Synthesis of (−)-2-Fluoroshikimic Acid

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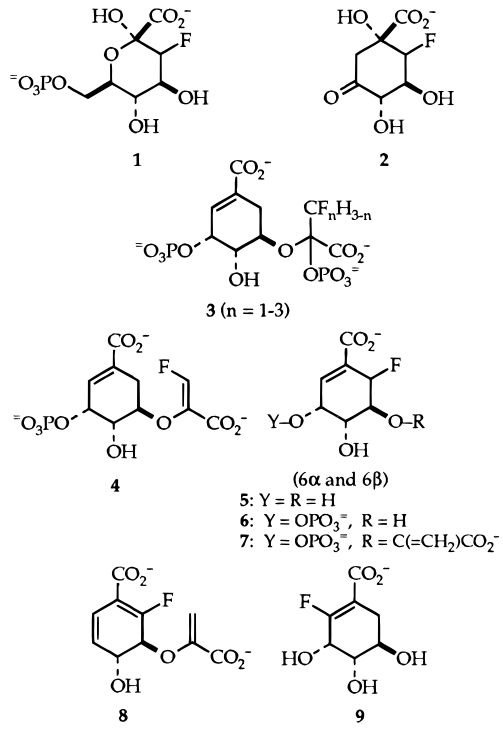
Fluorinated substrate analogs are useful as mechanistic probes and inhibitors of enzymatic reactions. Fluorine and hydrogen are similar sterically, yet dramatically different electronically,[1] so this substitution can reveal the nature of charged species in a reaction mechanism through its influence on the rate.[2] Fluorine also serves as a leaving group in an important class of suicide inhibitors of amino acid metabolism.[3] Depicted in Scheme 1 are the fluorinated derivatives of a number of intermediates along the shikimic acid pathway[4,5] that have been prepared synthetically[6−10] and enzymatically.[11−14] As anticipated, fluorine has a significant effect on the reactivity of these analogs. For example, the 6-fluoro derivatives of 5-enolpyruvylshikimate 3-phosphate (EPSP), **7**, have played an important role in deciphering the mechanism of the 1,4-elimination of phosphate catalyzed by chorismate synthase.[13,15] Bornemann et al. have recently demonstrated the enzymatic conversion of 6α-fluoro-EPSP, **7**, to 6-fluorochorismic acid, **8**, which for the *E. coli* enzyme occurs at 0.3% the rate with the normal substrate.[14]

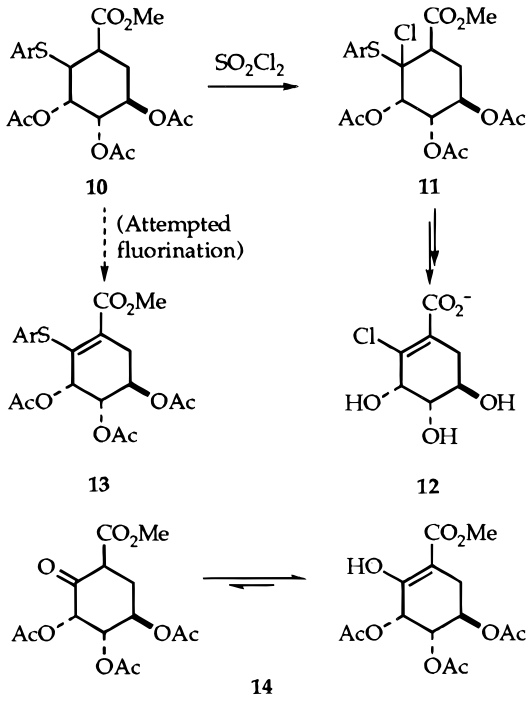
The 2-fluoro derivative of shikimic acid, **9**, has not been reported previously; we now describe a synthesis of this material by chemical conversion from shikimic acid itself. The new derivative provides access to the fluorinated analogs of shikimate 3-phosphate, EPSP, and, potentially, chorismic acid, which are isomeric to the 6-fluoro derivatives so far described.

In an earlier report, we outlined the synthesis of 2-chloroshikimic acid, **12**, with chlorination of sulfide **10** as the key step in the sequence (Scheme 2).[16] That route did not prove to be adaptable to the synthesis of the fluorine analog, since elimination to the unsaturated sulfide (e.g., **13**) occurred in preference to fluorination under a variety of conditions. We also explored a route involving the 2-keto analog **14**, with the intention of using (diethylamino)sulfur trifluoride (DAST) to introduce the unsaturated fluoride directly. However, the desired transformation was blocked by the highly enolic character of this intermediate, as a result of the conjugating carboxyl group at C-1. Therefore, to allow manipulation at the 2-position without interference from the carboxyl group, we developed the sequence depicted in Scheme 3,

Scheme 1



Scheme 2



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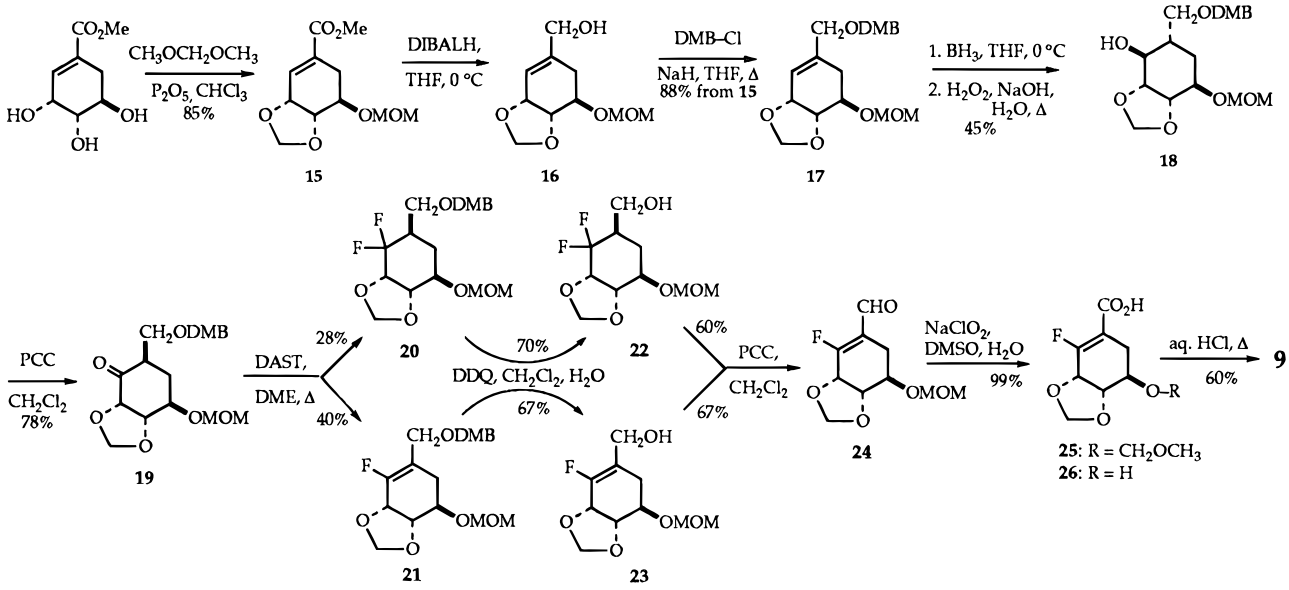
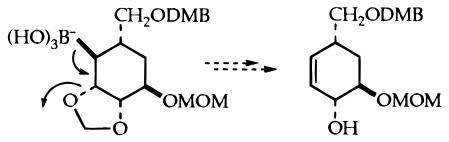
Scheme 3



MOM = CH_2OCH_3; DMB = 2,5-dimethoxybenzyl; DME = 1,2-dimethoxyethane

in which the carboxyl group is reduced at the outset and restored at the end.

The vigorous conditions anticipated for the DAST reaction dictated robust protection for the hydroxyl groups of shikimic acid. Methyl shikimate[17] was therefore protected as the methylene acetal and methoxymethyl ether,[18] **15**, and then reduced to the allylic alcohol **16** with DIBALH.[19] A number of protecting groups were evaluated for the primary hydroxyl group; the 2,5-dimethoxybenzyl ether proved to be stable to the succeeding reaction conditions, and, importantly, can be removed by an oxidative process that preserves the vinyl fluoride moiety and leaves the acetal protecting groups intact.[20] Hydroboration of the double bond of **17**, followed by oxidation with alkaline hydrogen peroxide, leads to the saturated alcohol **18**, albeit in moderate yield (45% from **17**). The major side reaction appears to be Grob-like fragmentation of the intermediate organoborane with opening of the acetal ring (e.g., **26** → **27**), since the byproducts have lost their methylene acetal hydrogens by ^{1}H NMR.



Oxidation of alcohol **18** with PCC[21] to ketone **19** is straightforward, setting the stage for introduction of fluorine.[22] Reaction with DAST[23] produces both geminal difluoride **20** and vinyl fluoride **21**, in a combined yield of 68%. These compounds are separately deprotected at the primary position by oxidation with DDQ[24] to give alcohols **22** and **23**, respectively, which in turn are oxidized by the Dess–Martin procedure[25] or, in better yield, by PCC,[21] to provide the fluoro enal **24** in each case. It appears that the difluoro derivative undergoes spontaneous elimination under the reaction conditions.

Further oxidation of the aldehyde **24** to the carboxylic acid **25** is carried out with sodium chlorite as oxidant in DMSO/water in quantitative yield.[26] Finally, the robust nature of the methylene acetal protecting groups was manifested when it came time to remove them. Cleavage of the methoxymethyl ether at C-5 is accomplished readily in aqueous hydrochloric acid, but the cyclic acetal is more resistant, requiring prolonged reflux in 3 N HCl. Nonetheless, 2-fluoroshikimic acid, **9**, is stable to these conditions and can be isolated as a hygroscopic powder in 60% overall yield after purification by reversed-phase HPLC and lyophilization.

Preliminary experiments with shikimate kinase suggest that 2-fluoroshikimate is accepted as a substrate and that the product, 2-fluoroshikimate 3-phosphate, can be further converted to 2-fluoro-EPSP by EPSP synthase. The results of these investigations will reported separately.

Experimental Section[27,28]

Methyl 5β-Methoxymethoxy-3α,4α-methylenedioxycyclohex-1-enecarboxylate (15). To a stirred solution of methyl shikimate, **14**[17] (6.68 g, 35.5 mmol), in chloroform (175 mL, dried over P_2O_5) were added dimethoxymethane (175 mL) and P_2O_5

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(27) **General Methods.** All reactions involving moisture-sensitive reagents were performed under a dry argon atmosphere. ^{19}F chemical shifts are reported in ppm from $CFCl_3$ as 0 ppm (downfield positive). *J* values are given in Hz. Chromatography refers to the method of Still, Kahn, and Mitra[28] using silica gel 60 (E. Merck, Darmstadt).
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(90 g), and the mixture was allowed to stir at rt for 20 h. The reaction mixture was partitioned between ice-cold saturated $NaHCO_3$ and CH_2Cl_2 (400 mL each). The reaction flask was carefully washed with more $NaHCO_3$ and CH_2Cl_2 (100 mL each), and the solutions were combined. The organic phase was washed with $NaHCO_3$ (100 mL) and brine (100 mL), dried, filtered, and evaporated under reduced pressure. The crude product was chromatographed (25% ethyl acetate/hexane) to give fully protected acetal **15** (7.36 g, 85%) as a colorless oil: ^{1}H NMR δ 6.85 (m, 1), 5.00 (s, 1), 4.95 (s, 1), 4.70 (s, 2), 4.66 (m, 1), 4.13 (t, 1, J = 6.4), 3.94 (td, 1, J = 6.6, 4.4), 3.75 (s, 3), 3.36 (s, 3), 2.69 (m, 1), 2.38 (m, 1); ^{13}C NMR δ 166.4, 133.1, 130.8, 95.6, 94.3, 75.4, 72.3, 72.2, 55.4, 52.0, 26.8. FAB-MS (NBA − LiCl) 251.1 (100, MLi^+). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.05; H, 6.66.

5β-(Methoxymethoxy)-3α,4α-(methylenedioxy)cyclohex-1-enemethanol (16). To a stirred solution of ester **15** (7.36 g, 30 mmol) in THF (150 mL) at −78 °C was added a 1.0 M solution of diisobutylaluminum hydride in hexane (120 mL, 4 equiv). The solution was stirred for 20 min, allowed to warm to 0 °C, and stirred for an additional 30 min. Isopropyl alcohol (30 mL) was added to decompose excess reagent, and the resulting solution was allowed to stir for 10 min before it was poured into a mixture of potassium sodium tartrate (170 g, 603 mmol, 20 equiv) in 50% water/ethyl acetate (800 mL). This mixture was stirred vigorously for 17.5 h, the layers were separated, and the aqueous phase was extracted with ethyl acetate (two 400-mL portions). The combined organic layer was dried, filtered, and evaporated under reduced pressure. Chromatography (ethyl acetate) of the crude residue gave alcohol **16** (6.47 g) as a colorless oil: ^{1}H NMR δ 5.75 (br s, 1), 5.01 (s, 1), 4.87 (s, 1), 4.68 (AB-q, 2, J = 6.8), 4.45 (br s, 1), 4.03 (t, 1, J = 6.9), 3.98 (br s, 2), 3.75 (m, 1), 3.31 (s, 3), 2.68 (m, 1), 2.31 (m, 1), 2.02 (m, 1); ^{13}C NMR δ 140.8, 117.2, 100.2, 95.8, 94.0, 76.2, 73.2, 65.2, 55.2, 29.1. FAB-MS (NBA + LiCl) 223.2 (40, MLi^+); HRMS calcd for $C_{10}H_{16}LiO_5$ 223.1158, found 223.1163. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.75; H, 7.40.

1-[[(2,5-Dimethoxybenzyl)oxy]methyl]-5β-(methoxymethoxy)-3α,4α-(methylenedioxy)cyclohexene (17). To a stirred solution of allylic alcohol **16** (3.4 g, 16 mmol) in THF (200 mL) were added consecutively 2,5-dimethoxybenzyl chloride[29] (7.3 g, 39 mmol, 2.5 equiv) and sodium hydride (4.5 g, 94 mmol, 6.0 equiv), and the suspension was heated to reflux for 6 h. The mixture was allowed to cool, NH_4OH (50 mL) was added, and stirring was continued for 5 min. The mixture was diluted with ether (600 mL), the layers were separated, and the organic phase was washed with NH_4Cl (600 mL), $NaHCO_3$ (600 mL), and brine (600 mL), dried, filtered, and evaporated under reduced pressure. The crude oil was chromatographed (20% ethyl acetate/hexane) to give 2,5-dimethoxybenzyl ether **17** (5.1 g, 88% from **15**) as an oil: ^{1}H NMR δ 6.95 (br s, 1), 6.76 (br s, 2), 5.86 (br s, 1), 5.08 (s, 1), 4.94 (s, 1), 4.73 (AB-q, 2, J = 6.8), 4.51 (m, 1), 4.48 (s, 2), 4.09 (m, 1), 3.99 (s, 2), 3.82 (m, 1), 3.76 (s, 3), 3.75 (s, 3), 3.35 (s, 3), 2.4 (m, 1), 2.11 (m, 1); ^{13}C NMR δ 153.5, 151.1, 138.3, 127.4, 119.4, 114.7, 112.9, 111.2, 95.8, 94.1, 76.2, 73.3, 73.11, 73.07, 66.8, 55.8, 55.6, 55.3, 29.5. Anal. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 61.89; H, 7.09.

1α-[[(2,5-Dimethoxybenzyl)oxy]methyl]-5β-(methoxymethoxy)-3α,4α-(methylenedioxy)cyclohexan-2β-ol (18). To a solution of alkene **17** (5.92 g, 16.2 mmol) in THF (200 mL) at 0 °C was added a 1.0 M solution of BH_3·THF in THF (113 mL, 7 equiv), and the solution was stirred for 1.7 h. Alkaline hydrogen peroxide (600 mL, 2:1 30% hydrogen peroxide/3.0 M NaOH) was then added carefully through a reflux condenser. The mixture was stirred for 15 min and warmed to room temperature. After 35 min, the solution was heated to 60 °C for 2.2 h. The mixture was allowed to cool and diluted with ether (500 mL), and the organic phase was washed successively with $NaHCO_3$ (500 mL) and brine (500 mL), dried, filtered, and evaporated under reduced pressure. The residue was chromatographed (40% ethyl acetate/hexanes) to give the starting olefin **17** (310 mg, 5%) as a colorless oil. Further elution with 60% ethyl acetate gave the desired alcohol **18** (2.79 g, 45%) as a colorless oil: ^{1}H NMR δ 6.86 (br s, 1), 6.74 (br s, 2), 5.09 (s, 1), 4.93 (s, 1), 4.63 (s, 2), 4.48 (s, 2), 4.05 (m, 2), 3.93 (m, 1), 3.73 (s, 3), 3.71 (s, 3), 3.60 (m, 1), 3.50 (m, 2), 3.32 (s, 3), 2.04 (m, 1), 1.68 (m, 1), 1.49 (m, 1); ^{13}C NMR δ 153.4, 151.4, 127.0, 115.1, 113.1, 111.3, 95.4, 94.4, 79.6, 77.4, 73.9, 73.2, 71.6, 68.6, 55.9, 55.7, 55.5, 35.1, 27.6. Anal. Calcd for $C_{19}H_{28}O_8$: C, 59.36; H, 7.34. Found: C, 59.37; H, 7.50.

1α-[[(2,5-Dimethoxybenzyl)oxy]methyl]-5β-(methoxymethoxy)-3α,4α-(methylenedioxy)cyclohexan-2-one (19). A solution of alcohol **18** (2.79 g, 7.2 mmol) and pyridinium chlorochromate (4.69 g, 21.8 mmol, 3.0 equiv) in CH_2Cl_2 (200 mL) was stirred for 24 h. The crude orange solution was loaded directly on a silica gel column (equilibrated with 40% ethyl acetate/hexane) and chromatographed (40% ethyl acetate/hexane) to give ketone **19** (2.18 g, 78%) as a colorless oil: ^{1}H NMR δ 6.94 (br s, 1), 6.74 (br s, 2), 5.0 (AB-q, 2), 4.74 (AB-q, 2), 4.51 (m, 3), 4.31 (m, 1), 4.21 (m, 1), 3.85 (m, 1), 3.74 (s, 6), 3.50 (m, 1), 3.39 (s, 3), 3.1 (m, 1), 2.35 (m, 1), 1.8 (m, 1); ^{13}C NMR δ 206.3, 153.6, 151.1, 127.8, 114.5, 112.7, 111.2, 95.7, 95.2, 81.0, 77.9, 71.0, 68.3, 67.9, 55.9, 55.8, 55.7, 43.4, 30.4. Anal. Calcd for $C_{19}H_{26}O_8$: C, 59.68; H, 6.85. Found: C, 59.50; H, 7.24. Further elution of the column with 50% ethyl acetate/hexane led to recovery of starting alcohol **18** (300 mg, 11%).

2,2-Difluoro-1α-[[(2,5-dimethoxybenzyl)oxy]methyl]-5β-(methoxymethoxy)-3α,4α-(methylenedioxy)cyclohexane (20) and 2-Fluoro-1-[[(2,5-dimethoxybenzyl)oxy]methyl]-5β-methoxymethoxy-3α,4α-(methylenedioxy)cyclohexene (21). To a stirred solution of ketone **19** (2.18 g, 5.7 mmol) in anhydrous dimethoxyethane (350 mL) was added (diethylamino)sulfur trifluoride (DAST) (3.77 mL, 28.5 mmol, 10.0 equiv), and the solution was heated to 80 °C. While heating was continued, additional portions of DAST (3.77 mL, 28.5 mmol, 10.0 equiv) were added through the top of the reflux condenser at 2, 8.5, and 22.5 h total time. The solution was allowed to cool after a total of 27 h. Excess reagent was carefully decomposed through the addition of $NaHCO_3$ (500 mL), and the mixture was extracted with ether (500 mL). The organic phase was washed with $NaHCO_3$ (500 mL) and brine (500 mL), dried, filtered, and evaporated under reduced pressure. Chromatography of the crude product (20% ethyl acetate/hexane) gave difluoride **20** (657 mg, 28%) as a colorless oil: ^{1}H NMR δ 6.95 (br s, 1), 6.76 (br s, 2), 5.23 (s, 1), 4.99 (s, 1), 4.68 (AB-q, 2, J = 6.9, 15.1), 4.52 (d, 2, J = 10.8), 4.24 (br m, 1), 4.17 (br s, 1), 4.08 (br s, 1), 3.88 (dd, 1, J = 4.0, 9.6), 3.76 (s, 3), 3.75 (s, 3), 3.51 (d, 1, J = 9.0), 3.36 (s, 3), 2.45 (br m, 1), 2.17 (m, 1), 1.81 (m, 1); ^{13}C NMR δ 171.0, 153.6, 151.0, 127.7, 114.4, 112.7, 111.2, 96.5, 95.5, 78.1, 74.5, 70.2, 67.8, 67.0, 55.8, 55.7, 55.6, 37.0, 26.4. ^{19}F NMR δ −104.7 (d, J = 244.4), −120.3 (ddd, J = 244.5, 27.5, 15.4); FAB-MS (NBA) 404 (100, M^+); HRMS calcd for $C_{19}H_{26}O_7F_2$ 404.1647, found 404.1646.

Further elution gave vinyl fluoride **21** (871 mg, 40%) as a colorless oil: ^{1}H NMR δ 6.93 (br s, 1), 6.77 (br s, 2), 5.10 (s, 1), 5.03 (s, 1), 4.69 (s, 2), 4.67 (m, 1), 4.45 (s, 2), 4.23 (m, 1), 4.16 (m, 2), 3.94 (m, 1), 3.76 (s, 3), 3.75 (s, 3), 3.35 (s, 3), 2.55 (m, 1), 2.34 (m, 1); ^{19}F NMR δ −121.0 (s); ^{13}C NMR δ 153.0, 151.2, 151.0 (d), 127.3, 114.9, 113.6, 113.1, 111.2, 95.6, 94.7, 77.1, 71.7, 71.5, 66.7, 64.8, 55.8, 55.6, 55.4, 27.4. FAB-MS (G) 384 (100, M^+); HRMS calcd for $C_{19}H_{25}O_7F$ 384.1584, found 384.1587.

2,2-Difluoro-1α-(hydroxymethyl)-5β-(methoxymethoxy)-3α,4α-(methylenedioxy)cyclohexane (22). A mixture of 2,5-dimethoxybenzyl ether **20** (657 mg, 1.62 mmol) and 2,3-dichloro-5,6-dicyanoquinone (DDQ, 443 mg, 1.95 mmol, 1.2 equiv) in 20:1 CH_2Cl_2/water (210 mL) was stirred for 22 h. The mixture was diluted with CH_2Cl_2 (50 mL), washed with brine (three 250-mL portions), dried, filtered, and evaporated under reduced pressure. The crude oil was chromatographed (40% ethyl acetate/hexane) to give the desired difluoro alcohol **22** (290 mg, 70%) as a colorless oil: ^{1}H NMR δ 5.24 (s, 1), 4.99 (s, 1), 4.69 (m, 2), 4.24 (br m, 1), 4.20 (br s, 1), 4.08 (br s, 1), 3.96 (dd, 1, J = 11.4, 5.3), 3.74 (dd, 1, J = 11.3, 5.8), 3.38 (s, 3), 2.33 (br m, 1), 1.97 (m, 1), 1.87 (m, 1); ^{19}F NMR δ −104.0 (d, J = 244.0), −120.1 (ddd, J = 244.0, 27.5, 15.0); ^{13}C NMR δ 122.0, 96.5, 95.5, 78.0, 74.4, 70.2, 59.7, 55.7, 38.7, 25.9; FAB-MS (NBA) 255.0 (65, MH^+). Anal. Calcd for $C_{10}H_{16}F_2O_5$: C, 47.24; H, 6.34. Found: C, 47.40; H, 6.57.

2-Fluoro-1-(hydroxymethyl)-5β-(methoxymethoxy)-3α,4α-(methylenedioxy)cyclohexene (23). A mixture of 2,5-dimethoxybenzyl ether **21** (220 mg, 0.57 mmol) together with 2,3-dichloro-5,6-dicyanoquinone (DDQ, 156 mg, 0.69 mmol, 1.2 equiv) in 21:1 CH_2Cl_2/water (157 mL) was stirred for 22 h. The

(29) O'Shea, K. E.; Fox, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 611−615.

mixture was diluted with CH_2Cl_2 (30 mL) and washed with brine (three 180-mL portions), and the organic phase was dried, filtered, and evaporated under reduced pressure. The crude oil was chromatographed (45% ethyl acetate/hexane) to give the fluoro alcohol **23** (90 mg, 67%) as a colorless oil: ^{1}H NMR δ 5.06 (s, 1), 4.98 (s, 1), 4.67 (s, 2), 4.58 (m, 1), 4.19 (m, 3), 3.93 (m, 1), 3.33 (s, 3), 2.51 (m, 1), 2.26 (m, 1); ^{19}F NMR δ −20.5 (s); ^{13}C NMR δ 149.2 (d, J = 256), 115.5 (d, J = 9), 95.8, 94.7, 76.9, 71.9, 71.6 (d, J = 26), 57.6 (d, J = 7), 55.4, 27.2 (d, J = 4). Anal. Calcd for $C_{10}H_{15}FO_5$: C, 51.28; H, 6.45. Found: C, 51.21; H, 6.56.

2-Fluoro-5β-(methoxymethoxy)-3α,4α-(methylenedioxy)-cyclohex-1-enecarboxaldehyde (24). A solution of difluoro alcohol **22** (333 mg, 1.31 mmol), $NaHCO_3$ (220 mg, 2.62 mmol, 2.0 equiv), and pyridinium chlorochromate (1.411 g, 6.54 mmol, 5.0 equiv) in CH_2Cl_2 (25 mL) was stirred for 2 h. The orange solution was loaded directly onto a silica gel column (equilibrated with 20% ethyl acetate/hexane) and eluted (20% ethyl acetate/hexane) to give aldehyde **24** (184 mg, 60%) as a colorless oil: ^{1}H NMR δ 10.15 (s, 1), 5.09 (s, 1), 5.04 (s, 1), 4.79 (m, 1), 4.65 (AB-q, 2, J = 6.9), 4.32 (m, 1), 4.14 (m, 1), 3.33 (s, 3), 2.58 (m, 1), 2.47 (m, 1); ^{19}F NMR δ −113.0; ^{13}C NMR δ 187.7 (d, J = 12), 166.0 (d, J = 285), 116.1, 95.7, 95.3, 76.8 (d, J = 7), 71.2 (d, J = 23), 70.7, 55.6, 22.0 (d, J = 2). Anal. Calcd for $C_{10}H_{13}FO_5$: C, 51.72; H, 5.64. Found: C, 52.09; H, 5.71.

Fluoro aldehyde **24** was also prepared as follows: A solution of fluoro alcohol **23** (102 mg, 0.44 mmol) and pyridinium chlorochromate (470 mg, 2.18 mmol, 5.0 equiv) in CH_2Cl_2 (10 mL) was stirred for 2 h. The orange solution was worked up as described above to give aldehyde **24** (68 mg, 67%).

2-Fluoro-5β-(methoxymethoxy)-3α,4α-(methylenedioxy)-cyclohex-1-enecarboxylic Acid (25). To a stirred solution of aldehyde **24** (132 mg, 0.57 mmol) in 1:2 DMSO/H_2O (6 mL) was added NaH_2PO_4 (16 mg, 0.11 mmol, 0.2 equiv) followed by sodium chlorite (72 mg, 0.80 mmol, 1.4 equiv), and the resulting solution was allowed to stir for 20 h. The reaction mixture was neutralized with $NaHCO_3$ (20 mL) and washed with CH_2Cl_2 (three 50-mL portions). The aqueous phase was acidified to pH 1 with 3 N HCl and extracted with CH_2Cl_2 (three 50-mL portions). The organic extract was dried, filtered, and evaporated under reduced pressure to give free acid **25** (141 mg, 99%) as a colorless oil: ^{1}H NMR δ 5.08 (s, 1), 5.02 (s, 1), 4.67 (m, 3), 4.27 (m, 1), 4.09 (m,1), 3.36 (s, 3), 2.64 (m, 2); ^{13}C NMR δ 165.9, 158.1 (d, J = 280), 108.2 (d, J = 3), 95.2, 94.6, 76.4 (d, J = 7), 71.4 (d, J = 25), 70.7, 55.2, 26.1; ^{19}F NMR δ −95.2 (s); FAB-MS (NBA) 247 (M^- − H, 100), 249 (M^+, 25); HRMS calcd for $C_{10}H_{14}O_6F$ 249.0774, found 249.0770.

2-Fluoroshikimic Acid (9) and 2-Fluoro-5β-hydroxy-3α,4α-(methylenedioxy)cyclohex-1-enecarboxylic Acid (26). A stirred solution of carboxylic acid **25** (135 mg, 0.54 mmol) and concd HCl (2 mL) in water (5 mL) was heated to reflux for 17.5 h. The solution was cooled, diluted with water (15 mL), filtered through a 0.1 μm filter, and lyophilized. The crude white solid was purified by preparative reversed-phase HPLC (C-18 Vydac column, 10 mL/min flow rate, 0.9 mL injection volume, 0.1% trifluoroacetic acid/water mobile phase). The first product to elute from the column (7.5 min retention time) was 2-fluoroshikimic acid, **9** (42 mg, 40%), which could be isolated as a hygroscopic white solid after lyophilization: $[\alpha]^{23}_D$ = −137° (c = 0.99 in H_2O); ^{1}H NMR (D_2O) δ 4.36 (m, 1), 3.82 (m, 1), 3.67 (dd, 1, J = 9.2, 4.6), 2.67 (m, 1), 2.13 (m, 1); ^{13}C NMR (D_2O) δ 167.9, 161.1 (d, J = 282), 107.9, 71.2 (d, J = 9), 66.3 (d, J = 24), 65.5, 29.4; ^{19}F NMR (D_2O) δ −100.5 (s); ϵ_{187} = 13 100; IR (KBr) 3481, 3354, 3215, 2900 br, 1692, 1662, 1440, 1262, 1147, 1100, 997, 938, 774, 668 cm^{-1}; FAB-MS (NBA) 191 (M^- − H, 100); HRMS calcd for $C_7H_8O_5F$ 191.0356, found 191.0352.

Continued elution with an increasing concentration of 0.1% trifluoroacetic acid/acetonitrile in the mobile phase led to the isolation of methylene acetal **26** (62 mg, 30%) as a hygroscopic white solid: ^{1}H NMR (D_2O) δ 5.01 (s, 1), 4.95 (s, 1), 4.73 (m, 1), 4.22 (m, 1), 3.95 (dd, 1, J = 11.0, 6.6), 2.57 (m, 1), 2.34 (m, 1); ^{13}C NMR (D_2O) δ 167.4, 159.9, 108.7, 94.3, 77.4 (d, J = 8), 71.2 (d, J = 25), 65.1, 27.9; ^{19}F NMR (D_2O) δ −101.0 (s). This material was converted to 2-fluoroshikimic acid on further treatment in aqueous HCl at reflux and purification (35 mg, 62%).

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