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STEREOSPECIFIC SYNTHESES OF 4-METHYLNAPHTHOQUINOL EPOXIDE

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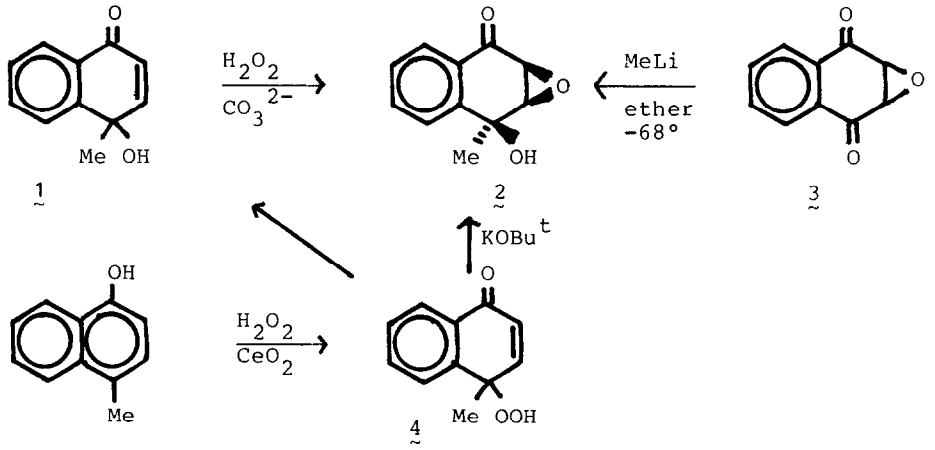
Summary: Epoxidation of 4-methylnaphthoquinol (1) with alkaline hydrogen peroxide and addition of methyllithium to naphthoquinone epoxide both lead stereospecifically to the cis hydroxyepoxide (2).

Synthetic routes to 2,3-epoxy-4-hydroxycyclohexanones are of interest since this system is present in a number of natural products[1] and because the factors controlling the relative stereochemistry in such syntheses are not fully understood. We have examined several routes to 4-methylnaphthoquinol epoxide which contains this system.



Epoxidation of 4-methylnaphthoquinol (1) with alkaline hydrogen peroxide might occur cis or trans to the hydroxyl group. In other enones, steric hindrance,[2] angle strain,[3] conformational factors[4] and interaction with charged or polar neighbouring groups[5] have been used to explain stereoselective epoxidations, but only the last of these effects would apply to the epoxidation of 1. We prepared the quinol (1)[6] from 4-methyl-1-naphthol by addition of singlet oxygen[7] and reduction of the hydroperoxide (4). Epoxidation of 1 with hydrogen peroxide and sodium carbonate in aqueous ethanol gave, in 65% yield, a single epoxide [m.p. 165-167°, δ ($CDCl_3$) 1.5 (3H, s), 3.75 and 3.8 (2H, AB quartet, J = 4 Hz)]. No trace of the epimeric epoxide was detected by NMR or TLC. The same epoxide was formed in 75% yield by epoxidation of 1 with t-butylhydroperoxide and Triton B in dioxan. This same epoxide was the major product (64% isolated)

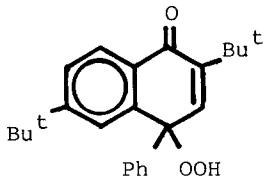
from prolonged epoxidation of 1 using m-chloroperoxybenzoic acid in refluxing methylene chloride. This result and a weak intramolecular hydrogen bond evident from the IR spectrum of 2 suggest the epoxide and the hydroxyl group are cis.

The cis stereochemistry is confirmed by the finding that $KOBu^t$ in $HOBu^t$/petrol isomerises the hydroperoxide cleanly to the same epoxide (2) (75% conversion in one minute at 20°). Such self-epoxidations by the anions of γ-hydroperoxy-enones often occur during alkaline autoxidation of phenols and have been assumed to give the cis product since there is kinetic evidence that the reaction is intramolecular.[8] In one case the cis stereochemistry of a hydroxyepoxide prepared in this way was confirmed by X-ray diffraction.[9] More recently other X-ray work[10] established the cis stereochemistry of the naphthoquinol epoxide (5) obtained by the action of base on the hydroperoxide (6) which closely resembles our hydroperoxide (4).

The exclusive formation of the cis isomer (2) in the alkaline hydrogen peroxide epoxidation cannot be due to steric or conformational factors and may be due to interaction of the hydroxyl group with the incoming HOO^- ion or with the departing HO^- ion in the ring closure step, so favouring cyclisation of one of the diastereomeric adducts (8). The observed cis stereochemistry can be contrasted with the trans stereochemistry observed in the epoxidation of the carboxylate (9),[5b] which is perhaps controlled by charge repulsion, and to the trans stereochemistry we found for the epoxidation of the hydroxynaphthalenone (10).[11]

An alternative approach to the quinol epoxide is its direct synthesis by reaction of naphthoquinone epoxide (3) with methyllithium. Previous studies of addition of organometallic reagents to (3) have encountered problems due to deprotonation leading to hydroxynaphthoquinone and opening of the epoxide by a nucleophile, often catalysed by the Lewis acids present.[12,13] Furthermore addition might occur from either face and recent work[14] has shown that, at least for reaction of an α-alkoxyaldehyde with an allyl tin, the stereochemistry of the addition is unpredictably dependent on the solvent and the nature of any Lewis acid present. In two cases the stereochemistry of the quinol epoxide formed from a naphthoquinone epoxide has been rigorously established. Read[15] found that reduction of naphthoquinone epoxide with sodium borohydride gives an 11:1 mixture of quinol epoxides, the major one (11) having the epoxide and hydroxyl cis, and Rieker[10] has reported that phenylmagnesium bromide adds to the substituted naphthoquinone epoxide (7) regio and stereospecifically giving the epoxide (5), the oxygens of which were shown to be cis by X-ray crystallography.

We find that addition of 1.6 moles per mole of methyllithium to a dilute solution of naphthoquinone epoxide in ether at -68° under argon gives immediate precipitation of a lithium alkoxide. After 45 minutes' stirring, workup by addition of ethyl acetate, water and acid gives a mixture from which the cis epoxide (2) was isolated in 50% yield. The other components of the mixture



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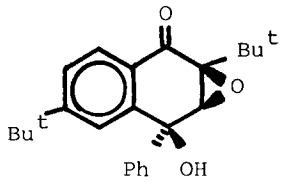

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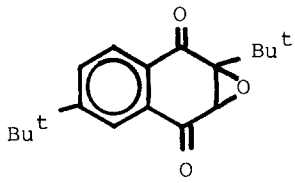

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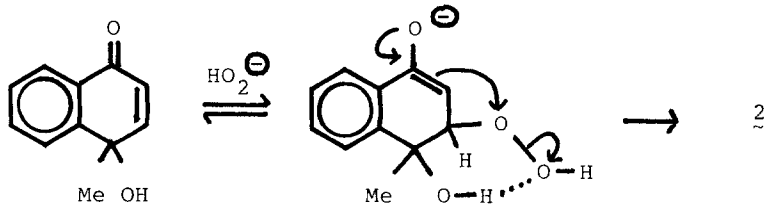

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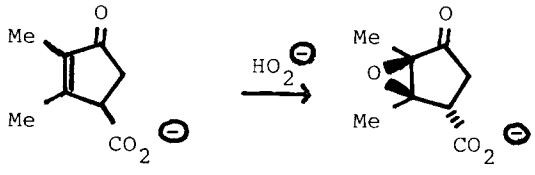

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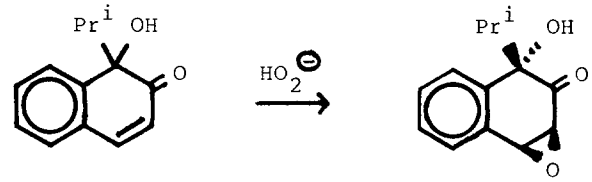

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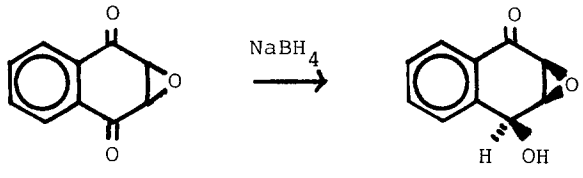

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include starting material, the dimethyldiol resulting from double addition and some hydroxynaphthoquinone. No stereoisomeric epoxide could be detected by NMR. This successful and stereospecific addition of methyllithium to naphthoquinone epoxide in cold ether solution contrasts with failures reported[13] with methylmagnesium iodide, butyllithium and dibutyl cuprate. It follows the same stereochemical path as the hydride addition to 3 and the addition of aryl Grignard to the hindered quinone epoxide (7).

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