

Reductive Alkylation of α -Epoxyketones

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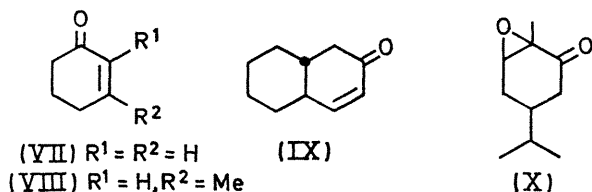
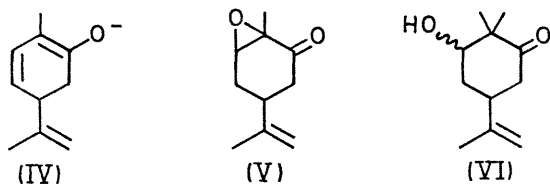
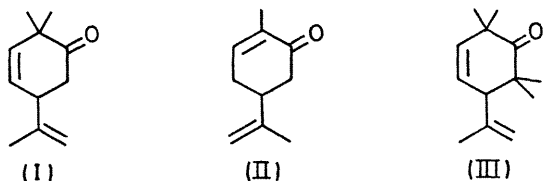
Summary α -Epoxyketones have been found to be useful intermediates for the specific alkylation of ketones to mono- or di-alkylated products.

In an attempt¹ to prepare $\alpha\alpha$ -dimethyl- $\beta\gamma$ -unsaturated ketone (I) by direct methylation of optically active carvone (II)[†], using standard conditions² the tetramethyl unsaturated ketone (III) was obtained as the major product (70%) along with recovered starting carvone. If the failure of the direct methylation was due to the lack of formation of the

expected enolate (IV), then a functionality such as an α -epoxyketone which would produce the desired methylation and still introduce unsaturation is required.

α -Epoxyketone (V) (yield >90%) was prepared by reaction of carvone with basic hydrogen peroxide.³ Reductive alkylation was carried out (yield ca. 80%) in liquid ammonia with lithium and methyl iodide,⁴ with ether or tetrahydrofuran as solvent. The presence or absence of t-alcohols did not affect the reaction appreciably. The intermediate alcohol (VI) was dehydrated with phosphoryl chloride in pyridine.⁵

The results of the reductive methylation of the epoxides of compounds (VII)—(IX) and of the alkylation of compound (X) with benzyl bromide are given in the Table. The intermediate alcohols in the reactions of the ketones (VII)—(IX) were not isolated but were directly dehydrated to yield the α -substituted $\beta\gamma$ -unsaturated ketones.



TABLE

Yields of epoxidation and reductive alkylation products^a

Ketone	% Yield of epoxyketone	% Yield of alkylation product
L-Carvone (II)	92	80
Cyclohexenone (VII)	92	65 ^b
3-Methylcyclohexenone (VIII)	83	55 ^b
$\Delta^{3,4}$ - <i>trans</i> -2-octalone (IX)	79	40 ^b
L-Carvotanacetone	>90	80

^a Reported yields are based on purified product; ^b Yield of isolated dehydrated products.

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[†] All compounds reported gave satisfactory analyses and physical data including i.r., u.v., n.m.r., and mass spectral determinations.

¹ C. H. Jarboe, L. A. Porter, and R. T. Buckler, *J. Medicin. Chem.*, 1968, **11**, 729.

² C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *J. Amer. Chem. Soc.*, 1961, **83**, 4433.

³ R. L. Wasson and H. D. House, *Org. Synth.*, 1963, **4**, 522.

⁴ L. E. Hightower, L. R. Glasgow, K. M. Stone, D. A. Albertson, and H. A. Smith, *J. Org. Chem.*, 1970, **35**, 1881 and references therein.

⁵ K. L. Rinehart and E. G. Perkins, *Org. Synth.*, 1963, **4**, 444.