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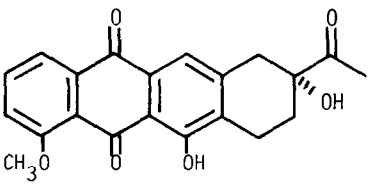
REGIOSPECIFIC SYNTHESIS OF (±)-DEOXYANTHRACYCLINONES

Jhillu Yadav, Paul Corey, Chi-Tung Hsu, Kato Perlman and Charles J. Sih*
School of Pharmacy, University of Wisconsin, Madison, WI 53706

Summary - A versatile regiospecific route to tetracyclic anthracyclinones is described; the synthetic strategy entails the attachment of a nucleophilic C-D ring synthon, 2b, to a suitably functionalized A ring intermediate such as 3.

The anthracycline antibiotic, doxorubicin is widely used in the combined chemotherapy of human cancers.[1] However, its severe dose limiting side effects[2] (myelosuppression, ECG abnormalities and cardiomyopathy) have prompted the search for new anthracycline compounds with improved antitumor efficacy and/or with reduced toxicity. Recently, a new group of anthracycline antibiotics lacking a hydroxyl group at the C-11 position have attracted the attention of synthetic chemists because clinical studies of aclacinomycin A[3] showed that it has a low incidence of cumulative dose-dependent cardiomyopathy. In contrast to doxorubicin which interferes with DNA synthesis and function[4], aclacinomycin A appears to preferentially inhibit RNA synthesis[3]. Although numerous total syntheses of daunomycinone have been achieved[5], to our knowledge only one synthesis of an 11-deoxy tetracyclic intermediate has recently appeared[6]. Because the 11-deoxyanthracycline antibiotics, glycosides of aklavinone[3], pyrromycinone[7], 11-deoxydaunomycinone[8] and congeners may possess an improved therapeutic index and thus constitute the so called "second generation" anthracycline antibiotics, we herein report a general regiospecific approach to 11-deoxyanthracyclinones, which has resulted in the first synthesis of (±)-7,11-dideoxydaunomycinone (1).



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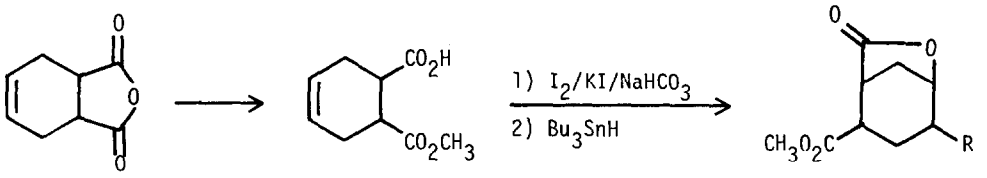
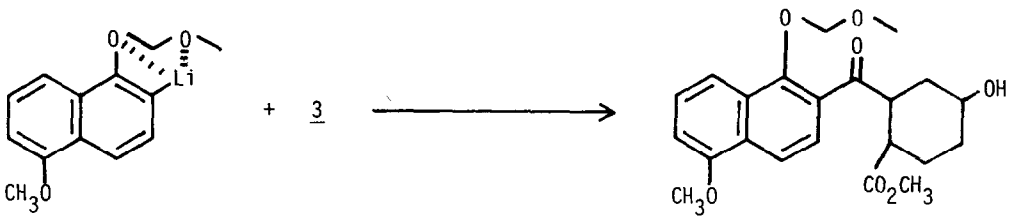
Our synthetic strategy entails the attachment of a nucleophilic C-D ring synthon to a suitably functionalized A-ring intermediate, followed by subsequent cyclization of the B-ring to complete the tetracyclic aglycone skeleton.

The methoxymethyl ether of monomethyl naphthalene-1,5-diol 2a (prepared by the treatment of 2a with NaH in DMF and chloromethyl methyl ether[9] in 96% yield), was chosen as the nucleophilic C-D ring synthon because it was relatively stable to butyllithium and was readily metalated at the ortho position[10]. The lactone, 3[11], was used as the complementary functionalized A ring synthon, efficiently prepared from the inexpensive cis-tetrahydrocyclophthalic anhydride 4 in three steps: Methanolysis of 4 afforded 5 in quantitative yields, which upon iodolactonization gave 6 in 88% yield. Reduction of 6 with tri-n-butyltin hydride[12] afforded 3 (97%).



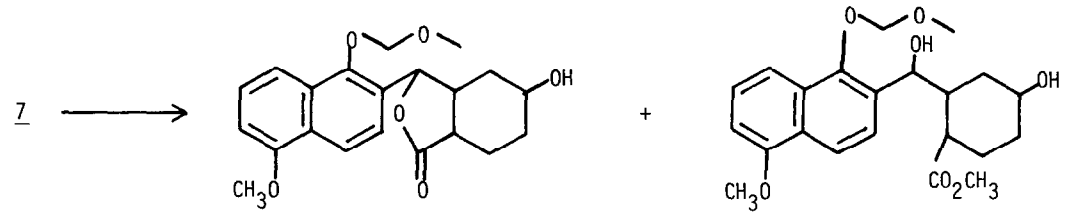
4 5 6 R = I 3 R = H

Reaction of 3 with the metalated naphthalene 2b (two equivalents of t-butyllithium in DME, -25°C) at -25°C furnished the acylated adduct, 7[12] (73%), m.p. 153-154°C; PMR δ 3.45, 3.58 and 3.97 (three s, 9H, $-OCH_3$), 5.10 (AB q, 2H, $-OCH_2O$), 6.86 (d, J = 8 Hz, ArH), 7.3-8.06 (m, 4H, ArH).



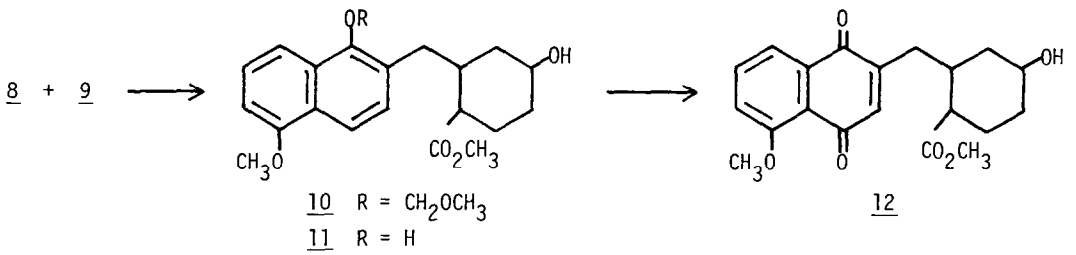
2b 7

Hydrogenation of 7 under acidic conditions [5% Pd/C, HAc-MeOH (1:20), 50 psi, 25°C, 4 hrs] afforded a mixture of 8 and 9 in variable proportions. This mixture was further hydrogenated under basic conditions (5% Pd/C, 2 mol equivalent KOH in MeOH, 50 psi, 25°C, 30 hrs) which after esterification with CH_2N_2 gave 10 (83% from 7). After removal of the methoxymethyl ether (5% conc HCl in MeOH, 25°C, 79%), 11, m.p. 132-135°C; PMR δ 3.80 (s, 3H, OCH_3), 3.97 (s, 3H, Ar-OCH_3), 7.12-7.85 (m, 5H, ArH), 8.36 (br, 1H, Ar-OH) was oxidized[13] [$Tl(NO_3)_3$-$3H_2O$, MeOH, 0°C, 15 min] to yield 12 (95%), m.p. 154-155°C; PMR δ 3.69 (s, 3H, OCH_3), 4.00 (s, 3H, Ar-OCH_3), 6.66 (s, 1H, quinone-H), 7.23-7.78 (m, 3H, ArH).

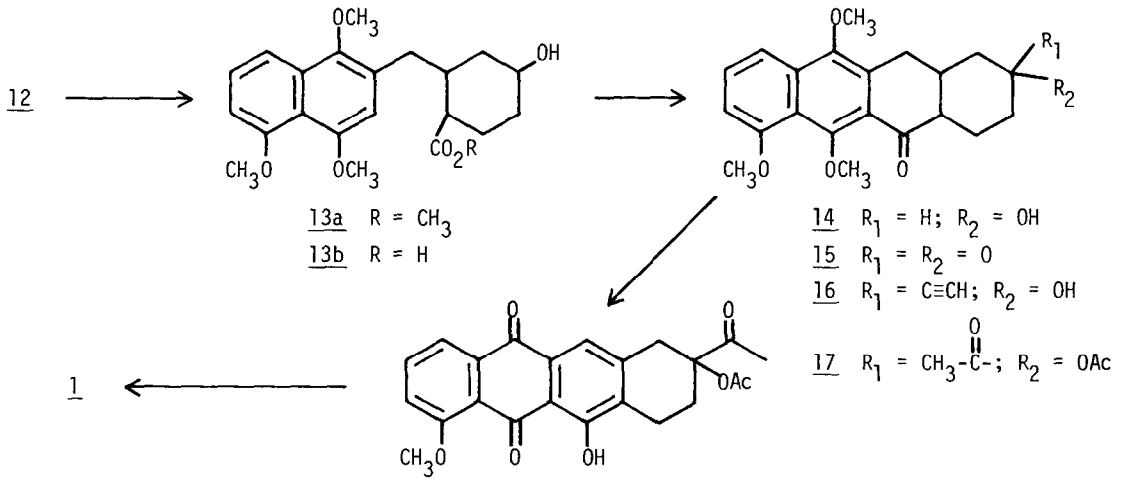


8 9

After reduction ($Na_2S_2O_4$) of 12, the resulting leuco product was methylated [K_2CO_3, $(CH_3)_2SO_4$, acetone reflux] to give 13a (60%), which was immediately hydrolyzed (KOH) to 13b (98%), m.p. 172-174°C, PMR δ 3.78, 3.86, 3.92 (three s, 9H, $ArOCH_3$), 6.61 (s, 1H, ArH), 6.81 (d, 1H, ArH), 7.3-7.7 (m, 2H, ArH). The acid, 13b was readily cyclized[14] [$(CF_3CO)_2O$:CF_3COOH (2:1), 0°C, 1 hr] to yield 14 (81%), m.p. 191-193°C, PMR δ 3.86, 3.90, 3.99 (three s, 9H, $ArOCH_3$), 6.86 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 1H, ArH), 7.39-7.70 (m, 2H, ArH). Oxidation of 14 (pyridinium chlorochromate, CH_2Cl_2, 25°C) gave the tetracyclic dione 15 (92%), m.p. 218-220°C.



Treatment of 15 with HC≡CMgBr (1.2 mol equivalent, THF, -20°C) gave 16 (81%), m.p. 231-235°C (dec), PMR δ 2.49 (s, 1H, C≡CH), 3.86, 3.91 and 3.99 (three s, 9H, $ArOCH_3$), 6.86 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H, ArH), 7.39-7.70 (m, 2H, ArH), which was hydrolyzed [$Hg(OAc)_2$-H_2S, EtOAc] into 17 (95%), m.p. 219-221°C, PMR δ 2.10 (s, 6H, $COCH_3$), 3.84, 3.89 and 3.98 (three s, $ArOCH_3$), 6.83 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 1H, ArH), 7.39-7.71 (m, 2H, ArH). Cleavage of the methoxyl groups and ring B aromatization were simultaneously effected by reaction of 17 with SeO_2 to yield 18 (30%), m.p. 258-260°C; PMR δ 2.05 and 2.22 (two s, 6H, $COCH_3$), 4.08 (s, 3H, $ArOCH_3$), 7.31-8.03 (m, 4H, ArH), 13.41 (s, 1H, ArOH). Alternatively, 18 may also be obtained by oxidative demethylation[15] of 17 with ceric ammonium nitrate, followed by bromination-debromination [Br_2, CH_2Cl_2-CCl_4 (1:1)] of the resulting dihydro quinone in overall yield of 50%. Deacetylation of 18 with CH_3OH in the presence of catalytic amount of $NaOCH_3$, gave 1 (75%), m.p. 210-211°C ($CHCl_3$), PMR δ 2.38 (s, 3H, $COCH_3$), 4.11 (s, 3H, $ArOCH_3$), 7.31-8.06 (m, 4H, ArH), 13.38 (1H, ArOH).



The introduction of the C-7 hydroxyl; the conversion of 16 into aklavinone, the aglycone of aclacinomycin A; and the possibility of utilizing a more highly functionalized A ring synthon than the lactone 3 leading to still more convergent syntheses of 11-deoxyanthracyclinones, are under investigation.

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References and Notes

1. R. H. Blum and S. K. Carter, Ann. Intern. Med., 80, 249(1974); D. W. Henry, ACS Symp. Ser., No. 30, Chapter 2, (1976); F. Arcamone, "Topics in Antibiotic Chemistry"; P. G. Sammes, Ed., Halsted Press, New York, Vol. 2, Chapter 3, 1978.
2. E. A. Lefrak, J. Pitha, S. Rosenheim and J. A. Gottlieb, Cancer (Philadelphia), 32, 302(1973); L. Lenaz and J. A. Page, Cancer Treat. Rev., 3, 111(1976).
3. T. Oki, Biotech. & Bioengineering, 22, Suppl. 1, 83(1980); T. Oki, J. Antibiotics (Japan), 30, S-70(1977).
4. S. Neidle, "Topics in Antibiotic Chemistry", P. G. Sammes, Ed., Halsted Press, New York, Vol. 2, Chapter 4, 1978.
5. T. R. Kelly, J. Vaya and L. Ananthasubramanian, J. Am. Chem. Soc., 102, 5983(1980) and ref. cited therein.
6. J. P. Gesson, J. C. Jacquesy and M. Mondon, Tetrahedron Lett., 3351(1980).
7. T. Oki, N. Shibamoto, Y. Matsuzawa, T. Ogasawara, A. Yoshimoto, I. Kitamura and T. Inui, J. Antibiotics (Japan), 683(1977).
8. F. Arcamone, G. Cassinelli, F. DiMatteo, S. Forenza, M. C. Ripamonti, G. Rivola, A. Vigevani, J. Clardy and T. McCabe, J. Am. Chem. Soc., 102, 1462(1980).
9. H. Christensen, Syn. Commun., 5, 65(1975).
10. R. A. Ellison and F. N. Kotsonis, J. Org. Chem., 38, 4192(1973). For a comprehensive review on hetero atom-facilitated lithiations see, H. W. Gschwend and H. R. Rodriguez, Org. React., 26, 1(1979).
11. J. Kelin, E. Dunkelblum and D. Avrahami, J. Org. Chem., 32, 935(1967).
12. All intermediates gave correct C, H analyses. The yields reported are unoptimized and melting points are uncorrected. PMR spectra (δ) were taken in $CDCl_3$ solution.
13. A. McKillop, D. H. Perry, M. Edwards, A. Antus, L. Farkas, M. Nogradi and E. C. Taylor, J. Org. Chem., 41, 282(1976).
14. K. A. Parker and J. L. Kallmerten, Tetrahedron Lett., 1197(1979).
15. P. Jacob, P. S. Calley, A. T. Shulgin and N. Castagnoli, J. Org. Chem., 41, 3627(1976).

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