The Stereochemistry of a Nucleophilic Enone Epoxidation: An Unusual Neighbouring Group Effect

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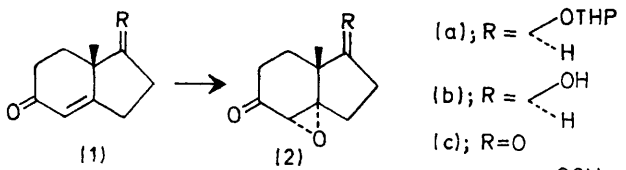
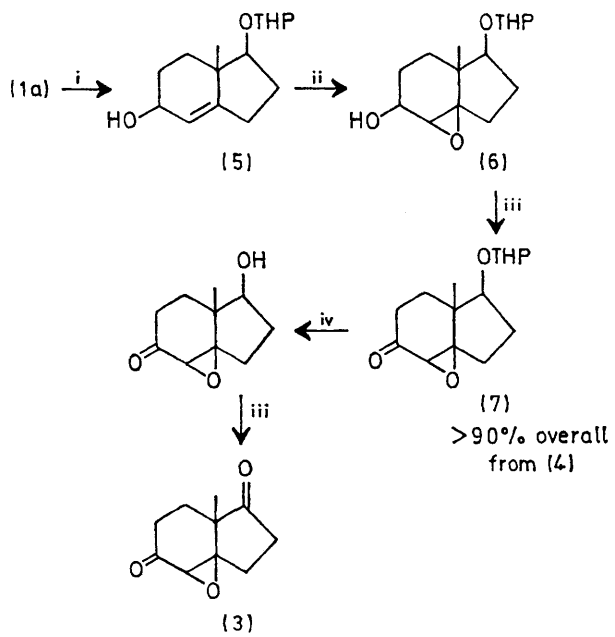
Summary Epoxidation of 7,7a-dihydro-7a-β-methyl-indane-1,5-(6*H*)-dione with alkaline hydrogen peroxide produces the *trans*-fused perhydroindanone exclusively.

THE alkaline hydrogen peroxide epoxidation of bicyclic and steroidal enones has been reported by many workers to give predominantly or exclusively the *cis*-fused ring system.[1] It appears that many of these assignments are based on 'literature precedent' even though studies by Henbest and Jackson[2] have shown that, in the case of 3-keto-Δ^4-steroids, the stereochemistry of epoxidation is dependent on the presence of polar functionality. The stereochemistry



for the related tetrahydroindanones has not been established although it might have been assumed that the normally higher tendency for formation of the *cis*-isomer in this ring system would lead to an even higher preference for



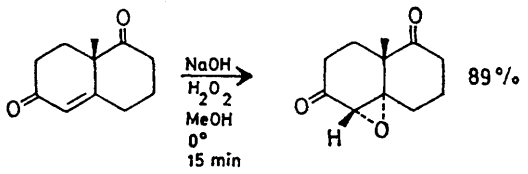
SCHEME 1

i; $LiAlH_4$, ether, reflux, ii; Bu^tOOH, $Mo(CO)_6$, PhH, iii; $CrO_3 \cdot py_2$, CH_2Cl_2, room temp., iv; 2:1 HOAc–H_2O, 40 °C.

formation of the β-epoxide. In contrast to this expectation, we now report that a tetrahydroindanone gives only the *trans*-fused isomer.

Treatment of (**1a**)[3] or (**1b**) with 30% aqueous H_2O_2 and 4N-NaOH in MeOH[4] gives only recovered starting material but (**1c**)[5] gives a 94% yield of a single epoxy ketone (**2c**),[6] m.p. 74—76° [i.r. 1745, 1712 cm^{-1}, n.m.r. δ 3·60 (epoxide methine), 1·16 (angular methyl)].

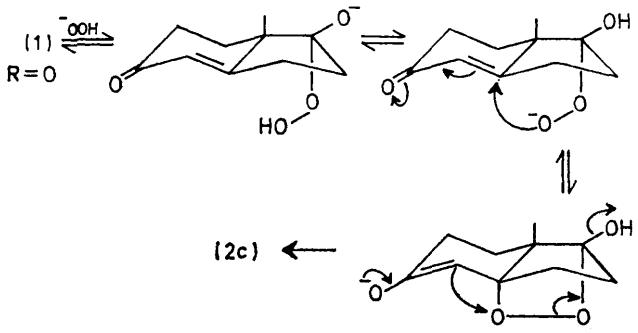
To establish the stereochemistry of (**2c**), we prepared a sample of the *cis*-fused epoxide (**3**) (Scheme 1). The stereochemistry of (**3**) relies on the reduction of the ketone and the epoxidation of the allylic alcohol. Previous work has established that reduction of (**1d**) under identical conditions gives the pseudoequatorial alcohol virtually exclusively, a fact which is confirmed by lanthanide induced shifts. Furthermore, the stereochemistry of epoxidation by peroxides catalysed by transition metals has been shown to be completely directed by the allylic alcohol.[8] Thus, the epoxy alcohol (**6**) must be the *cis*-fused isomer as depicted. Since oxidation and hydrolysis to (**3**), m.p. 141—142°, does not affect the ring junction, it too must be *cis* [i.r. 1745, 1720 cm^{-1}, n.m.r. δ 3·23 (epoxide methine), 1·32 (angular methyl)]. With the firm establishment of the stereochemistry of (**3**) that of (**2c**) may be now assigned as *trans*.



The n.m.r. data, in which the angular methyl group appears at higher field in the *trans* than the *cis* isomer,[10] and the epoxide methine appears at lower field in the *trans* than the *cis* isomer, supports the assignment.[1c] This same trend holds in comparing (**7**) to its epoxide isomer and may be general.

The ease of the reaction of (**1c**) led us to re-examine the nucleophilic epoxidation of the Wieland–Miescher ketone. Under our conditions, reaction was rapid and again a single isomer, m.p. 56—57° [n.m.r. δ3·10 (epoxide methine) 1·37 (angular methyl)] was produced. This was isomeric with that obtained in an internal Darzen's condensation.[1b] Using the previous trends in the n.m.r. chemical shifts for the epoxide methine proton, we assign *trans* stereochemistry to the product of nucleophilic epoxidation in this case as well.

The fact that only (**1c**) reacts, combined with the stereochemical result, suggests that the hydroperoxide anion initially attacks at the less hindered face of the nonconjugated carbonyl group to provide an intramolecular delivery to the β carbon of the enone (Scheme 2).† This



SCHEME 2

novel neighbouring group effect provides one of the rare methods that allow direct formation of the *trans*-perhydroindanone system.[10] These results also seem to suggest that a re-evaluation of the methods, by which the stereochemistry of the products of epoxidation by alkaline hydrogen peroxide of polycyclic enones is assigned,[1b] is required.

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† An alternative explanation based on the Henbest model rationalizes the result but fails to account for the total lack of reactivity of (**1a**) and (**1b**).

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