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A NOVEL ROUTE TO THE TETRACYCLIC RING OF ANTHRACYCLINONES

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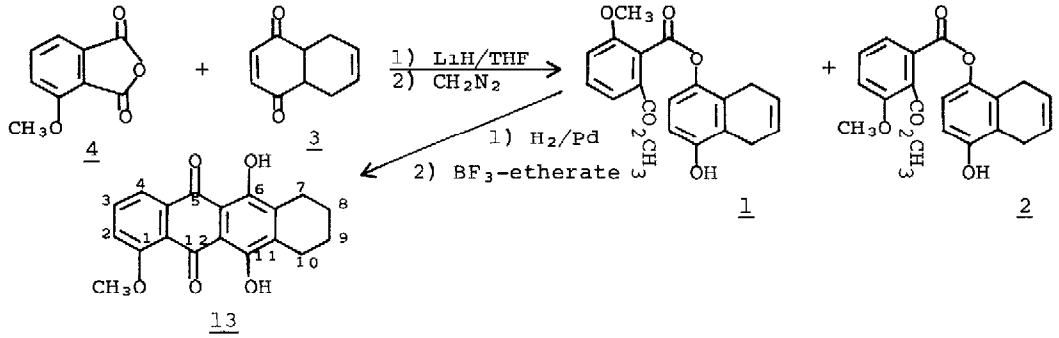
Recent reports on the effectiveness of Daunorubicin[1] and Adriamycin[2] for the treatment of a variety of human cancers has aroused considerable interest in the total synthesis of this group of anthracycline compounds. The anthracycline antibiotics[3], metabolites of Streptomyces sp., are made up of anthracyclinones[4] (the aglycone moiety) attached to aminosugars. Although a total synthesis of adriamycin has already been formally achieved[5,6,7,8], the need for an efficient regiospecific route to daunomycinone and adriamycinone persists, to furnish an alternative method possibly competitive with the biosynthetic process[9] for the preparation of these antitumor anthracyclines.

Several syntheses of tetracyclic hydroquinone systems have been accomplished starting with a Friedel-Craft reaction[10,11], a photo-Fries reaction[12], and a Diels-Alder reaction[13,14]. As part of the program directed to the total synthesis of daunomycinone and adriamycinone, we have developed a facile method for the construction of the tetracyclic hydroquinone ring system, featuring an efficient one-step cyclization of the tetrahydronaphthyl esters of 3-methoxyphthalic acid.

1,4,5,8,9,10-cis-Hexahydronaphthalene-1,4-dione (3)[15], the well known Diels-Alder adduct derived from p-benzoquinone and 1,3-butadiene was treated with two equivalents of lithium hydride to generate the dilithiophenolate of 1,4-dihydroxy-5,8-dihydronaphthalene, which was reacted with 3-methoxyphthalic anhydride[16] (4). After the products were methylated with diazomethane 4'-hydroxy-5',8'-dihydronaphthyl-2-methoxy-6-carbomethoxybenzoate[17], 1, m.p. 188.5-189° C, m/e 354 (M^+), 323 (M-31), 193 ($M-C_{10}H_9O_2$); pmr[17]: δ8.00 (s, 1, phenolic OH), 7.8-7.2 (m, 3, aromatic H), 7.15, 6.77 (AB, q, 2, J = 6 Hz, aromatic H), 5.90 (broad s, 2), 3.92 (s, 6, OCH_3) and 3.33 ppm (broad s, 4, benzylic H); uv_{max} (CH_3OH) 285 nm (ϵ3,600), 298 (ϵ4,600), and 4'-hydroxy-5',8'-dihydro

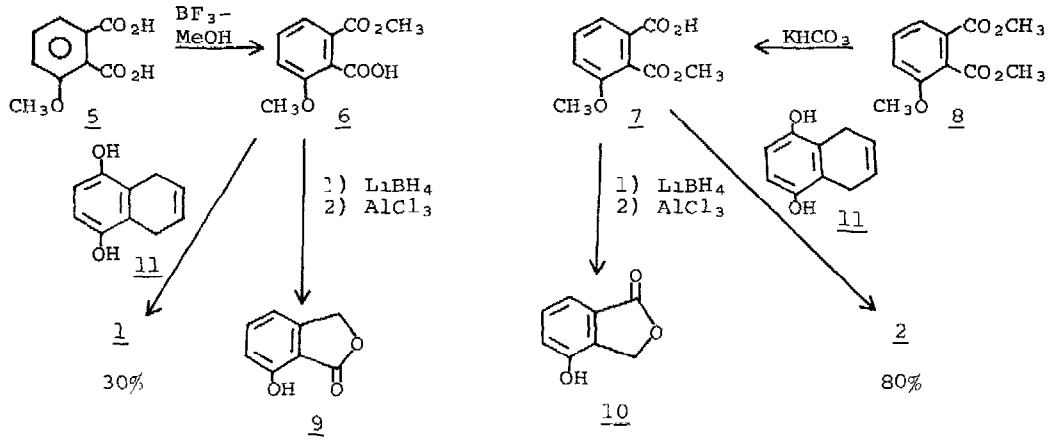
naphthyl-2-carbomethoxy-3-methoxybenzoate, 2, m.p. 175.5-176° C; m/e 354 (M^+), 323 (M-31), 143 (M-$C_{10}H_9O_2$); Pmr: δ8.75 (s, 1, phenolic OH), 7.8, 7.5, 7.23 (AMX^3, J = 5.0, 5.5 Hz aromatic H), 6.75 (s, 2H), 5.83 (broad s, 2H), 3.89 (s, 3H), 3.83 (s, 3H) and 3.22 ppm (broad s, 4, benzylic H); uv_{max} (CH_3OH) 283 nm (ε3,800), 302 (ε4,300) were obtained in a ratio of 95:5 (57%), indicating that the reaction proceeded with considerable regioselectivity as the phenolate attacked predominantly the more hindered carbonyl of 4.



4 3 1 2 13

To establish the identity of the isomeric esters 1 and 2, we conducted the following series of experiments. Refluxing of 5 with BF_3-methanol in methanol for 5 hours afforded 2-methoxy-6-carbomethoxybenzoic acid, 6, m.p. 151.5-153.5° in 82% yield 2-Carbomethoxy-3-methoxybenzoic acid, 7[18], m.p. 141.5-143° was obtained in 80% by hydrolysis of 8 with one equivalent of $KHCO_3$ in refluxing ethanol. Reduction of 6 with $LiBH_4$ afforded 7-methoxyphthalide, m.p. 105-108° (lit.[19] 107-109°), which was demethylated using $AlCl_3$ to yield 7-hydroxyphthalide, 9, m.p. 134-136° (lit. 134-136°[19], 135-136.5°[20]). Similarly, $LiBH_4$ reduction of 7 gave 4-methoxyphthalide, m.p. 126-128° (lit.[21,22] 127°), which upon $AlCl_3$ treatment yielded 4-hydroxyphthalide, 10, m.p. 257-258° dec. (lit.[21,22,23] 254-260° dec.). Having affirmed the structures of 6 and 7, it was possible to correlate them with 1 and 2 respectively by their reaction with 1,4-dihydroxy-5,8-dihydronaphthalene, 11, following the procedure of Brewster-Ciotti[24].

Hydrogenation of 1 over Pd/C afforded 4'-hydroxy-5',6',7',8'-tetrahydro-naphthyl-2-methoxy-6-carbomethoxy-benzoate, 12, m.p. 163-166°; Pmr: δ7.66 (d of d, 1H, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.45 (d of d, 1H, J_1 = J_2 = 7.8 Hz), 7.16 (d of d, 1H, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.20 (d, 1H, J = 8.5 Hz), 6.6 (d, 1H, J = 8.5 Hz), 5.08 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.5-2.9 (m, 4H),



1.65-1.95 ppm (m, 4H). When 11 was treated with BF_3-etherate at elevated temperature (90°, 1 hr) it underwent an apparent Fries rearrangement and subsequent dehydrative cyclization to give 1-methoxy-6,11-dihydroxy-7,8,9,10-tetrahydronaphthacene-5,12-dione, 13 in 60-80% yield, m.p. 234-235°; Pmr: δ13.83 (s, 1H), 13.43 (s, 1H), 7.98 (d of d, 1H, J_1 = 8.0 Hz, J_2 = 1.2 Hz), 7.70 (d of d, 1H, $J_1 = J_2$ = 1.2 Hz), 4.05 (s, 3H), 2.73 (m, 4H) and 1.80 ppm (m, 4H); uv_{max} ($CHCl_3$) 537 nm (ε8,800), 501 (ε13,400), 475 (ε11,200), 370 (ε3,700) and 292 (ε9,000).

The mechanism and regioselectivity of this cyclization reaction and its application to the synthesis of adriamycinone is currently under investigation.

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