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A NOVEL ANTHRAQUINONE ANNELATION. A NEW APPROACH TO AKLAVINONES.

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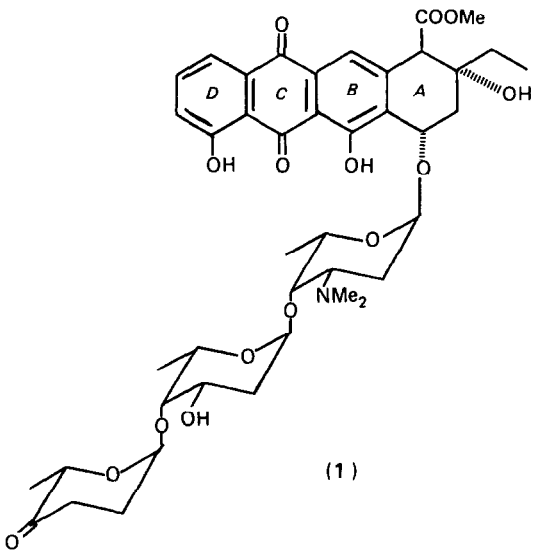
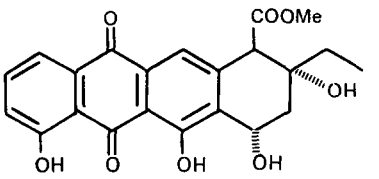
Summary: 1-Hydroxyanthraquinone has been annelated to a tetracyclic ketoester containing the major structural features of 4-deoxyaklavinone. The cyclization of the A-ring involves the first case of an anionic alkylation of an anthraquinone at a position which is not ortho to a phenolic function.

The clinical utility of the anthracycline antibiotics daunomycin and adriamycin (doxorubicin) in the treatment of certain human cancers has generated many studies on the synthesis of these compounds and related structures over the past decade.[1] The subsequently described anthracycline aclacinomycin A (1)[2] has been reported to have similar anticancer activity, but considerably lower toxicity,[3] thus making it a synthetic target of considerable importance. Very recently, the synthesis of the aglycone of (1), aklavinone (2), has been achieved by three different groups.[4-6]



(1)

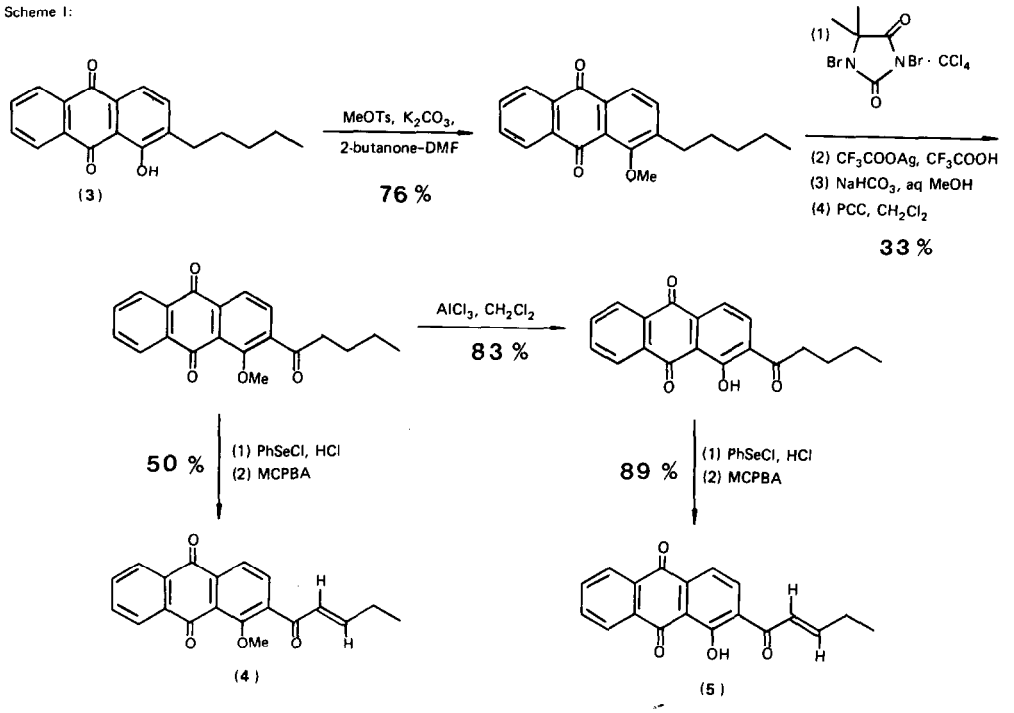


(2)

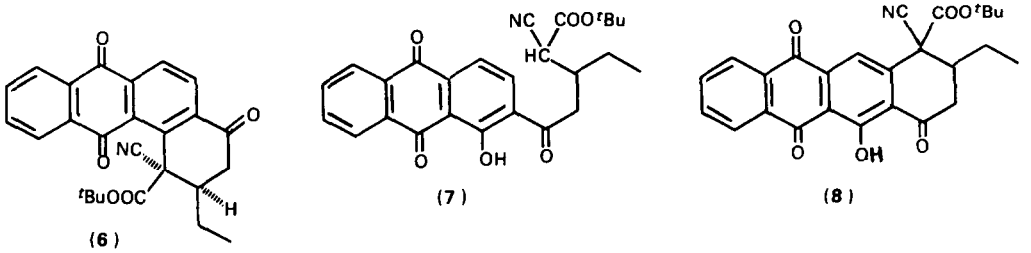
These syntheses, while quite varied in conception, all involve the construction of either ring B or C from a bicyclic precursor as a key step. We now report our initial success in the synthesis of an aklavinone-related structure by use of a new methodology, in which an appropriately substituted A-ring is grafted onto a simple and cheap anthraquinone.

1-Hydroxyanthraquinone was subjected to a Marschalk alkylation using n-valeraldehyde to give a 38% yield of 1-hydroxy-2-pentylanthraquinone (3),[7] which was further elaborated to the enones (4)[7] and (5)[7] as shown in Scheme I.

Scheme I:



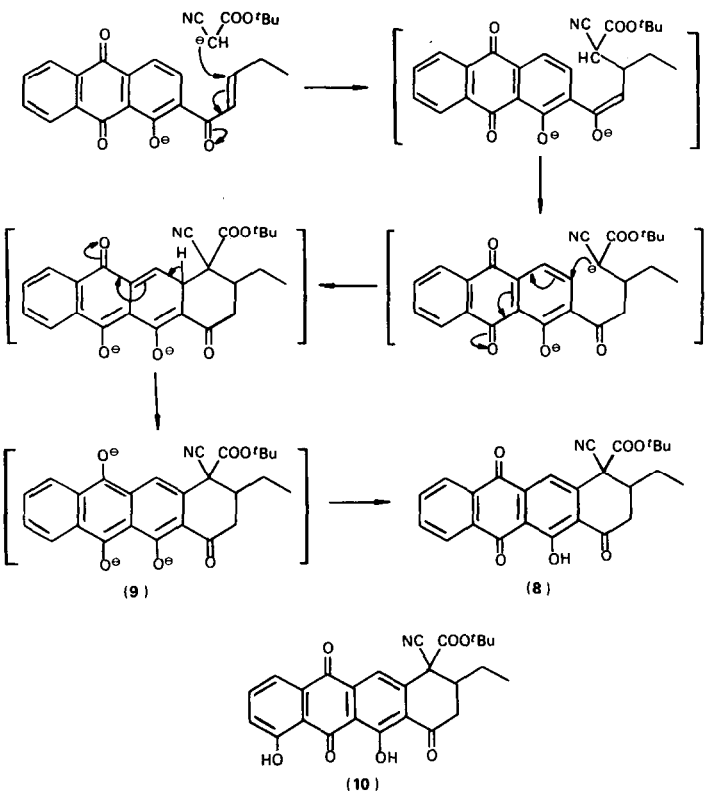
Michael addition of tert-butyl cyanoacetate to the methoxyenone (4) (NaH, DMF, RT, 14 hr) lead directly to a single isomer of the 1,2-benzanthraquinone (6) (mp 202-204° C) in 73% yield, mass spectrum [m/e, 430, 374, 356, 330, 301, 300], nmr in $CDCl_3$ [δ 8.56 (s, 2 H); 8.31-8.26 (m, 2 H); 7.86-7.82 (m, 2 H); 3.07-3.00 (m, 2 H); 2.94-2.83 (m, 1 H); 2.55-2.19 (m, 1 H); 1.64-1.56 (br, s, 10 H); and 1.10-1.04 (t, J = 7 Hz, 3 H)]. Formation of (6) can be explained by addition of the anion of the Michael adduct of (4) to the α-position of the anthraquinone system followed by expulsion of a methoxide ion.



A similar Michael addition of tert-butyl cyanoacetate to the hydroxyenone (5) afforded only the expected Michael adduct (7) (mp 127-131° C), when the reaction was quenched after 1 h. However, when the reaction was quenched after 6 h, the β-cyclization product (8)[7] (mp 157-159° C) was obtained in 75% yield, mass spectrum {m/e 445, 389, 345, 316 and 289}, nmr in $CDCl_3$ [δ 14.05 (s, 1 H); 8.364-8.261 (m, 2 H); 7.909 (s, 1 H); 7.880-7.832 (m, 2 H); 3.051-2.959 (m, 1 H); 2.844-2.754 (m, 2 H); 1.813-1.726 (m, 2 H); 1.633 (s, 9 H) and 1.108-1.048 (t, 3 H)].

To our knowledge, the formation of (6) from (7) involves the first case of an anionic alkylation of an anthraquinone which bears no phenolic hydroxyl ortho to the alkylation site.[8] We believe that the anthraquinone system is acting as an electron sink in this reaction, giving the intermediate hydroquinone anion (9), which is oxidized to the quinone (8) on work-up (Scheme II).

Scheme II:



Ring A of the ketoester 8 contains most of the functionalization found in this ring of aklavinone. Application of the methodology described above to the case of the inexpensive dye intermediate 1,8-dihydroxyanthraquinone should lead to the attractive intermediate (10), and subsequently to aklavinone itself. Studies having this objective are underway in our laboratories.

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7. This substance gave satisfactory elemental analysis and spectroscopic data. The mp, mass spectral data and nmr ($CDCl_3$) for some of the key intermediates in Scheme I are given below.
methoxyenone (4): mp 105-109° C; mass spectrum [m/e 320, 305, 292, 275, 265 and 251]; nmr [δ 8.177-8.313 (m, 3H); 7.744-7.86 (m, 3H); 6.827-6.915 (m, 1H); 6.579-6.654 (d, 1H); 3.928 (s, 3H); 2.290-2.350 (m, 2H) and 1.075-1.134 (t, J = 7 Hz, 3H)].
hydroxyenone (5): mp 116-120° C; mass spectrum [m/e 306, 291, 277, 252 and 251]; nmr [δ 13.34 (s, 1H); 8.245-8.313 (m, 2H); 7.808-7.964 (m, 4H); 7.049-7.32 (m, 1H); 6.843-6.909 (d, 1H); 2.337-2.392 (m, 2H) and 1.121-1.18 (t, J = 7 Hz, 3H)].
dihydroprecursor of (5): mp 125-126.5° C; mass spectrum [m/e 308, 279, 267, 266, 252 and 251]; nmr [δ 13.591 (s, 1H); 8.265-8.344 (m, 2H); 8.076-8.109 (d, 1H); 7.803-7.871 (m, 3H); 3.104-3.161 (t, J = 7 Hz, 2H); 1.655-1.774 (m, 2H); 1.339-1.457 (m, 2H) and 0.923-0.983 (t, J = 7 Hz, 3H)].

8. The addition of anions to C-2 of quinizarin has been observed. In these cases, the quinizarin dianion seems to behave as the dianion of the Michael acceptor tautomer 9,10-dihydroxy-1,4-anthraquinone: (a) K. Krohn and Ch. Hemme, Liebigs Ann. Chem., Part I, (1979), 35.
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