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SYNTHESIS OF (-)-3-HOMOSHIKIMIC ACID AND (-)-3-HOMOSHIKIMATE-3-PHOSPHATE

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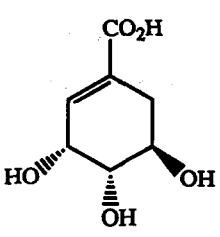
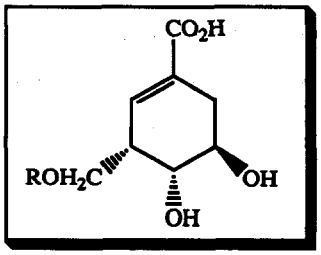
Abstract -- The title compounds **2** and **3** were synthesized in good yield from shikimic acid **1**, and are of mechanistic and synthetic interest as a prospective shikimate pathway inhibitors.

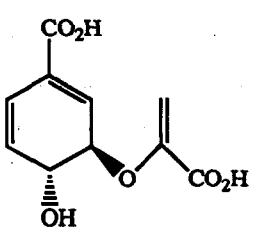
The shikimic acid biosynthetic pathway figures prominently in the metabolic chemistry of plants and microorganisms.[1,2] Besides leading to the aromatic amino acids phenylalanine, tyrosine and tryptophan, the pathway also produces such essential cofactors as folic acid and the isoprenoid quinones. Shikimic acid itself **1** has been a popular target for synthesis.[3] However structural variants,[4,5] analogs[6,7] and stereoisomers[8] are of particular contemporary interest as enzyme inhibitors and metabolic regulators with potentially valuable herbicidal and antibiotic activity. Described herein are short, highly stereoselective syntheses of (-)-3-homoshikimic acid **2**, and (-)-3-homoshikimate-3-phosphate **3**. These structures were designed for use as mechanistic probes and potential inhibitors of the enzymes shikimate kinase and enolpyruvylshikimate phosphate synthase, which catalyze reactions on the main biosynthetic pathway to the key branchpoint metabolite (-)-chorismic acid **4**.



1



2 R= H
3 R= PO_3H_2



4

3-Dehydroshikimic acid, which can be prepared by an improved oxidation[9] of (-)-**1** or by fermentation,[10] was esterified (CH_2N_2, methanol-ether, -20°C) to afford ketoester **5** (Scheme) in 65% overall yield. After silylation of the diol grouping in **5** (2.4 equiv TBDMSCl, imidazole, DMF, rt, 6 h), methylenation was accomplished by the addition of 1.2 equiv $Ph_3P{=}CH_2$ to ketoether **6** (THF, reflux)[11] thus affording diene **7** (70% overall from **5**). Deprotection (4 equiv Bu_4NF, THF, 0°C, 3 h) furnished enediol **8** in 80% yield.[12] Stereoselective epoxidation of **8** using *m*-chloroperoxybenzoic acid (1.3 equiv peracid, Na_2HPO_4, CH_2Cl_2, reflux, 19 h) gave *syn*-epoxyol **9** in ca. 80% yield.[13] It should be noted that all attempts to generate **9** directly by reaction of $(CH_3)_2S{=}CH_2$ with ketoether **6** gave a complex mixture apparently resulting from nucleophilic attack at both carbonyl groups of **6**.

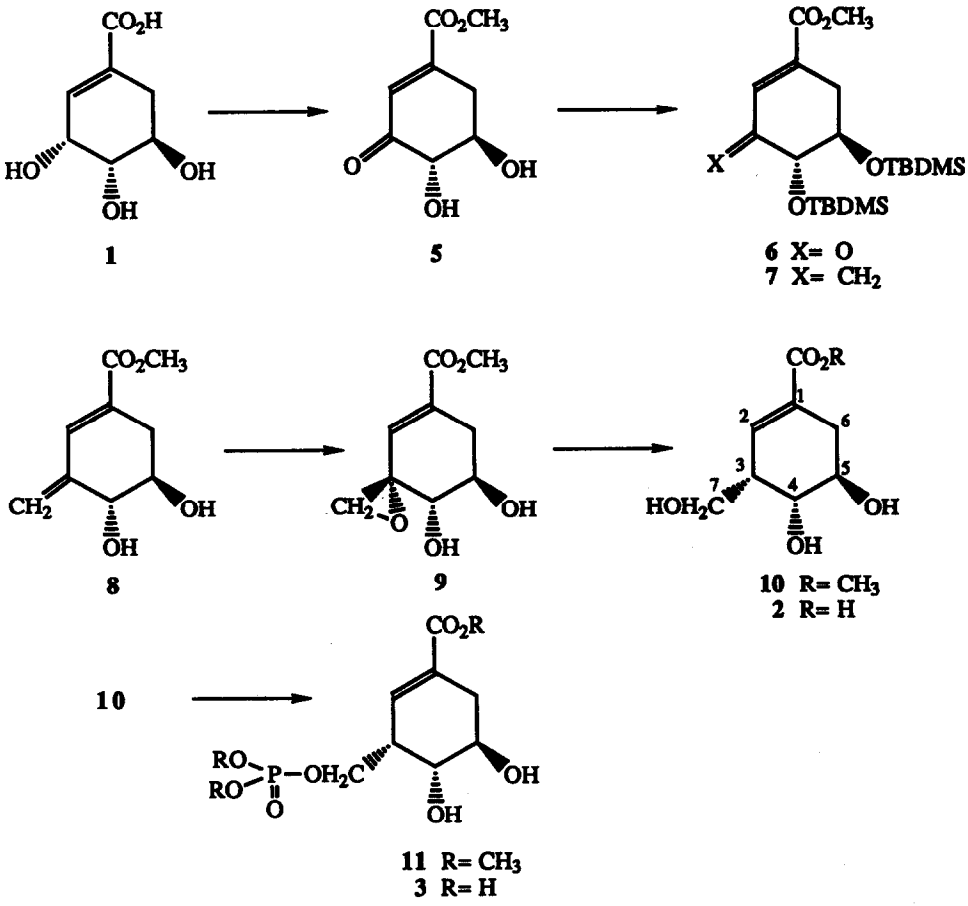
Reduction of the exocyclic epoxide in **9** with $NaBH_3CN$ in the presence of BF_3-etherate (5°C, 30 min, 50% yield).[14] proceeded with the expected inversion of configuration at the tertiary center to afford methyl 3-homoshikimate **10**. Saponification of **10** (0°C, H_2O) afforded **2** in 87% yield having $[\alpha]_D^{25} = -80°$.[15] The assigned regio and stereochemistry of reductive epoxide opening was supported by the NMR spectrum of **2** ($J_{3,4}$ = 4.9 Hz) and also by the significant nuclear Overhauser enhancement (10%) observed at H3 of **2** upon irradiation of H4.

No reaction occurred when phosphorylation of **10** was attempted with tetrabenzylpyrophosphate, but with dimethylchlorophosphate (1.1 equiv in pyridine, 0°C, 1 h) triester **11** was generated in 35% yield. Deprotection of the phosphate (TMSBr, CH_2Cl_2, 0°C, 1h) and carboxylate groups (3.3 equiv NaOH, H_2O, 0°C, 4 h) in **11** furnished (-)-homoshikimate-3-phosphate **3** which was obtained pure after anion exchange chromatography (DEAE-Sephadex A-25, HCO_3^- form, gradient elution with 0-0.5 M NH_4CO_3) in 67% yield.[16]

This stereoselective homologation of shikimic acid should provide access to a variety of potential inhibitors at intermediate and late stages of the aromatic biosynthetic pathway. The biological activity of such structures is currently under investigation.

ACKNOWLEDGMENT: We thank the National Institutes of Health (GM 24054) for generous financial assistance. We also thank Genencor International for a generous gift of microbiologically produced 3-dehydroshikimic acid. Support of the Cornell Nuclear Magnetic Resonance Facility by the NSF (CHE 7904825; PGM 8018643) and NIH (RR02002) is gratefully acknowledged.

SCHEME



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11. For **6**: R_f 0.34 (9:1 hexane:EtOAc); $[\alpha]_D$ -56° (c= 6.3, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$) 6.68 (br. s, 1 H), 4.06 (m, 1 H), 3.88 (d, 1 H, J= 6.9 Hz), 3.80 (s, 3 H), 2.89 (dq, 1 H, J= 18.7, 1.8 Hz), 2.55 (ddd, 1 H, J= 18.7, 5.3, 1.6 Hz), 0.85 (s, 9 H), 0.81 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 9 H); ^{13}C-NMR ($CDCl_3$) 197.5, 166.7, 143.6, 131.2, 71.6, 52.5, 31.7, 25.8, 18.3, 18.0, -4.6, -4.8, -4.9; IR (film) 2950, 2925, 2900, 2875, 1725, 1700, 1250, 1150, 825 cm^{-1}; CIMS m/z 415 (M+1, 100%).

12. For **8**: m.p. 112-113°C; R_f 0.46 (EtOAc); $[\alpha]_D$ -197° (c= 2.16, EtOAc); ^{1}H-NMR (d_6-acetone) 7.13 (d, 1 H, J= 2.1 Hz), 5.59 (s, 1 H), 5.39 (s, 1 H), 4.05 (dt, 1 H, J= 9.1, 2.0 Hz), 3.71 (s, 3 H), 3.63 (dt, 1 H, J= 9.1, 5.3 Hz), 2.80 (dd, 1 H, J= 17.7, 5.3 Hz), 2.27 (ddd, 1 H, J= 17.7, 9.1, 2.3 Hz); ^{13}C-NMR (d_6-acetone) 167.6, 145.8, 137.2, 128.6, 118.9, 74.5, 71.6, 51.9, 32.9; IR (film) 3300, 2975, 1705, 1450, 1275, 1100, 1075 cm^{-1}; CIMS (m/z 185 (M+1, 100%).

13. For **9**: R_f 0.32 (EtOAc); $[\alpha]_D$ -90° (c= 0.61, acetone); ^{1}H-NMR (d_6-acetone) 6.29 (t, 1 H, J= 1.7 Hz), 3.95 (m, 1 H), 3.71 (s, 3 H), 3.61 (d, 1 H, J= 7.4 Hz), 3.09 (d, 1 H, J= 5.4 Hz), 2.92 (d, 1 H, J= 5.4 Hz), 2.78 (ddd, 1 H, J= 18.0, 4.6, 1.7 Hz), 2.34 (ddd, 1 H, J= 18.0, 6.0, 1.7 Hz); ^{13}C-NMR (d_6-acetone) 166.9, 137.7, 134.7, 72.5, 70.3, 57.8, 53.0, 52.1, 31.7; IR (film) 3450, 2975, 1725, 1650, 1440, 1200, 1100, 1075 cm^{-1}; CIMS m/z 201 (M+1, 88%), 183 (M+1-H_2O, 100%).

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15. For **2**: $[\alpha]_D$ -80° (c= 1.2, H_2O); ^{1}H-NMR (D_2O) 6.74 (br. s, 1 H), 4.01 (m, 1 H), 3.90 (t, 1 H, J= 4.9 Hz), 3.70, 3.65 (AB quartet, 2 H, J= 10.9, 7.1 Hz), 2.63 (br. s, 1 H), 2.49 (br. d, 1 H, J= 19 Hz), 2.22 (br. d, 1 H, J= 19 Hz); ^{13}C-NMR (D_2O) 170.8, 138.4, 127.7, 67.5, 66.9, 60.9, 39.3, 28.3; IR (KBr) 3300, 2900, 1700, 1650, 1425, 1250, 1050 cm^{-1}; CIMS m/z 189 (M+1, 6%), 171 (M+1-H_2O, 46%), M+1-H_2O, 100%).

16. For **3**: $[\alpha]_D$ -12° (c= 0.57, H_2O); ^{1}H-NMR (D_2O) 6.64 (br. s, 1 H), 4.01 (m, 1 H), 3.85-3.93 (m, 3 H), 2.46 (br. s, 1 H), 2.40 (br. d, 1 H, J= 18 Hz), 2.19 (br. d, 1 H, J= 18 Hz); ^{13}C-NMR (D_2O) 176.7, 140.1, 134.0, 71.6, 71.3, 68.7, (d, $J_{C,P}$ = 5.3 Hz), 42.6 (d, $J_{C,P}$= 4.1 Hz), 33.1; IR (KBr) 3065, 1660, 1550, 1467, 1157, 1045, 970 cm^{-1}; CIMS m/z 305 (diammonium salt, M+1, 5%), 287 (14%), 269 (15%), 171 (26%), 153 (100%).

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