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SYNTHESIS OF ANTHRACYCLINONES VIA BASE-CATALYZED CYCLIZATIONS OF DIHYDROANTHRAQUINONE DERIVATIVES

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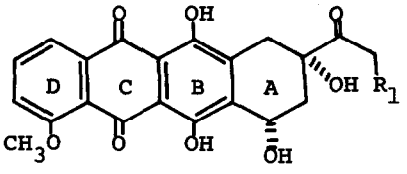
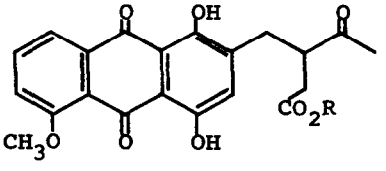
Efficient preparations of anthracyclinones (1 and 2), the aglycones of the clinically important anthracycline antibiotics, daunorubicin[1] and adriamycin[2] require a regiospecific synthesis of the tetracyclic skeleton with proper orientation of rings A and D substituents. One attractive route to 1 would entail the direct regiospecific cyclization of the anthraquinone intermediate,[3] 3. However, numerous attempts to catalyze the cyclization of 3 using conventional strong acidic (HF, conc. H_2SO_4, PPA, $BF_3 \cdot Et_2O$) or basic (NaH) reagents were unsuccessful. By altering the electronic configuration of the anthraquinone ring system, we were able to transform dihydroanthraquinone derivatives into anthracyclinones via intramolecular Claisen and aldol type condensations, which is the subject of this letter.



1 R_1 = H

2 R_1 = OH



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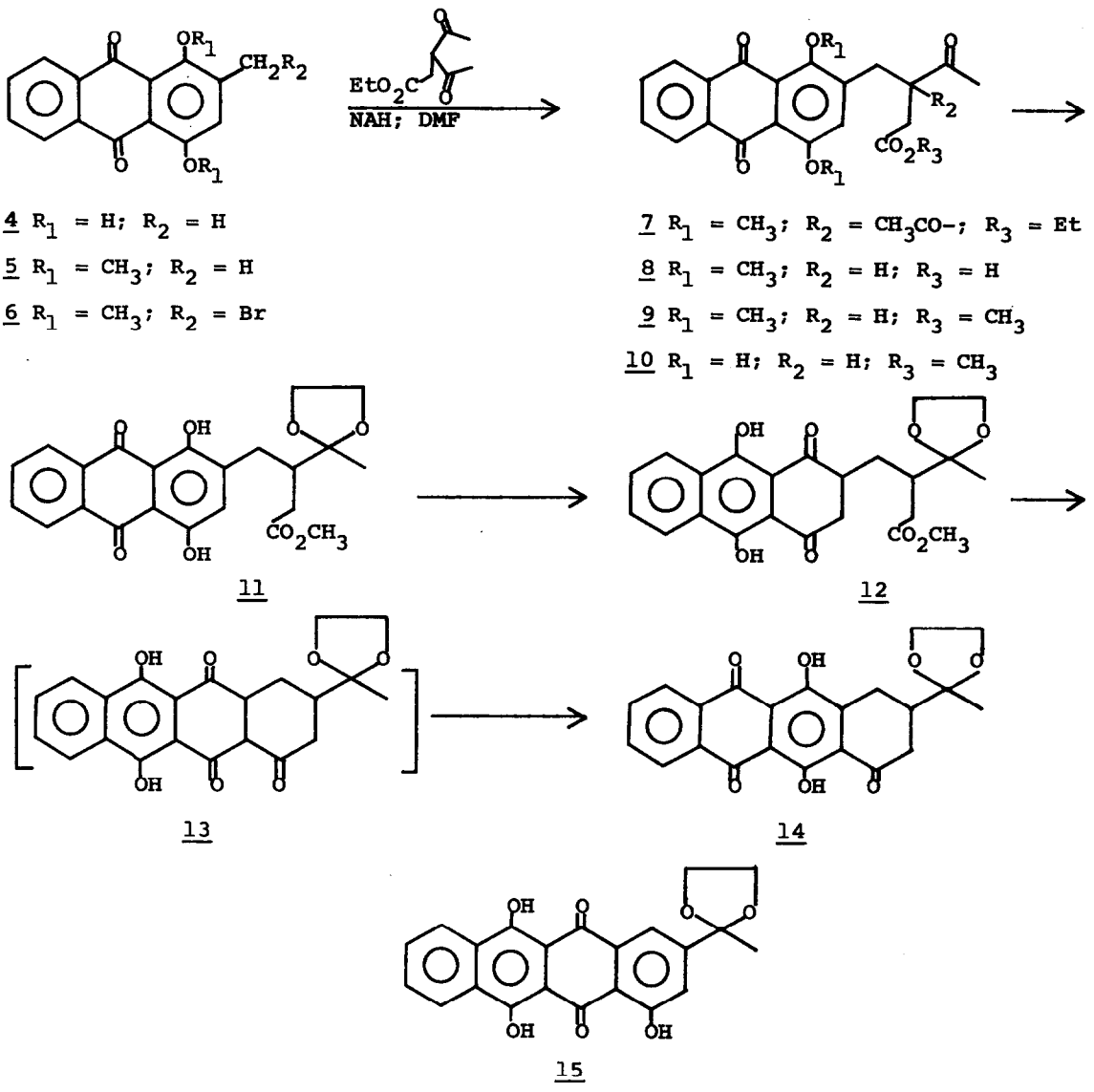
R = H or CH_3

Condensation of phthalic anhydride with methylhydroquinone ($AlCl_3/NaCl$[4], 190° C) afforded 2-methyl-1,4-dihydroxyanthraquinone (4), m.p. 178-179° in 80% yield. Methylation of 4 ($(CH_3)_2SO_4/K_2CO_3$) afforded 5 (85%, m.p. 132.5-133.5° C), which was brominated (NBS/CCl_4) to give 6 (50%, m.p. 184-186°), Nmr[5] ($CDCl_3$) δ 8.15 (m, 2H), 7.70 (m, 2H), 7.38 (s, 1H), 4.61 (s, 2H), 4.01 (s, 3H), 4.00 (s, 3H). Alkylation (NaH/DMF, 0° C) of 6 with 3-acetyl-4-oxo-valeric acid

ethyl ester gave 7, m.p. 163-163.5°, δ 8.13 (m, 2H), 7.69 (m, 2H), 7.12 (s, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 3.78 (s, 3H), 3.57 (s, 2H), 2.90 (s, 2H), 2.20 (s, 6H), 1.19 (t, J = 7.2 Hz, 3H) in 80% yield. Hydrolysis of the ester grouping and cleavage of the β-diketone were simultaneously effected by reaction of 7 with 8% NaOH at 60° C for 3 hrs to give 8 (85%), m.p. 200-202°, δ 8.73 (br. 1H), 8.24 (m, 2H), 7.76 (m, 2H), 7.16 (s, 1H), 4.03 (s, 3H), 3.97 (s, 3H), 2.4-3.6 (m, 5H), 2.22 (s, 3H). Esterification (CH_2N_2) of 8 afforded 9, m.p. 129-130° C, which was demethylated (BBr_3/CH_2Cl_2, -78° C) to 10 (90%), m.p. 178-180° C, δ 13.36 (s, 1H), 12.81 (s, 1H), 8.34 (m, 2H), 7.82 (m, 2H), 7.11 (s, 1H), 3.62 (s, 3H), 2.4-3.6 (m, 5H), 2.28 (s, 3H). After conversion of 10 into the ketal, 11 (ethylene glycol, p-TSA, C_6H_6, 4 hrs reflux), m.p. 140.5-141° C, δ 13.38 (s, 1H), 12.86 (s, 2H), 8.31 (m, 2H), 7.78 (m, 2H), 7.16 (s, 1H), 3.96 (s, 4H), 3.51 (s, 3H), 2.0-3.3 (m, 5H), 1.39 (s, 3H) in 90% yield, 11 was reduced[6] (6 eq. Zn metal in HOAc, 25° C, 0.5 hrs) to 12, δ 13.53 (s, 1H), 13.50 (s, 1H), 8.44 (m, 2H), 7.69 (m, 2H), 3.92 (br. s, 4H), 3.66 (s, 3H), 1.29 (s, 3H) in 80% yield, which was then subjected to base-catalyzed intramolecular cyclization as follows: To 20 mg of 12, suspended in 0.5 ml of ethylene glycol, was added 3 equivalents of Zn metal and 8 equivalents of CaO at -78° C (to minimize ester exchange). After repeated flushing of the system with N_2 to remove the last traces of molecular oxygen, conversion of 12 into 14 via the unstable intermediate 13 was accomplished by heating the reaction mixture to 140° C for 3 minutes. After preparative TLC ($CHCl_3$:acetone, 95:5) on silica gel plates, 9 mg (49%) of 14, m.p. 185-187° C, δ 13.97 (s, 1H), 13.17 (s, 1H), 8.28 (m, 2H), 7.80 (m, 2H), 4.0 (s, 4H), 2.3-3.7 (m, 5H), 1.38 (s, 3H) was obtained.

Substitution of NaH or CaH_2 for CaO or omission of the Zn metal from the reaction mixture led to the formation of 11 only. If DMF or diglyme was used as the solvent, 15, m.p. 231-233° C, δ 13.35 (s, 1H), 12.25 (s, 1H), 10.37 (s, 1H), 8.48 (m, 2H), 8.10 (d, 1H, J = 1.6 Hz), 7.80 (m, 2H), 7.44 (d, 1H, J = 1.6 Hz), 4.10 (m, 2H), 3.85 (m, 2H), 1.72 (s, 3H) was the predominant product accompanied by 11 and 14. Similarly, if the heating period was extended (e.g., 7 min), 15 became the major product instead of the desired 14.



4 R_1 = H; R_2 = H

5 R_1 = CH_3; R_2 = H

6 R_1 = CH_3; R_2 = Br

7 R_1 = CH_3; R_2 = CH_3CO-; R_3 = Et

8 R_1 = CH_3; R_2 = H; R_3 = H

9 R_1 = CH_3; R_2 = H; R_3 = CH_3

10 R_1 = H; R_2 = H; R_3 = CH_3

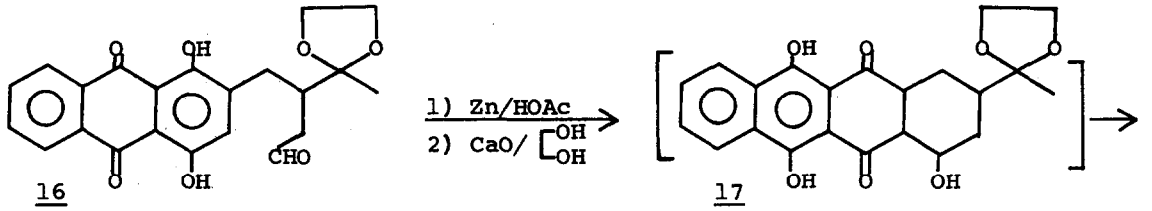
11 12

13 14

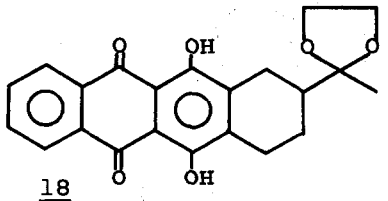
15

Since the ester grouping in 12 underwent exchange with the ethylene glycol solvent and the resulting glycolic ester failed to undergo cyclization under these reaction conditions, 11 was transformed into 16, δ 13.41 (s, 1H), 12.88 (s, 1H), 9.53 (m, 1H), 8.31 (m, 2H), 7.83 (m, 2H), 7.14 (s, 1H), 3.94 (s, 4H), 1.44 (s, 3H) (30%) via a five step reaction sequence involving: benzylation ($C_6H_5CH_2Br/K_2CO_3$/acetone/reflux), hydrolysis (aq. 8% NaOH/60° C/3 hrs), selective reduction of COOH → CH_2OH (B_2H_6/THF/25° C), debenzylation (H_2/Pd-$BaCO_3$/EtOAc) and oxidation of CH_2OH → CHO (pyridine chlorochromate/CH_2Cl_2/25° C).

Reduction of 16 with Zn metal in HOAc gave the dihydroanthraquinone derivative, which was similarly cyclized (CaO, ethylene glycol, Zn metal) via the transient intermediate 17 followed by dehydration and tautomerism to give 18[7] (> 50%), m.p. 183-184° C, δ 13.51 (s, 1H), 13.48 (s, 1H), 8.35 (m, 2H), 7.78 (m, 2H), 4.00 (s, 4H), 1.40 (s, 3H).



16 17



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Further refinement of the efficiencies of these Claisen and aldol type cyclizations and their applications to the regiospecific synthesis of 4-methoxyanthracyclinones are currently in progress.

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References and Notes

1. J. Bernard, R. Paul, M. Boiron, C. Jacquillat and R. Maral, Ed., "Rubidomycin", Springer-Verlag, New York, N.Y., 1969.
2. R. H. Blum, Cancer Chemother. Rep., Part 3, 6, 247 (1975).
3. The synthesis of intermediate 3 from 1,5-dihydroxyanthraquinone will be published separately.
4. D. B. Bruce, A. J. S. Sorrie and R. H. Thomson, J. Chem. Soc., 2403 (1953).
5. All intermediates gave C, H analyses and/or mass spectra; IR and NMR spectra consistent with the assigned structures. The yield reported was unoptimized and melting points were uncorrected. Unless stated otherwise, NMR (δ) were taken in $CDCl_3$ solutions.
6. W. W. Lee, A. P. Martinez, T. H. Smith and D. W. Henry, J. Org. Chem., 41, 2296 (1976).
7. This intermediate 18 was found to be identical to a sample, prepared by the condensation of phthalic anhydride with 1,4-dihydroxy-7-acetyl-5,6,7,8-tetrahydronaphthalene catalyzed by BF_3-etherate at 120° C, followed by ketalization.