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A NEW SYNTHESIS OF THE NAPHTHOPYRAN ANTIBIOTICS

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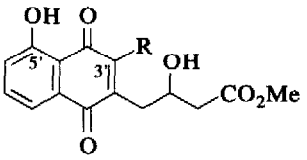
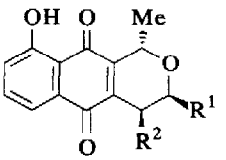
Summary. A known precursor (1) of the naphthopyran antibiotics has been synthesised from the naphthoquinones (11) and (12) by reaction with the diene (5) and subsequent elaboration.

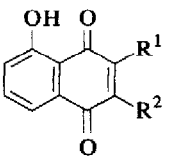
The biological importance of naphtho[2,3-*c*]pyran-5,10-quinones as antineoplastic antibiotics has earned them considerable interest, leading to their synthesis by several groups.[1-5] The hydroxy ester (1) and its 5'-*O*-methyl ether are known precursors to these naphthopyran antibiotics and hence (1) represents a highly desirable relay point for their synthesis. Reduction of (1) to its quinol, condensation with the appropriate aldehyde at position 3' and reoxidation to the quinone has provided a simple conversion to racemic nanaomycin A (2)[3] and thence nanaomycins C (3) and D (4) as well as kalafungin, the enantiomer of (4).[1]



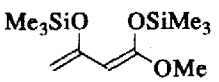
(1) R = H
(14) R = Br
(15) R = Cl



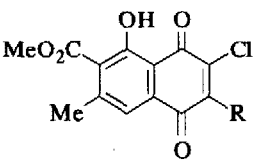
(2) $R^1 = CH_2COOH$, $R^2 = H$
(3) $R^1 = CH_2CONH_2$, $R^2 = H$
(4) $R^1, R^2 =$ $-CH_2COO-$



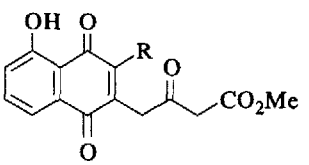
(8) $R^1, R^2 = H$
(9) $R^1 = Cl$, $R^2 = H$
(11) $R^1, R^2 = Cl$
(12) $R^1, R^2 = Br$



(5)



(6) R = H
(7) $R = CH_2COCH_2CO_2Me$



(10) R = Cl
(13) R = Br

This paper reports a simple, direct approach to (1) based on attachment of a four-carbon nucleophile, the diene (5), to an appropriate naphthoquinone. This approach reflects indications[6,7] that, for a strongly polarised diene like (5) combining with a quinonoid dienophile, conjugate addition competes with, and sometimes dominates, conventional Diels-Alder cycloaddition. For example, in related work here[6] uncatalysed addition of (5) to the highly substituted quinone (6) has been found to give the product (7) (59%); hydrolysis of the silyloxy groups and reoxidation to the quinone occurred as part of the isolation. Competitive cycloaddition was observed to only a minor extent (13%). Extrapolation to simpler naphthoquinonoid electrophiles relevant to (1) has therefore been investigated. Recent work[8]

has studied conjugate additions involving cyclic trioxy dienes fixed in s-*trans*-conformations.

Direct reaction of diene (5) and juglone (8) has been observed to lead to cycloaddition as the only detected process.[9] Similar treatment of (5) with the chlorojuglone (9) gave the same anthraquinonoid products resulting from cycloaddition but also led to a minor amount of the keto ester (10) (16%), m.p. 119-20°; δ 3.66 (2-CH_2), 4.12 (4-CH_2), 11.69 (OH). Carrying out this reaction in the presence of various Lewis acids, so as to enhance the polarisation and electrophilicity of the dienophile, was then explored. The most effective outcome of this approach resulted from adding the reactants (5) and (9) in the presence of zinc bromide at -78°, which caused the yield of (10) to be increased to 39%.

A more efficient conversion still, resulted from reaction of the diene (5) with dichlorojuglone (11).[10] This gave the same keto ester (10) in higher yield (53%). The process did not require addition of Lewis acid nor accompanying oxidation and was not accompanied by detectable cycloaddition. Similar uncatalysed reaction of dibromojuglone (12) and (5) gave the bromo analogue (13) (71%; 88% based on consumed starting material), m.p. 138-9°; δ 3.66 (2-CH_2), 4.18 (4-CH_2), 11.74 (OH) (lit.[8] 130°; 3.60, 4.10, 11.66). These one-step combinations leading to the chloro and bromo products (10), (13) respectively, offer potentially simple access to the target system (1), provided dehalogenation and reduction of the 3-carbonyl can be accomplished.

Reduction of the keto carbonyl group of (13) proceeded readily with sodium borohydride in tetrahydrofuran at -78° to give the hydroxy ester (14) (71%), m.p. 128-30°; δ 3.09 (3-OH), 4.39 (H3). Similar reduction of (10) gave (15), m.p. 127-9°.

Dehalogenation of the hydroxy esters (14), (15) was investigated by several reagents with essentially the same outcome from each, ranging from no reaction to complete decomposition. The most effective conditions involved treatment with stannous chloride in hydrochloric acid - methanol. Following aerial reoxidation, this gave the desired product (1), m.p. 94-5° (lit.[3] 87-8°); δ 2.60 (2-CH_2), 2.78 (4-CH_2), 3.18 (3-OH), 3.73 (CO_2Me), 4.33 (H3), 6.94 (H3'), 11.95 (5'-OH). This important relay compound was thereby conveniently obtained in overall yield of 21%, based on the simple sequence from (12).

All new compounds gave satisfactory analyses and spectroscopic data. ^1H N.m.r. spectra were run in $CDCl_3$. We acknowledge financial support from the Australian Research Council and an Australian Postgraduate Research Award (to I.T.C.).

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