Annelation Reactions of Levoglucosenone. Chiral Intermediates for the Synthesis of Naphtho[2.3-*c*]pyran-5,10-quinone Antibiotics

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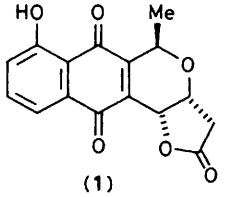
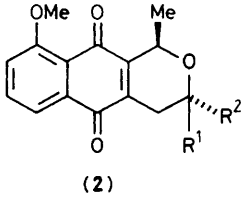
Reaction of the anion of 3-cyano-4-methoxy-3*H*-isobenzofuran-1-one (**4b**) with levoglucosenone affords a chiral annelation product useful for the synthesis of naphtho[2.3-*c*]pyran-5,10-quinone antibiotics.

The synthesis[1—3] and biosynthesis[4] of naphtho[2.3-*c*]pyran-5,10-quinone type antibiotics are of current interest since the molecules show interesting biological properties.[5] The syntheses of racemic kalafungin (**1**),[1] nanomycins,[2] and the eleutherins[3] [(**2a**) eleutherin; (**2b**) isoeleutherin] have been reported, but no chiral approach has been published. We report here an annelation strategy[6] for preparation of the chiral naphthopyran ring system which is central to these antibiotics.

Levoglucosenone[7] (**3**) is a chiral enone which is readily available by pyrolysis of waste paper. It possesses the same stereochemistry as the right-hand ring of kalafungin.[8] Annelation of (**3**) with (**4a**),[9] a useful reagent in anthracyclinone chemistry,[10] afforded an unstable naphthohydroquinone deri-



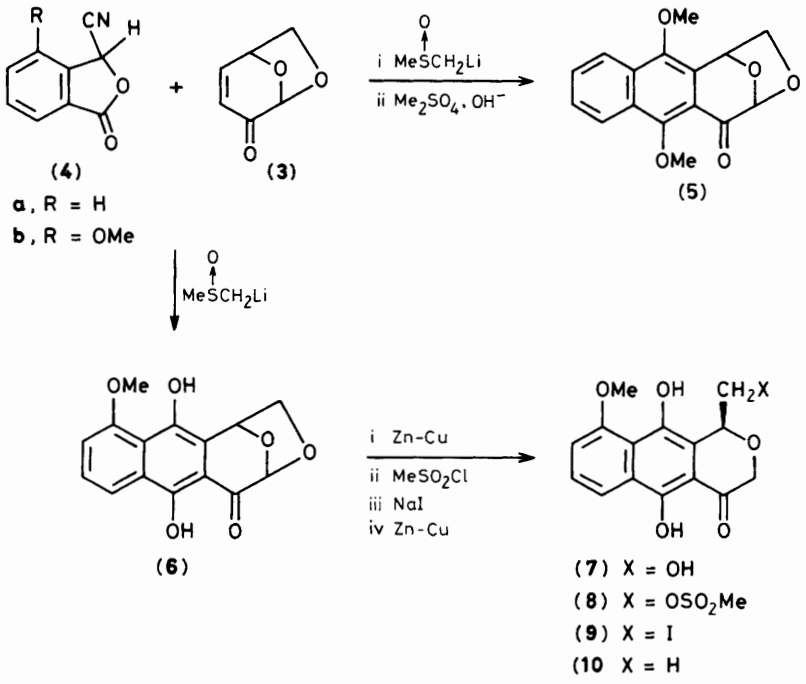
(1)



(2)

a; R^1 = Me, R^2 = H

b; R^1 = H, R^2 = Me



vative which was directly methylated to afford (**5**)† in 40% overall yield. In contrast, reaction of (**4b**) (1.2 equiv.)‡ with (**3**) (1 equiv.) gave crystalline, stable naphthohydroquinone (**6**)† in 65% yield after simple workup of the reaction mixture. This bicyclic acetal (**6**) was reductively opened with zinc–copper couple in tetrahydrofuran to afford chiral (**7**) (72%),† thus forming in two steps the basic ring system of the naphtho[2.3-*c*]pyran-5,10-quinones.

After several attempts to remove the primary hydroxy group of (**7**) failed, (**7**) was converted into the methanesulphonate (**8**) (85%),† and the methanesulphonate was then displaced with sodium iodide in acetone to give the iodide, (**9**) (85%).† Finally, reduction of (**9**) with zinc–copper couple in moist tetrahydrofuran gave the desired (**10**) (60%).† Addition of a lactone ring would afford kalafungin while conversion of (**7**)—(**10**) into their enantiomers would provide valuable intermediates for preparation of nanomycin and related systems.

The strategy outlined above serves as a convergent route to a number of substituted derivatives of (**7**)—(**10**) since the hydroxy phthalides required for preparation of (**4**) are readily available.[11]

We acknowledge partial support from the National Science Foundation.

Received, 14th January 1985; Com. 060

† All new compounds showed spectroscopic properties (^{13}C and ^{1}H n.m.r., i.r.) in agreement with the assigned structures: (**5**) m.p. 99—100 °C, $[\alpha]_D^{20}$ −200° ($CHCl_3$, *c* 1.0); (**6**) m.p. 144—145 °C, $[\alpha]_D^{20}$ −282° ($CHCl_3$, *c* 1.0); (**7**) m.p. 191—193 °C, $[\alpha]_D^{20}$ +14° ($CHCl_3$, *c* 0.2); (**8**) m.p. 164—166 °C (decomp.), $[\alpha]_D^{20}$ +32.5° ($CHCl_3$, *c* 0.23); (**9**) m.p. 158—159 °C (decomp.), $[\alpha]_D^{20}$ +81.6° ($CHCl_3$, *c* 0.18); (**10**) m.p. 152—154 °C, $[\alpha]_D^{20}$ +11° ($CHCl_3$, *c* 0.1). The m.p.s are uncorrected, and concentrations for the rotations are given in g/100 ml of solvent.

‡ The reactions were performed as described in ref. 10.

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