Synthesis of 11-Deoxyanthracyclinone *via* (Arene)tricarbonylchromium Complexes

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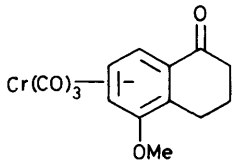
11-Deoxydaunomycinone (**1b**) has been synthesized *via* nucleophilic addition to the alicyclic part and directed lithiation at the aromatic part in the (η^6-arene)tricarbonylchromium complexes of the hydronaphthalene derivatives.

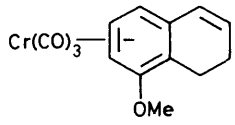
11-Deoxyanthracyclines, such as 11-deoxydaunomycin (**1a**), 11-deoxyadriamycin (**2a**), and 11-deoxycarminomycin (**3a**), are known to show a significant anticancer activity and less cardiotoxicity[1] than the 11-hydroxy analogues.[2,3] As a part of our investigation on the directed regioselective lithiation of aromatic compounds,[4] we now report the short, regioselective synthesis of 11-deoxydaunomycinone (**1b**).

Tricarbonyl(η^6-styrene)chromium was recognized as being equivalent to a Michael acceptor, in which nucleophilic addition occurs at the β-position of the styrene ligand.[5] Nucleophilic addition to this system can be used to introduce an acyl group at the C-9 position of anthracyclinones. The alternative method of carbanion addition to the carbonyl group of the corresponding β-tetralone usually proceeds in low yield with a large excess of the reagent, because of easy enolization of the carbonyl group.[6] Also, the directed lithiation of (arene)tricarbonylchromium is known to be useful for regioselective introduction of various substituents at positions on the arene ring, different from those that are substituted in the corresponding chromium-free arenes.[7] These two important concepts are effectively incorporated in this synthesis.

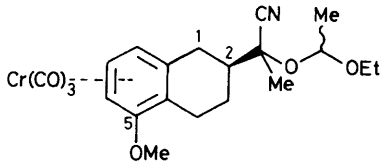
Tricarbonyl(5-methoxy-α-tetralone)chromium (**4**) (m.p. 114 °C), easily obtained from $Cr(CO)_6$ and the corresponding parent arene, was converted into tricarbonyl(3,4-dihydro-5-methoxynaphthalene)chromium (**5**) (m.p. 90—91 °C) by reduction ($LiAlH_4$, diethyl ether, 0 °C) and subsequent dehydration ($KHSO_4$, benzene, reflux) in 88% overall yield. The reaction of complex (**5**) with the carbanion of a protected acetaldehyde cyanohydrin [tetrahydrofuran (THF), −78—*ca.* 0 °C, 3 h] gave the tricarbonyl(2-*exo*-substituted-5-methoxytetralin)chromium (**6**) (m.p. 131—134 °C) in 87% yield.[8] *ortho*-Directed lithiation [Bu^nLi, tetramethylethylenediamine (TMEDA), −78 °C, THF, 2 h] of (**6**), followed by quenching with 2-formyl-3-methoxy-*N*,*N*-diethylbenzamide[9] and subsequent decomplexation (exposure to sunlight) gave a crude condensation product, which was converted into a diastereoisomeric mixture of keto-phthalide derivatives (**7**) (m.p. 142 °C), by treatment with dilute acid and then with base, in 38% overall yield after purification by silica gel chromatography. Reductive ring cleavage of the phthalide (**7**) with Zn dust (10% aqueous KOH, pyridine, reflux, 2 days),



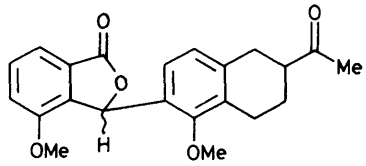
(**4**)



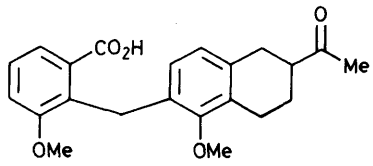
(**5**)



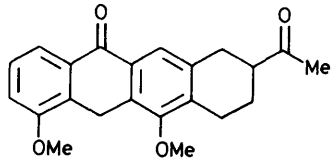
(**6**)



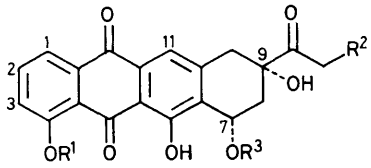
(**7**)



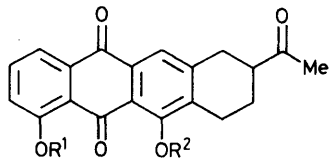
(**8**)



(**9**)



(**1**) R^1 = Me, R^2 = H
(**2**) R^1 = Me, R^2 = OH
(**3**) R^1 = R^2 = H
a; R^3 = Daunosamine
b; R^3 = H



(**10**) R^1 = R^2 = Me
(**11**) R^1 = R^2 = H
(**12**) R^1 = Me, R^2 = H

and subsequent Jones' oxidation† gave an oily keto-acid (**8**) in 95% yield. Treatment of the acid (**8**) with trifluoroacetic anhydride and trifluoroacetic acid (CH_2Cl_2, −15 °C, 1 h, and then room temp., 2 h) gave an anthrone derivative (**9**) (m.p. 201 °C) in 99% yield. The anthrone (**9**) was smoothly converted into the dimethoxyanthraquinone (**10**) (m.p. 191—193 °C) by CrO_3 oxidation (acetone, room temp., 20 h) in 96% yield. Demethylation of (**10**) with $AlCl_3$ gave a 4,6-dihydroxyanthraquinone (**11**). Regioselective monomethylation at the C-4 hydroxy group of (**11**) by the reported procedure[10] was not easy, but the dimethyl compound (**10**) could be demethylated cleanly and selectively at the 6-position with 1:1 HBr/AcOH (50 °C, 2 h) to give the monomethylanthraquinone (**12**) in 65% yield. Since (**12**) has been converted into 11-deoxydaunomycinone,[11] our synthesis *via* (arene)tricarbonylchromium complexes provides an alternative shorter route to the 11-deoxyanthracyclinones.[12]

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† Since some reduction of the acetyl group of (**8**) occured to give the secondary alcohol group, a mixture of the reduction products, without purification, was oxidized to (**8**) with Jones' reagent.

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