Regioselective Synthesis of Anthraquinones *via* (Arene)chromium Tricarbonyl Complexes

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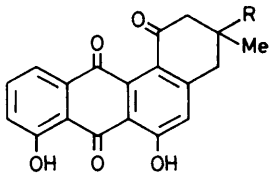
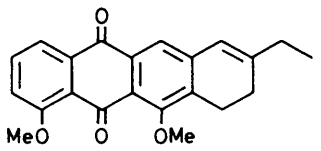
(±)-3-Deoxyrabelomycin (**2**) and the linear anthraquinone (**3**), an intermediate for synthesis of de(methoxycarbonyl)aklavinone (**5**), have been synthesized by regioselective lithiation of (η^6-arene)chromium tricarbonyl complexes.

7-Methoxy-1-tetralol and related compounds are lithiated at the 8-position *via* intramolecular co-ordination between lithium and the two proximal oxygen atoms.[1] On the other hand, we have recently reported[2] that proton abstraction from the corresponding (η^6-arene)chromium tricarbonyl complexes, easily obtained from the parent arenes and $Cr(CO)_6$, occurs with different regioselectivity (at the 6-position) under mild conditions. Since the $Cr(CO)_3$ group, as a temporary activating group, is easily removed oxidatively in quantitative yield, the directed lithiation of (η^6-arene)chromium complexes provides another useful method for the synthesis of substituted arenes. We now report the application of this procedure to the short, regioselective syntheses of natural anthraquinones 3-deoxyrabelomycin[3] (**2**), and the linear tetracyclic anthraquinone (**3**), a key intermediate for the synthesis of aklavinone[4] (**4**).

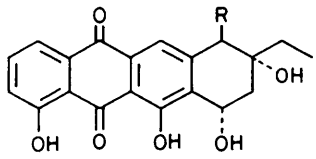
The tetralone complex (**6**) was methylated with MeI and NaH in dimethylformamide (DMF) and benzene to give the 2-*exo*-methyl complex[5] (**7**) (m.p. 71—72 °C), which was converted into the tetralol complex (**8**) (m.p. 113—114 °C) by stereoselective reduction[5] ($LiAlH_4$, ether, 0 °C) in 72% overall yield. Directed lithiation[2] [Bu^{n}Li (2 equiv.), tetramethylethylenediamine (TMEDA), −78 °C, 2 h] of (**8**), followed by quenching with 2-formyl-3-methoxy-*N*,*N*-diethylbenzamide[6] and subsequent decomplexation (exposure to sunlight), gave a diastereoisomeric mixture of hydroxy-phthalide derivatives in 40—50% yield without formation of regioisomeric products.



(**1**) R=OH, Rabelomycin
(**2**) R=H



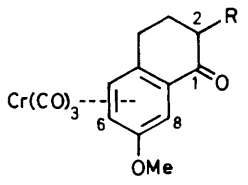
(**3**)



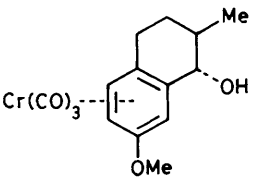
(**4**) R=CO_2Me, Aklavinone
(**5**) R=H

Dehydration of the hydroxy-phthalides with $KHSO_4$ gave the olefinic phthalide (**9**) (m.p. 174 °C) in quantitative yield.

The phthalide (**9**) was also obtained by the following sequence. Treatment of the dilithio-compound of complex (**8**) with DMF, followed by decomplexation and subsequent dehydration, afforded the 6-formyldihydronaphthalene (**10**)



(6) R = H
(7) R = Me



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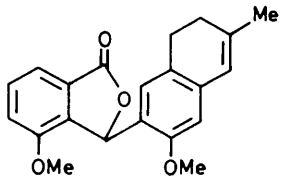

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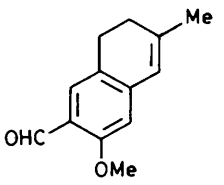

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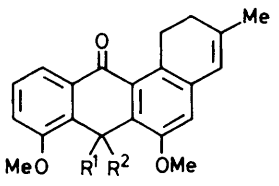
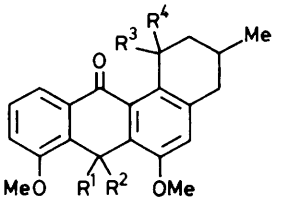
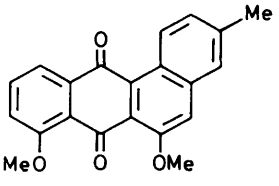


(11) $R^1 = R^2 = H$
(12) $R^1R^2 = O$
(13) $R^1 = H$, $R^2 = OOH$



(15) $R^1 = R^2 = R^3 = R^4 = H$
(16) $R^1R^2 = R^3R^4 = O$

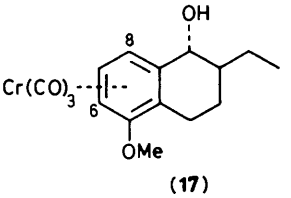


(14)

(m.p. 85 °C) in 92% yield. Condensation of (**10**) with the dilithio-compound of 3-methoxybenzanilide[7] gave the phthalide (**9**) in 80% yield.

Reduction of the phthalide (**9**) with Zn dust, followed by ring closure with trifluoroacetic anhydride and trifluoroacetic acid by the usual method, gave the anthrone (**11**) (m.p. 185 °C) in 89% overall yield. Conversion of (**11**) into the anthraquinone (**12**) was troublesome.† Air oxidation of (**11**) (Bu^tOK, Me_2SO–Bu^tOH) and subsequent treatment with base of the unstable hydroperoxide intermediate (**13**) gave the desired anthraquinone (**12**) in <10% yield, accompanied by the aromatized anthraquinone (**14**) in 50% yield. However, the anthrone (**15**), obtained by catalytic hydrogenation of (**11**) with 10% Pd–C, was smoothly converted into the anthraquinone (**16**) (m.p. 236—239 °C) with CrO_3 in AcOH. Demethylation of (**16**) with $AlCl_3$ gave 3-deoxyrabelomycin (**2**); λ_{max} (EtOH) 229, 267, and 434 nm: δ ($CDCl_3$) 1.24 (d, *J* 5 Hz, 3H), 6.89 (s, 1H), 7.16—7.26 (m, 1H), 7.52—7.70 (m, 2H), 11.76 (s, 1H), and 12.36 (s, 1H).

5-Methoxy-1-tetralone was converted into the (η^6-arene)-chromium complex (**17**) in 51% overall yield by the following sequence: (i), $Cr(CO)_6$; (ii) $LiPr^i{}_2N$; (iii) $B(OC_2H_4)_3N$, EtI; (iv) $LiAlH_4$. Treatment of the dilithio-compound of complex (**17**) with DMF, followed by air oxidation, gave a mixture of 6- and 8-formyl compounds in a ratio of 6:4. This undesirable lithiation at the 8-position was attributed to the co-ordination of the lithium to the benzylic alkoxide group.[8] Exclusive introduction of the formyl group at the 6-position could be achieved in 73% overall yield by protection of the hydroxy-group as the trimethylsilyl ether (i, Et_3N, Me_3SiCl; ii, Bu^nLi, TMEDA; iii, DMF; iv, *hν*–O_2). Deprotection and dehydration of (**18**) with $KHSO_4$ gave the 6-formyldihydronaphthalene (**19**), which was converted into the anthrone in 64% overall yield by the same method as just described. The anthrone (**20**) was easily oxidized (O_2, K_2CO_3) to the corresponding quinone (**3**), in contrast with the anthrone (**11**). The anthraquinone (**3**) has already been converted into de(methoxycarbonyl)aklavinone[7] (**5**).



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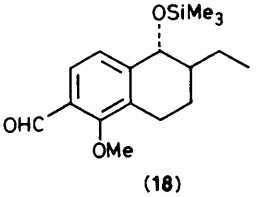

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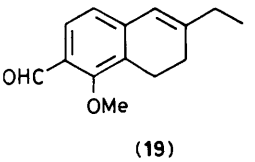

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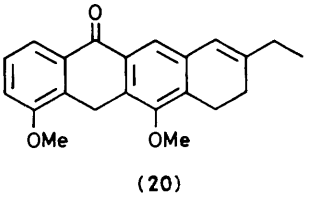

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Although a similar anthraquinone synthetic sequence has been reported,‡ the directed lithiation of the (η^6-arene)-chromium complexes provides a shorter route to the tetracyclic key intermediates.

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† Air oxidation of the anthrone (**11**) with Triton B or K_2CO_3 gave an unidentified dimeric product and CrO_3 or $(NH_4)_2Ce(NO_3)_6$ afforded only the quinone (**14**).

‡ In the strategy of Kende's group,[7] introduction of the formyl group required many steps and the product from the Claisen rearrangement was a mixture of the 6- and 8-substituted compounds.