Preparation of Optically Pure 2,3-Epoxycyclohexanones

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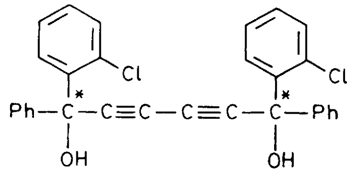
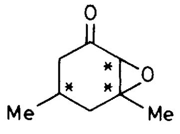
One hundred per cent optically pure methyl-substituted 2,3-epoxycyclohexanones [(**2**)—(**4**)] were obtained using a complexation method with optically active 1,6-di(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (**1**).

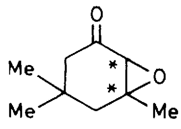
An optically active epoxy ketone is a useful chiral synthon. Optically active 2,3-epoxycyclohexanones are especially important starting materials for the preparation of various physiologically active compounds.[1] However, no attempt to prepare optically active 2,3-epoxycyclohexanone was successful until 1980 when Wynberg and Marsmann obtained 20 ± 3% e.e. 2,3-epoxycyclohexanone by the enantioselective epoxidation of cyclohex-2-enone with t-butyl hydroperoxide in the presence of quininium benzyl chloride.[1] The enantioselectivity of this method is not high, and it is not applicable to 3-methylcyclohex-2-enone because the olefin is too sterically crowded to be epoxidized by t-butyl hydroperoxide. We now report a very simple preparation of 100% e.e. 3,5-dimethyl- (**2**), 3,5,5-trimethyl- (**3**), and 3-methyl-2,3-epoxycyclohexanone (**4**) by an optical resolution method involving complexation with optically active 1,6-di(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (**1**).[2]



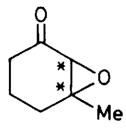
(**1**)



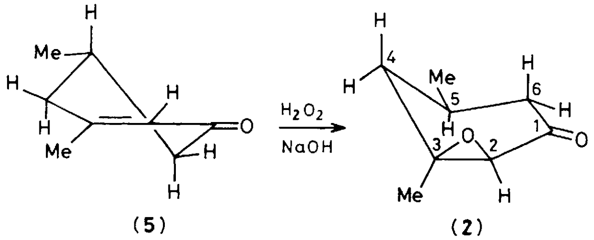
(**2**)



(**3**)



(**4**)



Scheme 1

When a solution of (−)-(**1**) (5.10 g, 10.6 mmol) and (**2**) (5.94 g, 42.4 mmol) in 1:1 diethyl ether–light petroleum (20 ml) was kept at room temperature for 6 h, a 1:1 complex of (−)-(**1**) and (−)-(**2**) (4.68 g, 58%) was obtained as colourless prisms, which upon Kugelrohr distillation *in vacuo* gave 90% e.e. (−)-(**2**)† (51%),‡ $[\alpha]_D$ −122°.§ Two recrystallisations of the 1:2 complex of (−)-(**1**) and 90% e.e. (−)-(**2**)

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† The enantiomeric excess (% e.e.) of (−)-(**2**) and (+)-(**4**) was determined by n.m.r. analysis in $CDCl_3$ using the chiral shift reagents, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) and tris(trifluorocamphorato)europium(III), respectively. Although these chiral shift reagents could not be used to determine the % e.e. of (+)-(**3**), (+)-(**3**) with $[\alpha]_D$ +13.5° is 100% optically pure, because the $[\alpha]_D$ value does not increase on further resolution.

‡ All yields of the optically resolved compounds were based on the theoretical amount of the optical isomer contained in the initial (±)-compound.

§ All the $[\alpha]_D$ values were measured in MeOH (*c* 0.15) in a 1 dm cell at 25 °C.

(4.68 g) from 1 : 1 diethyl ether–light petroleum (50 ml each) gave the complex of (−)-(**1**) and 100% e.e. (−)-(**2**) (2.74 g, 34%), m.p. 117—118 °C, which upon Kugelrohr distillation *in vacuo* gave 100% e.e. (−)-(**2**) (0.9 g, 30%), $[\alpha]_D$ −136°.

In the % e.e. determination of (**2**) by n.m.r. spectroscopy,† the chiral shift reagent was effective only for the methyl group at the 5-position, and hence the % e.e. of the other two asymmetric carbons at the 2- and 3-positions could not be determined. Nevertheless, the C-2 and C-3 carbon atoms of the 100% e.e. (−)-(**2**) should also be completely optically pure, because the sample of (**2**) used for the resolution was uncontaminated by any diastereoisomer (confirmed by n.m.r. spectroscopy). In the epoxidation of 3,5-dimethylcyclohex-2-enone (**5**), by the same method used to obtain 3,5,5-trimethyl-2,3-epoxycyclohexanone (**3**),[3] oxygen probably attacks from the sterically less hindered direction to give one stereoisomer only (Scheme 1).

The other two 2,3-epoxycyclohexanones [(**3**), (**4**)] were also easily resolved. When a solution of (−)-(**1**) (6.0 g, 12.4 mmol) and (**3**) (7.64 g, 49.6 mmol) in 1 : 4 diethyl ether–light petroleum (20 ml) was kept at room temperature for 6 h, a complex of (−)-(**1**) and (+)-(**3**) (5.5 g, 56%) was obtained as colourless prisms. Two recrystallisations of the complex from 1 : 1 diethyl ether–light petroleum (50 ml each) gave the complex of 100% e.e. (+)-(**3**) (3.4 g, 35%), m.p. 134—136 °C, which upon Kugelrohr distillation *in vacuo* gave 100% e.e. (+)-(**3**)† (1.2 g, 31%), $[\alpha]_D$ +13.5°. When a solution of (−)-(**1**) (5.9 g, 12.2 mmol) and (**4**) (6.15 g, 48.8 mmol) in 1 : 4 diethyl ether–light petroleum (25 ml) was kept at room temperature for 6 h, a 1 : 1 complex of (−)-(**1**) and (+)-(**4**) (5.7 g, 63%) was obtained as colourless prisms. Two recrystallisations of the complex from 1 : 1 diethyl ether–light petroleum (50 ml each) gave the complex of 100% e.e. (+)-(**4**) (1.8 g, 20%), m.p. 72—73 °C which upon Kugelrohr distillation *in vacuo* gave 100% e.e. (+)-(**4**)† (0.55 g, 18%), $[\alpha]_D$ +58.3°.

This resolution method is not applicable to 2,3-epoxycyclohexanone and 2-methyl- and 4,4-dimethyl-2,3-epoxycyclohexanones.

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