Ring-opening Reactions of an Epoxycyclopentene

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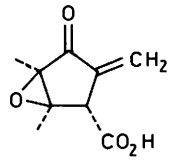
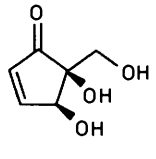
Under a range of conditions, the 5,5-dimethyl-1-methylsulphonyl-2-phenyl-3,4-epoxycyclopentene (**1**) ring-opens almost exclusively at the allylic terminus of the epoxide.

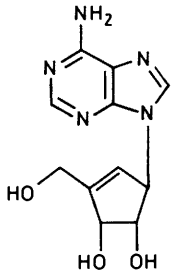
Highly functionalised cyclopentanoids[1] are of increasing interest because of their occurrence in a wide range of natural products, many of which are of biological or medicinal significance *e.g.* prostanoids, cyclopentanoid antibiotics like methylenomycin A[2] or pentenomycin I,[3] and cyclopentanoid nucleoside analogues, such as neplanocin A[4] and



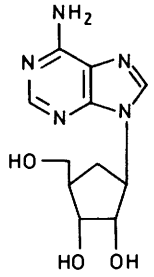
Methylenomycin A



Pentenomycin I



Neplanocin A

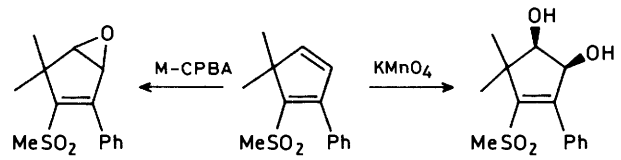


Aristeromycin

aristeromycin.[5] The synthetic challenge offered by these complex structures has resulted in a large number of publications devoted to stereocontrolled synthesis of cyclopentanoids in general.[6] Following the recent development of a new synthesis of 4-chlorocyclopentenes,[7] we were able to prepare a range of 5,5-disubstituted cyclopentadienes,[8] many of which bear a sulphur ligand at position 1. This paper reports the preparation of an epoxide derived from one of these dienes, and a study of its ring-opening reactions.

Epoxide ring-opening is important in organic synthesis, because the ring can be opened with a wide variety of reagents, and because, in favourable circumstances, ring-opening can be both regiospecific and stereospecific.[9] When the epoxide is derived from a 1,3-diene, this control is even more crucial, since the ring-opened product may have four adjacent functionalised carbons. The depth of study given to the ring-opening reactions of buta-1,3-diene monoepoxide, and of isoprene epoxide, is testimony to the importance attached to recognition and understanding of the factors influencing the mode of ring-opening.[9b]

Our chosen epoxide was 5,5-dimethyl-1-methylsulphonyl-2-phenyl-3,4-epoxycyclopentene (**1**), prepared in 96% yield from



(**1**) (**2**) (**3**)

the dienyl sulphone (**2**), using *m*-chloroperbenzoic acid. Selective epoxidation of the unsubstituted double bond of (**2**) was expected on account of the influence of the sulphone group on the other double bond. Thermolysis of (**1**) in refluxing xylene led cleanly to the sulphonyl enone (**10**), formed as a result of ring-opening at the allylic terminus of the epoxide, and then rearrangement to (**10**) in which the phenyl and enone entities are conjugated. The structure of (**10**) followed uniquely from its spectral data, notably the ^{1}H n.m.r., in which all the protons, including those of the diastereotopic gem-dimethyl groups (δ 1.35 and 1.60) and the non-conjugated methyl sulphone (δ 2.50), appeared as isolated singlets. This reaction is shown in Scheme 1, along with all the other reactions reported in this study of the ring-opening of (**1**). For convenience, the remaining reactions are discussed in two groups, according to the nature of the ring-opening conditions.

Ring-opening in Acidic Conditions.—Given the mode of thermal ring opening of (**1**), it was expected that acidic ring-opening would follow the same initial pathway. With sulphuric acid as catalyst, the product was a vicinal diol, (**9**), in which the conjugated methyl sulphone group (δ 2.52) was intact. The vicinal coupling constant (^3J 7.5 Hz) across the diol entity was compatible[10] with the *trans*-diol stereochemistry expected on chemical grounds, although this concurrence was not regarded as adequate proof of structure.

An alternative method of assigning relative configuration in cyclopentanoid rings relies on the *syn*-upfield rule developed by Anteunis,[11] and others.[12] The method depends upon the vicinal shielding effect of *cis* functional groups upon adjacent protons, but it is usually used with confidence when both isomers are available for analysis. It was therefore deemed wise to prepare the *cis*-cyclopentene-1,2-diol (**3**) by an unambiguous chemical route. This was achieved from the diene (**2**), using potassium permanganate, and (**3**) was found to have a vicinal coupling constant of 5.5 Hz. In the event, there were only very small differences in ^{1}H shift between the two diastereoisomers, and shielding effects were clearly not appropriate for stereochemical assignment. This situation is in marked contrast to cyclopentanol[10] and methylcyclopentenes,[13] in which the *syn*-upfield effect produces large Δδ values, which can be used with confidence in structure assignment.

Treatment of epoxide (**1**) with boron trifluoride–diethyl ether at room temperature yielded three products, one of which was the enone (**10**) described above. The other products were the dienal (**12**) and the hydroxy ether (**7**). Of these, the former may

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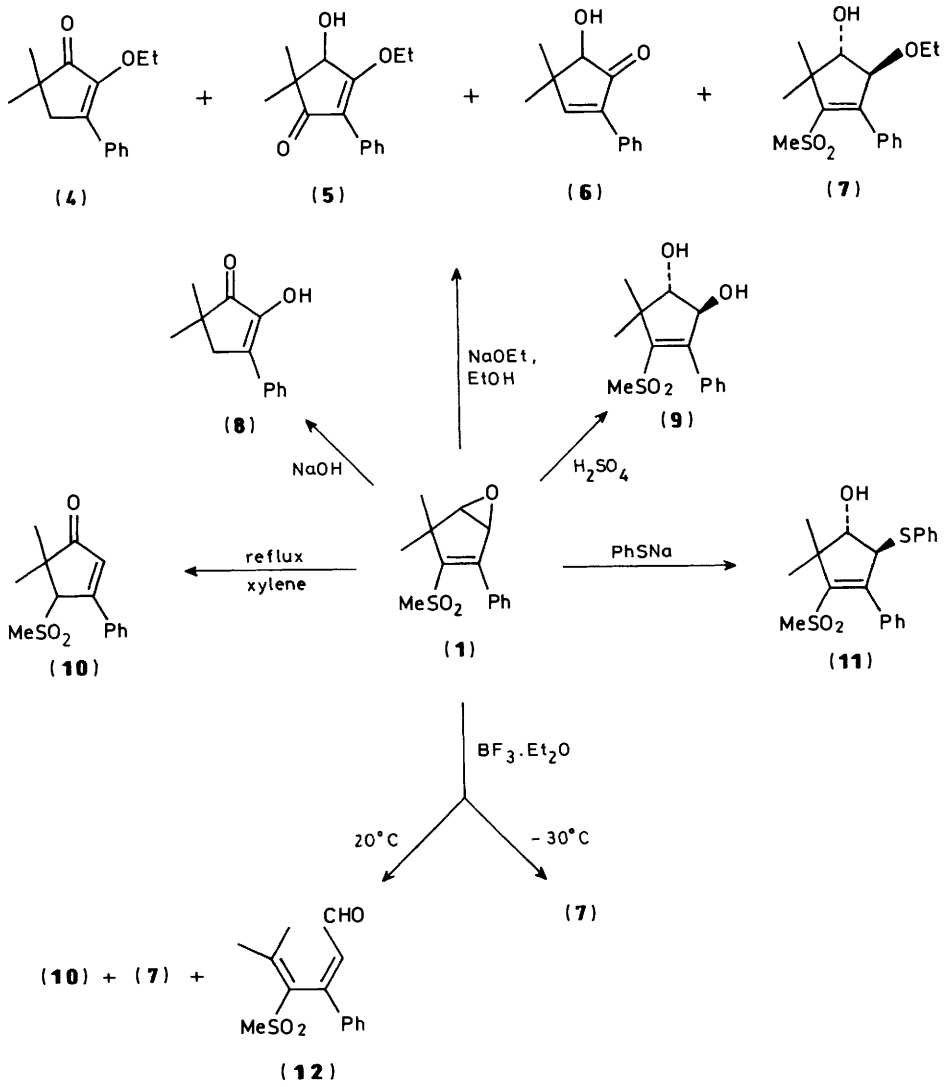
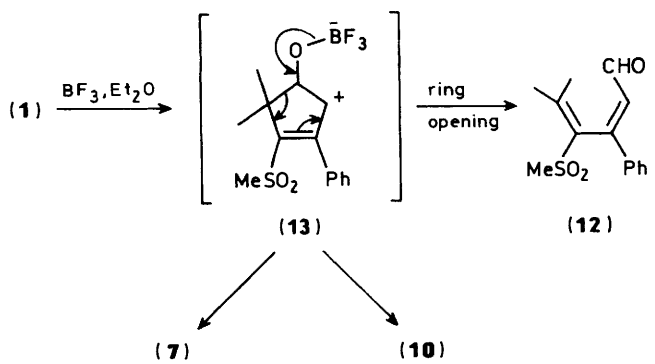


Scheme 1.

reasonably be deduced to have arisen *via* an intermediate, such as (13), produced directly from epoxide-opening. The formation of the ether (7) seems also to be explicable in terms of the same intermediate (13), although the apparent trapping by an ethoxy group was totally unexpected. Since each of the products (10), (12), and (7) could have been formed *via* (13), as indicated in Scheme 2, it seemed possible that a change in reaction conditions, notably temperature, could influence the partitioning from (13) into the products. When epoxide-opening was repeated at −30 °C, the hydroxy ether (7) was the only product, thereby removing any suspicion that (7) had been an artefact in the room temperature reaction. A survey of reviews on epoxide-opening by boron trifluoride–diethyl ether has not revealed other examples of this kind of reaction. Structure assignment for the ether (7) is discussed below—see ring-opening by ethoxide ion. The structure of the conjugated aldehyde (12) is clearly established on the basis of the i.r. (1 650 cm^{-1}) and n.m.r. (δ 6.7, d, *J* 8.0 and δ 9.8, d, *J* 8.0 Hz) data, which also indicate that the geminal methyls are now allylic.



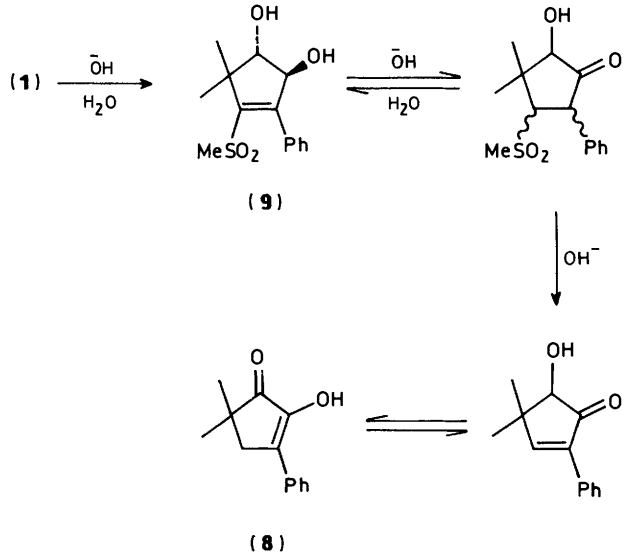
Scheme 2.

Nucleophilic Ring-opening.—Many nucleophiles attack 1,3-diene monoepoxides to give mixtures of 1,4- and 1,2-addition products.[9] The epoxide (1) is clearly not a typical structure, in that the gem-dimethyl group might inhibit attack at either of the flanking carbons [*i.e.* position 1 or 4 in (1)]. Moreover, the presence of the sulphonyl group is likely to influence the mode of ring-opening.

Reaction of the epoxide (1) with sodium benzenethiolate was studied as a prototype, and it was found to give only one product, isolated as a crystalline solid in 93% yield. From its spectral features, this product was clearly a β-hydroxy sulphide.

The key aspects were the OH stretch (3 500—3 400 cm^{-1}) and sulphone S=O bands (1 290 and 1 130 cm^{-1}) in the i.r. spectrum, and the n.m.r. evidence for a conjugated methyl sulphone (δ 2.50), two different phenyl groups, and a double doublet (δ 3.90 and 4.20) for the cyclopentene ring protons. Chemical considerations led us to expect a *trans*-hydroxy sulphide, and the vicinal coupling (^3J 7.0 Hz) was quite compatible with this assignment. The regiochemistry of the ring-opening follows from the small chemical-shift difference (Δδ 0.03 p.p.m.) between the vicinal protons of the PhS–C*H*–C*H*–OH entity. Of the two carbons in this sub-unit, one is allylic and hence one methine will be deshielded (*ca.* 0.8 p.p.m.) relative to other. However, the deshielding of methine protons by directly linked OH or SPh groups generally differs by *ca.* 1.0 p.p.m. This means that the protons of the PhS–CH–CH–OH entity, depending on adduct regiochemistry, will differ in chemical shift by either 1.8 or 0.2 p.p.m., approximately, if no other major shielding or deshielding influence is operating. These perceptions are confirmed by other observations[14] made on simpler cyclopentenes containing a Me_2C–CH(SPh)–CHOH sequence, and which show a Δδ of 1.7 ± 0.1 p.p.m. Clearly the present adduct must have structure (**11**) on this basis, and it is therefore formed by the same allylic-opening mode as observed under both thermal and acidic conditions.

By contrast, ring-opening of the epoxide (**1**) with sodium hydroxide was a sluggish reaction. The product (**8**) was readily identified by i.r. (OH stretch at 3 400—3 100; chelated C=O at 1 680 cm^{-1}) and n.m.r. (δ 1.23, equivalent Me groups; δ 2.7, s, CH_2). This reaction had obviously proceeded beyond a simple epoxide ring-opening, and this probably relates to the basicity of the medium. Previous experience has demonstrated the acidity of allylic protons at the 3-position in 1-sulphonylcyclopentenes [*e.g.* as in the preparation[8] of diene (**2**)], and this would offer a reasonable explanation for the desulphonylation of the initial ring-opened material. A possible sequence is presented in Scheme 3, although it should be stressed that the



Scheme 3.

details are speculative and not supported by direct experimental evidence.

When the epoxide (**1**) was refluxed in ethanol containing sodium ethoxide, four products were formed, as shown in Scheme 1. Two of these were readily identified as the ethyl enol ether (**4**), related to the hydroxy ketone (**8**), and the hydroxy ether (**7**) discussed above [see boron trifluoride opening of (**1**)]. Once again, this latter type of compound poses problems of structural assignment, both on stereo- and regio-chemical grounds. Given the fact that (**7**) is also formed from boron trifluoride–diethyl ether catalysed ring opening, and that sodium benzenethiolate ring opens (**1**) at the allylic centre, it is likely that the ethoxy group in (**7**) is placed at the allyic carbon [as it is in adduct (**11**)]. The presumed *trans* ring opening is again reasonable, given the vicinal coupling (^3J 6.0 Hz) observed in (**7**), and the close similarity of the n.m.r. data for (**7**) to that for the parent diol (**9**). The products (**4**) and (**7**) assumed less importance after it was discovered that, when increased amounts of sodium ethoxide were used in the ring-opening reaction, only (**5**) and (**6**) were produced from (**1**). In each case their structures were uniquely defined by their i.r. n.m.r. and mass spectra, as detailed in the Experimental section.

Conclusions.—Of the ring-opening reactions investigated in this study, four lead to single products, each of which is a highly substituted cyclopentene. Where mechanistic deductions can be made, they suggest that (**1**) ring-opens at the allylic epoxide terminus. This represents a sharp contrast to comparable reactions on simpler diene epoxides, which usually open *via* competing pathways. The presence of the gem-dimethyl group may be the factor which directs incoming nucleophiles to the 3-position in (**1**), although the experience of others[15] suggests caution over this interpretation. A further factor of possible relevance is the placement of the sulphonyl group.[16]

Given that the methylsulphonyl group represents a range of disguised functionality, the chemistry described here suggests ways in which this kind of epoxide opening may be applied in natural product synthesis and in the preparation of biologically active molecules.

Experimental

I.r. spectra were recorded on a Perkin-Elmer 157G I.R. spectrophotometer. ^1H N.m.r. spectra were recorded on Varian EM360A (60 MHz) spectrometer with tetramethylsilane as internal standard. Preparative t.l.c. plates were prepared in-house from Kieselgel G_{254} (Merck or Fluka), and were heated at 105 °C for 2—3 h prior to use. Ether refers to diethyl ether.

Preparation of the Epoxide (**1**).—5,5-Dimethyl-1-methylsulphonyl-2-phenylcyclopentadiene (**2**) (0.50 g, 2.0 mmol) was dissolved in dichloromethane (25 ml) at room temperature with stirring, and solid *m*-chloroperbenzoic acid (6.0 mmol) was added in small portions over 15 h. The reaction flask was wrapped in aluminium foil and the mixture was stirred for 3 days at room temperature. Saturated aqueous potassium iodide was added and the reaction mixture was extracted with chloroform (3 × 20 ml). The combined extracts were washed with aqueous sodium thiosulphate (2 × 10 ml) and water (2 × 10 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product. This, when recrystallised from ether–light petroleum (b.p. 40—60 °C) (1:1), afforded 4,4-dimethyl-3-methylsulphonyl-2-phenyl-6-oxabicyclo[3.1.0]hex-2-ene (**1**) (0.51 g, 96.2%) as a white solid, m.p. 129—132 °C; $\nu_{max.}$(solid film) 1 345, 1 290, and 1 120 cm^{-1} ($MeSO_2$); δ_H($CDCl_3$) 1.47 and 1.53 (6 H, 2 s, Me_2C), 2.52 (3 H, s, $MeSO_2$), 3.52 (1 H, d, *J* 3.0 Hz, CH), 3.87 (1 H, d, *J* 3.0 Hz, CH), and 7.42 (5 H, m, ArH) (Found: M^+, 264.0820. $C_{14}H_{16}O_3S$ requires *M*, 264.0820).

Ring-opening Reactions of the Epoxide (**1**) *under Various Conditions.*—(a) *Heat.* The epoxide (**1**) (0.10 g, 0.38 mmol) in dry xylene (10 ml) was refluxed for 7 days with exclusion of moisture. The xylene was removed under reduced pressure and the crude product purified by preparative t.l.c., with ether–light petroleum (b.p. 40—60 °C), (9:1) as eluant. Pure 5,5-dimethyl-4-methylsulphonyl-3-phenylcyclopent-2-enone (**10**) (0.07 g,

70%) was obtained as a white solid, m.p. 152—155 °C; $\nu_{max.}$(solid film) 1 695 cm^{-1} (conj. C=O); $\delta_H(CDCl_3)$ 1.35 and 1.60 (6 H, 2 s, Me_2C), 2.50 (3 H, s, $MeSO_2$), 4.5 (1 H, s, CH), 6.6 (1 H, s, HC=C), and 7.45 (5 H, s, ArH) (Found: M^+, 264.0823. $C_{14}H_{16}O_3S$ requires M, 264.0820).

(b) *Aqueous sulphuric acid.* The epoxide (**1**) (0.15 g, 0.57 mmol) in acetone–2.5% sulphuric acid (4:1 v/v; 10 ml) was refluxed for 2 days. The solvent was removed under reduced pressure and the residue added to water and extracted with ether (3 × 20 ml). The ether extracts were washed with water (10 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product. This was purified by preparative t.l.c. with ethyl acetate as eluant to afford *trans*-3,3-dimethyl-2-methylsulphonyl-1-phenylcyclopent-4-ene-1,2-diol (**9**), (0.08 g, 50% as a white solid, m.p. 145—148 °C; $\nu_{max.}$(solid film) 3 600—3 100br (OH), 1 290—1 270, and 1 120 cm^{-1} ($MeSO_2$); $\delta_H(CDCl_3)$ 1.30 and 1.50 (6 H, 2 s, Me_2C), 2.52 (3 H, s, $MeSO_2$), 2.73 (2 H, br s, OH), 3.70 (1 H, d, *J* 7.5 Hz, –C*H*OH), 4.67 (1 H, d, *J* 7.5 Hz, =C–C*H*–OH), and 7.27 (5 H, s, ArH) (Found: M^+, 282.0927. $C_{14}H_{18}O_4S$ requires M, 282.0926).

(c) *Boron trifluoride–diethyl ether.* The epoxide (**1**) (0.10 g, 0.38 mmol) was dissolved in dry ether (7 ml) under nitrogen. To the stirred solution, under nitrogen at room temperature, boron trifluoride–diethyl ether (0.5 ml) was added, *via* a syringe through the rubber septum. The mixture was then stirred for 4 h after which the reaction was carefully quenched with water and extracted with chloroform (3 × 20 ml). The combined extracts were washed with water (2 × 20 ml), dried ($MgSO_4$), and evaporated to afford a yellow solid which was purified by preparative t.l.c. with ether as eluant: three products (**10**), (**12**), and (**7**) were isolated in an approximate ratio of 3:2:1. 5-Methyl-4-methylsulphonyl-3-phenylhexa-2,4-dienal (**12**) was obtained as a syrup, $\nu_{max.}$(film) 1 650 cm^{-1} (conj. C=O aldehyde); $\delta_H(CDCl_3)$ 1.90 (6 H, s, Me_2C=), 2.8 (3 H, s, $MeSO_2$), 6.7 (1 H, d, *J* 8.0 Hz, =C*H*CHO), 7.4 (5 H, s, ArH), 9.8 (1 H, d, *J* 8.0 Hz, =CHC*H*O); and *trans*-2-ethoxy-5,5-dimethyl-4-methylsulphonyl-3-phenylcyclopent-3-enol (**7**), as a white solid, m.p. 137—139 °C; $\nu_{max.}$(solid film) 3 600—3 200br cm^{-1} (OH); $\delta_H(CDCl_3)$ 0.95 (3 H, t, *J* 7.0 Hz, OCH_2CH_3), 1.40 and 1.50 (6 H, 2 s, Me_2C), 2.0 (1 H, br s, OH), 2.53 (3 H, s, $MeSO_2$), 3.33 (2 H, m, OCH_2CH_3), 3.85 (1 H, d, *J* 6.0 Hz, C*H*OH), 4.40 (1 H, d, *J* 6.0 Hz, C*H*OEt), and 7.30 (5 H, s, ArH) (Found: M^+, 310.1237. $C_{16}H_{22}O_4S$ requires M, 310.1239). Product (**10**) was identical with that prepared earlier (*a*).

(d) *Sodium benzenethiolate.* Sodium hydride as a suspension in oil, was washed with dry ether (3 × 5 ml) and dried under nitrogen. To the dry sodium hydride (0.02 g, 0.42 mmol) dry tetrahydrofuran (THF) (5 ml) was added and the suspension was stirred under nitrogen at room temperature. Thiophenol (0.20 ml, 1.14 mmol) was then added to it and the mixture warmed to 40 °C; sodium benzenethiolate was precipitated as a white solid. A solution of the epoxide (**1**) (0.10 g, 0.38 mmol) in dry THF (0.5 ml) was added to the reaction mixture, which was then stirred under gentle reflux for 1 h. After dilution with cold water, the reaction mixture was extracted with ether (3 × 20 ml) and the combined extracts were washed with 10% aqueous sodium hydrogen carbonate (2 × 10 ml) and water (20 ml), dried ($MgSO_4$), and evaporated under reduced pressure to afford the crude product. This was purified by preparative t.l.c. using ether–light petroleum (b.p. 40—60 °C), (1:1), to give 2,2-dimethyl-3-methylsulphonyl-4-phenyl-5-phenylthiocyclopent-3-enol (**11**), (0.13 g, 92.8%) as a white solid, m.p. 135—136 °C; $\nu_{max.}$(solid film) 3 500—3 400 (OH), and 1 350, 1 290, and 1 130 cm^{-1} ($MeSO_2$); $\delta_H(CDCl_3)$ 1.40 and 1.53 (6 H, 2 s, Me_2C), 2.50 (4 H, s, with broad base, $MeSO_2$ and OH overlapped), 3.90 (1 H, d, *J* 7.0 Hz, CH), 4.20 (1 H, d, *J* 7.0 Hz, CH), 7.08 (5 H, s, ArH), and 7.23 (5 H, s, ArH) (Found: M^+, 374.1010. $C_{20}H_{22}O_3S_2$ requires M, 374.1010).

(e) *Sodium hydroxide.* The epoxide (**1**) (0.20 g, 0.76 mmol) was dissolved in a mixture of water and THF (1:1, v/v; 10 ml) with stirring at room temperature. Sodium hydroxide pellets (0.60 g, 15 mmol) were added and the reaction mixture was refluxed for 2 days with vigorous stirring. Solvent was removed under reduced pressure and the residue was added to saturated aqueous ammonium chloride solution and extracted with ether (3 × 20 ml). The ether extracts were combined, washed with water (2 × 10 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product. This was purified by preparative t.l.c. using ether–light petroleum (b.p. 40—60 °C) (1:1) as eluant to give pure 2-hydroxy-5,5-dimethyl-3-phenylcyclopent-2-enone (**8**) (0.11 g, 73.3%) as a white solid, m.p. 138—140 °C; $\nu_{max.}$(solid film) 3 400—3 100 (OH) and, 1 680 cm^{-1} (conj. C=O); $\delta_H(CDCl_3)$ 1.23 (6 H, s, Me_2C), 2.70 (2 H, s, CH_2), 6.50 (1 H, s, OH), 7.27 (3 H, m, ArH), and 7.80 (2 H, m, ArH) (Found: M^+, 202.0994. $C_{13}H_{14}O_2$ requires M, 202.0994.

(f) *Sodium ethoxide.* The epoxide (**1**) (0.20 g, 0.76 mmol), was added to a solution of sodium (0.60 g, 26.1 mmol) in dry ethanol (20 ml). The reaction mixture was refluxed for 2 days with exclusion of moisture, after which the reaction was quenched with cold water (50 ml). The mixture was then neutralised with dilute hydrochloric acid, and extracted with ether (3 × 20 ml). The combined extracts were washed with water (2 × 10 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give a crude product which was purified by preparative t.l.c. using ether–light petroleum (b.p. 40—60 °C) (10:3). Four products were isolated: (*a*) *trans*-2-ethoxy-5,5-dimethyl-4-methylsulphonyl-3-phenylcyclopent-3-enol (**7**); (*b*) 2-ethoxy-5,5-dimethyl-3-phenylcyclopent-2-enone (**4**) as an oil, $\nu_{max.}$ (film) 1 680 cm^{-1} (conj. C=O); $\delta_H(CDCl_3)$ 1.2—1.4 (9 H, m, 3 Me), 2.67 (2 H, s, CH_2), 4.4 (2 H, q, *J* 7.0 Hz, OCH_2CH_3), 7.30 (3 H, m, ArH), and 7.78 (2 H, m, ArH); (*c*) 3-ethoxy-4-hydroxy-5,5-dimethyl-2-phenylcyclopent-2-enone (**5**), as a white solid, m.p. 75—77 °C; $\nu_{max.}$(solid film) 3 500—3 100 (OH), 1 670 cm^{-1} (conj. C=O); $\delta_H(CDCl_3)$ 1.2—1.45 (9 H, m, 3 Me), 4.43 (2 H, m, OCH_2), 5.12 (1 H, s, C*H*OH), 7.35 (3 H, m, ArH), 7.92 (2 H, m, ArH) and 8.23 (1 H, s, OH) (Found: M^+, 246.1251. $C_{15}H_{18}O_3$ requires M, 246.1256; and (*d*) 5-hydroxy-4,4-dimethyl-2-phenylcyclopent-2-enone (**6**) as a thick oil; $\nu_{max.}$(film) 3 600—3 100 (OH) 1 710 and 1 695 cm^{-1} (conj. C=O); $\delta_H(CDCl_3)$ 1.17 and 1.38 (6 H, 2 s, Me_2C), 2.93 (1 H, br s, OH), 4.03 (1 H, s, C*H*OH), 7.27 (3 H, m, ArH), 7.53 (1 H, s, HC=C) and 7.67 (2 H, m, ArH) (Found: M^+, 202.0996. $C_{13}H_{14}O_2$ requires M, 202.0994).

Preparation of cis-3,3-*Dimethyl*-2-*methylsulphonyl*-1-*phenylcyclopent*-4-*ene*-1,2-*diol* (**3**).—This compound was prepared by *cis* oxidation of the diene (**2**), using potassium permanganate, as described by Wiberg *et al.*[17] The crude product was purified by preparative t.l.c. using ether–light petroleum (b.p. 40—60 °C) (1:1) as eluant to give the pure title compound (**3**), isolated (30% yield) as a solid, m.p. 132—135 °C; $\nu_{max.}$(solid film) 3 600—3 100 (OH) and 1 290 and 1 120 cm^{-1} ($MeSO_2$); $\delta_H(CDCl_3)$ 1.40 and 1.45 (6 H, 2 s, Me_2C) 2.52 (3 H, s, $MeSO_2$), 2.80 (2 H, br s, OH groups), 3.80 (1 H, d, *J* 5.5 Hz, C*H*OH), 4.70 (1 H, d, *J* 5.5 Hz, =C–C*H*OH), and 7.30 (5 H, s, ArH).

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