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BRIEF SYNTHESES OF (±)-METHYL SHIKIMATE, (±)-METHYL EPISHIKIMATE AND STRUCTURAL VARIANTS

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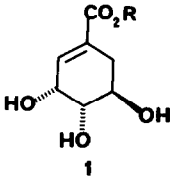
Abstract - Two brief syntheses of (±)-methyl shikimate are described in a strategy which offers potentially flexible access to a range of analogues. New intramolecular rearrangement reactions of epoxides derived from methyl 7-oxabicyclo[2.2.1]hept-3-ene 6-carboxylate and methyl bicyclo[2.2.1]hept-3-ene 6-carboxylate are described.

Shikimic acid (1,R=H) is a key biosynthetic intermediate, leading from carbohydrates to the aromatic amino acids. Many synthetic studies have been prompted[1], not only by the challenge of stereospecific and chiral synthesis of this trihydroxycarboxylic acid, but also because of the possibility of preparing structural variants as potential regulators of a range of biological mechanisms.



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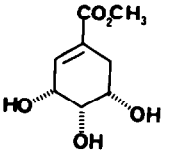
Our preliminary communication[2] described a brief and efficient stereocontrolled route to (±)-methyl epishikimate (2), offering possible entries not only to shikimic acid, but also to related systems. The synthesis, outlined in Scheme 1, depends upon the Diels-Alder reaction of furan with methyl acrylate, uniquely mediated by zinc iodide. Although the exo and endo adducts (3) are separable, they are most efficiently progressed as a mixture. Reaction of adducts (3) with osmium(IV) oxide and hydrogen peroxide, and then with 2,2-dimethoxypropane and p-toluene-sulphonic acid yields the acetonides (4,R,R=CMe_2). Lithium hexamethyldisilazane effects ring opening to give the O,O-isopropylidine derivative (5,R=H) of (±)-methyl epishikimate. Deprotection (aqueous acetic acid) gives the trihydroxy ester (2), the stereochemistry of which was rigorously defined by 2D J-decoupled analyses and NOSY measurements at 400 MHz.



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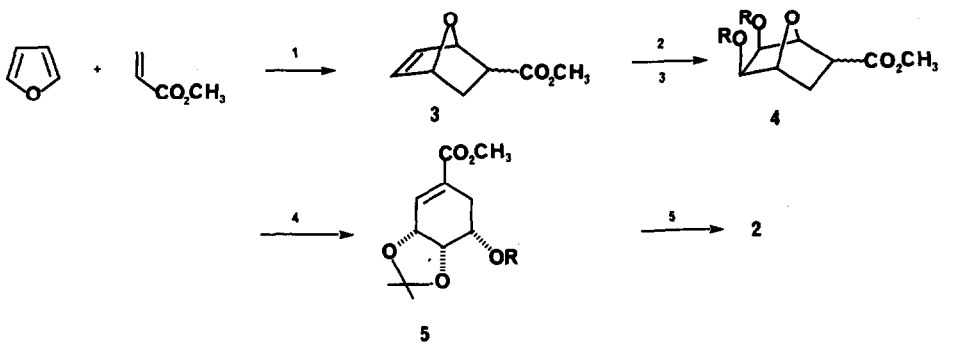
Attempts to invert the stereochemistry at C(5) by, for example, reacting the tosylate (5,R=$C_7H_7SO_2$) with lithium hydroxide resulted only in hydrolysis of the methyl ester. Reaction with potassium acetate led to elimination of toluene p-sulphonic acid and oxidation, to give the acetonide of methyl 3,4-dihydroxybenzoate (6). Reaction with potassium superoxide and dibenzo 18-crown-6 resulted in preferential hydrolysis to the acid (7,R=$C_7H_7SO_2$), together with a small amount of the epoxides (8).

Scheme 1

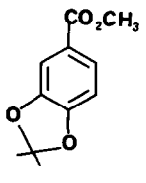


1. ZnI_2 ; 2. OsO_4; 3. $(MeO)_2C(Me)_2$,H^+; 4. $(Me_3Si)_2NH$, n-BuLi; 5. H^+(R=H)

The mesylate (5,R=CH_3SO_2) also reacted with lithium hydroxide to give the acid (7,R=CH_3SO_2). The unusual reluctance of (5,R=$C_7H_7SO_2$) and (5,R=CH_3SO_2) to undergo S_N2 displacement is indicative of the steric bulk of the adjacent acetonide, which apparently disfavours the S_N2 transition state. Acid treatment of the acetonide gave the diol (9,R=H), but attempts to diacetylate this and then invert at C(5) were thwarted by the ease of aromatization of the diacetate.

Oxidation of the acetonide of methyl 5-epishikimate (5,R=H) with pyridinium chlorochromate gave the highly unstable β,γ-unsaturated ketone (10). Although elemental analysis was precluded, support for the structural assignment was obtained from the u.v. spectrum (λ_{max}220nm), indicating (10) rather than (11). Reduction of (10) with sodium borohydride returned the acetonide of methyl 5-epishikimate almost exclusively, because of steric approach control. Reduction of the ketone (10) with sodium and liquid ammonia led to complex mixtures.

Another approach to inversion of the 5-hydroxyl involved the Mitsunubu system[4]. However, the acetonide of methyl 5-epishikimate (5,R=H) reacted with triphenylphosphine-diethyl azodicarboxylate - sodium benzoate, to give the diene (12,R,R=CMe_2). It was subsequently established that this elimination can be effected in the absence of sodium benzoate.



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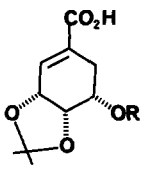

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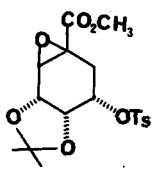

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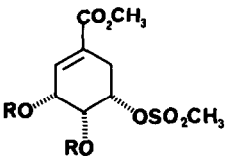

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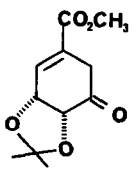

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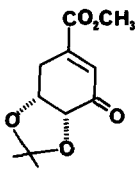

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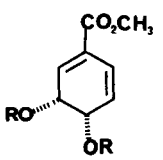

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Diene (12,R,R=CMe_2) is surprisingly stable, and when deprotected (aqueous acetic acid), gave the stable methyl cis-3,4-dihydroxybenzoate (12,R=H) together with a minor by-product, methyl 3-hydroxybenzoate, formed by a regioselective dehydration. Concurrent with our disclosure[2] of the cis-dihydrodihydroxybenzoate was a communication from an ICI group of cis-dihydrodihydroxybenzene formed microbiologically[5]. The unexpected stability of these molecules is noteworthy.

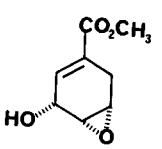
Consideration of electronic and steric factors suggested that hydroboration-oxidation of the diene (12,R,R=CMe_2) would afford (±)-methyl 0,0-isopropylidine shikimate. This was realized in practice, the sole isolable product being the acetonide in 45% yield. Since this compound has previously been synthesized and converted into shikimic acid,[9] our route represents a remarkably brief synthesis of the racemic natural product from readily available starting materials.

Berchtold reported[6] the transformation of methyl shikimate into the epoxide (13) by treatment with diethyl azodicarboxylate-triphenylphosphine in tetrahydrofuran, followed by distillation of the intermediate complex. We report a complementary reaction in which the acetonide (5,R=H) was subjected to DEAD-PPh_3 and zinc(II) tosylate in tetrahydrofuran in an attempted inversion at C(5). Only 2-hydrazinyltetrahydrofuran (14) was isolated, in high yield, in a reaction presumably mediated by Zn(II) tosylate functioning as a Lewis acid in an initial complex with tetrahydrofuran, highlighting an unexpected problem in the use of this solvent.

An even more expeditious route to the shikimate structure from adducts (3), was achieved by ring-opening[6] with lithium hexamethyldisilazane, giving the 5-hydroxydiene (15) in high yield. Cis-dihydroxylation with osmium (IV) oxide gave a mixture of (±)-methyl shikimate (1,R=Me) and the 5-epimer (2) in 74% yield, the ratio being 5:1 in favour of methyl shikimate. The two isomers were readily separated by chromatography the overall yield of (1,R=Me) being 26% from furan. Complete selectivity was achieved by conversion of (15) into the tert-butyldimethylsilyl ether (95%) followed by cis-hydroxylation (78%) and ring-opening (85%), the overall yield in this sequence from furan being (23%).

A further route to methyl shikimate from the adducts (3) would involve cis-hydroxylation under Prevost conditions[7] which should yield the endo-cis-diols (16). Ring-opening should give, directly, the correct triol relative stereochemistry. In practice, however, a wide range of Prevost variations led only to iodoacetate products, and not to the target cis-diols.

Other studies directed towards the synthesis of structural variants of shikimic acid uncovered unexpected intramolecular ring-opening processes. Thus, adducts (3) were transformed into epoxides (17,X=O), but reaction of these epoxides with lithium



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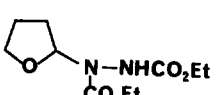

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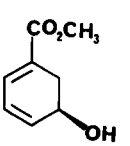

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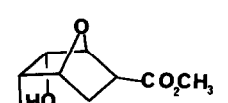

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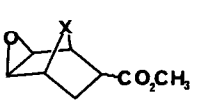

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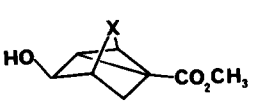

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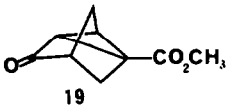
hexamethyldisilizane did not result in ring-opening of the 7-oxa[3.3.1]bicycloheptanes, as for acetonides (4,R,R=CMe_2). Instead, the tricyclic alcohol (18,Z=O) was isolated. The carbocyclic analogue (17,X=CH_2)[8] behaved similarly, yielding the alcohol (18,X=CH_2). Interestingly, the oxygen-bridged tricyclic alcohol (18,Z=O) could not be oxidized under a wide range of conditions, but the carbocyclic analogue was readily converted into the ketone (19) and thence to lactone (20) by Bayer Villiger reaction. Access to highly-functionalized bicyclo[3.1.0]pentanes is therefore possible.



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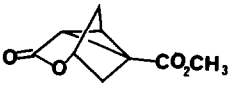
The principal discoveries within these studies therefore allow the briefest and potentially most flexible routes into racemic shikimic acid and its structural variants. Our present studies, concerned with enantiospecific Diels Alder reaction of chiral acrylates with furan, and with chiral hydroborations of cyclohexadienyl esters, will be reported in due course.

Acknowledgments We thank SERC for a grant towards a mass spectrometer, and for a SERC Studentship (A.D.K.). Dr. O.W. Howarth, University of Warwick, provided 400 MHz spectral analyses confirming structure and stereochemistry of intermediates and products. Drs., Gallagher, Floyd and Brown are also thanked for advice and suggestions.

Experimental Unless specified all the solvents used were dried prior to use. ^1H n.m.r. spectra were recorded at 100MHz or 400MHz with tetramethylsilane as an internal standard. The same standard was employed in the determination of ^{13}C n.m.r. data. All melting points are uncorrected and yields are unoptimised.

Exo-cis-2,3-dihydroxy-endo(exo)-6-methoxy-carbonyl-7-oxabicyclo[2,2,1]heptane (4,R=H) The adducts (3)[3] 10g) in acetone (25cm³) and diethyl ether (60cm³) were treated with 30% hydrogen peroxide solution (8cm³) and a solution containing 10% osmium (IV) oxide in t-butanol (10cm³). After stirring for 10 days, the solvents were removed from the reaction mixture and the residual oil taken up in hot ethyl acetate (5cm³). On cooling, the title compounds crystallized together as colourless prisms (11.2g). They were separated by chromatography on silica (200g) eluting the column with ethyl acetate. The exo-isomer which was obtained from the



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first fractions has m.p. 102-103°C; ν_{max} ($CHCl_3$) 3350, 1740cm^{-1}, δ_H ($CDCl_3$) 1.58 (dd, 1H, Jgem =12Hz, $J_{5\alpha,6}$ =8Hz,H-5α), 2.10 (qd,1H,Jgem=12Hz,$J_{5\beta,6}$ =4Hz, $J_{5\beta,6}$ =4Hz, H-5β, 2.52 (dd,1H $J_{6,5\alpha}$=8Hz, $J_{6,5\beta}$=4Hz, H-6), 3.30(s,2H,2xOH,2xOH, signal eliminated by addition of D_2O), 3.70(s, 3H, OCH_3), 3.85 (s,2H, H-2 H-3), 4.38(d,1H,$J_{4,5}$ β=4Hz,H-4), 4.54 (s, 1H, H-1); m/z (CI,isobutane) 189 (M+1, 100%), 171 (37%), 157 (32%) [Found: C, 51.2; H, 6.4 $C_8H_{12}O_5$ requires: C, 51.1; H, 6.4%]

The endo-isomer has m.p. 109-111°C; ν_{max} ($CHCl_3$) 3350, 1740cm^{-1}; δ_H($CDCl_3$) 1.60 (m, 1H, H-5α), 2.10 (m, 1H, H-5β), 3.1(m,1H, H-6), 3.25(bs,2H, 2xOH, signal eliminated by addition of D_2O), 3.68, (s,3H,OCH_3), =4Hz, H-4), 4.42(d,1H,$J_{1,6}$=4Hz, H-1); m/z (CI isobutane) 189 (M+1, 100%), 171 (37%), 157 (32%) [Found: C,51.5; H,6.2 $C_8H_{12}O_5$ requires. C, 51.1; H 6.4%]

Exo-2,3-O,O-isopropylidine-2,3-dihydroxy-endo(exo)-6-methoxycarbonyl-7-oxabicyclo [2,2,1]heptane (4,R,R=$C(CH_3)_2$. To the mixed diols (4,R=H) (1.2g) in acetone (15cm³) were added 2,2-dimethoxypropane (20cm³), 4-toluene sulphonic acid (0.1g) and anhydrous calcium chloride (3g) and the reaction mixture stirred and heated at

50°C for one hour. The calcium chloride was then filtered off and the solvents evaporated to leave a solid which was redissolved in ethyl acetate (50cm³) and the solution washed with cold water (20cm³), dried and reevaporated to yield the mixed acetonides (4,R,R=$C(CH_3)_2$) as a colourless solid (1.37g, 94%). The individual exo- and endo-isomers were separated by column chromatography on silica (50g) eluting with ethyl acetate: 60-80°C petrol (4:6).

The more polar exo-isomer has m.p. 66-67°C; ν_{max} ($CHCl_3$) 1740, 1380, 1360cm^{-1}; δH ($CDCl_3$) 1.30, 1.47 (2xs, 2x3H, $C(CH_3)_2$), 1.58 (dd, 1H, Jgem=10Hz, $J_{5\alpha,6}$=4Hz, H-5α), 2.11 (qd, 1H, Jgem=10Hz, $J_{5\beta,6}$=8Hz, $J_{5\beta,4}$=4Hz, H-5β), 2.42 (dd, 1H, $J_{6,5\alpha}$=4Hz, H-2), 3.70 (s, 3H, OCH_3), 4.24 (s, 2H, H-2 H-3), 4.44 (d,1H, $J_{4,5\beta}$=4Hz, H-4), 4.66, s,1H, H-1); δ_c ($CDCl_3$) 25.1, 25.9 (2xq,2x$C(CH_3)_2$), 27.3 (t, C-5), 43.1(d, C-6), 52.1 (q,OCH_3), 79.4, 79.7, 80.1, 88.2 (4xd, C-1, C-2, C-3, C-4, 111.2 (s,$C(CH_3)_2$); 172.1 (s, C=O) [Found:C, 57.9; H, 7.2 $C_{11}H_{16}O_5$ requires: C, 57.9; H, 7.0%].

The less polar endo-isomer has m.p. 96-98°C; ν_{max} ($CHCl_3$) 1740, 1380, 1360cm^{-1}; δH($CDCl_3$) 1.26, 1.47 (2xs, 2x 3H, $C(CH_3)_2$; 1.70 (dd, 1H, Jgem = 10Hz, $J_{5\alpha,6}$=4Hz, H-5α), 1.86 (m,1H, H-5β), 3.0 (qd,1H,$J_{6,5\beta}$=8Hz, $J_{6,1}$=4Hz, $J_{6,5\alpha}$ =4Hz, H-6), 3.72(s, 3H, OCH_3), 4.26 (bs, 2H, H-2, H-3), 4.43 (d, 1H, $J_{4,5\beta}$=4Hz, H-4), 4.54 (d,1H,$J_{1,6}$ =4Hz, H-1); m/z 213.0752 (M-CH_3, 98%, $C_{10}H_{13}O_5$ requires: 213.0762), 98%, 197 (M-CH_3O, 20%), 43 (100%).

(±)-3,4-O,O-Isopropylidine-1-methoxycarbonyl-3α,4α,5α-trihydroxycyclohexene (5,R=H) n-Butyl lithium (1.56M) in tetrahydrofuran (6.1cm³) was added to hexamethyldisilazane (3.1cm³) in tetrahydrofuran (30cm³) maintained at -78°C under a nitrogen atmosphere. After stirring for 20 minutes, the mixed acetonides (4,R,R=$C(CH_3)_2$) (3.34g) in tetrahydrofuran were introduced and the reaction mixture stirred for a further 30 minutes at -78°C before being allowed to warm to 0°C.

Water (20cm³) was added, and then chloroform (60cm³). The organic phase was removed, dried and evaporated to yield an oil which after chromatography on silica (60g) (elution with ethyl acetate: 60-80°C petrol (4:6) crystallised to give the title compound (1.64g) 49%) as a colourless solid, m.p. 78-79°C; λ_{max}(ε) 210(10,900)nm; ν_{max}($CHCl_3$) 3600, 3500, 1720, 1680cm^{-1}; δH($CDCl_3$) 1.30, 1.41 (2xs, 2x3H, $C(CH_3)_2$), 2.40(m, 1H, H-6), 2.52(d,1H, J=7.6Hz, OH), 2.62 (m,1H,H-6), 3.71(s,3H,OCH_3), 3.92(m,1H,H-5), 4.40(dd,1H,J=6.4Hz,J=3.2Hz, H-4), 4.70(m,1H,H-3), 6.72(m,1H,H-2); δ_C($CDCl_3$) 26.1, 27.5 (2xq, 2x$C(CH_3)_2$), 27.8(t,C-6), 52.0 (q,OCH_3), 67.1(d,C-5), 73.1(d,C-4), 75.7(d,C-3), 110.1(s,$C(CH_3)_2$), 129.4(s,C-1), 134.9(d,C-2), 166.7(s,C=O); m/z 213(M-CH_3, 100%), 197(M-CH_3O, 4%), 153(36%), 139(33%) [Found: C, 57.8; H, 7.1 $C_{11}H_{16}O_5$ requires: C,57.9; H,7.0%]. The 5-O-toluenesulphonyl derivate has m.p. 102-103°C; ν_{max} ($CHCl_3$) 1720, 1660, 1605cm^{-1}; δH($CDCl_3$) 1.34(s,6H,$C(CH_3)_2$), 2.41(s,3H,ArCH_3), 2.60(m,2H,H_2-6), 3.68(s,3H,OCH_3), 4.35(m,1H, H-4), 4.75(m,2H,H-3,H-5), 6.60(m,1H,H-2), 7.25(d,2H,J=8Hz, H-3′, H-5′, 7.73(d,2H,J=8Hz, H-2′, H-6′); m/z 367(M-CH_3, 100%), 213(70%), 173(38%).

The 5-O-methanesulphonyl derivative is a colourless crystalline solid, m.p. 109-110°C; ν_{max}($CHCl_3$) 1724, 1664cm^{-1}; δH($CDCl_3$) 1.40(d, 6H,$C(CH_3)_2$), 2.81(m,2H,H_2-6), 3.15(s,3H,SO_2CH_3) 3.80(s,3H, OCH_3), 4.56(m,1H,H-4), 4.82(m,1H, H-3), 4.97(m,1H,H-5), 6.78(m,1H,H-2); δ_C($CDCl_3$) 25.3(t,C-6), 26.5, 27.6(2xq, $C(CH_3)_2$), 39.1 (q,SO_2CH_3), 52.2(q,OCH_3), 73.5(d,C-4), 73.8(d, C-3), 75.3(d,C-5), 111.1 (s,$C(CH_3)_2$), 128.0 (s,C-1, 135.2(d,C-2), 166.0(s,C=O); m/z (CI, isobutane), 307(M+1, 10%), 249 (100%).

(±)-Methyl 5-epishikimate (2). The alcohol (5,R=H) (0.20g) was heated with 50% acetic acid (10cm³) at 55°C for 3 hours and then water and acetic acid were removed in vacuo using a "cold finger". The residue was crystallised from ethyl acetate to give the title ester as colourless prisms (0.16g), 96%), m.p. 111-112°C; λ_{max}(ε) 220(6200)nm; $\delta_H[(CD_3)_2CO]$ 2.38(dd,1H,J_1=17.2Hz,J_2=9.2Hz, H-6); 2.49(dd,1H,J_1=17.2Hz, J_2=5.2Hz, H-6); 3.70(s,3H,OCH_3), 3.82(dd,1H,J_1=9.2Hz, J_2=5.2, H-5), 3.94(bs,3H,3xOH, this signal disappears when D_2O is added), 3.96(m,1H,H-4), 4.3(m,1H,H-3), 6.61(m,1H,H-2); δC[$(CD_3)_2CO$/ $(CD_3)_2SO$] 29.8(t,C-6), 51.8(q,OCH_3), 68.8(d, C-5), 69.0(d,C-4), 71.6(d,C-3), 128.8(s,C-1),

140.5(d,C-2), 167.2(s,C=O); m/z (CI, isobutane) 189 (M+1, 11%), 171(M+1-H_2O, 100%) [Found: C, 50.9; H, 6.5 $C_8H_{12}O_5$ requires: C, 51.1; H, 6.4%].

Methyl 3,4-O,O-isopropylidine-3,4-dihydroxy benzoate(6). The O-tosyl derivative (5,R=tosyl) (0.18g) in dimethylformamide (10cm³) containing potassium acetate (0.5g) was stirred at 90°C for 6 days. After cooling, water (5cm³) was added and the mixture extracted with diethylether (25cm³). The combined extracts were then washed with water (25cm³), dried and evaporated to yield an oil which was chromatographed on silica (20g) eluting with ethyl acetate: 60-80° petrol (3:7) to give the title compound which remained as an oil (0.059g, 60%); λ_{max} 262nm; ν_{max} 1718, 1610cm^{-1}; δ_H($CDCl_3$) 1.50(s,6H,C(CH_3)$_2$), 3.71(s,3H,OCH_3), 6.55(d, 1H, J=8Hz, H-5), 7.20(d,1H,J=1Hz, H-2) 7.44 (dd,1H,J_1=8Hz, J_2=1Hz, H-6); m/z (EI), 208(M, 6%), 193(16%), 149(199%).

(±)-3,4-O,O-Isopropylidine-3α,4α-dihydroxy-5α-(4-toluenesulphonyloxy)cyclohexene-1-carboxylic acid (7,R=$C_7H_7SO_2$). The ester (5,R=tosyl)(9.95g) in benzene (8cm³) containing 18-crown-6 (0.2g) was treated with potassium superoxide. After stirring for 30 minutes, the reaction mixture was diluted with ethyl acetate (10cm³) and water (5cm³), followed by 1M hydrochloric acid(5cm³). The two phases were separated and the aqueous portion extracted with ethyl acetate (20cm³), the combined organic phase and extract were then dried and evaporated to give an oil which was chromatographed on silica (10g) eluting with ethyl acetate: (60-80°C petrol (4:1). The title compound was eluted first as a colourless solid (0.24g, 50%), m.p. 156-158°C, ν_{max}($CHCl_3$) 3550, 1710, 1660cm^{-1}; δ_H($CDCl_3$) 1.34(s,6H,C(CH_3)$_2$), 2.47(s,3H,4'CH_3), 2.63(m,2H,H_2-6), 4.42(m,1H, H-4), 4.73(m,2H,H-3,H-5), 6.81(m,1H,H-2), 7.35(d,2H,J8Hz,H-3', H-5'), 7.83(d,2H,J=8Hz, H-2',H-6'; m/z (EI) 353.0696(M-15, 47%, $C_{16}H_{17}SO_7$ requires: 353.0694); m/z (CI, isobutane) 369(M+1, 10%), 353(22%), 311(100%), 293(94%).

Subsequent fractions from the column afforded the epoxide(s) (8) (0.009g) as an oil, which proved to be unstable and was only partially characterized: ν_{max}($CHCl_3$) 3300, 1720, 1590cm^{-1}; δH[$(CD_3)_2CO$] 1.23, 1.33(2xs; C(CH_3)$_2$), 2.37(s,3H,4'-CH_3), 2.7(m,2H,H_2-6), 4.40(m,4H,H-2, H-3, H-4,H-5), 7.30(d,2H,J=8Hz, H-3', H-5'), 7.68(d,2H,J=8Hz, H-2',H-6'); m/z (CI, isobutane) 385(M+1, 100%), 369(12%), 231(30%), 213(24%).

(±)-3 ,4 -Dihydroxy-5 -methanesulphonyloxycyclo hexene-1-carboxylic acid (9,R=Ac). The O-mesylate (7,R=CH_3SO_2) (0.21g) in 50% aqueous acetic acid (8cm³) was stirred at 65°C for 15 hours. Water and acetic acid were then removed and the residual oil chromatographed on silica (5g) eluting with acetone. The product, also an oil (0.12g), 63%),, slowly crystallised to give a solid, m.p. 145-147°C; δ_H[$(CD_3)_2SO$] 2.72 (m,2H,H_2-6), 3.20(s,3H,SO_2CH_3), 4.28(m,1H,H-4), 4.50(m, 1H,H-3), 4.91(m,1H,H-5), 6.74(m,1H,H-2); δ_C[$(CD_3)_2SO$] 28.1(t,C-6), 38.2(q,SO_2CH_3), 69.1(d,C-4), 69.9(d,C-3), 79.9(d,C-5), 128.8(s, C-1), 141.1(d,C-2), 168/7(s,C=O); m/z (CI, isobutane) 253(M+1, 1%), 157(34%), 139(100%). Due to difficulties in detecting the molecular ion an accurate mass measurement was not possible.

3,4-O,O-Isopropylidine-3 ,4 -dihydroxy-5 -methanesulphonyloxycyclohexene-1-carboxylic acid (7,R=CH_3SO_2). The O-mesyl derivative of the alcohol (5,R=H) (0.05g) in tetrahydrofuran (4cm³) and water (1cm³) was treated with lithium hydroxide (0.03g) and stirred at room-temperature for 3 hours. Ethyl acetate (15cm³) was then added and the solution acidified with 1M hydrochloric acid (5cm³). The organic phase was separated, dried and evaporated to give a colourless solid which, after chromatography on silica (5g) eluting with ethyl acetate, afforded the title compound (0.034g, 72%), m.p. 157-159°C; δ_H[$(CD_3)_2SO$] 1.34(d,6H,C(CH_3)$_2$), 2.62(m,2H,$H_2$6), 3.31(s,3H,SO_2CH_3), 4.52(m, 1H,H-4), 4.98(m,2H,H-3,H-5), 6.66(m,1H,H-2); δ_C[$(CD_3)_2SO$] 25.2(t,C-6), 26.3, 27.2 (2xq, C(CH_3)$_2$), 38.6(q,SO_2CH_3), 72.6(d,C-4), 73.2(d, C-3), 75.7(d,C-5), 109.6(s,C(CH_3)$_2$). 128.1(s, C-1), 134.5(d,C-2), 166.7(s,C=O; m/z (EI) 277.0387 (M-CH_3, 85%, $C_{10}H_{13}SO_7$ requires 277.0381), 199(100%).

(±)-Methyl 4,5-O,O-isopropylidine-4α,5α-dihydroxycyclohexen-3-one-2-carboxylate(10) Pyridinium chlorochromate (0.3g) was suspended in dichloromethane (1cm³) containing sodium acetate (0.05g), to this was added the alcohol (5,R=H) (0.15g) in dichloromethane (1.5cm³). After stirring for 5 days, during which time an additional amount of pyridinium chlorochromate (0.15g) was added, a black solid separated out. This was collected, crushed and washed with diethyl ether (5x15cm³), the filtrate and washings were combined and filtered through a column of florisil (30g). Removal of the solvent yielded an oil (0.065, 44%); λ_{max} 220nm; ν_{max} ($CHCl_3$) 1740, 1690cm^{-1}; δ_H($CDCl_3$) 1.22, 1.24 (2xs, 3H, C(CH_3)$_2$), 3.77(bs, 1H, H-5), 3.92(s,3H,OCH_3), 4.48(1H, Jgem=8Hz H-2), 4.62(dd,1H,Jgem=8Hz, $J_{2,4}$=1.5Hz, H_2-2), 4.99(d,H-1,$J_{4,2}$=1.5Hz, H-4), 6.98(s,1H, H-6). This product is very unstable and meaningful mass spectrometric data were not obtained.

(±)-Methyl 5,6-O,O-isopropylidinecyclohexa-1,3-diene-2-carboxylate (12,R,R=C(CH_3)$_2$). 12;R,R=C(CH_3)$_2$). The hydroxy ester (5,R=H) (0.25g) and triphenylphosphine (0.57g) were dissolved in tetrahydrofuran (5cm³) and diethyl azodicarboxylate (0.35cm³) was added. The reaction mixture was protected with a nitrogen atmosphere and, after stirring for 2 hours, the solvent was removed to yield an oil which was chromatographed on silica (30g) eluting with ethyl acetate: 60°-80° petrol (1:4). The title compound was obtained from the early fractions as a colourless solid (0.09g, 39%), m.p. 47-49°C; λ_{max}272nm; $\nu$$CHCl_3$ 1730, 1660, 1610cm^{-1}; δH($CDCl_3$) 1.40(s,6H,C(CH_3)$_2$), 3.81(s,3H,OCH_3), 4.62(dd,1H,J=8Hz, J=3Hz, H-5); 4.82(dd,1H,J=8Hz, J=3Hz, H-6), 6.02 (dd,1H,J=10Hz,J=3Hz, H-4), 6.54(d,1H,J=10Hz, H-3), 6.86(m,1H,H-1); m/z (EI) 195.0657(M-CH_3, 27%, $C_{10}H_{11}O_4$ requires: 195.0657); m/z (CI, isobutane, %) 211(M+1,22), 153(100). Subsequent fractions from the column contained methyl 3-hydroxybenzoate (0.078g, 47%), m.p. and mixed m.p. 66-67°C, sample prepared from authentic 3-hydroxybenzoic acid (Aldrich H2, 000-8).

Cis-5,6-dihydroxy-2-methoxycarbonylcyclohexa-1,3-diene(12,R=H). The isopropylidene derivative (12;R,R=C(CH_3)$_2$) (0.09g) was stirred in 50% aqueous acetic acid (4cm³) at 55°C for 1.5hours. The water and acid were removed in vacuo and the residual oil chromatographed on silica (20g) eluting with ethyl acetate. The early fractions contained methyl 3-hydroxybenzoate (0.31g, 48%), followed by the title compound which was crystallised from ethyl acetate as a colourless solid (0.035, 48%), m.p. 91-92°C; λ_{max}(ε) 272(2500)nm; ν_{max} ($CHCl_3$) 3575, 3400, 1725, 1648, 1592cm^{-1}; δ_H[(CD_3)$_2$CO] 3.74(s,3H,OCH_3), 3.82(s,1H,OH, this signal is eliminated when D_2O is added), 4.10(dd, 1H, J=4.8Hz, H-5), 4.11(s,1H,OH, this signal is eliminated when D_2O is added), 4.34(dd, 1H,J=7Hz,J=4Hz, H-6), 6.05(dd,1H,J=10Hz, J=4.8Hz, H-4), 6.34(d,1H,J=10Hz, H-3), 6.38(m,1H,H-1); m/z 170(M,1%), 152(47%), 121(100%), [Found: C,56.4;H,6.0 $C_8H_{10}O_4$ requires: C,56.5; H; 5.9%].

(±)Methyl shikimate (1,R=Me) (a) The diene (12,R,R=C(CH_3)$_2$) (0.25g) in tetrahydrofuran (5cm³) at 0°C was treated with 1M diborane in tetrahydrofuran (7cm³) and the reaction then allowed to warm to room-temperature and stirred for 1 hour. A small quantity of ice was added and the temperature was then reduced to 0°C. Sodium hydroxide (0.045g) in water (2cm³) was added, followed by 30% hydrogen peroxide (0.25cm³), and after a further 30 minutes, the reaction mixture was extracted with diethyl ether (3x10cm³). The extracts were washed with water (5cm³), dried and evaporated to yield an oil which after chromatography on silica (75g) eluting with ethyl acetate: 60-80°C petrol (2:3), gave the 3,4-O,O-isopropylidene derivative of (±)-methyl shikimate as a colourless oil (0.122g), 45%); ν_{max}($CHCl_3$) 3580, 3390, 1715, 1659cm^{-1}; δ_H($CDCl_3$) 1.38, 1.42, (2xs,2x3H, C(CH_3)$_2$), 2.20, 2.72 (2xm, 2x1H,H_2-6), 2.80(bs,1H,OH, this signal is eliminated when D_2O is added), 3.76(s,3H, OCH_3), 4.00(m,2H,H-4,4-5), 4.73(m,1H,H-3), 6.91)m,1H,H-2); δ_C($CDCl_3$) 25.8, 27.9(2xq, C(CH_3)$_2$), 29.4(t,C-6), 52.1(q,OCH_3), 68.6(d, C-5), 72.3(d,C-4), 77.8(d,C-3), 109.7(s,C(CH_3)$_2$), 130.4(s,C-1), 134.1(d,C-2), 166.7(s,c=0); m/z CI, isobutane (229(M+1, 83%), 197(30%), 171(100%). Deacetonation under literature conditions[9] (Dowex W X-8 resin, protonated

form, methanol, room-temperature) gave (±)-methyl shikimate in 85% yield. This compound is identical, spectroscopically and chromatographically, with the methyl ester of naturally occurring shikimic acid; m.p. 113-113°C (lit.[9], 115-116°C); ν_{max}(KBr) 3445, 1660cm^{-1}; ($\delta_H(D_2O)$ 2.20(dd,1H, Jgem = 16Hz, J_2=8Hz, H-6α), 2.80(dd,1H, Jgem=16Hz, J_2=7Hz, H-6β), 3.76(s,3H,OCH$_3$), 3.77(m,1H,H-5), 4.04(m,1H,H-4), 4.46(m,1H,H-3), 6.82 m,1H,H-2); $\delta_C(D_2O)$ 31.6(t,C-6), 53.7(q,OCH$_3$), 67.0,67.8 (2xd,C-4,C-5), 72.3(d,C-3), 130.7(s,C-1), 138.4(d,C-2), 170.1(s,C=0).

(b) The diene (15) (0.22g) in acetone (5cm^3) and diethyl ether (8cm^3) was treated with a solution containing 10% osmium (IV) oxide in t-butanol (2cm^3) and 30% hydrogen peroxide (0.13cm^3). The reaction mixture was left stirring overnight, the solvents removed and the residue redissolved in acetone, dried and added to the top of a silica (25g) column. Elution with ethyl acetate gave a mixture of (±)-methyl shikimate and (±)-methyl 5-epishikimate as an oil. Further chromatography of the mixture using acetone as eluent separated the isomers, giving (±)-methyl shikimate, colourless prisms, m.p. 110-112°C, as the major product (0.16g); together with (±)-methyl epishikimate (0.06g) also a colourless solid, m.p. 110-112°C. The former compound is identical in every respect with the sample prepared by hydroboration of the diene (12; R,R=C(CH$_3$)$_2$). (±)-Methyl epishikimate has Rf 0.55 (silica-acetone) whereas (±)-methyl shikimate has Rf 0.65 in this solvent system. A mixed m.p. of the two compounds is depressed.

c) tButyldimethylsilyl triflate (0.7cm^3) was added to 2,6-lutidine (0.5cm^3) at 0°C and stirred for 30 minutes. The diene (15) (0.31g) in dichloromethane (2cm^3) was then introduced slowly and the mixture stirred for a further 30 minutes. After this time TLC analysis showed that all the diene had reacted to give a single product (Rf 0.77, SiO_2/EtOAc: 60-80°C petrol (1:3). The reaction mixture was poured onto ice and saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane (3x15cm^3). The dry, combined extracts were evaporated to yield the O-silyl derivative of the diene (15) as an oil which was purified by chromatography on a short-path silica column eluting with 30% ethyl acetate in 60-80°C petrol. Yield 0.51g, 95%; λ_{max} 272nm; νmax ($CHCl_3$) 1710cm^{-1}; $\delta_H(CDCl_3)$ 0.20(s,6H, CH$_3$)$_2$ Si, 0.91(s,9H, (CH$_3$)$_3$ CSi , 2.62(2xdd, 2H,$J_{6,5}$=8Hz,$J_{6,2}$=3Hz,H$_2$-6), 3.68((s,3H,OCH$_3$), 4.45(bt,1H,H-5), 5.95(m,2H,H-3,H-4), 6.86(m,1H, H-2;$\delta_C(CDCl_3)$ 19.4(s), 27.1(q), 32.7(t), 52.8(q), 66.6(q), 124.8(d), 129.5(s), 130.8(d), 133.0(d), 168.7(s). This compound was used directly in the next step which was accomplished in precisely the same manner as described in (b)above to givethe 5-O-tButyl dimethylsilyl derivative of (±)-methyl shikimate as an oil. Purification was achieved by chromatography on silica eluting with ethyl acetate: (60-80°C petrol (1:3), Rf 0.34 (single spot). Yield 78%; $\nu_{max}(CHCl_3)$ 3450, 1720cm^{-1}; $\delta_H(CDCl_3)$ 0.40(s,6H,(CH$_3$)$_2$Si), 1.88(s,9H,(CH$_3$)$_3$CSi ,2.15(bd, 1H,Jgem=9Hz, J=3Hz, H-6), 2.75(bdd,1H,Jgem=9Hz, J=3Hz,H-6), 3.75(s,3H,OCH$_3$), 3.78(m,1H,5-H), 4.05(m,1H, 4-H), 4.48(m,1H,3-H), 6.81(m,1H,H-2); $\delta_C(CDCl_3)$ 18.1(s), 22.5(q), 29.8(q), 31.4(t), 52.1(q), 66.0 (d), 68.3(d), 71.9(d), 129.9(s), 136.6(d), 166.8(s). Deprotection was accomplished by treating the silylderivative (0.11g) in tetrahydrofuran (1cm^3) with tetrabutylammonium fluoride (0.175g) in tetrahydrofuran (2cm^3) at 0°C. After 30 minutes the solvent was removed, and the residue chromatographed (SiO_2-acetone) to give (±)-methyl shikimate which proved to be identical in all respects with the compound obtained previously. Yield 86%.

2-[1 ,2 -Diethoxycarbonylhydrazinyl]-tetrahydrofuran (14). The alcohol (5,R=H) (0.05g) in dry tetrahydrofuran (3cm^3) containing triphenylphosphine (0.06g) and zinc(II) tosylate (0.09g) was treated with diethyl diazodicarboxylate (0.04cm^3) in tetrahydrofuran (1cm^3). The mixture was stirred for 18 hours and the solvents then evaporated to leave an oil which was chromatographed on silica (50g) eluting with ethyl acetate: 60-80°C petrol (2:3). This gave the title compound as a colourless oil (0.05g, 89%); $\nu_{max}(CHCl_3)$ 3390, 1720cm^{-1}; $\delta_H(CDCl_3)$ 1.28(2xt,2x3H,

2xOCH$_2$CH$_3$), 2.00(m,4H,H$_2$-3,H$_2$-4), 3.82(m,2H, H$_2$-5), 4.15(2xq,2x2H,2xOCH$_2$CH$_3$), 5.9(t,1H, J=7Hz,H-2), 6.91(bs,1H,NH, this signal is eliminated when D$_2$O is added); δ_C(CDCl$_3$) 14.5(q,OCH$_2$CH$_3$), 25.2(t,OCH$_2$CH$_3$), 28.3(t, OCH$_2$CH$_3$), 28.3(t,OCH$_2$CH$_3$), 62.0(t,C-4), 62.7(t,C-3), 68.6(t,C-5), 87.6(d,C-2), 155.6(s,C=O), 156.9(s,C=O); m/z (CI, isobutane 247(M+1, 7%), 177(98%), 71(100%).

(±)-Methyl 5β-hydroxy-5,6-dihydrobenzoate(15) The mixed adducts (3) (1.12g) in tetrahydro furan (9cm^3) were added dropwise to lithium hexamethylsilazane [generated from hexamethyl silazane (1.29g) and 1.85M) n-butyl lithium in tetrahydrofuran (50cm^3)] maintained at -78°C. The reaction mixture was stirred at this temperature for 1.5hours before being allowed to warm to 0°C. Saturated aqueous ammonium chloride solution (130cm^3) was added, and the reaction mixture extracted with chloroform (5x100cm^3). The combined extracts were then dried, evaporated, and the residue chromatographed on silica (50g) eluting with ethyl acetate: 60-80°C petrol (2:3) to afford the title compound (0.90g) as an oil; λ_{max}290nm; ν_{max}3420, 1700cm^{-1}; δ_H(CDCl$_3$) 2.75(m,2H,Jgem=16Hz, J$_1$=8Hz, J$_2$=2Hz, H$_2$-6), 3.76(s,3H,OCH$_3$), 3.76(s,1H,OH, this signal is eliminated by addition of D$_2$O), 4.36(bs,1H,H-5), 6.18(m,2H, H-3,H-4), 7.08(m,1H,H-2); δ_C(CDCl$_3$) 31,0(t, C-6), 51.7(q,OCH$_3$), 63.2(d,C-5), 124.2, 126.8(2xd, C-3, C-4), 131.8(d,C-2), 134(s, C-1), 167.6(s,C=O); m/z (EI) 154(M,40%), 139(28%), 122(23%), 95(100%), 94(31%), 77(50%). This compound is unstable in air and accurate carbon and hydrogen analytical data were not obtained.

Exo-2,3-epoxy-exo(endo)-6-methoxycarbonyl-7-oxatricyclo[2,2,1]heptane (17,X=O). The mixed adducts (3) (5.56g) in dichloromethane (50cm^3) was added to a solution of 3-chloroperbenzoic acid (7.86g) in dichloromethane (200cm^3) maintained at 0°C. After 12 hours the reaction mixture was filtered and the filtrate, washed in succession with 10% aqueous sodium sulphite (5x50cm^3), 5% aqueous sodium bicarbonate (3x50cm^3) and brine (2x50cm^3). It was then dried and the solvent removed to yield the title compounds (4.3, 70%). Column chromatography on silica, eluting with ethyl acetate - 60-80°C petrol mixtures afforded the exo-6-methoxycarbonyl isomer (3.46g, 56%), m.p. 45-47°; ν_{max} (CHCl$_3$) 1740cm^{-1}; δ_H(CDCl$_3$) 1.6-2.8(m,3H,H$_2$-5, H-6), 3.25(s,1H,H-2), 3.8(s,3H,OCH$_3$), 4.55(d,1H, J=4Hz, H-4), 4.8(s,1H,H-1); δ_C(CDCl$_3$) 31.5(t, C-5), 44.7(d,C-6), 49.4(d,C-3), 49.9(d,C-2), 52.2(q,OCH$_3$), 74.0(d,C-1), 76.9(d,C-4), 172.8(s,C=O); m/z (CI, isobutane) 171(M+1, 100%), 139(28%), 111(28%) [Found: C,56.3, H,6.0 C$_8$H$_{10}$O$_4$ requires: C,56.5, H,5.9%].

3-Hydroxy-6-methoxycarbonyl-7-oxa-tricyclo [2,2,1,0^{2,6}]heptane (18,X=O) The epoxides (17,X=O) (2.65g) in tetrahydrofuran (15cm^3) were slowly added to a solution of lithium hexamethylsilazane generated from hexamethyl silazane (2.76g) and 1eq. of n-butyl lithium in tetrahydrofuran (30cm^3) maintained at -78°C. After 1 hour at this temperature the reaction mixture was allowed to warm to 0°C and saturated ammonium chloride (300cm^3) was then introduced. Extraction with chloroform (5x50cm^3) and removal of the solvent from the combined extracts afforded an oil, which remained as a liquid after chromatography on silica (40g) eluting with ethyl acetate: 60-80°C petrol (1:1). Yield (1.67g) (63%); ν_{max}3450, 1730cm^{-1}; δ_H(CDCl$_3$) 1.74(m,2H,H$_2$-3), 2.16(d,1H,J$_{6,1}$=4Hz, H-6), 3.20(bs,1H,OH, this signal is eliminated when D$_2$O is added), 3.67(s,3H,OCH$_3$), 3.99(bs,1H,H-5), 4.13(m,1H,H-4), 4.43(dd,J$_{1,6}$=4Hz, J$_{1,4}$=1.1Hz, H-1); δ_C(CDCl$_3$) 25.7(d,C-6), 29.3(s,C-2), 30.2(t,C-3), 51.8(q,OCH$_3$), 59.3(d,C-1), 74.3(d,C-4), 76.4(d,C-5), 171.0(s,C=O); m/z (EI) 170(M,3%), 138(67%), 110(100%), 81(92%) [Found: C,56.5; H,5.9 C$_8$H$_{10}$O$_4$ requires: C, 56.5; H,6.0%].

Exo-2,3-epoxy-exo(endo)-6-methoxycarbonyl bicyclo[2,2,1]heptane (17,X=CH$_2$) The mixed adducts of cyclopentadiene and methyl acrylate[11] (0.55g) in dichloromethane (10cm^3) maintained at 0°C were treated with 3-chloroperbenzoic acid (0.68g) in dichloromethane (15cm^3). After 24 hours, the reaction mixture was washed with 10% aqueous sodium sulphite (3x15cm^3), 5% aqueous sodium bicarbonate (3x15cm^3) and

brine (3x10cm³). The dried organic phase was then evaporated to yield the title compounds as an oil which was purified by column chromatography on silica (50g) eluting with ethyl acetate: 60-80°C petrol (3:7), without separation (0.40g), 65%; ν_{max} 1760cm^{-1}; $\delta_H(CDCl_3)$ 3.70(s,3H,OCH$_3$, endo isomer), 3.72(s,3H,OCH$_3$, exo isomer). Integral ratios show proportions of isomers to be 2:1 exo:endo; m/z (EI) 168.0785(M,20%, calculated for $C_9H_{12}O_3$ 168.0786).

3-Hydroxy-6-methoxycarbonyltricylco[2,2,1,$0^{2,6}$]heptane (18,X=CH$_2$). This compound was prepared by treatment of epoxide (19,X=CH$_2$) with lithium hexamethylsilazane under exactly the same conditions as those used in the conversion of the epoxide (19,X=O) into the oxa-analogue (20,X=O). Yield 70%. The product is an oil; ν_{max} 3460, 1720cm^{-1}; $\delta_H(CDCl_3)$ 1.47(qd,1H,Jgem=10.9Hz, $J_{7,2}$=2.8Hz, $J_{7,5\alpha}$=1.5Hz, H-7$_1$), 1.52(dd,1H,Jgem=10.8Hz, $J_{5\beta,2}$=1.5Hz, H-5β, 1.59(qd,s,1H, Jgem=10.8Hz, $J_{5\alpha,2}$=2.9Hz, $J_{5\alpha,7}$=1.4Hz, "W effect", H-5α), 1.63(brs,1H,OH, this signal is removed by addition of D_2O), 1.90(m,1H,H-1), 1.92(m, 1H,H$_2$-7), 1.96(m,1H,H-2), 1.98(m,1H,H-4), 3.64(s,3H,OCH$_3$); $\delta_C(CDCl_3)$ 23.2(d,C-2), 27.3(d,C-1), 28.6(s,C-6), 30.0, 30.7(2xt, C-5, C-7), 37.2(d,C-4), 51.6(q,OCH$_3$), 78.5 (d,C-3), 173.6(s,C=0) [Found: C,64.3; H,7.1 $C_9H_{12}O_3$ requires: C,64.2; H 7.1%].

6-Methoxycarbonyltricyclo[2,2;1,$0^{2,6}$]heptane-3-one(19) The alcohol (17,X=CH$_2$) (0.35g) in dichloromethane (5cm³) was added to a suspension of pyridinium chlorochromate (0.97g) in dichloromethane (5cm³). After stirring for 3 hours, diethyl ether (50cm³) was added to the reaction mixture and the solvent decanted from a black solid which had formed. This material was crushed and washed with more diethyl ether (3x10cm³). Filtrate and washings were combined, filtered through florisil (40g) and evaporated to yield the title compound as an oil (0.23g, 78%); ν_{max} 1770, 1735cm^{-1}; $\delta_H(CDCl_3)$ 2.1(m,6H, H-1,H-4,H$_2$-5, H$_2$-7), 2.66(bd,1H,J=4Hz, H-2), 3.74(s,3H,OCH$_3$); δc(CDCl$_3$) 26.5(d,C-2), 27.4 (d,C-1), 31.8(2xt,C-5,C-7), 40.0(d,C-4), 52.1(q,OCH$_3$), 171.0 (s,CO$_2$CH$_3$), 209.2(s,C=O) [Signal for C-6 not detected; m/z (EI) 166.0637 (M,27%, $C_9H_{10}O_3$ requires: 166.0630), 149(100%).

7-methoxycarbonyl-4-oxatricyclo[3,2,1,$0^{2,7}$]octan-3-one(20) The tricyclic ketone (19) (0.58g) in dichloromethane (2cm³) was treated with solid sodium hydrogencarbonate (0.19g) and 3-chloroperbenzoic acid (0.089g). The mixture was stirred for 48 hours and 10% aqueous sodium sulphite (15cm³) then added. More solvent (15cm³) was introduced and the organic phase separated, washed with water (3x5cm³), dried and evaporated to give the title compound as an oil which was chromatographed on silica (25g) eluting with ethyl acetate: 60-80°C petrol. Yield 0.57g, 90%;ν_{max} br.1750cm^{-1}; $\delta_H(CDCl_3)$ 2.00(m, 1H,H-2), 2.01(m,1H,H-1), 2.18(d,1H,Jgem=12Hz, H-6α), 2.30(dd,1H,Jgem=12Hz,$J_{6\beta 5}$=3.5Hz,H-6β), 2.55(dd,1H,Jgem,=8Hz,$J_{8,1}$=2Hz, H-8), 2.75(d, 1H,Jgem=8Hz,H-8), 3.76 (s,3H,OCH$_3$), 4.72(m, 1H,H-5); $\delta_{(C)}(CDCl_3)$ 26.9(d,C-1), 29.6(d, C-2), 30.6(t,C-8), 31.9(t,C-6), 74.4(d,C-5), 168.0, 170.0(2xs, 2xC=0). [The signal corresponding to C-7 was not detected]; m/z (EI) 182.0576 (M,13%, $C_9H_{10}O_4$ requires: 182.0578), 151(32%), 137(81%).

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