**)* from the corresponding phenol (**4**) and on its palladium-catalysed reduction.[4] We chose this method of deoxygenation of phenols because it requires mild reaction conditions with concomitant high chemoselectivity.[4c]

Compound (**4**) was easily obtained from daunomycinone (**3**) by demethylation with $AlCl_3$ followed by ketalization of the side-chain carbonyl group,[5] in 79% yield from (**3**). The triflation with trifluoromethanesulphonic anhydride afforded, after washing with MeOH, (**5**) in 67% yield.[6] The selectivity of this reaction can be explained by the higher acidity of the 4-OH phenol with respect to that of 6-OH and 11-OH. In fact, spectrophotometric titration[7] in aqueous solution of carmino-

* All compounds gave satisfactory spectroscopic and analytical data. For (**4**): δ_H(200 MHz, $CDCl_3$, TMS) 1.47 (3 H, s, CH_3), 1.97 (1 H, dd, *J* 14.6, 4.8 Hz, 8-Hβ), 2.46 (1 H, d, *J* 15.1 Hz, 8-Hα), 2.79 (1 H, d, *J* 19.0 Hz, 10-Hβ), 3.03 (1 H, s, 9-OH), 3.25 (1 H, d, *J* 19.0 Hz, 10-Hα), 3.81 (1 H, d, *J* 7.1 Hz, 7-OH), 4.08 (4 H, s, CH_2CH_2), 5.25 (1 H, br s, 7-H), 7.30 (1 H, br d, *J* 8.4 Hz, 3-H), 7.69 (1 H, bt, *J* 8.3 Hz, 2-H), 7.87 (1 H, bd, *J* 7.6 Hz, 1-H), 12.20 (1 H, s, 4-OH), 12.95 (1 H, s, 6-OH), and 13.56 (1 H, s, 11-OH); *m/z* (FD-MS) 428 (M^+, 100%). For (**5**): δ_H(200 MHz, $CDCl_3$) 1.47 (3 H, s, CH_3), 1.98 (1 H, dd, *J* 14.7, 5.0 Hz, 8-Hβ), 2.47 (1 H, d, *J* 14.5 Hz, 8-Hα), 2.78 (1 H, d, *J* 19.0 Hz, 10-Hβ), 3.12—3.32 (2 H, m, 10-Hα + 9-OH), 3.82 (1 H, d, *J* 6.8 Hz, 7-OH), 4.08 (4 H, s, CH_2CH_2), 5.12–5.34 (1 H, m, 7-H), 7.62 (1 H, d, *J* 8.2 Hz, 3-H), 7.90 (1 H, t, *J* 8.0 Hz, 2-H), 8.48 (1 H, dd, *J* 7.9, 1.2 Hz, 1-H), 13.30 (1 H, s, 11-OH), and 13.60 (1 H, s, 6-OH), δ_F(188 MHz, $CDCl_3$, $CFCl_3$) −72.27 (3 F, s, CF_3); *m/z* (FD-MS) 560 (M^+, 100%). For (**2**): δ_H(200 MHz, $CDCl_3$, TMS) 2.16 (1 H, dd, *J* 14.6, 4.8 Hz, 8-Hβ), 2.35 (1 H, dt, *J* 14.4, 1.8 Hz, 8-Hα), 2.42 (3 H, s, CH_3), 2.94 (1 H, d, *J* 18.7 Hz, 10-Hβ), 3.18 (1 H, dd, *J* 18.8, 2 Hz, 10-Hα), 3.82 (1 H, d, *J* 5.8 Hz, 7-OH), 4.55 (1 H, s, 9-OH), 5.19–5.40 (1 H, m, 7-H), 7.73 (2 H, m, 2-H + 3-H), 8.24–8.38 (2 H, m, 1-H + 4-H), 13.26 (1 H, s, 11-OH), 13.55 (1 H, s, 6-OH); *m/z* (EI-MS) 368 (M^+, 40%), 187 (100%); $[\alpha]_D$ −170° (*c* 0.1 in dioxane).



Scheme. *Reagents and conditions*: i, $AlCl_3$ (10.0 equiv.), CH_2Cl_2, reflux, 2 h, (88%); ii, $(CH_2OH)_2$ (10.0 equiv.), PTSA (catalyst), benzene, reflux, 2 h, (90%); iii, Tf_2O (2.5 equiv.), Pr^i_2EtN (5.0 equiv.), 4-Me_2N-Py (1.0 equiv.), Py, 0 °C, 1 h, (67%); iv, $Pd(AcO)_2$/DPPF 0.5 mol%, HCO_2H Et_3N (4.0 equiv.), DMF, 40 °C, 8 h, (82%); v, CF_3CO_2H, 0 °C, 20 min (90%).

mycin (4-demethyldaunorubicin) assigns to 4-OH a value of $pK_a = 8.64$; the next ionization step is related to 11-OH with a value of $pK_a = 10.94$.

The triflate (**5**) requires very mild reduction conditions in order to avoid the hydrogenolysis of 7-OH or the formation of large amounts of A ring aromatization product.

The palladium-catalysed reduction of (**5**) has been carried out with a catalyst generated *in situ* from $Pd(AcO)_2$/DPPF[8] (0.5 mol%) and triethylammonium formate as hydride source, according to our previous experience with a model substrate.[9] After deprotection of the carbonyl group and crystallization from CH_2Cl_2 we obtained the target compound (**2**) in 74% yield from (**5**).

This semisynthetic approach to 4-demethoxydaunomycinone (**2**) is highly competitive with respect to a total chemical synthesis. We are currently studying the scope and limitation of palladium catalysis in anthracycline chemistry.

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5 The protection of the 13-carbonyl group enhances the yield of the following triflation step.
6 Structure (**5**) was assigned to the product of triflation since it could be converted into the final product (**2**); the latter afforded analytical data consistent with its identification as 4-demethoxydaunomycinone, independently obtained by total synthesis. Moreover the chemical shifts for the phenolic OH protons in the ^1H NMR spectra of (**5**) are in agreement with the predictions for substituted anthracyclinones described earlier (A. Vigevani, M. Ballabio, E. Gandini, and S. Penco, *Magn. Reson. Chem.*, 1985, **23**, 344).
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