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TETRAHEDRON: *ASYMMETRY*

Synthesis of 3-deoxy-3,3-difluoroshikimic acid and its 4-epimer from quinic acid

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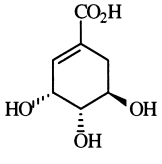
Abstract

3-Deoxy-3,3-difluoroshikimic acid **2** and its 4-epimer **3** as new analogues of shikimic acid have been synthesised from quinic acid in overall yields of 30% and 12%, respectively.

Shikimic acid **1** is an important intermediate in the biosynthetic sequence known as the shikimate pathway which operates in plants, fungi and microorganisms to convert carbohydrate precursors to essential aromatic α-amino acids (L-phenylalanine, L-tyrosine and L-tryptophan).[1] The lack of the shikimate pathway in mammals has spurred an intense search for specific enzyme inhibitors along the pathway as potential herbicides and antimicrobial agents, particularly following the discovery of *N*-phosphonomethylglycine which specifically inhibits the enzyme 5-enolpyruvylshikimate-3-phosphate synthase.[2] Very recently the existence of a functional shikimate pathway in apicoplexan parasites was reported,[3] which thus provides attractive targets for the development of new antiparasite agents. As a consequence of the interest shown in the pathway, increasing effort has been directed towards the synthesis of analogues of the pathway intermediates, particularly that of shikimic acid.[4] So far, the functionalisation of the cyclohexene ring of shikimic acid includes the introduction of 2-fluoro,[5,6] 2-bromo,[6] 2-chloro,[7] 3α-hydroxymethyl,[8] 3α-amino,[9,10] 3α- and 3β-fluoro,[11] 3β-chloro,[11b] 5β-amino,[12,13] 5β-hydroxymethyl,[14] 6α- and 6β-amino,[15] 6α- and 6β-fluoro,[15,16] 6β-hydroxy,[15,17,18] and 6β-mercapto[15] groups. In this communication, we describe the first examples of the synthesis of difluoro-substituted shikimic acids **2** and **3** from natural quinic acid.



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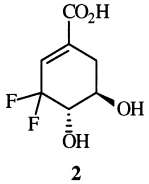

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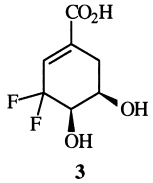

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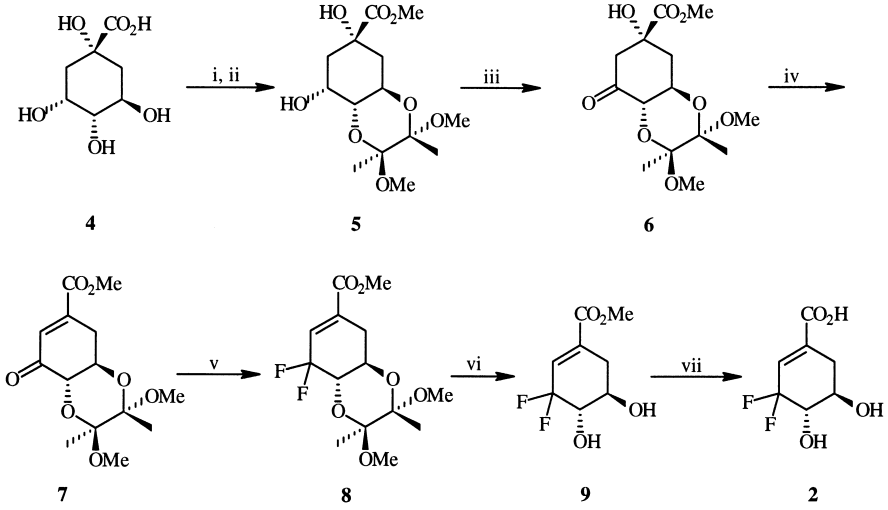
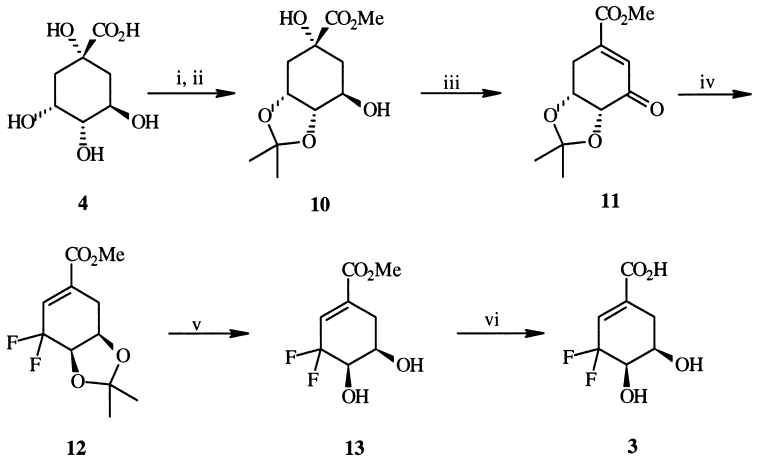
As a semi-detached member of the shikimate pathway, (−)-quinic acid **4** has been used extensively as a cheap chiral template for the synthesis of shikimic acid and analogues.[4] Recent developments in the protecting groups for *trans* diequatorial vicinal diols in carbohydrate chemistry[19] have enabled the selective protection of *trans*-4,5-dihydroxyl groups in quinic acid with 2,2,3,3-tetramethoxybutane to form the corresponding butane diacetal **5**[20] (Scheme 1). Oxidation of the remaining 3-hydroxyl group in **5** under Swern conditions gave the ketone **6** in 70% yield, m.p. 209–211°C, $[\alpha]_D$ +115.0 (*c* 0.55 in $CHCl_3$) {lit.[9] m.p. 212–214°C, $[\alpha]_D$ +82.7 (*c* 1.05 in $CHCl_3$)}, together with some spontaneous β-elimination product **7** (15%), m.p. 123.5–125°C, $[\alpha]_D$ +85.8 (*c* 1.28 in $CHCl_3$) {lit.[9] m.p. 98–99°C, $[\alpha]_D$ +73.3 (*c* 1.25 in $CHCl_3$)}.[21] Dehydration of ketone **6** was effected either by treatment with phosphorus oxychloride in pyridine (81%) or under normal acetylation conditions (85%). We have also found that the product of methoxymethylation of ketone **6** underwent rapid and complete elimination during chromatography on silica gel to give compound **7** in almost quantitative yield. *gem*-Difluorination of the α,β-unsaturated ketone **7** was achieved by using excess *N*,*N*-diethylaminosulphur trifluoride (DAST) in CH_2Cl_2 at room temperature to give compound **8**[22] (94%), $[\alpha]_D$ +75.8 (*c* 0.69 in $CHCl_3$), which was then treated with aqueous trifluoroacetic acid to remove the butane diacetal group to afford compound **9** (94%), $[\alpha]_D$ −100.1 (*c* 0.83 in $CHCl_3$). Hydrolysis (NaOH, H_2O) of the methyl ester **9** delivered the desired acid **2** (37%), m.p. 168.5–170°C, $[\alpha]_D$ −90.6 (*c* 0.76 in CH_3OH), and also protocatechuic acid (12%) which resulted from the elimination of hydrogen fluoride and subsequent aromatisation. An improved yield of 67% for acid **2** was achieved without aromatisation by treating the methyl ester **9** with potassium trimethylsilanolate.[23]



Scheme 1. Reagents and conditions: i, Dowex 50WX4-50 resin (H^+), methanol, reflux, 20 h; ii, 2,2,3,3-tetramethoxybutane, $CH(OMe)_3$, CSA (cat.), methanol, reflux, 20 h (84% for two steps); iii, DMSO, $(COCl)_2$, CH_2Cl_2, −78°C, 60 min, then Et_3N, −78°C to rt (70%); iv, $POCl_3$, pyridine, rt, 4 h (81%) or Ac_2O, DMAP (cat.), pyridine, rt, 10 h (85%); v, DAST, CH_2Cl_2, rt, 14 days (94%); vi, aq. TFA, rt, 1.5 h (94%); vii, NaOH, H_2O:THF (1:1), rt, 20 h, then Amberlite IR-120 (H^+) resin (37%) or $KOSiMe_3$, THF, rt, 20 h, then Amberlite IR-120 (H^+) resin (67%)

Having prepared 3-deoxy-3,3-difluoroshikimic acid **2**, we then looked at the synthesis of its 4-epimer from quinic acid (Scheme 2). By employing known literature procedures,[24] the α,β-unsaturated ketone **11** was obtained from quinic acid in three steps with an overall yield of 34%, m.p. 89–91°C, $[\alpha]_D$ −51.7 (*c* 1.20 in $CHCl_3$) {lit.[24d] m.p. 84–85°C, $[\alpha]_D$ −51.7 (*c* 0.5 in $CHCl_3$)}. Reaction of ketone **11** with excess of *N*,*N*-diethylaminosulphur trifluoride (DAST) produced the difluoroshikimate **12** (60%), $[\alpha]_D$ +22.3 (*c* 0.63 in $CHCl_3$), which was deprotected with aqueous trifluoroacetic acid to give compound **13**

(80%), $[\alpha]_D$ −37.9 (*c* 0.71 in $CHCl_3$). Further deprotection using potassium trimethylsilanolate furnished the free acid **3** (71%), m.p. 142–144°C, $[\alpha]_D$ −51.8 (*c* 1.41 in CH_3OH), together with 15% of eliminated and aromatised product which was identified as 3-fluoro-4-hydroxybenzoic acid, m.p. 220–221.5°C.



Scheme 2. Reagents and conditions: i, $CMe_2(OMe)_2$, *p*-TsOH (cat.), PhH, reflux, 18 h (80%); ii, NaOMe, methanol, rt, 4 h (78%); iii, PCC, 4 Å molecular sieve, pyridine, CH_2Cl_2, rt, 30 h (55%); iv, DAST, CH_2Cl_2, rt, 20 h (60%); v, aq. TFA, rt, 4 h (80%); vi, $KOSiMe_3$, THF, rt, 20 h, then Amberlite IR-120 (H^+) resin (71%)

Initial testing of acid **2** against the type II dehydroquinase from *M. tuberculosis*[25] showed active inhibition. More detailed biochemical studies on these compounds are currently under way, the results of which will be reported in due course.

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References

1. Haslam, E. *Shikimic Acid, Metabolism and Metabolites*; John Wiley & Sons: Chichester, 1993.
2. Grossbard, E.; Atkinson, D. *The Herbicide Glyphosate*; Butterworths: Boston, 1985.
3. 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.
4. For reviews, see: (a) Jiang, S.; Singh, G. *Tetrahedron* **1998**, *54*, 4697–4753; (b) Campbell, M. M.; Sainsbury, M.; Searle, P. A. *Synthesis* **1993**, 179–193.
5. Rich, R. H.; Bartlett, P. A. *J. Org. Chem*. **1996**, *61*, 3916–3919.
6. González-Bello, C.; Manthey, M. K.; Harris, J. H.; Hawkins, A. R.; Coggins, J. R.; Abell, C. *J. Org. Chem*. **1998**, *63*, 1591–1597.
7. Rich, R. H.; Lawrence, B. M.; Bartlett, P. A. *J. Org. Chem*. **1994**, *59*, 693–694.
8. Wood Jr., H. B.; Ganem, B. *Tetrahedron Lett*. **1993**, *34*, 1403–1406.
9. Alves, C.; Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 8443–8456.
10. (a) Brettle, R.; Cross, R.; Frederickson, M.; Haslam, E.; Davies, G. M. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 291–294; (b) Adams, H.; Bailey, N. A.; Brettle, R.; Cross, R.; Frederickson, M.; Haslam, E.; MacBeath, F. S.; Davies, G. M. *Tetrahedron* **1996**, *52*, 8565–8580.

11. (a) Brettle, R.; Cross, R.; Frederickson, M.; Haslam, E.; MacBeath, F. S.; Davies, G. M. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1275–1278; (b) Brettle, R.; Cross, R.; Frederickson, M.; Haslam, E.; MacBeath, F. S.; Davies, G. M. *Tetrahedron* **1996**, *52*, 10547–10556.
12. Pansegrau, P. D.; Anderson, K. S.; Widlanski, T.; Ream, J. E.; Sammons, R. D.; Sikorski, J. A.; Knowles, J. R. *Tetrahedron Lett*. **1991**, *32*, 2589–2592.
13. Marzabadi, M. R.; Gruys, K. J.; Pansegrau, P. D.; Walker, M. C.; Yuen, H. K.; Sikorski, J. A. *Biochemistry* **1996**, *35*, 4199–4210.
14. Campbell, M. M.; Mahon, M. F.; Sainsbury, M.; Searle, P. A. *Tetrahedron Lett*. **1991**, *32*, 951–954.
15. Sutherland, J. K.; Whitehead, R. C.; Davies, G. M. *J. Chem. Soc., Chem. Commun*. **1993**, 464–465.
16. Sutherland, J. K.; Watkins, W. J.; Bailey, J. P.; Chapman, A. K.; Davies, G. M. *J. Chem. Soc., Chem. Commun*. **1989**, 1386–1387.
17. Carless, H. A.; Dove, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 649–652.
18. Tran, C. H.; Crout, D. H. G.; Errington, W.; Whited, G. M. *Tetrahedron: Asymmetry* **1996**, *7*, 691–698.
19. Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Poisson, J.-F.; Warriner, S. L.; Wesson, K. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2023–2031 and references cited therein.
20. (a) Montchamp, J.-L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem*. **1996**, *61*, 3897–3899; (b) Tian, F.; Montchamp, J.-L.; Frost, J. W. *J. Org. Chem*. **1996**, *61*, 7373–7381; (c) Montchamp, J.-L.; Frost, J. W. *J. Am. Chem. Soc*. **1997**, *119*, 7645–7653.
21. Alternatively we have prepared the α,β-unsaturated ketone **7** directly from natural shikimic acid by sequential esterification, transacetalisation and oxidation. The key step was the transacetalisation in which methyl shikimate was treated with 2,2,3,3-tetramethoxybutane to form a separable mixture of the desired butane 2,3-diacetal (formed with the pseudo-*trans*-diequatorial 4,5-dihydroxyl groups in the shikimate) together with butane 2,2-diacetal (formed with the 3,4-dihydroxyl groups) in a ratio of 2:1.
22. All new compounds reported had spectral data in accord with the assigned structure and gave satisfactory elemental analyses and/or high resolution mass spectral data. Selected data: compound **2**: ν_{max} (KBr)/cm^{-1} 3394, 2927, 1712 (C=O), 1662 (C=C), 1430, 1295, 1164, 1114, 1014; δ_H (270 MHz, CD_3OD) 2.26 (1H, dm, *J* 18.47 Hz, C*H*HC=), 2.90 (1H, ddt, *J* 0.67, 18.47 and 4.61 Hz, CH*H*C=), 3.68–3.90 (2H, m, 2×C*H*OH), 6.63 (1H, apparent dt, *J* 7.91 and 2.64 Hz, CH=C); δ_C (67.8 MHz, CD_3OD) 33.41 (CH_2), 68.87 (d, J_{FC} 7.27 Hz, CH_2*C*HOH), 75.14 (dd, J_{FC} 19.73 and 20.77 Hz, CF_2*C*HOH), 121.30 (t, J_{FC} 237.80 Hz, CF_2), 130.00 (dd, J_{FC} 27.0 and 32.19 Hz, *C*H=C), 137.54 (dd, J_{FC} 10.38 and 11.43 Hz, CH=*C*), 168.14 (C=O); δ_F (254 MHz, $CDCl_3$) −103.4 (dm, J_{FF} 284.1 Hz), −105.4 (dm, J_{FF} 284.1 Hz) (found: C, 43.25; H, 4.07. $C_7H_8F_2O_4$ requires: C, 43.31; H, 4.15%). Compound **3**: ν_{max} (KBr)/cm^{-1} 3347, 2958, 2927, 1704 (C=O), 1654 (C=C), 1257, 1153, 1060, 1044; δ_H (270 MHz, CD_3OD) 2.38–2.54 (1H, m, C*H*HC=), 2.67 (1H, dm, *J* 18.47 Hz, CH*H*C=), 3.95–4.01 (2H, m, 2×C*H*OH), 6.61 (1H, dm, *J* 7.26 Hz, CH=C); δ_C (67.8 MHz, CD_3OD) 29.94 (CH_2), 68.03 (d, J_{FC} 6.23 Hz, CH_2*C*HOH), 72.25 (dd, J_{FC} 18.69 and 31.15 Hz, CF_2*C*HOH), 119.88 (dd, J_{FC} 233.13 and 242.50 Hz, CF_2), 129.01 (dd, J_{FC} 25.96 and 34.27 Hz, *C*H=C), 138.93 (t, J_{FC} 10.39 Hz, CH=*C*), 168.31 (C=O) [m/z HRMS (CI, NH_3). Found MNH_4^+, 212.0727; $C_7H_{12}F_2NO_4$ requires *MNH*$_4$, 212.0734]. Compound **8**: ν_{max} (film)/cm^{-1} 2996, 2954, 2911, 2838, 1731 (C=O), 1658 (C=C), 1438, 1373, 1303, 1265, 1230, 1118, 1037; δ_H (270 MHz, $CDCl_3$) 1.32 (3H, s, Me), 1.40 (3H, s, Me), 2.27–2.46 (1H, m, C*H*HC=), 2.90 (1H, dt, *J* 18.47 and 5.28 Hz, CH*H*C=), 3.28 (3H, s, OMe), 3.32 (3H, s, OMe), 3.81 (3H, s, CO_2Me), 3.87–4.09 (2H, m, 2×C*H*OR), 6.72 (1H, dt, *J* 8.57 and 2.64 Hz, CH=C); δ_C (67.8 MHz, $CDCl_3$) 17.48 (Me), 17.61 (Me), 29.60 (CH_2), 48.07 (OMe), 48.10 (OMe), 52.56 (CO_2*Me*), 64.08 (d, J_{FC} 8.3 Hz, CH_2*C*HOR), 70.86 (dd, J_{FC} 18.69 and 20.77 Hz, CF_2*C*HOR), 99.27 (CHOR), 99.94 (CHOR), 116.86 (dd, J_{FC} 239.35 and 242.47 Hz, CF_2), 130.02 (dd, J_{FC} 24.93 and 33.23 Hz, *C*H=C), 134.94 (t, J_{FC} 10.39 Hz, CH=*C*), 165.30 (C=O) [m/z HRMS (CI, NH_3). Found MNH_4^+, 340.1572; $C_{14}H_{24}F_2NO_6$ requires *MNH*$_4$, 340.1572].
23. Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett*. **1984**, *25*, 5831–5834.
24. (a) Lesuisse, D.; Berchtold, G. A. *J. Org. Chem*. **1985**, *50*, 888–890; (b) Hanessian, S.; Beaulieu, P.; Dubé, D. *Tetrahedron Lett*. **1986**, *27*, 5071–5074; (c) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1991**, *47*, 4571–4578; (d) Wang, Z.-X.; Shi, Y. *J. Org. Chem*. **1997**, *62*, 8622–8623.
25. Moore, J. D.; Lamb, H. K.; Garbe, T.; Servos, S.; Gougan, G.; Charles, I. G.; Hawkins, A. R. *Biochem. J*. **1992**, *287*, 173–181.