Regiochemistry of Nucleophilic Opening of β-Substituted Styrene Oxides with Thiolate Anions: Model Experiments in the Synthesis of Leukotriene Analogues

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β-Substituted *trans*-styrene oxides are cleaved with thiolate anions highly regioselectively by attack at the α-carbon whereas the *cis*-isomers are cleaved by attack at the α- and β-carbons. Cysteine, in a suitably protected form, similarly cleaves β-substituted *trans*-styrene oxides, thus allowing the synthesis of a simple LTE model.

Slow reacting substances, *e.g.*, leukotriene C_4 (**1**), are recognized as important regulators of the immune response and are mediators, *inter alia*, of airways constriction and bronchial spasm in human asthma.[1-3] The possibility that analogues of leukotrienes may be useful antagonists is attractive and we have sought to synthesize simple models (**2**) of leukotriene E_4, in which an aromatic ring may be regarded as replacing the 7,9-diene system in a *cisoid* conformation.

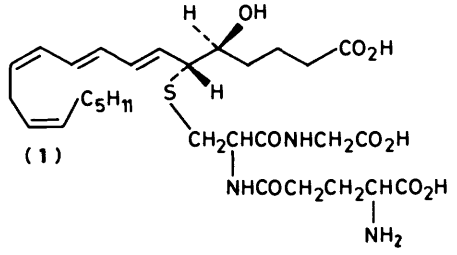
It was expected that the models (**2**) might easily be prepared by the addition of cysteine to the epoxides (**3**). The addition of simple thiols to styrene oxide has been studied[4] and there are a number of reports[5-12] of the additions of other nucleophiles to styrene oxides and some of their β-substituted derivatives.

In general, the regiochemistry of such reactions is determined by the substitution of the phenyl ring, the stereochemistry of the epoxide, and the reaction conditions. There appear to be no studies of the reactions of thiols with β-substituted styrene oxides. We report here some reactions of the β-methylstyrene oxides (**4**)—(**7**) with thiols, preparatory to similar reactions of methyl 6-phenyl-5,6-epoxyhexanoate (**8**) which are also described.

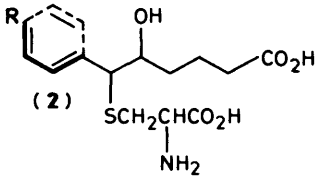
Additions to β-Methylstyrene Oxides.—The *trans*-epoxides (**4**) and (**6**)[13] were prepared by MCPBA oxidation of (*E*)-β-methylstyrene and by treatment of 4-methoxy-β-methylstyrene successively with HOBr and KOH.[14] The *cis*-epoxides† (**5**) and (**7**)[9] were prepared by MCPBA oxidation of the (*Z*)†-methylstyrenes which were obtained by reaction of the aromatic aldehyde with the ylide derived from ethyltriphenylphosphonium bromide. The peracid oxidation of (*Z*)-4-methoxy-β-methylstyrene was carried out in methylene chloride–aqueous sodium hydrogen carbonate.[15]

Reaction of the *trans*-epoxides (**4**) and (**6**) with thiophenol–triethylamine and the similar reaction of (**4**) with toluene-α-thiol–triethylamine gave only the *erythro*-products (**9**), (**10**), and (**11**) respectively, of nucleophilic attack at the α-carbon. The mass spectra of the adducts (**9**)—(**11**) showed important fragment ions at *m/z* 199, 229, and 213, respectively, corresponding to the ions (**15**), (**16**), and (**17**) and demonstrating the attachment of the sulphur atom to the α-carbon. The base peaks in the mass spectra of (**9**)—(**11**) at *m/z* 200, 165, and 91 are assigned to the ions (**18**), (**19**), and the tropyllium ion respectively. It is presumed that the ion (**18**) arises by a hydrogen transfer process with loss of acetaldehyde. The equivalent ion *m/z* 214 is quite intense in the mass spectrum of the adduct (**11**). Further support for the regiochemistry of the adducts comes from their ^{1}H n.m.r. spectra and those of the acetates (**12**)—(**14**). For example in the ^{1}H n.m.r. spectrum of (**9**), the α- and β-methine proton signals overlap at δ 3.96—4.30 whereas in the acetate (**12**) the β-methine proton signal is clearly visible as a doublet of quartets at 5.33 (*J* *ca.* 6 and 7 Hz). Double irradiation of the methyl doublet (δ 1.30) in the ^{1}H n.m.r. spectrum of the acetate (**12**) caused the signal at δ 5.33 to collapse to a doublet (*J* *ca.* 6 Hz) and double irradiation of the α-methine doublet (δ 4.30, *J* *ca.* 6 Hz) caused the signal at δ 5.33 to collapse to a quartet (*J* *ca.* 7 Hz).

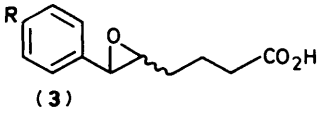
The reaction of the *cis*-epoxide (**5**), containing the *trans*-epoxide (**4**) (25%), with thiophenol–triethylamine gave a mixture of the *erythro*-adduct (**9**), the *threo*-adduct (**20**), and the *threo*-regioisomeric adduct (**25**). Similarly, reaction of the same mixture of (**5**) and (**4**) with toluene-α-thiol–triethylamine gave the *erythro*-adduct (**11**), the *threo*-adduct (**21**), and the *threo*-



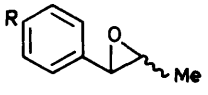
(**1**)



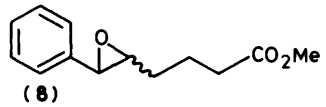
(**2**)



(**3**)

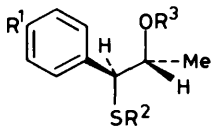


(**4**) R = H, *trans*
(**5**) R = H, *cis*
(**6**) R = MeO, *trans*
(**7**) R = MeO, *cis*

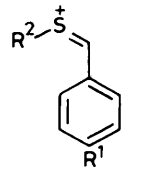


(**8**)

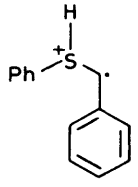
† Shown by g.l.c. to contain up to 25% of the diastereoisomer.



(9) $R^1 = R^3 = H, R^2 = Ph$
(10) $R^1 = MeO, R^2 = Ph, R^3 = H$
(11) $R^1 = R^3 = H, R^2 = CH_2Ph$
(12) $R^1 = H, R^2 = Ph, R^3 = Ac$
(13) $R^1 = MeO, R^2 = Ph, R^3 = Ac$
(14) $R^1 = H, R^2 = CH_2Ph, R^3 = Ac$



(15) $R^1 = H, R^2 = Ph$
(16) $R^1 = MeO, R^2 = Ph$
(17) $R^1 = H, R^2 = CH_2Ph$



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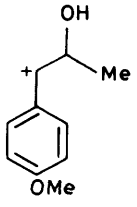

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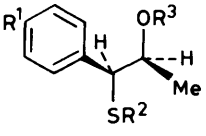
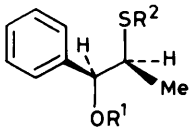


(20) $R^1 = R^3 = H, R^2 = Ph$
(21) $R^1 = R^3 = H, R^2 = CH_2Ph$
(22) $R^1 = MeO, R^2 = Ph, R^3 = H$
(23) $R^1 = H, R^2 = Ph, R^3 = Ac$
(24) $R^1 = H, R^2 = CH_2Ph, R^3 = Ac$



(25) $R^1 = H, R^2 = Ph$
(26) $R^1 = H, R^2 = CH_2Ph$
(27) $R^1 = Ac, R^2 = Ph$
(28) $R^1 = Ac, R^2 = CH_2Ph$

regioisomeric adduct (**26**). The diastereoisomeric mixture (48%) of (**9**) and (**20**) was separated by preparative t.l.c. from the regioisomer (**25**) (46%) as was the mixture (31%) of (**11**) and (**21**) from regioisomer (**26**) (23%). The ratios of (**9**) to (**20**) and (**11**) to (**21**), 1:1 and 1.3:1 respectively, were determined by integration of the methyl signals in the ^1H n.m.r. spectra at δ 1.20, 1.05, 1.17, and 1.02 for (**9**), (**20**), (**11**), and (**21**) respectively. Acetylation of the mixtures of (**9**) and (**20**) and (**11**) and (**21**) gave the mixed acetates (**12**) and (**23**) and (**14**) and (**24**). The ^1H n.m.r. spectra of the mixtures of (**12**) and (**23**) and (**14**) and (**24**) showed the expected lowfield multiplets for the β-methine protons at δ 5.33 and 5.28. The base peak in the mass spectrum of the *threo*-adduct (**25**), at *m/z* 138, and an intense peak at *m/z* 137 are asssigned to the ions (**29**) and (**30**), respectively, and lend support to the structural assignments in which the sulphur is attached to the β-carbon. This is further supported by the ^1H n.m.r. spectra of the *threo*-adduct (**25**) and its acetate (**27**). In the spectrum of the latter, the α-methine doublet (δ 5.80, *J ca.* 7 Hz) is at much lower field and the β-methine doublet of quartets (δ 3.62, *J ca.* 7 and 7 Hz) is correspondingly at much higher field than the corresponding signals (δ 4.33 and 5.33 respectively) in the *threo*-regioisomer (**23**). The spectroscopic data for the *threo*-adduct (**26**) and its acetate (**28**) were similar to those of (**25**) and (**27**) and were consistent with the assigned structure. The *threo*-adduct (**22**) (64%) was isolated by crystallisation of the product of the reaction of the 4-methoxy-*cis*-epoxide (**7**), containing 15% of the 4-methoxy *trans*-epoxide (**6**), with thiophenol–triethylamine. The mass spectrum of the *threo*-adduct (**22**) shows important peaks at *m/z* 229 and 165 (100%) similar to that of its diastereoisomer (**10**). The ^1H n.m.r. spectrum of (**22**) is similar to that of (**10**) but the methyl doublet (*J ca.* 7 Hz) occurs at δ 1.10 rather than δ 1.22.

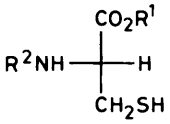
It is apparent that the *trans*-β-methylstyrene oxides (**4**) and (**6**) cleave highly regioselectively with thiophenol and toluene-α-thiol by attack of the sulphur atom at the α-carbon. The *cis*-β-methylstyrene oxide (**5**) cleaves by attack at both the α- and β-carbon. Assuming that the *erythro*-adducts (**9**) and (**11**) largely arise from the *trans*-β-methylstyrene oxide (**4**) (25%) in our sample of (**5**), the ratio of α:β attack for the reactions of thiophenol and toluene-α-thiol may be estimated at *ca.* 1:2. Preferential β-attack in the reactions of *cis*-β-methylstyrene oxide (**5**) with hydroxide ion[12] and ethylenimine[8] has been observed whereas the reactions with the *trans*-isomer (**4**) gave products predominantly of α-attack. Interestingly, *trans*-β-methylstyrene oxide (**4**) has been reported to react selectively with benzylamine at the β-carbon whereas the 4-methoxy derivative (**6**) reacted with 4-benzylpiperidine mainly at the α-carbon.[11] A variety of 4-substituted *cis*-β-methylstyrene oxides react preferentially at the β-carbon with isopropylamine,[9] and in contrast with our observation of the reaction of (**7**) with thiophenol.

Although the reactions with amines and thiols do not conform to an entirely consistent pattern, presumably owing to subtle steric and electronic effects, we were encouraged by our studies with thiols since the *trans*-β-methylstyrene oxides (**4**) and (**6**) gave the regiochemistry required in the target molecules (**2**). Additionally, this approach to (**2**) from (**3**) would give the *erythro*-configuration which is present in LTC_4 (**1**), and, if required, the *threo*-configuration could possibly be obtained by use of the *cis*-epoxides, particularly those containing an electron donating *para*-substituent.

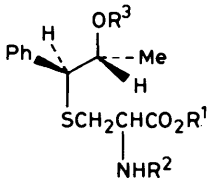
Reaction of *trans*-β-methylstyrene oxide (**4**) with cysteine in methanol–triethylamine[16] did not allow the isolation of any well defined products. However, its reaction with methyl *N*-acetylcysteine (**31**)[17] under similar conditions gave the hydroxy sulphide (**33**) which, being a mixture (*ca.* 1:1) of diastereoisomers, showed largely duplicated signals in the ^1H n.m.r. spectrum. Assignments in support of the structure (**33**) were as follows: δ 6.50—7.00 (br m, NH), 4.7—4.9 (m, C*H*NHAc), 3.95—4.25 (m, C*H*Me), 3.82 and 3.88 (d, *J ca.* 6 Hz, PhC*H*), 3.62 and 3.73 (s, OMe), 2.7—3.0 (m, CH_2SR), 2.58 (br s, exch. with D_2O, OH), 1.88 and 2.02 (s, *Me*CONH), and 1.20 (d, *J ca.* 6 Hz, *Me*CH). The mass spectrum of the hydroxy sulphide (**33**) did not show a molecular ion but showed important peaks at *m/z* 266 and *m/z* 267 corresponding to the ions (**37**) and (**38**), thus supporting the assigned regiochemistry of the addition process. Further support for this assignment was evident from the ^1H n.m.r. spectrum of the acetoxy sulphide which showed a multiplet at δ 5.10—5.40 (MeC*H*OAc). The diastereoisomers of the hydroxy sulphide (**33**) and its acetate were not readily separable by t.l.c. However, the diastereoisomers of the hydroxy sulphide (**35**), which were similarly prepared by the reaction of ethyl cysteine (**32**) with *trans*-β-methylstyrene oxide (**4**), were separated by preparative t.l.c.; the less polar fraction (isomer 1) and the more polar fraction (isomer 2) were then each acetylated to afford the diacetates (**36**) (isomers 1 and 2). Neither isomer of (**36**) showed a molecular ion in its mass spectrum, but showed important ions at *m/z* 307 and *m/z* 280 corresponding to *M* − 60 and the ion equivalent to (**37**) which was observed in the mass spectrum of the hydroxy sulphide (**33**). The 400 MHz ^1H n.m.r. spectra of isomers 1 and 2 of (**36**) confirmed the regiochemistry of the adducts showing the α-methine proton doublets (*J ca.* 6 Hz) at δ 3.91 and 3.97 and the β-methine proton double quartets (*J ca.* 6 and 6 Hz) at δ 5.23 and 5.25,

(29)

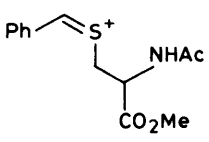
(30)



(31) R^1 = Me, R^2 = Ac
(32) R^1 = Et, R^2 = H



(33) R^1 = Me, R^2 = Ac, R^3 = H
(34) R^1 = Me, R^2 = R^3 = Ac
(35) R^1 = Et, R^2 = R^3 = H
(36) R^1 = Et, R^2 = R^3 = Ac



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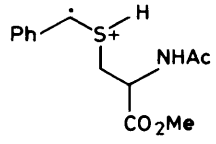
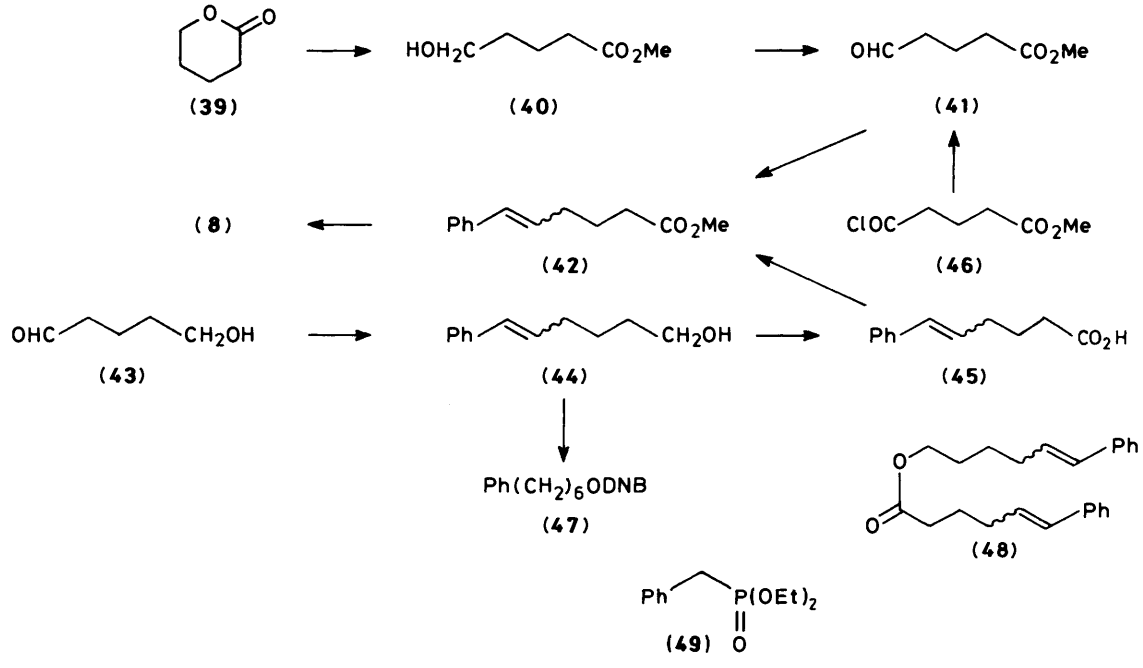


(38)

6.20 (br d, H_M, J_{MX} *ca.* 8 Hz). In both isomers the methylene groups of the OEt showed the expected multiplicity arising from the proximity of the chiral carbon of the cysteine residue.

Preparation of Methyl 6-Phenyl-5,6-epoxyhexanoate (**8**).—The two approaches used for the synthesis of the epoxide (**8**) are shown in the Scheme. The first required the synthesis of methyl 5-oxopentanoate (**41**) which is a commonly used intermediate in the synthesis of leukotrienes. Usually this intermediate is synthesized by Rosenmund reduction of the acid chloride (**46**). We have found this rather unreliable and have converted δ-valerolactone (**39**) into methyl 5-hydroxypentanoate (**40**) by sodium methoxide catalysed methanolysis. Oxidation of (**40**) with PCC afforded methyl 5-oxopentanoate (**41**). During the course of this work a similar route to (**41**) was reported which employed acid-catalysed transesterification of (**39**) to (**40**).[18] Conversion of the aldehyde (**41**) into methyl 6-phenylhex-5-enoate (**42**) was achieved by reaction with benzylidenetriphenylphosphorane in benzene. The *E*:*Z* ratio was established as 75:25 by g.l.c. The alternative route to (**42**) employed the reaction between 5-hydroxypentanal (**43**) and benzylidenetriphenylphosphorane in dimethyl sulphoxide to give the unsaturated alcohol (**44**) which was characterized as the corresponding saturated 3,5-dinitrobenzoate (**47**). Jones oxidation of (**44**) to the unsaturated acid (**45**) was followed by esterification with diazomethane. A by-product of the Jones oxidation of the unsaturated alcohol (**44**) was the ester (**48**) which showed a molecular ion at *m*/*z* 348 in the mass spectrum. The *E*:*Z* ratio of the unsaturated ester (**42**) was variable and maximally was



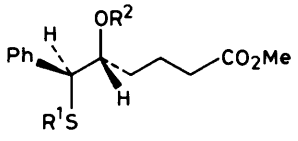
Scheme.

respectively. Additionally, the cysteinyl residues in each isomer gave rise to well defined ABX patterns in which the additional spin–spin coupling of Hx with the NH was observed [$AcNH_MCH_X(CO_2Et)CH_AH_BSR$]: for isomer 1, δ 2.9 (dq, H_AH_B, J_{AB} *ca.* 13.5 Hz), 4.73 [dt, Hx, J_{MX} *ca.* 7.5 Hz, $J_{AX} \simeq J_{BX}$ (apparent) *ca.* 5 Hz], and 6.09 (br d, H_M, J_{MX} *ca.* 7.5 Hz); for isomer 2, δ 2.8 (dq, H_AH_B, J_{AB} *ca.* 13.5 Hz), 4.74 [dq, Hx, J_{MX} *ca.* 7.5 Hz, J_{AX} (apparent) *ca.* 4.5 and J_{BX} (apparent) *ca.* 6 Hz], and 80:20. Reaction of the 5-hydroxypentanal (**43**) with diethyl benzylphosphonate (**49**) and potassium hydride in 1,2-dimethoxyethane (DME) also gave (**44**) which was converted into the unsaturated ester (**42**) in which the *E*:*Z* ratio was 85:15. The ^1H n.m.r. spectrum of methyl 6-phenylhex-5-enoate (**42**) showed a 2H multiplet of δ 5.25—6.58 typical of a (largely) (*E*)-β-substituted styrene and singlets at δ 3.52 and 3.55 were assigned to the OMe of the (*Z*)- and (*E*)-isomers, respectively.

The i.r. ($\nu_{max.}$ 1 740 cm^{-1}) and u.v. ($\lambda_{max.}$ 248 nm) spectra further confirmed the structure.

Oxidation of methyl 6-phenylhex-5-enoate (**42**) (*E*:*Z* *ca.* 80:20) with MCPBA in methylene chloride gave the expected mixture of *trans*- and *cis*-epoxides (**8**). The ^1H n.m.r. spectrum showed the presence of both the *trans*- and *cis*-isomers which exhibited important signals at δ 3.6 (s, OMe), 3.48 (d, *J* *ca.* 3 Hz, PhC*H*), 3.53 (s, OMe), and 4.0 (d, *J* *ca.* 4.5 Hz, PhC*H*), respectively.

Additions to Methyl 6-Phenyl-5,6-epoxyhexanoate (**8**).—The reactions of thiophenol and toluene-α-thiol under normal conditions with the epoxide (**8**) gave the adducts (**50**) and (**52**), respectively, which were purified by preparative t.l.c. The assignment of regiochemistry of adducts (**50**) was supported by the appearance in the mass spectrum of the ions (**18**) and (**15**). Similarly, the appearance of the ion (**17**) in the mass spectrum of the adduct (**52**) supported the assigned regiochemistry [*cf.* the adducts (**9**) and (**11**)]. The ^1H n.m.r. spectra of the acetates (**51**) and (**53**) further confirmed the regiochemistry since they exhibited multiplets for C*H*OAc at δ 5.15—5.40 and 5.10—5.32, respectively. There was no spectroscopic evidence that the adducts (**50**) and (**52**) or their acetates (**51**) and (**53**), respectively were contaminated with diastereoisomeric materials and it is assumed they are largely the *erythro*-adducts.



(**50**) R^1 = Ph, R^2 = H
(**51**) R^1 = Ph, R^2 = Ac
(**52**) R^1 = CH_2Ph, R^2 = H
(**53**) R^1 = CH_2Ph, R^2 = Ac
(**54**) R^1 = $CH_2CHNHAc$, CO_2Me, R^2 = H
(**55**) R^1 = $CH_2CHNHAc$, CO_2Me, R^2 = DNB

Reaction of the epoxide (**8**) (*E*:*Z* *ca.* 80:20) with methyl *N*-acetyl-cysteine (**31**) under normal conditions gave the hydroxy sulphide (**54**) as a diastereoisomeric mixture. The ^1H n.m.r. spectrum showed important bands at δ 6.3—6.8 (br m, NH), 4.50—4.95 (m, C*H*NHAc), 3.8—4.1 (m, PhC*H* and C*H*OH), 3.65 and 3.75 (s, OMe, cys), 3.62 (s, CO_2Me), 2.66—3.00 (m, CH_2S), 2.13—2.40 (m, CH_2CO_2Me), 1.90 and 2.02 (s, NHCO*Me*), and 1.1—2.0 (m, 4 H, $-CH_2-CH_2$). The appearance of the important ions (**37**) and (**38**) in the mass spectrum supports the structural assignment, as do the spectroscopic data for the 3,5-dinitrobenzoate (**55**). In particular, the ^1H n.m.r. spectrum of (**55**) showed a lowfield multiplet for C*H*ODNB at δ 5.3—5.65 and two doublets (*J* *ca.* 6 Hz) at δ 4.15 and 4.26 for PhC*H*. It is assumed that the adducts (**54**) and (**55**) are most likely to be largely *erythro* as for (**50**)—(**53**). Although the diastereoisomeric mixtures (**54**) and (**55**) could not be separated chromatographically or crystallized and the reaction of ethyl cysteine (**32**) with the epoxide failed to give well defined products [*cf.* *trans*-β-methylstyrene oxide (**4**)], we believe these preliminary results are encouraging. Further investigation of the reactions of the epoxide (**8**) with cysteine and its other derivatives (*e.g.* methyl *N*-trifluoroacetylcysteine) and with glutathione and its derivatives are proposed. Additionally, it is expected that other aromatic systems (carbocyclic or heterocyclic) may be substituted for the phenyl residue in the epoxide (**8**).

Experimental

^1H N.m.r. spectra were recorded at 60 and 90 MHz in deuteriochloroform or $(CD_3)_2SO$ (10% in deuteriochloroform) using Varian EM 360A and Perkin-Elmer R32 spectrometers. ^1H N.m.r. spectra, at 400 MHz, were recorded using a Bruker WH400 spectrometer and ^{13}C n.m.r. spectra using a Bruker WP80 spectrometer. I.r. spectra were recorded for thin films (liquids) or Nujol mulls (solids) using a Perkin-Elmer 257 spectrophotometer. U.v. spectra were obtained for ethanolic solutions using a Pye-Unicam SP8-100 spectrophotometer. Mass spectra were recorded with AEI MS 12 or Kratos MS80 and MS50 spectrometers. M.p.s were determined on a Kofler hot stage microscope and are uncorrected. Preparative t.l.c. was performed on silica gel (Merck 60 PF254 + 366) or alumina (Merck 60 PF254) spread on 1M plates at a thickness of 0.75 mm. Column chromatography was carried out using silica gel or alumina (Camag) with a stationary phase to product ratio of > 30:1. G.l.c. employed a Pye 104 series chromatograph with hydrogen flame ionization detector and a 5 ft column (3% SE30 on Chromaborb W), and was used for a determination of *Z*:*E* and *cis*:*trans* ratios for β-substituted styrenes and epoxides. Unless otherwise stated, all solutions of products in organic solvents were routinely dried over anhydrous magnesium sulphate and evaporated under reduced pressure on a rotary evaporator.

(*Z*)-β-*Methylstyrene and* cis-β-*Methylstyrene Oxide* (**5**).—A suspension of ethyltriphenylphosphonium bromide (16 g) in dry benzene (100 ml) was stirred under a nitrogen atmosphere and treated with a solution (28 ml) of butyl-lithium (1.5M) in hexane. After 0.5 h, a solution of benzaldehyde (2.3 g) in benzene (20 ml) was added dropwise over 10 min and stirring was continued at room temperature for 6 h. The reaction mixture was poured into light petroleum (b.p. 40—60 °C; 200 ml) and filtered. The filtrate was washed with water (2 × 100 ml) and dried. Evaporation gave a residue which, after column chromatography on silica gel, elution with hexane, and distillation, gave β-methylstyrene (2.3 g, 90%), b.p. at 20 mm Hg, 65—70 °C, *Z*:*E* *ca.* 75:25 (lit.,[19] b.p. at 20 mm Hg for *Z*-isomer, 64.5 °C); $\lambda_{max.}$ 247 nm (ε 10 900). Use of benzene–HMPA (3:1) gave 94% of a product with b.p. at 20 mm Hg, 64—68 °C, *Z*:*E* ratio *ca.* 85:15.

A solution of the β-methylstyrene (5 g) (*Z*:*E* *ca.* 75:25) in dichloromethane (100 ml) was cooled in ice and treated with *m*-chloroperoxybenzoic acid (85%, 9.5 g). The solution was allowed to warm to room temperature and after 4 h the reaction mixture was diluted with dichloromethane (100 ml) and then washed with saturated aqueous sodium sulphite (50 ml), aqueous sodium hydrogen carbonate (5%; 3 × 50 ml), and water, and dried. The residue obtained by evaporation was subjected to column chromatography on silica gel (eluting with ether) to afford β-methylstyrene oxide (4.05 g, 59%), *cis* : *trans* ratio *ca.* 75:25 [Found: *m*/*z* 134 ($M^{+\cdot}$). $C_9H_{10}O$ requires $M^{+\cdot}$ 134].

(*Z*)-4-*Methoxy*-β-*methylstyrene and* cis-4-*Methoxy*-β-*methylstyrene Oxide* (**7**).—Using a procedure similar to that outlined above, ethyltriphenylphosphonium bromide (37 g) in THF (200 ml) and HMPA (65 ml) was allowed to react with a solution (66 ml) of butyl-lithium (1.5M) in hexane. Addition of *p*-anisaldehyde (10 g), followed by work-up and column chromatography on silica gel afforded, after distillation, 4-methoxy-β-methylstyrene (9.2 g, 85%), b.p. at 15 mm Hg, 100—112 °C, *Z*:*E* *ca.* 85:15 (lit.,[20] b.p. at 16 mm Hg, 106—112 °C); $\lambda_{max.}$ 257 nm (ε

15 700). A solution of 4-methoxy-β-methylstyrene (5.0 g) (*Z*:*E* *ca.* 85:15) in dichloromethane (10 ml) was added to a stirred solution of *m*-chloroperoxybenzoic acid (85%, 7.5 g) in dichloromethane (100 ml) and aqueous sodium hydrogen carbonate (5%; 30 ml). After 2 h, the reaction mixture was poured into ether (100 ml) and the organic layer was washed with aqueous sodium carbonate (5%; 3 × 50 ml) and water, and then dried. The residue obtained by evaporation was subjected to column chromatography on basic alumina (eluting with ether), to afford 4-methoxy-β-methylstyrene oxide (5.7 g, 86%), *cis*:*trans* ratio *ca.* 85:15 [Found: *m/z* 164 ($M^{+\cdot}$). $C_{10}H_{12}O_2$ requires $M^{+\cdot}$ 164].

General Procedure for Thiol Additions to Epoxides.—The epoxide (200 mg), triethylamine (4 equiv.), thiol (3 equiv.), and methanol (1 ml) were stirred under an atmosphere of nitrogen until t.l.c. on silica gel (benzene–ethyl acetate 10:1) indicated complete reaction. The reaction mixture was diluted with ether (30 ml), washed with aqueous sodium hydrogen carbonate (5%, 3 × 10 ml), dilute hydrochloric acid (3 × 10 ml), and water (10 ml), dried, and evaporated. Products were isolated by preparative t.l.c. on silica gel with benzene–ethyl acetate (10:1). By the above procedure, the following results were obtained.

(*a*) *trans*-Methylstyrene oxide (**4**) with thiophenol gave erythro-1-*phenyl*-1-*phenylthiopropan*-2-*ol* (**9**) as a pale yellow oil (93%), $\nu_{max.}$ 3 500 cm^{-1} (OH); δ 7.10—7.45 (m, 2 × Ph), 3.96—4.30 (m, PhSC*H* and MeC*H*OH), 2.50 (br s, exch. with D_2O, OH), and 1.20 (d, *J ca.* 7 Hz, *Me*CH) [Found: *m/z* 244.0922 ($M^{+\cdot}$), 200.0664 ($M - C_2H_4O)^{+\cdot}$ (100%), and 199.0593 ($M - C_2H_5O)^+$. $C_{15}H_{16}OS$, $C_{13}H_{12}S$, and $C_{13}H_{11}S$ require 244.0922, 200.0660, and 199.0581, respectively].

(*b*) *trans*-4-Methoxy-β-methylstyrene oxide (**6**) with thiophenol gave erythro-1-(4-*methoxyphenyl*)-1-*phenylthiopropan*-2-*ol* (**10**) as a pale yellow oil (90%), $\nu_{max.}$ 3 420 cm^{-1} (OH); δ 6.70—7.35 (m, Ph and $MeOC_6H_4$), 3.90—4.25 (m, PhSC*H* and MeC*H*OH), 3.75 (s, MeO), 2.25 (br s, exch. with D_2O, OH), and 1.22 (d, *J* 6 Hz, *Me*CH) [Found: *m/z* 274.1017 ($M^{+\cdot}$), 229.0663 ($M - C_2H_5O)^+$, and 165.0917 ($M - C_6H_5S)^+$ (100%). $C_{16}H_{18}O_2S$, $C_{14}H_{13}OS$, and $C_{10}H_{13}O_2$ require 274.1028, 229.0687, and 165.0916, respectively].

(*c*) *trans*-β-Methylstyrene oxide (**4**) with toluene-α-thiol gave erythro-1-*benzylthio*-1-*phenylpropan*-2-*ol* (**11**) as a pale yellow oil (76%), $\nu_{max.}$ 3 430 cm^{-1} (OH); δ 7.0—7.35 (m, 2 × Ph), 4.04 (dq, *J* 6 and 6 Hz, MeC*H*OH), 3.66 (d, *J* 6 Hz, PhCH$_2$SC*H*), 3.52 (ABq, *J* 14 Hz, PhCH_2S), 2.60 (br s, exch. with D_2O, OH), and 1.17 (d, *J* 6 Hz, *Me*CH) [Found: *m/z* 214.0808 ($M - C_2H_4O)^{+\cdot}$, 213.0737 ($M - C_2H_5O)^+$, and 91.0560 ($M - C_9H_{11}OS)^+$. $C_{14}H_{14}S$, $C_{14}H_{13}S$, and C_7H_7 require 214.0816, 213.0738, and 91.0548, respectively].

(*d*) *cis*-Methylstyrene oxide (**5**) [containing 25% of (**4**)] with thiophenol gave a mixture (48%) of the erythro-*adduct* (**9**) and the threo-*adduct* (**20**), $\nu_{max.}$ 3 500 cm^{-1} (OH); δ 7.10—7.50 (m, 2 × Ph), 3.95—4.30 (m, PhSC*H* and MeC*H*OH), 2.45 (br s, exch. with D_2O, OH), 1.20 (d, *J* 7 Hz, *erythro Me*CH), and 1.05 (d, *J* 7 Hz, *threo Me*CH) (Found: $M^{+\cdot}$ 244.0925. $C_{15}H_{16}OS$ requires 244.0922); and threo-1-*phenyl*-2-*phenylthiopropan*-1-*ol* (**25**) as a pale yellow oil (46%), $\nu_{max.}$ 3 440 cm^{-1} (OH); δ 7.00—7.55 (m, 2 × Ph), 4.35 (d, *J* 9 Hz, PhC*H*OH), 3.26 (dq, *J* 7 and 9 Hz, PhSC*H*), and 1.05 (d, *J* 7 Hz, *Me*CH) [Found: *m/z* 244.0920 ($M^{+\cdot}$), 138.0491 ($M - C_7H_6O)^{+\cdot}$ (100%), and 137.0416 ($M - C_7H_7O)^+$. $C_{15}H_{16}OS$, $C_8H_{10}S$, and C_8H_9S require 244.0922, 138.0503, and 137.0425, respectively].

(*e*) *cis*-β-Methylstyrene oxide (**5**) [containing 25% of (**4**)] with toluene-α-thiol gave a mixture (31%) of the erythro-*adduct* (**11**) and the threo-*adduct* (**21**), $\nu_{max.}$ 3 430 cm^{-1} (OH); δ 7.05—7.4 (m, 2 × Ph), 3.85—4.20 (m, MeC*H*OH), 3.3—3.8 (m, PhCH$_2$SC*H* and PhCH_2S), 2.10 (br s, exch. with D_2O, OH), 1.17 (d, *J* 6 Hz, *erythro Me*CH), and 1.02 (d, *J* 6 Hz, *threo Me*CH) [Found: *m/z* 214.0811 ($M - C_2H_4O)^{+\cdot}$, 213.0734 ($M - C_2H_5O)^+$, and 91.0555 ($M - C_9H_{11}OS)^+$. $C_{14}H_{14}S$, $C_{14}H_{13}S$, and C_7H_7 require 214.0816, 213.0738, and 91.0548, respectively); and threo-1-*phenyl*-2-*benzylthiopropan*-2-*ol* (**26**) as a pale yellow oil (23%), $\nu_{max.}$ 3 440 cm^{-1} (OH); δ 7.20—7.50 (m, 2 × Ph), 4.43 (d, *J* 7 Hz, PhC*H*OH), 3.70 (s, PhCH_2S), 2.60—3.25 (br s, exch. with D_2O, OH), 2.93 (dq, *J* 7 and 7 Hz, PhCH$_2$SC*H*), and 1.03 (d, *J* 7 Hz, *Me*CH) [Found: *m/z* 258.1046 ($M^{+\cdot}$), 152.0664 ($M - C_7H_6O)^{+\cdot}$, and 151.0569 ($M - C_7H_7O)^+$. $C_{16}H_{18}OS$, $C_9H_{12}S$, and $C_9H_{11}S$ require 258.1078, 152.0660, and 151.0582, respectively].

(*f*) *cis*-4-Methoxy-β-methylstyrene oxide (**7**) [containing 15% of (**6**)] with thiophenol gave threo-1-(4-*methoxyphenyl*)-1-*phenylthiopropan*-2-*ol* (**22**) (64%), m.p. 60—62 °C (from ethyl acetate–hexane), $\nu_{max.}$ 3 420 cm^{-1} (OH); δ 6.70—7.35 (m, Ph and $MeOC_6H_4$), 3.85—4.20 (m, PhSC*H* and MeC*H*OH), 3.72 (s, MeO), 2.80 (br s, exch. with D_2O, OH), and 1.10 (d, *J* 6 Hz, *Me*CH) [Found: C, 70.0; H, 6.7; S, 11.5%. *m/z* 274.1025, ($M^{+\cdot}$), 229.0686 ($M - C_2H_5O)^+$, and 165.0918 ($M - C_6H_5S)^+$ (100%). $C_{16}H_{18}O_2S$ requires C, 70.05; H, 6.55; S, 11.70%; $M^{+\cdot}$, 274.1028; $C_{14}H_{13}OS$ and $C_{10}H_{13}O_2$ require 229.0687 and 165.0916, respectively].

General Procedure for Acetylation of Hydroxy Sulphides.—The hydroxy sulphide (100 mg) was dissolved in a mixture of pyridine (2 ml) and acetic anhydride (1 ml) and was left at room temperature for 24 h. The reaction mixture was poured into ether (30 ml) and washed with aqueous sodium hydrogen carbonate (5%; 3 × 10 ml), dilute hydrochloric acid (3 × 10 ml), and water (1 × 10 ml), and then dried. Evaporation followed by preparative t.l.c. on silica gel, eluting with benzene, gave the acetate. Using this procedure, the hydroxy sulphides were converted into the corresponding acetates as follows.

(*a*) The *erythro*-hydroxy sulphide (**9**) gave erythro-2-*acetoxy*-1-*phenyl*-1-*phenylthiopropane* (**12**) as a pale yellow oil (93%), $\nu_{max.}$ 1 740 and 1 240 cm^{-1} ($MeCO_2$); δ 7.05—7.40 (m, 2 × Ph) 5.33 (dq, *J* 6 and 7 Hz, MeC*H*OAc), 4.30 (d, *J* 6 Hz, PhSC*H*), 1.90 (s, $MeCO_2$), and 1.30 (d, *J* 7 Hz, *Me*CH) [Found: *m/z* 286 ($M^{+\cdot}$). $C_{17}H_{18}O_2S$ requires $M^{+\cdot}$ 286].

(*b*) The *erythro*-hydroxy sulphide (**10**) gave erythro-2-*acetoxy*-1-(4-*methoxyphenyl*)-1-*phenylthiopropane* (**13**), as a pale yellow oil (82%), $\nu_{max.}$ 1 740 and 1 240 cm^{-1} ($MeCO_2$); δ 6.52—7.56 (m, Ph and $MeOC_6H_4$), 5.20 (dq, *J* 6 and 6 Hz, MeC*H*OAc), 4.20 (d, *J* 6 Hz, PhSC*H*), 1.90 (s, MeCOO), and 1.22 (d, *J* 7 Hz, *Me*CH) [Found: *m/z* 316 ($M^{+\cdot}$). $C_{18}H_{20}O_3S$ requires $M^{+\cdot}$ 316].

(*c*) The *erythro*-hydroxy sulphide (**11**), gave erythro-2-*acetoxy*-1-*benzylthio*-1-*phenylpropane* (**14**) as a pale yellow oil (79%), $\nu_{max.}$ 1 735 and 1 235 ($MeCO_2$) cm^{-1}; δ 7.05—7.40 (m, 2 × Ph), 5.28 (dq, *J* 7 and 7 Hz, MeC*H*OAc), 3.79 (d, *J* 7 Hz, PhCH$_2$SC*H*), 3.55 (ABq, *J* 14 Hz, PhCH_2S), 1.91 (s, $MeCO_2$), and 1.24 (d, *J* 7 Hz, *Me*CH) [Found: *m/z* 300 ($M^{+\cdot}$). $C_{18}H_{20}O_2S$ requires $M^{+\cdot}$ 300].

(*d*) A mixture (1:1) of the *erythro*- and *threo*-hydroxy sulphides (**9**) and (**20**) gave a mixture of *erythro*- and *threo*-acetoxy sulphides (**12**) and (**23**) as a pale yellow oil (92%), $\nu_{max.}$ 1 730 and 1 230 cm^{-1} ($MeCO_2$); δ 7.1—7.4 (m, 2 × Ph), 5.33 (m, MeC*H*OAc), 4.33 (d, *J* 8 Hz, *threo*, PhSC*H*), 4.30 (d, *J* 6 Hz, *erythro*, PhSC*H*), 1.98 (s, *threo*, $MeCO_2$), 1.90 (s, *erythro*, $MeCO_2$), 1.30 (d, *J* 7 Hz, *erythro*, *Me*CH), and 1.20 (d, *J* 7 Hz, *threo*, *Me*CH) [Found: *m/z* 286 ($M^{+\cdot}$). $C_{17}H_{18}O_2S$ requires $M^{+\cdot}$ 286].

(*e*) A mixture (1:1.3) of the *erythro*- and *threo*-hydroxy sulphides (**11**) and (**21**) gave a mixture of *erythro*- and *threo*-acetoxy sulphides (**14**) and (**24**) as a pale yellow oil (91%), $\nu_{max.}$ 1 740 and 1 235 cm^{-1} ($MeCO_2$); δ 7.05—7.45 (m, 2 × Ph), 5.28 (m, *Me*CHOAc), 3.82 (d, *J* 7 Hz, *threo*, PhCH$_2$SC*H*), 3.79 (d, *J* 7 Hz, *erythro*, PhCH$_2$SC*H*), 3.55 (m, PhCH_2S), 2.07 (s, *threo*, $MeCO_2$), 1.91, (s, *erythro*, $MeCO_2$), 1.24 (d, *J* 7 Hz, *erythro*,

*Me*CH), and 1.13 (d, *J* 7 Hz, *threo*, *Me*CH) [Found: *m/z* 300 ($M^{+\cdot}$). $C_{18}H_{20}O_2S$ requires $M^{+\cdot}$ 300].

(*f*) The *threo*-hydroxy sulphide (**25**) gave threo-1-*acetoxy*-1-*phenyl*-2-*phenylthiopropane* (**27**) as a colourless oil (91%), $\nu_{max.}$ 1 740 and 1 230 cm^{-1} ($MeCO_2$); δ 7.05—7.55 (m, 2 × Ph), 5.80 (d, *J* 7 Hz, PhC*H*OAc), 3.62 (dq, *J* 7 and 7 Hz, PhSC*H*), 1.96 (s, $MeCO_2$), and 1.15 (d, *J* 7 Hz, *Me*CH) [Found: *m/z* 286 ($M^{+\cdot}$). $C_{17}H_{18}O_2S$ requires $M^{+\cdot}$ 286].

(*g*) The *threo*-hydroxy sulphide (**26**) gave threo-1-*acetoxy*-2-*benzylthio*-1-*phenylpropane* (**28**) as a pale yellow oil (85%), $\nu_{max.}$ 1 740 and 1 235 cm^{-1} ($MeCO_2$); δ 7.18—7.50 (m, 2 × Ph), 5.80 (d, *J* 7 Hz, PhC*H*OAc), 3.70 (s, PhCH_2S), 3.0 (dq, *J* 7 and 7 Hz, PhCH$_2$SC*H*), 2.05 (s, $MeCO_2$), and 1.10 (d, *J* 7 Hz, *Me*CH) [Found: *m/z* 300 ($M^{+\cdot}$). $C_{18}H_{20}O_2S$ requires $M^{+\cdot}$ 300].

Reactions of Cysteine Derivatives with trans-β-*Methylstyrene Oxide* (**4**).—(*a*) *Reaction with methyl* N-*acetylcysteinate* (**31**). The reaction of methyl *N*-acetylcysteinate (**31**) with (**4**) under the general conditions described above gave 1-(2-*acetamido*-2-*methoxycarbonylethylthio*)-1-*phenylpropan*-2-*ol* (**33**) as a viscous yellow oil (44%), $\nu_{max.}$ 3 380 and 3 300 (NH and OH), 1 745 (CO_2Me), and 1 660 cm^{-1} (NHAc); δ 7.33 (br s, Ph), 6.5—7.0 (br m, NH), 4.7—4.9 (m, C*H*NHAc), 3.95—4.25 (m, MeC*H*OH), 3.82 and 3.88 (d, *J* 6 Hz, PhC*H*), 3.62 and 3.73 (s, OMe), 2.7—3.0 (m, RSCH_2), 2.58 (br s, exch. with D_2O, OH), 1.88 and 2.00 (s, *Me*CONH), and 1.20 (d, *J* 6 Hz, *Me*CH) [Found: *m/z* 267.0920 ($M - C_2H_4O)^{+\cdot}$ and 266.0828 ($M - C_2H_5O)^+$. $C_{13}H_{17}NO_3S$ and $C_{13}H_{16}NO_3S$ require 267.0929 and 266.0851, respectively].

Acetylation of the hydroxy sulphide (**33**) under the usual conditions gave the *2-acetoxy*-1-(2-*acetamido*-2-*methoxycarbonylethylthio*)-1-*phenylpropane* (**34**) as a pale yellow oil (73%), $\nu_{max.}$ 3 340 (NH), 1 740 (CO_2Me and $MeCO_2$), 1 665 (NHAc), and 1 240 cm^{-1} (C–O of $MeCO_2$); δ 7.35 (br s, Ph), 5.95—6.4 (br m, NH), 5.1—5.4 (m, MeC*H*OAc), 4.6—4.85 (m, C*H*NHAc), 3.95 and 3.98 (d, *J* 6 Hz, PhC*H*), 3.65 and 3.75 (s, OMe), 2.95—3.7 (m, RSCH_2), 1.88 and 2.05 (s, *Me*CONH), 1.95 (s, $MeCO_2$), and 1.25 (d, *J* 6 Hz, *Me*CH) [Found: *m/z* 353 ($M^{+\cdot}$). $C_{17}H_{23}NO_5S$ requires $M^{+\cdot}$ 353].

(*b*) *Reaction with ethyl cysteinate*.[21] A solution of the *trans*-epoxide (**4**) (200 mg) in methanol–water (10:1, 2 ml) was treated with ethyl cysteinate (**32**) (300 mg) and triethylamine was added to bring the pH to *ca.* 8.5. The reaction mixture was stirred at room temperature for 24 h and worked up to afford, after preparative t.l.c. on silica gel (eluting with cyclohexane–ethyl acetate 10:1), 1-(2-*ethoxycarbonylethylthio*)-1-*phenylpropan*-2-*ol* (**35**), as a colourless oil (257 mg, 60%), $\nu_{max.}$ 3 250—3 500 (NH_2 and OH) and 1 740 cm^{-1} (CO_2Et); δ 7.2—7.5 (br s, Ph), 3.7—4.35 (m, MeCH_2O, MeC*H*OH, and PhC*H*), 3.3—3.7 (m, C*H*NH$_2$), 2.5—3.0 (m, RSCH_2), 2.2 (br, s, exch. with D_2O, NH_2 and OH), and 1.1—1.4 (m, *Me*CH and CO_2CH_2*Me*) [Found: *m/z* 283 ($M^{+\cdot}$). $C_{14}H_{21}NO_3$ requires $M^{+\cdot}$ 283].

Acetylation of the hydroxy sulphide (**35**) under the usual conditions gave 2-*acetoxy*-1-(2-*acetamido*-2-*ethoxycarbonylethylthio*)-1-*phenylpropane* (**36**) (67%), m.p. 78—82 °C (from aqueous methanol), $\nu_{max.}$ 3 340 (NH), 1 740 (CO_2Et and $MeCO_2$), 1 660 (NHAc), and 1 235 cm^{-1} (C–O of $MeCO_2$) [Found: C, 58.3; H, 7.0; N, 3.7; S, 8.45%; *m/z* 307 ($M - C_2H_4O_2)^+$. $C_{18}H_{21}NO_5S$ requires C, 58.85; H, 6.85; N, 3.8; S, 8.7%; $C_{16}H_{21}NO_3S$ requires $M^{+\cdot}$ 307].

Preparative t.l.c. on silica gel, eluting with benzene–ethyl acetate–triethylamine (66:33:1), allowed the separation of the hydroxy sulphide (**35**) into two isomers, isomer 1 (R_F 0.4) being less polar than isomer 2 (R_F 0.3). Both isomers, which had similar ^1H n.m.r. spectra to that recorded for their mixture, were acetylated under the usual conditions to afford the *acetoxy sulphide* (isomer 1) (**36**) (82%), m.p. 89—91 °C, $[\alpha]_D$ ($CHCl_3$) +62.4°; δ (400 MHz) 7.25—7.38 (m, Ph), 6.09 (br d, *J* 7.5 Hz, N*H*COMe), 5.23 (dq, *J* 6 and 6 Hz, MeC*H*OAc), 4.73 (dt, *J* 7.5 and 5 Hz, C*H*NHAc), 4.22 (m, OCH_2Me), 3.91 (d, *J* 6 Hz, PhC*H*), 2.90 (dq, J_{AB} 13.5 Hz, RSCH_AH_B), 1.96 (s, $MeCO_2$), 1.90 (s, MeCONH), 1.30 (t, *J* 7 Hz, OCH$_2$*Me*), and 1.25 (d, *J* 6 Hz, *Me*CH) [Found: *m/z* 307.1243 ($M - C_2H_4O_2)^{+\cdot}$ and 280.0992 ($M - C_4H_7O_2)^+$. $C_{16}H_{21}NO_3S$ and $C_{14}H_{18}NO_3S$ require 307.1242 and 280.1007]; and the *acetoxy sulphide* (isomer 2) (**36**) (90%), m.p. 102—105 °C, $[\alpha]_D$ ($CHCl_3$) −79.2°; δ (400 MHz) 7.24—7.36 (m, Ph), 6.20 (br d, *J* 7.5 Hz, N*H*COMe), 5.25 (dq, *J* 6 and 6 Hz, MeC*H*OAc), 4.74 (dq, *J* 7.5, 6, and 4.5 Hz, C*H*NHAc), 4.13 (m, OCH_2Me), 3.97 (d, *J* 6 Hz, PhC*H*), 2.80 (dq, J_{AB} 13.5 Hz, RSCH_AH_B), 2.04 (s, $MeCO_2$), 1.96 (s, *Me*CONH), 1.25 (d, *J* 6 Hz, *Me*CH), and 1.21 (t, *J* 7 Hz, OCH$_2$*Me*) [Found: *m/z* 307.1238 ($M - C_2H_4O_2)^{+\cdot}$ and 280.1023 ($M - C_4H_7O_2)^+$. $C_{16}H_{21}NO_3S$ and $C_{14}H_{18}NO_3S$ require 307.1242 and 280.1007].

Methyl 5-*Oxopentanoate* (**41**).—δ-Valerolactone (**39**) (20 g) was dissolved in a solution of sodium methoxide which was prepared from sodium (1 g) and anhydrous methanol (50 ml). After being heated under reflux for 3 h, the reaction mixture was poured into water and extracted with ether (3 × 50 ml) and chloroform (3 × 50 ml). The combined organic extracts were washed with water, dried, and evaporated to give methyl 5-hydroxypentanoate (**40**) as a yellow oil (22 g, 83%), $\nu_{max.}$ 3 480 (OH) and 1 740 cm^{-1} (CO_2Me); δ 3.67 (s, OMe), 3.2—3.75 (m, CH_2OH), 2.36 (br s, exch. with D_2O, OH), 2.05—2.60 (m, CH_2CO_2Me), and 1.25—2.0 (m, 2 × CH_2). Without further purification, the hydroxy ester (**40**) (14 g) in dry dichloromethane (10 ml) was added to a stirred suspension of pyridinium chlorochromate in dry dichloromethane (200 ml). After 2 h, ether (500 ml) was added and the supernatant was decanted from a black residue which was washed with ether (3 × 100 ml). The combined organic solutions were filtered through HyFlo and evaporated. Distillation gave methyl 5-oxopentanoate (**41**) (12.1 g, 88%), b.p. at 1.5 mmHg, 52—60 °C (lit.,[22] b.p. at 23 mmHg, 100—103 °C); $\nu_{max.}$ 1 735 (CHO and CO_2Me) cm^{-1}; δ 9.60 (br s, CHO), 3.70 (s, OMe), 2.12—2.78 (m, 2 × CH_2COR), and 1.5—2.12 (m, CH_2).

6-*Phenylhex*-5-*en*-1-*ol* (**44**).—Benzyltriphenylphosphonium bromide (75.5 g) was added to a solution of NaH (60% dispersion; 7.15 g) in dry DMSO (400 ml) at room temperature and under a nitrogen atmosphere. After 0.5 h, a solution of 5-hydroxypentanal (**43**) (10 g) in DMSO (100 ml) was added dropwise over 10 min and with stirring. After 18 h, the reaction mixture was poured into ether (250 ml) and filtered. The organic layer was washed with water (3 × 200 ml), dried, and evaporated to afford a residue which on column chromatography on silica gel (eluting with cyclohexane–ethyl acetate (10:1) gave the *alcohol* (**44**) as a colourless oil (9.6 g, 69%), $\nu_{max.}$ 3 400 cm^{-1} (OH), $\lambda_{max.}$ 246 nm (ε 6 430); δ 7.28 (br s, Ph), 5.35—6.6 (m, CH=CH), 3.2—3.83 (m, CH_2OH), 2.50 (br s, exch. with D_2O, OH), 2.0—2.6 (m, CH_2–CH=CH), and 1.05—1.95 (2 × CH_2). A similar product was obtained (45%) by reaction of 5-hydroxypentanal (**43**) (0.005 mol) with diethyl benzylphosphonate (**49**) (0.01 mol) and potassium hydride (0.01 mol) in DME.

6-*Phenylhexyl* 3,5-*Dinitrobenzoate* (**47**).—A solution of (**44**) (126 mg) in ethyl acetate (5 ml) was added to a suspension of prehydrogenated Pd–C catalyst (10%; 10 mg) in ethyl acetate (20 ml) in an atmosphere of hydrogen. After 18 h, the solution was filtered and evaporated to afford the crude hydrogenated product which was esterified under standard conditions with 3,5-dinitrobenzoyl chloride in pyridine. The usual work-up afforded the *dinitrobenzoate* (**47**), m.p. 58—60 °C (from methanol) (Found: C, 61.3; H, 5.5; N, 7.5. $C_{19}H_{20}N_2O_6$ requires C, 61.3; H, 5.4; N, 7.5%).

Methyl 6-Phenylhex-5-enoate (**42**).—(*a*) A suspension of benzyltriphenylphosphonium bromide (17.7 g) in dry benzene (100 ml) was stirred under an atmosphere of nitrogen and treated with a solution (26.6 ml) of butyl-lithium (1.5M) in hexane. After 0.5 h, the aldehyde (**41**) (5.2 g) was added and stirring was continued for a further 3 h at room temperature. The reaction mixture was poured into dry hexane (500 ml), filtered, and evaporated and the resultant residue was subjected to column chromatography on silica gel eluting with ethyl acetate–cyclohexane (1:10), to afford the *unsaturated ester* (**42**) as a pale yellow oil (4.8 g, 59%), *E*:*Z* *ca.* 75:25, $\nu_{max.}$ 1 740 cm^{-1} (CO_2Me); $\lambda_{max.}$ 248 nm (ε 7 570); δ 7.25 (br s, Ph), 5.25—6.58 (m, CH=CH), 3.55 (s, *E*-CO_2Me) and 3.52 (s, *Z*-CO_2Me), 2.0—2.55 (m, CH_2–CH=CH and CH_2CO_2Me), and 1.35—2.0 (m, CH_2) [Found: *m/z* 204 ($M^{+\cdot}$). $C_{13}H_{16}O_2$ requires $M^{+\cdot}$ 204].

(*b*) A solution of the unsaturated alcohol (**44**) (9.6 g) in acetone (150 ml) was cooled in an ice bath and treated with Jones reagent (50 ml) and stirred for 45 min, after which the reaction mixture was diluted with water (200 ml) and extracted with ether (3 × 200 ml). The extracts were combined, washed with water, dried, and evaporated. Column chromatography of the residue on silica gel, eluting with ethyl acetate–cyclohexane, gave 6-phenylhex-5-enoic acid (**45**)[23] as a pale yellow oil (7.5 g, 70%), $\nu_{max.}$ 2 480—3 440 and 1 710 cm^{-1} (CO_2H); $\lambda_{max.}$ 248 nm (ε 9 100); δ 11.0 (br s, exch. with D_2O, CO_2H), 7.32 (br s, Ph), 5.3—6.6 (m, CH=CH), 2.15—2.76 (m, CH_2–CH=CH and CH_2CO_2H), and 1.46—2.12 (m, CH_2) [Found: *m/z* 190.0995 ($M^{+\cdot}$). $C_{12}H_{14}O_2$ requires $M^{+\cdot}$ 190.0993] and 6-phenylhex-5-enyl 6-phenylhex-5-enoate (**48**) as a pale yellow oil (0.67 g, 7%), $\nu_{max.}$ 1 740 cm^{-1} (CO_2R); $\lambda_{max.}$ 248 (ε 10 100); δ 7.35 (m, 2 × Ph), 5.38—6.6 (m, 2 × CH=CH), 3.8—4.20 (m, OCH_2R), and 1.05—2.5 (m, 6 × CH_2) [Found: *m/z* 348 ($M^{+\cdot}$). $C_{24}H_{28}O_2$ requires $M^{+\cdot}$ 348]. The unsaturated acid (**45**) (5.2 g) was esterified under standard conditions with an ethereal solution of diazomethane and afforded the *unsaturated ester* (**42**) (5.6 g, 100%), *E*:*Z* maximally 80:20 when derived from (**43**) by the Wittig reaction and 85:15 when derived from (**43**) by the Horner-Emmons reaction.

Methyl 6-Phenyl-5,6-epoxyhexanoate (**8**).—The unsaturated ester (**42**) (5 g) (*E*:*Z* 80:20) was oxidised with *m*-chloroperoxybenzoic acid in dichloromethane as described above to give, after chromatography, the epoxide (**8**) as a colourless oil (3.7 g, 65%), $\nu_{max.}$ 1 735 cm^{-1} (CO_2Me); δ 7.22 (br s, Ph), 4.0 (d, *J* 4.5 Hz, *cis* PhC*H*), 3.6 (s, *trans* OMe), 3.53 (s, *cis* OMe), 3.48 (d, *J* 3 Hz, *trans* PhC*H*), 2.7—3.35 (m, OCH–CH_2), 2.05—2.62 (m, CH_2CO_2Me), and 1.2—2.0 (m, 2 × CH_2) [Found: *m/z* 220.1099 ($M^{+\cdot}$). $C_{13}H_{16}O_3$ requires $M^{+\cdot}$ 220.1100].

Thiol Additions to Methyl 6-Phenyl-5,6-epoxyhexanoate (**8**).—(*a*) The epoxide (**8**) (*trans*:*cis* *ca.* 80:20) was treated with thiophenol under the general conditions specified above and gave *methyl* erythro-5-*hydroxy*-6-*phenyl*-6-*phenylthiohexanoate* (**50**) (90%), m.p. 84—86 °C (from aqueous methanol), $\nu_{max.}$ 3 500 (OH) and 1 730 cm^{-1} (CO_2Me); δ 6.9—7.5 (m, 2 × Ph), 4.20 (d, *J* 5 Hz, PhSC*H*), 3.75—4.05 (m, CH_2CHOH), 3.58 (s, OMe), 2.55 (br s, exch. with D_2O, OH), 2.0—2.4 (m, CH_2CO_2Me), and 1.1—1.95 (m, 2 × CH_2) [Found: C, 69.1; H, 6.95; S, 9.6% *m/z*. 200.0659 ($M - C_6H_{10}O_3$)$^{+\cdot}$ and 199.0599 ($M - C_6H_{11}O_3$)$^+$ (100%). $C_{19}H_{22}O_3S$ requires C, 69.05; H, 6.7; S, 9.7%; $C_{13}H_{12}S$ and $C_{13}H_{11}S$ require 200.0660 and 199.0581, respectively]. Using the general acetylation procedure described above, the hydroxysulphide (**50**) gave *methyl* erythro-5-*acetoxy*-6-*phenyl*-6-*phenylthiohexanoate* (**51**) as a colourless oil (84%), $\nu_{max.}$ 1 740 cm^{-1} ($MeCO_2$ and CO_2Me); δ 6.9—7.4 (m, 2 × Ph), 5.15—5.40 (m, CH_2CHOAc), 4.30 (d, *J* 6 Hz, PhSC*H*), 3.60 (s, OMe), 2.05—2.36 (m, CH_2CO_2Me), 1.90 (s, $MeCO_2$), and 1.38—1.78 (m, 2 × CH_2) [Found: *m/z* 372 ($M^{+\cdot}$). $C_{21}H_{24}O_4S$ requires $M^{+\cdot}$ 372].

(*b*) The epoxide (**8**) (*trans*:*cis* *ca.* 80:20) was treated with toluene-α-thiol under the general conditions specified above and gave *methyl* erythro-6-*benzylthio*-5-*hydroxy*-6-*phenylhexanoate* (**52**) (70%), m.p. 76—77.5 °C (from aqueous methanol), $\nu_{max.}$ 3 500 (OH) and 1 730 cm^{-1} (CO_2Me); δ 6.9—7.4 (m, 2 × Ph), 3.7—3.95 (m, CH_2CHOH), 3.68 (d, *J* 7 Hz, $PhCH_2SCH$), 3.58 (s, OMe), 3.49 (ABq, *J* 14 Hz, $PhCH_2S$), 2.05—2.4 (m, CH_2CO_2Me), and 1.0—1.95 (m, 2 × CH_2) [Found: C, 69.3; H, 7.0; S, 9.6%. *m/z* 214.0811 ($M - C_6H_{10}O_3$)$^{+\cdot}$, 213.0741 ($M - C_6H_{11}O_3$)$^+$, and 91.0558 ($M - C_{13}H_{17}O_3S$)$^+$ (100%). $C_{20}H_{24}O_3S$ requires C, 69.7; H, 7.0; S, 9.3%; $C_{14}H_{14}S$, $C_{14}H_{13}S$, and C_7H_7 require 214.0816, 213.0738, and 91.0548, respectively]. Using the general acetylation procedure described above, the hydroxy sulphide (**52**) gave *methyl* erythro-5-*acetoxy*-6-*benzylthio*-6-*phenylhexanoate* (**53**) as a pale yellow oil (63%), $\nu_{max.}$ 1 745 cm^{-1} ($MeCO_2$ and CO_2Me); δ 7.03—7.42 (m, 2 × Ph), 5.1—5.32 (m, $CHOAc$) 3.76 (d, *J* 7 Hz, $PhCH_2SCH$), 3.62 (s, OMe), 3.52 (ABq, *J* 14 Hz, $PhCH_2S$), 2.0—2.35 (m, CH_2CO_2Me), 1.88 (s, $MeCO_2$), and 1.3—1.8 (m, 2 × CH_2) [Found: *m/z* 386 ($M^{+\cdot}$). $C_{22}H_{26}O_4S$ requires $M^{+\cdot}$ 386].

Reaction of the Epoxide (**8**) *with Methyl* N-*Acetylcysteinate* (**31**).—Using the standard conditions described above afforded *methyl* erythro-6-(2-*acetamido*-2-*methoxycarbonylethylthio*)-5-*hydroxy*-6-*phenylhexanoate* (**54**) as a yellow viscous oil (64%), $\nu_{max.}$ 3 370—3 500 (NH and OH), 1 740 (CO_2Me), and 1 665 cm^{-1} (NHAc); δ 7.3 (br s, Ph), 6.3—6.8 (br m, NH), 4.5—4.95 (m, $CHNHAc$), 3.8—4.1 (m, PhC*H* and CH_2CHOH), 3.65 and 3.75 (s, CO_2Me, cys), 3.62 (s, CO_2Me), 2.66—3.0 (m, $RSCH_2$), 2.13—2.4 (m, CH_2CO_2Me), 1.90 and 2.02 (s, *Me*CONH), and 1.1—2.0 (m, 2 × CH_2) [Found: *m/z* 267.0928 ($M - C_6H_{10}O_3$)$^{+\cdot}$ and 266.0867 ($M - C_6H_{11}O_3$)$^+$. $C_{13}H_{17}NO_3S$ and $C_{13}H_{16}NO_3S$ require 267.0929 and 266.0851). Reaction of the hydroxy sulphide (**54**) with 3,5-dinitrobenzoyl chloride in pyridine under standard conditions followed by work-up afforded *methyl* erythro-6-(2-*acetamido*-2-*methoxycarbonylethylthio*)-5-(3,5-*dinitrobenzoyloxy*)-6-*phenylhexanoate* (**55**) as a yellow oil, $\nu_{max.}$ 1 740 (CO_2R) and 1 670 cm^{-1} (NHAc); δ 9.15 [m, *p*-H of $C_6H_3(NO_2)_2$] and 8.95 [m, *o*-H of $C_6H_3(NO_2)_2$], 7.1—7.5 (m, Ph), 6.0—6.35 (br m, NH), 5.3—5.65 (m, $CH_2CHOCOR$, 4.5—4.9 (m, $CHNHAc$), 4.15 and 4.26 (d, *J* 6 Hz, PhC*H*), 3.65 and 3.75 (s, CO_2Me, cys), 3.75 (s, CO_2Me), 2.7—3.0 (m, $RSCH_2$), 2.2—2.5 (m, CH_2CO_2Me), 1.95 and 2.03 (s, *Me*CONH), and 1.55—2.15 (m, 2 × CH_2) [Found: *m/z* 591 ($M^{+\cdot}$). $C_{26}H_{29}N_3O_{11}S$ requires $M^{+\cdot}$ 591].

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