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The Shikimate Pathway. Part 9.[1] Halogenation at C-3 of the Shikimate Nucleus

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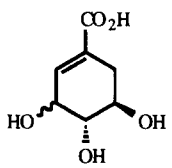
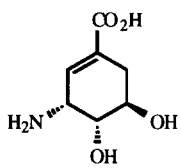
Abstract: The use of (-)-shikimic acid as starting material in the syntheses of a series of C-3 halogenated derivatives including the analogous 3α- and 3β-fluoro and 3β-chloro acids is described together with the first *stereospecific* synthesis of (-)-3-*epi*-shikimic acid directly from the parent acid.

The shikimate pathway[3,4] is a biosynthetic pathway utilized by plants, fungi and micro-organisms for the synthesis of several essential aromatics including L-α-amino acids (Phe, Tyr and Trp), precursors to the folate coenzymes and various isoprenoid quinones. Inhibitors of the enzymes that catalyse the various transformations from acyclic C_3 and C_4 precursors to aromatics have become the subject of intense research following the discovery that *N*-phosphonomethylglycine (glyphosate) possesses post-emergence herbicidal properties[5] as a result of its extreme affinity for the enzyme 5-enolpyruvyl-shikimate-3-phosphate synthase.

The idea that transition state analogues and compounds closely related to shikimate pathway intermediates may show potent enzyme inhibitory activity has encouraged the syntheses of several specifically substituted shikimate derivatives over recent years; syntheses of analogues of (-)-shikimic acid **1** containing 3α-hydroxymethyl,[6] 5β-hydroxymethyl,[7] 6α- and 6β-fluoro,[8-11] 2-chloro[12] and 6β-hydroxy[13-15] functionalities have been reported by several research groups.



1 α-OH
2 β-OH



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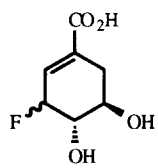
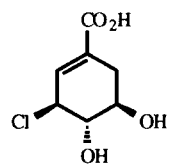


4 α-F
5 β-F



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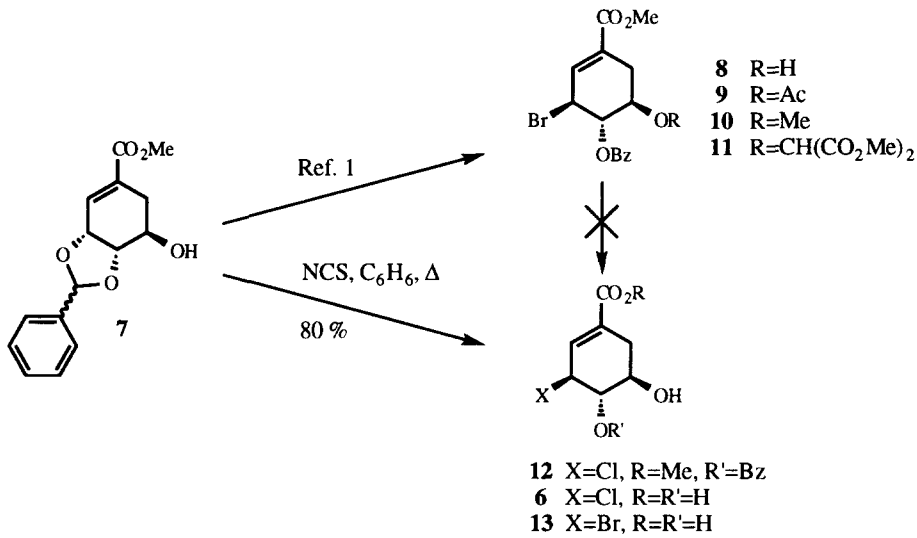
Our interest in this area has focused on the synthesis of C-3 derivatized shikimate mimics since in the main stem of the pathway, reactions at the C-3 hydroxyl group of (-)-shikimic acid **1**, and its precursors, play a vital role in the ultimate derivation of the aromatic skeleton *viz.* oxidation-reduction, phosphorylation and finally elimination. We have previously reported on our successful attempts to introduce nitrogen at C-3 of the shikimate nucleus and have described the preparation of the γ-amino acid **3** directly from the parent acid **1**;[1,16] we have also recently communicated the syntheses of both the 3α- and 3β-fluoro acids **4** and **5**.[17] In this paper

we wish to report more fully on our studies concerned with C-3 halogenation of the shikimate ring and we describe herein the synthesis of 3α-fluoro, 3β-fluoro and 3β-chloro acids **4-6** together with the first *stereospecific* synthesis of the 3-*epi*-acid **2** directly from the parent acid **1**.

Our attempts to introduce nitrogenous functionality at C-3 of the shikimate nucleus[16] resulted in a detailed study of methods suitable for the introduction of bromine at C-3; we have previously described the synthesis of a series of 3β-bromides **8-11** from the protected shikimate **7**.[1] We were similarly interested in the development of methods by which to prepare other C-3 halogenated shikimate derivatives with particular emphasis being given to the introduction of both of the smaller halogens at C-3 (fluorine and chlorine), our initial attempts being based upon methods analogous to those that proved successful for bromination of the shikimate ring.

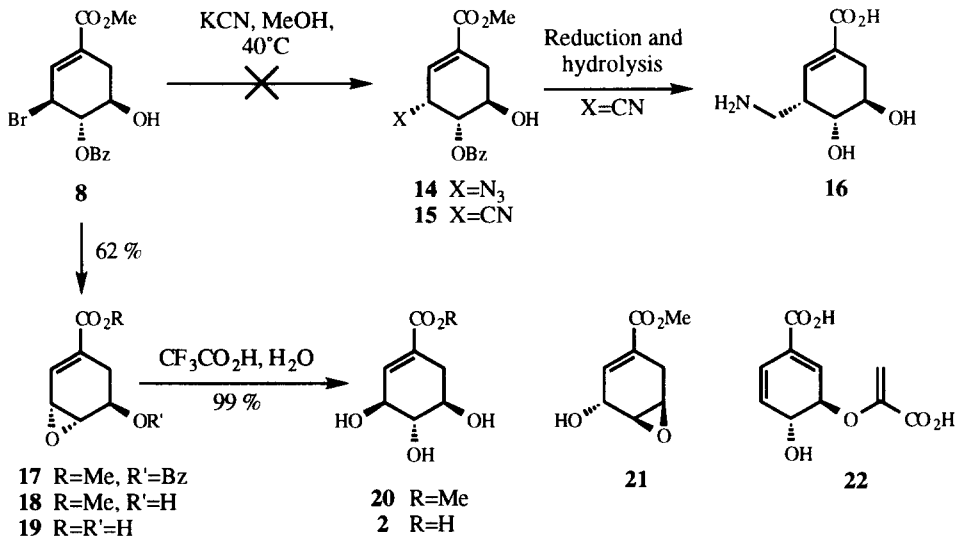


Incorporation of chlorine at C-3 proved to be possible using a radical source of chlorine. Treatment of 3,4-*O*-benzylidene protected shikimate **7** with *N*-chlorosuccinimide in refluxing benzene afforded the corresponding 3β-chloro-4α-benzoate **12** in high yield (80%). Unfortunately, all attempts to prepare both the 3β-chloro acid **6** and the 3β-bromo acid **13** by hydrolytic methods from esters **8**, **9** or **12** failed, the substrates preferentially decomposing under the reaction conditions as a result of the high lability of both the allylic bromide and chloride functionalities. Attempts to replace halide in the more reactive bromoesters **8-11** with fluoride to prepare 3-fluorinated shikimates failed under a variety of conditions, presumably due to the poor nucleophilicity of fluoride ion; similarly attempts to increase reactivity of **8-11** by precipitation of bromide with a soluble silver salt followed by the addition of a source of fluoride ion failed. In all cases either starting materials were recovered unchanged or aromatized products were isolated.

Instead we switched our attention to the use of 3,4-α-epoxides as precursors to 3-halogenated shikimate derivatives following an observation in our laboratories that bromide **8** could be smoothly converted to the epoxy benzoate **17** under extremely mildly basic conditions. We had initially envisaged that treatment of bromide **8** with cyanide ion (under similar conditions to those used to prepare the 3α-azide **14** required for the

synthesis of the amino acid **2**)[1,16] would furnish the 3-nitrile **15** from which the amino acid **16** (the homologue of **2**) would follow after nitrile reduction and ester hydrolysis. Surprisingly, none of the required 3α-nitrile **15** could be prepared by these means, instead a rapid benzoyl migration-epoxidation sequence occured to afford **17** (62%) which was readily debenzoylated with methoxide anion at 0°C to yield the known[18-20] epoxyol **18** (70%).

Epoxyol **18** (a natural product from *Chalara microspora*)[18] has been the subject of some controversy since the two groups to have reported its synthesis have offered widely differing values for its specific rotation. Workers in New York[19,20] have suggested a previously overlooked Payne rearrangement[21] (**18**→**21**) to be the cause of this discrepancy and have successfully developed methods for this isomerization; an elegant synthesis of (-)-chorismic acid **22** has been reported by workers in Massachusetts from epoxyol **21**[22] (prepared by an alternative enzymic route). Whilst the isomerization of **18** to **21** formally constitutes a seven step synthesis of (-)-chorismic acid **22** from (-)-shikimic acid **1** it is perhaps somewhat of a humbling experience for the synthetic chemist to note that the overall molecular conversion offered by this relatively low yielding synthetic procedure is achieved essentially quantitatively *in vivo* by a triad of enzymes working under extremely mild conditions of pH and temperature.

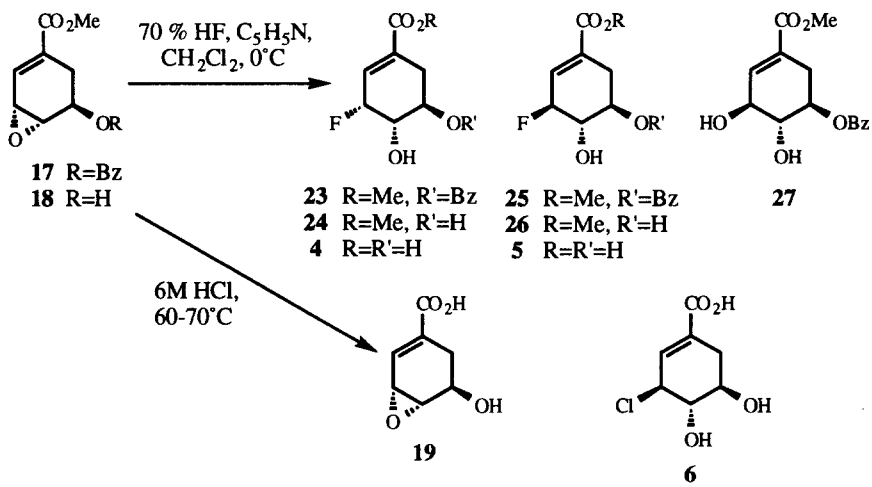


Whilst we have noted a similar dextrorotation for **18** to the New York researchers[19,20] we have found the proposed rearrangement to be far less facile and far more base specific than previously noted, indeed we have only observed the isomerization of **18**→**21** using methoxide ion in methanol at room temperature or above. In our hands, when treated with excess potassium carbonate at 40°C in a methanol-tetrahydrofuran mixture, bromide **8** was smoothly converted solely to epoxyol **18** (82%). Saponification of **18** (NaOH, H_2O, 20°C) afforded a 1:1 mixture of epoxy acid **19** and 3-*epi*-shikimic acid **2** (74%) which upon attempted separation by

reverse phase HPLC (elution with MeCN:H_2O containing 1% trifluoroacetic acid) was converted cleanly to 3-*epi*-acid **2** (65%).

We thus exploited the acid lability of epoxyol **18** to develop a new synthesis of (-)-3-*epi*-acid **2**. Treatment of an aqueous solution of **18** with catalytic amounts of trifluoroacetic acid resulted in smooth regiospecific and stereospecific epoxide cleavage to yield the 3-*epi*-ester **20** quantitatively; subsequent hydrolysis of ester **20** (NaOH, H_2O, 20°C) afforded the free acid **2** (81%) after ion-exchange chromatography. Both ester **20** and acid **2** have, to the best of our knowledge, only previously been prepared either in racemic form[23] or contaminated with their naturally occuring C-3 epimers from which the desired 3-*epi*-compounds **20** and **2** were isolated by fractional crystallization;[23,24] our approach thus allows the first *stereospecific* synthesis of both laevorotatory ester **20** and acid **2** on a preparative scale from the parent acid **1**.

Using a similar protocol we were successfully able to prepare both 3α- and 3β-fluorinated shikimate derivatives from the epoxy benzoate **17**. Treatment of **17** with fluoride ion under the acidic conditions offered by Olah's reagent[25] (polyhydrogen fluoride in pyridine, *ca.* 70% hydrogen fluoride) at 0°C resulted in the regiospecific opening of the epoxide ring to afford a mixture of the 3β-alcohol **27** (17%) together with both the 3α-fluoride **23** (8%) and 3β-fluoride **25** (48%) (by ^1H nmr of the crude reaction mixture) from which both 3β-fluoride **25** and 3β-alcohol **27** could be isolated in pure form. Careful analysis of a mixture of **23** and **25** using a combination of ^1H, ^{13}C and ^{19}F nmr spectroscopy showed clearly that fluoride ion had been incorporated at C-3 of the ring; neither regioisomeric 4-fluorinated products nor 1-fluorinated products resulting from oxirane cleavage *via* an alternative S_N2' mechanism could be detected.



Methoxide catalysed debenzoylation of a crude mixture of **23**, **25** and **27** (NaOMe, MeOH, 0°C) afforded a mixture of esters **20**, **24** and **26** from which both 3α- and 3β-fluorides **24** and **26** could be isolated in pure form by reverse phase HPLC (53% and 8% yields respectively). Acid induced hydrolysis of a mixture of **23** and **25** in acidic aqueous 1,4-dioxane afforded a mixture of the 3α- and 3β-fluoro acids **4** (5%) and **5** (91%) (by ^1H nmr spectroscopy) from which pure 3β-fluoro acid **5** could be isolated after separation by

reverse phase HPLC; interestingly the 3β-fluoride **5** has a melting point identical (183-186°C) to that of the parent acid **1**.

A similar protocol has allowed the synthesis of the 3β-chloro acid **6**. Epoxide cleavage in epoxyol **18** under somewhat more forcing acidic conditions (6M HCl, 60-70°C) resulted in formation of both chloro acid **6** and the 3,4-α-epoxy acid **19** (3,4-anhydroshikimic acid) which could be separated from the large amounts of material (arising from the aromatization of the shikimate nucleus) by reverse phase HPLC to afford pure samples of each albeit in low yields (13% and 12% respectively). Interestingly, none of the 3-*epi*-acid **2** could be observed in the reaction mixture despite the presence of a vast excess of water relative to chloride ions, presumably the non-nucleophilic nature of the trifluoroacetate ion accounts for the successful formation of **2** from **18** using trifluoroacetic acid as catalyst.

Unfortunately, all attempts to prepare the corresponding 3β-bromo acid **13** from **18** in acidic media under similar conditions (HBr in either H_2O or AcOH) failed presumably due to the instability of either the resulting brominated product or starting material under such forcing acidic conditions.

In summary, we have successfully developed methods that allow the synthesis of a series of shikimate analogues directly from the parent acid **1** in which the 3-hydroxyl functionality has been replaced with both fluorine and chlorine. We have demonstrated the synthetic utility of these methods by describing the synthesis of both the 3α- and 3β-fluoro acids **4** and **5** together with the 3β-chloro acid **6**. As part of the synthesis of fluoro and chloro acids **4**, **5** and **6**, we have prepared the naturally occuring epoxyol **18** (first isolated from the fungus *Chalara microspora*) and have utilized the acid lability of this fungal metabolite to develop the first *stereospecific* synthesis of (-)-3-*epi*-shikimic acid **2** as well as a synthesis of 3,4-anhydroshikimic acid **19**.

Acknowledgements: We thank the SERC and Zeneca Pharmaceuticals for CASE studentships (to FSM, RC and MF) and The University of Sheffield for support.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Specific rotations were measured with a Perkin-Elmer 141 polarimeter. Microanalyses were performed by The University of Sheffield Department of Chemistry Microanalytical Service and by the Microanalysis Department at Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire. Mass spectra were recorded by electron impact (+EI) or by chemical ionisation (+CI) (ammonia as the ionising agent) using a Kratos MS-25 mass spectrometer or by either positive or negative fast atom bombardment (+FAB or -FAB) (ammonia or xenon as the ionising agent) using a Kratos MS-80 mass spectrometer as indicated. Infra-red spectra were recorded on a Perkin-Elmer 457 spectrophotometer in a nujol mull or as a neat film as indicated. All nuclear magnetic resonance spectra were recorded in the solvents specified. ^1H and ^{13}C Spectra were recorded using either a Bruker AM-250 spectrometer (operating at 250·1 MHz and 62·9 MHz respectively) or using a Bruker AM-400 spectrometer (operating at 400·1 MHz and 100·6 MHz respectively); ^{19}F spectra were recorded using a Bruker WSP-80 spectrometer (operating at 32·4 MHz). Flash column chromatography was performed using silica gel 60 (Merck 9385). Ethyl acetate, methanol, petroleum ethers (b.p. 40-60°C and b.p. 60-80°C) and

water were distilled prior to use. Benzene was dried over sodium wire prior to use. Tetrahydrofuran was distilled from sodium-benzophenone ketyl immediately prior to use. Preparative reverse phase high performance liquid chromatography was performed on a Dynamax 60A HPLC column (41·6 mm internal diameter) using the specified solvents as eluent.

3(*S*),4(*S*),5(*R*)-Trihydroxy-1-cyclohexene-1-carboxylic acid 2. A solution of methyl 3(*S*),4(*S*),5(*R*)-trihydroxy-1-cyclohexene-1-carboxylate **20** (134 mg, 0·71 mmol) in water (5 ml) was treated with sodium hydroxide (30 mg, 0·75 mmol) and the solution was stirred at room temperature overnight. The resulting solution was neutralized by the addition of Amberlite IR-120 (H) cationic exchange resin (*ca.* 100 mg) together with a small spatula of charcoal and the mixture was stirred for 5 minutes, filtered and the solvent removed *in vacuo* to afford a colourless oil. Trituration with diethyl ether afforded the *product* **2** (101 mg, 81%) as a pale yellow solid that crystallized from ethyl acetate and methanol as colourless prisms, m.p. 164-165°C; [Lit.,[23] m.p. 167°C]; $[\alpha]_D$ -31·0° (*c* 0·1, H_2O); (Found: C, 48·15; H, 5·75. $C_7H_{10}O_5$ requires C, 48·3; H, 5·8%); ν_{max} (nujol) 3700-3100, 1700, 1650 cm^{-1}; *m/z* (+CI) 192, $M+NH_4^+$; δ_H (D_2O) 6·43 (1H, t, *J* 3 Hz, H-2), 4·24 (1H, dtd, *J* 8, 3, 2·5 Hz, H-3), 3·76 (1H, td, *J* 10·5, 6·5 Hz, H-5), 3·46 (1H, dd, *J* 10·5, 8 Hz, H-4), 2·74 (1H, ddd, *J* 18, 6·5, 2·5 Hz, H-6α), 2·19 (1H, ddt, *J* 18, 10·5, 3 Hz, H-6β); δ_C (D_2O) 172·9 (C=O), 135·5 (C-2), 131·7 (C-1), 76·7, 71·9 and 69·1 (C-3, C-4 and C-5), 32·8 (C-6).

3(*S*)-Fluoro-4(*S*),5(*R*)-dihydroxy-1-cyclohexene-1-carboxylic acid 5. A solution of methyl 5(*R*)-benzoyloxy-3(*S*)-fluoro-4(*S*)-hydroxy-1-cyclohexene-1-carboxylate **25** (250 mg, 0·85 mmol) in 1,4-dioxane (4 ml) was treated with 6M hydrochloric acid (4 ml) and the resulting solution was stirred at 60-65°C for 6 hours. After cooling the solvent was removed *in vacuo* and the residue purified by reverse phase HPLC. Elution with 100:0·5 v/v water-trifluoroacetic acid afforded the *product* **5** (136 mg, 91%), R_t 14·3 min, as a colourless solid. m.p. 183-186°C; (Found: C, 48·15; H, 5·3. $C_7H_9O_4F$ requires C, 47·75; H, 5·15%); *m/z* (-FAB) 175, $M-H^-$; δ_H (D_2O) 6·87 (1H, dm, *J* 10 Hz, H-2), 5·25 (1H, dm, *J* 42·5 Hz, H-3), 3·90 (2H, m, H-4 and H-5), 2·90 (1H, dm, *J* 18 Hz, H-6α), 2·35 (1H, dm, *J* 18 Hz, H-6β); δ_C (D_2O) 169·1 (C=O), 135·1 (J_{CF} 22·5 Hz, C-2), 132·7 (J_{CF} 9·5 Hz, C-1), 94·0 (J_{CF} 170 Hz, C-3), 76·6 (J_{CF} 17·5 Hz, C-4), 69·9 (J_{CF} 9 Hz, C-5), 33·9 (C-6); δ_F (D_2O) -186·7 (ddm, J_{HF} 42·5, 10 Hz).

3(*S*)-Chloro-4(*S*),5(*R*)-dihydroxy-1-cyclohexene-1-carboxylic acid 6 and **3(*R*),4(*R*)-epoxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylic acid 19.** A solution of methyl 3(*R*),4(*R*)-epoxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **18** (250 mg, 1·47 mmol) in 6M hydrochloric acid (4 ml) was stirred and held at 60-70°C for 8 hours. After cooling the solvent was removed *in vacuo* and the residue purified by reverse phase HPLC. Elution with 100:0·5 v/v water-trifluoroacetic acid afforded the *product* **19** (28 mg, 12%), R_t 12·6 min, as a colourless solid. m.p. 166-167°C; (Found: C, 54·15; H, 5·25. $C_7H_8O_4$ requires C, 53·85; H, 5·15%); *m/z* (+CI) 156, MH^+; ν_{max} (nujol) 3500-3300, 1700, 1660 cm^{-1}; δ_H (D_2O) 6·98 (1H, m, H-2), 5·00 (1H, m, H-3), 4·20 (1H, ddd, *J* 6·5, 4, 3·5 Hz, H-5), 4·02 (1H, dd, *J* 6·5, 3·5 Hz, H-4), 2·90 (1H, ddm, *J* 18·5, 4 Hz, H-6α), 2·38 (1H, ddm, *J* 18·5, 6·5 Hz, H-6β); δ_C (CD_3OD) 169·6 (C=O), 135·4 (C-2), 130·0 (C-1), 70·4 (C-3), 66·1 (C-4), 57·5 (C-5), 31·1 (C-6). Further elution afforded the *product* **6** (37 mg, 13%), R_t 16·6 min, as a colourless solid. (Found: C, 43·45; H, 4·75. $C_7H_9O_4Cl$ requires C, 43·65; H, 4·7%); *m/z* (-FAB) 191, $M-H^-$; ν_{max} (nujol) 3500-3300, 1700, 1660 cm^{-1}; δ_H (D_2O)

6·82 (1H, m, H-2), 3·87 (3H, m, H-3, H-4 and H-5), 2·90 (1H, dm, *J* 18 Hz, H-6α), 2·39 (1H, m, H-6β); δ_C (CD_3OD) 169·1 (C=O), 138·0 (C-2), 131·3 (C-1), 79·5 (C-3), 71·0 (C-4), 62·4 (C-5), 33·6 (C-6).

Methyl 4(*S*)-benzoyloxy-3(*S*)-chloro-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate 12. A solution of methyl 3(*R*),4(*S*)-benzylidenedioxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **7**[1] (1·00 g, 3·62 mmol) in benzene (80 ml) was treated with *N*-chlorosuccinimide (700 mg, 5·24 mmol) and the resulting solution was stirred and held at reflux for 4 hours. After cooling the solvent was removed *in vacuo* and the residues subjected to column chromatography. Elution with 3:2 v/v petroleum ether (b.p. 60-80°C)-ethyl acetate afforded the *product* **12** (900 mg, 80%), R_f 0·60, as a colourless oil. (Found: C, 58·1; H, 4·8; Cl, 11·6. $C_{15}H_{15}O_5Cl$ requires C, 58·0; H, 4·8; Cl, 11·4%); *m/z* (+CI) 311, MH^+; ν_{max} (film) 3500-3300, 1700 cm^{-1}; δ_H ($CDCl_3$) 8·10 (2H, d, *J* 8 Hz, *o*-ArH), 7·61 (1H, t, *J* 8 Hz, *p*-ArH), 7·47 (2H, t, *J* 8 Hz, *m*-ArH), 6·63 (1H, td, *J* 3, 1 Hz, H-2), 5·42 (1H, dd, *J* 10, 8 Hz, H-4), 4·81 (1H, m, H-3), 4·03 (1H, m, H-5), 3·81 (3H, s, $-CO_2Me$), 3·03 (1H, ddm, *J* 17·5, 6 Hz, H-6α), 2·51 (1H, dddd, *J* 17·5, 9, 3·5, 3 Hz, H-6β); δ_C ($CDCl_3$) 166·5 and 165·7 (C=O), 135·5, 133·5, 129·9, 129·7, 129·2 and 128·4 (aromatic CH, aromatic C, C-1 and C-2), 78·5 (C-4), 68·6 (C-3), 56·4 (C-5), 52·3 (C-8), 32·4 (C-6).

Methyl 5(*R*)-benzoyloxy-3(*R*),4(*R*)-epoxy-1-cyclohexene-1-carboxylate 17. A solution of methyl 4(*S*)-benzoyloxy-3(*S*)-bromo-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **8**[1] (981 mg, 2·76 mmol) in methanol (30 ml) was added potassium cyanide (200 mg, 3·08 mmol) and the mixture was stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and the residues partitioned between chloroform (30 ml) and water (30 ml). The organics were dried over sodium sulphate, filtered and the solvent was removed *in vacuo* to afford a pale yellow oil which was subjected to column chromatography. Elution with 5:1 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **17** (465 mg, 62%), R_f 0·37, as a colourless oil. $[\alpha]_D$ +249·9° (*c* 2·1, $CHCl_3$); (Found: C, 65·4; H, 5·5. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·15%); ν_{max} (film) 1720, 1650, 1600, 1585, 1495 cm^{-1}; *m/z* (+CI) 275, 292, MH^+, $M+NH_4^+$; δ_H ($CDCl_3$) 7·97 (2H, dt, *J* 7·5, 1·5 Hz, *o*-ArH), 7·57 (1H, tt, *J* 7·5, 1·5 Hz, *p*-ArH), 7·43 (2H, tt, *J* 7·5, 1·5 Hz, *m*-ArH), 7·21 (1H, dd, *J* 4, 3 Hz, H-2), 5·88 (1H, ddd, *J* 5, 3, 2 Hz, H-5), 3·78 (1H, ddd, *J* 4, 3, 2 Hz, H-4), 3·78 (3H, s, $-CO_2Me$), 3·57 (1H, t, *J* 4 Hz, H-3), 2·98 (1H, dt, *J* 18, 2 Hz, H-6α), 2·47 (1H, ddd, *J* 18, 5, 3 Hz, H-6β); δ_C ($CDCl_3$) 166·1 and 165·7 (C=O), 133·3 and 133·1 (C-2 and aromatic CH), 131·0 (C-1), 129·7 (aromatic CH), 129·6 (aromatic C), 128·4 (aromatic CH), 66·2 (C-5), 54·0 (C-3), 52·1 (OMe), 46·6 (C-4), 26·5 (C-6).

Methyl 3(*R*),4(*R*)-epoxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate 18. A solution of methyl 4(*S*)-benzoyloxy-3(*R*)-bromo-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **8**[1] (1·47 g, 4·14 mmol) in methanol (10 ml) and tetrahydrofuran (30 ml) was added anhydrous potassium carbonate (600 mg, 4·35 mmol) and the mixture was stirred at *ca.* 40°C overnight. After cooling the solvent was removed *in vacuo* to afford a pale yellow oil that was subjected to column chromatography. Elution with 3:1 v/v petroleum ether (b.p. 40-60°C)-ethyl acetate afforded the *product* **18** (577 mg, 82%), R_f 0·25, as a colourless oil. (Found: C, 56·8; H, 5·8. $C_8H_{10}O_4$ requires C, 56·45; H, 5·9%); $[\alpha]_D$ +224·3° (*c* 1·1, $CHCl_3$), [Lit.,[19,20] $[\alpha]_D$ +248° (*c* 0·5, EtOH)]; ν_{max} (film) 3700-3100, 1715, 1650 cm^{-1}; *m/z* (+CI) 171, 188, MH^+, $M+NH_4^+$; δ_H ($CDCl_3$) 7·15 (1H, dd, *J* 4, 3 Hz, H-2), 4·58 (1H, broad m, H-5), 3·77 (3H, s, $-CO_2Me$), 3·59 (1H, ddd, *J* 4, 3, 2 Hz, H-4), 3·50 (1H, t, *J* 4 Hz, H-3), 2·82 (1H, dt, *J* 18, 2 Hz, H-6α), 2·32 (1H, ddd, *J* 18, 5, 3 Hz, H-6β),

2·04 (1H, broad d, *J* 6Hz, -OH); δ_C ($CDCl_3$) 166·2 (C=O), 133·4 (C-2), 130·7 (C-1), 63·2 and 56·0 (C-3 and C-5), 52·0 (OMe), 46·2 (C-4), 29·2 (C-6).

Methyl 3(*S*),4(*S*),5(*R*)-trihydroxy-1-cyclohexene-1-carboxylate 20. A solution of methyl 3(*R*),4(*R*)-epoxy-5(*R*)-hydroxy-1-cyclohexene-1-carboxylate **18** (158 mg, 0·93 mmol) in water (5 ml) was treated with trifluoroacetic acid (3 drops) and the solution was stirred overnight at room temperature. Removal of the solvent *in vacuo* afford the *product* **20** (173 mg, 99%) as a colourless oil which upon trituration with diethyl ether afforded a white solid that crystallized from ethyl acetate as colourless prisms. m.p. 132°C; $[\alpha]_D$ -13·4° (*c* 0·5, MeOH); [Lit.,[24] m.p. 133°C; $[\alpha]_D$ -13·2° (MeOH)]; (Found: C, 51·0; H, 6·45. $C_8H_{12}O_5$ requires C, 51·05; H, 6·45%; ν_{max} (film) 3700-3100, 1710, 1660 cm^{-1}; *m/z* (+CI) 206, $M+NH_4^+$; δ_H (D_2O) 6·66 (1H, td, *J* 4·5, 1 Hz, H-2), 4·25 (1H, dddd, *J* 8·5, 4·5, 3, 2 Hz, H-3), 3·77 (1H, td, *J* 10, 6 Hz, H-5), 3·74 (3H, s, $-CO_2Me$), 3·46 (1H, dd, *J* 10, 8·5 Hz, H-4), 2·79 (1H, dddd, *J* 18, 6, 2, 1 Hz, H-6α), 2·21 (1H, dddd, *J* 18, 10, 4·5, 3 Hz, H-6β); δ_C (D_2O) 168·8 (C=O), 139·0 (C-2), 128·2 (C-1), 76·4, 71·7 and 68·8 (C-3, C-4 and C-5), 52·6 (OMe), 31·9 (C-6).

Methyl 5(*R*)-benzoyloxy-3(*S*)-fluoro-4(*S*)-hydroxy-1-cyclohexene-1-carboxylate 25 and **methyl 5(*R*)-benzoyloxy-3(*S*),4(*S*)-dihydroxy-1-cyclohexene-1-carboxylate 27.** A solution of methyl 5(*R*)-benzoyloxy-3(*R*),4(*R*)-epoxy-1-cyclohexene-1-carboxylate **17** (250 mg, 0·91 mmol) in dichloromethane (5 ml) held at 5°C was treated with 70% hydrogen fluoride/pyridine (2 ml) and the resulting mixture was stirred for 5 minutes, poured onto a saturated solution of sodium hydrogen carbonate and stirred for a further 10 minutes. The organics were extracted into dichloromethane (50 ml), washed with sodium hydrogen carbonate solution (30 ml), 2M hydrochloric acid (30 ml) and water (30 ml). The organic layer was dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to afford a pale yellow oil which was subjected to column chromatography. Elution with 4:1 v/v petroleum ether (b.p. 60-80°C)-ethyl acetate afforded the *product* **25** (130 mg, 48%) as a colourless oil. (Found: C, 61·4; H, 5·5. $C_{15}H_{15}O_5F$ requires C, 61·2, H, 5·15%); ν_{max} (film) 3500-3400, 1720 cm^{-1}; *m/z* (+EI) 294, M^+; δ_H ($CDCl_3$) 8·06 (2H, dt, *J* 8, 1 Hz, *o*-ArH), 7·60 (1H, tt, *J* 8, 1 Hz, *p*-ArH), 7·46 (2H, tt, *J* 8, 1 Hz, *m*-ArH), 6·80 (1H, ddm, *J* 11, 2·5 Hz, H-2), 6·23 (1H, ddm, *J* 48, 8 Hz, H-3), 5·27 (1H, ddd, *J* 16, 8, 6 Hz, H-4), 4·19 (1H, m, *J* 8, 7, 5 Hz, H-5), 3·79 (3H, s, $-CO_2Me$), 3·13 (1H, ddm, *J* 17·5, 6, 2·5 Hz, H-6α), 2·50 (1H, dm, *J* 17·5 Hz, H-6β); δ_C ($CDCl_3$) 166·1 and 165·5 (C=O), 133·4 (J_{CF} 21 Hz, C-2), 133·3 (aromatic CH), 130·2 (aromatic C), 130·1 (J_{CF} 9·5 Hz, C-1), 129·7 and 128·4 (aromatic CH), 91·5 (J_{CF} 172 Hz, C-3), 72·4 (J_{CF} 19·5 Hz, C-4), 70·6 (J_{CF} 9·5 Hz, C-5), 52·2 (OMe), 29·6 (C-6); δ_F ($CDCl_3$) -186·8 (dddd, J_{HF} 48, 16, 11, 5 Hz). Further elution afforded the *product* **27** (45 mg, 17%) as colourless needles. m.p. 136-138°C; (Found: C, 61·4; H, 5·5. $C_{15}H_{16}O_6$ requires C, 61·65, H, 5·5%); *m/z* (+EI) 292, M^+; δ_H ($CDCl_3$) 8·06 (2H, dt, *J* 7, 1 Hz, *o*-ArH), 7·60 (1H, tt, *J* 7, 1 Hz, *p*-ArH), 7·47 (2H, tt, *J* 7, 1 Hz, *m*-ArH), 6·83 (1H, m, H-2), 5·25 (1H, m, *J* 9·5, 4·5, 4 Hz, H-5), 4·47 (1H, m, H-3), 3·90 (1H, dd, *J* 9·5, 7·5 Hz, H-4), 3·70 (3H, s, $-CO_2Me$), 3·11 (1H, dddd, *J* 17·5, 6, 2, 1·5 Hz, H-6α), 2·62 (1H, broad s, -OH), 2·49 (1H, dddd, *J* 17·5, 9·5, 3·5, 2·5 Hz, H-6β); δ_C ($CDCl_3$) 166·5 and 166·0 (C=O), 138·0 (aromatic CH), 133·4 (C-2), 129·7 (aromatic CH), 129·6 (aromatic C), 128·5 (aromatic CH), 127·9 (C-1), 75·2 (C-5), 72·3 (C-3), 72·0 (C-4), 52·1 (OMe), 30·3 (C-6).

Methyl 3(*R*)-fluoro-4(*S*),5(*R*)-dihydroxy-1-cyclohexene-1-carboxylate 24 and **methyl 3(*S*)-fluoro-4(*S*),5(*R*)-dihydroxy-1-cyclohexene-1-carboxylate 26.** A solution of crude fluorinated

material [prepared from methyl 5(*R*)-benzoyloxy-3(*R*),4(*R*)-epoxy-1-cyclohexene-1-carboxylate **17** as above] (300 mg, 1·02 mmol) in dry methanol (30 ml) was treated with sodium methoxide (50 mg, 0·93 mmol) and the resulting solution was stirred at 0°C for 3 hours after which sodium dihydrogen phosphate (500 mg) was added and the resulting mixture stirred for a further 10 minutes. After addition of dichloromethane (100 ml) the insoluble material was removed by filtration, the solvent removed *in vacuo* and the residues subjected to column chromatography. Elution with 4:1 v/v petroleum ether (b.p. 60-80°C)-ethyl acetate afforded an inseparable mixture of the *products* **24** and **26**. Reverse phase HPLC separation of the mixture eluting with water, acetonitrile and trifluoroacetic acid (97:3:0·5) afforded the *product* **26** (100 mg, 53%), R_t 23·4 min, as a colourless oil. (Found: C, 50·15; H, 5·75. $C_8H_{11}O_4F$ requires C, 50·55; H, 5·85%); *m/z* (+CI) 208, $M+NH_4^+$; δ_H ($CDCl_3$) 6·76 (1H, dt, *J* 11, 2·5 Hz, H-2), 5·06 (1H, dm, *J* 49·5 Hz, H-3), 3·78 (3H, s, $-CO_2Me$), 3·70 (2H, m, H-4 and H-5), 2·87 (1H, dm, *J* 18 Hz, H-6α), 2·27 (1H, dm, *J* 18 Hz, H-6β); δ_C ($CDCl_3$) 166·1 (C=O), 133·7 (J_{CF} 22·5 Hz, C-2), 130·5 (J_{CF} 10 Hz, C-1), 92·3 (J_{CF} 171 Hz, C-3), 75·1 (J_{CF} 17·5 Hz, C-4), 68·4 (J_{CF} 9 Hz, C-5), 52·2 (OMe), 32·1 (C-6). Further elution afforded the *product* **24** (15 mg, 8%), R_t 36·4 min, as a colourless oil. (Found: C, 50·3; H, 5·6. $C_8H_{11}O_4F$ requires C, 50·55; H, 5·85%); *m/z* (+CI) 208, $M+NH_4^+$; δ_H (CD_3OD) 6·80 (1H, dm, *J* 8, 3·5, 2 Hz, H-2), 5·18 (1H, ddt, *J* 47, 5, 2 Hz, H-3), 4·01 (1H, m, H-5), 3·85 (1H, ddd, *J* 13·5, 7·5, 5 Hz, H-4), 3·76 (3H, s, $-CO_2Me$), 2·74 (1H, dm, *J* 18·5, 5, 2 Hz, H-6α), 2·24 (1H, dm, *J* 18·5, 5·5, 2 Hz, H-6β); δ_C (CD_3OD) 168·4 (C=O), 133·9 (J_{CF} 20 Hz, C-2), 130·6 (J_{CF} 9·5 Hz, C-1), 88·7 (J_{CF} 169·5 Hz, C-3), 71·6 (J_{CF} 16·5 Hz, C-4), 68·6 (J_{CF} 3 Hz, C-5), 52·9 (OMe), 32·2 (C-6); δ_F (D_2O) -191·0.

REFERENCES AND NOTES

1. Part 8. Adams, H.; Bailey, N.A.; Cross, R.; Frederickson, M.; Haslam, E.; MacBeath, F.S.; Davies, G.M. *Tetrahedron*, **1996**, *52*, 8568-8583.
2. *Present address:* School of Chemistry, The University of Leeds, Leeds, U.K., LS2 9JT.
3. Haslam E. *Shikimic acid: Metabolism and Metabolites*; John Wiley and Sons: Chichester, 1993.
4. Campbell, M.M.; Sainsbury, M.; Searle, P.A. *Synthesis*, **1993**, 179-193.
5. Grossbard, E.; Atkinson, D. *The Herbicide Glyphosate*; Butterworths: Boston, 1985.
6. Wood, H.B. Jr.; Ganem, B. *Tetrahedron Lett.*, **1993**, *34*, 1403-1406.
7. Campbell, M.M.; Mahon, M.F.; Sainsbury, M.; Searle, P.A. *Tetrahedron Lett.*, **1991**, *32*, 951-954.
8. Sutherland, J.K.; Watkins, W.J.; Bailey, J.P.; Chapman, A.K.; Davies, G.M. *J. Chem. Soc., Chem. Commun.*, **1989**, 1386-1387.
9. Sutherland, J.K.; Whitehead, R.C.; Davies, G.M. *J. Chem. Soc., Chem. Commun.*, 1993, 464-465.
10. Bowles, S.A.; Campbell, M.M.; Sainsbury, M.; Davies, G.M. *Tetrahedron*, **1990**, *46*, 3981-3992.
11. Duggan, P.J.; Parker, E.; Coggins, J.; Abell, C. *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 2347-2352.
12. Rich, R.H.; Lawrence, B.M.; Bartlett, P.A. *J. Org. Chem.*, **1994**, *59*, 693-694.
13. Blacker, J.A.; Booth, R.J.; Davies, G.M.; Sutherland, J.K. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2861-2870.
14. Carless, H.A.J.; Dove, Y. *Tetrahedron: Asym.*, **1996**, *7*, 649-652.
15. Tran, C.H.; Crout, D.H.G.; Errington, W.; Whited, G.M. *Tetrahedron: Asym.*, **1996**, *7*, 691-698.
16. Brettle, R.; Cross, R.; Frederickson, M.; Haslam, E.; Davies, G.M. *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 291-294.

17. Brettle, R.; Cross, R.; Frederickson, M.; Haslam, E.; MacBeath, F.S.; Davies, G.M. *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 1275-1278.
18. Fex, T.; Trofast, J.; Wickberg, B. *Acta Chem. Scand., Ser. B*, **1981**, *35*, 91-95.
19. Wood, H.B.; Ganem, B. *Tetrahedron Lett.*, **1989**, *30*, 6257-6258.
20. Wood, H.B.; Ganem, B. *J. Am. Chem. Soc.*, **1990**, *112*, 8907-8909.
21. Payne, G.B. *J. Org. Chem.*, **1962**, *27*, 3819-3822.
22. Pawlak, J.L.; Berchtold, G.A. *J. Org. Chem.*, **1987**, *52*, 1765-1771.
23. Grewe, R.; Hinrichs, I. *Chem. Ber.*, **1964**, *97*, 443-448.
24. Grewe, R.; Jeschke, J.-P. *Chem. Ber.*, **1956**, *89*, 2080-2088.
25. Olah, G.A.; Welch, J.T.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.*, **1979**, *44*, 3872-3881.

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