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AN UNUSUALLY SIMPLE ROUTE TO 4-DEMETHOXY-7-DEOXYDAUNOMYCINONE

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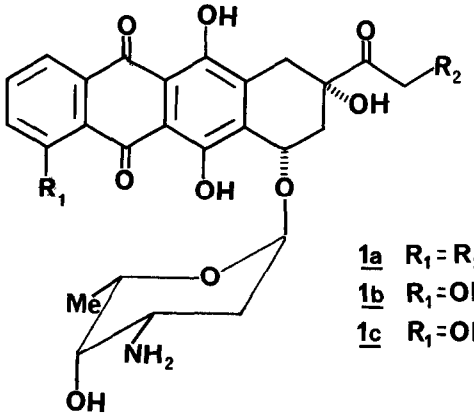
Summary: 4-Demethoxy-7,9-dideoxy-9-bromodaunomycinone reacts rapidly with cold dilute sodium hydroxide to give, in high yield, 4-demethoxy-7-deoxydaunomycinone. Evidence is presented in support of a transient enol epoxide intermediate in this unexpected reaction.

The improved antineoplastic activity of 4-demethoxydaunomycin (1a)[1] as compared with the naturally occurring daunomycin (1b) and/or adriamycin (1c), coupled with its non availability through the natural process of fermentation, has provided the stimulus for many studies on the synthesis of the corresponding aglycone, 4-demethoxydaunomycinone (2).[2]

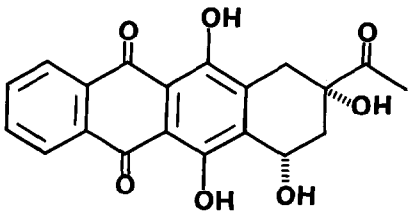
Our own studies on the synthesis of 2 made use of the key intermediate ketone 3, which could be prepared readily and in appreciable quantity from the cheap dye intermediate quinizarin.[3] The introduction of a 9-hydroxyl substituent into 3 to give 4-demethoxy-7-deoxydaunomycinone (4) was best achieved by vigorous acetylation of 3, followed by epoxidation of the resulting enol acetate and subsequent alkaline hydrolysis.[4] Although this procedure is reasonably effective, it is quite laborious and the final products must always be separated chromatographically from a considerable amount of starting material. We now report a surprisingly simple, yet novel, conversion of 3 into 4.

Direct bromination of ketone 3 under acidic equilibrating conditions affords almost exclusively the 9-bromoketone 5; as expected, 5 undergoes dehydrohalogenation readily on warming with a variety of bases, giving high yields of the enone 6.[5] We have now observed however, that treatment of 5 with cold, dilute sodium hydroxide rapidly produces the 9-hydroxyketone 4 in almost quantitative yield.[6a] The important anthracycline intermediate 4 is, consequently, now available from 3 in high yield by two experimentally trivial operations.

The mechanism of the ready conversion of 5 to 4 is by no means obvious since, as a tertiary α-bromoketone, it should be incapable of reacting with hydroxide ion by either an



1a $R_1 = R_2 = H$
1b $R_1 = OMe$; $R_2 = H$
1c $R_1 = OMe$; $R_2 = OH$



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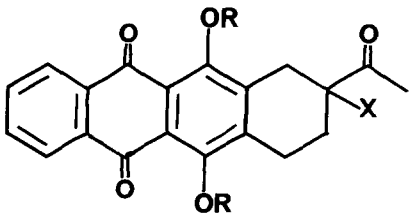
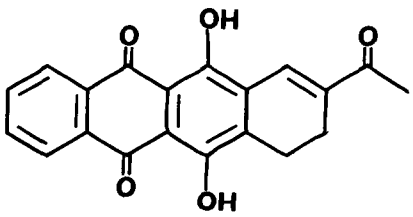


3 X = R = H
4 X = OH ; R = H
5 X = Br ; R = H
7 X = Br ; R = $COCMe_3$
8 X = OH ; R = $COCMe_3$



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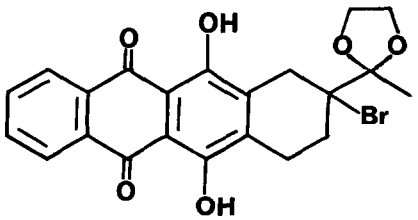

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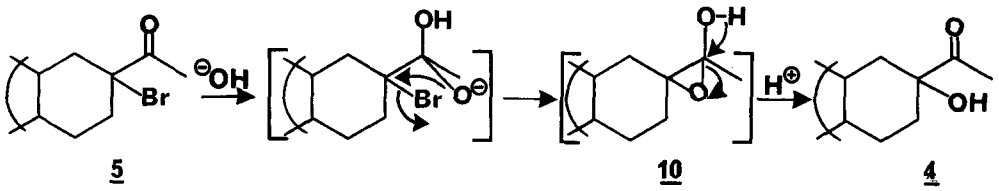
S_N1 or S_N2 process. The phenolic hydroxyls of 5 are not required for the displacement, since conversion of 5 to its dipivalate (7),[6b] followed by reaction with cold dilute base, cleanly affords the dipivalate (8) of 4. On the other hand, conversion of 5 to its ethylene ketal (9), followed by similar treatment with base, led only to the recovery of unchanged ketal 9. The carbonyl group of 5 is, therefore, involved in the displacement reaction. We propose that hydroxide ion adds to the ketonic carbonyl of 5 to give an alkoxide which internally displaces the tertiary bromine to give a transient epoxyenol intermediate (10), which is immediately isomerized to give the α-hydroxyketone 4 (Scheme 1). In support of this mechanism, a number of epoxyenol ethers have actually been isolated by the action of methoxide ion on certain α-haloketones under controlled conditions, including at least one case derived from a tertiary halide.[7]



5 10 4

Scheme 1

References and Notes

1) F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, A. M. Casazza, G. Pratessi and P. Reggiani, Cancer Treat. Rep., 60, 829 (1976).

2) For a recent comprehensive review, see F. Arcamone. "Doxorubicin", Academic Press: New York, 1981.

3) F. A. J. Kerdesky, R. J. Ardecky, M.V. Lakshmikantham and M. P. Cava, J. Am. Chem. Soc. 103, 1992 (1981).

4) D. Dominguez, R. J. Ardecky and M. P. Cava, J. Am. Chem. Soc., 105, 1608 (1983).

5) D. Dominguez and M. P. Cava, J. Org. Chem., 48, 2820 (1983).

6) a) In a typical experiment, to a stirred solution of the bromo ketone 5 (0.5 g, 1.2 mmol) in THF (30 ml) and water (40 ml) at RT under N_2 atm. was added very slowly 50 ml (1% w/v) aq. NaOH over a period of 10 min. After stirring for an additional 5 min, the deep purple solution was poured over crushed ice and acidified. The orange solid was filtered, dried and carefully crystallized ($CHCl_3$-EtOH) to yield 4 (0.4 g, 94%), identical in all respects (mp. MS, PMR) with an authentic sample.[4]

b) Pivalate 7 was made by treating a chloroform solution of 5 with an excess of pivalic anhydride in the presence of H_2SO_4 (cat.) at RT; mp 159-61°C. ^1H NMR ($CDCl_3$). δ 1.34 (s, 9H), 1.55 (s, 9H), 2.10 (m, 2H), 2.54 (s, 3H), 2.80-3.77 (m, 4H), 7.72 (m, 2H), 8.15 (m, 2H).

7) a) C. L. Stevens, W. Malik and R. Pratt, J. Am. Chem. Soc., 4758 (1950).

b) C. L. Stevens and A. J. Weinheimer, ibid, 80 4072 (1958).

Acknowledgements

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