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Synthesis of (6*S*)-6-fluoroshikimic acid

Chuanjun Song, Shende Jiang and Gurdial Singh*

Department of Chemistry, University of Sunderland, Sunderland, SR1 3SD, UK

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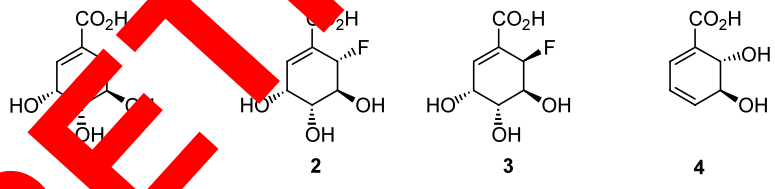
Abstract—(6*S*)-6-Fluoroshikimic acid **2** and (6*R*)-6-hydroxyshikimic acid **16** have been synthesised via an OsO_4-catalysed dihydroxylation of diene **8**, which was derived from (−)-shikimic acid **1**.

The shikimate biosynthetic pathway is utilised in plants, fungi and microorganisms for the synthesis of the aromatic amino acids (L-phenylalanine, L-tyrosine and L-tryptophan) and precursors to the folate coenzymes.[1] The focus of attention on the shikimate pathway has been heightened by the fact that this pathway is inoperative in mammals.[2] Consquently the design and synthesis of inhibitors of the enzymes found on this pathway with the specific aims of developing new herbicidal and antimicrobial agents[3] has been invigorated. The most potent inhibitor of this biosynthetic pathway is glyphosate (*N*-phosphonomethylglycine), which specifically inhibits 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase, the sixth enzyme of the shikimate pathway.[4] The recent finding that the shikimate pathway is also operative in apicomplexan parasites,



further adds to the urgency to discover and develop inhibitors as antiparasitic agents.

The synthesis of shikimic acid **1** and its analogues has been an active area of research and considerable emphasis has been devoted to the functionalisation of the ring.[6] Amongst all the analogues of shikimic acid, (6*S*)-6-fluoroshikimic acid **2** has been found to exhibit the most potent antibacterial properties and additionally it has been very useful as a mechanistic probe for studying the enzymology of the shikimate pathway.[7] The synthesis of (6*S*)-6-fluoroshikimic acid **2** from quinic acid and from the *cis*-dihydrodiols,[6c,8] has been reported but are somewhat lengthy. Abell et al.[9] have recently reported an enzymatic synthesis of **2** from 3-fluorophosphoenolpyruvate.

Our approach for the synthesis of **2** uses (−)-shikimic acid as the enantiomerically pure starting material for the synthesis of diene **8**. The access to such dienes has been recently enhanced by the ability to engineer microbial cells. Genetic engineering of *Escherichia coli*. has resulted in the production of (*S*,*S*)-2,3-dihydroxy-2,3-dihydrobenzoic **4** acid in a high yielding process and represents an attractive alternative starting point for synthesis.

Due to the prohibitive commercial price of (−)-shikimic acid **1** we isolated it from Chinese star anise (*Illicium verum* Hook) in fairly large quantities.[6d,12,13] Esterification of **1** in refluxing methanol with a catalytic amount of camphorsulfonic acid produced the crystalline methyl ester **5**,[14] which was used directly for the next reaction, alternatively it could be further purified by recrystallisation from ethyl acetate. Treatment of the methyl ester **5** with 2,2-dimethoxypropane in the presence of camphorsulfonic acid gave the acetonide **6**[15] in 91% overall yield (Scheme 1). The hydoxyl group in the acetonide **6** was reacted with trifluoromethanesulfonic

* Corresponding author. Tel.: +44 191 515 3094; fax: +44 191 515 3148; e-mail: gurdial.singh@sunderland.ac.uk

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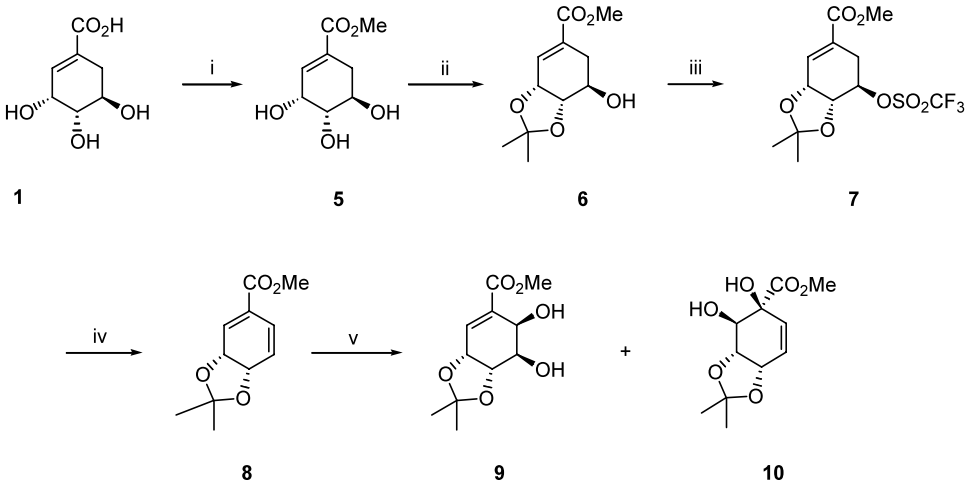
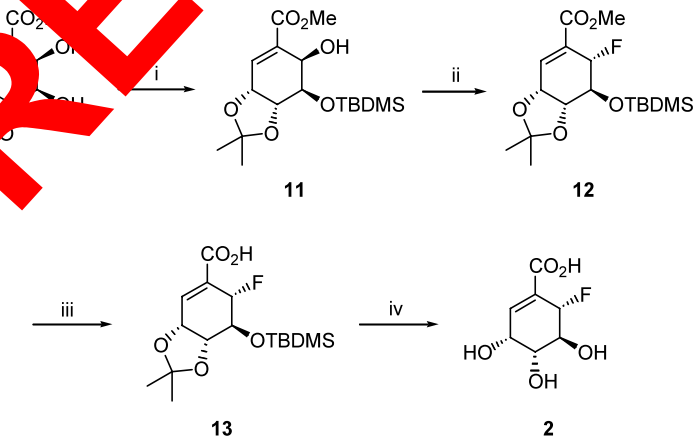


Scheme 1. *Reagents and conditions*: i, CSA, MeOH, reflux, 10 h, 96%; ii, $CMe_2(OMe)_2$, CSA, rt, 2 h, 95%; iii, Tf_2O, DMAP, pyridine, CH_2Cl_2, –40°C, 40 min, 98%; iv, CsOAc, DMF, rt, 2 h, 81%; v, OsO_4, NMO, *t*-BuOH–H_2O (1:1), 0°C, rt, 8 h, 38% for **9**, 35% for **10**.

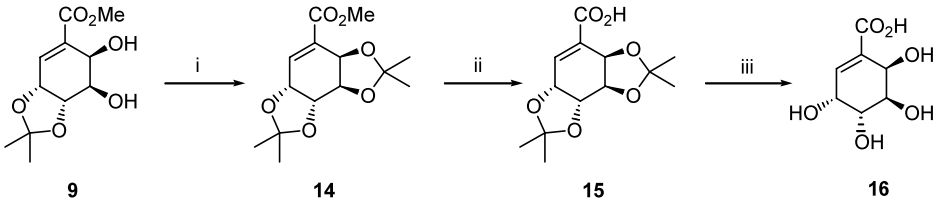
anhydride with pyridine and a catalytic amount of DMAP to afford the triflate **7** in 98% yield. The triflate **7** was relatively stable, however it decomposes slowly during prolonged storage at 4°C yielding a black residue. Treatment of triflate **7** with cesium acetate in DMF at room temperature gave the diene **8** in 81% yield.[16] We found that the elimination of the triflate group was complete after 2 h. The diene **8** proved to be somewhat unstable in that prolonged reaction time 18h or warming of the reaction mixture invariably led further elimination affording methyl 3-hydroxybenzoate as the only product. Dihydroxylation of the diene **8** with *N*-methylmorpholine *N*-oxide and a catalytic amount of osmium tetroxide gave the diols **9** and **10** (ratio 1:1) which were separated by flash chromatography in a combined yield of 75%.

Selective protection of the diol **8** with *tert*-butyldimethylsilyl triflate gave the monosilyl ether **11** (78%) as colourless crystals (Scheme 2). Treatment of silyl ether **11** with an excess of *N*,*N*-diethylaminosulfur trifluoride (DAST) at room temperature afforded exclusively[17] the fluoride (6*S*)-6-fluoromethylshikimate **12** in 92% yield. The methyl ester group of **12** was hydrolysed with lithium hydroxide to afford acid **13** in 92% yield. Removal of both the *tert*-butyldimethylsilyl and isopropylidene functionality with aqueous trifluoroacetic acid resulted in the formation of the desired (6*S*)-6-fluoroshikimic acid **2** in 88% yield whose spectroscopic data were in accord with those reported in the literature.[6a,b]

Protection of the diol **9** gave the (6*R*)-6-hydroxyshikimic acid **16** (Scheme 3). For the removal of the protecting group to proceed in an efficient manner we found it necessary to first convert **9** to the diacetonide **14** (95%). Subsequent hydrolysis with lithium hydroxide afforded the acid **15** (99%). Although flash chromatography had been used to purify the acid **15**,[8b] in our hands we found that it was somewhat labile to silica gel. As a result of these observations we proceeded with the removal of the acetonide functions of the acid **15**, used without further purification, followed by treat-



Scheme 2. *Reagents and conditions*: i, TBDMSOTf (1.05 equiv.), Et_3N, CH_2Cl_2, –78°C, 50 min, 78%; ii, DAST, CH_2Cl_2, rt, 4 h, 92%; iii, LiOH, dioxane–H_2O (1:1), rt, 1 h, 92%; iv, TFA–H_2O (9:1), rt, 2 h, 88%.



Scheme 3. *Reagents and conditions*: i, $CMe_2(OMe)_2$, CSA, rt, 3 h, 98%; ii, LiOH, THF–H_2O (1:4), rt, 1 h, 99%; iii, aq. HCl, MeOH, 30 h, 91%.

ment with aqueous hydrochloric acid to obtain **16**[8b] in 91% yield.

In conclusion, we have devised a short and efficient synthesis of (6*S*)-6-fluoroshikimic acid **2** and (6*R*)-6-hydroxyshikimic acid **16**. These compounds are useful tools for biologists to study the enzymes in the shikimate pathway, and they can also be further elaborated into other synthetic targets.

1. Experimental

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. IR spectra were recorded on a UNICAM Research series FT-IR instrument. ^{1}H NMR spectra were obtained on JEOL JNM GSX 270 and Bruker DRX 500 spectrometers. ^{13}C NMR spectra were obtained on the JEOL JNM-GSX 270 instrument operating at 67.8 MHz with proton decoupling. Chemical shifts were measured relative to tetramethylsilane (δ TMS = 0) using either tetramethylsilane or the solvent as internal reference. All the coupling constants, *J* values, are given in Hz. Unless otherwise stated, solutions in deuterochloroform were used for the determination of NMR spectra. Mass spectra were recorded by EPSRC Mass Spectrometry Service Centre at Swansea using a Micromass Quattro II low resolution triple quadrupole mass spectrometer and a Finnigan MAT 900 XL high resolution double focussing mass spectrometer. Microanalyses were performed by MEDAC Ltd. Optical rotations were measured at room temperature using a Bellingham & Stanley ADP 220 digital polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Flash chromatography was performed on Fluka silica gel 60 (220–440 mesh), and the solvent petroleum ether (petrol) refers to the fraction boiling in the range of 40–60°C was distilled prior to use. Thin layer chromatography was carried out using pre-coated aluminium plates (Merck Kieselgel 60 F_{254}) which were visualised with UV light and then with either basic aqueous potassium permanganate or acidic ammonium molybdate as appropriate. All commercially available reagents and solvents were dried and purified according to standard procedures. Reactions requiring anhydrous conditions were performed in oven-dried apparatus under argon or nitrogen.

1.1. Methyl (3*R*,4*S*,5*R*)-3,4-isopropylidenedioxy-5-trifluoromethanesulfonyloxycyclohexa-1,5-diene-1-carboxylate 7

To a cooled solution (–40°C) of the acetonide **6** (2.14 g, 9.39 mmol) in dichloromethane (50 ml), DMAP (100 mg, 0.82 mmol) and pyridine (2.3 ml, 28.2 mmol) were added. To the stirred trifluoromethanesulfonic anhydride (3.16 ml, 18.8 mmol) was added dropwise. The reaction mixture was stirred at –40°C for a further 1 h before being allowed to warm to room temperature, diluted with dichloromethane (50 ml), and washed with water (80 ml). The aqueous layer was extracted with dichloromethane (2×80 ml), the combined organic extracts were dried (Na_2SO_4) and evaporated to afford a residual oil which was purified by column chromatography on silica gel with petrol–diethyl ether (3:1) as eluent to give the triflate **7** (3.32 g, 98%) as a colourless oil, $[\alpha]_D = -71.4$ (*c* 0.64, $CHCl_3$); ν_{max} (film)/cm^{-1} 2992, 2954, 1724, 1658, 1415, 1245, 1214 and 1145; δ_H (270 MHz) 1.42 (3 H, s), 1.46 (3 H, s), 2.62 (1 H, ddt, *J* 17.8, 8.6, 2.0), 3.05 (1 H, dd, *J* 17.8, 4.6), 3.80 (3 H, s), 4.31 (1 H, dd, *J* 7.6, 6.3), 4.81–4.85 (1 H, m), 5.01 (1 H, dt, *J* 7.9, 4.6), 6.99 (1 H, q, *J* 1.3); δ_C (67.8 MHz) 25.74, 27.48, 28.01, 52.44, 72.25, 74.23, 85.44, 111.07, 128.92, 134.03 165.43 (Note: the CF_3 resonance was not observed due to fluorine coupling).

1.2. Methyl (3*R*,4*S*)-3,4-isopropylidenedioxycyclohexa-1,5-diene-1-carboxylate 8

Cesium acetate (1.81 g, 9.43 mmol) was added to a solution of triflate **7** (3.09 g, 8.58 mmol) in DMF (4 ml). The reaction mixture was stirred at room temperature for 2 h, and then partitioned between light petrol (60 ml) and water (60 ml). The aqueous layer was extracted with petrol (2×50 ml), the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with petrol–diethyl ether (5:1) as eluent to afford the diene **7** (1.46 g, 81%) as a colourless oil, δ_H (270 MHz) 1.39 (3 H, s), 1.41 (3 H, s,), 3.80 (3 H, s), 4.65 (1 H, ddd, *J* 9.9, 4.0, 0.7), 4.82 (1 H, dddd, *J* 9.2, 4.0, 2.0, 0.7), 6.04 (1 H, dd, *J* 9.9, 4.0), 6.54 (1 H, d, *J* 9.9) and 6.85–6.87 (1 H, m); δ_C (67.8 MHz) 24.36, 26.38, 51.89, 69.27, 70.43, 105.23, 122.03, 125.27, 126.67, 133.32, 165.40.

1.3. Methyl (3*R*,4*R*,5*R*,6*R*)-5,6-dihydroxy-3,4-isopropylidenedioxycyclohex-1-ene-1-carboxylate 9 and methyl (1*S*,2*R*,3*S*,4*S*)-1,2-dihydroxy-3,4-isopropylidenedioxycyclohex-5-ene-1-carboxylate 10

To a solution of diene **8** (2.92 g, 13.88 mmol) in *tert*-butanol (18 ml) and water (2 ml) at 0°C were added *N*-methylmorpholine *N*-oxide (1.95 g, 16.65 mmol) and osmium tetroxide (100 mg, 0.39 mmol). The mixture was stirred at 0°C for 8 h. Aqueous sodium thiosulfate was added, the mixture was stirred at room temperature for 30 min and then filtered through Celite. The filtrate was diluted with water (30 ml) and extracted with ethyl acetate (3×80 ml). The organic phases were combined and dried (Na_2SO_4). Concentration under reduced pressure followed by column chromatography of the residue using petrol–ethyl acetate (2:3) as eluent afforded the diol **9** (1.29 g, 38%) and diol the **10** (1.18 g, 35%) as colourless solids. Both diols were recrystallised (separately) from petrol–diethyl ether and gave colourless crystals. Data for **9**: m.p. 97–99°C; $[\alpha]_D=-31.3$ (*c* 0.80, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3436, 2987, 2940, 2917, 1716, 1656, 1434, 1380, 1268, 1205, 1162, 1041; δ_H (270 MHz) 1.40 (3 H, s), 1.43 (3 H, s), 3.55–3.62 (1 H, br s), 3.81 (3 H, s), 3.93–3.98 (1 H, m), 4.10–4.14 (1 H, br s), 4.45 (1 H, t, *J* 6.6), 4.68 (1 H, br s), 4.83 (1 H, dd, *J* 5.9, 3.3), 6.95 (1 H, d, *J* 3.3); δ_C (67.8 MHz) 25.42 (Me), 27.59, 52.25, 65.22, 70.69, 71.91, 75.17, 109.85, 131.30, 136.85, 166.54; *m*/*z* HRMS (CI, NH_3), Found: MNH_4^+ 262.1288, $C_{11}H_{20}NO_6$ requires 262.1291. Microanalysis: Found: C, 54.07; H, 6.67. $C_{11}H_{16}O_6$ requires C, 54.09; H, 6.60%. Data for **10**: m.p. 91–92°C; $[\alpha]_D=+82.7$ (*c* 1.05, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3436, 2998, 2981, 2948, 2931, 1743, 170[illegible] 1440, 1380, 1245, 1137, 1035; δ_H (270 MHz) 1.41 ([illegible]H, s), 1.53 (3 H, s), 3.24 (1 H, d, *J* 6.6), 3.84 (3[illegible] s), 3.95–4.05 (1 H, m), 4.03 (1 H, s), 4.33 (1 H, [illegible], *J* 6.6), 4.73–4.77 (1 H, m), 5.89 (1 H, d, *J* 9.9[illegible].11 (1 H, dd, *J* 9.9, 4.0); δ_C (67.8 MHz) 25.32, [illegible] 53.33, 72.35, 72.88, 74.56, 76.14, 109.97, 127.98, [illegible]9.41, 173.99; *m*/*z* HRMS (CI, NH_3), Found: M[illegible]H_4^+ 262.1289, $C_{11}H_{20}NO_6$ requires 262.[illegible]91. Microanalysis: Found: C, 54.06; H, 6.67. $C_{11}H_{[illegible]}$ requires C, 54.09; H, 6.60%.

1.4. Methyl (3*R*,4*R*,5*R*,6*R*)-5-*tert*-butyldimethylsilyloxy-6-hydroxy-3,4-isopropylidenedioxycyclohex-1-ene-1-carboxylate 11

tert-Butyldimethylsilyl trifluoromethanesulfonate (0.76 ml, 3.3 mmol) was added dropwise to a stirred solution of diol **9** (767 mg, 3.14 mmol) and triethylamine (0.88 ml, 6.28 mmol) in dichloromethane (60 ml) at −78°C, the reaction mixture was stirred at −78°C for 50 min, and was then quenched with water (40 ml). The mixture was allowed to warm to room temperature and extracted with dichloromethane (3×40 ml). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness. Chromatography of the residue on silica gel with petrol–diethyl ether (3:1) gave the monosilyl ether **10** (878.3 mg, 78%) as a white solid, which was recrystallised from petrol as colourless crystals, m.p. 66–67.5°C; $[\alpha]_D=-79.3$ (*c* 0.92, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3521, 3444, 2954, 2927, 2894, 2856, 1716, 165, 1276, 1251, 1209, 1126, 1051; δ_H (270 MHz) 0.12 (3 H, s), 0.16 (3 H, s), 0.93 (9 H, s), 1.38 (3 H, s), 1.45 (3 H, s), 2.85 (1 H, d, *J* 2.0), 3.77 (1 H, dd, *J* 7.3, 3.3), 3.81 (3 H, s), 4.32 (1 H, t, *J* 7.3), 4.54 (1 H, dd, *J* 3.3, 2.0), 4.84 (1 H, dd, *J* 7.3, 3.3), 7.03 (1 H, d, *J* 3.3); δ_C (67.8 MHz) (4.94, (4.51, 18.02, 25.23, 25.75, 27.59, 52.24, 66.36, 72.52, 73.12, 75.84, 109.57, 131.99, 137.48, 165.94; *m*/*z* HRMS (CI, NH_3). Found: MH^+ 359.1894, $C_{17}H_{31}O_6Si$ requires 359.1890. Microanalysis: Found: C, 57.06; H, 8.51. $C_{17}H_{30}O_6Si$ requires C, 56.95; H, 8.43%).

1.5. Methyl (3*R*,4*R*,5*S*,6*S*)-5-*tert*-Butyldimethylsilyloxy-6-fluoro-3,4-isopropylidenedioxycyclohex-1-ene-1-carboxylate 12

N,*N*-Diethylaminosulfur trifluo[illegible]e (1.80 [illegible]ml, 13.59 mmol) was added to a sol[illegible]on o[illegible]e m[illegible]osilyl ether **11** (590 mg, 1.65 mmol)[illegible] dichlore[illegible]ane (25 ml). The reaction mixture [illegible]s sti[illegible]d at ro[illegible]m temperature for 4 h, then quench[illegible] w[illegible]ater ([illegible] ml). The aqueous phase was extract[illegible] with [illegible]hlo[illegible]methane (3×50 ml). The combined [illegible]nic extra[illegible] were dried (Na_2SO_4) and concentra[illegible]d u[illegible]r reduced pressure. Chromatography on silica gel w[illegible] petrol–diethyl ether (5:1) as eluent yi[illegible]d the title co[illegible]pound **12** (547.2 mg, 92%) as a colo[illegible]ess oil, $[\alpha]_D=+41.1$ (*c* 1.22, $CHCl_3$); ν_{max} (film)/c[illegible]$^{-1}$ 2954, [illegible]31, 2857, 1731, 1664, 1463, 1371, 1249, 11[illegible] 1072, [illegible]0; δ_H (270 MHz) 0.13 (6 H, s), 0.86 ([illegible] H, s), 1.4[illegible], s), 3.84 (3 H, s), 4.24 (1 H, t, *J* 4.6), [illegible] (1 H), 4.68–4.74 (1 H, m), 5.15 (1 H, d, J_{FH} [illegible]2), [illegible].02 (1 H, m); δ_C (67.8 MHz) −5.08, 17.90, 25[illegible]26.35, 27.86, 52.27, 68.89 (d, J_{FC} 25.96), 71.15 (d, J_{FC} [illegible]08), 74.62 (d, J_{FC} 2.08), 84.42 (d, J_{FC} 174.46), 111.[illegible], 127.06 (d, J_{FC} 17.65), 139.50 (d, J_{FC} 6.23), [illegible]59 *m*/*z* HRMS (CI, NH_3), Found: MNH_4^+ 378.2109, $C_{17}H_{33}FNO_5Si$ requires 378.2112.

1.6. (3*R*,4*R*,5*S*,6*S*)-5-*tert*-Butyldimethylsilyloxy-6-fluoro-3,4-isopropylidenedioxycyclohex-1-ene-1-carboxylic acid 13

Lithium hydroxide (127 mg, 5.3 mmol) was added to a solution of ester **12** (190.2 mg, 0.53 mmol) in dioxane (1 ml) and water (1 ml). The reaction mixture was stirred at room temperature for 1 h, diluted with water (15 ml) and diethyl ether (20 ml), and acidified with Amberlite IR-120(plus) ion-exchange resin. After stirring for 15 min, the mixture was filtered and the filtrate was extracted with diethyl ether (2×60 ml). The combined ethereal extracts were dried (Na_2SO_4) and evaporated to afford the acid **13** (169 mg, 92%) as an oil, $[\alpha]_D=+44.4$ (*c* 0.63, $CHCl_3$); ν_{max} (film)/cm^{-1} 2956, 2931, 2892, 2857, 1725, 1660, 1455, 1382, 1255, 1122; δ_H (270 MHz) 0.13 (3 H, s), 0.14 (3 H, s), 0.87 (9 H, s), 1.40 (6 H, s), 4.26 (1 H, dd, *J* 5.3, 4.6), 4.43 (1 H, ddd, *J* 10.6, 4.6, 3.3), 4.74 (1 H, dd, *J* 8.9, 3.6), 5.15 (1 H, dd, J_{FH} 46.2, *J* 3.6), 7.08 (1 H, t, *J* 2.6), 8.00–8.50 (1 H, br s); δ_C (67.8 MHz) (5.17, 17.82, 25.46, 26.24, 27.74, 68.83 (d, J_{FC} 25.96), 71.10 (d, J_{FC} 2.07), 74.55, 84.08 (d, J_{FC} 174.45), 111.11, 126.82 (d, J_{FC} 17.66), 140.87 (d, J_{FC} 6.23), 168.77; *m*/*z* HRMS (ES). Found: M^+-H 345.1541, $C_{16}H_{26}FO_5Si$ requires 345.1533.

1.7. (3*R*,4*R*,5*S*,6*S*)-6-Fluoro-3,4,5-trihydroxycyclohex-1-ene-1-carboxylic acid 2

The acid **13** (150 mg, 0.43 mmol) was dissolved in trifluoroacetic acid (3.6 ml) and water (0.4 ml), and the solution was stirred at room temperature for 2 h. The reaction mixture was evaporated to dryness, and the residue was co-evaporated repeatedly with absolute ethanol to give the acid **2** (72.7 mg, 88%) as a white solid, R_f 0.5 in ethyl acetate:acetic acid:water (4:1:1); δ_H (270 MHz, CD_3OD) 3.62 (1 H, dd, *J* 7.9, 4.6), 4.09 (1 H, ddd, J_{FH} 17.2, *J* 7.9, 4.6), 4.33–4.37 (1 H, m), 5.07 (1 H, dd, J_{FH} 47.5, 5.2) and 6.90 (1 H, d, *J* 4.0); δ_C (67.8 MHz, CD_3OD) 66.93 (d, J_{FC} 2.08), 70.58 (d, J_{FC} 6.23), 71.65 (d, J_{FC} 20.76), 90.38 (d, J_{FC} 172.38), 131.58 (d, J_{FC} 19.73), 141.50 (d, J_{FC} 6.23), 168.39.

1.8.Methyl(3*R*,4*R*,5*R*,6*R*)-3,4:5,6-bis(isopropylidenedioxy)-cyclohex-1-ene-1-carboxylate 14

To a solution of diol **9** (298.7 mg, 1.22 mmol) in 2,2-dimethoxypropane (15 ml) was added 10-camphorsulfonic acid (170 mg, 0.73 mmol). The reaction mixture was stirred at room temperature for 2 h. Saturated aqueous sodium hydrogen carbonate (40 ml) was added, and the mixture was extracted with ethyl acetate (3×50 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to leave a residue which was purified by column chromatography on silica gel with petrol–diethyl ether (3:1) as eluent to give the diacetonide **14** (340 mg, 98%) as a colourless oil, $[\alpha]_D$ = +41.9 (*c* 0.86, $CHCl_3$); ν_{max} (film)/cm^{-1} 2987, 2935, 1727, 1662, 1371, 1247, 1060; δ_H (500 MHz) 1.34 (3 H, s), 1.35 (3 H, s), 1.40 (3 H, s), 1.43 (3 H, s), 3.85 (3 H, s), 4.61 (1 H, ddd, *J* 4.9, 3.0, 1.2), 4.68–4.70 (2 H, m), 4.99 (1 H, d, *J* 6.0) and 6.75 (1 H, dd, *J* 2.4, 1.2); δ_C (67.8 MHz) 25.86, 26.24, 27.54, 27.83, 52.21, 69.08, 70.57, 72.29, 73.45, 109.19, 109.68, 129.00, 136.75, 166.43; *m*/*z* HRMS (CI, NH_3). Found: MNH_4^+ 302.160[illegible] $C_{14}H_{24}NO_6$ requires 302.1604.

1.9. (3*R*,4*R*,5*R*,6*R*)-3,4:5,6-Bis(isopropylidene[illegible]ox[illegible] cyclohex-1-ene-1-carboxylic acid 15

Lithium hydroxide (105 mg, 4.38 mmol) was added to a solution of diacetonide **14** (161 mg, 0[illegible] mmol) in THF (1 ml) and water (4 ml). The reaction mixture was stirred at room temperature for [illegible] diluted with water (10 ml) and diethyl ether (2[illegible] ml), and acidified with Amberlite IR-120(plus) ion [illegible] resin. After stirring for 15 min, the mixture was filtered and the filtrate was extracted with diethyl ether (3×30 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford **15** (150 mg, 99%) as a colourless oil, $[\alpha]_D$ = +61.7 δ_c 1.5, $CHCl_3$) [lit.,[8b] $[\alpha]_D$ = +50.9 (*c* 0.122, $CHCl_3$)]; ν_{max} (film)/cm^{-1} 2989, 2935, 1702, 1656, 1373, 1226, 1060; δ_H (270 MHz) 1.25 (3 H, s), 1.28 (3 H, s), 1.32 (3 H, s), 1.34 (3 H, s), 4.52–4.55 (1 H, m), 4.61–4.64 (2 H, m), 4.89 (1 H, d, *J* 5.9), 6.78 (1 H, d, *J* 2.0), 8.00–9.00 (1 H, br s); δ_C (67.8 MHz) 25.84, 26.24, 27.54, 27.80 (4 C, 2×C*Me*$_2$), 68.84, 70.52, 72.26, 73.35 (4 C, 4×CHOR), 109.40, 109.83, 128.48, 138.67, 170.52; *m*/*z* HRMS (CI, NH_3). Found: MNH_4^+ 288.1445, $C_{13}H_{22}NO_6$ requires 288.1447.

1.10. (3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetrahydroxycyclohex-1-ene-1-carboxylic acid 16

Concentrated hydrochloric acid (3 drops) was added to a solution of acid **15** (150 mg, 0.56 mmol) in methanol (5 ml) and water (5 ml). The reaction mixture was stirred at room temperature for 30 h, and concentrated under reduced pressure to dryness. The residue was co-evaporated repeatedly with absolute ethanol to give the acid **16** (95 mg, 91%) as a white solid, R_f 0.47 in ethyl acetate:acetic acid:water (4:1:1); $[\alpha]_D$ = −172.6 (*c* 0.95, MeOH) [lit.,[8b] $[\alpha]_D$ = −169 (*c* 0.23, MeOH)]; ν_{max} (KBr)/cm^{-1} 3369, 2929, 2984, 1704, 1652, 1409, 1249, 1095; δ_H (270 MHz, CD_3OD) 3.87 (1 H, dd, *J* 9.2, 4.0), 3.95 (1 H, dd, *J* 9.2, 4.0), 4.39 (1 H, dd, *J* 4.6, 4.0), 4.62 (1 H, d, *J* 4.0), 6.87 (1 H, d, *J* 4.0); δ_C (67.8 MHz, CD_3OD) 66.99, 67.19, 70.00, 70.38, 133.93, 140.46, 169.44. *m*/*z* HRMS (ES). Found: [illegible] 189.0397, $C_7H_9O_6$ requires 189.0399.

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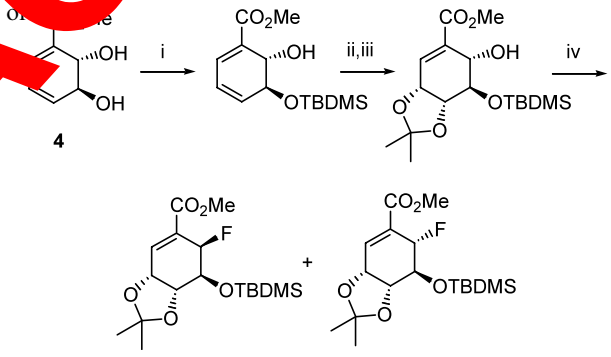
References

1. (a) [illegible]lam, E. *Shikimic Acid, Metabolism and Metabo-*[illegible] John Wiley & Sons: Chichester, 1993; (b) Abell, C. In *Comprehensive Natural Products Chemistry*; Barton, D. H. R.; Nakanishi, K.; Meth-Cohn, O.; Sankawa, U., Eds. Enzymology and Molecular Biology of the Shikimate Pathway; Elsevier: Amsterdam, 1999; Vol. 1, pp. 573–607.
2. Kishore, G. M.; Shah, D. M. *Annu. Rev. Biochem.* **1988**, *57*, 627–663.
3. Jiang, S.; Singh, G. *Tetrahedron* **1998**, *54*, 4697–4753.
4. Franz, J. E.; Mao, M. K.; Sikorski, J. A. *Glyphosate: A Unique Global Herbicide*; Americal Chemical Society: Washington, DC, 1997.
5. (a) Roberts, F.; Roberts, C. W.; Johnson, J. J.; Kyle, D. E.; Krell, T.; Coggins, J. R.; Coombs, G. H.; Milhous, W. K.; Tzipori, S.; Ferguson, D. J. P.; Chakrabarti, D.; McLeod, R. *Nature* **1998**, *393*, 801–805; (b) Keeling, P. J.; Palmer, J. D.; Donald, R. G. K.; Roos, D. S.; Waller, R. F.; McFadden, G. I. *Nature* **1999**, *397*, 219–220; (c) Roberts, C. W.; Finnerty, J.; Johnson, J. J.; Roberts, F.; Kyle, D. E.; Krell, T.; Coggins, J. R.; Coombs, G. H.; Milhous, W. K.; Tzipori, S.; Ferguson, D. J. P.; Chakrabarti, D.; McLeod, R. *Nature* **1999**, *397*, 220.
6. (a) Sutherland, J. K.; Watkins, W. J.; Bailey, J. P.; Chapman, A. K.; Davies, G. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1386–1387; (b) Sutherland, J. K.; Whitehead, R. C.; Davies, G. M. *J. Chem. Soc., Chem. Com-*

mun. **1993**, 464–465; (c) Blacker, A. J.; Booth, R. J.; Davies, G. M.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2861–2870; (d) Adams, H.; Bailey, N. A.; Brettle, R.; Cross, R.; Frederickson, M.; Haslam, E.; MacBeath, F. S.; Davies, G. M. *Tetrahedron* **1996**, *52*, 8565–8580; (e) Brettle, R.; Cross, R.; Frederickson, M.; Haslam, E.; MacBeath, F. S.; Davies, G. M. *Tetrahedron* **1996**, *52*, 10547–10556; (f) Jiang, S.; Singh, G.; Boam, D. J.; Coggins, J. R. *Tetrahedron: Asymmetry* **1999**, *10*, 4087–4090.

7. (a) Davies, G. M.; Barrett-Bee, K. J.; Jude, D. A.; Lehan, M.; Nichols, W. W.; Pinder, P. E.; Thain, J. L.; Watkins, W. J.; Wilson, R. G. *Antimicrob. Agents Chemother*. **1994**, *38*, 403–406; (b) Ewart, C. D. C.; Jude, D. A.; Thain, J. L.; Nichols, W. W. *Antimicrob. Agents Chemother*. **1995**, *39*, 87–93; (c) Jude, D. A.; Ewart, C. D. C.; Thain, J. L.; Davies, G. M.; Nichols, W. W. *Biochim Biophys. Acta* **1996**, *1279*, 125–129.
8. (a) Carless, H. A.; Dove, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 649–652; (b) Tran, C. H.; Crout, D G.; Errington, W.; Whited, G. M. *Tetrahedron: ymm y* **1996**, *7*, 691–698.
9. Duggan, P. J.; Parker, E.; Coggins, J.; bell, oorg. *Med. Chem. Lett*. **1995**, *5*, 2347–2352.
10. Song, C.; Jiang, S.; Singh, G. *Tetra Lett*. **200 2**, 9069–9071.
11. Franke, D.; Sprenger, G. A.; ller, M. *A Chem., Int. Ed*. **2001**, *40*, 555–557.
12. Grewe, R.; Lorenzen, W. em. **1953**, *86*, 928–938.
13. Shikimic acid has been pro by fe entation using recombinant *E. coli* Drat K .; Knop, D. R.; Frost, J. W. *J. A Ch Soc.* **9**, *121*, 1603–1604. This methodolo as b to produce shikimic acid on a large indust ale for the manufacture of the Gilead/Roche antiinfluenza drug Tamiflu™ (oseltamivir phosphate), see: Karpf, M di, R. *J. Org. Chem*. **2001**, *66*, 2044–2051.
14. (a) Fleet, G. W. J.; Sh T. K. Warr, S. M. *J. Chem. Soc., Perki rans.* **984**, 05–908; (b) Meier, R.-M.; Tamm, C *Helv. Chim.* **1991**, *74*, 807–818.
15. Chahoua, L.; ltas M.; Gorrichon, L.; Tisnès, P.; Zedde, C. *Org m.* **19** *57*, 5798–5800.
16. Huntley F. M.; B.; Ganem, B. *Tetrahedron Lett*. 2031–20 .
17. The diene **4** be converted to **2** and **3** via selective tion of C- OH group, followed by reaction with smium tetraoxide. The DAST reaction of the C-6 hydroxy up rseulted in formation of both (6*R*)- and *S*)-shiki ates, in a 1:1 ratio, in a poor combined yield o



Reagents and conditions: i, TBDMSOTf (1.05 equiv.), Et_3N, CH_2Cl_2, −78°C; ii, OsO_4, NMO, *t*-BuOH–H_2O (10:1), 0°C to rt; iii, $CMe_2(OMe)_2$, CSA, rt; iv, DAST, CH_2Cl_2, rt, 16 h.