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SYNTHESIS OF 5-HOMOSHIKIMIC ACID AND SOME FLUORINATED DERIVATIVES AS POTENTIAL INHIBITORS OF 5-ENOLPYRUVYLSHIKIMATE-3-PHOSPHATE SYNTHASE

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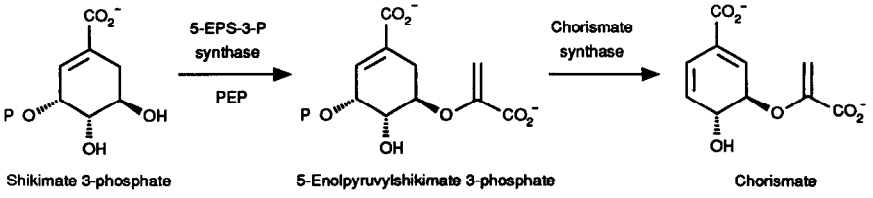
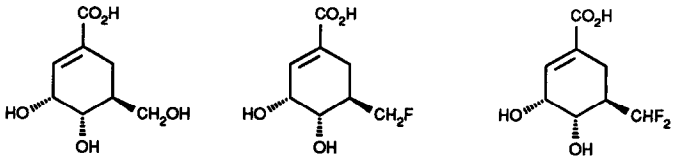
Abstract: The synthesis of (±)-5-homoshikimic acid, its 5-fluoromethyl and difluoromethyl analogues are described from the cycloadducts of 5,6-dihydro-1-^{t}butyloxycarbonylpyridine and methyl acrylate. The adducts on ring opening afford methyl 5-^{t}butoxycarbonylmethyl-5,6-dihydrobenzoate, which may be 3,4-*cis*-dihydroxylated and converted in a series of steps into the title compounds

The shikimic acid pathway is of major biosynthetic importance leading from glucose to the aromatic amino acids[1]. At a comparatively late stage in the sequence shikimic acid 3-phosphate is converted into 5-enolpyruvylshikimic acid 3-phosphate and thence into chorismic acid (scheme 1)[2]. From chorismic acid the pathway branches, leading to the aromatic amino acids, and a diverse group of compounds. Consequently there is much interest in the possibility of selectively inhibiting the enzymes which regulate various steps along the pathway[3]. We have thus targeted 5-homoshikimic acid (1) and its fluoro analogues (2) and (3) as potential inhibitors of the enzyme 5-ESP-3-phosphate synthetase.

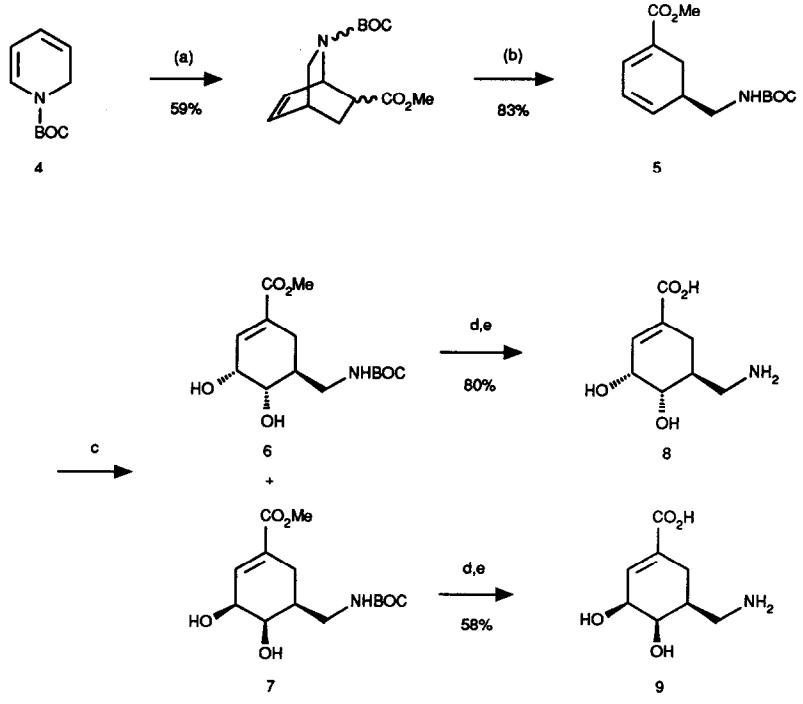
In a preliminary account we have described[4] the synthesis of the racemic cyclohexadienylcarbamate (5) from the Diels Alder addition of methyl acrylate and 1-^{t}butoxycarbonyl-1,2-dihydropyridine (4)[5]. When this product is reacted with N-methylmorpholine-N-oxide/osmium tetraoxide the diastereomeric diols (6) (29%) and (7)(39%) are formed.

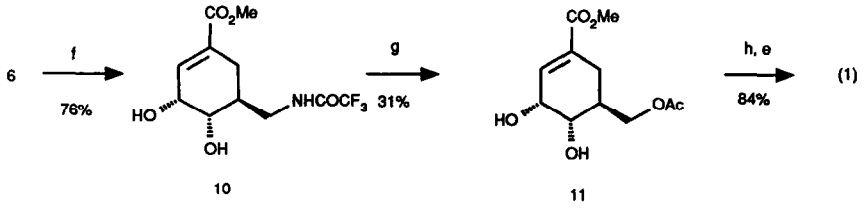


Scheme 1 Biosynthetic relationship of shikimic acid and chorismic acid



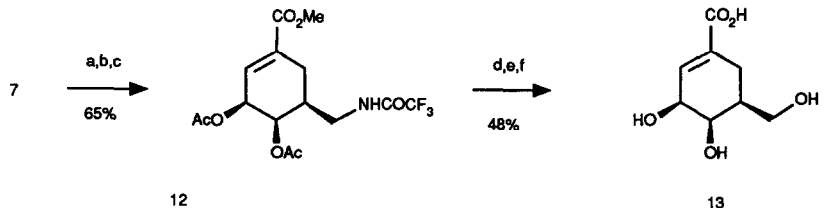
Deprotection of each of the diols by reaction with trifluoroacetic acid, and then ester hydrolysis with aqueous sodium hydroxide affords the amino acids (8) and (9). The trifluoroacetamide (10) was obtained from the diol (6) by treatment first with trifluoroacetic acid and then with trifluoroacetic anhydride. When reacted with sodium nitrite[6] this compound afforded the acetate (11), which was O-deacetylated and hydrolysed to 5-homoshikimic acid (1) by consecutive reactions with ammonia/methanol and then aqueous sodium hydroxide at 20 C°.





Scheme 2 Reagents: (a) CH_2CHCO_2Me, PhMe, Δ; (b) $(TMS)_2NLi$, THF, -78°C; (c) OsO_4, NMO, Me_2CO; (d) TFA, 20°C; (e) NaOH, H_2O, 20°C 20h; (f) TFA then TFAA, py., DMAP, 20°C; (g) $NaNO_2$, HOAc, Ac_2O, -4-10°C; (h) NH_3, H_2O, MeOH, 20°C.

A different sequence (scheme 3) was established for the β,β-diol (7), which was first bisacetylated and then converted into the trifluoroacetamide (12). Deprotection then gave the isomeric trihydroxy acid (13).

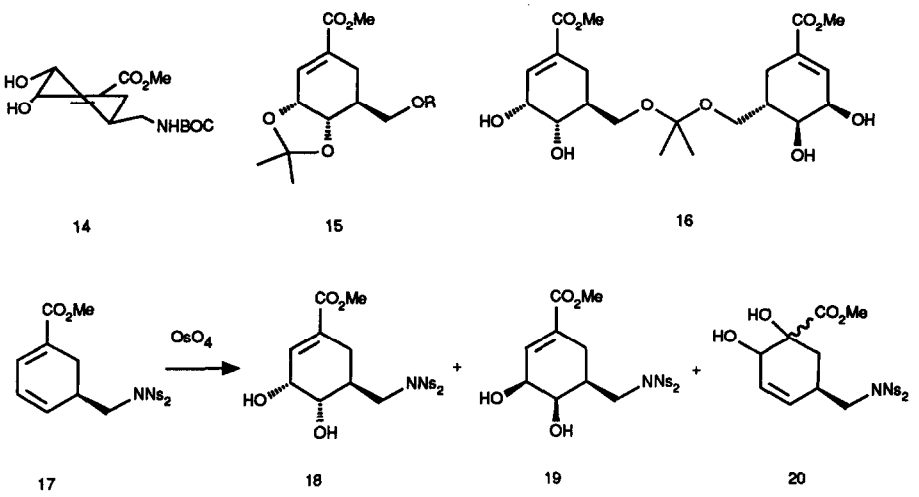


Scheme 3 Reagents: (a) Ac_2O, DMAP, Et_3N; (b) TFA, 20°C; (c) TFAA, py., DMAP, 20°C; (d) $NaNO_2$, HOAc, Ac_2O, -4-10°C; (e) NH_3, H_2O, MeOH, 20°C; (f) NaOH, H_2O, 20°C.

An X-ray crystallographic analysis of diol (6) shows it to adopt the half- chair conformation (14). ^1H NMR data confirm that this spacial arrangement is also favoured in solution, and this geometry seems to be adopted by most of the other cyclohexene derivatives described in this paper.

In order to form the fluoromethyl derivative (2) of 5-homoshikimic acid the acetonide (15,R=H) was prepared, in two steps, from the acetoxymethyl compound (11). Acetonide formation from methyl homoshikimate also gave product (15) together with the bimolecular acetal (16). The monofluoro compound (2) was obtained by reaction of the acetonide (15, R=H) with morpholinosulphur trifluoride (morph-DAST), followed, by diol deprotection ($HOAc/H_2O$) and hydrolysis ($NaOH/H_2O$). Oxidation of the acetonide (15, R=H) with pyridinium chlorochromate gave the corresponding aldehyde which following reaction with morph-DAST, and deprotection, as above, yielded the difluoro analogue (3).

In an alternative route to 5-homoshikimate the cyclohexadienylcarbamate (5) was converted in three steps into the disulphonimide[7] (17, Ns = 4-nitrobenzenesulphonyl) and this product reacted with N-methyl-morpholine-N-oxide/OsO_4. Three diols (18)(16%), (19)(8%), and (20)(10%) were obtained.



14 15 16

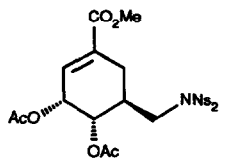
17 18 19 20

Better selectivity and yields were observed when the disulphonimide (17) was reacted with iodine/silver acetate/water ('wet' Prévost conditions[8]). Although this reaction gave six products (21), (22), (23), (24), (25), and (18), the major components (23) and (24), isolated as a mixture, have the correct relative stereochemistry for conversion into the desired product. The diacetate (21) also has the correct stereochemistry for conversion into 5-homoshikimic acid, but this compound could not be separated from its isomeric diacetate (22).

O-Deacetylation of the mixed hydroxyacetates (23) and (24) afforded the diol (18) in 69% yield. This compound was protected as the acetonide and treated with potassium iodide in DMF at 130° C. This gave the iodide (26) (32%), the exocyclic methylene compound (27)(11%), and the O-formyl derivative (28) (17%). This last compound was unexpected, but forms as a result of an interaction of the iodide (26) with solvent DMF: there is precedent for this type of reaction[9].

An improved yield of the iodide was obtained by reacting the disulphonimide with potassium iodide in the presence of 18-crown-6 in toluene solution. The iodide was then converted into the acetoxy derivative (15, R=Ac)(63%) by treatment with sodium acetate in DMF at 110° C. Both the O-formyl compound (28) and the O-acetate (15, R=Ac) were deprotected to give 5-homoshikimic acid in 64% and 61% yields, respectively. An X-ray crystallographic structure determination shows the iodide to adopt a half-chair conformation (29)[10].

The methodology described above provides ready access to a range of homologues of shikimic acid, some of which have potential as inhibitors, at a relatively late stage, of the biosynthetic pathway leading from carbohydrates to aromatic amino acids. We[11] and others[12] have shown that related synthetic routes lead to homochiral products, thus it will be possible to follow similar procedures in the case of the homoshikimic acids disclosed here.



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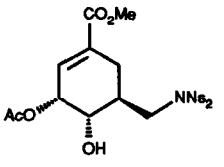

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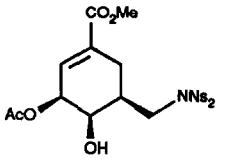
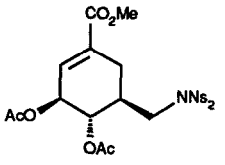
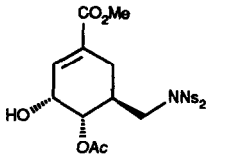


25 (3%)



22

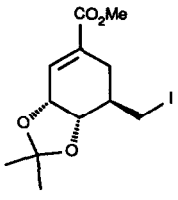
(21+22 20%)



24

(23+24 52%)

plus 18 (3%)



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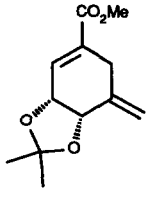

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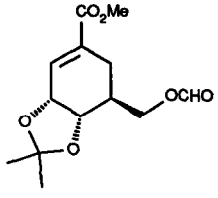

28

Experimental

All solvents were dried and distilled before use. Petrol refers to petroleum ether boiling in the range 60-80°C and light petrol refers to that boiling in the range 40-60°C. Tetrahydrofuran was pre-dried over sodium wire and then boiled over sodium benzophenone ketyl under a nitrogen atmosphere until anhydrous. This was redistilled immediately prior to use. Osmium tetroxide was used as a solution in *t*-butanol.

Medium pressure flash column chromatography was routinely employed using Amicon Matrex or Merck 9385 silica gel. All dilute aqueous solutions used were 2.0 M unless otherwise stated.

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1310 spectrophotometer and peaks are reported in wavenumbers (cm^{-1}). Samples were prepared as liquid films, Nujol mulls or chloroform solutions, as indicated. ^1H NMR spectra were recorded on a JEOL GX FT 270 (270 MHz) spectrometer although, where indicated, JEOL GX FT 400 (400 MHz) or Varian EM-360 (60 MHz) instruments were used.

^{13}C NMR spectra were recorded on a JEOL GX FT 270 spectrometer at 67.8 MHz. Chemical shifts (δ) are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded using a VG Analytical 7070E instrument with a VG 2000 data system. Chemical ionisation (C.I.) was employed using *i*-butane as the reagent gas, although where indicated, ammonia was also used.

2-(*t*-Butoxycarbonyl)-7-(methoxycarbonyl)-2-azabicyclo[2.2.2]oct-5-ene

A solution of the dihydropyridine (4)[4] (15.0 g, 82.8 mmol) and methyl acrylate (14.9 cm^3, 165 mmol) in toluene (40 cm^3) was heated to reflux under a nitrogen atmosphere. After 2 days the solvent and excess methyl acrylate was evaporated under reduced pressure to leave an oil-solid mixture. Repeated crystallisation from toluene yielded the *endo* isomer as a colourless crystalline solid (6.58 g, 30%). Column chromatography (petrol-ethyl acetate 9:1) of the remaining material yielded the *exo* isomer as a colourless oil (6.52 g, 29%).
endo isomer: m.p. 113-114°C (toluene); R_F 0.50 (petrol-ethyl acetate 4:1); (Found: C, 63.0; H, 8.0; N, 5.3. $C_{14}H_{21}NO_4$ requires C, 62.9; H, 7.9; N, 5.2%); $\nu_{max}(CHCl_3)$ 1725 (C=O), 1665 (C=) cm^{-1}; $\delta_H(CDCl_3)$ 1.46 (9H, s, C*Me*$_3$), 1.85 (2H, m, 2 x 8-H), 2.80 (1H, m, 4-H), 2.90 (1H, d, J_{gem} 10.3 Hz, 3-H), 3.06 (1H, m, 7-H), 3.22 (1H, dd, J_{gem} 10.3, $J_{3,4}$ 2.2 Hz, 3-H), 3.65 (3H, s, OMe), 5.06 (1H, br s, 1-H), 6.34 (1H, m, 5-H), 6.43 (1H, , 6-H); /z (C.I., NH_3) 285 (MNH_4^+, 2%), 268 (MH^+, 3), 229 (26), 212 (30), 168 (51), 81 (100).
exo isomer: R_F 0.50 (petrol-ethyl acetate 4:1); $\nu_{max}(CHCl_3)$ 1725 (C=O), 1665 (C=) cm^{-1}; $\delta_H(CDCl_3)$ 1.43 (9H, 2 x s, CMe_3), 1.50 (1H, m, 8-H), 2.10 (1H, , 8-H), 2.54 (1H, m, 7-H), 2.77 (1H, m, 4-H), 2.93 (1H, m, 3-H), 3.34 (1H, m, 3-H), 3.70 (3H, 2 x s, OMe), 4.94 (1H, m, 1-H), 6.44 (2H, m, 5-H, 6-H); m/z (C.I.) 268 (MH^+, 4%), 212 (100).

Methyl 5-[N-(*t*-butoxycarbonyl)aminomethyl]cyclohexa-1,3-diene-1-carboxylate (5)

A solution of 1,1,1,3,3,3-hexamethyldisilazane (7.30 cm^3, 34.6 mmol) in dry THF (35 cm^3) at -78°C was treated with a solution of *n*-butyl lithium in hexanes (1.6 M, 34.6 mmol) under a nitrogen atmosphere. After 20 min a solution of the adducts prepared above (8.40 g, 31.5 mmol) in THF (90 cm^3) was added dropwise *via* a cannula. The reaction mixture was stirred for 10 min at this temperature, allowed to warm to 20°C and quenched with saturated aqueous ammonium chloride solution (100 cm^3). The mixture was extracted with dichloromethane (600, 2 x 200 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (petrol-ethyl acetate 4:1) yielded the title compound as a colourless solid (7.00 g, 83%): m.p. 69-70°C (petrol-ethyl acetate); R_F 0.30 (petrol-ethyl acetate 4:1); (Found: C, 62.8; H, 8.0; N, 5.1. $C_{14}H_{21}NO_4$ requires C, 62.9; H, 7.9; N, 5.2%); $\nu_{max}(CHCl_3)$ 3450 (NH), 1695 (C=O), 1640 (C=) cm^{-1}; $\delta_H(CDCl_3)$ 1.44 (9H, s, CMe_3), 2.34 (1H, ddd, J_{gem} 19.5, $J_{6\beta,5}$ 13.5, $J_{6\beta,2}$ 1.5 Hz, 6β-H), 2.58 (1H, ddd partially obscured by 5-H, J_{gem} 19.5, $J_{6\alpha,5}$ 8.5, $J_{6\alpha,2}$ 1.5 Hz, 6α-H), 2.60 (1H, m, 5-H), 3.06 (1H, m, 1′-H), 3.23 (1H, m, 1′-H), 3.76 (3H, s, OMe), 4.72 (1H, br s , N-H), 6.03 (1H, dd, $J_{4,3}$ 9.5, $J_{4,5}$ 3.0 Hz, 4-H), 6.12 (1H, ddd, $J_{3,4}$ 9.5, $J_{3,2}$ 5.0, $J_{3,5}$ 1.5 Hz, 3-H), 6.99 (1H, dt, $J_{2,3}$ 5.0, $J_{2,6\alpha}$ 1.5, $J_{2,6\beta}$ 1.5 Hz, 2-H); $\delta_C(CDCl_3)$ 14.1 (C*Me*$_3$), 24.7 (C-6), 28.3 (*C*Me$_3$), 34.3 (C-5), 43.2 (C-1′), 51.6 (OMe), 124.6 (C-3), 126.5

(C-1), 132.6 (C-4), 134.8 (C-2), 155.9 (C=O), 167.5 (C=O); m/z (C.I) 268 (MH^+, 2%), 168 (100), 137 (70).

Osmium tetroxide catalysed *cis*-hydroxylation of the cyclohexadienylcarbamate (5)

A solution of the cyclohexadienylcarbamate (**5**) (7.00 g, 26.2 mmol) in acetone (100 cm^3) was treated with a solution of osmium tetroxide in *t*-butanol (0.5% w/v, 1.0 cm^3), N-methylmorpholine N-oxide (3.37 g, 28.8 mmol) and water (1.0 cm^3). The reaction mixture was stirred at 20°C for 48 h and then concentrated under reduced pressure to yield a black oil-solid mixture. Trituration with diethyl ether and crystallisation from ethyl acetate yielded methyl 3α,4α-dihydroxy-5β-[N-(*t*-butoxycarbonyl)-aminomethyl]cyclohex-1-ene--1- carboxylate (6) as a colourless solid (2.25 g, 29%): m.p. 181-182°C (ethyl acetate); R_F 0.28 (petrol-ethyl acetate 1:1); (Found: C, 56.0; H, 7.8; N, 4.65. $C_{14}H_{23}NO_6$ requires C, 55.8; H, 7.7; N, 4.65%); ν_{max}(Nujol) 3400 (OH), 3280 (OH), 1705 (C=O), 1670 (C=C) cm^{-1}; δ_H(D_6-DMSO) 1.38 (9H, s, CMe_3), 1.86 (1H, br dd, J_{gem} 18.0, $J_{6\beta,5}$ 8.5 Hz, 6β-H), 1.96 (1H, m, 5-H), 2.38 (1H, br dd, J_{gem} 18.0, $J_{6\alpha,5}$ 4.0 Hz, 6α-H), 2.84 (1H, ddd, J_{gem} 14.0, $J_{1',5}$ 8.0, $J_{1',NH}$ 5.5 Hz, 1'-H), 3.12 (1H, dt, J_{gem} 14.0, $J_{1',5}$ 5.5, $J_{1',NH}$ 5.5 Hz, 1'-H), 3.39 (1H, m, 4-H), 4.06 (1H, m, 3-H), 4.52 (1H, d, $J_{OH,4}$ 5.5 Hz, 4-OH), 4.89 (1H, d, $J_{OH,3}$ 6.0 Hz, 3-OH), 6.66 (1H, br d, $J_{2,3}$ 4.0 Hz, 2-H), 6.80 (1H, br t, *J* 5.5 Hz, NH); δ_C(D_6-DMSO) 26.7 (C-6), 28.4 (CMe_3), 35.8 (C-5), 41.6 (C-1'), 51.8 (OMe), 65.0 (C-4), 69.6 (C-3), 77.7 (*C*Me_3), 130.0 (C-1), 138.6 (C-2), 156.1 (C=O), 166.9 (C=O); m/z (C.I.) 302 (MH^+, 1%), 228 (100).

The remaining material was purified by column chromatography (petrol-ethyl acetate 1:1) to yield methyl-3β,4β-dihydroxy-5β-[N-(*t*-butoxy-carbonyl)amino-methyl]cyclohex-1-ene-1-carboxylate (7) as a colourless oil (3.08 g, 39%): R_F 0.28 (petrol-ethyl acetate 1:1); (Found: C, 56.2; H, 7.6; N, 4.7. $C_{14}H_{23}NO_6$ requires C, 55.8; H, 7.7; N, 4.65%); ν_{max}(liquid film) 3380 (OH), 1700 (C=O) cm^{-1}; δ_H(D_6-DMSO) 1.38 (9H, s, CMe_3), 1.82 (2H, m, 5-H, 6-H), 2.15 (1H, d m, J_{gem} 16.0 Hz, 6α-H), 2.99 (2H, m, 2 x 1'-H), 3.67 (3H, s, OMe), 3.70 (3H, br s, 4-H), 4.12 (1H, br s, 3-H), 4.39 (1H, br s, 4-OH), 5.00 (1H, br s, 3-OH), 6.53 (1H, br s, 2-H), 6.83 (1H, br t, *J* 5.5 Hz, NH); δ_C(D_6-DMSO) 24.1 (C-6), 28.2 (CMe_3), 37.0 (C-5), 42.5 (C-1'), 51.5 (OMe), 66.9 (C-4), 68.8 (C-3), 77.5 (*C*Me_3), 129.1 (C-1), 140.8 (C-2), 155.8 (C=O), 166.5 (C=O); m/z (C.I.) 302 (MH^+, 28%), 246 (95), 228 (90), 202 (100).

3α,4α-Dihydroxy-5β-(aminomethyl)cyclohex-1-ene-1-carboxylic acid (8)

The ester carbamate (6) (61 mg, 0.20 mmol) was treated with trifluoroacetic acid (4 cm^3), the solution stirred at 20°C for 5 min and then concentrated under reduced pressure. The residue was dissolved in water (4 cm^3) and a 1.0 M aqueous sodium hydroxide solution was added dropwise until the solution was alkaline and then a further 0.3 cm^3 was added. The solution was stirred at 20°C under an argon atmosphere for 20 h. Amberlite IR 120 (+) ion exchange resin was added and the mixture filtered. The resin was washed with water (3 x 10 cm^3), the washings discarded and the product washed from the resin with dilute aqueous ammonia solution (3 x 8 cm^3). Lyophilisation yielded the title compound as an off-white powder (30.5 mg, 80%): R_F 0.55 (reverse phase silica, water); δ_H(D_2O) 2.02 (1H, dd m, J_{gem} 17.0, $J_{6\beta,5}$ 11.0 Hz, 6β-H), 2.15 (1H, m, 5-H), 2.59 (1H,

dd, J_{gem} 17.0, $J_{6\alpha,5}$ 4.5 Hz, 6α-H), 3.03 (1H, dd, J_{gem} 13.0, $J_{1',5}$ 6.0 Hz, 1'-H), 3.24 (1H, dd, J_{gem} 13.0, $J_{1',5}$ 7.0 Hz, 1'-H), 3.72 (1H, dd, $J_{4,5}$ 10.8, $J_{4,3}$ 4.0 Hz, 4-H), 4.25 (1H, dd, $J_{3,4}$ 4.0, $J_{3,2}$ 5.0 Hz, 3-H), 6.49 (1H, m, 2-H); $\delta_C(D_2O)$ 28.7 (C-6), 32.2 (C-5), 42.0 (C-1'), 65.2 (C-4), 71.8 (C-3), 129.6 (C-2), 137.3 (C-1), 175.0 (C=O); m/z (C.I., NH_3) 188 (MH^+, 100%), 172 (35), 152 (44).

3β,4β-Dihydroxy-5β-(aminomethyl)cyclohex-1-ene-1-carboxylic acid (9)

The ester carbamate (7) (93 mg, 0.31 mmol) was treated with trifluoroacetic acid (5 cm^3), the solution stirred at 20°C for 10 min and then concentrated under reduced pressure. The residue was dissolved in water (5 cm^3) and a 1.0 M aqueous sodium hydroxide solution was added dropwise until the solution was alkaline and then a further 0.4 cm^3 was added. The solution was stirred at 20°C under an argon atmosphere for 20 h. Amberlite IR 120 (+) ion exchange resin was added and the mixture filtered. The resin was washed with water (3 x 10 cm^3), the washings discarded and the product washed from the resin with dilute aqueous ammonia solution (3 x 9 cm^3). Lyophilisation yielded the title compound as an off-white powder (34 mg, 58%): R_F 0.55 (reverse phase silica, water); $\delta_H(D_2O)$ 2.14 (2H, m, 5-H, 6β-H), 2.41 (1H, d m, J_{gem} 16.0 Hz, 6α-H), 3.13 (1H, dd, J_{gem} 13.0, $J_{1',5}$ 6.8 Hz, 1'-H), 3.24 (1H, dd, J_{gem} 13.0, $J_{1',5}$ 6.0 Hz, 1'-H), 4.04 (1H, m, 4-H), 4.44 (1H, m, 3-H), 6.35 (1H, br s, 2-H); $\delta_C(D_2O)$ 24.1 (C-6), 35.0 (C-5), 41.3 (C-1'), 67.3 (C-4), 68.2 (C-3), 132.3 (C-2), 135.1 (C-1), 175.0 (C=O); m/z (C.I., NH_3) 188 (MH^+, 100%), 170 (62), 126 (68).

Methyl 3α,4α-dihydroxy-5β-[N-(trifluoroacetyl)aminomethyl]cyclohex-1-ene-1-carboxylate (10)

The carbamate (6) (3.85 g, 12.8 mmol) was added slowly to trifluoroacetic acid (45 cm^3). After stirring at 20°C for 30 min the reaction mixture was concentrated under reduced pressure and taken up in pyridine (50 cm^3). The solution was treated with trifluoroacetic anhydride (9.60 cm^3, 68.0 mmol), DMAP (catalytic) and stirred at 20°C for 3 days. The reaction mixture was then concentrated under reduced pressure and poured into water (100 cm^3). Dilute aqueous hydrochloric acid (200 cm^3) was added and the mixture extracted with ethyl acetate (3 x 150 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (petrol-ethyl acetate 1:3) yielded the title compound as a colourless crystalline solid (2.90 g, 76%): m.p. 116-117°C (petrol-ethyl acetate); R_F 0.33 (petrol-ethyl acetate 1:3); (Found: C, 44.5; H, 4.8; N, 4.65. $C_{11}H_{14}F_3NO_5$ requires C, 44.4; H, 4.75; N, 4.7%); ν_{max}(Nujol) 3400 (OH), 3310 (OH), 1735 (C=O), 1705 (C=O), 1655 (C=C) cm^{-1}; $\delta_H(D_6$-Acetone) 2.00 (1H, dddd, J_{gem} 18.0, $J_{6\beta,5}$ 9.5, $J_{6\beta,2}$ 2.4, $J_{6\beta,3}$ 1.2 Hz, 6β-H), 2.20 (1H, m, 5-H), 2.58 (1H, br dd, J_{gem} 18.0, $J_{6\alpha,5}$ 5.0 Hz, 6α-H), 3.45 (1H, m, 1'-H), 3.60 (2H, m, 4-H, 1'-H), 3.71 (3H, s, OMe), 3.90 (2H, br s, 2 x OH), 4.26 (1H, br t, $J_{3,4}$ 4.5, $J_{3,2}$ 4.5 Hz, 3-H), 6.82 (1H, ddd, $J_{2,3}$ 4.5, $J_{2,6\beta}$ 2.4, $J_{2,6\alpha}$ 1.0 Hz, 2-H), 8.50 (1H, br s, NH); $\delta_C(D_6$-Acetone) 27.7 (C-6), 35.3 (C-5), 41.8 (C-1'), 51.4 (OMe), 65.5 (C-4), 71.1 (C-3), 116.5 (q, $J_{C,F}$ 268 Hz, CF_3), 131.3 (C-1), 137.2 (C-2), 157.4 (C=O), 166.9 (C=O); m/z (C.I., NH_3) 315 (MNH_4^+, 100%), 297 (M^+, 38).

Homonuclear decoupling experiment data for (10):

Signal Irradiated (Chemical shift, δ)	Observed Resonance 2-H	3-H	6α-H	6β-H
Original resonance	ddd	br dd	br dd	dddd
3-H (4.26)	dd		ddd 18.0, 5.0, 1.0 Hz	ddd
6α-H (2.58)	dd	ddd 4.5, 4.5, 1.2 Hz		ddd

Methyl 3α,4α-dihydroxy-5β-(acetoxymethyl)cyclohex-1-ene-1-carboxylate (11)

A solution of the trifluoroacetamide (10) (0.38 g, 1.28 mmol) in acetic anhydride (100 cm^3) and glacial acetic acid (50 cm^3), was cooled to -4°C under a nitrogen atmosphere. Sodium nitrite (0.88 g, 12.8 mmol) was added, and the reaction mixture was stirred at -4 to 10°C for 17 h. The solution was concentrated under reduced pressure and poured into water (50 cm^3). Saturated brine (50 cm^3) was added and the mixture extracted with ethyl acetate (3 x 100 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure (azeotroping with toluene). Column chromatography (petrol-ethyl acetate 1:3) yielded the title compound as a yellow oil (98 mg, 31%): R_F 0.43 (petrol-ethyl acetate 1:3); $\nu_{max}(CHCl_3)$ 3450 (OH), 1710 (C=O), 1655 (C=C) cm^{-1}; $\delta_H(CDCl_3)$ 2.10 (3H, s, Me), 2.18 (2H, m, 5-H, 6β-H), 2.64 (1H, m, 6α-H), 2.73 (1H, br s, OH), 3.21 (1H, br s, OH), 3.58 (1H, dd, $J_{4,5}$ 9.5, $J_{4,3}$ 4.5 Hz, 4-H), 3.77 (3H, s, OMe), 4.15 (1H, dd, J_{gem} 11.4, $J_{1',5}$ 3.4 Hz, 1'-H), 4.34 (1H, dd, $J_{3,2}$ 5.0, $J_{3,4}$ 4.5 Hz, 3-H), 4.43 (1H, dd, J_{gem} 11.4, $J_{1',5}$ 4.4 Hz, 1'-H), 6.90 (1H, ddd, $J_{2,3}$ 5.0, $J_{2,6\beta}$ 2.0, $J_{2,6\alpha}$ 1.0 Hz, 2-H); $\delta_C(CDCl_3)$ 20.8 (Me), 27.0 (C-6), 34.6 (C-5), 52.0 (OMe), 64.7 (C-1'), 65.3 (C-4), 69.2 (C-3), 132.2 (C-1), 135.8 (C-2), 167.0 (C=O), 171.8 (C=O); m/z (C.I.) 245 (MH^+, 1%), 167 (100).

3α,4α-Dihydroxy-5β-(hydroxymethyl)cyclohex-1-ene-1-carboxylic acid (5-homoshikimic acid) (1)

(1a) A solution of the diol acetate (11) (30 mg, 0.12 mmol) in methanol (3 cm^3) was treated with aqueous ammonia solution (1 cm^3) and stirred at 20°C under a nitrogen atmosphere for 21 h. The solvents were evaporated under reduced pressure. Column chromatography (ethyl acetate) yielded methyl 3α,4α-dihydroxy-5β-(hydroxymethyl)cyclohex-1-ene-1-carboxylate as a colourless powder (21 mg, 84%): m.p. 115-115.5°C (ethyl acetate); R_F 0.25 (ethyl acetate); (Found: C, 53.3; H, 7.1. $C_9H_{14}O_5$ requires C, 53.5; H, 7.0%); ν_{max}(Nujol) 3250 br (OH), 1715 (C=O), 1655 (C=C) cm^{-1}; $\delta_H(D_2O)$ 2.11 (2H, m, 5-H, 6β-H), 2.55 (1H, m, 6α-H), 3.64 (1H, dd, J_{gem} 12.0, $J_{1',5}$ 6.0 Hz, 1'-H), 3.73 (2H, m, 4-H, 1'-H), 3.75 (3H, s, OMe), 4.28 (1H, dd, $J_{3,2}$ 4.5, $J_{3,4}$ 4.5 Hz, 3-H), 6.83 (1H, dd, $J_{2,3}$ 4.5, $J_{2,6\beta}$ 1.5 Hz, 2-H); $\delta_C(D_2O)$ 25.4 (C-6), 35.9 (C-5), 51.9 (OMe), 61.7 (C-1'), 64.8 (C-4), 68.7 (C-3), 131.4 (C-1), 135.9 (C-2), 168.9 (C=O); m/z (C.I., NH_3) 220

(MNH_4^+, 100%), 202 (M^+, 22).

(1b) The acetonide formate (28) (38 mg, 0.14 mmol) was dissolved in dry methanol (3 cm^3), Amberlyst-15 ion exchange resin was added and the reaction mixture stirred at 20°C for 17 h. The resin was filtered off and the methanol evaporated under reduced pressure. The residue was dissolved in glacial acetic acid (1 cm^3), water (1 cm^3) and THF (1 cm^3) and heated at 60°C under an argon atmosphere for 3.5 h. Removal of the solvents under reduced pressure and column chromatography (ethyl acetate) yielded methyl 3α,4α-dihydroxy-5β-(hydroxymethyl)cyclohex-1-ene-1-carboxylate as a colourless powder (18 mg, 64%), identical with the sample described above.

(1c) A solution of the acetonide (15,R=H) (40 mg, 0.17 mmol) in glacial acetic acid (1.5 cm^3), water (1.5 cm^3) and THF (1.5 cm^3) was heated to 50-60°C under an argon atmosphere for 17 h. Evaporation of the solvents under reduced pressure and column chromatography (ethyl acetate) yielded methyl 3α,4α-dihydroxy-5β-(hydroxymethyl)cyclohex-1-ene-1-carboxylate as a colourless powder (23.5 mg, 70%), identical with the sample described above.

(2a) Methyl 3α,4α-dihydroxy-5β-(hydroxymethyl)cyclohex-1-ene-1-carboxylate (34 mg, 0.17 mmol) in water (3 cm^3) was treated with aqueous sodium hydroxide solution (1.0 M, 0.17 cm^3) and stirred at 20°C under an argon atmosphere for 5.5 h. The solution was acidified by the addition of IR-120 ion-exchange resin. The resin was filtered off and washed with water. The combined aqueous phases were lyophilised to yield the 5-homoshikimic acid as a colourless microcrystalline solid (32 mg, quantitative): R_F 0.83 (reverse phase silica, water); ν_{max}(Nujol) 3410 (OH), 3370 (OH), 3280 (OH), 1685 (C=O), 1645 (C=C) cm^{-1}; $\delta_H(D_2O)$ 2.09 (2H, m, 5-H, 6β-H), 2.53 (1H, dd, J_{gem} 22.0, $J_{6\alpha,5}$ 9.0 Hz, 6α-H), 3.64 (1H, dd, J_{gem} 11.2, $J_{1',5}$ 6.0 Hz, 1′-H), 3.74 (2H, m, 4-H, 1′-H), 4.28 (1H, dd, $J_{3,4}$ 4.5, $J_{3,2}$ 4.5 Hz, 3-H), 6.79 (1H, dd, $J_{2,3}$ 4.5, $J_{2,6\beta}$ 2.0 Hz, 2-H); $\delta_C(D_2O)$, 25.8 (C-6), 36.2 (C-5), 62.0 (C-1′), 65.1 (C-4), 69.0 (C-3), 132.4 (C-1), 135.6 (C-2), 170.9 (C=O); m/z (C.I., NH_3) 206 (MNH_4^+, 100%).

Homonuclear decoupling experiment data for (**1**):

Signal Irradiated	**Observed Resonance**				
(Chemical shift, δ)	2-H	3-H	4-H	1′-H	1′-H
Original resonance	dd	dd	m	m	dd
3-H (4.28)	d 2.0 Hz		d 9.0 Hz	dd 11.0 Hz 4.2 Hz	dd
4-H, 1′-H (3.74)	dd	d			m
6β-H, 5-H (2.09)	d 4.5 Hz	dd	m	d 11.0 Hz	d 11.0 Hz

(2b) A solution of methyl 5-homoshikimate (see below) (34 mg, 0.17 mmol) in water (3 cm^3) was treated with aqueous sodium hydroxide solution (1.0 M, 0.17 cm^3) and stirred at 20°C under an argon atmosphere for

5.5 h. The solution was acidified by the addition of IR-120 ion-exchange resin. The resin was filtered off and washed with water. The combined aqueous phases were lyophilised to yield 5-homoshikimic acid as a microcrystalline solid (32 mg, quantitative).

Methyl 3β,4β-diacetoxy-5β-[N-(trifluoroacetyl)aminomethyl]cyclohex-1-ene-1-carboxylate (12)

(1) A solution of the diol (7) (9.90 g, 32.9 mmol) in dichloromethane (100 cm^3) was treated with triethylamine (11.5 cm^3, 82.3 mmol), acetic anhydride (7.76 cm^3, 82.3 mmol) and DMAP (catalytic). The reaction mixture was stirred at 20°C under a nitrogen atmosphere for 21 h. The solution was diluted with dichloromethane (100 cm^3), washed with dilute aqueous hydrochloric acid (2 x 100 cm^3), saturated aqueous sodium bicarbonate solution (100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (petrol-ethyl acetate 7:3) yielded methyl 3β,4β-diacetoxy-5β-[N-(t-butoxycarbonyl)aminomethyl]cyclohex-1-ene-1-carboxylate as a colourless oil which crystallised on standing (9.00 g, 71%): m.p. 94-96°C (petrol-ethyl acetate); R_F 0.70 (petrol-ethyl acetate 1:1) (Found : C, 56.1; H, 7.1; N, 3.6. $C_{18}H_{27}NO_8$ requires C, 56.1; H, 7.1; N, 3.6%); $\nu_{max}(CHCl_3)$ 3420 (NH), 1710 br (C=O) cm^{-1}; $\delta_H(CDCl_3)$ 1.44 (9H, s, CMe_3), 2.06 (3H, s, Me), 2.08 (2H, m, 5-H, 6β-H), 2.09 (3H, s, Me), 2.47 (1H, d m, J_{gem} 17.0 Hz, 6α-H), 2.85 (1H, m, 1′-H), 3.28 (1H, m, 1′-H), 3.78 (3H, s, OMe), 4.95 (1H, br t, *J* 6.0 Hz, NH), 5.45 (1H, m, 4-H), 5.57 (1H, m, 3-H), 6.64 (1H, m, 2-H); $\delta_C(CDCl_3)$ 20.7 (2 x Me), 24.4 (C-6), 28.3 (CMe_3), 36.4 (C-5), 41.2 (C-1′), 52.0 (OMe), 66.3 (C-4), 69.3 (C-3), 79.5 (CMe_3), 132.0 (C-1), 134.4 (C-2), 155.8 (C=O), 166.2 (C=O), 170.0 (C=O), 171.1 (C=O); m/z (C.I.) 386 (MH^+, 1%), 368 (1), 330 (55), 286 (50), 226 (100).

(2) Methyl 3β,4β-diacetoxy-5β-[N-(t-butoxycarbonyl)aminomethyl]cyclohex-1-ene-1-carboxylate (1.05 g, 2.72 mmol) was added portionwise to trifluoroacetic acid (10 cm^3). After stirring for 10 min at 20°C the reaction mixture was concentrated under reduced pressure, taken up in pyridine (8 cm^3). Trifluoroacetic anhydride (0.37 cm^3, 3.90 mmol) and DMAP (catalytic) were added and the reaction mixture stirred at 20°C for 1.5 h. After diluting with ethyl acetate (200 cm^3), the solution was washed with dilute aqueous hydrochloric acid (2 x 100 cm^3), saturated aqueous sodium bicarbonate solution (100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (petrol-ethyl acetate 7:3) yielded the title compound as a colourless solid (1.01 g, 97%): m.p. 117-118°C (petrol-ethyl acetate); R_F 0.70 (petrol-ethyl acetate 1:1); (Found : C, 47.0; H, 4.6; N, 3.6. $C_{15}H_{18}F_3NO_7$ requires C, 47.25; H, 4.8; N, 3.7%); ν_{max}(Nujol) 3280 (NH), 1710 (C=O) cm^{-1}; $\delta_H(CDCl_3)$ 2.08 (3H, s, Me), 2.12 (1H, m, 6β-H), 2.13 (3H, s, Me), 2.30 (1H, m, 5-H), 2.54 (1H, br dd, J_{gem} 17.5, $J_{6\alpha,5}$ 5.5 Hz, 6α-H), 3.00 (1H, m, 1′-H), 3.61 (1H, m, 1′-H), 3.79 (3H, s, OMe), 5.37 (1H, m, 4-H), 5.58 (1H, m, 3-H), 6.67 (1H, br s, 2-H), 7.32 (1H, br t, *J* 6.0 Hz, NH); m/z (C.I.) 382 (MH^+, 3%), 322 (100).

3β,4β-Dihydroxy-5β-(hydroxymethyl)cyclohex-1-ene-1-carboxylic acid (13)

(1) A solution of the trifluoroacetamide (12) (0.70 g, 1.84 mmol) in glacial acetic acid (70 cm^3) and acetic anhydride (140 cm^3) was cooled to -4°C under a nitrogen atmosphere. Sodium nitrite (1.27 g, 18.4 mmol) was

added and the solution was stirred at -4 to 10°C for 18 h. The reaction mixture was concentrated under reduced pressure and poured into water (50 cm^3). Brine (50 cm^3) was added and the mixture extracted with ethyl acetate (3 x 100 cm^3). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure (azeotroping with toluene) to leave a yellow oil (0.70 g). This crude product was dissolved in methanol (40 cm^3) and treated with dilute aqueous ammonia solution. After stirring at 20°C for 19 h the reaction mixture was concentrated under reduced pressure. Column chromatography (ethyl acetate) yielded the methyl 3β,4β-dihydroxy-5β-(hydroxymethyl)cyclohex-1-ene-1-carboxylate as a pale yellow solid (0.18 g, 48%), m.p. 127-128°C (ethyl acetate); R_F 0.28 (ethyl acetate); (Found : C, 53.6; H, 6.7. $C_9H_{14}O_5$ requires C, 53.5; H, 7.0%); ν_{max}(Nujol) 3320 (OH), 3220 (OH), 1710 (C=O), 1640 (C=C) cm^{-1}; $\delta_H(D_2O)$ 1.97 (2H, m, 5-H, 6β-H), 2.35 (1H, br d, 6α-H), 3.58 (1H, dd, J_{gem} 11.0, $J_{1',5}$ 6.0 Hz, 1'-H), 3.70 (1H, dd, J_{gem} 11.0, $J_{1',5}$ 7.2 Hz, 1'-H), 3.76 (3H, s, OMe), 4.08 (1H, m, 4-H), 4.42 (1H, m, 3-H), 6.68 (1H, br s, 2-H); $\delta_C(D_2O)$ 22.2 (C-6), 38.3 (C-5), 52.0 (OMe), 62.1 (C-1'), 66.2 (C-4), 68.7 (C-3), 130.0 (C-1), 138.8 (C-2), 168.8 (C=O); m/z (C.I.) 185 (M^+-OH, 70%), 167 (39), 153 (100), 137 (62).

(2) A solution of methyl 3β,4β-dihydroxy-5β-(hydroxymethyl)cyclohex-1-ene-1-carboxylate (81 mg, 0.40 mmol) in water (8 cm^3) was treated with aqueous sodium hydroxide solution (1.0 M, 0.42 cm^3) and stirred at 20°C under a nitrogen atmosphere for 18 h. The solution was acidified by adding Amberlite IR 120 (+) ion exchange resin and filtered. The resin was washed with water (3 x 5 cm^3) and the combined filtrate and washings lyophilised to yield the title compound as an off-white solid (75 mg, quantitative): m.p. 192-193°C (acetonitrile); R_F 0.72 (reverse phase silica , water); $\delta_H(D_2O)$ 1.94 (2H, m, 5-H, 6β-H), 2.31 (1H, br d, J_{gem} 16.0 Hz, 6α-H), 3.57 (1H, dd, J_{gem} 11.0, $J_{1',5}$ 6.0 Hz, 1'-H), 3.69 (1H, dd, J_{gem} 11.0, $J_{1',5}$ 7.5 Hz, 1'-H), 4.06 (1H, m, 4-H), 4.41 (1H, m, 3-H), 6.65 (1H, br s, 2-H); $\delta_C(D_2O)$ 22.2 (C-6), 38.3 (C-5), 62.1 (C-1'), 66.2 (C-4), 68.7 (C-3), 130.6 (C-1), 138.5 (C-2), 170.4 (C=O); m/z (C.I.) 189 (MH^+, 5%), 171 (46), 153 (100).

Methyl 3β,4β-diacetoxy-5β-(acetoxymethyl)cyclohex-1-ene-1-carboxylate

A solution of the trifluoroacetamide (12) (5.00 g, 13.1 mmol) in glacial acetic acid (120 cm^3) and acetic anhydride (240 cm^3) was cooled to -4°C under a nitrogen atmosphere. Sodium nitrite (9.06 g, 131 mmol) was added and the solution was stirred at 0°C for 18 h. The reaction mixture was concentrated under reduced pressure and partitioned between ethyl acetate (400 cm^3) and water (150 cm^3). The aqueous phase was extracted with ethyl acetate (2 x 200 cm^3) and the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure and azeotroped with toluene. Column chromatography (petrol-ethyl acetate 4:1 to 7:3) yielded the title compound as a colourless oil (0.48 g, 11%): R_F 0.43 (petrol-ethyl acetate 7:3); ν_{max}(liquid film) 1740 (C=O), 1650 (C=C) cm^{-1}; $\delta_H(CDCl_3)$ 2.05 (3H, s, Me), 2.07 (3H, s, Me), 2.08 (3H, s, Me), 2.18 (1H, m, 6β-H), 2.33 (1H, m, 5-H), 2.50 (1H, br dd, J_{gem} 17.5, $J_{6\alpha,5}$ 5.5 Hz, 6α-H), 3.79 (3H, s, OMe), 3.97 (1H, dd, J_{gem} 11.2, $J_{1',5}$ 6.3 Hz, 1'-H), 4.03 (1H, dd, J_{gem} 11.2, $J_{1',5}$ 8.2 Hz, 1'-H), 5.51 (1H, m, 4-H), 5.60 (1H, m, 3-H), 6.65 (1H, br s, 2-H); $\delta_C(CDCl_3)$ 20.7 (2 x Me), 20.8 (Me), 23.4 (C-6), 52.0 (OMe), 63.4 (C-1'), 65.4 (C-4), 68.9 (C-3), 131.7 (C-1), 134.4 (C-2), 166.1 (C=O), 170.0 (C=O), 170.4 (C=O), 170.8 (C=O), m/z (C.I.) 329 (MH^+, 3%), 269 (100).

Methyl 3α,4α-isopropylidenedioxy-5β-(acetoxymethyl)cycloclohex-1-ene-1-carboxylate (15,R=Ac)

The diol (11) (80 mg, 0.33 mmol) and *p*-TSA (*trace*) were dissolved in acetone (3 cm^3) and 2,2-dimethoxypropane (3 cm^3). The reaction mixture was stirred at 20°C under a nitrogen atmosphere for 18 h after which solvents were evaporated under reduced pressure. Column chromatography (petrol-ethyl acetate 3:1) yielded the title compound as a colourless oil (88 mg, 94 %): R_F 0.80 (petrol-ethyl acetate 1:1); $\nu_{max}(CHCl_3)$ 1710 (C=O), 1645 (C=C) cm^{-1}; $\delta_H(CDCl_3)$ 1.36 (3H, s, Me), 1.40 (3H, s, Me), 2.02 (2H, m, 5-H, 6β-H), 2.03 (3H, s, Me), 2.61 (1H, dd, J_{gem} 21.0, $J_{6\alpha,5}$ 8.0 Hz, 6α-H), 3.74 (3H, s, OMe), 4.04 (1H, dd, J_{gem} 11.0, $J_{1',5}$ 6.0 Hz, 1'-H), 4.07 (1H, dd, $J_{4,5}$ 8.5, $J_{4,3}$ 6.0 Hz, 4-H), 4.24 (1H, dd, J_{gem} 11.0, $J_{1',5}$ 4.0 Hz, 1'-H), 4.58 (1H, m, 3-H), 6.89 (1H, m, 2-H); $\delta_C(CDCl_3)$ 20.8 (Me), 24.8 (C-6), 25.7 (Me), 28.0 (Me), 36.5 (C-5), 52.0 (OMe), 64.3 (C-1'), 71.0 (C-4), 73.9 (C-3), 109.2 (CMe_2), 132.8 (C-1), 133.7 (C-2), 166.6 (C=O), 170.8 (C=O); m/z (C.I.) 285 (MH^+, 1%), 269 (36), 167 (100), 149 (67).

Methyl 3α,4α-isopropylidenedioxy-5β-(hydroxymethyl)cyclohex-1-ene-1-carboxylate (15, R=H)

(a) A solution of the acetate (15, R=Ac) (85 mg, 0.30 mmol) in methanol (4 cm^3) was treated with aqueous ammonia solution (1 cm^3) and stirred at 20°C under a nitrogen atmosphere for 48 h. The solvents were evaporated under reduced pressure. Column chromatography (petrol - ethyl acetate 1:1) yielded the title compound as a colourless oil which crystallised on standing (63.5 mg, 87%): m.p. 52-53°C (petrol-diethyl ether); R_F 0.40 (petrol-ethyl acetate 1:1); (Found: C, 59.3; H, 7.6. $C_{12}H_{18}O_5$ requires C, 59.5; H, 7.5%); $\nu_{max}(CHCl_3)$ 3500 (OH), 1710 (C=O), 1655 (C=C) cm^{-1}; $\delta_H(CDCl_3)$ 1.40 (3H, s, Me), 1.47 (3H, s, Me), 1.96 (1H, m, 5-H), 1.98 (1H, m, 6β-H), 2.13 (1H, br s, OH), 2.60 (1H, dd, J_{gem} 22.0, $J_{6\alpha,5}$ 9.0 Hz, 6α-H), 3.75 (2H, m, 2 x 1'-H), 3.77 (3H, s, OMe), 4.16 (1H, dd, $J_{4,5}$ 8.5, $J_{4,3}$ 6.0 Hz, 4-H), 4.62 (1H, ddd, $J_{3,4}$ 6.0, $J_{3,2}$ 3.5, $J_{3,6\beta}$ 1.0 Hz, 3-H), 6.94 (1H, m, 2-H), $\delta_C(CDCl_3)$ 24.8 (C-6), 25.8 (Me), 28.0 (Me), 39.0 (C-5), 52.1 (OMe), 64.9 (C-1'), 71.4 (C-4), 76.4 (C-3), 109.4 (CMe_2), 133.5 (C-1, C-2), 166.7 (C=O); m/z (E.I.) 242 (M^+, 1%), 227 (65), 153 (45), 137 (100).

(b) Methyl 5-homoshikimate (60mg, 0.30 mmol) and *p*-TSA (*trace*) were dissolved in acetone (3 cm^3) and 2,2-dimethoxypropane (3 cm^3). The reaction mixture was stirred at 20°C under a nitrogen atmosphere for 22 h, after which the solvents were evaporated under reduced pressure. Column chromatography (petrol-ethyl acetate 4:1 then 1:1) yielded the title compound as a colourless oil which crystallised on standing (60.5 mg, 84%), identical with the sample described above and the ketal (16) as a colourless oil (12.5 mg, 8%): R_F 0.80 (petrol-ethyl acetate 1:1); $\delta_H(CDCl_3)$ 1.33 (3H, s, Me), 1.39 (3H, s, Me), 1.42 (3H, s, Me), 1.95-2.20 (2H, m, 5-H, 6β-H), 2.64 (1H, m, 6α-H), 3.35-3.57 (2H, m, 1'-H), 3.76 (3H, s, OMe), 4.15 (1H, m, 4-H), 4.58 (1H, m, 3-H), 6.87 (1H, m, 2-H); $\delta_C(CDCl_3)$ 24.8 (Me), 26.0 (Me), 28.2 (Me), 37.3 (C-5), 52.0 (OMe), 60.5 and 60.7 (C-1'), 71.1 (C-4), 74.0 and 74.1 (C-3), 99.8 (CMe_2), 108.8 (CMe_2), 132.9 (C-1), 133.8 and 133.9 (C-2), 167.0 (C=O).

Methyl 3α,4α-diacetoxy-5β-(acetoxymethyl)cyclohex-1-ene-1-carboxylate

A solution of methyl 5-homoshikimate (12 mg, 0.06 mmol) in pyridine (1 cm^3) was treated with acetic anhydride (0.5 cm^3) and DMAP (catalytic) and stirred at 20°C for 15 h. The reaction mixture was poured into ethyl acetate (10 cm^3) and washed with dilute aqueous hydrochloric acid (3 x 10 cm^3) and water (10 cm^3). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure (azeotroping with toluene) to yield the title compound as a colourless oil (17 mg, 87%): R_F 0.74 (petrol-ethyl acetate 1:1); $\delta_H(CDCl_3)$ 2.04 (3H, s, Me), 2.06 (3H, s, Me), 2.09 (3H, s, Me), 2.33 (1H, dddd, J_{gem} 18.0, $J_{6\beta,5}$ 9.9, $J_{6\beta,2}$ 2.4, $J_{6\beta,3}$ 1.2 Hz, 6β-H), 2.49 (1H, m, 5-H), 2.75 (1H, br dd, J_{gem} 18.0, $J_{6\alpha,5}$ 5.2 Hz, 6α-H), 3.78 (3H, s, OMe), 4.09 (1H, dd, J_{gem} 11.2, $J_{1',5}$ 3.8 Hz, 1'-H), 4.20 (1H, dd, J_{gem} 11.2, $J_{1',5}$ 5.5 Hz, 1'-H), 5.04 (1H, dd, $J_{4,5}$ 10.8, $J_{4,3}$ 3.9 Hz, 4-H), 5.65 (1H, br dd, $J_{3,2}$ 5.3, $J_{3,4}$ 3.9 Hz, 3-H), 6.78 (1H, ddd, $J_{2,3}$ 5.3, $J_{2,6\beta}$ 2.4, $J_{2,6\alpha}$ 1.3 Hz, 2-H); $\delta_C(CDCl_3)$ 20.8 (3 x Me), 27.3 (C-6), 32.5 (C-5), 52.2 (OMe), 63.2 (C-1'), 64.9 (C-4), 69.0 (C-3), 131.8 (C-2), 134.3 (C-1), 166.3 (C=O), 170.1 (C=O), 170.9 (2 x C=O)

3α,4α-Dihydroxy-5β-(fluoromethyl)cyclohex-1-ene-1-carboxylic acid (2)

(1) A polythene reaction vessel fitted with a septum cap was charged with dichloromethane (4 cm^3) and morpholino-DAST (0.14 cm^3, 1.14 mmol) under a nitrogen atmosphere and cooled to -78°C. A solution of the alcohol (15, R=H) (275 mg, 1.14 mmol) in dichloromethane (2 cm^3) was added via cannula and the solution stirred for 30 min before warming to 20°C and stirring for a further 2 days. Silica gel was added and the dichloromethane evaporated under reduced pressure. The pre-absorbed product was added to the top of a silica gel column and eluted with petrol-ethyl acetate (9:1) to yield methyl 3α,4α-isopropylidenedioxy--5β-(fluoromethyl)cyclohex-1-ene-1-carboxylate as a colourless oil (180 mg, 65%): R_F 0.50 (petrol-ethyl acetate 4:1); $\nu_{max}(CHCl_3)$ 1715 (C=O), 1645 (C=C) cm^{-1}; $\delta_H(CDCl_3)$ 1.41 (3H, s, Me), 1.44 (3H, s, Me), 1.99 (1H, d m, $J_{5,F}$ 25.6 Hz, 5-H), 2.15 (1H, ddt, J_{gem} 17.3, $J_{6\beta,5}$ 9.7, $J_{6\beta,2}$ 1.9, $J_{6\beta,3}$ 1.9 Hz, 6β-H), 2.70 (1H, br dd, J_{gem} 17.3, $J_{6\alpha,5}$ 4.1 Hz, 6α-H), 3.78 (3H, s, OMe), 4.16 (1H, dd, $J_{4,5}$ 9.0, $J_{4,3}$ 6.0 Hz, 4-H), 4.54 (1H, ddd, $J_{1',F}$ 49.0, J_{gem} 9.5, $J_{1',5}$ 4.0 Hz, 1'-H), 4.59 (1H, ddd, $J_{1',F}$ 49.0, J_{gem} 9.5, $J_{1',5}$ 5.1 Hz, 1'-H), 4.65 (1H, m, 3-H), 6.94 (1H, ddd, $J_{2,3}$ 3.5, $J_{2,6\beta}$ 1.9, $J_{2,6\alpha}$ 1.0 Hz, 2-H); $\delta_C(CDCl_3)$ 24.4 (d, $J_{6,F}$ 4 Hz, C-6), 25.7 (Me), 28.1 (Me), 38.3 (d, $J_{5,F}$ 18 Hz, C-5), 52.1 (OMe), 71.1 (C-4), 72.9 (d, $J_{3,F}$ 4 Hz, C-3), 83.7 (d, $J_{1',F}$ 170 Hz, C-1'), 109.2 (CMe_2), 133.1 (C-1), 133.7 (C-2), 166.6 (C=O); m/z (E.I.) 244 (M^+, 1%), 229 (M^+-CH_3, 229.0867 $C_{12}H_{17}FO_4$ requires 229.0876, 55%).
Further elution with petrol-ethyl acetate (4:6) yielded the unreacted alcohol (15, R=H) (65 mg, 23%).

(2) A solution of methyl 3α,4α-isopropylidenedioxy-5β-(fluoromethyl)cyclohex-1-ene-1-carboxylate (175 mg, 0.72 mmol) in THF (5 cm^3), glacial acetic acid (5 cm^3) and water (4 cm^3) was heated to 50-60°C under a nitrogen atmosphere for 2 days. The solution was concentrated under reduced pressure and chromatographed (petrol-ethyl acetate 1:3) to yield methyl 3α,4α-dihydroxy-5β-(fluoromethyl)cyclohex-1-ene-1-carboxylate as a colourless oil which crystallised on standing (142 mg, 97%): m.p. 78-79°C (petrol-ethyl acetate); R_F 0.25

(petrol-ethyl acetate 1:1); (Found : C, 52.95; H, 6.45. $C_9H_{13}FO_4$ requires C, 52.9; H, 6.4%); $\nu_{max}(CHCl_3)$ 3550 (OH), 3400 (OH), 1715 (C=O), 1650 (C=C) cm^{-1}; $\delta_H(CDCl_3)$ 2.06-2.32 (2H, m, 6β-H), 2.47 (2H, br s, 2 x OH), 2.67 (1H, m, 6α-H), 3.77 (3H, s, OMe), 3.78 (1H, m, 4-H), 4.33 (1H, dd, $J_{3,4}$ 4.0, $J_{3,2}$ 5.0 Hz, 3-H), 4.55 (1H, ddd, $J_{1',F}$ 47.0, J_{gem} 9.0, $J_{1',5}$ 3.8 Hz, 1'-H), 4.72 (1H, ddd, $J_{1',F}$ 47.0, J_{gem} 9.0, $J_{1',5}$ 4.0 Hz, 1'-H), 6.91 (1H, ddd, $J_{2,3}$ 5.0, $J_{2,6\beta}$ 2.0, $J_{2,6\alpha}$ 1.0 Hz, 2-H); $\delta_C(CDCl_3)$ 26.2 (d, $J_{6,F}$ 7 Hz, C-6), 36.0 (d, $J_{5,F}$ 18 Hz, C-5), 52.1 (OMe), 65.5 (C-4), 69.0 (d, $J_{3,F}$ 4 Hz, C-3), 84.1 (d, $J_{1',F}$ 168 Hz, C-1'), 132.8 (C-1), 135.4 (C-2), 166.9 (C=O); m/z (E.I.) 204 (M^+, 2%), 96 (100).

(3) A solution of methyl 3α,4α-dihydroxy-5β-(fluoromethyl)cyclohex-1-ene-1-carboxylate (68 mg, 0.33 mmol) in THF (5 cm^3) was treated with aqueous sodium hydroxide solution (1.0 M, 0.35 cm^3). Water (*ca.* 4 cm^3) was added to give a homogeneous solution, which was stirred at 20°C under a nitrogen atmosphere for 3 h. Amberlite IR 120 (+) ion exchange resin was added and the mixture filtered. The resin was washed with water and the combined filtrate and washings were concentrated under reduced pressure and lyophilised to yield 3α,4α-dihydroxy-5β-(fluoromethyl)cyclohex-1-ene-1-carboxylic acid as an off-white solid (59 mg, 93%): R_F 0.50 (reverse phase silica, water); ν_{max}(Nujol) 3300 (OH), 3140 (OH), 1685 (C=O), 1650 (C=C) cm^{-1}; $\delta_H(D_2O)$ 2.17 (2H, m, 5-H, 6β-H), 2.54 (1H, m, 6α-H), 3.75 (1H, dd, $J_{4,5}$ 10.3, $J_{4,3}$ 4.0 Hz, 4-H), 4.27 (1H, dd, $J_{3,4}$ 4.0, $J_{3,2}$ 5.0 Hz, 3-H), 4.55 (1H, ddd, $J_{1',F}$ 47.0, J_{gem} 9.3, $J_{1',5}$ 3.2 Hz, 1'-H), 4.66 (1H, ddd, $J_{1',F}$ 47.0, J_{gem} 9.3, $J_{1',5}$ 4.2 Hz, 1'-H), 6.70 (1H, dm, $J_{2,3}$ 5.0 Hz, 2-H); $\delta_C(D_2O)$ 26.0 (d, $J_{6,F}$ 4 Hz, 6-H), 34.8 (d, $J_{5,F}$ 18 Hz, 5-H), 64.9 (C-4), 68.2 (d, $J_{3,F}$ 4 Hz, 3-H), 84.3 (d, $J_{1',F}$ 163 Hz, 1'-H), 133.7 (C-1), 134.0 (C-2), 171.8 (C=O); m/z (E.I.) 190 (M^+, 190.0643 $C_8H_{11}FO_4$ requires 190.0641, 1%), 96 (100).

3α,4α-Dihydroxy-5β-(difluoromethyl)cyclohex-1-ene-1-carboxylic acid (3)

(1) A solution of the alcohol (15,R=H) (260 mg, 1.07 mmol) in dichloromethane (12 cm^3) was treated with pyridinium chlorochromate (0.35 g, 1.61 mmol) and stirred at 20°C for 4 h. The reaction mixture was added directly to the top of a silica gel column and eluted with petrol-ethyl acetate (7:3) to yield methyl 3α,4α-isopropylidenedioxy-5β-formylcyclohex-1-ene-1-carboxylate as a colourless oil (182 mg, 71%): R_F 0.55 (petrol-ethyl acetate 7:3); ν_{max}(liquid film) 1715 (C=O), 1650 (C=C) cm^{-1}; $\delta_H(CDCl_3)$ 1.42 (3H, s, Me), 1.43 (3H, s, Me), 2.49 (1H, ddt, J_{gem} 18.0, $J_{6\beta,5}$ 7.0, $J_{6\beta,2}$ 1.6, $J_{6\beta,3}$ 1.6 Hz, 6β-H), 2.75 (1H, ddt, J_{gem} 18.0, $J_{6\alpha,5}$ 5.7, $J_{6\alpha,2}$ 1.5, $J_{6\alpha,3}$ 1.5 Hz, 6α-H), 2.93 (1H, ddd, $J_{5,6\beta}$ 7.0, $J_{5,4}$ 6.3, $J_{5,6\alpha}$ 5.7 Hz, 5-H), 3.78 (3H, s, OMe), 4.51 (1H, dd, $J_{4,5}$ 6.3, $J_{4,3}$ 6.3 Hz, 4-H), 4.72 (1H, m, 3-H), 6.89 (1H, ddd, $J_{2,3}$ 3.5, $J_{2,6\beta}$ 1.6, $J_{2,6\alpha}$ 1.5 Hz, 2-H), 9.79 (1H, d, *J* 0.5 Hz, CHO); $\delta_C(CDCl_3)$ 20.5 (C-6), 25.7 (Me), 27.7 (Me), 49.6 (C-5), 52.0 (OMe), 70.6 (C-4), 71.8 (C-3), 109.2 (CMe_2), 130.4 (C-1), 134.8 (C-2), 166.2 (C=O), 201.3 (CHO); m/z (E.I.) 241 (MH^+, 1%), 225 (M^+-CH_3, 225.0768 $C_{11}H_{13}O_5$ requires 225.0763, 21), 156 (100).

Homonuclear decoupling experiment data for methyl 3α,4α-isopropylidenedioxy-5β-formylcyclohex-1-ene--1-carboxylate:

Signal Irradiated (Chemical shift, δ)	Observed Resonance					
	2-H	3-H	4-H	5-H	6α-H	6β-H
Original resonance	ddd	m	dd	ddd	ddt	ddt
2-H (6.89)		d m 6.3 Hz	dd	ddd	ddd	ddd
3-H (4.72)	dd		m	ddd	ddd	ddd
4-H (4.51)	ddd	m simplifies		dd 5.7, 7.0 Hz	ddt	ddt
5-H (2.93)	ddd	m	d		dt	dt
6α-H (2.75)	dd	m simplifies	dd	m		m
6β-H (2.49)	dd	m simplifies	dd	m	m	

(2) A polythene reaction vessel fitted with a septum cap was charged with dichloromethane (10 cm^3) and morpholino-DAST (0.11 cm^3, 0.91 mmol) under a nitrogen atmosphere. A solution of methyl 3α,4α-isopropylidenedioxy-5β-formylcyclohex-1-ene-1-carboxylate (182 mg, 0.76 mmol) in dichloromethane (4 cm^3) was added via cannula and the reaction mixture stirred at 20°C for 2 days. Silica gel was added and the dichloromethane evaporated under reduced pressure. The pre-absorbed product was added to the top of a silica gel column and eluted with petrol-ethyl acetate (9:1) to yield methyl 3α,4α-isopropylidenedioxy-5β-(difluoromethyl)cyclohex-1-ene-1-carboxylate as a colourless oil (181 mg, 91%): R_F 0.74 (petrol-ethyl acetate 7:3); $\nu_{max}(CHCl_3)$ 1715 (C=O), 1645 (C=C) cm^{-1}; $\delta_H(CDCl_3)$ 1.41 (3H, s, Me), 1.46 (3H, s, Me), 2.14 (2H, m, 5-H, 6β-H), 2.78 (1H, m, 6α-H), 3.79 (3H, s, OMe), 4.20 (1H, dd, $J_{4,3}$ 6.2, $J_{4,5}$ 9.0 Hz, 4-H), 4.66 (1H, m, 3-H), 6.02 (1H, td, $J_{1',F}$ 56.0 Hz, $J_{1',5}$ 2.0 Hz, 1'-H), 6.97 (1H, ddd, $J_{2,3}$ 3.5, $J_{2,6\beta}$ 2.0, $J_{2,6\alpha}$ 1.0 Hz, 2-H); $\delta_C(CDCl_3)$ 19.7 (t, $J_{6,F}$ 5 Hz, 6-H), 25.5 (Me), 27.9 (Me), 41.4 (t, $J_{5,F}$ 20 Hz, 5-H), 52.1 (OMe), 70.9 (C-4), 72.0 (d, $J_{3,F}$ 7 Hz, 3-H), 109.5 (CMe_2), 116.0 (t, $J_{1',F}$ 241 Hz, 1'-H), 132.4 (C-1), 133.3 (C-2), 166.2 (C=O); m/z (E.I.) 248 (M^+-CH_2, 248.0853 $C_{11}H_{14}F_2O_4$ requires 248.0860, 3%), 247 (M^+-CH_3, 39) (C.I.) 263 (MH^+, 100%), 247 (42), 205 (63).

(3) A solution of methyl 3α,4α-isopropylidenedioxy-5β-(difluoromethyl)cyclohex-1-ene-1-carboxylate (178 mg, 0.68 mmol) in THF (5 cm^3), glacial acetic acid (5 cm^3) and water (4 cm^3) was heated at 60°C under a nitrogen atmosphere for 3 days. The solution was concentrated under reduced pressure. Column chromatography (petrol-ethyl acetate 4:6) yielded methyl 3α,4α-dihydroxy-5β-(difluoromethyl)cyclohex-1-ene-1-carboxylate as a colourless oil which crystallised on standing (148 mg, 98%): m.p. 100-101°C (petrol-ethyl acetate); R_F 0.32 (petrol-ethyl acetate 1:1); (Found: C, 48.4; H, 5.5. $C_9H_{12}F_2O_4$ requires C, 48.65; H, 5.4%); ν_{max}(Nujol) 3260 (OH), 1700 (C=O), 1640 (C=C) cm^{-1}; $\delta_H(D_6$-acetone, $D_2O)$ 2.26 (1H, dddd, J_{gem} 17.6, $J_{6\beta,5}$ 10.5, $J_{6\beta,2}$ 2.5, $J_{6\beta,3}$ 1.0 Hz, 6β-H), 2.46 (1H, m, 5-H), 2.61 (1H, br dd, J_{gem} 17.6, $J_{6\alpha,5}$

5.3 Hz, 6α-H), 3.72 (1H, dd, $J_{4,5}$ 10.4, $J_{4,3}$ 4.0 Hz, 4-H), 3.77 (3H, s, OMe), 4.30 (1H, m, 3-H), 6.26 (1H, td, $J_{1',F}$ 57.0, $J_{1',5}$ 2.2 Hz, 1'-H), 6.89 (1H, ddd, $J_{2,3}$ 5.2, $J_{2,6\beta}$ 2.5, $J_{2,6\alpha}$ 1.1 Hz, 2-H); δ_C($CDCl_3$ + D_6-acetone) 21.2 (t, $J_{6,F}$ 5 Hz, C-6), 38.6 (t, $J_{5,F}$ 20 Hz, C-5), 51.7 (OMe), 64.7 (C-4), 67.7 (d, $J_{3,F}$ 9 Hz, C-3), 116.3 (t, $J_{1',F}$ 240 Hz, 1'-H), 131.3 (C-1), 135.3 (C-2), 166.4 (C=O); m/z (E.I.) 222 (M^+, 3%), 96 (100).

(4) A solution of methyl 3α,4α-dihydroxy-5β-(difluoromethyl)cyclohex-1-ene-1-carboxylate (26 mg, 0.12 mmol) in water (3 cm^3) was treated with aqueous sodium hydroxide solution (1.0 M, 0.12 cm^3,) and stirred at 20°C for 5 h. Amberlite IR-120 (+) ion exchange resin was added and the mixture filtered. The resin was washed with water (3 x 3 cm^3) and the combined filtrate and washings were lyophilised to yield 3α,4α-dihydroxy-5β-(fluoromethyl)cyclohex-1-ene-1-carboxylic acid (2)

as a colourless solid (21 mg, 86%): R_F 0.35 (reverse phase silica, water); ν_{max}(Nujol) 3350 (OH), 3240 (OH), 1680 (C=O), 1630 (C=C) cm^{-1}; δ_H(400 MHz, D_2O) 2.28 (1H, br dd, J_{gem} 17.5, $J_{6\beta,5}$ 10.1 Hz, 6β-H), 2.40 (1H, m, 5-H), 2.60 (1H, dd, J_{gem} 17.5, $J_{6\alpha,5}$ 5.2 Hz, 6α-H), 3.86 (1H, dd, $J_{4,5}$ 10.6, $J_{4,3}$ 4.1 Hz, 4-H), 4.29 (1H, m, 3-H), 6.14 (1H, td, $J_{1',F}$ 57.0, $J_{1',5}$ 2.3 Hz, 1'-H), 6.84 (1H, d m, $J_{2,3}$ 4.1 Hz, 2-H); δ_C(D_2O) 21.6 (t, $J_{6,F}$ 5 Hz, C-6), 37.8 (t, $J_{5,F}$ 20 Hz, C-5), 64.9 (C-4), 67.7 (d, $J_{3,F}$ 7 Hz, C-3), 117.0 (t, $J_{1',F}$ 239 Hz, 1'-H), 131.6 (C-1), 135.6 (C-2), 170.4 (C=O); m/z (C.I., NH_3) 226 (MNH_4^+, 100%), 210 (88), 208 (M^+, 13); (E.I.) 190 (M^+-H_2O, 190.0432 $C_8H_8F_2O_3$ requires 190.0442, 18%).

Methyl 5-[N,N-di(p-nitrobenzenesulphonyl)aminomethyl]cyclohexa-1,3-diene-1-carboxylate (17)

(1) The cyclohexadienylcarbamate (5) (28.8 g, 0.11 mol) was added portion-wise to trifluoroacetic acid (100 cm^3). After stirring for 5 mins, excess TFA was evaporated under reduced pressure to leave a yellow oil. Sodium hydroxide (1.0 M, *ca.* 400 cm^3) was added cautiously until the solution was alkaline to litmus. The solution was extracted with ethyl acetate (2 x 500 cm^3), dried ($MgSO_4$) and evaporated to give methyl 5-(aminomethyl)cyclohexa-1,3-diene-1-carboxylate as a yellow oil (15.7 g, 85%): R_F 0.80 (dichloromethane - methanol - aqueous ammonia 20:8:1); ν_{max}(liquid film) 1700 (C=O), 1630 (C=C), 1565 cm^{-1}; δ_H($CDCl_3$) 2.35 (1H, m, 6β-H), 2.51 (1H, m, 5-H), 2.60 (1H, m, 6α-H), 2.77 (2H, m, 2 x 1'-H), 3.73 (3H, s, OMe), 4.29 (2H, br s, NH_2), 6.02 (1H, dd, $J_{4,3}$ 9.5, $J_{4,5}$ 3.0 Hz, 4-H), 6.11 (1H, dd, $J_{3,4}$ 9.5, $J_{3,2}$ 5.3 Hz, 3-H), 6.96 (1H, d, $J_{2,3}$ 5.3 Hz, 2-H); δ_C($CDCl_3$) 24.8 (C-6), 37.1 (C-5), 45.1 (C-1'), 51.6 (OMe), 124.3 (C-3), 126.1 (C-1), 132.8 (C-4), 135.8 (C-2), 167.8 (C=O); m/z (C.I) 168 (MH^+,100%), 151 (22).

(2) A solution of methyl 5-(aminomethyl)cyclohexa-1,3-diene-1-carboxylate (15.7 g, 93.9 mmol) in dry THF (250 cm^3) was treated with *p*-nitrobenzenesulphonyl chloride (22.9 g, 0.103 mol) and triethylamine (14.4 cm^3, 0.103 mol). After stirring for 40 h at 20°C the reaction mixture was poured into water (500 cm^3) and extracted with ethyl acetate (3 x 500 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a dark brown oil. Column chromatography (petrol-ethyl acetate 4:1 to 1:1) yielded methyl 5-[N-(p-nitrobenzenesulphonyl)aminomethyl]cyclohexa-1,3-diene-1-carboxylate as a pale yellow solid (20.7 g, 63%): m.p. 130-132°C (petrol-ethyl acetate); R_F 0.30 (petrol-ethyl acetate 7:3); (Found: C, 51.1; H, 4.6; N, 7.9. $C_{15}H_{16}N_2O_6S$ requires C, 51.1; H, 4.6; N, 7.95%); ν_{max}($CHCl_3$) 1695 (C=O), 1350 (SO_2), 1160 (SO_2) cm^{-1}; δ_H(D_6-acetone) 2.31 (1H, ddd, J_{gem} 16.9, $J_{6\beta,5}$ 10.9, $J_{6\beta,2}$ 1.7 Hz, 6β-H), 2.53 (1H, ddd, J_{gem}

16.9, $J_{6\alpha,5}$ 8.4, $J_{6\alpha,2}$ 1.5 Hz, 6α-H), 2.62 (1H, m, 5-H), 3.03 (2H, m, 1′-H), 3.70 (3H, s, OMe), 6.06 (1H, ddd, $J_{4,3}$ 9.5, $J_{4,5}$ 3.5, $J_{4,2}$ 1.5 Hz, 4-H), 6.12 (1H, ddd, $J_{3,4}$ 9.5, $J_{3,2}$ 5.1, $J_{3,5}$ 1.5 Hz, 3-H), 6.93 (1H, m, 2-H), 7.01 (1H, br t, *J* 6.2 Hz, N-H), 8.12 (2H, d, *J* 9.0 Hz, Ar-H), 8.42 (2H, d, *J* 9.0 Hz, Ar-H); $\delta_C(CDCl_3)$ 24.5 (C-6), 33.8 (C-5), 45.6 (C-1′), 51.8 (OMe), 124.4 and 128.2 (aromatic CH), 125.4 (C-3), 126.2 (C-1), 132.5 (C-4), 133.1 (C-2), 145.8 and 150.0 (aromatic C), 167.5 (C=O); m/z (C.I) 353 (MH^+, 9%), 321 (100).

(3) Sodium hydride (0.28 g, 11.6 mmol) was added slowly to a stirred solution of methyl 5-[N-(p--nitrobenzenesulphonyl)aminomethyl]cyclohexa-1,3-diene-1-carboxylate (3.15 g, 8.94 mmol) in dry DMF (50 cm^3) over 7 min. The resultant black solution was stirred at 20°C for 1 h and then *p*-nitrobenzenesulphonyl chloride (2.57 g, 11.6 mmol) added. After 1.5 h water (200 cm^3) was added and the mixture extracted with ethyl acetate (3 x 200 cm^3). The combined extracts were washed with brine (100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to leave a dark brown oil. Column chromatography petrol-ethyl acetate 4:1 to 1:1) yielded 5-[N,N-di(p-nitrobenzenesulphonyl)aminomethyl]cyclohexa-1,3-diene-1-carboxylate (140) as a pale yellow solid (3.37 g, 70%): m.p. 178-179°C (petrol-ethyl acetate); R_F 0.50 (petrol-ethyl acetate 7:3); (Found: C, 46.9; H, 3.4; N, 7.6. $C_{21}H_{19}N_3O_{10}S_2$ requires C, 46.9; H, 3.6; N, 7.8%); $\nu_{max}(CHCl_3)$ 1700 (C=O), 1350 (SO_2), 1170 (SO_2) cm^{-1}; $\delta_H(CDCl_3)$ 2.39 (2H, m, 6-H), 2.92 (1H, m, 5-H), 3.73 (2H, m partially obscured by OMe, 2 x 1′-H), 3.75 (3H, s, OMe), 5.88 (1H, dd, $J_{4,3}$ 9.3, $J_{4,5}$ 4.4 Hz, 4-H), 6.16 (1H, ddd, $J_{3,4}$ 9.3, $J_{3,2}$ 5.2, $J_{3,5}$ 1.6 Hz, 3-H), 7.01 (1H, d, $J_{2,3}$ 5.2 Hz, 2-H), 8.28 (4H, d, *J* 9.0 Hz, Ar-H), 8.45 (4H, d, *J* 9.0 Hz, Ar-H); $\delta_C(CDCl_3)$ 24.3 (C-6), 32.7 (C-5), 51.0 (C-1′), 51.8 (OMe), 124.4 and 129.9 (aromatic CH), 126.0 (C-3), 126.6 (C-1), 131.4 (C-4), 132.1 (C-2), 144.5 and 150.9 (aromatic C), 166.7 (C=O); m/z (C.I., NH_3) 555 (MNH_4^+, 100%), 538 (MH^+, 18).

Reaction of dienyl disulphonimide (17) with potassium iodide

The dienyl disulphonimide (17) (195 mg, 0.36 mmol) and potassium iodide (132 mg, 0.80 mmol) were suspended in DMF (2 cm^3) and heated at 110°C under a nitrogen atmosphere for 16 h. TLC on silica gel indicated one major product plus a trace of unreacted starting material. The reaction mixture was diluted with water (35 cm^3) and extracted with ether (3 x 30 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to leave a brown oil. Column chromatography (petrol-ethyl acetate 9:1 to 17:3) gave recovered starting material (3.5 mg, 2%) and methyl 3-methylbenzoate (32) (35 mg, 64%) as a colourless oil: δ_H(60 MHz, $CDCl_3$) 2.50 (3H, s, Me), 3.98 (3H, s, OMe), 7.20-8.00 (4H, m, Ar-H); m/z (C.I.) 151 (MH^+, 100%), 119 (54), 91 (34).

Osmium tetroxide catalysed *cis*-hydroxylation of dienyl disulphonimide (17)

N-Methylmorpholine N-oxide (0.62 g, 5.29 mmol) in acetone (10 cm^3) and water (25 cm^3) was treated with a 0.5% (w/v) solution of osmium tetoxide in *t*-butanol (11.1 cm^3, 0.05 equiv). The diene disulphonimide (17) (2.37 g, 4.41 mmol) in THF (50 cm^3) was added slowly and the reaction mixture stirred at 20°C for 24 h. TLC (petrol-ethyl acetate 1:1) indicated three close running products and baseline material. THF and acetone were

evaporated under reduced pressure and the reaction mixture diluted with water (400 cm^3), acidified with 2M hydrochloric acid and carefully extracted with ethyl acetate (1000 cm^3, 2 x 500 cm^3). The combined extracts were dried ($MgSO_4$) and preabsorbed onto silica gel. Column chromatography (petrol-ethyl acetate 54:46) yielded (in order of elution):

Methyl 1,2-dihydroxy-5β-[N,N-di(p-nitrobenzenesulphonyl)aminomethyl]cyclohex-3-ene-1-carboxylate (20) (0.25 g, 10%): m.p. 217-218°C (ethyl acetate); R_F 0.32 (petrol-ethyl acetate 1:1); (Found: C, 44.0; H, 3.7; N, 7.2. $C_{21}H_{21}N_3O_{12}S_2$ requires C, 44.1; H, 3.7; N, 7.35%); ν_{max}(Nujol) 1735 (C=O), 1360 (SO_2), 1170 (SO_2) cm^{-1}; δ_H(D_6-DMSO) 1.52-1.72 (2H, m, 2 x 6-H), 2.84 (1H, m, 5-H), 3.65 (3H, s, OMe), 3.74 (1H, m, 1′-H), 4.00 (1H, m, 1′-H), 4.30 (1H, m, 2-H), 4.91 (1H, s, 1-OH), 5.03 (1H, d, $J_{2,OH}$ 7.9 Hz, 2-OH), 5.51 (2H, m, 3-H, 4-H), 8.21 (4H, d, *J* 9.2 Hz, Ar-H), 8.47 (4H, d, *J* 9.2 Hz, Ar-H); δ_C(D_6-DMSO) 32.4 (C-5), 34.9 (C-6), 52.1 (OMe), 53.8 (C-1′), 69.1 (C-2), 74.8 (C-1), 124.9 and 129.8 (aromatic CH), 126.8 (C-4), 130.9 (C-3), 143.5 and 150.9 (aromatic C), 175.2 (C=O); m/z (C.I) 554 (MH^+-H_2O, 4%), 536 (MH^+-$2H_2O$, 46%), 504 (100), 402 (52), 349 (60), 319 (70).

Methyl 3β,4β-dihydroxy-5β-[N,N-di(p-nitrobenzenesulphonyl)aminomethyl]cyclo-hex-1-ene-1-carboxylate (19) (0.20 g, 8%): m.p. 212-213°C (ethyl acetate); R_F 0.25 (petrol-ethyl acetate 1:1); (Found: C, 43.7; H, 3.7; N, 7.2. $C_{21}H_{21}N_3O_{12}S_2$ requires C, 44.1; H, 3.7; N, 7.35%); ν_{max}(Nujol) 3420 (OH), 1685 (C=O), 1350 (SO_2), 1175 (SO_2) cm^{-1}; δ_H(D_6-DMSO) 1.90 (2H, m, 6-H), 2.23 (1H, m, 5-H), 3.63 (3H, s, OMe), 3.65 (1H, m partially obscured by OMe, 4-H), 3.98 (2H, m, 1′-H), 4.16 (1H, m, 3-H), 4.73 (1H, d, $J_{4,OH}$ 3.3 Hz, 4-OH), 5.17 (1H, d, $J_{3,OH}$ 6.4 Hz, 3-OH), 6.53 (1H, s, 2-H), 8.26 (4H, d, *J* 8.9 Hz, Ar-H), 8.49 (4H, d, *J* 8.9 Hz, Ar-H); δ_C(D_6-DMSO) 23.4 (C-6), 37.1 (C-5), 51.6 (OMe), 52.1 (C-1′), 66.3 (C-4), 68.5 (C-3), 124.9 and 129.8 (aromatic CH), 128.4 (C-1), 140.7 (C-2), 143.5 and 150.9 (aromatic C), 166.2 (C=O); m/z (C.I) 536 (MH^+-$2H_2O$, 11%), 388 (100).

Methyl 3α,4α-dihydroxy-5β-[N,N-di(p-nitrobenzenesulphonyl)aminomethyl]cyclo-hex-1-ene-1-carboxylate (18) (0.40g, 16%): m.p. 198-199°C (petrol-ethyl acetate); R_F 0.21 (petrol-ethyl acetate 1:1); (Found: C, 44.0; H, 3.7; N, 7.3. $C_{21}H_{21}N_3O_{12}S_2$ requires C, 44.1; H, 3.7; N, 7.35%); ν_{max}(Nujol) 3480 (OH), 3360 (OH), 1715 (C=O), 1350 (SO_2), 1165 (SO_2) cm^{-1}; δ_H(D_6-DMSO) 1.88 (1H, dd, J_{gem} 17.8, $J_{6\beta,5}$ 9.0 Hz, 6β-H), 2.18 (1H, dd, J_{gem} 17.8, $J_{6\alpha,5}$ 4.8 Hz, 6α-H), 2.37 (1H, m, 5-H), 3.43 (1H, m, 4-H), 3.62 (3H, s, OMe), 3.85 (1H, m, 1′-H), 4.10 (1H, m, 3-H), 4.14 (1H, m, 1′-H), 4.69 (1H, d, $J_{4,OH}$ 6.8 Hz, 4-OH), 5.11 (1H, d, $J_{3,OH}$ 6.2 Hz, 3-OH), 6.70 (1H, m, 2-H), 8.23 (4H, d, *J* 9.0 Hz, Ar-H), 8.48 (4H, d, *J* 9.0 Hz, Ar-H); δ_C(D_6-DMSO) 26.8 (C-6), 34.6 (C-5), 51.7 (OMe), 52.5 (C-1′), 64.7 (C-4), 70.2 (C-3), 124.9 and 129.8 (aromatic CH), 129.4 (C-1), 138.4 (C-2), 143.5 and 150.9 (aromatic C), 166.5 (C=O); m/z (C.I) 536 (MH^+-$2H_2O$, 6%), 388 (100).

'Wet' Prévost reaction upon diene disulphonimide (17)

A mixture of silver acetate (0.31 g, 1.86 mmol) and iodine (0.24 g, 0.93 mmol) in glacial acetic acid (20 cm^3) was stirred at 20°C until all the iodine was consumed. The diene disulphonimide (17) (0.50 g, 0.93 mmol) was added and the reaction mixture heated to reflux under a nitrogen atmosphere for 2 h. Water (0.2 cm^3) was added and heating continued for a further 2 h. The reaction mixture was allowed to cool, filtered and concentrated under reduced pressure (azeotroping with toluene). TLC indicated four products which were

separated by column chromatography (petrol-ethyl acetate 7:3 then 1:1) to yield (in order of elution): Methyl 3α,4α-diacetoxy-5β-[N,N-di(p-nitrobenzenesulphonyl)aminomethyl]cyclo-hex-1-ene-1-carboxylate (21) and methyl 3β,4α-diacetoxy-5β-[N,N-di(p-nitro-benzenesulphonyl)aminomethyl]cyclohex-1-ene-1-carboxylate (22) as an inseparable mixture, pale yellow solid (124 mg, 20%): R_F 0.78 (petrol - ethyl acetate 1:1).

Diacetate (21): $\delta_H(CDCl_3)$ 1.99 (3H, s, Me), 2.10 (1H, m, 6β-H), 2.12 (3H, s, Me), 2.53 (1H, dd, J_{gem} 18.4, $J_{6\alpha,5}$ 5.4 Hz, 6α-H), 2.73 (1H, m, 5-H), 3.75 (3H, s, OMe), 3.76 (1H, dd, J_{gem} 15.0, $J_{1',5}$ 8.2 Hz, 1'-H), 3.89 (1H, dd, J_{gem} 15.0, $J_{1',5}$ 6.0 Hz, 1'-H), 4.97 (1H, dd, $J_{4,5}$ 10.1, $J_{4,3}$ 4.0 Hz, 4-H), 5.67 (1H, dd, $J_{3,2}$ 5.0, $J_{3,4}$ 4.0 Hz, 3-H), 6.74 (1H, d m, $J_{2,3}$ 5.0 Hz, 2-H), 8.32 (4H, d, *J* 9.0 Hz, Ar-H), 8.45 (4H, d, *J* 9.0 Hz, Ar-H);

Diacetate (22): $\delta_H(CDCl_3)$ 2.05 (3H, s, Me), 2.06 (3H, s, Me), 2.10-2.60 (3H, m, 5-H, 2 x 6-H), 3.73 (3H, s, OMe), 3.70-3.83 (2H, m, 2 x 1'-H), 5.04 (1H, dd, $J_{4,5}$ 10.2, $J_{4,3}$ 7.1 Hz, 4-H), 5.56 (1H, d m, $J_{3,4}$ 7.1 Hz, 3-H), 6.62 (1H, t, $J_{2,3}$ 2.0, $J_{2,6}$ 2.0 Hz, 2-H), 8.30 (4H, d, *J* 9.0 Hz, Ar-H), 8.45 (4H, d, *J* 9.0 Hz, Ar-H).

Methyl 3β-acetoxy-4β-hydroxy-5β-[N,N-di(p-nitrobenzenesulphonyl)aminomethyl]-cyclohex-1-ene-1-carboxylate (25) as a pale yellow solid (19 mg, 3%): R_F 0.59 (petrol-ethyl acetate 1:1); $\delta_H(D_6DMSO)$ 2.00 (2H, m, 2 x 6-H), 2.06 (3H, s, Me), 2.35 (1H, m, 5-H), 3.65 (3H, s, OMe), 3.81 (1H, m, 4-H), 3.90 (1H, dd, J_{gem} 15.0, $J_{1',5}$ 7.5 Hz, 1'-H), 4.09 (1H, dd, J_{gem} 15.0, $J_{1',5}$ 6.8 Hz, 1'-H), 5.24 (2H, br s, 4-OH, 3-H), 6.45 (1H, br s, 2-H), 8.29 (4H, d, *J* 9.0 Hz, Ar-H), 8.49 (4H, d, *J* 9.0 Hz, Ar-H).

Methyl 3α-acetoxy-4α-hydroxy-5β-[N,N-di(p-nitrobenzenesulphonyl)aminomethyl]cyclohex-1-ene-1-carboxylate (23) and methyl 4α-acetoxy-3α-hydroxy-5β-[N,N-di(p-nitrobenzenesulphonyl)aminomethyl]cyclohex-1-ene-1-carboxylate (24) as an inseparable mixture, pale yellow solid (294 mg, 52%): R_F 0.51 (petrol-ethyl acetate 1:1); m/z (E.I.) 613 (M^+, 3%), 186 (32), 153 (45), 122 (35), 43 (100).

Hydroxyacetate (23): $\delta_H(CDCl_3)$ 1.95-2.21 (1H, m, 6β-H), 2.16 (3H, s, Me), 2.40-2.59 (2H, m, 5-H, 6α-H), 3.70-3.92 (2H, m, 2 x 1'-H), 3.73 (3H, s, OMe), 4.18 (1H, dd, $J_{4,5}$ 11.0, $J_{4,3}$ 4.4 Hz, 4-H), 5.45 (1H, dd, $J_{3,2}$ 4.6, $J_{3,4}$ 4.4 Hz, 3-H), 6.79 (1H, dd, $J_{2,3}$ 4.6, $J_{2,6\beta}$ 1.6 Hz, 2-H), 8.33 (4H, d, *J* 9.2 Hz, Ar-H), 8.45 (4H, d, *J* 9.2 Hz, Ar-H).

Hydroxyacetate (24): $\delta_H(CDCl_3)$ 1.95-2.21 (1H, m, 6β-H), 2.02 (3H, s, Me), 2.40-2.59 (1H, m, 6α-H), 2.82 (1H, m, 5-H), 3.70-3.92 (2H, m, 2 x 1'-H), 3.74 (3H, s, OMe), 4.53 (1H, dd, $J_{3,2}$ 4.5, $J_{3,4}$ 4.0 Hz, 3-H), 4.87 (1H, dd, $J_{4,5}$ 10.0, $J_{4,3}$ 4.0 Hz, 4-H), 6.84 (1H, d m, $J_{2,3}$ 4.5 Hz, 2-H), 8.32 (4H, d, *J* 9.2 Hz, Ar-H), 8.44 (4H, d, *J* 9.2 Hz, Ar-H).

3α,4α-Dihydroxy-5β-[N,N-di(p-nitrobenzenesulphonyl)aminomethyl]cyclohex-1- ene-1-carboxylate (26) as a pale yellow solid (15 mg, 3%): R_F 0.21 (petrol-ethyl acetate 1:1), identical with the sample prepared via the osmium tetroxide route.

Methyl 3α,4α-dihydroxy-5β-[N,N-di(p-nitrobenzenesulphonyl)aminomethyl]-cyclohex-1-ene-1-carboxylate (18)

A solution of the mixed hydroxyacetates (23 + 24) (3.00 g, 4.89 mmol) in methanol (140 cm^3) was treated with dilute aqueous ammonia solution and stirred at 20°C under a nitrogen atmosphere for 23 h. Methanol was evaporated under reduced pressure and the resultant slurry was lyophilised to leave a pale yellow solid.

Crystallisation from ethyl acetate yielded the title compound as a cream coloured solid (1.94 g, 69%), identical with the sample prepared *via* the osmium tetroxide route.

General procedure for acetylation of methyl 3,4-dihydroxy-3,4,5,6-tetrahydrobenzoates

A solution of the diol in pyridine (4 cm^3) was treated with acetic anhydride (0.5 cm^3), DMAP (catalytic) and stirred at 20°C for 24 h. The reaction mixture was poured into chloroform (30 cm^3) and washed with dilute aqueous hydrochloric acid (4 x 25 cm^3) and water (25 cm^3). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure (azeotroping with toluene). Column chromatography (petrol-ethyl acetate 7:3) yielded the diacetate.

Methyl 3α,4α-diacetoxy-5β-[N,N-di(p-nitrobenzenesulphonyl)aminomethyl]-cyclohex-1-ene-1-carboxylate (21)

Acetylation of the diol (18) (64.5 mg, 0.11 mmol) using the general procedure described above gave the title compound as a pale yellow solid (60 mg, 81%): m.p. 214-215°C (dec.) (petrol-ethyl acetate); R_F 0.78 (petrol-ethyl acetate 1:1); (Found C, 45.8; H, 3.8; N, 6.3. $C_{25}H_{25}N_3O_{14}S_2$ requires C, 45.8; H, 3.8; N, 6.4%); ν_{max}(Nujol) 1730 (C=O), 1705 (C=O), 1375 (SO_2), 1170 (SO_2) cm^{-1}; δ_H($CDCl_3$) 1.99 (3H, s, Me), 2.10 (1H, m, 6β-H), 2.12 (3H, s, Me), 2.53 (1H, dd, J_{gem} 18.4, $J_{6\alpha,5}$ 5.4 Hz, 6α-H), 2.73 (1H, m, 5-H), 3.75 (3H, s, OMe), 3.76 (1H, dd, J_{gem} 15.0, $J_{1',5}$ 8.2 Hz, 1'-H), 3.89 (1H, dd, J_{gem} 15.0, $J_{1',5}$ 6.0 Hz, 1'-H), 4.97 (1H, dd, $J_{4,5}$ 10.1, $J_{4,3}$ 4.0 Hz, 4-H), 5.67 (1H, dd, $J_{2,3}$ 5.0, $J_{3,4}$ 4.0 Hz, 3-H), 6.74 (1H, d m, $J_{2,3}$ 5.0 Hz, 2-H), 8.32 (4H, d, *J* 9.0 Hz, Ar-H), 8.45 (4H, d, *J* 9.0 Hz, Ar-H); δ_C($CDCl_3$) 20.8 (2 x Me), 27.6 (C-6), 33.1 (C-5), 51.1 (C-1'), 52.3 (OMe), 64.8 (C-4), 70.5 (C-3), 124.4 and 130.1 (aromatic CH), 132.0 (C-2), 133.0 (C-1), 144.1 and 151.0 (aromatic C), 165.8 (C=O), 169.8 (C=O), 170.0 (C=O); m/z (C.I., NH_3) 673 (MNH_4^+, 81%), 488 (100).

Methyl 3α,4α-isopropylidenedioxy-5β-[N,N-di(p-nitrobenzenesulphonyl)aminomethyl]cyclohex-1-ene-1-carboxylate

The diol disulphonimide (18) (2.80 g, 4.90 mmol) was suspended in 2,2-di-methoxypropane (10 cm^3) and acetone (10 cm^3). A catalytic amount of *p*-TSA was added and the reaction mixture stirred at 20°C under a nitrogen atmosphere for 22 h. The suspension cleared and then a fine white precipitate formed. Evaporation under reduced pressure and trituration with acetone yielded the title compound as a white powder (2.80 g, 94%): m.p. 220-220.5°C (ethyl acetate); R_F 0.72 (petrol-ethyl acetate 1:1); (Found : C, 47.1; H, 4.2; N, 6.9. $C_{24}H_{25}N_3O_{12}S_2$ requires C, 47.1; H, 4.1; N, 6.9%); ν_{max}(Nujol) 1715 (C=O),1350 (SO_2), 1240, 1165 (SO_2) cm^{-1}; δ_H(D_6-DMSO) 1.30 (3H, s, Me), 1.38 (3H, s, Me), 1.85 (1H, dd, J_{gem} 16.5, $J_{6\beta,5}$ 9.0 Hz, 6β-H), 2.11 (1H, m, 5-H), 2.20 (1H, dd, J_{gem} 16.5, $J_{6\alpha,5}$ 3.7 Hz, 6α-H), 3.64 (3H, s, OMe), 4.02 (3H, m, 4-H, 2 x 1'-H), 4.68 (1H, m, 3-H), 6.79 (1H, m, 2-H), 8.21 (4H, d, *J* 9.0 Hz, Ar-H), 8.49 (4H, d, *J* 9.0 Hz, Ar-H); m/z (C.I.,

NH_3) 629 (MNH_4^+, 100%), 612 (MH^+, 5).

Reaction of acetonide disulphonimide with potassium iodide

The acetonide disulphonimide from the previous experiment (309 mg, 0.51 mmol) and dry potassium iodide (419 mg, 2.53 mmol) were suspended in dry DMF (4 cm^3) and heated at 130°C under a nitrogen atmosphere for 21 h. The reaction mixture was poured into water (50 cm^3) and extracted with ethyl acetate (3 x 50 cm^3). The combined extracts were washed with aqueous sodium thiosulphate solution (2% w/v, 25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. TLC on silica gel (petrol-ethyl acetate 4:1) indicated three products and baseline material. Column chromatography (petrol-ethyl acetate 17:3 to 4:1) gave (in order of elution):

Methyl 3α,4α-isopropylidenedioxy-5-methylenecyclohex-1-ene-1-carboxylate (27) as a colourless oil (12.5 mg, 11%): R_F 0.49 (petrol-ethyl acetate 4:1); $\nu_{max}(CHCl_3)$ 1715 (C=O), 1660 (C=C) cm^{-1}; $\delta_H(CDCl_3)$ 1.38 (3H, s, Me), 1.41 (3H, s, Me), 3.04 (1H, d, J_{gem} 19.0 Hz, 6-H), 3.17 (1H, dm, J_{gem} 19.0 Hz, 6-H), 3.78 (3H, s, OMe), 4.63 (1H, d, $J_{4,3}$ 5.2 Hz, 4-H), 4.70 (1H, m, 3-H), 5.14 (1H, m, 1′-H), 5.26 (1H, m, 1′-H), 6.74 (1H, m, 2-H); $\delta_C(CDCl_3)$ 26.6 (Me), 28.0 (Me), 28.6 (C-6), 52.0 (OMe), 74.3 (C-4), 76.9 (C-3), 109.6 (CMe_2), 115.7 (C-1′), 130.6 (C-1), 135.3 (C-2), 139.9 (C-5), 166.8 (C=O); m/z (E.I.) 209 (M^+-CH_3, 209.0799 $C_{11}H_{13}O_4$ requires 209.0812, 75%).

Methyl 3α,4α-isopropylidenedioxy-5β-(iodomethyl)cyclohex-1-ene-1-carboxylate (26) as colourless crystals (56.5 mg, 32%): m.p. 69-71°C (light petrol); R_F 0.44 (petrol-ethyl acetate 4:1); (Found: C, 40.8; H, 4.9. $C_{12}H_{17}IO_4$ requires C, 40.9; H, 4.9%); $\nu_{max}(CHCl_3)$ 1710 (C=O), 1655 (C=C) cm^{-1}; $\delta_H(CDCl_3)$ 1.40 (3H, s, Me), 1.44 (3H, s, Me), 1.56 (1H, m, 5-H), 2.05 (1H, ddt, J_{gem} 17.7, $J_{6\beta,5}$ 10.3, $J_{6\beta,3}$ 2.2, $J_{6\beta,2}$ 2.2 Hz, 6β-H), 2.69 (1H, br dd, J_{gem} 17.7, $J_{6\alpha,5}$ 4.4 Hz, 6α-H), 3.34 (1H, dd, J_{gem} 10.1, $J_{1',5}$ 6.4 Hz, 1′-H), 3.47 (1H, dd, J_{gem} 10.1, $J_{1',5}$ 3.7 Hz, 1′-H), 3.78 (3H, s, OMe), 4.01 (1H, dd, $J_{4,5}$ 9.2, $J_{4,3}$ 6.2 Hz, 4-H), 4.63 (1H, ddd, $J_{3,4}$ 6.2, $J_{3,2}$ 3.9, $J_{3,6\beta}$ 2.2 Hz, 3-H), 6.94 (1H, ddd, $J_{2,3}$ 3.9, $J_{2,6\beta}$ 2.2, $J_{2,6\alpha}$ 0.7 Hz, 2-H); $\delta_C(CDCl_3)$ 10.2 (C-1′), 25.8 (Me), 28.2 (Me), 29.0 (C-6), 38.6 (C-5), 52.1 (OMe), 71.3 (C-4), 76.7 (C-3), 109.5 (CMe_2), 133.4 (C-1), 133.5 (C-2), 166.5 (C=O); m/z (E.I.) 352 (M^+, 2%), 337 (66), 149 (33).

Methyl 3α,4α-isopropylidenedioxy-5β-(O-formylhydroxymethyl)cyclohex-1-ene-1-carboxylate (28) as a colourless oil (24 mg, 17%): R_F 0.25 (petrol-ethyl acetate 4:1); $\nu_{max}(CHCl_3)$ 1715-1725 (C=O) cm^{-1}; $\delta_H(CDCl_3)$ 1.40 (3H, s, Me), 1.44 (3H, s, Me), 2.05 (2H, m, 5-H, 6β-H), 2.68 (1H, br dd, J_{gem} 21.0, $J_{6\alpha,5}$ 9.0 Hz, 6α-H), 3.78 (3H, s, OMe), 4.10 (1H, dd, $J_{4,5}$ 8.5, $J_{4,3}$ 6.0 Hz, 4-H), 4.20 (1H, dd, J_{gem} 11.0, $J_{1',5}$ 5.5 Hz, 1′-H), 4.38 (1H, dd, J_{gem} 11.0, $J_{1',5}$ 3.5 Hz, 1′-H), 4.63 (1H, ddd, $J_{3,4}$ 6.0, $J_{3,2}$ 3.5, $J_{3,6\beta}$ 1.5 Hz, 3-H), 6.95 (1H, ddd, $J_{2,3}$ 3.5, $J_{2,6\beta}$ 2.0, $J_{2,6\alpha}$ 1.0 Hz, 2-H), 8.10 (1H, d, J 0.5 Hz, CHO); $\delta_C(CDCl_3)$ 25.0 (C-6), 25.8 (Me), 28.1 (Me), 36.7 (C-5), 52.1 (OMe), 63.9 (C-1′), 71.1 (C-4), 73.9 (C-3), 109.4 (CMe_2), 133.0 (C-1), 133.7 (C-2), 160.8 (CHO), 166.6 (C=O); m/z (E.I) 270 (M^+, 0.4%), 255 (39), 149(100).

Homonuclear decoupling experiment data for (26):

Signal Irradiated (Chemical shift, δ)	**Observed Resonance** 2-H	3-H	4-H	1′-H	1′-H	6α-H	6β-H
Original resonance	ddd	ddd	dd	dd	dd	br dd	dddd
2-H (6.94)		dd	dd	dd	dd	dd	ddd
3-H (4.63)	dd		d	dd	dd	dd	ddd
5-H (4.63)	ddd	ddd	d	d	d	br d	ddd

Homonuclear decoupling experiment data for (28):

Signal Irradiated (Chemical shift, δ)	**Observed Resonance** 2-H	3-H	4-H	1′-H	1′-H	6α-H
Original resonance	ddd	ddd	dd	dd	dd	br dd
6α-H (2.68)	dd	ddd	dd	dd	dd	
6β-H & 5-H (4.28)	dd	dd	d	d	d	d 1.0 Hz

Methyl 3α,4α-isopropylidenedioxy-5β-(iodomethyl)cyclohex-1-ene-1-carboxylate (26)

A suspension of 18-crown-6 (0.57 g, 2.16 mmol) and dry potassium iodide (0.65 g, 3.93 mmol) in toluene (130 cm^3) was stirred at 20°C for 10 mins. The disulphonimide (17) was added and the reaction mixture heated to reflux under a nitrogen atmosphere. After 3 days additional potassium iodide (0.50 g, 3.01 mmol) and 18-crown-6 (0.50 g, 1.89 mmol) were added. After a total of 7 days, toluene was evaporated under reduced pressure, ethyl acetate was added and the suspension was filtered and concentrated under reduced pressure. Column chromatography (petrol-ethyl acetate 4:1) yielded the title compound as colourless crystals (435 mg, 63%), identical with the sample described above.

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References

1.(a) Haslam E.; *The Shikimate Pathway*, Butterworths, London, 1974.

(b) Herbert R.B.; *The Biosynthesis of Secondary Metabolites*, Chapman and Hall, London, 1981.

(c) Torssell K.B.G.; *Natural Product Chemistry*, Wiley, Chichester, 1983.

(d) Ganem B.; *Tetrahedron*, **34**, 3353-3383 (1978).

2.(a) Levin J.G.; Sprinson D.B.; *J. Biol. Chem.*, **239**, 1142-1150 (1964).

(b). Anderson K.S.; Sikorski, J.A.; A. J. Benesi A.J.; Johnson K.A.; *J. Am. Chem. Soc.*, **110**, 6577-6579 (1988).

(c) Anderson K.S.; Sammons R,D.; Leo G.C.; Sikorski J.A.; Benesi A.J.; Johnson K.A.;, *Biochem.*, **29**, 1460-1465 (1990).

(b) Sliwa H; Le Bot Y.; *Tetrahedron Lett.*, **18**, 4129-4132 (1977).

3.(a) Alberg D.G.; Bartlett P.A.; *J. Am. Chem. Soc.*, **111**, 2337-2338 (1989).

(b) Pansegrau P.D.; Anderson K.S.; Widlanski T.; Ream J.E.; Sammons R. D.; Sikorski J.A.; Knowles J.R.; *Tetrahedron Lett.*, **32**, 2589-2592 (1991).

4.(a) Fowler F.W.; *J. Org. Chem.*, **37**, 1321-1323 (1972).

5. Campbell M.M.; Mahon M.F.; Sainsbury M.; Searle P.A.; and Davies, *Tetrahedron Lett.*, **32**, 181-185 (1991).

6. Nikolaides N.; Ganem B.; *J. Org. Chem.*, **54**, 5996-5998 (1989).

7.(a) Baumgarten R.J.; DeChristopher P.J.; Adamek J.P; Lyon G.D.; Klein S.A.; *J. Org. Chem.*, **39**, 3525-3532 (1974).

(b) DeChristopher P.J.; Adamek J.P.; G.D. Lyon, Galante J.J.; Haffner H.E.; Boggio R.J.; Baumgarten R.J.; *J. Am. Chem. Soc.*, **91**, 2384-2385 (1969).

8.(a) Woodward R.B.; Brutcher F.B. Jr.; *J. Am. Chem. Soc.*, **80**, 209-211 (1958).

(b) Campbell M.M.; Sainsbury M.; Yavarzadeh R.; *Tetrahedron*, **40**, 5063-5070 (1984).

9. DeChristopher P.J.; Adamek J.P.; Klein S.A.; Lyon G.D.; Baumgarten J.R.; *J. Org. Chem.*, **40**, 3288-3291 (1975).

10. We anticipated that the iodide could also be synthesised through reaction of the disulphonimide (17) with potassium iodide and subsequent osmylation of the product methyl 5,6-dihydro-5-iodomethylbenzoate. In practice, however, the only compound obtained from the first reaction was methyl 3-methylbenzoate. This suggests that methyl 5,6-dihydro-5-iodomethylbenzoate is formed, but that it readily undergoes elimination and rearrangement to methyl benzoate.

11. Campbell M.M.; Mahon M.F.; Sainsbury M.; Searle P.A.; Davies G.M;, *Tetrahedron Lett.*, **33**, 3181-3184 (1992).

12. Birch A.J.; Kelly L.F.; Weerasuria D.V.; *J. Org. Chem.*, **53**, 278-281 (1988).