

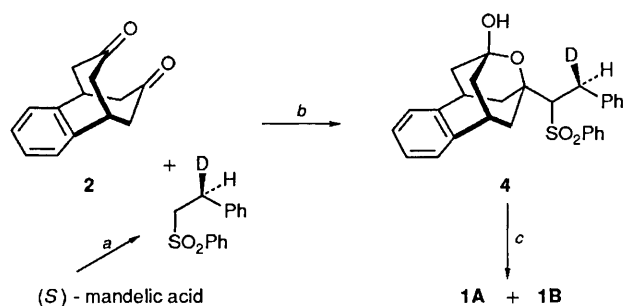
Partial Kinetic 'Resolution' Resulting from a Deuterium Isotope Effect

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The 'racemate' **1A/1B** cyclises on heating to the enol **5** via an 'ene' reaction; at two-thirds completion, the recovered enone **1A/1B** has $[\alpha]_D -62^\circ$ (**1B** has $[\alpha]_D -132^\circ$); kinetic 'resolution' results from a deuterium isotope effect for the cyclisation (k_H/k_D ca. 1.8); the absolute stereochemistry of compound **6a** is determined by X-ray analysis.

In the course of other work we had reason to prepare a 1:1 mixture of the diastereoisomers **1A** and **1B**, *i.e.* a 'racemate' of **1**, but for the identical configurations in both 'enantiomers' at the deuterium-bearing carbon. The preparation of the **1A/1B** 'racemate'[†] is summarised in Scheme 1. Enone **1**, when it is heated in the melt at 165°C for 20 min, cyclises to the enol **5**.[‡] The *Z*-alkene is not formed. The cyclisation presumably occurs, under the thermal conditions, via an 'ene' reaction (Fig. 1) that will be subject to a deuterium isotope effect: the 'enantiomer' **1A** has hydrogen in the appropriate position for transfer to oxygen, while the 'enantiomer' **1B** has deuterium so placed. If one assumes a deuterium isotope effect of 2 for this 'ene' reaction,¹ **1A** will react twice as quickly as **1B**. It can,



Scheme 1 Compound **2**: see ref. 2; step *a*, ref. 3; step *b*: BuⁿLi/THF, ref. 4; step *c*: i, (CF₃CO)₂O/THF; ii, Na-Hg/THF-MeOH, ref. 5

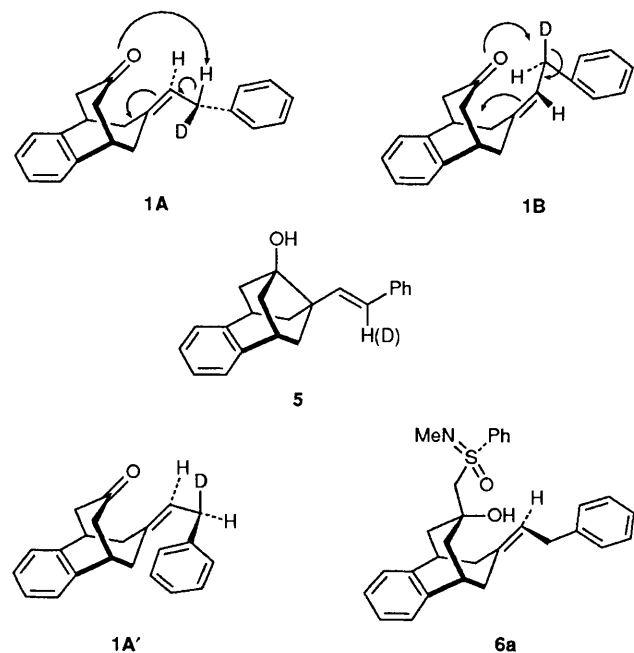


Fig. 1

[†] $[\alpha]_D +1.79 (\pm 0.03)^\circ$; because of a secondary deuterium isotope effect in step *b* (see Scheme 1), **1A** and **1B** will not be formed in exactly equal amounts, but the chirality of the deuterium-bearing carbon must also contribute to the net $[\alpha]_D$.

[‡] All new compounds have satisfactory elemental analyses and spectroscopic properties.

therefore, be predicted that when 'racemic' enone **1A** + **1B** is cyclised thermally to **5**, then at incomplete reaction, recovered enone should be 'resolved', the degree of 'resolution' depending on the deuterium isotope effect for cyclisation. An estimate of the deuterium isotope effect is derivable independently from (i) the $[\alpha]_D$ of recovered enone and (ii) the deuterium content of product enol (see below).

Enone **1** (unlabelled) was resolved via the adducts (**6a-d**; *exolendo*, *R/S*), obtained with (+)-(*S*)-*N,S*-dimethyl-*S*-phenylsulphoximine,⁶ which are separable by preparative TLC and which regenerated **1A** or **1B** (unlabelled), $[\alpha]_D \pm 132^\circ$, on heating to 140°C. The absolute configuration of adduct **6a** (which generates **1A**, $[\alpha]_D +132^\circ$) has been determined by X-ray crystallographic analysis.[§]

The thermal transformation of the resolved enone **1A** into **5** takes place cleanly by an 'ene' reaction via the 'extended' conformation **1A'**, rather than via the more crowded alternative **1A''**, and similarly for resolved **1B**. Thus, the (*R*)-enone **1A** (96.13% d₁), having the (*R*)-configuration at the deuterium-bearing carbon, affords enol **5** (96.9% d₁), with complete retention of deuterium, whereas the (*S*)-enone **1B** (96.13% d₁) affords enol **5** (96.06% d₀) with total loss of deuterium. These experiments also demonstrate that the configurational integrity of the (*S*)-mandelic acid is preserved in **1A** and **1B** (see Scheme 1).

§ *Crystal data* for **6a**: C₃₀H₃₃NO₂S, *M* = 471.63, orthorhombic, space group *P*₂₁₂₁, *a* = 8.464(2), *b* = 13.193(2), *c* = 22.977(2), *V* = 2568.8 Å³, *Z* = 4, *D*_c = 1.22 g cm⁻³. Cu-Kα X-radiation (graphite monochromator), λ = 1.5418 Å, μ(Cu-Kα) = 12.80 cm⁻¹, *F*(000) = 1008. Data were collected at 296 K using a θ - 2θ scan to a 2θ limit of 60° on an Enraf-Nonius CAD-4 diffractometer. Each reflection measurement was followed by its Friedel pair. 5024 reflection intensities were measured, they were corrected for absorption by a Gaussian method and merged to give 3794 unique reflections with an *R*_{merge} = 0.063. The maximum and minimum transmission factors were 0.84 and 0.76, respectively. The Friedel pairs were not merged and used throughout the analysis as independent measurements, except for the initial stages of structure solution and refinement. The structure was solved by the direct methods program MITHRIL⁷ and refined without the inclusion of anomalous scattering to give *R* = 0.052. The Δ*f*' values for S, N and O atoms were then included in the calculations. The *R*_w values for the two possible enantiomers of **6a** were 0.0899 and 0.0892, respectively after least-squares refinement. The Hamilton *R*-factor ratio test⁸ thus establishes the absolute configuration for **6a** at a significance exceeding 0.005. As a final test, refinement of the Rodgers η-factor was carried out on the *R*-factor preferred absolute configuration.⁹ From any starting point in the range -1.0 to 01.0 (except zero) refinement converged at 1.07(5). The absolute configuration is thus fully established. The final *R*-factor for 3576 reflections having *F* > 3.0σ(*F*) was 0.0529 (*R*_w = 0.0825); the final model included anisotropic temperature factors for all non-hydrogen atoms, and a correction for extinction was applied. All H atoms were included initially in their calculated positions; where there was an ambiguity, peaks in the relevant difference Fourier were used to resolve the problem. The H atoms were given individual, refined isotropic thermal parameters, but their coordinates were not refined. The total number of refined parameters was 341. Weights were assigned as 1/σ²(*F*), where σ(*F*) was derived from counting statistics. The upper and lower limits in the final difference electron density map were 0.26 and -0.46 eÅ⁻³, respectively. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, see Notice to Authors, Issue No. 1.

When 'racemic' enone **1A** + **1B** (51 mg, 98.0% d₁, [α]_D +7.2°) was heated in the melt for 20 min at 165 °C, the reaction product (88% recovery), separated by preparative TLC, consisted of recovered enone **1B** > **1A** (13.5 mg, [α]_D -60.5°) and enol **5** (31.4 mg, 64.85% d₁). The calculated values for *k_H*/*k_D* of 1.7 (from [α]_D of recovered enone) and 1.8 (from deuterium content of product enol) are in reasonable agreement.

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