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THE ortho-QUINODIMETHANE ROUTE TO ANTHRACYCLINONES
A NEW SYNTHESIS OF 4-DEMETHOXYDAUNOMYCINONE

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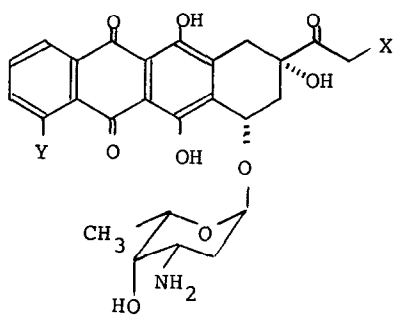
The anthracycline[1] antibiotics adriamycin (1),[2] daunomycin (2)[3] and carminomycin (3)[4] are of interest because of their potent activity against experimental tumors and human cancers.[5] A serious limitation to the use of these drugs in chemotherapy is toxicity; in particular, cardiotoxicity limits the total accumulative dose which can be administered. Structural modification of the natural drugs has led to improvements in biological activity as exemplified by the recent report that 4-demethoxydaunomycin (4) is more active than daunomycin (2) itself.[6]



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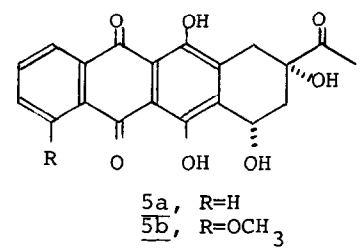
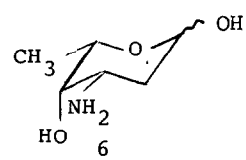
2: X=H Y=OCH_3
3: X=H Y=OH
4: X=H Y=H



5a, R=H
5b, R=OCH_3



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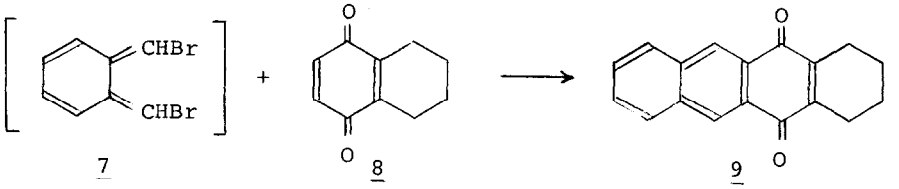
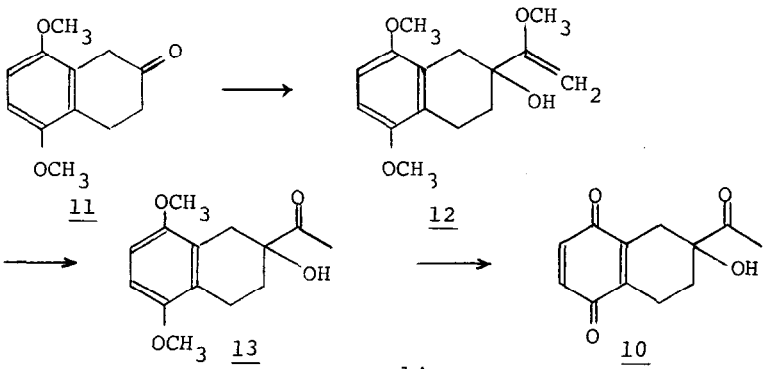
Intense interest in the synthesis of the anthracyclines has produced a number of different approaches to construction of the tetracyclic aglycones[7] and the amino sugar[8] L-daunosamine (6). Methods for coupling of the aglycones to appropriately protected daunosamine derivatives complete the synthesis of the glycosidic antibiotics.[9]

We have developed a simple and direct synthesis of the aglycone 4-demethoxydaunomycinone (5a), an intermediate in the synthesis of 4. The key feature in our synthetic strategy is construction of the tetracyclic nucleus by a Diels-Alder reaction between an appropriately substituted quinone and a reactive o-quinodimethane 7.[10] Reaction of 7, generated from tetrabromo-o-xylene 14, with quinone 8 produces an adduct which spontaneously loses HBr to give quinone 9, mp 182.5-183°, 72%.

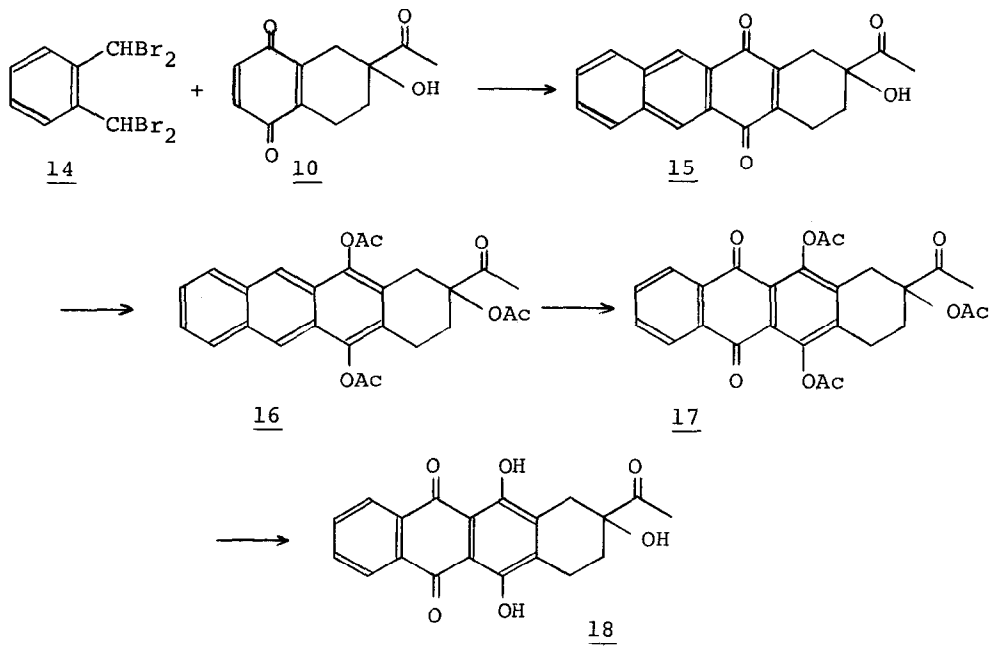


7 8 9

Quinone 10 was prepared as shown below. Reaction of 5,8-dimethoxy-2-tetralone (11)[11] with methoxyvinyllithium[12], followed by workup with aqueous ammonium chloride gave 12. The conversion of 11 into 12 proceeds in 40% yield (easily monitored by doublets in the pmr spectrum at δ 4.0 and 4.4), but the reaction can be repeated on the mixture of 11 and 12. After four reactions, the crude enol ether 12 was hydrolyzed (3 N $HClO_4$,MeOH-H_2O,25°) to produce hydroxyketone 13 (87% yield, mp 100.5-102.5°).[7a] Oxidation of 13 with argentic oxide[13] gives quinone 10, 98%, mp 100-102°. The overall yield of 10 prepared in this way from 11 is 85%.

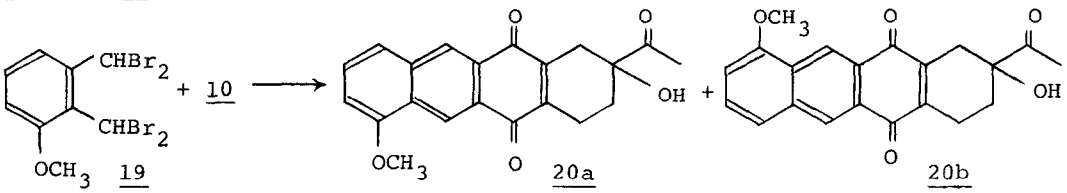


Reaction of tetrabromo-o-xylene 14[14] with NaI in DMF in the presence of quinone 10 produced quinone 15 in 33% yield after chromatography (SiO_2, 10% EtOAc-CH_2Cl_2), mp 233-235°(d) [nmr: δ 1.92 (m 2H), 2.39 (s 3H), 2.90 (m 4H), 7.68 (dd 2H), 8.06 (dd 2H), 8.625 (s 1H), 8.638 (s 1H)]. Reduction of 15 (Zn,Et_3N,Ac_2O,100°,12 hr) gave hydroquinone triacetate 16, mp 213-215° [nmr: δ 2.0 (s 3H), 2.15 (s 3H), 2.0-2.4 (m 2H),2.57 (s 6H), 2.95 (m 2H), 3.25 (m 2H), 7.39 (dd 2H), 7.92 (dd 2H), 8.20 (s 2H); ir ($CHCl_3$): 1760, 1735, 1720 cm^{-1}] in 94% yield. Oxidation of 16 (CrO_3,AcOH-H_2O,25°,2 hr) gave the quinone triacetate 17, mp 244.5-245.5° [nmr: δ 2.05 (s 3H), 2.23 (s 3H), 2.0-2.4 (m 2H), 2.53 (s 3H), 2.54 (s 3H), 2.8-3.1 (m 2H), 3.2 (bs 2H), 7.75 (dd 2H),



8.17 (dd 2H); ir ($CHCl_3$) 1770, 1740, 1720(sh), 1680, 1590 cm^{-1}], which was hydrolyzed (HCl,AcOH-H_2O,75°,2 hr) to (±)-4-demethoxy-7-deoxydaunomycinone 18, mp 210-212° [nmr: δ 2.01 (m 2H), 2.41 (s 3H), 3.02 (m 4H), 3.81 (s 1H), 7.84 (dd 2H), 8.37 (dd 2H), 13.48 (s 2H); ir (KBr) 3500, 1700, 1620, 1590 cm^{-1}].[15] The yield of 18 from 16 is 69%.[16] Since the conversion of 18 into 4-demethoxydaunomycinone (5a) has been reported[7d], our synthesis also constitutes a new synthesis of 5a.

This approach is being extended to the methoxy series corresponding to daunomycinone (5b). Reaction of tetrabromo-o-xylene 19 (prepared from 2,3-dimethylanisole by NBS bromination, 80%, mp 147-148°) with sodium iodide in the presence of quinone 10 gave a mixture of the two regioisomeric quinones 20a and 20b.[17] Details of this work will be published in a future paper.



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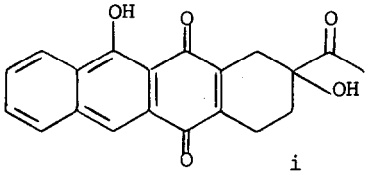
15. While the melting point of 17 is higher than that reported (160-162°), the pmr spectrum of 17 is in exact agreement with the reported spectrum. 7d
16. A by-product of the oxidation and hydrolysis of 15 is a hydroxyquinone, mp 160-163°, tentatively assigned structure i and/or ii [ms: m/e 336; nmr: δ 1.94 (m 2H), 2.38 (s 3H), 2.83 (m 4H), 3.60 (1H), 7.6-8.5 (m 5H), 13.37 (1H)].



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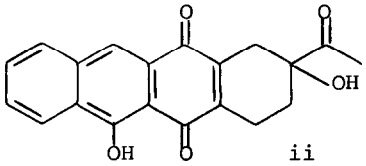

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17. All new compounds gave satisfactory combustion and spectroscopic data consistent with assigned structures.

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