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Syntheses of (6*S*)-6-fluoro- and (6*R*)-6-hydroxyshikimic acids

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Abstract—(6*S*)-6-Fluoroshikimic acid **2** and (6*R*)-6-hydroxyshikimic acid **3** have been synthesised via an OsO_4-catalysed dihydroxylation of diene **6**, which was derived from (–)-shikimic acid **1**. © 2001 Elsevier Science Ltd. All rights reserved.

The shikimate pathway is the biosynthetic sequence that exists in plants, fungi and microorganisms to synthesise the aromatic amino acids (L-phenylalanine, L-tyrosine and L-tryptophan) from carbohydrates.[1] It has recently been discovered that the shikimate pathway is also present in apicomplexan parasites.[2] Since the shikimate pathway is absent from mammals,[3] enzymes along this pathway are therefore attractive targets for the development of antimicrobial agents against bacterial, fungal and parasitical pathogens. There have been increasing efforts to design and synthesise analogues of the shikimate pathway intermediates as potential enzyme inhibitors.[4] Shikimic acid **1** is a key intermediate in the shikimate pathway, and the synthesis of its analogues has been a particularly active area of research.[5] Among various analogues of shikimic acid, (6*S*)-6-fluoroshikimic acid **2** has been reported to have antibacterial properties and also to be useful as a mechanistic probe for studying the enzymology of the shikimate pathway.[6] Both (6*S*)-6-fluoroshikimic acid **2** and (6*R*)-6-hydroxyshikimic acid **3** have been previously synthesised in a lengthy synthesis from quinic acid[5a,b] as well as arene *cis*-dihydrodiols,[5c,7] with the derivatives of (6*R*)-6-hydroxyshikimic acid **3** being precursors for the synthesis of (6*S*)-6-fluoroshikimic acid **2**. An enzymatic synthesis of **2** from 3-fluorophosphoenolpyruvate on a small scale has also been reported.[8] However, with the intense interest shown in the shikimate pathway, there still exists an urgent need for the efficient synthesis of (6*S*)-6-fluoroshikimic acid **2** to cater for the mechanistic studies of the shikimate pathway, and in this communication we report our facile syntheses of (6*S*)-6-fluoroshikimic acid **2** and (6*R*)-6-hydroxyshikimic acid **3** using shikimic acid as the starting material.

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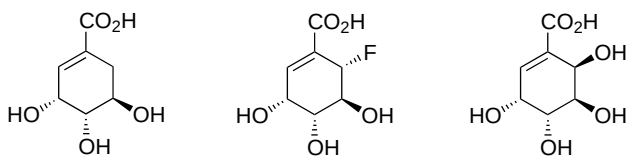
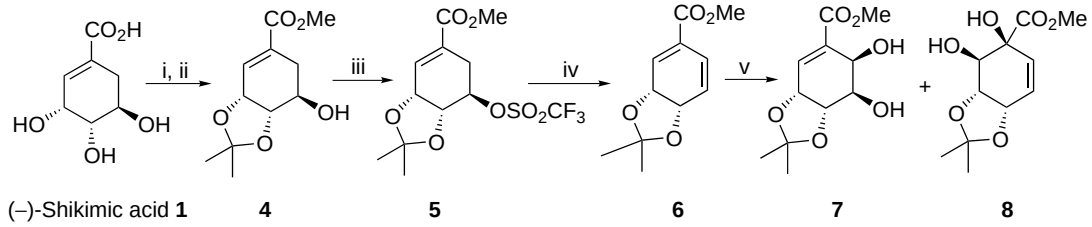
Esterification of (–)-shikimic acid[9] with methanol using a catalytic amount of camphorsulphonic acid produced the crystalline methyl ester, which was protected with 2,2-dimethoxypropane, also in the presence of camphorsulphonic acid, to give the acetonide **4**[10] in 91% overall yield (Scheme 1). Activation of the hydroxyl group in acetonide **4** with trifluoromethanesulphonic anhydride yielded the triflate **5** (98%). Treatment of triflate **5** with cesium acetate in DMF at room temperature produced the diene **6** in 81% yield.[11] After some experimentation, we found that the elimination of the triflate group was normally complete within 2 h, prolonged reaction time and heating up the reaction mixture invariably led to the diene **6** eliminating further to give methyl 3-hydroxybenzoate as the sole product. When a mesylate group was installed rather than the triflate group, the elimination reaction with cesium acetate in DMF either did not occur at room temperature or, when being heated, instead affording methyl 3-hydroxybenzoate. Catalytic dihydroxylation of the diene **6** with *N*-methylmorpholine *N*-oxide and osmium tetroxide gave the diols **7**,[12] mp 97–99°C, $[\alpha]_D$ –31.3 (*c* 0.80 in $CHCl_3$), and **8**, mp 91–92°C, $[\alpha]_D$ +82.7 (*c* 1.05 in $CHCl_3$), ratio 1:1, in 73% combined yield.



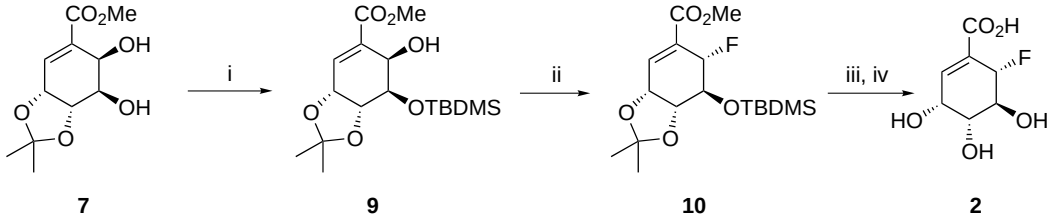
(–)-Shikimic acid **1** **2** **3**

Diol **7** was selectively protected with *tert*-butyldimethylsilyl triflate to give the monosilyl ether **9** (72%) as colourless crystals, mp 66–67.5°C, $[\alpha]_D$ –79.3 (*c* 0.92 in $CHCl_3$). Treatment of silyl ether **9** with an excess of *N*,*N*-diethylaminosulphur trifluoride (DAST)

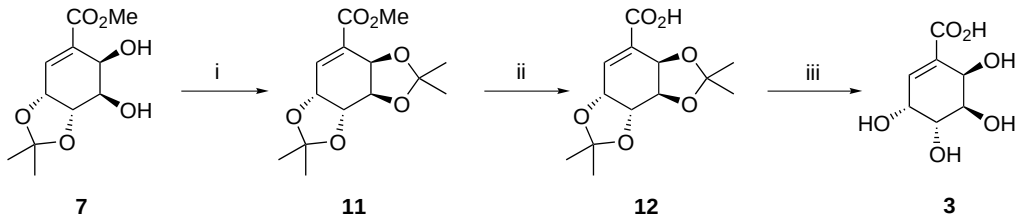
PII: S0040-4039(01)01976-1



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, −20°C, 40 min, 98%; (iv) CsOAc, DMF, rt, 2 h, 81%; (v) OsO_4, NMO, *t*-BuOH–H_2O (10:1), 20°C, 8 h, 38% for **7**, 35% for **8**.



Scheme 2. *Reagents and conditions*: (i) TBDMSOTf (1.05 equiv.), Et_3N, CH_2Cl_2, −20°C, 30 min, 72%; (ii) DAST, CH_2Cl_2, rt, 4 h, 92%; (iii) LiOH, dioxane–H_2O (1:1), rt, 1 h; (iv) TFA–H_2O (9:1), rt, 2 h, 81% for two steps.



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, 98%; (iii) aq. HCl, MeOH, 30 h, 91%.

at room temperature afforded the fluorinated compound **10** in 92% yield, $[\alpha]_D$ +41.1 (*c* 1.22 in $CHCl_3$) (Scheme 2). Hydrolysis of the methyl ester group in **10** with lithium hydroxide gave the free acid, which was further deprotected using aqueous trifluoroacetic acid to remove both the silyl and isopropylidene groups to furnish the desired (6*S*)-6-fluoroshikimic acid **2**[5a,b,8] in an overall yield of 65%.

Diol **7** could be directly deprotected to give the (6*R*)-6-hydroxyshikimic acid **3**. Here, for the convenience of isolating the free acid intermediate, diol **7** was first converted to the diacetonide **11** (98%), $[\alpha]_D$ +41.9 (*c* 0.86 in $CHCl_3$), which was then hydrolysed with lithium hydroxide and further deprotected with aqueous hydrochloric acid to afford the free acid **3** in 89% overall yield, $[\alpha]_D$ −172.6 (*c* 0.95 in MeOH) {lit.[7b] $[\alpha]_D$ −169 (*c* 0.23 in MeOH)} (Scheme 3).

In conclusion, we have demonstrated a short and efficient synthesis of (6*S*)-6-fluoroshikimic acid **2** and (6*R*)-6-hydroxyshikimic acid **3**. These compounds are useful tools for biologists to study the enzymes in the shikimate pathway.

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12. All new compounds reported were characterised (IR, ^{1}H and ^{13}C NMR, HRMS and/or elemental analyses). Selected data: Compound **7**: ν_{max} (KBr)/cm^{-1} 3436 (OH), 2987, 2940, 2917, 1716 (C=O), 1656 (C=C), 1434, 1380, 1268, 1205, 1162, 1041; δ_H (270 MHz, $CDCl_3$) 1.40 (3H, s, Me), 1.43 (3H, s, Me), 3.55–3.62 (1H, br s, OH), 3.81 (3H, s, CO_2Me), 3.93–3.98 (1H, m, C*H*OH), 4.10–4.14 (1H, br s, OH), 4.45 (1H, t, *J* 6.6 Hz, CHOR), 4.68 (1H, br s, C*H*OH), 4.83 (1H, dd, *J* 5.9 and 3.3 Hz, CHOR), 6.95 (1H, d, *J* 3.3 Hz, CH=C); δ_C (67.8 MHz, $CDCl_3$) 25.42 (Me), 27.59 (Me), 52.25 (CO_2*Me*), 65.22, 70.69, 71.91, 75.17 (CHOR), 109.85 (*C*Me$_2$), 131.30 (CH=*C*), 136.85 (*C*H=C), 166.54 (C=O). [*m*/*z* HRMS (CI, NH_3). Found: MNH_4^+ 262.1288, $C_{11}H_{20}NO_6$ requires 262.1291] (found: C, 54.07; H, 6.67. $C_{11}H_{16}O_6$ requires C, 54.09; H, 6.60%). Compound **10**: ν_{max} (neat film)/cm^{-1} 2954, 2931, 2857, 1731 (C=O), 1664 (C=C), 1463, 1371, 1249, 1108, 1072, 840; δ_H (270 MHz, $CDCl_3$) 0.13 (6H, s, SiMe$_2$), 0.86 (9H, s, CMe$_3$), 1.40 (6H, s, CMe$_2$), 3.84 (3H, s, CO_2Me), 4.24 (1H, t, *J* 4.6 Hz, CHOR), 4.37–4.45 (1H, m, CHOR), 4.68–4.74 (1H, m, CHOR), 5.15 (1H, d, J_{FH} 46.2 Hz, CHF), 6.95–7.02 (1H, m, C=CHR); δ_C (67.8 MHz, $CDCl_3$) −5.08 (SiMe$_2$), 17.90 (Si*C*Me$_3$), 25.54 (C*Me*$_3$), 26.35 (Me), 27.86 (Me), 52.27 (CO_2*Me*), 68.89 (d, J_{FC} 25.96 Hz, CHOR), 71.15 (d, J_{FC} 2.08 Hz, CHOR), 74.62 (d, J_{FC} 2.08 Hz, CHOR), 84.42 (d, J_{FC} 174.46 Hz, CHF), 111.08 (*C*Me$_2$), 127.06 (d, J_{FC} 17.65 Hz, CH=*C*), 139.50 (d, J_{FC} 6.23 Hz, *C*H=C), 165.59 (C=O) [*m*/*z* HRMS (CI, NH_3). Found: MNH_4^+ 378.2109, $C_{17}H_{33}FNO_5Si$ requires 378.2112].