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# SYNTHESIS OF (3*R*)- AND (3*S*)-FLUORO-(4*R*,5*R*)-DIHYDROXY-1-CYCLOHEXENE-1-CARBOXYLIC ACIDS: THE (3*R*)- AND (3*S*)-FLUORO ANALOGUES OF (-)-SHIKIMIC ACID

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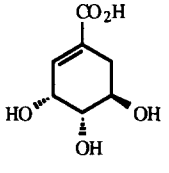
**Abstract:** (3*R*)-and (3*S*)-Fluoro-(4*R*,5*R*)-dihydroxy-1-cyclohexene-1-carboxylic acids (the (3*R*)-and (3*S*)-fluoro analogues of (-)-shikimic acid) have been synthesised from (-)-shikimic acid *via* an intermediate epoxide (a fungal metabolite from *Chalara microspora*) that underwent acid catalysed hydrolysis to afford the first stereospecific synthesis of (-)-3-*epi*-shikimic acid. Copyright © 1996 Elsevier Science Ltd

The shikimate pathway[2-4] is a biosynthetic pathway utilized by plants, fungi and micro-organisms for the synthesis of several essential aromatic metabolites including the three commonly occurring aromatic L-α-amino acids (Phe, Tyr, Trp), the folate coenzymes and various isoprenoid quinones. Compounds that inhibit the enzymes which catalyse the diverse biochemical transformations *en route* from acyclic $C_3$ and $C_4$ units to aromatics have been highlighted as potential anti-fungal, bacteriocidal or herbicidal agents following the discovery that *N*-phosphonomethylglycine (glyphosate, marketed by Monsanto as Roundup®) possesses post-emergence herbicidal properties[5] as a result of its extreme affinity for the enzyme 5-enolpyruvyl-shikimate-3-phosphate synthase (5-EPS-3-P synthase).

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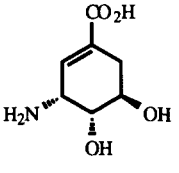


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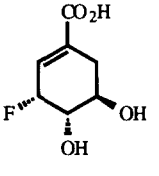


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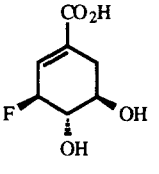


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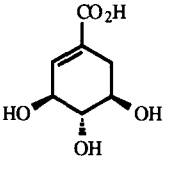


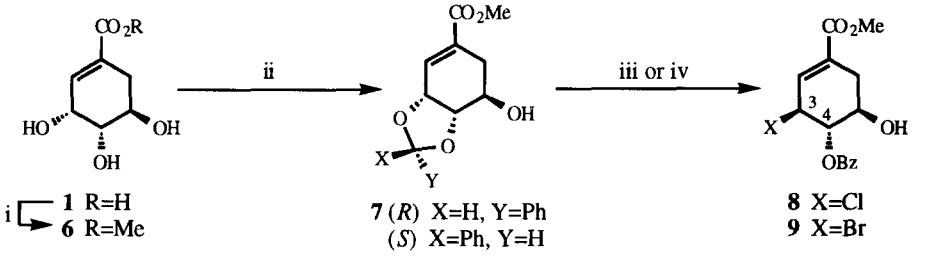

**5**

We have for some time been interested in the development of synthetic routes to compounds that closely mimic shikimate pathway intermediates and have embarked upon a program of research in this area utilizing (-)-shikimic acid **1** as a precursor concentrating our efforts on the synthesis of 3-substituted shikimate derivatives. We have recently described[6] the first successful methods for the incorporation of nitrogenous functionality at C-3 of the shikimate nucleus and have highlighted the synthesis of the (3*R*)-amino shikimate derivative **2** directly from the parent acid **1**.

The syntheses of both 6α- and 6β-fluoroshikimic acids by several research groups[7-9] together with a recent report of 2-chloroshikimic acid[10] has led us to investigate methods suitable for the incorporation of a fluorine atom at C-3 of the shikimate ring as a mimic of the natural hydroxyl group (both on steric and electronic grounds) but with the distinction that, where hydrogen bonding is possible, unlike an -OH group

fluorine may act only as a hydrogen bond acceptor and not as a donor. In this communication we wish to report methods for the incorporation of fluorine, chlorine and bromine at C-3 of the shikimate ring and we describe herein the synthesis of both the 3α- and 3β-fluoro acids **3** and **4** together with the first stereospecific[11] synthesis of 3-*epi*-shikimic acid **5** directly from the natural acid **1**.

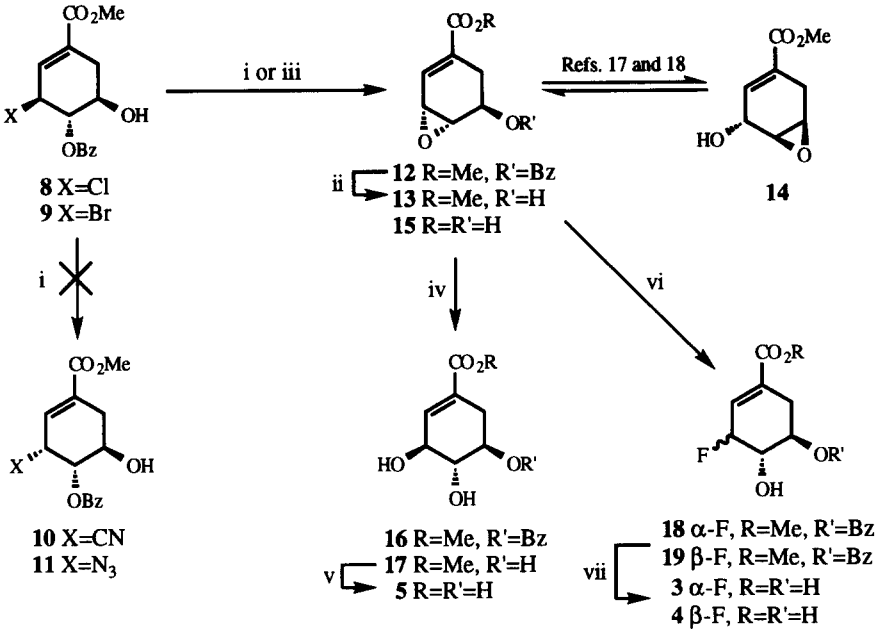
(-)-Shikimic acid **1** was isolated from the ground seeds and carpels of star aniseed[12] according to a known procedure.[13] Treatment of **1** with acidified methanol gave the known ester **6** quantitatively;[14] selective 3,4-*cis*-diol protection of **6** was effected with benzaldehyde dimethyl acetal in refluxing acidic THF to yield acetals **7** (72%, *R:S* 3:2).[6] Radical bromination of **7** using *N*-chlorosuccinimide ($C_6H_6$, Δ) or *N*-bromosuccinimide[15] ($CCl_4$, 20°C) afforded the 3β-chloride **8** (80%) and 3β-bromide **9** (62%) respectively; the *trans*-3,4-stereochemistry in halides **8** and **9** was clearly evident from the larger coupling constants between H-3 and H-4 ($J_{3,4}$ 7·5-8 Hz) when compared to those resulting from the 3,4-*cis*-sterochemical arrangements of **1**, **6** and **7** ($J_{3,4}$ 4-5 Hz).




*Reagents and conditions:* i, 1% HCl, MeOH, reflux; ii, $PhCH(OMe)_2$, $TsOH{\cdot}H_2O$, THF, reflux; iii, NCS, $C_6H_6$, reflux; iv, NBS, $CCl_4$

Attempted replacement of halide in both **8** and **9** with cyanide in warm methanol to afford nitrile **10** (in a manner analogous to that used to prepare azide **11**)[6] failed, instead rapid benzoyl migration followed by ring closure resulted in the formation of epoxide **12** (64%). Methoxide induced debenzoylation of **12** afforded the known epoxyol **13** (a fungal metabolite isolated from *Chalara microspora*);[16] alternatively, treatment of **9** with potassium carbonate in tetrahydrofuran (64°C) afforded 5-benzoate **12** and addition of methanol to the reaction mixture resulted in concomitant debenzoylation to **13** (82%). Epoxyol **13** has proven to be the subject of some controversy since the two groups[16-18] to have reported its synthesis have offered widely differing values for its specific rotation. Ganem[17,18] has suggested that a rapid base induced Payne rearrangement[19] of **13** to the 'more stable epoxyol isomer'[18] **14** may be the cause of this discrepancy; epoxyol **14** has been elegantly utilized by Berchtold in a synthesis of (-)-chorismic acid.[20]

In our hands, epoxide **13** has proven to be far less susceptible to rearrangement to **14** under basic conditions than suggested previously,[18] indeed epoxyol **13** was found to be stable under a variety of basic conditions (NaH, $K_2CO_3$ etc.) in various solvents (THF, MeOH etc.); formation of **14** from **13** could only be observed using methoxide ion in neat methanol at room temperature or above. Hydrolysis of **13** (NaOH, $H_2O$) afforded a 1:1 mixture of epoxy acid **15** and 3-*epi*-acid **5** (80%) which was smoothly converted to solely **5** upon attempted separation by reverse-phase HPLC under acidic conditions (using $MeCN:H_2O:CF_3CO_2H$ as eluent); the *trans*-3,4-stereochemistry in **5** was clearly evident from coupling constant data ($J_{3,4}$ 8 Hz).




*Reagents and conditions:* i, KCN, MeOH, 40°C; ii, NaOMe, MeOH, 0°C; iii, $K_2CO_3$, MeOH, THF, reflux; iv, $CF_3CO_2H$, $H_2O$, 20°C; v, NaOH, $H_2O$, 20°C; vi, 70% HF, $C_5H_5N$, 0°C; vii, 6M HCl, dioxane, 60-70°C

The discovery of the acid lability of epoxyol **13** allowed us to develop a new and stereospecific synthesis of (-)-3-*epi*-shikimic acid **5**. Treatment of **13** with aqueous trifluoroacetic acid afforded methyl ester **17** quantitatively which was readily saponified (NaOH, $H_2O$, 20°C) to yield acid **5** (81%) after ion-exchange chromatography. Both ester **17** and acid **5** have, to the best of our knowledge, only previously been prepared either in racemic form[11] or as mixtures contaminated with their C-3 epimers from which the desired compounds were isolated by fractional crystallization;[11,21] our approach thus allows the first *stereospecific* synthesis of both laevorotatory ester **17** and acid **5** on a preparative scale.

A similar protocol using polyhydrogen fluoride/pyridine complex has allowed the synthesis of the (3*R*)- and (3*S*)-fluoro acids **3** and **4**. Treatment of 5-benzoate **12** with an excess of Olah's reagent[22] at 0°C resulted in the regiospecific opening of the epoxide ring to afford a mixture of the 3β-alcohol **16** (17%; $J_{3,4}$ 7·5 Hz), together with both the 3α-fluoride **18** (8%) and 3β-fluoride **19** (48%, $J_{3,4}$ 8 Hz). Careful analysis of a mixture of **18** and **19** using a combination of $^1H$, $^{13}C$ and $^{19}F$ nmr spectroscopy showed clearly that fluoride ion had been incorporated at C-3 of the ring; no regioisomeric 4-fluorinated products or 1-fluorinated products (resulting from oxirane cleavage *via* an alternative $S_N2'$ mechanism) could be detected. Acid induced hydrolysis of **18** and **19** in acidic aqueous dioxane afforded a mixture of the 3α- and 3β-fluoro acids **3** (5%) and **4** (91%) from which pure 3β-fluoro acid **4** could be isolated by HPLC; notably **4** has an identical melting point to the parent acid **1** (183-186°C).

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