Tetrahedron Vol. 46, No 11, pp. 3981–3992, 1990
Printed in Great Britain

0040–4020/90 $3.00+.00

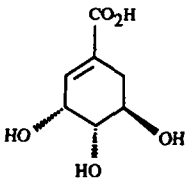
REACTIVITY STUDIES IN THE SHIKIMIC ACID SERIES: THE SYNTHESIS OF RACEMIC METHYL 6α-FLUOROSHIKIMATE

Stephen A.Bowles, Malcolm M. Campbell*, and Malcolm Sainsbury*
School of Chemistry, University of Bath, Claverton Down, Bath,
BA2 7AY, UK
and Gareth M.Davies
ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield,
Cheshire, SK10 4TG, U.K.

(*Received in UK* 2 *March* 1990)

Summary. The regio- and stereo-selective epoxidation of methyl 3,4-dihydrobenzoate derivatives has been investigated. Perbenzimidic acid leads only to epoxides formed at the $\Delta^{1,2}$ bond. More electrophilic reagents such as MCPBA also give products of this type, as well as epoxides formed through attack at the $\Delta^{5,6}$ bond. Reactions of the 3,4-dihydrobenzoates with thiophenate anion have been undertaken as a means of protecting the $\Delta^{1,2}$ bond and thence controlling the regioselectivity of epoxidation. A synthesis of racemic methyl 6α-fluoroshikimate has been achieved through the ring-opening of an epoxide of methyl 3,4-dihydro-3,4-isopropylidenedioxybenzoate.

Aromatic compounds are ubiquitous in Nature and frequently arise through the so-called 'acetate pathway'. In plants and micro-organisms an alternative biosynthetic route may also operate leading *via* shikimic acid (1) to aromatic amino acids. As part of our continuing interest in the synthesis of compounds related to shikimic acid[1], we now report upon the regio- and stereo-selectivity of the epoxidation of methyl 3,4-dihydrobenzoate derivatives and the reactions of the products with electrophiles and nucleophiles. The main substrate for these reactions is the diene acetonide (2), which can be obtained by the dehydration of the hydroxy ester (3) using diethyl azodicarboxylate and triphenylphosphine[2] (Mitsunobu's conditions[3]), or less efficiently with Martin's reagent[4]. When reacted with *m*-chloroperbenzoic acid (MCPBA) the dieneacetonide gives a mixture of the two epoxides (4) and (5) in the ratio 8:3 and a small amount of the α-epoxide (6). The epoxides could not be obtained pure, thus the crude reaction mixture was treated with sodium thiophenate to afford the hydroxysulphides (7) and (8). These products, which can be separated, are derived from ring-opening of the epoxides (4) and (6) respectively, but no product from nucleophilic attack on the isomer (5) was detected. However, in later work we were able to show that this compound does indeed react with sodium thiophenate and forms the allylic alcohol (11), rather than expected hydroxysulphide (10). Sodium hydride alone does not effect this last reaction, thus participation of the thiophenate anion appears essential. A possible mechanism involves S_N2 displacement of the epoxide by thiophenol to form the sulphide (9), which then reacts with excess thiophenate to displace diphenyldisulphide and to generate the carbanion (10). This on protonation produces the conjugated hydroxy ester (11). There are some precedents for displacements of this type[5].



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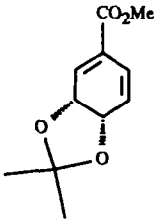

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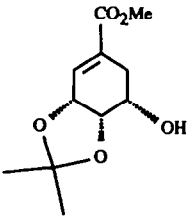

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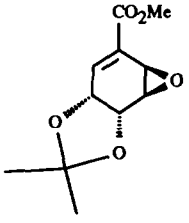

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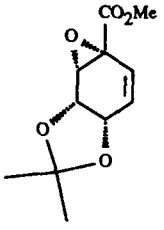

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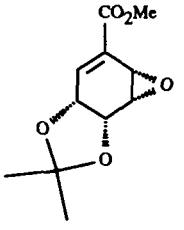
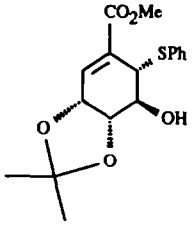


(6)

Treatment of the dieneacetonide (2) with trifluoroperacetic acid caused deprotection and aromatisation to give methyl 3-hydroxybenzoate, but reactions with either vanadylacetylacetonate-^{t}butylhydroperoxide or monoperphthalic acid yielded the same mixture of epoxides as obtained from the reaction with MCPBA[6]. However, when the less electrophilic perbenzimidic acid[7] was used the α-epoxide (5) was obtained in quantitative yield.



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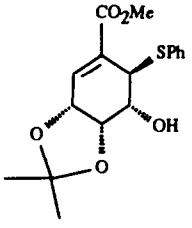

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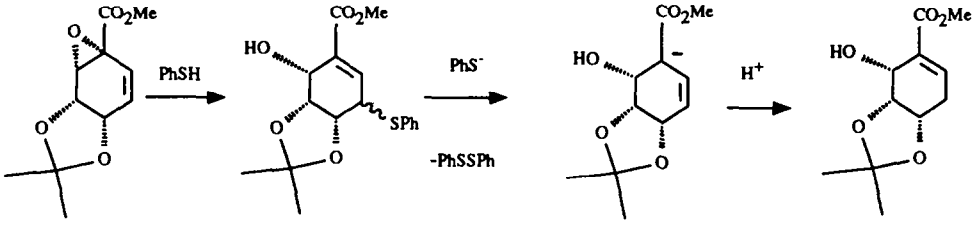
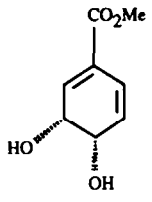


(5) (9) (10) (11)

The stereochemistry of the reaction can be explained if the approach of the reagent was assisted by initial complexation to the acetonide unit. Such an interaction might be enhanced in the dihydroxydiene (12)[8], and in fact this compound when reacted with MCPBA gave the epoxides (13) and (14) in the ratio 1:1[9,10]. The reaction is complete within 10 hours compared with the three days necessary for the reaction between the dieneacetonide and MCPBA, and none of the 5β, 6β-epoxide was isolated, or detected. To circumvent the formation of mixed products we considered using the susceptibility of the 3,4-dihydrobenzoates to conjugate addition[11] by protecting the $\Delta^{1,2}$ bond prior to epoxidation. Thus we envisaged that reaction of the hydroxy ester (3) with sodium thiophenate should give the adduct (15), which after dehydration, could be epoxidized and oxidized in one step to afford the sulphone (16). Elimination of benzenesulphinic acid would then complete the synthesis of the epoxide (4).



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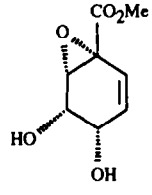

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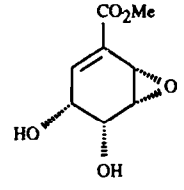

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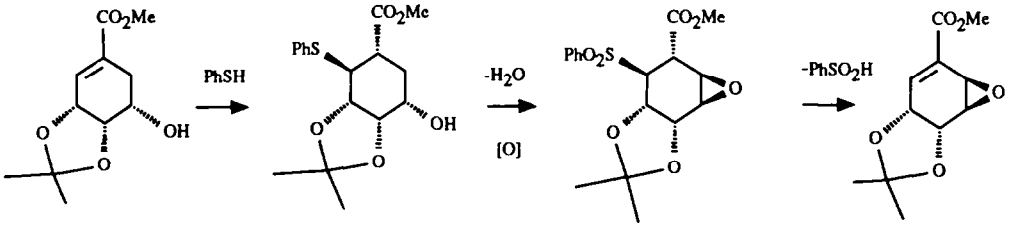
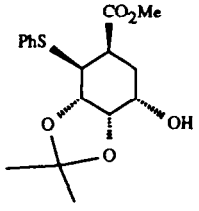


(3) (15) (16) (4)

In practice the reaction of the hydroxy ester (3) with sodium thiophenate progressed slowly at ambient temperature and, after 18 hours, furnished two hydroxysulphides (15) and (17), together with much unreacted starting material. The structure of the major product was established by a single crystal X-ray analysis of the deprotected 4-bromobenzoate ester (18, Ar=4-BrC_6H_4). When the reaction time was extended to 4 days three products were isolated. Two of these were the expected hydroxysulphides (15) and (17), but now only in 9% and 5% yields respectively. The major product was the lactone (19) (12% yield), the structure of which was also confirmed by X-ray crystallography.

Neither of the two hydroxysulphides (15) and (17) could be dehydrated under Mitsunobu conditions, so in an alternative approach to the epoxide (4) the dieneacetonide (2) was reacted with sodium thiophenate in expectation of forming the monosulphide (20). This could then be epoxidized and oxidized as in the previous route to give the sulphone (16), and then the desired product (4). The first step of this reaction, which was carried out at 0°C, afforded the disulphide (23) as the major product (47% yield) and small amounts of the two monosulphides (22) and (24). When the reaction was repeated using thiophenol in the

presence of a catalytic amount of triethylamine the *cis*-monosulphide (21) was obtained in 59% yield, rather than the anticipated *trans*-isomer (20). We consider that compound (20) is the initial product of the sodium thiophenate reaction, but under the basic conditions isomerisation to the allylic sulphide (22) occurs. A second Michael addition then affords the disulphide (23). The seemingly unusual relative stereochemistries of the monosulphide (21) and the disulphide (23) are occassioned by the fact that the presence of the acetonide function in both compounds determines that the phenylsulphide groups occupy 'equatorial' sites. In order to minimise non-bonded interactions the methoxycarbonyl functions must then be 'axially' orientated. These conclusions are supported by ^{1}H n.mr data including nuclear Overhauser effect experiments (see experimental section).



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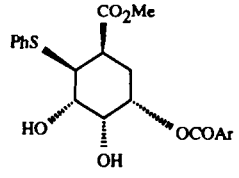

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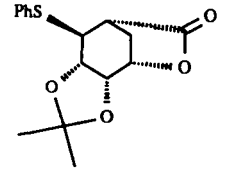

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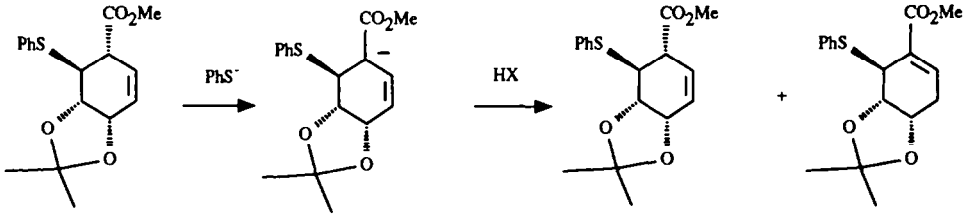
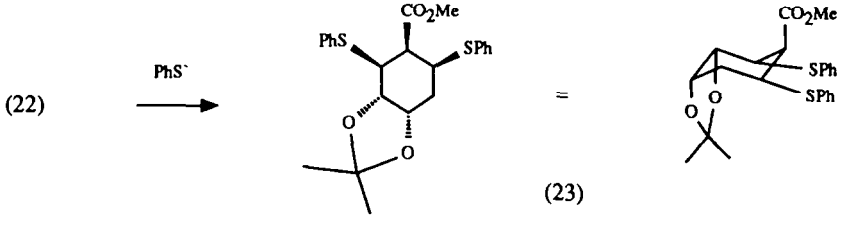


(20) (21) (22)



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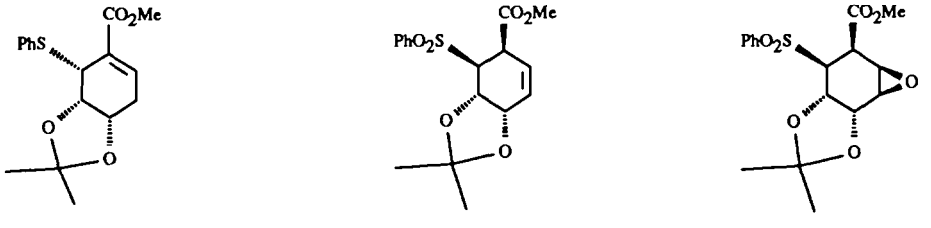
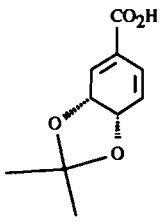


(24) (25) (26)

Unfortunately oxidation of the sulphide (21) merely gave the sulphone (25) and the epoxide (26) could not be formed. Considering the likely mechanisms by which MCPBA could attack the dieneacetonide (2)[11] we reasoned that Michael addition would be disfavoured for the corresponding acid (27). Hydrolysis of the dieneacetonide was achieved by treating it with pig liver esterase at pH7 in an aqueous medium buffered with phosphate. Oxidation of the acid with MCPBA gave the epoxide (28), which was converted into the epoxide (4) by treatment with diazomethane (an excess of the reagent must be avoided otherwise the pyrazoline (29) is produced by 1,3-dipolar addition to the $\Delta^{1,2}$ bond). The overall yield for the two steps was 56%.

When the epoxide (4) was reacted with hydrofluoric acid in pyridine racemic methyl 6α-fluoroshikimate (30) was obtained in 49% yield as a colourless oil, together with 3% of the isomers (31) and (32) in the ratio 4:1 [methyl 6α-fluoroshikimate has also recently been synthesised by Professor J.K.Sutherland's group at the University of Manchester[12]].



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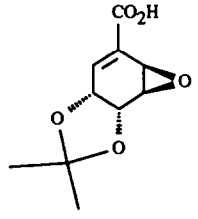

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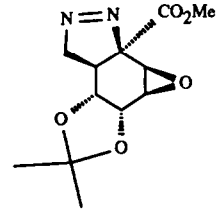

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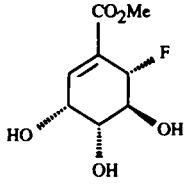

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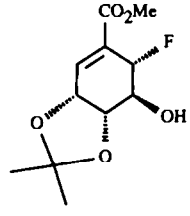

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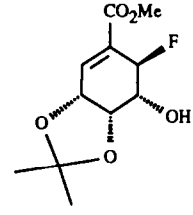

(32)

Experimental

U.v. spectra were recorded on a Perkin-Elmer 402 instrument for solutions in 95% ethanol. ^{1}H. N.m.r. spectra were obtained at 270MHz and 400MHz and ^{13}C n.m.r. spectra at 67.8 MHz using tetramethylsilane as internal standard in deuteriochlorform solution, unless stated otherwise. The instrument used was a JEOL MNGXFT spectrometer. Mass spectra were measured on a VG 7070E instrument. All solvents, other than ethanol, were distilled prior to use. Light petroleum refers to petroleum ether, b.p. 60-80°C.

Methyl 5β,6β-epoxy-3α,4α-isopropylidenedioxycyclohexenoate (4) and *methyl 1α,2α-epoxy-3α,4α-isopropylidenedioxy-cyclohex-5-en-1β-oate (5)*- (a) *With MCPBA*-A solution of the dieneacetonide (2)(466mg, 2.22 mmol) in dichloromethane (15cm^3) was heated and stirred at 40°C with *m*-CPBA (480 mg, 2.77 mmol). After 12h. the reaction mixture was allowed to cool, and was washed with 10% aq. sodium sulphite, saturated sodium hydrogen carbonate solution, and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting yellow oil was chromatographed with 10% ethyl acetate - light petroleum to yield a colourless oil, found by ^{1}H n.m.r. to be an 8:3 mixture of the epoxides (4) and (5). R_F = 0.65 [50% EtOAc - light petroleum]; υ_{max} 1720cm^{-1} (C=O).

Methyl 5β,6β-epoxy-3α,4α-isopropylidenedioxycyclohexenoate (4) has δ_H (400 MHz) 1.38 and 1.39 (2 x 3H, 2s, CMe_2), 3.65 (1H, ddd, $J_{5,6}$ = 3.5, $J_{5,4}$ = 2.0, $J_{5,3}$ = 0.5 Hz, 5-H), 3.81 (3H, s, OCH_3), 3.98 (1H, ddd,

$J_{6,5}$ = 3.5, $J_{6,2}$ = 1.5, $J_{6,4}$ = 0.5 Hz, 6-H), 4.56 (1H, dd, $J_{3,4}$ = 7.0, $J_{3,2}$ = 2.5Hz, 3-H), 4.79 (1H, m, $J_{4,3}$ = 7.0, $J_{4,5}$ = 2.0, $J_{4,2}$ = 0.5, $J_{4,6}$ = 0.5Hz, 4-H), 6.81 (1H, ddd, $J_{2,3}$ = 2.5, $J_{2,6}$ = 1.5, $J_{2,4}$ = 0.5Hz, 2-H).

NOEDS Data for (4), from the epoxide mixture

Signal irradiated (Chemical shift δ)	Observed n.O.e. (% enhancement)		
5-H (3.65)	4-H (9)		6-H (10)
6-H (3.98)		5-H (7)	
3-H (4.56)	2-H (9)	4-H (9)	
4-H (4.79)	3-H (11)		5-H (7)

(b) *With monoperphthalic acid* - The dieneacetonide (2) (100mg, 0.48 mmol) in ether (3cm^3) was treated with an etherial solution of monoperphthalic acid (0.49 mmol). After stirring for 5 days at ambient temperature, the reaction mixture was washed with saturated sodium hydrogen carbonate and brine, dried (Na_2SO_4), and evaporated to afford a yellow oil. This was chromatographed (eluting with 1:10 EtOAc - light petroleum) to yield, initially, unreacted (2) (32mg). Further elution afforded a colourless oil comprising the epoxides (4) and (5) (25mg, 34% corrected yield) in a 3:1 ratio.

(c) *With vanadium (IV) 2,4-pentadionate oxide - t-butyl hydroperoxide* - A solution of the dieneacetonide (2) (122mg, 0.58 mmol) and vanadium (IV) 2,4-pentadionate (0.4mg, 0.26 mol%) in benzene (1 cm^3) was stirred at ambient temperature, under nitrogen. A solution of *t*-butyl hydroperoxide in toluene (3M, 0.48cm^3, 1.44 mmol) was added, and after 12h., the solvents were evaporated to leave a golden-coloured oil. This was taken up in chloroform (5cm^3) and washed with 10% aq. sodium sulphite and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was chromatographed with 1:10 ethyl acetate - light petroleum, to yield a 3:1 mixture of the epoxides (4) and (5) (60mg, 46%).

Methyl 1α,2α-epoxy-3α,4α-isopropylidenedioxycyclohex-5-en-1β-oate (5). - The dieneacetonide (2) (62mg, 0.30 mmol), potassium carbonate (0.07g) and benzonitrile (*ca.* 0.03 cm^3, 0.3 mmol) were stirred in methanol (5 cm^3) at O°C, and 30% aqueous hydrogen peroxide (*ca.* 0.04 cm^3, 0.35 mmol) were added dropwise. After 2.5h., 10% aqueous sodium sulphite (*ca.* 2 cm^3) was added and the organic material extracted with dichloromethane (x 3), dried ($MgSO_4$) and the solvents evaporated to leave a colourless semi-solid. This was chromatographed, eluting with 10% ethyl acetate - light petroleum, to furnish an oil which crystallised on standing as needles of the title compound (67mg, quantitative) m.p. 60-71°C; R_F 0.79 (10% EtOAc - light petroleum]; υ_{max} 1720cm^{-1} (C=O); δ_H (400MHz) 1.38 (6H, s, CMe_2), 3.80 (3H, s, OCH_3), 3.88 (1H, d, $J_{2,3}$ = 2.0Hz, 2-H), 4.48 (1H, ddd, $J_{4,3}$ = 7.0, $J_{4,5}$ = 2.5, $J_{4,6}$ = 1.5Hz, 4-H), 4.77 (1H, br dd, $J_{3,4}$ = 7.0, $J_{3,2}$ = 2.0Hz, 3-H), 5.86 (1H, ddd, $J_{5,6}$ = 10.5, $J_{5,4}$ = 2.5, $J_{5,3}$ = 0.5Hz, 5-H), 6.40 (1H, dd, $J_{5,6}$ = 10.5, $J_{6,4}$ = 1.5Hz, 6-H); δ_C 25.75 and 27.49 (2q, $C(CH_3)_2$), 51.55 (s, 1-C), 52.78 (q, OCH_3), 54.71 (d, 2-C), 70.11 (d, 3-C), 70.55 (d, 4-C), 110.73 (s, $C(CH_3)_2$), 121.12 (d, 6-C), 131.72 (d, 5-C), 168.63 (C=O); *m/z* 227 (MH^+, 44%), 211 (9), 169 (100), 137 (34) (Found: C, 58.5; H, 6.3, $C_{11}H_{14}O_5$ requires: C, 58.4; H, 6.2%).

NOEDS Data for (5), from the epoxide mixture

Signal irradiated (Chemical shift, δ)	Observed n.O.e. (% enhancement)		
2-H (3.88)		3-H (21)	
4-H (4.47)	2-H (4)	3-H (5)	OMe (37)

Methyl 5β-hydroxy-3α,4α-isopropylidenedioxy-6α-phenylthiocyclohexenoate (7) and *methyl 5α-hydroxy-3α,4α-isopropylidenedioxy-6β-phenylthiocyclohexenoate* (8) - A 60% dispersion of sodium hydride in mineral oil (60mg) was washed with 40-60 petroleum ether and protected by a stream of N_2. THF (5cm^3) was added and the suspension cooled to O°C. Thiophenol (0.15cm^3, 1.43 mmol) was added in one portion and the resulting white suspension stirred for 15 min. before a solution of the three component epoxide mixture (4), (5) and (6) (300mg, 1.45 mmol) in THF (5cm^3) was added. After 1.5h., the reaction was washed with 10% aqueous sodium hydroxide (5cm^{3}x3). The aqueous phase was re-extracted with dichloromethane and the organic portions combined and dried (Na_2SO_4). Evaporation of the solvent gave a yellow oil which was chromatographed [1:2 ether - light petroleum (b.p. 30-40°C) to yield (7) as a white solid (158mg,35%) m.p. 126°C; R_F 0.56 [50% EtOAc-hexane]; υ_{max} 3680-3200 (OH), 1710cm^{-1} (C=O); δ_H (400MHz) 1.37 and 1.48 (2 x 3H), 2s, CMe_2), 2.45 (1H, d, $J_{5,OH}$ = 7.0 Hz, OH), 3.74 (3H, s, OCH_3), 3.90 (1H, ddd, $J_{5,4}$ = 9.0, $J_{5,OH}$ = 7.0 $J_{5,6}$ = 4.5Hz, 5-H), 4.29 (1H, dd, $J_{4,5}$ = 9.0, $J_{4,3}$ = 7.0Hz, 4-H), 4.40 (1H, d, $J_{6,5}$ = 4.5, 6-H), 4.60 (1H, dd, $J_{3,4}$ = 7.0, $J_{3,2}$ = 3.5Hz, 3-H), 6.90 (1H, d, $J_{2,3}$ = 3.5 Hz, 2-H), 7.30 and 7.55 (5H, 2m, SPh); *m/z* (E.I.) 336 (M^+, 100%), 226 (38), 168 (33) (Found: C, 60.7;

H, 6.0. $C_{17}H_{20}O_5S$ requires: C, 60.7; H, 5.6%).
Benzoate derivative: m.p. 108-109°C; R_F 0.36 [1:2 Et_2O - light petroleum (b.p. 30-40°]; υ_{max} 1715-1700cm^{-1} (2 C=O); δH (400MHz, C_6D_6) 1.20 and 1.40 (2 x 3H, 2s, CMe_2), 3.34 (3H, s, OCH_3), 4.42 (1H, dd, $J_{3,4}$ = 7.0, $J_{3,2}$ = 3.5 Hz, 3-H), 5.00 (1H, dd, $J_{4,5}$ = 9.0, $J_{4,3}$ = 7.0Hz, 4-H), 5.18 (1H, d, $J_{6,5}$ = 4.0Hz, 6-H), 5.56 (1H, dd, $J_{5,4}$ = 9.0, $J_{5,6}$ = 4.0 Hz, 5-H), 6.96 [d,(obscured by Ph), 2-H], 6.68, 7.02, 7.56 and 7.89 (10H, 4m, SPh and OCOPh); *m/z* (E.I.) 440 (M^+, 440.1278. $C_{24}H_{24}O_6S$ requires: 440.1291, 2%) 331 (1), 202 (25), 105 (56), 91 (100).
NOEDS data for methyl 5β-benzoyloxy-3α,4α-isopropylidenedioxy-6α-phenylthiocyclohexenoate

Signal irradiated (Chemical shift, δ*)	Observed Resonance (% enhancement)				
	2-H	5-H	6-H	4-H	3-H
5-H (5.56)	-		14	3	-
6-H (5.23)	-	13		13	-
4-H (5.00)	-	4	15		10
3-H (4.64)	13	-	-	16	

* Measured in $CDCl_3$ - C_6D_6
Further elution with 2:3 ether - light petroleum afforded (8) (89mg, 20%) as a colourless solid, m.p. 112°C; R_F = 0.47 [50% EtOAc-hexane]; υ_{max} (CH_2Cl_2) 3520 - 3600 (OH), 1710cm^{-1} (CO); δ_H (400MHz) 1.41 and 1.47 (2 X 3H), 2s, CMe_2), 2.26 (1H, br s, OH), 3.73 (3H, s, OCH_3), 4.02 (1H, dd, $J_{6,5}$ = 2.5, $J_{6,3}$ = 1.0Hz, 6-H), 4.37 (1H, dd, $J_{4,3}$ = 5.0, $J_{4,5}$ = 5.0Hz, 4-H), 4.58 (1H, br m, 5-H), 4.74 (1H, ddd, $J_{3,4}$ = 5.0, $J_{3,2}$ = 4.0, $J_{3,6}$ = 1.0Hz, 3-H), 6.78 (1H, d, $J_{2,3}$ = 4.0 Hz, 2-H), 7.29 and 7.60 (5H, 2m, SPh); *m/z* (E.I.) 336 (M^+, 336.1034. $C_{17}H_2O_5S$ requires: 336.1029, 100%), 168 (38), 137 (49), 110 (100).
NOEDS data for (8).

Signal irradiated (Chemical shift, δ)	Observed n.O.e. (% enhancement)				
	2-H	3-H	5-H	4-H	6-H
2-H (6.78)		6	-	-	-
3-H (4.74)	8		-	6	-
5-H (4.58)	-	-		9	7
4-H (4.37)	-	7	8		-
6-H (4.02)	-	-	7	-	

Benzoate derivative: m.p. 131-132°C; R_F 0.42 [1:2 Et_2O-light petroleum (b.p. 30-40°C)]; υ_{max} 1715-1700cm^{-1} (2x C=O); δ_H (400MHz) 1.44 and 1.54 (2 x 3H, 2s, CMe_2), 3.63 (3H, s, OCH_3), 4.22 (1H, dd, $J_{6,5}$ = 2.5, $J_{6,3}$ = 1.0 Hz, 6-H), 4.53 (1H, br m, 4-H), 4.86 (1H, ddd, $J_{3,4}$ = 5.0, $J_{3,2}$ = 3.5, $J_{3,6}$ = 1.0Hz, 3-H), 6.11 (1H, dd, $J_{5,4}$ = 3.5, $J_{5,6}$ = 2.0 Hz, 5-H), 6.85 (1H, d, $J_{2,3}$ = 3.5 Hz, 2-H), 7.22-7.62 and 7.93 (10H, 2m, SPh and OCOPh); *m/z* (E.I.) 440 (M^+, 440.1311 $C_{24}H_{24}O_6S$ requires: 440.1291, 2%) 311 (2), 105 (100).
Methyl 6α-hydroxy-4α,5α-isopropylidenedioxycyclohexenoate (11) - Sodium hydride (7.6mg, of 60% dispersion) was washed with light petroleum (b.p. 30-40°C) and dried in a stream of nitrogen. THF (0.5cm^3) was added and the stirred suspension cooled to 0°C. Thiophenol (10 µl, 0.19 mmol) was added and stirring continued for 20 mins. before a solution of epoxy ester (5) (40mg, 0.18 mmol) in THF (2.5cm^3) was added dropwise. After 1h., a few drops of water were introduced and the solvents were evaporated under reduced pressure (the last traces of water removed under high vacuum) and flash chromatography of the resulting oil (gradient elution with 25% to 50% EtOAc - light petroleum) afforded the title compound as a colourless oil (9mg, 23%). R_F 0.34 [50% Et_2O-light petroleum]; υ_{max} 3620-2220 (CO_2H,OH) 1705 cm^{-1} (C=O); δ_H 1.35 and 1.36 (2 x 3H, 2s, CMe_2), 2.55 (1H, ddd, J_{gem} = 18.0, $J_{5\alpha,6}$ = 5.5, $J_{5\alpha,4}$ = 3.0 5α-H), 2.66 (1H, ddd [partially obscured by OH], J_{gem} = 18.0, $J_{5\beta,4}$ = 5.0, $J_{5\beta,6}$ = 3.5Hz, 5β-H), 2.67 (1H, br s, OH), 3.79 (3H, s, OCH_3), 4.41 (1H, dd, $J_{3,4}$ = 6.5, $J_{3,2}$ = 2.5 Hz, 3-H), 4.54 (1H, ddd, $J_{4,3}$ = 6.5, $J_{4,5\beta}$ = 5.0, $J_{4,5\alpha}$ = 3.0 Hz, 4-H), 4.71 (1H, d, $J_{2,3}$ = 2.5 Hz, 2-H), 7.10 (1H, dd, $J_{6,5\alpha}$ = 5.5, $J_{6,5\beta}$ = 3.5 Hz, 6-H).
Methyl 3α,4α-dihydroxycyclohexa-1,5-dieneoate (12) - The diene ester (2) (86mg, 0.41 mol) was stirred at 56°C for 1.5h. with 50% aqueous acetic acid (4 cm^3). The aqueous acid was partially removed on a rotary evaporator, and the product evaporated to a yellow oil under high vacuum. Trituration with ethyl acetate

afforded the title compound as a white solid (36mg, 53%). The mother liquor was flash chromatographed with 50% EtOAc - light petroleum to give a further 23mg of (12) (33%, overall yield 86%) m.p. 98.5°C (lit.,[2] 91-92°C); R_F 0.15 [50% Et_2O) - petroleum ether]; υ_{max} 3560-3140 (OH), 1715 cm^{-1} (C=O); δ_H ($(CD_3)_2CO$) (3H, s, OCH_3), 3.80 (1H, br s, OH), 4.12 (1H, br s, OH), 4.15 [obscured by OH], 4-H), 4.40 (1H, dd, $J_{3,4}$ = 6.5, $J_{3,2}$ = 3.5 Hz, 3-H), 6.11 (1H, dd, $J_{5,6}$ = 10.0, $J_{5,4}$ = 5.0 Hz, 5-H), 6.39 (1H, br d, $J_{6,5}$ = 10.0 Hz, 6-H), 6.88 (1H, br m, 2-H); *m/z* (E.I.) 170 (M^+, 23%) 152 (100), 138 (78) (Found: C, 56.5; H, 5.9. Calc. for $C_8H_{10}O_4$: C, 56.5; H, 5.9%).

Methyl 3α,4α-dihydroxy-1α,2α-epoxycyclohex-5-en-1β-oate (13) *and methyl 5α,6α-epoxy-3α,4α-dihydroxycyclohexoate (14)* - A solution of the dihydroxydiene ester (12) (28mg, 0.16 mmol) and *m*-CPBA (30mg, 0.16 mmol) in dichloromethane (5cm^3), was stirred at ambient temperature for 12h. Removal of the solvent under reduced pressure left a white gum which was chromatographed with 50% ethyl acetate - light petroleum, to furnish a 1:1 mixture of the title compounds (16mg, 52%) as a white semi solid. R_F 0.49 [EtOAc]; υ_{max} 3600-3180 (OH), 1720cm^{-1} (C=O); The 5,6-epoxide (14) has δ_H ($(CD_3)_2CO$ - D_2O) 3.74 (1H, br dd, $J_{5,6}$ = 2.5 $J_{5,4}$ = 1.5Hz, 5-H), 3.83 (3H, s, OCH_3), 4.00 (1H, dd, $J_{6,5}$ = 2.5, $J_{6,2}$ = 1.5Hz, 6-H), 4.09 (1H, br d, $J_{4,3}$ = 3.0 Hz, 4-H), 4.32 (1H, ddd, $J_{3,2}$ = 4.0, $J_{3,4}$ = 3.0, $J_{3,5}$ = 1.5Hz, 3-H), 7.17 (1H, dd, $J_{2,3}$ = 4.0, $J_{2,6}$ = 1.5Hz, 2-H); and the 1,2-epoxide (13) has δ_H 3.81 (3H, s, OCH_3), 3.91 (1H, br d, $J_{2,3}$ = 1.5Hz, 2-H), 4.04 (1H, br d, $J_{3,4}$ = 3.0 Hz, 3-H), 4.18 (1H, ddd, $J_{4,5}$ = 3.5, $J_{4,3}$ = 3.0, $J_{4,2}$ = 1.0 Hz, 4-H), 6.27 (1H, dd, $J_{5,6}$ = 7.0, $J_{5,4}$ = 3.5Hz, 5-H), 6.48 (1H, d, $J_{6,5}$ = 7.0Hz, 6-H).

Reactions of the hydroxy ester (3) *with sodium hydride-thiophenol* - (A) - A 60% dispersion of sodium hydride (40mg) was washed with light petroleum (b.p. 30-40°C) (3cm^3x3) and dried in a stream of nitrogen. THF (2cm^3) was added and the suspension cooled to 0°C in an ice bath. Thiophenol (0.1 cm^3, 1 mmol) was added in one portion and the white suspension stirred for 1h., before a solution of the hydroxy ester (3) (228mg, 1mmol) in THF (3cm^3) was added dropwise. The ice bath was removed and the reaction stirred at ambient temperature for 18h., after which time the solvent was evaporated, and the resulting brown oil applied to a silica column. Elution with 1:2 ethyl acetate - light petroleum gave *methyl 5α-hydroxy- 3α,4α-isopropylidenedioxy-2β-phenylthiocyclohexan-1β-oate* (15) as a white solid (127mg, 50% corrected yield) m.p. 84.5-85°C (ether-light petroleum); R_F 0.45 [50% EtOAc - light petroleum]; υ_{max} 3570 (OH), 1270 cm^{-1} (C=O); δ_H (400MHz) 1.39 and 1.52 (2 x 3H, 2s, CMe_2), 1.95 (1H, ddd, J_{gem} = 14.0, $J_{6\alpha,5}$ = 9.0, $J_{6\alpha,1}$ = 6.5Hz, 6α-H), 2.17 (1H, ddd, J_{gem} = 14.0 $J_{6\beta,1}$ = 6.5, $J_{6\beta,5}$ = 6.0Hz, 6β-H), 2.27 (1H, d, $J_{OH,5}$ = 5.0 Hz, OH), 3.26 (1H, ddd, $J_{1,6\beta}$ = 6.5, $J_{1,6\alpha}$ = 6.5, $J_{1,2}$ = 4.5Hz, 1-H), 3.48 (1H, dd, $J_{2,3}$ = 6.0, $J_{2,1}$ = 4.5Hz, 2-H), 3.71 (3H, s, OCH_3), 4.15 (1H, br m, 5-H), 4.43 (1H, dd, $J_{4,3}$ = 6.0, $J_{4,5}$ - 3.5Hz, 4-H), 4.55 (1H., dd, $J_{3,2}$ = 6.0, $J_{3,4}$ = 6.0Hz, 3-H), 7.24-7.34 and 7.47 (5H, 2m, SPh); δ_C 25.27 and 27.29 (2q, $C(CH_3)_2$), 28.61 (t, 6-C), 40.80 (d, 1-C), 50.36 (d, 2-C), 51.96 (q, OCH_3), 65.23 (d, 5-C), 75.38 and 76.92 (2d, 3-, 4-C), 109.34 (s, C $(CH_3)_2$), 127.65 (d, aromatic *p*-CH), 129.12 and 132.42 (2d, aromatic *o*-*m*-CH) 134.57 (s, aromatic C-S), 173.42 (s, C=O); *m/z*. (E.I.) 338 (M^+, 100%), 171 (78), 110 (16) (Found : C 604; H, 6.6 $C_{17}H_{22}O_5S$ requires: C, 60.4; H, 6.5%).

NOEDS data for (15)

Signal irradiated (Chemical shift, δ)	Observed n.O.e. (% enhancement)
2-H (3.48)	1-H(21) 3-H(5) aromatic *o*-H(5)
3-H (4.55)	2-H(5) 4-H(32)

Continued elution yielded an oil, found by ^1H n.m.r. to be a 1:1 mixture of starting material (3) and *methyl 5α-hydroxy-3α,4α-isopropylidenedioxy-2β-phenylthiocyclohexan-1α-oate* (17) (113mg, 23% corrected yield). The R_F 0.31 [50% EtOAc - petroleum ether] was coincidental with that of the hydroxy ester (3). *Methyl 5α-hydroxy-3α,4α-isopropylidenedioxy-2β-phenylthiocyclohexan-1α-oate* has δ_H (400MHz) 1.38 and 1.51 (2 x 3H, 2s, CMe_2), 2.00 (1H, d, $J_{OH,5}$ = 8.0Hz, OH), 2.46 (3H, m, 1, 6α-, 6β-H), 3.21 (1H, dd, $J_{2,1}$ = 11.5, $J_{2,3}$ = 9.0Hz, 2-H), 3.69 (3H, s, OCH_3), 3.82 (1H, br m, 5-H), 4.01 (1H, dd, $J_{3,2}$ = 9.0, $J_{3,4}$ = 5.0Hz, 3-H), 4.29 (1H, dd, $J_{4,3}$ = 5.0, $J_{4,5}$ = 7.0Hz, 4-H), 7.28-7.33 and 7.56 (5H, m, SPh); δ_C 25.97 and 27.92 (2q, $C(CH_3)_2$), 32.00 (t, 6-C), 44. 73 (d, 1-C), 50.29 (d, 2-C), 52.00 (q, OCH_3), 67.08 (d, 5-C), 76.04 and 77.37 (2d, 3-, 4-C), 109.75 (s, $C(CH_3)_2$), 128.31, 128.79 and 131.61 (3d, aromatic CH), 135.12 (s, aromatic C-s), 172.86 (s, C=O); *m/z* 339 (MH^+, 79%), 281(41), 171(100).

(B) - A 60% dispersion of sodium hydride in mineral oil (180mg) was washed with pentane (3cm^3 x3) and protected by a stream of nitrogen. Anhydrous THF (5cm^3) was introduced and the suspension stirred at 0°C. Thiophenol (0.45cm^3, 4.4 mmol) was added and, after 30 mins., a solution of the hydroxy ester (3) (10.6g, 4.4 mmol) in THF (5cm^3) was added slowly. After four days at ambient temperature, a small amount of water (*ca.* 3cm^3) was added and the product extracted with chloroform. The solvent was dried ($MgSO_4$) and removed to leave a yellow oil which was flash chromatographed, eluting with 1:2 EtOAc - light petroleum to yield initially *endo-3,4-isopropylidenedioxy-exo-2-phenylthio-6-oxabicyclo [3.2.1]octan-7-one* (19), as a cream coloured solid (148mg, corrected yield 12%). m.p. 87-88°C (from ether-light petroleum); R_F 0.64 [50% EtOAc - light petroleum]; υ_{max} = 1760 (C=O), 1575cm^{-1} (C=C); δ_H

1.30 and 1.54 (2 x 3H, 2s, CMe_2), 2.30 (1H, br dd, J_{gem} = 13.0Hz, $J_{8endo,5}$ = 1.0 Hz, 8 *endo*-H), 2.38 (1H, ddd, J_{gem} = 13.0, $J_{8exo,5,1}$ = 5.5, J_{8exo} = 2.0Hz, 8 *exo*-H), 2.63 (1H, m, 1-H), 3.98 (1H, ddd, $J_{2,1}$ = 2.5, $J_{2,3}$ = 1.0, $J_{2,8endo}$ = 0.5Hz, 2-H), 4.21 (1H, dd, $J_{4,3}$ = 6.0, $J_{4,5}$ = 2.5Hz, 4-H), 4.40 (1H, br d, $J_{3,4}$ = 6.0Hz, 3-H), 4.67 (1H, ddd, $J_{5,8exo}$ = 5.5, $J_{5,4}$ = 2.5, $J_{5,8endo}$ = 1.0Hz, 5-H); δ_C 25.60 and 25.31 (2q, $C(CH_3)_2$), 28.74 (t, 8-C), 39.37 (d, 1-C), 44.94 (d, 2-C), 72.64 and 75.72 (2d, 3-, d-C), 78.07 (d, 5-C), 109.84 (s, CMe_2), 128.2 (d, aromatic *p*-C), 129.50 and 131.78 (2d, aromatic *o*-, *m*-C), 132.13 (s, aromatic C-S), 175.41 (s, C=O); *m/z* (E.I.) 306 (M^+, 70%), 291 (100) (Found : C, 62.7; H, 6.0. $C_{16}H_{18}O_4S$ requires: C, 62.7; H, 5.9%).
Continued elution afforded the following compounds (in order of elution): *methyl 5α-hydroxy-3α,4α-isopropylidenedioxy-2β-phenylthiocyclohexan-1β-oate* (15) as a colourless solid (125mg, corrected yield 9%,); and an oil containing *methyl 5α-hydroxy-3α,4α-isopropylidenedioxy-2β-phenylthiocyclohexan-1α-carboxylate* (17) (5% corrected yield) and unreacted (3) in the proportions 1:1 (125mg) R_F 0.24.
Methyl 5α-(4α-bromobenzoyloxy)-3α,4α-dihydroxy-2β-phenylthiocyclohexanoate (18, Ar=4-BrC_6H_4) - To a solution of the phenylthiohydroxy ester (17) (45mg, 0.13 mmol) and *p*-bromobenzoyl chloride (30mg, 0.14 mmol) in dichloromethane (3cm^3) under nitrogen was added freshly distilled triethylamine (19µl, 0.13 mmol). After 5 days at ambient temperature, the solvent was evaporated and the residue chromatographed eluting with 20% EtOAc-light petroleum to yield the *p*-bromobenzoate (18, Ar=4-BrC_6H_4) as a colourless solid (19mg, 30%) m.p. 140-142°C; R_F 0.73 [50% EtOAc - light petroleum]; υ_{max} 3640-3280 (OH), 1730-1720cm^{-1} (C=O); δ_H 2.05 (2H, br s, 2OH) 2.15 (1H, ddd, J_{gem} = 14.0, $J_{6\beta,1}$ = 8.0, $J_{6\beta,5}$ = 3.5Hz, 6β-H), 233 (1H, ddd, J_{gem} = 14.0, $J_{6\beta,5}$ = 7.0, $J_{6\alpha,1}$ = 4.5Hz, 6α-H), 3.44 (1H, br m, 1-H), 3.71 (4H, br s, OCH_3, 2-H), 4.28 (1H, dd, $J_{3,2}$ = 6.0, $J_{3,4}$ = 3.0Hz, 3-H), 4.40 (1H, dd, $J_{4,5}$ = 3.5, $J_{4,3}$ = 3.0Hz, 4-H), 5.44 (1H, dd, $J_{5,6\alpha}$ = 7.0, $J_{5,4}$ = 3.5, $J_{5,6\alpha}$ = 3.5Hz, 5-H), 7.25-7.60 and 7.92 (9H, 2m, SPh and $OCOC_6H_4Br$); *m/z* 465 and 463 (MH^+ -18, 2%), 385 (1), 383 (1), 294 (4), 279 (5), 203 (100), 202 (100), 201 (54), 200 (54).
Reaction of the dieneacetonide (2) with sodium hydride-thiophenol - Sodium hydride (30mg of a 60% dispersion) was washed with pentane (3x2cm^3) and dried in a stream of nitrogen. THF (2cm^3) was added and the suspension cooled in an ice-salt bath. Thiophenol (*ca.* 0.1cm^3) was added, and after 30 min. a solution of the dieneacetonide (81) (213mg, 1.01 mmol) in THF (2cm^3) was added dropwise. This was stirred for 1h., after which time a few drops of water were added, and the reaction mixture diluted with diethyl ether and dried ($MgSO_4$). The solvents were evaporated and the residual brown oil chromatographed with 20% ether-light petroleum (b.p. 30-40°C) to effect a partial separation. The more lipophilic product was columned twice more, and crystallised from hexane to give a fluffy colourless solid of *methyl 2β,6β-diphenylthio-3α,4α-isopropylidenedioxycyclohexan-1β-oate* (23) (204mg, 47%) m.p. 125.5-126.5°C (from hexane); R_F 0.67 [0.3 EtOAc - light petroleum]; υ_{max} 1725 cm^{-1} (C=O); δ_H (400MHz) 1.37 and 1.49 (2 x 3H, 2s, CMe_2), 1.77 (2H, m, 5α-,5β-H), 3.00 (1H, dd, $J_{2,3}$ = 9.5, $J_{2,1}$ = 4.5hZ, 2-H), 3.16 (1H, br d, $J_{1,2}$ = 4.5, $J_{1,6}$ = 4.0Hz, 1-H), 3.42 (1H, ddd, $J_{6,5\beta}$ = 10.5, $J_{6,5\alpha}$ = 6.5, $J_{6,1}$ = 4.0Hz, 6-H), 3.79 (3H, s, OCH_3), 4.40 (1H, dd, $J_{3,2}$ = 9.5, $J_{3,4}$ = 5.0Hz, 3-H), 4.43 (1H, m, $J_{4,5\beta}$ = 3.5Hz, 4-H), 7.26, 7.39 and 7.46 (10H, 3 x m, 2SPh); δ_C 26.14 and 28.66 (2q, $C(CH_3)_2$), 29.47 (t,5-C), 43.04 (d, 1-C), 50.10 (d, 6-C), 51.57 (q, OCH_3), 53.44 (d, 2-C), 74.36 and 75.25 (2d, 3-, 4-C), 108.56 (s $C(CH_3)_2$), 128.-04, 129.04 and 132.97 (3d, aromatic CH), 133.16 and 133.63 (2s, aromatic C-S), 171.23 (s, C=O); *m/z* 430 (E.I.) (M^+, 100%), 320 (17), 156 (18), 153 (8) (Found: C, 64.3, H, 6.2. $C_{23}H_{26}O_4S_2$ requires: C, 64.2; H, 6.05%).
NOEDS data for (23)

Signal irradiated (Chemical shift, δ)	Observed nOe (% enhancement)			
5α-H, 5β-H (2.30)	*o*-Ph(1%)	4-H(7%)	6-H(4%)	
2-H (3.00)	*o*-Ph(4%)	3-H(2%)	6-H(7%)	1-H(6%)
		5α-H(2%)	CMe_2(5%)	

The more hydrophilic fraction obtained from the partial chromatographic separation was found to comprise a mixture of *methyl 4α,5α-isopropylidenedioxy-6α-phenylthiocyclohexenoate* (24) and *methyl 4α,5α-isopropylidenedioxy-6β-phenylthiocyclohexenoate* (22) in a 1:5 ratio (74mg, 22%). R_F 0.62 [1:2 EtOAc - light petroleum]. An analytical sample of each was obtained by repeated chromaotgraphy of the mixture, eluting with 20% ether-light petroleum (b.p. 30-40°C). The less polar α-allylic sulphide (24) was eluted first as an oil, with υ_{max} 1710 cm^{-1}(C=O); δ_H 1.26 and 1.28 (2 x 3H, 2s, CMe_2), 2.20 (1H, ddd, J_{gem} = 13.5, $J_{5\beta,4}$ = 5.5, $J_{5\beta,6}$ = 3.5 Hz 5βp-H), 2.27 (1H, br m, [obscured by 5β-H), 3.77 (3H, s, OCH_3). 4.36 (1H, dd, $J_{2,3}$ = 3.5, $J_{2,5\alpha}$ = 3.0 Hz, 2-H), 4.65 (1H, dd, $J_{3,4}$ = 6.5, $J_{3,2}$ = 3.5Hz, 3-H), 4.84 (1H, ddd, $J_{4,5\alpha}$ = 7.0, $J_{4,3}$ = 6.5, $J_{4,5\beta}$ = 5.5 Hz, 4-H), 7.01 (1H, br d, $J_{6,5\beta}$ = 3.5Hz, 6-H), 7.25-7.60 (5H, m, SPh); δ_C 24.38 and 26.31 (2q, $C(CH_3)_2$), 28.61 (t, 5-C), 43.66 (d, 2-C), 52.03 (q, $OCH_3)_2$), 72.41 (d, 3-C), 76.81 (d, 4-C), 108.25 (s $C(CH_3)$), 127.63 AND 129.16 (2d, aromatic CH), 129.68 (s, 1-C), 132.21 (d, aromatic CH),

133.75 (s, aromatic C-S), 140.59 (d, 6-C), 165.60 (s, C=O); *m/z* (E.I.) 320 (M^+, 320.1073. $C_{17}H_{20}O_4S$ requires 320.1080, 78%), 262 (30), 153 (74), 110(100). The more polar β-allylic sulphide (22) was also obtained as a colourless oil: υ_{max} 1710 cm^{-1} (C=O); δ_H 1.27 and 1.30 (2 x 3H, 2s, CMe_2), 2.50 (1H, ddd, J_{gem} = 18.0, $J_{5\beta,4}$ = 4.0, $J_{5\beta,6}$ = 3.5Hz, 5β-H), 2.57 (1H, ddd, J_{gem} = 18.0, $J_{5\alpha,6}$ = 7.0, $J_{5\alpha,4}$ = 2.0Hz, 5α-H), 3.78 (3H, s, OCH_3, 4.52 (1H, d, $J_{2,3}$ = 1.5Hz, 2-H), 4.62 (1H, dd, $J_{3,4}$ = 7.0, $J_{3,2}$ = 1.5Hz, 3-H), 4.65 (1H, br m, 4-H), 7.17 (1H, dd, J6,5α = 7.0, $J_{6,5\beta}$ = 3.5, 6-H), 7.20-7.52 (5H, m, SPh); *m/z* (E.I.) 320 (M^+, 320.1084. $C_{17}H_{20}O_4S$ requires: 320.1080, 100%), 262 (52), 218 (40).

Methyl 3α,4α-isopropylidenedioxy-2β-phenylthiocyclohex-5-en-1β-oate (21) - To a solution of the dieneacetonide (3) (210mg, 1mmol) and thiophenol (0.21 cm^3, 2 mmol) in chloroform (1 cm^3) was added triethylamine (10μl). After stirring for 1h. at ambient temperature the reaction mixture was diluted with ether, washed successively with 5% aqueous NaOH, water and bring, and dried (Na_2SO_4). The solvents were removed under reduced pressure to leave a white residue which was purified by flash chromatography [eluting with 1:6 ether-light petroleum (b.p. 30-40°C)] to yield the title compound as a colourless solid (188mg, 59%). Recrystallisation of a sample from petroleum ether gave long, translucent needles, m.p. 100.5 - 101°C; R_F 0.34 [20% Et_2O - petroleum ether]; υ_{max} 1735cm^{-1} (C=O); δ_H 1.38 and 1.39 (2 x 3H, 2s, CMe_2), 3.72 (4H, s and m, OCH_3, 1-H), 3.81 (1H, dd, $J_{2,1}$ = 5.0, $J_{2,3}$ = 5.5Hz, 2-H), 4.62 (1H, dd, $J_{3,2}$ = 5.5, $J_{3,4}$ = 5.5Hz, 3-H), 4.76 (1H, br m, 4-H), 5.91 (1H, ddd, $J_{5,6}$ = 10.0, $J_{5,4}$ = 3.0, $J_{5,1}$ = 2.5Hz, 5-H), 6.12 (1H, dd, $J_{6,5}$ = 10.0, $J_{6,1}$ = 3.0Hz, 6-H), 6.92 and 7.41 (5H, 2m, SPh); δ_C 26.39 and 27.77 (2q, $C(CH_3)_2$), 42.34 (d, 1-C), 50.21 (d, 2-C), 52.08 (q, OCH_3), 71.44 and 75.23 (2d, 3-, 4- C), 109.73 (s, $C(CH_3)_2$), 125.64, 127.64, 128.07, 129.08 and 132.33 (5d, 5-, 6-, aromatic CH), 134.48 (s, aromatic C-S), 171.65 (s, C=O); *m/z* (E.I.) 320 (M^+, 100%), 245(23) (Found C, 63.9; H, 6.35. $C_{17}H_{20}O_4S$ requires C, 63.7; H, 6.3%).

NOEDS data for (21)

Signal irradiated	Observed nOe (% enhancement)						
(Chemical shift, δ)	*o*-H	*m/p*-H	6-H	5-H	3/4-H	2-H	1-H
aromatic 2-H (7.40)		10	-	-	1	6	-
6-H (6.11)	-	-		9	-	6	-
5-H (5.77)	-	-	20		5	-	-
3-/4-H (4.70)	2	-	-	15		11	-
2-H (4.02)	6	-	-	-	5		18
1-H (3.74)	-	-	13	-	-	11	

Methyl 3α,4α-isopropylidenedioxy-2β-phenylsulphonylcyclohex-5-en-1β-oate (25) - The phenylsulphide (21) (127mg, 0.40 mmol) was heated at 40°C with m-CPBA (0.22g, 1.29 mmol) in dichloromethane (6cm^3). T.l.c. analysis after 1h., showed that all the starting material has been converted to two spots of product R_F 0.59 and 0.48 [50% EtOAc - light petroleum]. After 3 days only the more hydrohilic product was detected. The reaction was diluted with dichloromethane, washed successively with 10% aq. sodium sulphite, saturated sodium hydrogen carbonate solution, and brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield a pale yellow oil, which solidified on standing to give the phenylsulphone (25) as a cream coloured solid [125mg, 89%], m.p. 108-109°C (from ether-light petroleum; R_F 0.48 [50% EtOAc-light petroleum]; μ_{max} 1730 (C=O), 1655 (C=C), 1310 (SO_2 asymmetric), 1150cm^{-1} (SO_2 symmetric); δ_H 1.06 and 1.31 (2 x 3H, 2s, CMe_2), 3.55 (1H, dd, $J_{2,3}$ = 9.0, $J_{2,1}$ = 4.5Hz, 2-H), 3.79 (3H, s, OCH_3), 3.87 (1H, br d, 1-H), 4.76 (1H, br dd, 4-H), 5 .18 (1H, dd, $J_{3,2}$ = 8.5, $J_{3,4H}$ = 6.5Hz, 3-H), 6.01 (1H, ddd, $J_{5,6}$ = 9.5, $J_{5,4}$ = 3.5, $J_{5,1}$ = 1.5Hz, 5-H), 6.12 (1H, ddd, $J_{6,5}$ = 9.5, $J_{6,1}$ = 1.0Hz, 6-H), 7.47-7.68 and 7.95 (5H, 2m, SO_2Ph); δ_C 24.49 and 26.80 (2q, $C(CH_3)_2$), 42.32 (d, 1-C), 52.26 (q, OCH_3), 65.58 (d, 2-C), 72.81 and 73.04 (2d,3-, 4-C), 109.07 (s, $C(CH_3)_2$), 127.01, 128.14 and 135.02 (4d, aromatic CH, 5-, 6-C), 142.99 (s, aromatic C-S), 170.08 (S, C=O); *m/z* 353 (MH^+, 7%), 337 (4), 295 (54), 157 (100) (Found: C, 57.4; H, 5.5 $C_{17}H_{20}O_6S$ requires: C, 57.95; H, 5.7%).

3α,4α-Isopropylidenedioxycyclohexa-1,5-diene-1-carboxylic acid (27) - The dieneacetonide (3) (212 mg, 1.0 mmol) was stirred in acetone-water (1:9, 20cm^3) at ambient temperature, and to the cloudy white solution was added pig liver esterase (300μl, 120U). 0.05M, pH7 phosphate buffer [Na_2HPO_4. $12H_2O$ (3.201G), KH_2PO_4 (0.484g) in 250cm^3 of H_2O] was added periodically to maintain the reaction at pH7. After 2h., the starting material had reacted completely (t.l.c., 50% EtOAc-hexane), the solvents were evaporated and the white residue taken up in 50cm^3 of water. This was acidified to pH3 with 2M HCl and the product extracted with ethyl acetate. Reacidification of the aqueous portion and extraction was carried out twice more, and the combined extracts dried ($MgSO_4$) and evaporated to a yellow oily solid. This was taken up in chloroform and washed with water, dried ($MgSO_4$) and concentrated to a yellow oil

(195mg, 99%) which solidified on standing. A sample was purified by flash chromatography eluting with 70:30:1 hexane-ethyl acetate-formic acid to furnish a white solid (m.p. 92-94°C). R_F 0.31 [70:30:1, hexane-EtOAc-HCO_2H]; υ_{max} 3850-2270 (COOH), 1695cm^{-1} (C=O); δ_H 1.41 and 1.43 (2 x 2H, 2s, CMe_2), 4.66 (1H, dd, $J_{4,3}$ = 9.0, $J_{4,5}$ = 4.0Hz, 4-H), 4.85 (1H, dd, $J_{3,4}$ = 9.0, $J_{3,2}$ = 3.5Hz, 3-H), 6.07 (1H, dd, $J_{5,6}$ = 10.0, $J_{5,4}$ = 4.0Hz, 5-H), 6.54 (1H, d, $J_{6,5}$ = 10.0Hz, 6-H), 6.88 (1H, br s, COOH), 7.00 (1H, dd, $J_{2,3}$ = 3.5, $J_{2,6}$ = 1.0Hz, 2-H); *m/z* 139 (MH^+, 100%), 138 (32), 121 (30) (Found : C, 60.9; H, 6.2. $C_{10}H_{12}O_4$ requires: C, 61.2; H, 6.1%).

Methyl 5β,6β-epoxy-3α,4a-isopropylidenedioxycyclohexenoate (4) - The diene acid (27) (106mg, 0.5mmol) in chloroform (3cm^3) was stirred overnight with *m*-CPBA (100mg, 0.5mmol) at ambient temperature. Removal of the white precipitate of *m*-chlorobenzoic acid by filtration, and evaporation of the filtrate under reduced pressure afforded a white gum (110mg) of *5β,6β-epoxy-3α,4α-isopropylidenedioxycyclohexenoic acid* (28) R_F 0.38 [60:40:1 light petroleum-EtOAc-HCO_2H]; δ_H (200MHz) 3.70 (1H, dd, $J_{5,6}$ = 3.5, $J_{5,4}$ = 2.5 Hz, 5-H), 4.01 (1H, dd, $J_{6,5}$ = 3.5, $J_{6,2H}$ = 1.5Hz, 6-H), 4.62 (1H, dd, $J_{3,4}$ = 7.0, $J_{3,2}$ = 2.5Hz, 3-H), 4.83 (1H, br dd, $J_{4,3}$ = 7.0, $J_{4,5}$ = 2.5Hz, 4-H), 6.98 (1H, dd, $J_{2,3}$ = 2.5, $J_{2,6}$ = 1.5Hz, 2-H), 8.70 (1H, br s, CO_2H). This was contaminated with *ca.* 10% *m*-chlorobenzoic acid, but was reacted without further purification. The gum (110mg) was dissolved in ether (5cm^3) and treated with an etherial solution of diazomethane. The ensuing reaction was monitored frequently the t.l.c. and when complete, the solvent was allowed to evaporate. The resulting yellow oil was chromatographed with 10% EtOAc - light petroleum to yield the title compound as a colourless oil (69mg, 56% overall yield) R_F 0.28 [10% EtOAc-light petroleum]; υ_{max} 1720 cm^{-1} (C=O); δ_H 1.37 and 1.41 (2 x 3H, 2s, CMe_2), 3.67 (1H, dd, $J_{5,6}$ = 3.5, $J_{5,4}$ = 2.0Hz, 5-H), 3.83 (3H, s, OCH_3), 4.00 (1H, dd, $J_{6,5}$ = 3.5, $J_{6,2}$ = 1.5, $J_{6,4}$ = 0.5Hz, 6-H), 4.58 (1H, dd, $J_{3,4}$ = 7.0, $J_{3,2}$ = 2.5Hz, 3-H), 4.81 (1H, m, $J_{4,3}$ = 7.0, $J_{4,5}$ = 2.0, $J_{4,2}$ = 0.5, $J_{4,6}$ = 0.5Hz, 4-H), 6.81 (1H, ddd, $J_{2,3}$ = 2.5, $J_{2,6}$ = 1.5, $J_{2,4}$ = 0.5Hz, 2-H); δ_C 25.94 and 27.79 (2q, $C(CH_3)_2$), 46.05 (d, 6-C), 49.24 (d, 5-C), 52.22 (q, OCH_3), 70.81 and 71.24 (2d, 3-, 4-C), 111.00 (s $C(CH_3)_2$), 127.47 (s, 1-C), 139.99 (d, 2-C), 165.39 (s, C=O); *m/z* 211 (M^+-15.31%), 169 (100), 137 (58) (Found : C, 58.4; H, 6.25. $C_{11}H_{14}O_5$ requires: C, 58.4; H, 6.2%).

1-Methoxycarbonyl-2,3-endo-epoxy-3,4-exo-isopropylidenedioxy-8, 9-diazabicyclo [4,3,0] non-8-ene (29) - The epoxy acid (28)-*m*-chlorobenzoic acid mixture (279mg, *ca.* 0.6 mmol of (28) by ^{1}H n.m.r.) was dissolved in diethyl ether (5cm^3) and swirled vigorously whilst an etherial solution of diazomethane was added dropwise. Addition was continued until the yellow colour persisted indicating a excess of diazomethane. The excess reagent and ether were allowed to evaporate to leave a pale yellow oil (331 mg). This was columned with 20% ethyl acetate-light petroleum, to furnish the title compound as a colourless solid (116mg, *ca.* 70%) m.p. 115-116°C; R_F 0.48 [50% EtOAc-light petroleum]; υ_{max} 1725cm^{-1} (C=O); δ_H 1.12 and 1.26 (2 x 3H, 2s, CMe_2), 2.66 (1H, ddd, $J_{6,7endo}$ = 11.5, $J_{6,7exo}$ = 10.0, $J_{6,5}$ = 3.0 Hz, 6-H), 2.92 (1H, ddd, $J_{3,2}$ = 3.5, $J_{3,4}$ = 1.0, $J_{3,5}$ = 1.0Hz, 3-H), 3.33 (3H, s, OCH_3), 3.60 (1H, dd, J_{gem} = 16.5, $J_{7endo,6}$ = 11.5Hz, 7endo-H), 3.66 (1H, ddd, $J_{5,4}$ = 5.5, $J_{5,6}$ = 3.0, $J_{5,3}$ = 1.0 Hz, 5-H), 3.78 (1H, br d, $J_{4,5}$ = 5.5Hz, 4-H), 3.97 (1H, br d, $J_{2,3}$ = 3.5Hz, 2-H), 4.16 (1H, dd, J_{gem} = 16.5, $J_{7exo,6}$ = 10.0Hz, 7exo-H); δ_C 26.13 and 27.81 (2q, $C(CH_3)_2$), 35.79 (d, 6-C), 52.78 (q, OCH_3), 53.20 and 54.86 (2d, 2-, 3-C), 69.19 and 71.56 (2d, 4-, 5-C), 79.37 (t, 7-C), 91.89 (s, 1-C), 109.24 (s, CMe_2), 169.65 (s, C=O); *m/z* 269 (MH^+, 100%), 225 (21), 183 (43), 151 (85) (Found : C, 53.3; H, 6.2. N, 10.1. $C_{12}H_{16}O_5N_2$ requires: C, 53.7; H, 6.0; N, 10.45%).

NOEDS data for (29)

Signal irradiated	Observed nOe (% Enhancement)							
(Chemical shift, δ	7exo-H	2-H	4-H	5-H	7endo-H	3-H	6-H	CMe_2
7endo-H (3.60)	23	-	-	15		-	16	-
3-H (2.92)	-	7.5	3	-	-		-	-
6-H (2.66)	12	-	-	15	-	-		-
CMe_2 (1.26)	-	-	4	3	-	3	6	

Methyl 6α-fluoro-3α,4α,5β-trihydroxy-cyclohex-1-enoate (30) - The epoxy ester (4) (38mg, 0.18 mmol) in dichloromethane (1cm^3) was stirred at O°C in a polythene tube, and anhydrous hydrogen fluoride pyridine (*ca.* 70% HF, 0.5cm^3) added dropwise *via* a polythrene pipette. After 15 minutes the reaction mixture was added dropwise to aqueous calcium acetate (0.125g in 5cm^3), and the resulting fine white precipitate removed by filtration through a short pad of celite. The filtrate was shaken with dichloromethane (3x2cm^3) and the combined extracts washed once with brine, dried (Na_2SO_4) and concentrated to a colourless oil (1.4mg, 3%). ^{1}H N.m.r. showed this to be a 4:1 mixture of two fluoro alcohols (31) and (32) : *methyl 6α-fluoro-5β-hydroxy-3α,4α-isopropylidene- dioxycyclohex-1-enoate* (31), the major isomer, has δ_H 1.26 and 1.49 (2 x 3H, 2s, CMe_2), 3.85 (3H, s, OCH_3), 4.27 (1H, ddd, $J_{5,F}$ = 10.5, $J_{5,4}$ = 6.5, $J_{5,6}$ = 5.5 Hz, 5-H), 4.30 (1H, dd [partially obscured by 5-H) $J_{3,2}$ = 3.5Hz, 3-H), 4.75 (1H, ddd, $J_{4,5}$ = 6.5, $J_{4,3}$ = 2.5,

$J_{4,F}$ = 2.0 Hz, 4-H), 5.25 (1H, br ddd, $J_{6,F}$ = 46.0, $J_{6,5}$ = 5.5, $J_{6,2}$ = 1.0Hz, 6-H), 6.94 (1H, ddd, $J_{2,3}$ = 3.5, $J_{2,F}$ = 2.0, $J_{2,6}$ = 1.0 Hz, 2-H); *methyl (3α, 4α, 5α, 6β)-5α-Fluoro-6β-hydroxy-3α,4a-isopropylidenedioxy-cyclohex-1-enoate* (312, the minor isomer has δ_H 1.44 (6H, s, CMe_2), 3.85 (3H, s, OCH_3), 4.41 (1H, br ddd, $J_{4,F}$ = 8.0, $J_{4,3}$ = 6.5, $J_{4,5}$ = 1.5Hz, 4-H), 4.59 (1H, br dd, $J_{6,F}$ = 6.5, $J_{6,5}$ = 2.5Hz, 6-), 4.81 (1H, ddd, $J_{3,4}$ = 6.5, $J_{3,2}$ = 2.0, $J_{3,F}$ = 1.0Hz, 3-H), 5.49 (1H, br dd, $J_{5,F}$ = 48.0, $J_{5,6}$ = 2.5Hz, 5-H), 6.83 (1H, ddd, $J_{2,F}$ = 2.5, $J_{2,3}$ = 2.0, $J_{2,6}$ = 1.0Hz, 2-H). The washings and aqueous phase were combined and lyophilised, and the resulting white solid flash chromatographed on silica with 10% methanol-chloroform to furnish the title compound (30) as a colourless oil (17mg, 49%). R_F 0.33 [10% MeOH-$CHCl_3$]; υ_{max} 3720-3060(OH), 1710 cm^{-1} (C=O); δ_H (400MHz) 2.70 (3H, br s, 3OH), 3.69 (1H, dd, $J_{4,5}$ = 9.0, $J_{4,3}$ = 4.0Hz, 4-H), 3.82 (3H, s, OCH_3), 4.23 (1H, ddd, $J_{5,F}$ = 17.0, $J_{5,4}$ = 9.0, $J_{5,6}$ = 6.0Hz, 5-H), 4.49 (1H, br dd, $J_{3,2}$ = 5.0, $J_{3,4}$ = 4.0Hz, 3-H), 5.23 (1H, br dd, $J_{6,F}$ = 48.0 $J_{6,5}$ = 6.0Hz, 6-H), 6.95 (1H, dd, $J_{2,3}$ = 5.0, $J_{2,6}$ = 1.0Hz, 2-H); δ_C (CD_3OD) 52.97 (q, OCH_3), 66.70 (dd, $J_{2,F}$ = 2.0, 3-C), 70.23 (dd, $J_{4,F}$ = 7.7Hz, 4-C), 73.41 (dd, $J_{5,F}$ = 21.2Hz, 5-C), 90.15 (dd, $J_{6,F}$ = 173.2 Hz, 6-C), 130.67, (d, $J_{1,F}$ = 18.7 Hz, 1-C), 142.19 (dd, $J_{2,F}$ = 5.5Hz, 2-C), 167.40 (s, C=O); *m/z* (C.I. ammonia) 224 (MNH_4, 224.0932; $C_8H_{15}O_5NF$ requires: 224.0934, 47%), 204 (14), 188 (15), 80 (100).

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Note

We did not observe kinetic resolution during our experiment using pig liver esterase to effect the hydrolysis of the dieneacetonide (2), but when the epoxy ester (5) was treated with this reagent system partial resolution to afford the corresponding acid, $[\alpha]_D^{18}$ +12.8°(*c* 0.17, $CHCl_3$); m.p. 93-95.5°C, was noted. The yield of this product was only 19%: ν_{max}3600-2300, 1705 cm^{-1}; δ_H 1.40(6H, 2s, CMe_2), 3.95(1H, d, *J*=2.0Hz, 2-H), 4,51(1H, m, 4-H), 4.81(1H, dd, $J_{3,4}$=7.0Hz, $J_{3,2}$=2.0Hz, 3-H), 5.91 (1H, dd, $J_{5,6}$=10.0Hz, $J_{5,4}$=2.5Hz, 5-H), 6.38(1H, dd, $J_{6,5}$=10.0Hz, $J_{6,4}$=2.0Hz, 6-H); *m/z* (-ve FAB, H_2O-glycerol) 212(M^+,7%), 167(12%), 109(13%).

Acknowledgements

The authors thank the S.E.R.C. and ICI for a C.A.S.E. studentship awarded to S.A. Bowles. We are extremely grateful to Dr.Kieran.C.Molloy and Dr.Mary.F.Mahon, School of Chemistry, University of Bath, for determining the X-ray crystallographic structures of compounds (18, Ar=4-BrC_6H_4) and (19). Data relating to these compounds has been deposited with the Cambridge Crystallographic Data Base. We thank Professor J.K.Sutherland for providing spectra of methyl 6α-fluoroshikimate for comparative purposes, and for details of the experimental conditions required for the successful ring opening of the epoxide (28).