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THE ISOBENZOFURAN ROUTE TO ANTHRACYCLINONES

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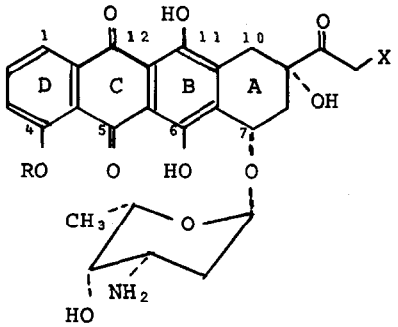
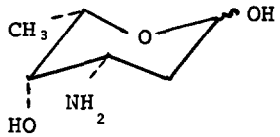
Current interest in the total synthesis of the clinically important anthracycline antibiotics[1] daunorubicin (1), adriamycin (2) and carminomycin-I (3) has led to development of a variety of strategies for the efficient construction of these complex molecules. Several routes to L-daunosamine (4) the amino sugar moiety, have been reported,[2] and its attachment to the aglycones of 1 and 2 has been described.[3] Recent total syntheses of the aglycones themselves have utilized Friedel-Crafts acylations[4] or cycloaddition to a diquinone dienophile[5] to reach the tetracyclic target. We now report a novel alternative route to anthracyclinones based on the chemistry of quinone-isobenzofuran adducts.





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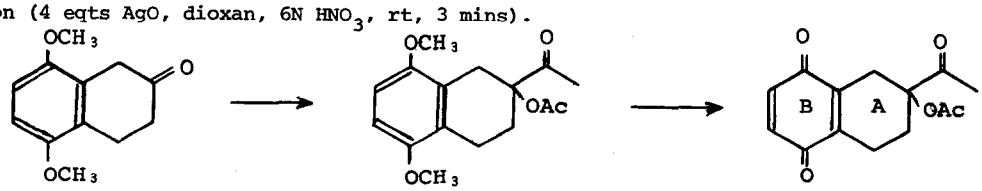
1, R = CH_3, X = H

2, R = CH_3, X = OH

3, R = H, X = H

Our new strategy rests upon the one-step construction of the complete anthracyclinone skeleton by addition of a C_8 isobenzofuran unit to the quinone form of a preformed AB synthon. In its simplest variant, our AB synthon is the yellow crystalline quinone 7, mp 86-87°, prepared in 64% yield from the readily available 1,4-dimethoxy-6-tetralone[6] 5 by ethinylation (3 eqts HC≡CMgBr, THF, rt), conversion to the acetoxy ketone 6, mp 120-122° (2 eqts $Hg(OAc)_2$, EtOAc, rt, 16 hrs) and oxidative demethylation (4 eqts AgO, dioxan, 6N HNO_3, rt, 3 mins).



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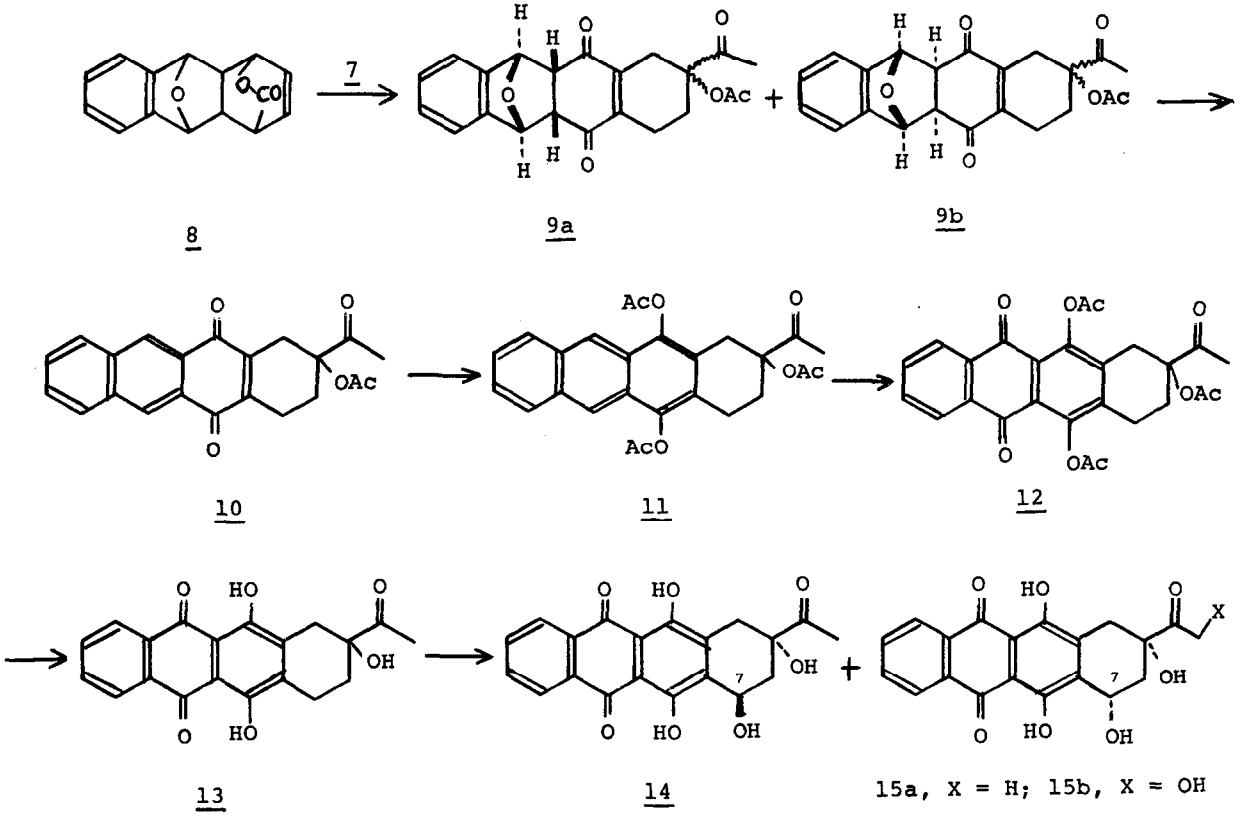
While 1,3-diarylisobenzofurans have long been employed as Diels-Alder dienes,[8] our knowledge of the parent system is relatively recent.[9] In 1965 Fieser and Haddadin showed that lactone 8, conve-

niently prepared by allowing a mixture of α-pyrone[10] and the benzyne-furan adduct to stand several days at room temperature, provided a high yield of the unstable isobenzofuran upon heating above 130°.[11] We have found that thermolysis of lactone 8 in the presence of the bicyclic quinone 7 (140°, diglyme) gave in 96% yield a mixture consisting of a 3:1 ratio of endo (9a) and exo (9b) adducts.[12] Aromatization of this mixture (NaOAc, HOAc, reflux, 16 hrs) gave 70% of the yellow quinone 10, mp 254-256°, which was reduced with zinc dust in acetic anhydride (110°, 20 min) to yield 93% of the sensitive triacetate 11. Oxidation of the C-ring[13] (4 eqts CrO_3, 80% aq HOAc, rt, 2 hrs) gave the yellow quinone triacetate 12, mp 247-248°, in 64% yield after chromatography (SiO_2, 1% MeOH:$CHCl_3$).

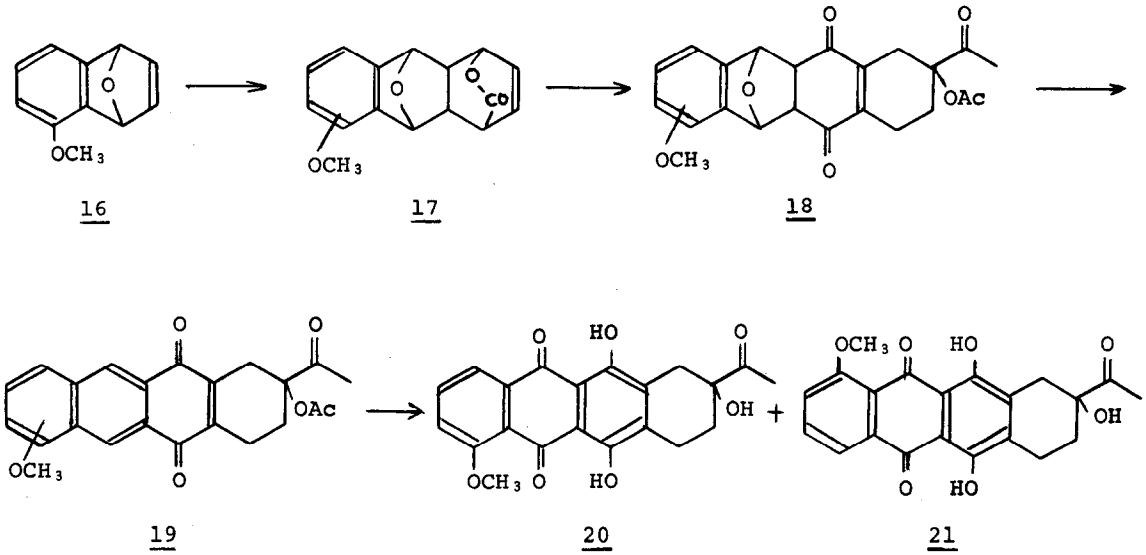
Acid hydrolysis of 12 (1:1 6N HCl-HOAc, 70°, N_2, 2 hrs) produced a quantitative yield of (±)-4-demethoxy-7-deoxydaunomycinone 13 [nmr δ 13.54 (s, 2H), 8.36 (m, 2H), 7.84 (m, 2H), 3.7 (s, broad, 1H), 2.99 (m, 4H), 2.40 (s, 3H), 1.96 (m, 2H)]. This product was identical in all respects with an analytical sample, mp 160-162°, independently prepared in our laboratory from quinizarinquinone and 2-acetoxybutadiene in 36% overall yield[14] using our earlier four-step sequence.[5]

Conversion of 13 to (±)-4-demethoxydaunomycinone (15a), the aglycone of the powerful antineoplastic agent 4-demethoxydaunorubicin (IMI-22),[15] was achieved by homolytic bromination at C-7 (1.5 eqts Br_2 in CCl_4, AIBN, reflux) followed by reaction with AgO_2CCF_3 (DMSO, rt, 10 mins) to give on aqueous workup a mixture of 15a and its 7-epimer 14 in approximately 1:2 ratio.[16] Equilibration in trifluoroacetic acid (rt, 1.5 hrs) followed by methanolysis gave, in ca. 45% yield from 12, the desired *racemic* aglycone 15a [nmr δ 2.31 (m, 2H), 2.44 (s, 3H), 3.08 (m, 2H), 4.56 (s, 1H, exch), 5.32 (m, 1H, $\nu_{\frac{1}{2}}$ = 8 Hz), 7.84 (m, 2H), 8.31 (m, 2H), 13.29 (s, 1H), 13.58 (s, 1H); R_f SiO_2 3% MeOH-$CHCl_3$)



= 0.25. The latter product could be transformed by C-14 bromination (Br_2, $CHCl_3$, rt, 16 hrs) and displacement (.002 M NaOH, 80% acetone, 60°, 5 mins)[17] in 55% overall yield to the interesting new aglycone (±)-4-demethoxyadriamycinone (15b), mp 227-228°.

Synthesis of daunomycinone by our isobenzofuran route required the generation of 4-methoxyisobenzofuran. To this end, the 3-methoxybenzyne-furan adduct[18] 16, mp 59-60°, was reacted with α-pyrone (neat, 10-15 das, rt) to give 83% of the stereoisomeric mixture of lactones 17. Thermolysis of 17 at 140° in the presence of quinone 7 gave a 93% yield of the tetracyclic adduct 18 as a mixture of stereoisomers. Direct aromatization (NaOAc, HOAc, reflux, 5 hrs) led in 70% yield to the orange quinones 19 (mp 214-226°). Reduction (Zn dust, Ac_2O, reflux, 20 mins), C-ring oxidation (6 molar eqts Jones rgt, 12 hrs, acetone, rt) and mild acid hydrolysis as before gave in 51% overall yield the regioisomeric mixture of (±)-7-deoxydaunomycinone (20) and its 1-methoxy counterpart 21.



Although the mixture of 20 and 21 thus formed was indistinguishable from authentic 7-deoxydaunomycinone by ir, uv, ms and proton magnetic resonance, regiochemical characterization could be achieved by C-13 nmr and analytical hplc. In $CDCl_3$ the wide-band ^1H-decoupled cmr spectrum of authentic 20 showed singlets at δ 19.9, 23.9, 29.1 and 32.3 which we tentatively assign to aliphatic carbons C-14, C-8, C-7 and C-10, respectively.[19] The cmr of our product mixture was nearly identical to that of 20 but showed extra peaks for the C-14 and C-10 carbons at δ 19.6 and 32.7, respectively. These signals were of the same intensity as the adjacent ones at δ 19.9 and 32.3, and were attributed to an equal amount of regioisomer 21 in the product mixture. This conclusion was confirmed by careful hplc analysis ($CHCl_3$, Corasil columns) which showed the presence of two compounds of nearly identical retention times, one of them shown to be 20 by coinjection with authentic material.

Despite its lack of regiospecificity our new strategy provides a convergent and efficient route to (±)-7-deoxydaunomycinone from tetralone 5 in eight steps and 10% overall yield. Although this compares favorably with existing routes, its main significance rests upon the likelihood that a more

highly functionalized AB synthon equivalent than quinone 7 would be compatible with the exceptionally mild conditions of our new sequence. This possibility, leading to still more convergent syntheses of the natural aglycones, is under investigation.[20]

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16. Pure trans diol 14 showed its C-7 proton signal as a multiplet at δ 5.40 ($\nu_{\frac{1}{2}}$ = 18 Hz) and could be independently isomerized to 15a by CF_3CO_2H in good yield. Diol 14: $R_f(SiO_2, 3\%MeOH\text{-}CHCl_3)=0.19$
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18. This compound, mp 59-60°, was prepared from 2-amino-6-methoxybenzoic acid and isoamyl nitrite added simultaneously to a refluxing 1:1 mixture of furan in 1,2-dimethoxyethane. The corresponding reaction with 2-amino-3-methoxybenzoic acid was unsuccessful.
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