

## Stereoselective Epoxidation of a 5,6,6-Trisubstituted Cyclohex-2-enone

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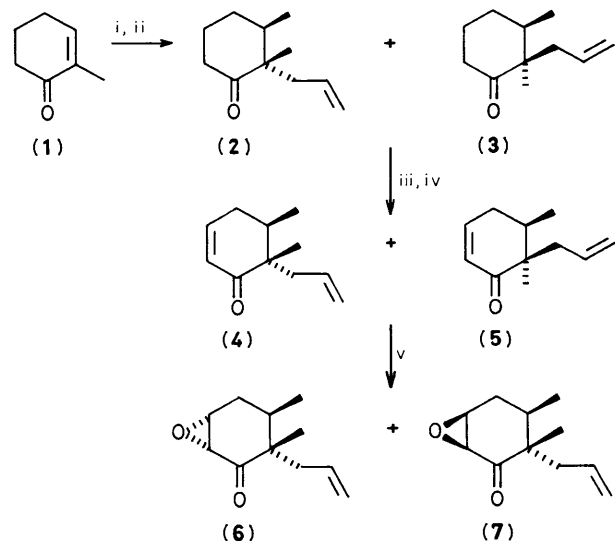
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Alkaline hydroperoxidation of a *cis/trans* mixture of 5,6-dimethyl-6-allylcyclohex-2-enone (4 : 1) has led to a pair of epoxides (ratio 3 : 1) derived only from the *cis* isomer, whose separation was achieved chromatographically and the relative stereochemistry defined by crystal structure analysis of an ozonolysis product.

As part of a larger programme directed towards the synthesis of upial,<sup>1</sup> we have investigated the extent and direction of stereoselectivity possible in the alkaline hydroperoxidation of cyclohex-2-enones that already carry an array of substituents. Our interest was heightened by an awareness that tandem cuprate addition-alkylations to acceptor molecules such as (1) seldom lead to stereochemically homogeneous products.<sup>2</sup> Therefore it was also necessary to find a better separation technique than preparative vapour phase chromatography.<sup>2</sup> Herein we demonstrate that a prototypical  $\alpha,\beta$ -epoxycyclohexanone is indeed capable of stereocontrolled formation,<sup>3</sup> and ideally suited to separation by medium pressure liquid chromatography. X-Ray analysis of a peroxide degradation product has provided the unequivocal basis for stereochemical assignment.

2-Methylcyclohex-2-enone (1) was treated sequentially with lithium dimethylcuprate and allyl bromide as previously detailed to give (2) and (3) in a 4 : 1 ratio.<sup>†</sup> Because these isomers could not easily be separated, the mixture was transformed into (4) and (5) by conventional selenenylation-oxidation (Scheme 1). Despite the presence of substantial amounts (20%) of (5), alkaline hydrogen peroxide in aqueous acetone at 20 °C acted uniquely on (4) to deliver stereoisomers (6) and (7) in a combined yield of 74%.<sup>‡</sup> The relative amount



**Scheme 1.** Reagents: i,  $\text{Me}_2\text{CuLi}$ ,  $\text{Et}_2\text{O}$ , 0 °C; ii,  $\text{CH}_2=\text{CHCH}_2\text{Br}$ , tetrahydrofuran (THF), hexamethylphosphoramide; iii, lithium diisopropylamide,  $\text{PhSeCl}$ , THF, -78 °C; iv, 30%  $\text{H}_2\text{O}_2$ , pyridine,  $\text{CH}_2\text{Cl}_2$ , 25 °C; v,  $\text{NaOH}$ , 30%  $\text{H}_2\text{O}_2$ ,  $\text{Me}_2\text{CO}$ , room temp.

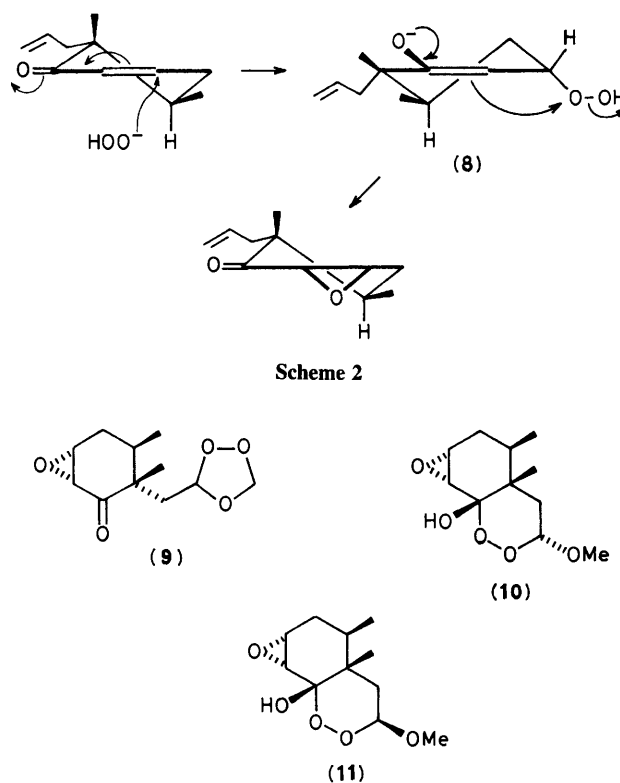
<sup>†</sup> Ref. 2 reports realization of a 9 : 1 ratio of these products. This percentage distribution was never approached in more than ten runs, each with slight modification of the procedure.

<sup>‡</sup> The failure of (5) to be epoxidized has precedent, see ref. 3.

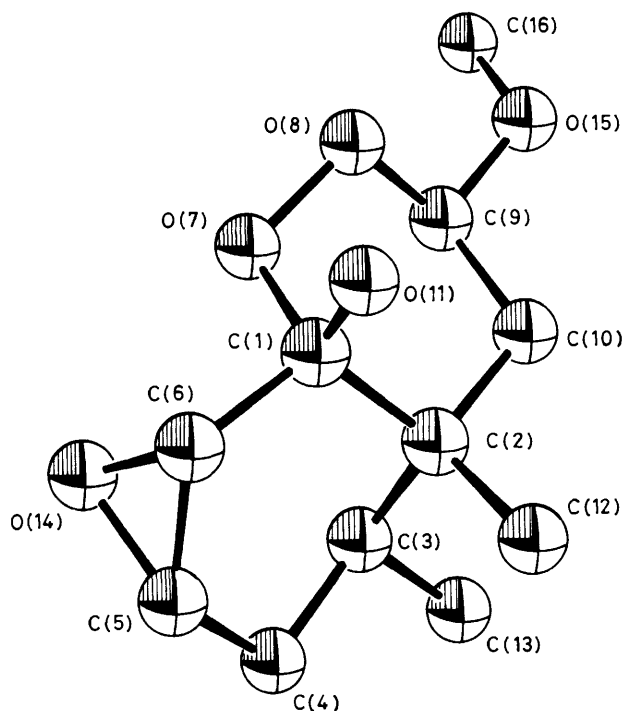
of (6)§ in the mixture was 75%.<sup>4</sup> In agreement with earlier observations,<sup>5</sup> the hydroperoxide anion is seen to add in a conjugate fashion to (4) preferentially from the axial direction to deliver intermediate enolate anion (8) (Scheme 2). The *trans* arrangement of the methyl groups in (5) seems to provide sufficient steric hindrance to both faces of the acceptor double bond to deter analogous Michael reaction.

The separation of (6) from (7) was conveniently accomplished by silica gel chromatography. Although the n.m.r. spectra of these colourless oils were distinctively different, unequivocal stereochemical assignments were not possible on this basis alone. Consequently, (6) was ozonolysed in a  $\text{CH}_2\text{Cl}_2$ - $\text{MeOH}$  (5 : 1) solvent system between -78 and 0 °C. Oxidative ( $\text{H}_2\text{O}_2$ ) workup produced not only ozonide (9) (15%), but also the crystalline peroxides (10) and (11) (40% and 27%, respectively).<sup>6</sup> The stereochemistry of (11) was rigorously established by X-ray crystallographic analysis (see Figure 1).

**Crystal data.** Suitable crystals of (11) formed from diethyl ether with symmetry  $C2/c$ . Preliminary experiments gave cell parameters of  $a = 11.027(3)$ ,  $b = 14.432(2)$ ,  $c = 14.064(2)$  Å



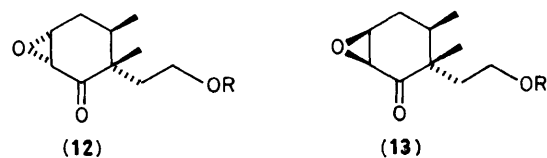
§ Satisfactory combustion analyses were obtained for (6). In all cases,  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r., and high-resolution mass spectra are in complete accord with the assigned structures.



**Figure 1.** A computer generated perspective of (11) derived from the X-ray co-ordinates (hydrogens omitted for clarity) showing the relative conformation.

and  $\beta = 95.85(1)^\circ$  for  $Z = 8$ . An automatic four circle diffractometer equipped with a sealed tube Cu X-ray source ( $\lambda = 1.5418 \text{ \AA}$ ) and graphite monochromator was used for data collection. Of the 1573 reflections measured with  $2\theta \leq 114^\circ$ , 1433 were observed ( $I \geq 3\sigma I$ ). A multi-solution tangent formula approach<sup>7</sup> to phase solution gave an initial model which was subsequently refined using full matrix least-squares techniques. The function minimized was  $\sum \omega(|F_o| - |F_c|)^2$  with  $\omega = 1/\sigma F_o$ . Hydrogens were added with fixed isotropic temperature factors. The final unweighted residual is 0.064. All intramolecular bond distances and angles are within normal ranges and the only short intermolecular contact is a hydrogen bond of 2.83 Å between O(11) and O(15). The peroxide containing ring is in a chair conformation while the cyclohexane ring, in a half chair conformation, has C(2) and C(3) above and below, respectively, the best plane through C(1), C(4), C(5), and C(6). The methoxy group occupies an equatorial site.¶

¶ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.



R=H, SiMe<sub>2</sub>But, tetrahydropyran-2-yl

Evidently, (6), (7), and derived substances such as (12) and (13) adopt mutually distinctive topographies that enable the oxirane ring in the two series to exert diagnostically different anisotropy effects<sup>8</sup> on the methyl substituents (CDCl<sub>3</sub> solution). In the all-*cis* series, the 6-methyl singlet appears at  $\delta$  1.07–1.00 and the 5-methyl doublet is seen in the region 0.95–0.93. For (6) and (12), both related absorptions are shifted to higher field ( $\delta$  0.93–0.88 and 0.88–0.86, respectively).

The alkaline peroxidation of acyclic enones is recognized to be nonstereospecific but highly stereoselective.<sup>9</sup> The above results established that stereoselectivity can also be realized in conformationally flexible cyclic,  $\alpha,\beta$ -unsaturated ketones at a level adequately suited for total synthesis.<sup>3–5</sup>

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## References

- G. Schulte, P. J. Scheuer, and O. J. McConnell, *J. Org. Chem.*, 1980, **45**, 552.
- R. K. Boeckman, Jr., *J. Org. Chem.*, 1973, **38**, 4450.
- For a review see: G. Berti, *Top. Stereochem.*, 1973, **7**, 172.
- Similar or higher stereoselectivities have been reported for other cyclohexenones: ref. 3; C. G. Chavdarian, S. L. Woo, R. D. Clark, and C. H. Heathcock, *Tetrahedron Lett.*, 1976, 1769; M. Miyashita, T. Kumazawa, and A. Yoshikoshi, *Chem. Lett.*, 1979, 163; B. C. Laguzza and B. Ganem, *Tetrahedron Lett.*, 1981, 1483.
- E. Klein and G. Ohloff, *Tetrahedron*, 1963, **19**, 1091.
- For previous examples of somewhat related chemistry, see P. S. Bailey, 'Ozonation in Organic Chemistry,' vol. 1, Academic Press, New York, 1978, chap. V.
- The following library of crystallographic programs was used: MULTAN 80, University of York, York, England, 1980; Structure Determination Package V17.0, Enraf-Nonius Corporation, Delft, Holland, 1981; ORTEP-II, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1970.
- L. A. Paquette, W. E. Fristad, C. A. Schumann, M. A. Beno, and G. G. Christoph, *J. Am. Chem. Soc.*, 1979, **101**, 4645 and relevant references cited therein; M. Kitadani, H. Uda, and A. Yoshikoshi *Tetrahedron Lett.*, 1966, 4843; G. Legler and B. Squiring, *Tetrahedron*, 1967, **23**, 2683.
- H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *J. Am. Chem. Soc.*, 1959, **81**, 108; H. O. House and R. S. Ro, *ibid.*, 1958, **80**, 2428; H. O. House and D. J. Reif, *ibid.*, 1955, **77**, 6525; H. H. Wasserman and N. E. Aubrey, *ibid.*, 1955, **77**, 590; H. H. Wasserman, N. E. Aubrey, and H. E. Zimmerman, *ibid.*, 1953, **75**, 96; N. H. Cromwell and R. A. Setterquist, *ibid.*, 1954, **76**, 5752; R. E. Lutz and J. O. Weiss, *ibid.*, 1955, **77**, 1814.