Synthesis of Substituted Indans as Prostacyclin Analogues

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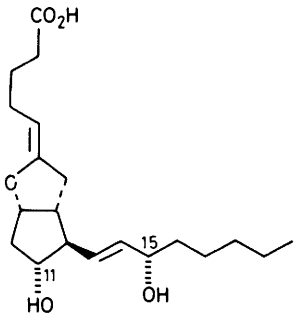
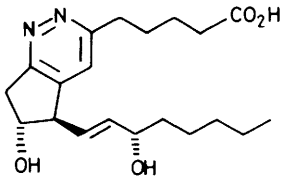
A route is described to the substituted indans (**8**) and (**10**), prepared as analogues of prostaglandin I_2 (prostacyclin). Two key steps in the synthesis involve the regiospecific attack of lithium salts from allylic sulphides onto indene oxides and, after oxidation to the corresponding sulphoxides, their reductive rearrangement to the required diols. Using model indene oxides, attempts have been made to direct the stereochemistry of the exocyclic hydroxy group by steric control during formation of the precursor sulphide.

Prostacyclin (**1**), discovered in 1976 by Vane and his collaborators,[1] has proven to be a clinically useful agent, particularly as an anti-platelet aggregating agent. The unstable nature of the natural product has spawned a number of attempts to prepare analogues with similar therapeutic properties but greater stability and accessibility. One of the earliest derivatives reported was the pyrazine (**2**), which is claimed to retain good anti-aggregating properties,[2] whilst one of the most recently reported derivatives is the furan analogue (**3**);[3] reviews on this subject are available.[4]



(1)



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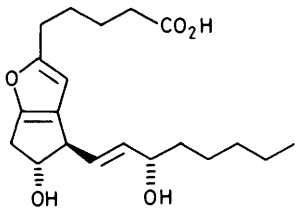
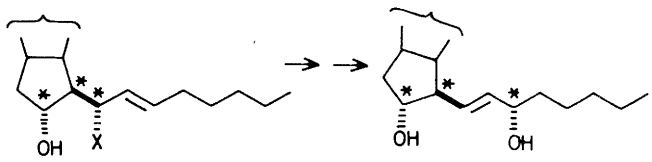


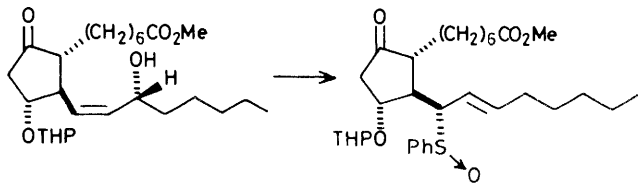
(3)

One of the key problems to be overcome in any synthetic approach to an analogue is control of the stereochemistry of the two alcohol groups, at positions C-11 and C-15 in prostacyclin, if these features are to be incorporated. Whilst several elegant solutions to this problem have been studied we wished to explore a different type of stereochemical control. One of the problems with introduction of the C-15 hydroxy group is its distance away from adjacent chiral centres. Our approach was to introduce a chiral control centre nearer to the other chiral centres, for example, nearer to the cyclopentane group, before transporting it to the more distant position in the side-chain (Scheme 1) by use of a [2,3]-sigmatropic rearrangement. That

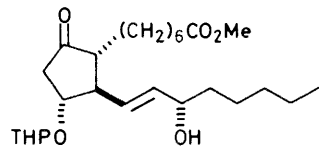


Scheme 1.

such chiral control during a sigmatropic rearrangement can occur has been illustrated by Stork,[5] who showed that the *cis*-alcohol (**4**) could be converted into the sulphoxide (**5**) by treatment with benzenesulphenyl chloride, followed by its reductive rearrangement to the isomeric *trans*-alcohol (**6**). More recently Hoffmann has made a detailed study on the stereochemical details of such [2,3]-sigmatropic rearrangements.[6]



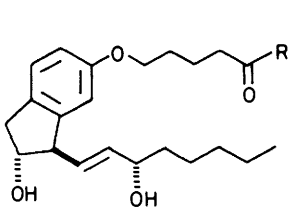
(4) (5)



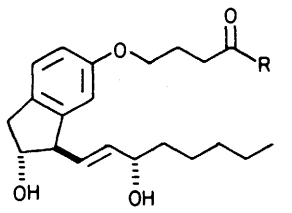
(6)

In this work the target prostacyclin analogues were the indan derivatives (**7**) and (**9**), chosen since molecular models suggested a similar spatial orientation between the carboxy and hydroxy groups when compared to that in compounds (**1**) and (**2**); the presence of the phenyl ether mimics the vinylic ether function in the natural product.

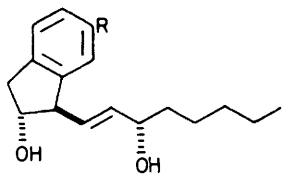
The current approach envisaged an initial study on the model indans (**11**) and (**12**) and the first problem was to examine the reaction of indene oxide (**13**) with the anion from allyl phenyl sulphide (**17**). Routes to optically active indene oxides have been reported,[7] thus opening possibilities for enantioselective synthesis. The alkylation of allyl phenyl sulphide (**17**) has been



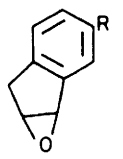
(7) R = OH
(8) R = N



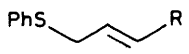
(9) R = OH
(10) R = N



(11) R = H
(12) R = OMe

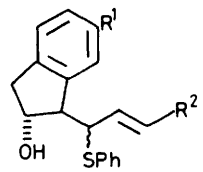


(13) R = H
(14) R = OMe
(15) R = $O(CH_2)_4CO_2Me$
(16) R = $O(CH_2)_3CO_2Me$

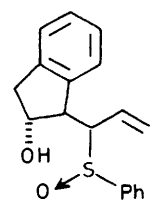


(17) R = H
(18) R = C_5H_{11}

studied and is known to give mainly α-alkylation,[8] γ-substituted allyl sulphides show an even higher regioselectivity for α-*versus* γ-alkylation.[9] The lithium salt of the sulphide (**17**) reacted with indene oxide (**13**)* at −70 to −50 °C to afford, as the major product (81%) a mixture of the diastereoisomers (**20**). The chemical shifts of the protons on the indene portion of the product indicated regioselective opening of the oxide at position 1, rather than at position 2, a result consistent with the known behaviour of indene oxide and related systems towards nucleophilic attack.[10] Recently similar studies on cyclopentadiene monoepoxide have been published.[11] The ratio of diastereoisomers was approximately 1:1 indicating no discrimination between the two possible transition studies of the types (**19a**) and (**19b**) (Scheme 2). Oxidation of the mixture of diastereoisomers (**20**) with sodium metaperiodate afforded four sulphoxides (**23**) which were not separated but treated with sodium benzenethiolate in methanol at 70 °C to give the diol (**24**), isolated in 40% yield. The diol (**24**) was also produced, in higher yield (76%), from the sulphoxides generated by attack of allyl 4-methoxyphenyl sulphide (**25**) on indene oxide and oxidation with sodium metaperiodate. The [2,3]-rearrangements of the sulphoxides, in both cases, proceeded with stereoselective migration of the double bond since formation of *cis*-olefin was not detected.



(20) $R^1 = R^2 = H$
(21) $R^1 = H$, $R^2 = C_5H_{11}$
(22) $R^1 = OMe$, $R^2 = C_5H_{11}$



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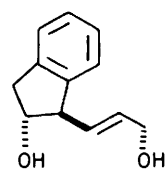

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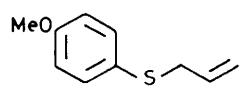
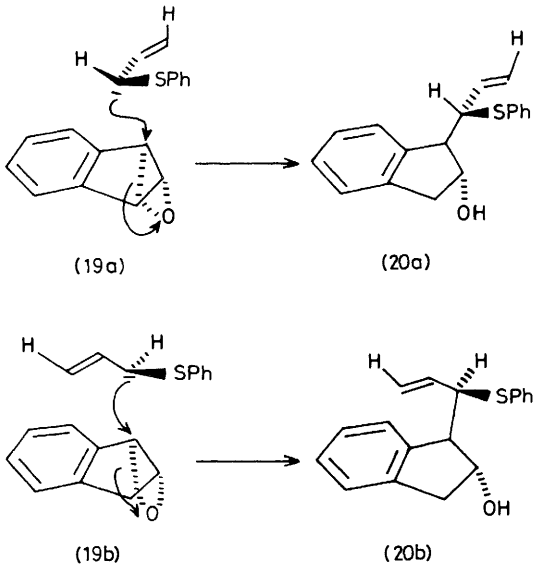


(25)

An attempt to produce the sulphoxides (**23**) directly from the indene oxide (**13**) and the corresponding sulphoxide of the sulphide (**17**) failed; no reaction occurred at low temperatures, whilst at higher temperatures complex mixtures formed. In the presence of sodium benzenethiolate, only traces of the required diol (24) could be observed and no further alkylations of sulphoxides with epoxides were attempted in the present work.

In order to introduce the appropriate octenol side-chain needed for the targets, phenyl oct-2-enyl sulphide (**18**) was prepared (see Experimental section) and its lithium salt allowed to react with indene oxide (**13**). Again a mixture of two diastereoisomers was formed and this was immediately oxidized to the corresponding sulphoxides, followed by [2,3]-sigmatropic rearrangement, either in the presence of sodium benzenethiolate or trimethyl phosphite, to produce a mixture of two diols; the more polar substance was assigned as the (1*RS*),(3′*SR*)-isomer (**11**) and the less polar compound as the (1*RS*),(3′*RS*)-isomer (**26**). These tentative assignments were made on the basis of the known chromatographic behaviour of the prostaglandin C-15 epimers.[12] Both reaction conditions gave approximately 1:1 ratios of the diols.

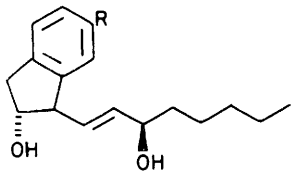
Before attempting preparation of the targets the influence of an oxygen ether function on the indene group was studied, using the methoxy derivative (**14**). During the preparation of the indene (**31**), by treatment of the corresponding alcohol (**30**) with



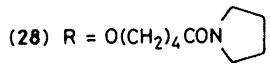
(19a) (20a)
(19b) (20b)

Scheme 2.

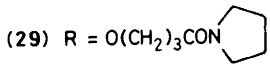
* All materials were prepared as racemates; for convenience only one enantiomer is depicted in the drawings.



(26) R = H
(27) R = OMe

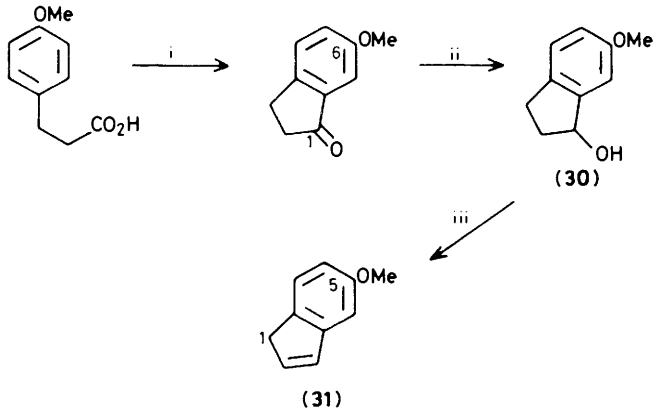


(28) R = $O(CH_2)_4CON$



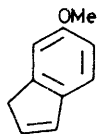
(29) R = $O(CH_2)_3CON$

acid, care had to be taken to avoid double bond isomerisation. The best route (Scheme 3) involved the acid-catalysed dehydration using toluene-*p*-sulphonic acid in benzene. 5-Methoxyindene (**31**) showed $\lambda_{max.}$ 252 nm, whereas the 6-isomer (**32**) showed $\lambda_{max.}$ 270 nm, consistent with the greater delocalisation of electrons possible in the latter substance.[13]



Scheme 3. *Reagents:* i, $SOCl_2$ then $AlCl_3/CH_2Cl_2$; ii, $NaBH_4$, CH_3OH; iii, TsOH, benzene

Bromohydrin formation from the indene (**31**), followed by base-catalysed epoxide formation, produced the indene oxide (**14**). The latter epoxide was more labile than the unsubstituted epoxide, for example, silica gel or neutral alumina chromatography catalysed its rearrangement to 5-methoxyindan-2-one (**33**). As a result of this instability the epoxide was utilised in further reactions without purification.



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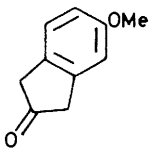
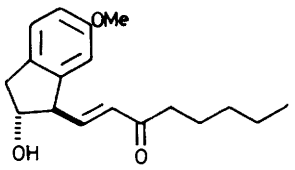


(33)

Attack of the lithium salt of 1-phenylthio-oct-2-ene (**18**) produced a mixture of the two diastereoisomeric sulphides (**22**) in good yield. Treatment of the corresponding sulphoxides from (**22**) with trimethyl phosphite produced the diols (**12**) and (**27**) in 42 and 34% yield respectively; again the relative stereochemical assignments were made on the basis of the polarity of the products, compound (**12**) being more polar than compound (**27**). Oxidation of either of the diols with manganese dioxide gave the corresponding αβ-unsaturated ketone (**34**), thus confirming the regiospecific attachment of the sulphide carbanion at C-1 rather than at C-2 of the epoxide.

Preparation of the targets (**7**) and (**9**) commenced with 6-hydroxyindan-1-one, itself obtained by demethylation of the methoxy derivative (Scheme 3) with aluminium bromide in refluxing benzene. Alkylation of the phenol (**35**) with either



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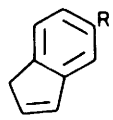
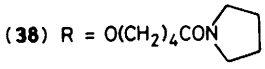
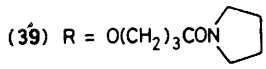


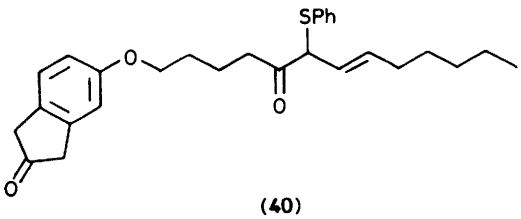
(35) R = OH
(36) R = $O(CH_2)_4CO_2Me$
(37) R = $O(CH_2)_3CO_2Me$



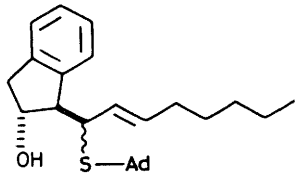
(38) R = $O(CH_2)_4CON$



(39) R = $O(CH_2)_3CON$



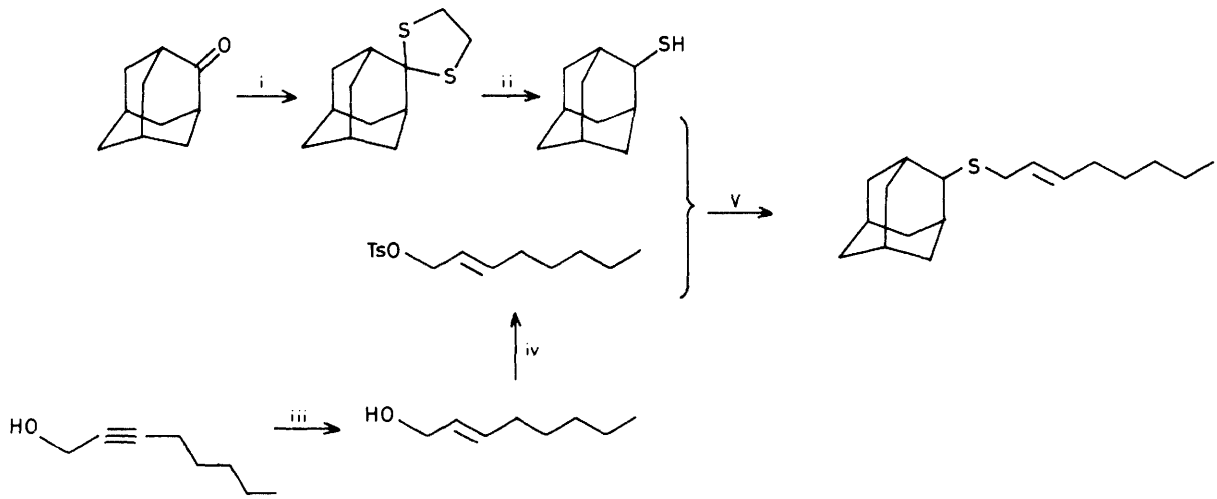
(40)



(42)

methyl 5-bromovalerate or ethyl 4-bromobutyrate, using sodium methoxide in methanol as base gave the methyl esters (**36**) and (**37**) respectively. Although these esters could be hydrolysed to the corresponding acids and then be oxidized to the corresponding bromohydrins, attempted cyclisation to the desired epoxides failed since the product epoxides were unstable to isolation; attempted *in situ* formation of the epoxides led only to precipitation of the acid salts. Direct use of the ester (**36**), as its epoxide (**15**) was also ruled out by the preferred condensation of the ester group with the lithium salt of the sulphide (**18**), yielding side products such as the ketone (**40**). For these reasons the esters (**36**) and (**37**) were converted into their corresponding pyrrolidides (**38**) and (**39**) before continuing. The amides were successfully converted into the desired adducts using the general sequence described above. Thus the valeramide (**38**) was converted, *via* the sulphides and the corresponding sulphoxides, into a mixture of the two diols (**8**) and (**28**), whilst the butyramide (**39**) gave the diols (**10**) and (**29**) respectively. In both series an approximately 1:1 ratio of the epimeric diols was produced.

The lack of chiral discrimination of the epoxides during reaction with the sulphides [see Scheme 2, (**19a**) and (**19b**)] was disappointing. Nevertheless, one attempt was made to test whether steric effects could impart some enantioselectivity into the transition states leading to the adduct sulphides [see Scheme 2, (**20a**) and (**20b**)]. As described above, if this were possible one could expect to control, after subsequent [2,3]-rearrangement, the stereochemistry of the final diols. Models showed that the products (**20a**) should be preferred to those, (**20b**), if the sulphide substituent is very large. To test this idea 2-adamantylthio-oct-2-ene (**41**) was prepared (Scheme 4) for use in place of the phenyl sulphide (**18**). Reaction of the sulphide (**41**) with the indene oxide (**13**) proceeded very slowly to



Scheme 4. *Reagents:* i, $HSCH_2CH_2SH$, TsOH, benzene; ii, 3–4 equiv. Bu^nLi, Et_2O; iii, $LiAlH_4$, reflux THF; iv, TsCl, pyridine; v, NaOEt, EtOH

produce the α-alkylated sulphide (**42**), together with other products, including some of the γ-alkylated product. The α-alkylated products (**42**), however, consisted of an unequal mixture of diastereoisomers. Assuming no equilibration of the isomers under the reaction conditions this observation must reflect the expected steric discrimination between the two types of transition states [(**19a**) and (**19b**), Scheme 2]. Subsequent oxidation of the sulphide mixture (**42**) to the corresponding sulphoxides and reductive rearrangement produced the diols (**11**) and (**26**), with the former isomer predominating by a ratio of 3:1. This result suggests a preference for transition state (**19a**) over (**19b**), as predicted assuming the steric size of the sulphide substituents increases in the series H < alkenyl < sulphide when steric repulsions are minimised in the transition state (**19a**) relative to (**19b**). More work will be required to show whether or not this observation can be exploited.

The possibility of influencing the diastereoisomeric ratio of the sulphide isomers, *e.g.* (**20a**) and (**20b**), by base-catalysed equilibration, were thwarted by competing isomerisation of the allylic double bond to form vinylic sulphides.

Experimental

Solvents were dried and distilled before use. Light petroleum refers to the fraction of boiling range 60—80 °C; brine refers to a saturated aqueous solution of sodium chloride. Di-isopropylamine was distilled from calcium hydride and stored over molecular sieves. n-Butyl-lithium in hexane was obtained from Aldrich Chemical Co. and standardised according to the method of Kofron.[14]

M.p.s were determined with a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 297 spectrophotometer as films for liquid or in $CHCl_3$ solution for solids; u.v. spectra were taken in ethanol solutions on a Unicam SP 800A spectrophotometer. ^1H N.m.r. spectra were obtained for solutions in [^2H]chloroform with tetramethylsilane as internal reference, using either a Perkin-Elmer R32 or a Jeol FX90Q spectrometer (90 MHz), whilst mass specta were recorded on either a Kratos /AEI MS902/50 or a Kratos MS25 instrument.

Thin-layer chromatography (t.l.c.) was carried out on 0.25 mm Merck pre-coated silica plates ($GF60_{254}$) or, where indicated, on neutral alumina plates. Preparative layer chromatography (p.l.c.) was carried out on 2 mm Merck pre-coated silica plates. Column chromatography was carried out on Merck silica plates (G60), generally using elution under medium pressure. Solvent mixtures refer to volumes before mixing. Reactions were generally carried out under a dry, oxygen-free nitrogen atmosphere.

(1RS),(2RS)-1-(1-*Phenylthioprop*-2-*enyl*)*indan*-2-*ol* (**20**).—To n-butyl-lithium (1.5M in hexane, 7.7 ml, 11.5 mmol) in tetrahydrofuran (20 ml) at 0 °C was added di-isopropylamine (1.17 g, 11.6 mmol); the solution was stirred for 20 min before the temperature was lowered to −64 °C and the sulphide[15] (**17**) (1.58 g. 10.5 mmol) in tetrahydrofuran (3 ml) added. The mixture was stirred for 30 min before a solution of indene oxide (**13**) (1.67 g, 12.6 mmol) in tetrahydrofuran (4 ml) at −74 °C was added slowly. After a further 3 h at −50 to −70 °C the reaction was quenched with aqueous ammonium chloride and extracted with ether. The organic extracts were washed with brine, dried over anhydrous sodium sulphate, and the solvent removed under reduced pressure to give the crude products. Chromatography through silica (65 g), using ether–hexane (3:7) as eluant, afforded a mixture of the diastereoisomers (**20**) as a viscous oil (2.39 g, 81%); the mixture showed $\nu_{max.}$ 3 550—3 150, 3 070, 1 635w, 1 585, 1 480, 1 440, 920, 745, and 690 cm^{-1}; δ 2.15 (1 H, br s, OH), 2.85 (1 H), 3.2—3.45 (2 H), 3.90 (1 H, C*H*SPh), 4.5—4.6 (1 H, C*H*OH), 4.8—5.0 (2 H, CH_2=CH), 5.6—5.9 (1 H, C*H*=CH_2), and 7.1—7.4 (9 H, m, ArH); *m/z* 282 (M^+, 9), 264 (5), 173 (5), 172 (12), 155 (8), 149 (100), 133 (22), 128 (43), 115 (62), 109 (22), 91 (27), and 77 (36) (Found: M^+, 282.107 74. $C_{18}H_{18}OS$ requires M^+, 282.107 83).

(1RS),(2RS)-1-[(1E)-3-*Hydroxypropenyl*]*indan*-2-*ol* (**24**).—The sulphide (**20**) (1.49 g, 5.3 mmol) in methanol (50 ml) was oxidized with a solution of sodium metaperiodiate (0.5M; 10.6 ml) at 0 °C for 2 h and then at room temperature for 48 h. The mixture was filtered, the residue washed with methanol, and the filtrates concentrated under reduced pressure before extraction with dichloromethane. The extract was washed with brine, dried, and rapidly chromatographed through silica, using ethyl acetate–light petroleum (1:3) as eluant, to give a mixture of the sulphoxides (1.11 g, 71%) and recovered sulphides (0.19 g, 13%).

The sulphoxide mixture (0.56 g, 1.87 mmol) in methanol (7 ml) was added to a solution of benzenethiol (1.42 g, 13.0 mmol) in methanol (40 ml), to which had previously been added sodium (69 mg, 3.0 mg-atom). The reaction mixture was heated, under nitrogen, at reflux point for 3.5 h, before removal of the solvent, under reduced pressure and addition of dichloromethane; the mixture was then washed with 2M-NaOH and brine, dried, and the products isolated. P.l.c. using ethyl acetate–dichloromethane (3:7) as eluant, gave the *title diol* (0.143 g, 40%), m.p. (ethyl acetate–hexane) 73—74 °C; $\nu_{max.}$ 3 500—3 100, 1 675w, 1 605, 1 080, 975, and 745 cm^{-1}; δ 2.59 (2 H, br s, exchangeable with D_2O, 2 × OH), 2.88 (1 H, q, *J* 7, 16 Hz, ArCH_2), 3.23 (1 H, q, *J* 6, 16 Hz, ArCH_2), 3.60 (1 H, dd, *J* 9.4, 7.0 Hz, ArC*H*), 4.17 (2 H, d, *J* 4.8 Hz, CH_2OH), 4.12—4.41 (1 H, m, C*H*OH), 5.6—5.9 (2 H, m, CH=CH), and 7.05—7.25 (4 H, m, ArH); *m/z* 172 (M^+ − H_2O) (63), 154 (15), 141 (27), 129 (100), 116 (45), 115 (42), 91 (26), and 77 (8) (Found: C, 75.7; H, 6.45. $C_{12}H_{14}O_2$ requires C, 75.8; H, 7.4%).

3-(4-*Methoxyphenylthio*)*prop*-1-*ene* (**25**).—4-Methoxybenzenethiol (11.2 g, 80 mmol) in ethanol (75 ml) containing dissolved sodium (1.86 g, 80 mg-atom) was treated with allyl bromide (10 g, 83 mmol) at room temperature overnight, before the mixture was poured into water and extracted with light petroleum. The organic layer was washed with brine, dried, and the crude sulphide isolated *in vacuo*. Distillation of the residual material gave the title sulphide (12.9 g, 90%), as a colourless oil, b.p. 82—83 °C/0.3 mmHg (lit.,[16] 94—95 °C/0.8 mmHg); $\nu_{max.}$ 2 840, 1 630, 1 595, 1 495, 1 285, 1 245, 1 030, 920, and 825 cm^{-1}; δ 3.40 (2 H, d, *J* 7 Hz, CH_2CH=CH_2), 3.72 (3 H, s, OCH_3), 4.86—5.01 (2 H, m, CH_2=CH), 5.63—6.0 (1 H, m, C*H*=CH_2), 6.8 (2 H, d, *J* 9 Hz, ArH), and 7.31 (2 H, d, *J* 9 Hz, ArH) (Found: C, 66.65; H, 6.8; S, 17.65. Calc. for $C_{10}H_{12}OS$: C, 66.6; H, 6.7; S, 17.8%).

Preparation of the Diol (**24**) *from the Sulphide* (**25**).—The sulphide (2.0 g, 11.2 mmol) was treated with lithium di-isopropylamide (11.7 mmol; *ex.* n-butyl-lithium and di-isopropylamine) in tetrahydrofuran (25 ml) at −75 °C for 15 min before the addition of a solution of indene oxide (1.45 g, 11.0 mmol) in tetrahydrofuran (3 ml). The reaction mixture was stirred at −70 °C for 3.5 h, quenched at −30 °C with saturated aqueous ammonium chloride, and extracted with ether. The organic extracts were washed with brine, dried, filtered, and the solvent removed under reduced pressure before purification of the product by chromatography through silica (230 g). Elution with ethyl acetate–light petroleum (1:6) afforded recovered sulphide (**25**) (0.22 g, 11%) followed by a diastereoisomeric mixture of (1*RS*),(2*RS*)-1-1-(4-methoxyphenylthioprop-2-enyl)indan-2-ol (2.9 g, 85%). This material, which was used directly in the next step, showed $\nu_{max.}$ 3 550—3 200, 1 585, 1 485, 1 280, 1 245, 1 030, 915, 825, and 745 cm^{-1}; *m/z* 312 (M^+, 57), 291 (1), 179 (100), 127 (7), 155 (8), 140 (97), 139 (24), 115 (23), 91 (24), and 77 (12) (Found: M^+, 312.118 15. $C_{19}H_{20}O_2S$ requires M^+, 312.118 39).

The sulphide mixture (2.15 g, 6.9 mmol) in dichloromethane (65 ml) was oxidized with *m*-chloroperbenzoic acid (1.54 g, 7.6 mmol) at −55 °C before being warmed to −10 °C over a period of 1.5 h; the mixture was then washed with 2M-aqueous sodium carbonate and brine, dried, filtered, and the solvent removed under reduced pressure to produce the sulphoxides (2.17 g, 100%), as a colourless foam. The mixture of sulphoxides (2.14 g, 6.52 mmol) was dissolved in methanol (25 ml) and trimethyl phosphite (1.54 ml, 13 mmol) was added before the solution was stirred at room temperature, under nitrogen for 4.5 h. The solvent was removed under reduced pressure, ethyl acetate was added, and the extract washed with 2M-aqueous sodium carbonate and brine and then dried and filtered. Removal of the solvent afforded the crude diol (**24**), which was purified by chromatography through silica, with ethyl acetate–dichloromethane (2:3) as eluant, to give crystalline material (0.94 g, 76%), m.p. 73—74 °C, identical in t.l.c. behaviour and spectral properties with the material described above.

(2E)-1-*Phenylthio-oct*-2-*ene* (**18**).—To a solution of oct-1-en-3-ol (2.37 g, 18.5 mmol) in tetrahydrofuran (100 ml) at −60 °C was added n-butyl-lithium (1.55M; 12 ml, 18.6 mmol) followed, after 15 min, by the dropwise addition over 10 min of a solution of freshly prepared benzenesulphenyl chloride (2.06 g, 14.3 mmol) in tetrahydrofuran (10 ml). The intense colour of the sulphenyl chloride was discharged immediately upon addition. After a further 1.5 h at −50 °C the solution was warmed to ambient temperature over 1 h and quenched with saturated aqueous ammonium chloride. The product was extracted with ether, and the extract washed with brine, before chromatography through silica (85 g) using ether–hexane (1:9) as eluant. The column initially afforded starting alcohol (0.65 g, 27%) followed by the sulphoxide (2.3 g, 68%) as a pale yellow oil, $\nu_{max.}$ 2 930, 1 445, 1 085, 1 045, 970, 745, and 690 cm^{-1}; δ 0.8—1.4 (9 H, m, aliphatic H), 1.8—2.1 (2 H, m, CH_2CH=CH), 3.49 (2 H, d, *J* 6.4 Hz, SO·CH_2), 5.1—5.75 (2 H, m, CH=CH), and 7.35—7.65 (5 H, m, ArH); *m/z* 236 (M^+, 1), 220 (4), 218 (2), 126 (100), 111 (36), 110 (14), 78 (27), 77 (18), and 55 (46) (Found: M^+, 236.123 04. $C_{14}H_{20}OS$ requires *M*, 236.123 48). This material was contaminated with a small quantity of the (*Z*)-isomer, as shown by the appearance of a small signal at δ 3.61 (d, *J* 8 Hz, SOCH_2) in its ^1H n.m.r. spectrum; the estimated presence of this was 8 ± 2%.

The sulphoxides (20 g, 82 mmol) in dimethylformamide (100 ml) at 0 °C were treated, dropwise, with phosphorus tribromide (229 g, 84.6 mmol), the mixture stirred for 10 min at 0 °C, poured into ice–water, and extracted with light petroleum. After being washed with water, the extract was dried, the solvents removed under reduced pressure and the residue distilled, boiling range 132—136 °C/11 mmHg, to yield the *title sulphide* (11.2 g, 61%) as a colourless oil, $\nu_{max.}$ 2 960, 2 930, 1 585, 1 480, 1 440, 965, 740, and 690 cm^{-1}; δ 0.75—1.40 (9 H, m, aliphatic H), 1.82—2.10 (2 H, m, CH_2CH=CH), 3.40—3.61 (2 H, m, SCH_2), 5.25—5.75 (2 H, m, CH=CH), and 7.10—7.41 (5 H, m, ArH); *m/z* 220 (M^+, 23), 149 (2), 110 (100), 109 (27), and 77 (6) (Found: C, 76.6; H, 9.25; S, 14.5. $C_{14}H_{20}O$ requires C, 76.3; H, 9.15; S, 14.55%).

(1RS),(2RS)-(2E)-1-[1-*Phenylthio-oct*-2-*enyl*]*indan*-2-*ol* (**21**).—The sulphide (**18**) (2.42 g, 11 mmol) was added dropwise to a solution of lithium di-isopropylamide (11.5 mmol, freshly prepared from n-butyl-lithium and di-isopropylamine) in tetrahydrofuran (25 ml) at −75 °C. Stirring was continued for a further 15 min after addition of the sulphide before the addition of indene oxide (**18**) (1.67 g, 12.6 mmol) in tetrahydrofuran (3 ml). The reaction mixture was stirred for 3.5 h at −70 to −60 °C before warming to −30 °C and quenching by addition of saturated aqueous ammonium chloride and extraction with ether. The extract was washed with brine, dried, the solvent removed under reduced pressure, and the residue chromatographed through silica (100 g), with ethyl acetate–light petroleum (1:19) as eluant to afford the recovered sulphide (**18**)

(0.94 g, 39%), recovered epoxide (0.60 g, 36%), and the product alcohols (1.35 g, 35%; 55% after allowing for recovery of starting epoxide), as a mixture of two diastereoisomers, $\nu_{max.}$ 3 200—3 550, 2 925, 1 585, 1 480, 1 440, 965, 745, and 690 cm^{-1}; δ 0.71—1.32 (9 H, m, aliphatic H), 1.60—1.90 (2 H, m, CH_2CH=CH), 2.36 (1 H, br s, exchanged by D_2O, HO), 2.84 (1 H, q, *J* 5, 16 Hz, $ArCH_2$), 3.10—3.41 (2 H, m, ArC*H* and one $ArCH_2$), 3.90—4.10 (1 H, m, C*H*SPh), 4.45—4.72 (1 H, m, C*H*OH), 5.17—5.42 (2 H, m, CH=CH), and 7.10—7.45 (9 H, m, ArH; *m/z* 352 (M^+, 7), 334 (3), 243 (14), 242 (41), 225 (12), 219 (81), 218 (100), 133 (36), 129 (30), 116 (32), 115 (33), 110 (58), 109 (88), 77 (28), and 69 (32) (Found: M^+, 352.186 04. $C_{23}H_{28}OS$ requires M^+, 352.186 08).

(1RS),(2RS)-1-[(1E),(3SR)-*Hydroxyoct*-1-*enyl*]*indan*-2-*ol* (**11**).—The sulphide mixture (**21**) (0.41 g, 1.16 mmol) in dichloromethane (25 ml) at −20 °C was oxidized with *m*-chloroperbenzoic acid (0.24 g, 1.16 mmol), the temperature being allowed to rise to ambient over 1 h. The reaction was quenched with 2M-aqueous sodium carbonate, before the organic layer was washed with brine, dried, and the solvent removed under reduced pressure. The mixture of sulphoxides (0.42 g, 1.1 mmol) was dissolved in methanol (7 ml) and added to a solution of benzenethiol (0.92 g, 8.3 mmol) in methanol (30 ml) to which had been added sodium (41 mg, 1.8 mmol). The mixture was heated to 70 °C under nitrogen for 2 h before concentration under reduced pressure. The residue was taken up in ethyl acetate, washed with 2.5M-sodium hydroxide (2 × 7 ml) and brine before being dried, filtered, and the solvent removed under reduced pressure. The residue was separated by p.l.c. using ethyl acetate–dichloromethane (1:2) as eluant. The more polar isomer (R_F 0.24, ethyl acetate–dichloromethane, 2:3) was the *title diol* (75 mg, 26%), m.p. (ethyl acetate–hexane) 97—99 °C, $\nu_{max.}$ 3 450—3 150, 1 065, 975, and 745 cm^{-1}; δ 0.8—1.0 (3 H, m, CH_3), 1.20—1.65 [8 H, m, $(CH_2)_4$], 2.87 (1 H, q, *J* 9, 15.2 Hz, $ArCH_2$), 3.16 (1 H, q, *J* 7, 15.2 Hz, $ArCH_2$), 3.55 (1 H, t, *J* 7 Hz, ArCH), 3.90 (2 H, br s, exchanged by D_2O, 2 × OH), 4.0—4.35 (2 H, m, 2 × C*H*OH), 5.42—5.81 (2 H, m, C*H*=C*H*), and 7.0—7.15 (4 H, m, ArH); *m/z* 260 (M^+, weak), 242 (57), 171 (23), 153 (21), 146 (36), 145 (60), 143 (70), 142 (77), 129 (99), 128 (88), 117 (35), and 116 (100) (Found: C, 78.3; H, 9.2. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.3%).

The less polar isomer (R_F 0.43, ethyl acetate–dichloromethane, 2:3) was identified as (1RS),(2RS)-1-[(1E),(33RS)-*hydroxyoct*-1-*enyl*]*indan*-2-*ol* (**26**) (50 mg, 17%), m.p. 84—86 °C; $\nu_{max.}$ 3 150—3 500, 1 065, 975, and 745 cm^{-1}; δ 0.8—1.0 (3 H, m, CH_3), 1.20—1.65 [8 H, m, $(CH_2)_4$], 2.48 (2 H, br s, exchanged by D_2O, 2 × OH), 2.87 (1 H, q, *J* 7, 16 Hz, $ArCH_2$), 3.18 (1 H, q, *J* 7, 15 Hz, $ArCH_3$), 3.50—3.70 (1 H, m, ArC*H*), 4.05—4.40 (2 H, m, 2 × C*H*OH), 5.55—5.85 (2 H, m, CH=CH), and 7.05—7.22 (4 H, m, ArH); *m/z* 260 (M^+, weak), 242 (62), 171 (21), 145 (56), 143 (66), 142 (85), 133 (68), 116 (84), 91 (40), and 77 (14) (Found: C, 78.3; H, 9.1. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.3%).

Repetition of the reductive rearrangement on the sulphoxides, using trimethyl phosphite in methanol as reductant, heating the mixture for 3 h at reflux, gave the more polar (**11**) in 27% yield and the less polar isomer (**26**) in 35% yield.

5-*Methoxyindene* (**31**).—6-Methoxyindan-1-one was prepared according to the method of House and Hudson,[17] m.p. 107—108 °C (lit.[17] 109—110 °C). The ketone (8 g, 49 mmol) in methanol was reduced with sodium borohydride (3.87 g, 100 mmol), added in portions, at room temperature over 30 min. After a further 20 min 2M-hydrochloric acid was added, followed by aqueous sodium hydrogen carbonate; the mixture was then extracted with dichloromethane and the extract washed with brine and dried. After removal of solvent the resulting indanol was dissolved in benzene (100 ml), toluene-*p*-sulphonic acid (50 mg) added and the solution heated to reflux with azeotropic removal of water. After reaction was complete (disappearance of alcohol followed by monitoring the reaction by t.l.c.) the solution was cooled, washed with aqueous sodium hydrogen carbonate and brine, and then dried; chromatography of the isolated product through silica (300 g), with ethyl acetate–light petroleum (1:15) as eluant gave 5-methoxyindene (**31**) (5.4 g, 75%) as a colourless liquid, b.p. 71—73 °C/0.8 mmHg (lit.[18] 110—145 °C/10 mmHg), $\nu_{max.}$ 3 070, 2 950, 2 850, 1 620, 1 610, 1 550, 1 470, 1 270, 1 145, 1 035, and 950 cm^{-1}; $\lambda_{max.}$ 252 nm (ε 5 500) (Found: M^+, 146.073 161). Calc. for $C_{10}H_{10}O$; M^+, 146.072 66). 5-Methoxyindene showed a blue-green colour when on silica gel and sprayed with a solution of formaldehyde in sulphuric acid; under similar conditions an authentic sample of 6-methoxyindene produced a violet colouration.

6-*Methoxy*-1,2-*epoxyindan* (**14**).—5-Methoxyindene (**31**) (4.12 g, 28 mmol) in tetrahydrofuran (250 ml) and water (65 ml) was treated with freshly recrystallised *N*-bromosuccinimide (5.44 g, 31 mmol) with stirring for 20 h at room temperature. The reaction mixture was filtered, quenched with cold water, and extracted with ether; the extract was washed with brine, dried, and concentrated to small bulk to give crystals of trans-2-*bromo*-6-*methoxyindan*-1-*ol* (4.9 g, 72%), m.p. 110—111 °C, $\nu_{max.}$(KBr) 3 1120—3 420, 1 585, 1 490, 1 290, 1 065, 810, and 730 cm^{-1}; δ 2.50 (1 H, br s, exchanged by D_2O, HO), 3.11 (1 H, q, *J* 7.7, 16 Hz, $ArCH_2$), 3.50 (1 H, q, *J* 7, 16 Hz, $ArCH_2$), 3.76 (3 H, s, MeO), 4.04—4.34 (1 H, m, CHBr), 5.25 (1 H, d, *J* 6 Hz, ArC*H*), and 6.85—7.25 (3 H, m, ArH); *m/z* 244 (45), 242 (49), 226 (1), 224 (1), 163 (100), 145 (29), 121 (24), 103 (22), 91 (36), 77 (20), and 55 (52) (Found: C, 49.6; H, 4.5; Br, 32.65. $C_{10}H_{11}BrO_2$ requires C, 49.4; H, 4.6; Br, 32.9%).

The bromohydrin (3.0 g, 12.3 mmol) in dioxane (30 ml) was treated with aqueous potassium hydroxide (13M; 1.7 ml, 22 mmol) at room temperature for 15 min before addition of water (250 ml) and extraction with ether. The organic layer was washed with water, dried, and the solvent removed under reduced pressure to afford the viscous epoxide (**14**) (1.85 g, 93%). The material was used directly in further reactions. A sample showed $\nu_{max.}$ 3 030, 2 840, 1 615, 1 590, 1 490, 1 250 (epoxide), 900, 820, and 745 cm^{-1}; δ 2.76 (1 H, dd, *J* 2.6, 16.6 Hz, $ArCH_2$), 3.0 (1 H, br d, *J* 16.8 Hz, $ArCH_2$), 3.65 (3 H, s, MeO), 3.90 (1 H, m, CH), 3.97 (1 H, m, ArC*H*), 6.58—6.70 (1 H, m, ArH) and 6.90—7.0 (2 H, m, ArH). The material was unstable to chromatography through silica, the product exhibiting a strong carbonyl signal at 1 750 cm^{-1}.

(1RS),(2RS)-1-[(1E)-3-*Hydroxyoct*-1-*enyl*]-6-*methoxyindan*-2-*ols* (**12**) and (**27**).—The oxide (**14**) (1.55 g, 9.6 mmol) in tetrahydrofuran (3 ml) was added dropwise to a freshly prepared solution of the lithium salt of the sulphide (**18**) (2.25 g, 10.2 mmol) (*ex.* use of lithium di-isopropylamide in the manner described above) in tetrahydrofuran (25 ml) at −70 °C over 30 min. After a further 3 h the mixture was warmed to −30 °C, and quenched with saturated aqueous ammonium chloride and extracted with ether. The organic extracts were washed with brine, dried, and the solvent removed under reduced pressure before the crude product was chromatographed through silica (270 g), with ethyl acetate–light petroleum (1:6) as eluant to afford, initially, unchanged sulphide (**18**) (0.23 g, 10%), and then the mixture of sulphides (**22**) (2.82 g, 77%), $\nu_{max.}$ 3 150—3 550, 2 920, 2 850, 1 610, 1 585, 1 490, 965, 745, and 695 cm^{-1} (Found: M^+, 382.196 49. $C_{24}H_{30}O_2S$ requires M^+, 382.196 64).

The sulphide mixture (1.77 g, 4.6 mmol) in dichloromethane (85 ml) at −65 °C was oxidized with *m*-chloroperbenzoic acid (0.94 g, 4.6 mmol), added in portions during 30 min. After being stirred between −50 and −15 °C for 1 h the mixture was worked up in the normal manner to produce a mixture of the

corresponding sulphoxides (1.83 g); the mixture showed 4 components by t.l.c. The mixture of sulphoxides (1.82 g) was dissolved in methanol (20 ml) and trimethyl phosphite (1 ml, 8.7 mmol) added. The reaction mixture was stirred under nitrogen at room temperature for 2 h before removal of the solvent under reduced pressure. Chromatography through silica (100 g), using ethyl acetate–dichloromethane (1:4) gave two main products. The less polar material was the (1RS),(2RS),(3RS)-*diol* (**27**) (0.45 g, 34%) isolated as a viscous oil, $\nu_{max.}$ 3 150, 3 600, 2 940, 2 860, 1 615, 1 495, 1 285, and 970 cm^{-1}; δ 0.80—1.0 (3 H, m, CH_3), 1.20—1.55 [8 H, m, $(CH_2)_4$], 2.65—3.15 (4 H, m, 2 × OH, $ArCH_2$), 3.50—3.60 (1 H, m, ArC*H*), 3.74 (3 H, s, MeO), 4.09—4.30 (2 H, m, 2 × CHOH), 5.64—5.76 (1 H, m, C*H*=C*H*), 6.65—6.73 (2 H, m, ArH), and 7.07 (1 H, d, *J* 8 Hz, ArH); *m/z* 290 (M^+, 6), 272 (8), 172 (19), 159 (32), 146 (24), 115 (20), 91 (18), 77 (19), 57 (36), 55 (60), 43 (100), and 41 (59) (Found: C, 74.35; H, 9.0. $C_{18}H_{26}O_3$ requires C, 74.45; H, 9.0%).

The more polar material was the (1RS),(2RS),(3RS)-*diol* (**12**) (0.56 g, 43%) as colourless crystals, m.p. 104—105 °C, $\nu_{max.}$ 3 050—3 500, 1 610, 1 495, 1 280, and 975 cm^{-1}; δ 0.84—0.97 (3 H, m, CH_3), 1.25—1.60 [8 H, m, $(CH_2)_4$], 1.91 (1 H, s, exchanged by D_2O, OH), 2.60 (1 H, s, exchanged by D_2O, OH), 2.81 (1 H, q, *J* 7.7, 15.5 Hz, $ArCH_2$), 3.15 (1 H, q, *J* 6.7, 15.4 Hz, $ArCH_2$), 3.50—3.63 (1 H, m, ArC*H*), 3.76 (3 H, s, OMe), 4.07—4.35 (2 H, m, 2 × C*H*OH), 5.60—5.71 (2 H, m, CH=CH), 6.61—6.76 (2 H, m, ArH), and 7.09 (1 H, d, *J* 8 Hz, ArH); *m/z* 290 (M^+, 6), 272 (30), 229 (11), 201 (15), 173 (36), 172 (28), 159 (100), 147 (25), 146 (43), 115 (23), 91 (17), 77 (12), 57 (19), 55 (39), and 43 (80) (Found: C, 74.2; H, 8.9. $C_{18}H_{26}O_3$ requires C, 74.45; H, 9.0%).

(1RS),(2RS)-1-[(1E)-3-*Oxo-oct*-1-*enyl*]-6-*methoxyindan*-1-*ol* (**34**).—To a suspension of manganese dioxide (0.99 g) in dichloromethane (15 ml) was added a mixture of the diastereoisomeric diols (**12**) and (**27**) (0.10 g); the mixture was stirred for 2.5 h, filtered, and the solvent removed under reduced pressure to afford an oil. Purification by p.l.c. [ethyl acetate–dichloromethane (1:4) as eluant] gave the recovered diol (21 mg, 21%) and the *title* compound (24 mg, 26%) as a pale yellow oil, $\nu_{max.}$ 3 200—3 600, 2 920, 1 665, 1 620, 1 490, 980, and 925 cm^{-1}; δ 0.80—1.0 (3 H, m, CH_3), 1.20—1.65 [6 H, m, $(CH_2)_3$], 2.40—3.10 (5 H, m), 3.70 (4 H, s and m, *Me*O and ArC*H*), 4.20—4.35 (1 H, m, C*H*OH), 6.17 (1 H, d, *J* 16 Hz, C*H*CO), 6.45—6.70 (3 H, m), and 7.0 (1 H, d, *J* 8 Hz, ArH); *m/z* 288 (M^+, 12), 270 (8), 199 (9), 172 (24), 146 (13), 99 (15), 77 (7), 71 (35), 57 (18), 55 (58), 43 (100), and 41 (51) (Found: M^+, 288.171 93. $C_{18}H_{24}O_3$ requires M^+, 288.172 53).

6-*Hydroxyindan*-1-*one*.—A mixture of 6-methoxyindan-1-one (7 g, 55 mmol) and aluminium bromide (48 g, 180 mmol) was heated in refluxing benzene (240 ml) for 4.5 h. The resulting mixture was cooled, decomposed with ice-cold 2M-hydrochloric acid and the benzene layer separated and the aqueous layer re-extracted with ethyl acetate. The combined organic extracts were washed with brine, dried, and concentrated. The solid product was recrystallised from ethanol to give the title indanone (6.48 g, 79%), m.p. 150—151 °C (lit.,[19] 151—153 °C).

6-(4-*Methoxycarbonylbutoxy*)*indan*-1-*one*.—6-Hydroxyindan-1-one (7.5 g, 51 mmol) was treated with sodium methoxide (from 1.41 g sodium, 61 mg-atom) in methanol (125 ml) at room temperature after which methyl 5-bromovalerate (11.9 g, 61 mmol) was added; the mixture was heated to reflux for 50 h, cooled, and the solvent removed under reduced pressure. The residue was extracted with ethyl acetate, and the extract washed with water, dried, and the solvent removed under reduced pressure to afford colourless crystals of the *title compound* (9.9 g, 74%), m.p. 72—74 °C, $\nu_{max.}$ 1 745, 1 695, 1 055, and 845 cm^{-1}; δ 1.72—1.96 [4 H, m, $(CH_2)_2$], 2.32—2.52 (2 H, m, $CH_2CO_2CH_3$), 2.63—2.80 (2 H, m, CH_2CO), 3.0—3.15 (2 H, m, $ArCH_2$), 3.67 (3 H, s, CH_3O), 3.90—4.10 (2 H, m, $ArOCH_2$), and 7.12—7.40 (3 H, m, ArH); *m/z* 262 (M^+, 4), 120 (15), 115 (100), 91 (13), 83 (28), 73 (35), and 55 (49) (Found: C, 68.7; H, 6.8. $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%).

5-(4-*Methoxycarbonylbutoxy*)*indene* (**36**).—Sodium borohydride (2.9 g, 77 mmol) was added in portions to a stirred solution of the corresponding indanone (9.33 g, 36 mmol) in methanol (100 ml) at room temperature. After addition the solution was stirred for a further 20 min before the addition of 2M-aqueous hydrochloric acid followed by 2M-aqueous sodium hydrogen carbonate. After extraction with dichloromethane, and drying and evaporation of the extract under reduced pressure, the residue was dissolved in benzene (110 ml), toluene-*p*-sulphonic acid (40 mg) added, and the mixture heated with azeotropic removal of water for 1.5 h. The benzene solution was then washed with aqueous sodium hydrogen carbonate and brine, dried, and the solvent removed under reduced pressure; the residue was chromatographed through silica (350 g) using ethyl acetate–light petroleum (1:13) to afford the *title indene* (6.0 g, 68%), m.p. 41—42 °C, $\nu_{max.}$ 1 740, 1 615, 1 550, 1 270, 1 160, 985, 825, and 700 cm^{-1}; δ 1.70—1.91 [4 H, m, $(CH_2)_2$], 2.30—2.50 (2 H, m, $CH_2CO_2CH_3$), 3.29—3.39 (2 H, m, $ArCH_2$), 3.65 (3 H, s, CH_3O), 3.90—4.09 (2 H, m, $ArOCH_2$), 6.48—6.60 (1 H, m, ArCH=C*H*), 6.69—6.97 (3 H, m, vinylic and 2 ArH), and 7.32 (1 H, d, *J* 8 Hz, ArH); *m/z* 246 (M^+, 19), 215 (15), 132 (37), 115 (100), 83 (18), 73 (26), 59 (12), and 55 (30) (Found: C, 72.95; H, 7.5. $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.4%).

5-(4-*Pyrrolidin*-1-*ylcarbonylbutoxy*)*indene* (**38**).—The ester (**36**) (5.85 g, 24 mmol) in dioxane (40 ml) and 2% (w/v) sodium carbonate in water (130 ml, 24.5 mmol) was heated under reflux for 5.5 h. It was then cooled, washed with ether, and the aqueous layer acidified with dilute hydrochloric acid before extraction with ethyl acetate. The extract was dried and the solvent removed under reduced pressure to give a crude product which upon recrystallisation from ether–hexane afforded 5-(4-*carboxybutoxy*)*indene* (4.4 g, 80%), m.p. 96—98 °C, $\nu_{max.}$ 2 600—3 250, 1 695, 1 620, and 1 265 cm^{-1}; δ 1.75—1.95 [4 H, m, $(CH_2)_2$], 2.35—2.55 (2 H, m, CH_2CO_2H), 3.34 (2 H, br s, $ArCH_2$), 3.95—4.05 (2 H, m, $ArOCH_2$), 6.38—6.59 (1 H, m, ArCH=C*H*), 6.70—7.05 (3 H, m, vinylic and 2 ArH), 7.20—7.40 (1 H, m, ArH), and 9.05 (1 H, br s, exchanged with D_2O, CO_2H); *m/z* 232 (M^+, 17) 133 (8), 132 (100), 115 (6), 103 (6), and 77 (4) (Found: C, 72.3; H, 6.95. $C_{14}H_{16}O_3$ requires C, 72.4; H, 6.9%).

The acid (3 g, 12.9 mmol) in dichloromethane (50 ml) and triethylamine (1.82 ml, 13 mmol) at room temperature was treated with ethyl chloroformate (1.3 ml, 13 mmol), followed by pyrrolidine (1.1 ml, 13 mmol). After being stirred for 70 min the solution was washed with aqueous sodium carbonate dilute hydrochloric acid, and brine; it was then dried and concentrated under reduced pressure. The solid was crystallised from ethyl acetate to afford the *title amide* (3.3 g, 90%), m.p. 74—75 °C, $\nu_{max.}$ 2 960, 1 650, and 1 450 cm^{-1}; δ 1.71—1.91 [8 H, m, $(CH_2)_4$], 2.20—2.40 (2 H, m, CH_2CON), 3.3—3.6 (6 H, m), 3.90—4.10 (2 H, m, $ArOCH_2$), and 6.40—7.40 (5 H, m); *m/z* 285 (M^+, 2), 154 (80), 131 (5), 98 (25), 70 (17), 56 (44), 55 (89), 43 (53), 42 (24), and 41 (48) (Found: C, 75.65; H, 8.1; N, 5.2. $C_{18}H_{23}NO_2$ requires C, 75.75; H, 8.1; N, 4.9%).

(1RS),(2RS)-1-[(1E),(3SR)-*Hydroxy*]*oct*-1-*enyl*-2-*hydroxy*-6-(4-*pyrrolidin*-1-*ylcarbonylbutoxy*)*indan* (**8**).—This was prepared, through the following intermediates, using the methods described for the preparation of the model methoxy derivative (**12**).

trans-2-*Bromo*-1-*hydroxy*-6-(4-*pyrrolidin*-1-*ylcarbonyl-butoxy*)*indan*. This was prepared on a 11.6 mmol scale and obtained as a viscous oil (4.4 g). A sample was crystallised from ethanol to give off-white crystals, m.p. 125—127 °C; δ 1.7—2.0 [8 H, m, $(CH_2)_4$], 2.2—2.4 (2 H, m, CH_2CO), 3.0—3.7 (7 H, m), 3.87—4.02 (2 H, m, $ArOCH_2$), 4.16—4.37 (1 H, m, CHBr), 5.22 (1 H, d, *J* 5 Hz, ArC*H*), 6.65—6.81 (2 H, m, ArH), and 7.28 (1 H, d, *J* 7 Hz, ArH) (Found: C, 56.6; H, 6.25; Br, 21.1; N, 3.6. $C_{18}H_{24}NO_3Br$ requires C, 56.55; H, 6.3; Br, 20.9; N, 3.7%).

1,2-*Epoxy*-6-(4-*pyrrolidin*-1-*ylcarbonylbutoxy*)*indene*. This was prepared on a 10.5 mmol scale. The crude product was extracted with ethyl acetate to give 2.24 g of the epoxide (Found: M^+, 301.167 83. $C_{18}H_{23}NO_3$ requires M^+, 301.167 78).

(1RS),(2RS)-1-*Hydroxy*-1-[(1E)-1-*phenylthio*-*oct*-2-*enyl*]-6-(4-*pyrrolidin*-1-*ylcarbonylbutoxy*)*indan*. This was prepared on a 7.8 mmol scale to afford the crude product which was purified by chromatography through silica gel (230 g); so obtained were unchanged sulphide (**18**) (1.27 g) and the required sulphide (0.44 g, 13%), $\nu_{max.}$ 3 150—3 550 (OH), 2 920, 2 860, 1 625 (amide CO), 1 445, 965, 740, and 690 cm^{-1}; δ 0.7—0.95 (3 H, m, CH_3), 1.0—1.3 [6 H, m, $(CH_2)_3$], 1.7—2.0 [10 H, m, $(CCH_2)_5$], 2.15—2.40 (3 H, m), 2.75 (1 H, 1, *J* 5, 16 Hz, $ArCH_2$), 3.05—3.53 (6 H, m), 3.8—4.0 (3 H, m), 4.4—4.7 (1 H, m, C*H*OH), 5.2—5.4 (2 H, m, CH=CH), and 6.7—7.45 (8 H, m, ArH) (Found: M^+, 521.2969. $C_{32}H_{43}NO_3S$ requires M^+, 521.2963).

Title indan (**8**). Oxidation of the sulphide to the corresponding sulphoxide was utilised on a 0.48 mmol scale to afford 0.255 g of the diastereoisomeric sulphoxides (Found: M^+, 537.2908. $C_{32}H_{43}NO_4$ requires M^+, 537.2913). The mixture of sulphoxides (0.25 g) was treated with trimethyl phosphite in methanol and the crude product chromatographed through silica gel (33 g). Elution with ethyl acetate–dichloromethane (2:3) gave first the less polar 3′-epi-*alcohol* (**28**) (73 mg, 36.5%) as a viscous oil, $\nu_{max.}$ 3 200—3 550, 2 920, 2 865, 1 630, and 970 cm^{-1}; δ 0.8—1.0 (3 H, m, CH_3), 1.2—2.0 [18 H, m, $(CH_2)_8$], 2.2—2.4 (2 H, m, CH_2CO), 2.80 (1 H, 1, *J* 7, 15 Hz, $ArCH_2$), 3.0—3.6 (6 H, m), 3.9—4.3 (4 H, m), 5.6—5.8 (2 H, m, CH=CH), 6.46—6.77 (2 H, m, ArH), and 7.04 (1 H, d, *J* 8 Hz, ArH) (Found: M^+, 429.287 56. $C_{26}H_{39}NO_4$ requires M^+, 429.287 89).

Further elution gave a mixture of the two alcohol epimers (28 mg, 14%), followed by the *required alcohol* (**8**) (65 mg, 32.5%) as a viscous oil, $\nu_{max.}$ 3 200—3 600, 2 930, 2 880, 1 630, and 970 cm^{-1}; δ 0.8—1.0 (3 H, m, CH_3), 1.1—2.0 [18 H, m, $(CH_2)_8$], 2.2—2.4 (2 H, m, CH_2CO), 2.79 (1 H, q, *J* 7, 16 Hz, $ArCH_2$), 3.0—3.6 (6 H, m), 3.85—4.35 (4 H, m), 5.6—5.8 (2 H, m, CH=CH), 6.6—6.8 (2 H, m, ArH), and 7.07 (1 H, d, *J* 7.7 Hz, ArH) (Found: M^+, 429.2870. $C_{26}H_{39}NO_4$ requires M^+, 429.2879) (Found: C, 72.6; H, 9.05; N, 3.0. $C_{26}H_{39}NO_4$ requires C, 72.7; H, 9.15; N, 3.3%).

6-(3-*Methoxycarbonylpropoxy*)*indan*-1-*one*.—The procedure described for the preparation of the corresponding butoxy-analogue (*vide supra*) was followed, using 6-hydroxyindan-1-one (11 g, 74 mmol) and ethyl 4-bromobutyrate (17.4 g, 89 mmol) and sodium methoxide (89 mmol) to give the crude ether. Recrystallisation from hexane afforded the *title ketone* (11 g, 60%), m.p. 80—81 °C, $\nu_{max.}$(Nujol) 1 740, 1 700, 1 180, 1 040, and 850 cm^{-1}; δ 2.0—2.2 (2 H, m, CH_2), 2.4—2.8 (4 H, m), 2.98—3.14 (2 H, m, $ArCH_2$), 3.67 (3 H, s, CH_3OCO), 4.01 (2 H, t, *J* 6 Hz, $ArOCH_2$), and 7.1—7.4 (3 H, ArH) (Found: C, 67.5; H, 6.75. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%).

5-(3-*Pyrrolidin*-1-*ylcarbonylpropoxy*)*indene* (**39**).—6-(3-Methoxycarbonylpropoxy)indan-1-one (10 g) was reduced with sodium borohydride (3.1 g) in refluxing ethanol (110 ml) and, after work-up, the crude indanol was dehydrated with toluene-*p*-sulphonic acid in the usual manner. The product was chromatographed through SiO_2 (350 g) using EtOAc–light petroleum (1:15) as eluant, to produce 5-(3-ethoxycarbonylpropoxy)indene (**37**) (4.0 g, 40%), $\nu_{max.}$(film) 2 960, 1 735, 1 620, 1 550, 1 465, 1 270, 1 180, and 700 cm^{-1} (Found: M^+, 246.125 11. $C_{15}H_{18}O_3$ requires M^+, 246.125 58). The ester (**37**) was hydrolysed in the same manner as the ester (36) to give the corresponding *acid* (94%), m.p. 93—94 °C (Found: C, 71.25; H, 6.45. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.5%). The acid (2.86 g) was coupled with pyrrolidine (1.2 ml) by use of allyl chloroformate (1.32 ml) and triethylamine (1.92 ml) in dichloromethane (50 ml). The crude amide was chromatographed through SiO_2 (100 g), using EtOAc–dichloromethane (1 : 4) as eluant, to give the title amide (**39**) (2.85 g, 80%) as a solid, m.p. 56—58 °C, $\nu_{max.}$ 1 635, 1 590, 1 245, and 1 045 cm^{-1}; δ 1.7—2.3 [6 H, m, $(CH_2)_3$], 2.40—2.25 (2 H, m, CH_2CON), 3.27—3.55 (6 H, m, $ArCH_2$ and 2 × CH_2N), 4.06 (2 H, t, *J* 5.8 Hz, $ArOCH_2$), 6.33—6.61 (1 H, m, ArCH=C*H*), 6.67—7.07 (3 H, m, aromatic and vinylic H), and 7.20—7.36 (1 H, m, ArH); *m/z*; *m/z* 271 (M^+, 1), 141 (9), 140 (100), 132 (8), 131 (7), 98 (9), 69 (11), 56 (11), 55 (20), 43 (10), and 41 (15) (Found: C, 75.4; H, 7.8; N, 4.95. $C_{17}H_{31}NO_2$ requires C, 72.25; H, 7.8; N, 5.2%).

(1RS),(2RS)-1-[(1R),(3SR)-*Hydroxyoct*-1-*enyl*]-2-*hydroxy*-6-(3-*pyrrolidin*-1-*ylcarbonylpropoxy*)*indan* (**10**).—The indene (**39**) was converted into the title compound in a manner similar to that used in the preparation of the butoxy analogue (**8**). Thus the indene (2.6 g, 9.5 mmol) was converted into the corresponding bromohydrin and then the corresponding epoxide (1.47 g, 54%), isolated as a viscous oil (Found: M^+, 287.151 37. $C_{17}H_{21}NO_3$ requires M^+, 287.152 13).

Reaction of the epoxide (1.4 g) with the lithium salt of the sulphide (**18**) (1.06 g), afforded the corresponding alkylated sulphide (0.6 g, 25%), as a mixture of diastereoisomers (Found: M^+, 507.281 83. $C_{13}H_{41}NO_3S$ requires M^+, 507.280 70).

Oxidation of the sulphide to the corresponding sulphoxide was carried out with one equivalent of *m*-chloroperbenzoic acid and the mixture of diastereoisomers (0.35 g) thus obtained was treated with trimethyl phosphite (0.16 ml) before chromatography through SiO_2 (30 g), with EtOAc–dichloromethane (3:2) as eluant. The first compound isolated was the less polar 3′-epi-*isomer* (29) (99 mg, 36%) isolated as a viscous oil, $\nu_{max.}$ 3 400, 2 930, 2 880, 1 630, 1 450, and 970 cm^{-1}; δ 0.9 (3 H, m, CH_3), 1.15—1.65 [8 H, m, $(CH_2)_4$], 1.75—2.25 [8 H, m, $(CH_2)_3$, and two OH], 2.31—2.50 (2 H, m, CH_2CON), 2.80 (1 H, q, *J* 15, 7.7 Hz, $ArCH_2$), 3.0—3.61 (6 H, m, CH_2NCH_2 and benzylic H), 3.90—4.42 (4 H, m, H–CO), 5.55—5.80 (2 H, m, CH=CH), 6.6—6.8 (2 H, m, ArH), and 7.05 (1 H, d, *J* 7.7 Hz, ArH); *m/z* 397 ($M^+ - H_2O$, 0.3), 141 (9), 140 (100), 113 (8), 98 (9), 70 (9), 69 (8), 56 (10), 55 (20), 44 (8), and 43 (18) (Found: M^+, 415.271 95. $C_{25}H_{37}NO_4$ requires M^+, 415.272 24).

The more polar material was the *title alcohol* (**10**) (92 mg, 34%), m.p. (EtOAc–hexane) 113—114 °C, $\nu_{max.}$ 3 400, 1 640, and 975 cm^{-1}; δ 0.9 (3 H, m, CH_3), 1.17—1.64 [8 H, m, $(CH_2)_4$], 1.73—2.25 [8 H, m, $(CH_2)_3$ and 2 OH], 2.32—2.52 (2 H, m, CH_2CON), 2.79 (1 H, q, *J* 15, 7 Hz, $ArCH_2$), 2.97—3.60 (6 H, m, CH_2NCH_2 and benzylic H), 3.90—4.40 (4 H, m, $ArOCH_2$ and C*H*OH), 5.55—5.73 (2 H, m, CH=CH), 6.6—6.8 (2 H, m, ArH), and 7.06 (1 H, d, *J* 8 Hz, ArH); *m/z* 297 ($M^+ - H_2$, 0.7), 141 (9), 140 (100), 113 (5), 98 (3), 70 (1), 56 (1), and 44 (2) (Found: C, 72.25; H, 8.9; N, 3.15. $C_{25}H_{37}NO_4$ requires C, 72.25; H, 9.0; N, 3.4%).

Attempted hydrolysis of the amide (**10**) with base resulted in its decomposition.

(2E)-1-(2-*Adamantylthio*)*oct*-2-*ene* (**41**).—A solution of *trans*-oct-2-en-1-ol (2 g) in dry tetrahydrofuran (12 ml) and hexamethylphosphoric triamide (5 ml) was treated, under nitrogen, with n-butyl-lithium (1.45M; 10.8 ml) at 0 °C followed

by toluene-*p*-sulphonyl chloride (3 g) in dry tetrahydrofuran (7 ml). The mixture was stirred for 5 min and sodium adamantane-2-thiolate [prepared from freshly prepared adamantane-2-thiol (27 g) and sodium (0.39 g) in ethanol (10)][20] was added. The mixture was stirred at 3 °C for 90 min, poured into water, and extracted with light petroleum; the extract was washed with brine. The crude extract was purified by chromatography through SiO_2 (160 g) with light petroleum as eluant, to give the *title sulphide* (2.6 g, 60%) as a colourless oil, $\nu_{max.}$ 2 920, 2 855, 1 450, 1 100, and 965 cm^{-1}; *m/z* 278 (M^+, 6), 167 (5), 135 (5), 110 (100), 93 (17), 91 (44), 79 (21), and 67 (28) (Found: C, 77.85; H, 10.75; S, 11.55. $C_{18}H_{30}S$ requires C, 77.6; H, 10.9; S, 11.5%).

Purification of the Sulphides (**42**).—The sulphide (**41**) (1.32 g) in dry tetrahydrofuran (5 ml) was added dropwise to a solution of lithium di-isopropylamide [*ex.* di-isopropylamine (0.7 ml) and butyl-lithium (1.45M; 3.3 ml)] in tetrahydrofuran (10 ml) at −76 °C. After 20 min, indene oxide (0.63 g) in tetrahydrofuran (2 ml) was added and the mixture stirred for a further 4 h at −70 °C before being warmed to −30 °C; it was then quenched with aqueous ammonium chloride and extracted with ether. The crude extract was purified by chromatography through SiO_2 (120 g) with EtOAc–light petroleum (1:6) as eluant to give, in order of elution, unchanged sulphide (**41**) (1.06 g), followed by a mixture of the α- and γ-alkylated sulphides (0.25 g, 13%) (ratio 77:23 by integration of the vinylic H atoms). Further elution of the column gave indan-1-ol (0.3 g, 48%).

Oxidation and Rearrangement of the Sulphides (**42**).—The sulphide mixture (0.18 g) was oxidised at −50 °C with *m*-chloroperbenzoic acid (0.089 g) in dichloromethane over 20 min. Work-up in the normal manner gave the mixture of crude sulphoxides (0.19 g), which was dissolved in methanol (10 ml) and treated with trimethyl phosphite (0.1 ml) at room temperature for 7 days. The solvent was removed under reduced pressure and the residue separated by h.p.l.c. through μ-Porasil using EtOAc–hexane (2:3) as solvent (Waters 6000A instrument). Two major products were detected and identified as the alcohols (**11**) and (**26**) by direct comparison with authentic samples. The ratio of the two alcohols was 3:1 in favour of the more polar isomer (**11**).

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