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# Arene *cis*-dihydrodiols—useful precursors for the preparation of antimetabolites of the shikimic acid pathway: application to the synthesis of 6,6-difluoroshikimic acid and (6*S*)-6-fluoroshikimic acid

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**Abstract**—The synthesis of 6,6-difluoroshikimic acid (**11**) has been achieved in ten steps from the enantiopure diol **16**, which is derived from enzymatic cis-dihydroxylation of iodobenzene. The versatility of the synthetic strategy has been demonstrated by the preparation of the known antimicrobial agent, (6*S*)-6-fluoroshikimic acid (**5**).
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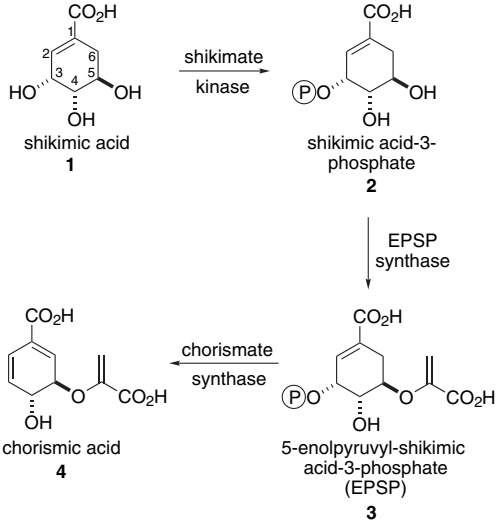
## 1. Introduction

Over recent years, there has been extensive interest in the efficient preparation of analogues of (−)-shikimic acid (**1**), which have been targeted as likely inhibitors of enzymes on the shikimic acid pathway and which are of relevance as potential antifungal, antibacterial and antiparasitic agents. A principal goal of our present research is the synthesis of analogues of (**1**), which may either inhibit shikimate kinase, or alternatively undergo intracellular phosphorylation by the kinase and thereby act as prodrugs for inhibitors of enzymes further downstream on the pathway (e.g., EPSP synthase or chorismate synthase (Scheme 1)).[1]

The feasibility of this approach is supported by the findings of extensive studies of the fluorinated analogues **5** and **6** of (−)-shikimic acid (**1**) (Scheme 2).[2] Both of these compounds display in vitro antibacterial activity against a range of *Escherichia coli* strains with (6*S*)-6-fluoroshikimic acid (**5**) being the more potent agent (MIC against *E. coli* K-12 of 0.1 μg/mL compared with 64 μg/mL for (6*R*)-6-fluoroshikimic acid (**6**)).[3] The fluorinated analogues are substrates for the shikimate transport system of *E. coli*[4] and importantly, the (6*S*)-isomer **5** has been shown to be protective against a range of bacterial intraperitoneal challenges in mice.[3] Both compounds are substrates for shikimate kinase from *E. coli* and are transformed to the corresponding 6-fluoro-




**Scheme 1.**

shikimate-3-phosphates **7** and **8** at rates comparable to (−)-shikimic acid itself. In turn, compounds **7** and **8** are transformed by EPSP synthase from *E. coli* to the corresponding 6-fluoro-EPSP analogues **9** and **10** at rates approximately one order of magnitude slower than the natural substrate.[5] Further studies have indicated that the antimicrobial activity of **6** is due, at least in part, to ultimate inhibition of chorismate synthase whereas **5** is proposed to act via ultimate inhibition of 4-amino-4-deoxychorismate synthase (ADCS), an enzyme on the post-chorismate branch of the pathway leading to *para*-aminobenzoic acid (PABA).[6]

*Keywords*: Shikimic acid; Fluorination; Antibacterial agents.
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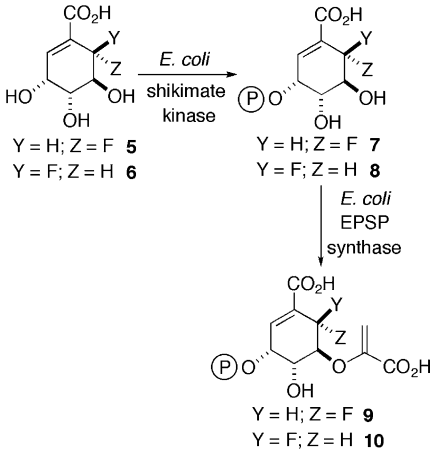
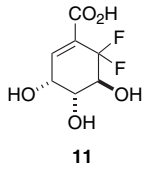



**Scheme 2.**

It has been disclosed quite recently that both **5** and **6** inhibit the growth of the parasite *Plasmodium falciparum*, the principal causative agent of malaria in humans.[7] In contrast to the situation with *E. coli*, the (6*R*)-compound **6** was significantly more potent than isomer **5** in this assay. This intriguing discovery has stimulated renewed interest in the design and synthesis of novel inhibitors of enzymes on the shikimate pathway. In this paper, we provide details of the synthesis of compound **11**, the final member of the series of 6-fluoroshikimic acids (Fig. 1). We also describe our investigations into modifications of the synthetic approach for the preparation of other 6-substituted analogues of (−)-shikimic acid.

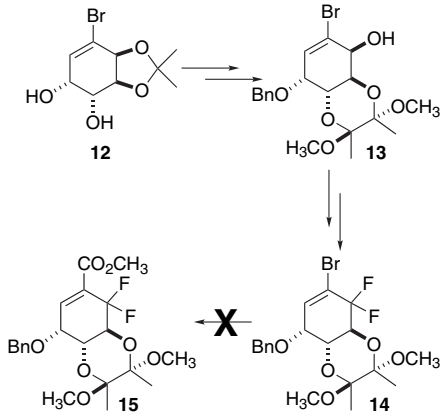


**11**

**Figure 1.**

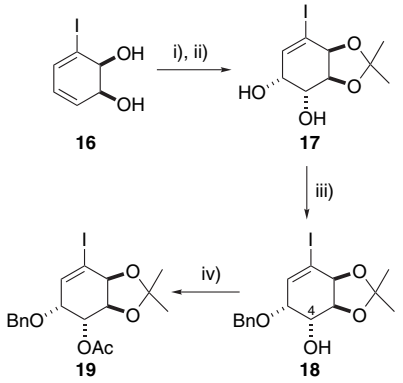
## 2. Results and discussion

Quite recently, we reported details of the synthesis of vinyl bromide **13** in four steps from commercially available diol **12** (Scheme 3).[1a] Oxidation of the allylic hydroxyl in **13** gave the expected α,β-unsaturated ketone which, on treatment with the nucleophilic fluorinating agent [bis-(2-methoxyethyl)]-aminosulfurtrifluoride (DeoxoFluor®)[8] was converted to the *gem*-difluoride **14**. Unfortunately, all attempts to introduce a carboxyl substituent at C1 of **14** using Pd(0) chemistry, as well as using other trans-metallation protocols, were unsuccessful.



**Scheme 3.**

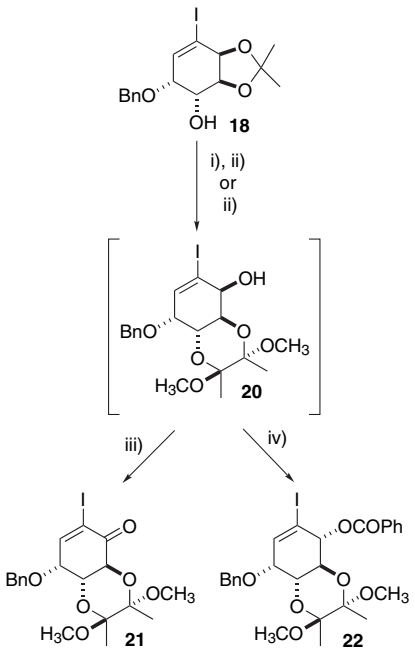
It is well documented that aryl and vinyl bromides exhibit diminished reactivity in Pd(0) catalysed C–C bond forming reactions when compared with the corresponding vinyl iodides. We decided, therefore, to turn our attention to the preparation of the analogue of **14**, which bears an iodine atom at C1. Our starting material for this synthesis was the enantiomerically pure diol **16**, which is obtained from the toluene-dioxygenase catalysed cis-dihydroxylation of iodobenzene (Scheme 4).[9,10]



**Scheme 4.** Reagents: (i) $(CH_3O)_2C(CH_3)_2$, *p*-TSA, $CH_2Cl_2$; (ii) $OsO_4$ (cat.), NMO, $^tBuOH$, $H_2O$, 81% over two steps; (iii) $Bu_2SnO$, $C_6H_5CH_3$, $CH_3OH$, Δ, then BnBr, $Bu_4NI$, $C_6H_5CH_3$, 130 °C, 91%; (iv) $Ac_2O$, DMAP, py, $CH_2Cl_2$, quant.

Following the general procedure of Hudlicky,[11] the vicinal diol in **16** was protected as an acetonide and subsequent face-selective cis-dihydroxylation of the less substituted 3,4-double bond gave diol **17** in good yield. Using the excellent protocol reported recently by Simas and co-workers,[12] a high-yielding and regioselective mono-benzylation of the vicinal diol in **17** was accomplished via an intermediate stannylene acetal, to give the benzyl ether **18**.[13] The regioselectivity of this reaction was confirmed by acetylation of the remaining free hydroxyl of **18** to give **19**: comparison of the $^1H$ NMR spectra of the two compounds confirmed a significant downfield shift of the resonance assigned to C(4)*H* in compound **19** [$\delta_H$ (300 MHz; $CDCl_3$): ~4.41 for **18**, 5.53 for **19**].

Over recent years, the protection of substrates bearing vicinal di-equatorial hydroxyl groups as their butane-diacetal (BDA) derivatives, has received a great deal of attention.[14] The enhanced stability of compounds protected in this way permits the use of a wide variety of reagents and conditions and furthermore, their conformational rigidity often has a beneficial influence on the stereoselectivity of subsequent transformations. Prompted by these observations, we initiated investigations into the conversion of **18** into the BDA protected compound **20**, which we believed would be a robust and versatile intermediate, not only for the synthesis of our target compound **11** but also for other analogues of (−)-shikimic acid (Scheme 5).

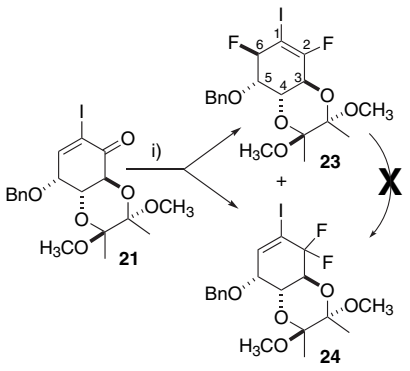



**Scheme 5.** Reagents: (i) TFA/$H_2O$ (1:1), rt; (ii) butan-2,3-dione, $(CH_3O)_3CH$, CSA, $CH_3OH$, Δ; (iii) DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$, −78 °C to rt, 15% over two steps; 36% over three steps; (iv) $Ph_3P$, DIAD, $C_6H_5CO_2H$, THF, 49% over three steps.

Direct trans-ketalisation of **18** with butan-2,3-dione gave an inseparable mixture of diacetals consisting predominantly of the desired isomer **20**. This mixture was then oxidised using Swern conditions[15] to give **21** in a disappointing 15% yield over two steps. A lengthier three-step procedure was thus developed, involving acid-catalysed hydrolysis of **18** to give the corresponding triol, followed by ketalisation to give an inseparable mixture of diacetals, which mostly comprised the desired isomer **20**. Oxidation of this mixture followed by chromatographic purification provided the enone **21** in an acceptable yield of 36% over three steps. Derivatisation of the inseparable mixture of diacetals with acetic anhydride and pyridine did not facilitate the purification of compound **20** (as the (6*S*)-acetate), however, exposure of the mixture of diacetals to Mitsunobu conditions[16] allowed isolation of the (6*R*)-benzoate **22** in 49% yield over three steps from **18**.

With the pivotal enone **21** in hand, we were able to investigate the key fluorodeoxygenation step necessary for the introduction of geminal fluorines at C6. Treatment of **21** with DeoxoFluor® in the absence of additional solvent for 72 h resulted in the formation of two isomeric difluorides. After chromatographic purification, the desired *gem*-difluoride **24** was isolated in 36% yield and the isomeric allylic fluoride **23** was isolated in 30% yield (Scheme 6).

The configuration at C6 of **23** was confirmed by comparison of its spectroscopic data with those of the corresponding vinyl bromide **25** (Fig. 2), the structure of which was previously assigned by the use of 2D heteronuclear Overhauser effect spectroscopy (HOESY).[1a] The formation of **23** is presumed to occur via allylic rearrangement during the difluorination reaction and the observed regiochemical outcome is likely to be a consequence of either a $S_N2'$ or a $S_N1'$ reaction of an activated intermediate of type **26** with ambient fluoride ion.




**Scheme 6.** Reagents: (i) DeoxoFluor®, rt, 72 h, 30% of **23**, 36% of **24**.

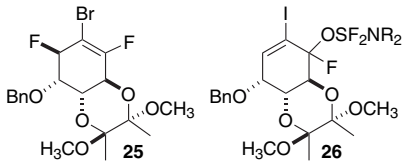
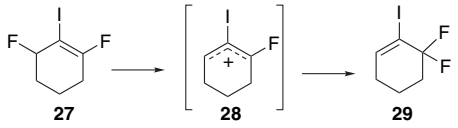


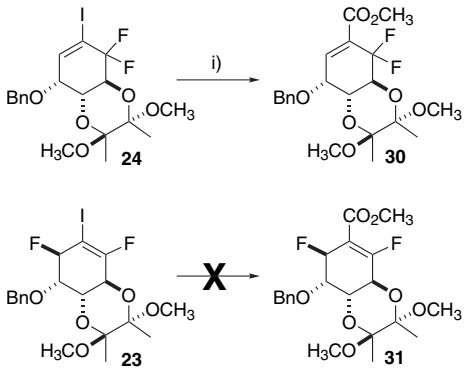

**Figure 2.**

Previous research efforts in our group have culminated in the development of mild reaction conditions for the isomerisation of the allylic fluoride **27** to the *gem*-difluoride **29** (Scheme 7).[17] In this model system, it transpired that simply stirring a solution of **27** in $CH_2Cl_2$ in the presence of 4 Å molecular sieves resulted in quantitative conversion of **27** to **29**. We have not carried out detailed investigations into the mechanism of this intriguing transformation, however, the reaction is presumed to proceed via the intermediacy of a transient allylic carbenium ion **28**. Unfortunately, despite extensive investigations, it proved impossible to discover conditions under which allylic fluoride **23** could be isomerised to *gem*-difluoride **24**. The contrasting reactivity of **23** and **27** is presumed to reflect the instability of the highly oxygenated carbenium ion, which is considered to be a necessary intermediate in the isomerisation of **23**.

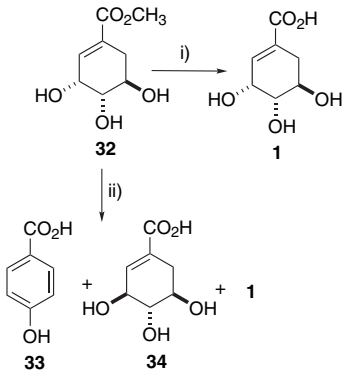



**Scheme 7.** Reagents: (i) 4 Å mol. sieves, $CH_2Cl_2$, rt, 8 h, quant.

Having successfully prepared the *gem*-difluoride **24**, we were in a position to investigate the key carbonylation reaction: the transformation that had thwarted progress in the corresponding vinyl bromide series.[1a] Previous model studies indicated that the vinyl iodide **29** was an excellent substrate in a variety of Pd(0)-mediated transformations. In particular, carbonylation using conditions modified from those described by Ortar[18] (tri-2-furyl phosphine and Hünigs base replacing triphenylphosphine and triethylamine, respectively) gave the corresponding unsaturated ester in 55% yield. Pleasingly, application of these reaction conditions to **24** yielded the desired ester **30** in comparable yield (56%) (Scheme 8).



**Scheme 8.** Reagents: (i) $Pd(OAc)_2$, diisopropylethylamine, tri-2-furylphosphine, $CH_3OH$, CO, DMF, rt, 24 h, 56%.

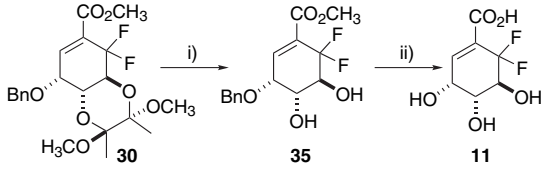


**Scheme 9.** Reagents: (i) concd $HCl/H_2O$ (1:1), 60–70 °C, 12 h, 86%; (ii) concd $HCl/H_2O$ (1:1), 100 °C, 30 h.

Exposure of the allylic rearrangement product **23** to the same carbonylation conditions failed to provide any of the expected unsaturated ester **31** and, indeed, starting material remained unchanged. This finding was particularly disappointing as we had envisaged that in the presence of fluoride ion, compound **31** might undergo relatively facile rearrangement to the *gem*-difluoride **30** via a conjugate addition–elimination sequence.

The successful preparation of unsaturated ester **30** meant that all that remained to be accomplished was complete deprotection to give the target material **11**. Several plausible sequences were considered with the main requirement being for conditions that would allow efficient removal of the benzyl protecting group without recourse to hydrogenolysis procedures. The possibility of effecting ester hydrolysis and concomitant debenzylation under acidic conditions was particularly attractive, however, we were cognizant of the pioneering work of J. F. Eykmann.[19] During his classic structural and reactivity studies of (−)-shikimic acid, Eykmann observed that the natural material underwent facile dehydrative aromatisation when heated in hydrochloric acid to give *para*-hydroxy benzoic acid. With a view to discovering reaction conditions under which aromatisation could be minimised, we carried out a brief investigation into the fate of methyl shikimate (**32**) when heated at different temperatures in ~6 M HCl. In accord with Eykmann's observations, heating **32** at 100 °C in ~6 M HCl for 30 h resulted in partial conversion to *para*-hydroxy benzoic acid **33**. A substantial quantity of 3-*epi*-shikimic acid (**34**) and a lesser quantity of **1** itself were also formed in the reaction (crude ratio **33**:**34**:**1** was 2:2:1). When the reaction time was shortened to 12 h, the product mixture was more complicated and analysis by $^1H$ NMR indicated the presence of other 'shikimate-like' materials as well as **33**, **34** and **1** (crude ratio **33**:**34**:**1** was 2:6:9). In contrast, when the temperature was decreased to ~60 °C and the reaction time maintained at 12 h, analysis of the crude reaction mixture indicated that no aromatisation or epimerisation had taken place and the only isolable product was (−)-shikimic acid (**1**) (Scheme 9).

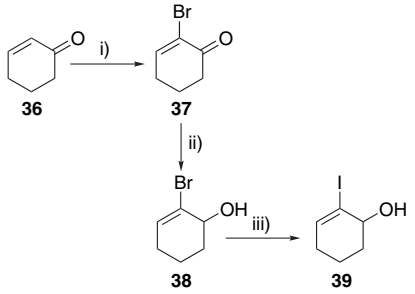
Encouraged by these observations, as well as the literature precedent for the cleavage of benzyl ethers under acidic conditions,[20] we embarked on the final deprotection sequence to give **11**. Ultimately, this was achieved in two straightforward steps (Scheme 10). Firstly, the BDA group was removed in quantitative fashion by stirring **30** in a mixture of TFA and water (6:1) at room temperature. Secondly, in accord with our model studies, removal of the benzyl protecting group and concomitant ester hydrolysis was accomplished by heating a solution of the diol **35** in ~6 M HCl at 60–70 °C for 12 h. Analysis of the crude product from this sequence by $^1H$ NMR spectroscopy indicated that no aromatisation had occurred and the target compound **11** was generated in essentially pure form.



**Scheme 10.** Reagents: (i) $TFA/H_2O$ (6:1), rt, 3 h; (ii) concd. $HCl/H_2O$ (1:1), 60–70 °C, 12 h then HPLC, 68% over two steps.

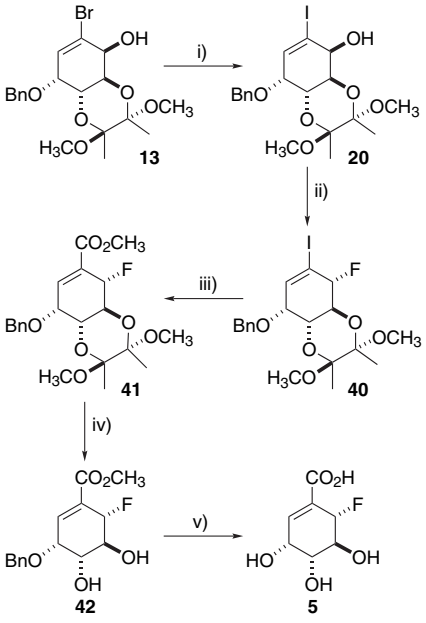
The shikimic acid pathway is a wonderful and elegant example of a divergent biosynthetic sequence: a plethora of aromatic end products is derived from a single, pre-branch-point intermediate of the pathway, chorismic acid (**4**).[21,22] Taking our lead from this impressive biosynthetic example, a major goal of our recent endeavours has been the development of a *divergent synthetic* strategy which will allow the efficient preparation of a range of analogues of shikimic acid. In this context, we envisaged vinyl iodide **20** (or an alternatively protected variant of **20**) to be a pivotal intermediate, however, high-yielding preparation of a sample of this compound had not been possible from the acetonide **18** (vide supra). During the course of our investigations, however, we became aware of the 'aromatic Finkelstein reaction' developed by Buchwald and co-workers.[23] This incredibly useful reaction effects the conversion of aryl bromides to the corresponding aryl iodides by the action of a catalytic quantity of CuI, KI and a 1,2-diamine additive. In the original publication, a single example of a halogen exchange of a vinyl bromide was reported and this prompted us to carry out a brief investigation into the halogen exchange of vinyl bromide **38**. This simple compound was readily prepared in two steps from 2-cyclohexenone (**36**)[24,25] and was selected as an appropriate model for the highly oxygenated vinyl bromide **13** (Scheme 11).

Reaction of **38** under the conditions described by Buchwald resulted in generation of crude product mixtures consisting




**Scheme 11.** Reagents: (i) $Br_2$, $Et_3N$, $CH_2Cl_2$, 0 °C to rt, 65%; (ii) $NaBH_4$, $CeCl_3$, $CH_3OH$, rt, 90%; (iii) KI, CuI, *N*,*N*′-dimethylethylenediamine, $^n$BuOH, 130 °C, 24 h.

predominantly of vinyl iodide **39** (ratios assessed by $^1$H NMR analysis). In our hands, the reaction was a little capricious and ratios of **39**:**38** generally varied unpredictably between 4:1 and 14:1. Interestingly, when the 1,2-diamine additive, *N*,*N*′-dimethylethylenediamine, was replaced with *trans*-1,2-diaminocyclohexane, the outcome was much inferior and ratios of **39**:**38** ranging from 1:3 to 1:7 were commonly obtained. The relative success of the conversion of **38** to **39** using *N*,*N*′-dimethylethylenediamine, encouraged us to attempt the halogen exchange of vinyl bromide **13**. Pleasingly, application of the conditions used in the model study resulted in good conversion to the vinyl iodide **20** (<10% contamination by **13**) (Scheme 12).




**Scheme 12.** Reagents: (i) CuI, KI, *N*,*N*′-dimethylethylenediamine, $^n$BuOH, 130 °C; (ii) $Et_2NSF_3$, $CH_2Cl_2$, −78 °C to rt, 38% over two steps from **13**; (iii) $Pd(OAc)_2$, diisopropylethylamine, tri-2-furylphosphine, $CH_3OH$, CO, DMF, rt, 24 h, 58%; (iv) TFA/$H_2O$ (6:1), rt, 3 h, 72%; (v) concd HCl/$H_2O$ (1:1), 60–70 °C, 10 h then HPLC, 61%.

Subsequent fluorodeoxygenation of **20** using the nucleophilic fluorinating agent DAST ($Et_2NSF_3$)[26] proceeded with inversion of configuration to give the allylic fluoride **40**, which could be obtained free of the corresponding vinyl bromide after chromatographic purification. Pd(0) mediated carbonylation of **40** occurred in comparable yield to the difluorinated analogue **24**, to give the α,β-unsaturated ester **41** and finally, two-stage removal of the protecting groups furnished (6*S*)-6-fluoroshikimic acid (**5**), which was identical in all respects to an authentic sample kindly provided by AstraZeneca.

## 3. Conclusions

In summary, we have prepared the novel compound, 6,6-difluoroshikimic acid (**11**), in ten steps from the enantiopure diol **16**. A key step in the synthesis, fluorodeoxygenation of enone **21**, was accomplished using the nucleophilic fluorinating agent DeoxoFluor®: although the total yield of difluorinated products from this reaction was reasonable, competing mechanistic processes resulted in the generation of only moderate quantities of the required *gem*-difluorinated product **24** together with equivalent amounts of an undesired vinyl fluoride **23**, arising from allylic rearrangement. In contrast to previous model studies, it proved impossible to isomerise the latter compound to *gem*-difluoride **24**, thus making the fluorine incorporation step the least efficient of the sequence.

Allylic alcohol **20**, an intermediate in the synthesis of 6,6-difluoroshikimic acid, was selected as an ideal candidate for a diversification point for the synthesis of other analogues of (−)-shikimic acid. Although not directly accessible in pure form from enantiopure diol **16**, compound **20** has been synthesised from the analogous vinyl bromide **13** via application of Buchwald's 'aromatic Finkelstein reaction'. The potential synthetic utility of **20** has been demonstrated by the preparation of the known antibacterial agent (6*S*)-6-fluoroshikimic acid (**5**).

## 4. Experimental

### 4.1. General

Solvents were dried and distilled before use. Chromatography was performed over Merck silica gel 60 (40–63 μm). IR spectra were recorded on a Perkin–Elmer 881 spectrometer or an AT1-Mattson Genesis Series FTIR spectrometer. $^1$H, $^{13}$C and $^{19}$F NMR spectra were recorded on a Varian Inova 400 MHz spectrometer or a Varian Inova 300 MHz spectrometer. Chemical shifts are referenced to the residual solvent peak. Mass spectra were recorded on Fisons VG Trio 2000 quadrupole (EI/CI, low resolution), Kratos Concept 1*S* (EI/CI, high resolution) and Micromass Platform (electrospray) spectrometers.

**4.1.1. (3*R*,4*R*,5*S*,6*S*)-1-Iodo-5-*O*,6-*O*-(propane-2′,2′-diyl)-cyclohex-1-ene-3,4,5,6-tetraol (17).** To a stirred solution of (5*S*,6*S*)-1-iodo-5,6-dihydroxycyclohexa-1,3-diene (**16**) (1.109 g, 4.66 mmol) in $CH_2Cl_2$ (36 mL) was added 2,2-dimethoxypropane (0.63 mL, 5.13 mmol) and a catalytic quantity of *p*-TSA. The reaction mixture was stirred at room temperature for 1 h after which time it was quenched by the addition of a saturated aqueous solution of sodium bicarbonate (40 mL). The organic phase was collected and combined with three further $CH_2Cl_2$ extracts (3×40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to provide the crude acetonide as a pale yellow oil (1.203 g). This material was dissolved in $^t$BuOH (15 mL) and *N*-methylmorpholine-*N*-oxide (0.56 g, 4.76 mmol) was

added followed by a solution of $OsO_4$ in $^tBuOH$ (1.8 mL of a 2.5% solution) and water (a few drops). The reaction mixture was stirred at room temperature for 36 h under an atmosphere of nitrogen when it was quenched by the addition of solid sodium metabisulphite (1.97 g) and filtered through a pad of silica, eluting with EtOAc. Concentration of the filtrate in vacuo gave the crude product as a dark-coloured solid, which was purified by flash column chromatography ($SiO_2$; EtOAc/petroleum ether (40–60), 7:13) to give the title compound as colourless crystals (1.175 g, 81%). $R_f$ 0.41 (EtOAc/petroleum ether (40–60), 2:5); mp 146–148 °C; $[\alpha]_D^{27}$ +23.6 (*c* 0.78, $CH_2Cl_2$); $\nu_{max}$ (film)/$cm^{-1}$ 3502s and 3376s (O–H), 2923w and 2882w (C–H), 1631w (C=C); $\delta_H$ (300 MHz; $CDCl_3$) 1.38 and 1.41 (2×3H, 2×s, 2×acetonide C$H_3$), 2.5 (2H, br, O*H*), 4.21 (1H, ~t, *J* 4.4, C(4)*H*), 4.28–4.33 (1H, m, C(3)*H*), 4.38 (1H, t, *J* 5.2, C(5)*H*), 4.63 (1H, br d, *J* 5.2, C(6)*H*), 6.41 (1H, d, *J* 3.0, C(2)*H*); $\delta_C$ (75 MHz; $CDCl_3$) 26.5 and 27.9 (2×acetonide *C*$H_3$), 67.9 (*C*(3)H), 69.5 (*C*(4)H), 76.4 (*C*(5)H), 78.6 (*C*(6)H), 100.8 (*C*(1)), 110.2 (acetonide *C*), 139.2 (*C*(2)H); *m/z* (EI) 312 ($M^+$, 3%), 297 (12), 254 (12), 127 (15), 109 (68), 101 (100) (Found 311.9853, $C_9H_{13}IO_4$ ($M^+$) requires 311.9860).

**4.1.2. (3*R*,4*R*,5*S*,6*S*)-1-Iodo-3-*O*-benzyl-5-*O*,6-*O*-(propane-2′,2′-diyl)-cyclohex-1-ene-3,4,5,6-tetraol (18).** A solution of the diol **17** (0.245 g, 0.79 mmol) and $Bu_2SnO$ (0.236 g, 0.95 mmol) in a 1:1 mixture of methanol and toluene (4 mL) was heated at 130 °C for 3 h. After this time, the solvent was evaporated under reduced pressure. Dry toluene (4 mL) was added and then evaporated under reduced pressure. The resulting crude stannylene acetal was redissolved in toluene (4 mL) and $Bu_4NBr$ (0.058 g, 0.16 mmol) and BnBr (0.19 mL, 1.58 mmol) were added. The mixture was then heated at 130 °C under an atmosphere of nitrogen for 6 h whereafter the solvent was removed in vacuo to give the crude product as a yellow oil. Purification by flash column chromatography ($SiO_2$; EtOAc/petroleum ether (40–60), 3:17), using a pad of KF at the top of the column to remove tin residues gave the title compound as colourless crystals (0.290 g, 91%). $R_f$ 0.32 (EtOAc/petroleum ether (40–60), 3:17); mp 73–74 °C; $[\alpha]_D^{22}$ −28.5 (*c* 1.20, $CH_2Cl_2$); $\nu_{max}$ (film)/$cm^{-1}$ 3464br (O–H), 2985m and 2890m (C–H), 1630w (C=C); $\delta_H$ (300 MHz; $CDCl_3$) 1.42 and 1.43 (2×3H, 2×s, 2×acetonide C$H_3$), 2.51 (1H, d, *J* 2.3, O*H*), 4.13 (1H, dd, *J* 4.1, 3.6, C(3)*H*), 4.40–4.43 (1H, m, C(4)*H*), 4.45 (1H, t, *J* 4.8, C(5)*H*), 4.64–4.73 (3H, m, C(6)*H* and benzyl C$H_2$), 6.46 (1H, d, *J* 3.6, C(2)*H*), 7.34–7.45 (5H, m, aromatic C*H*); $\delta_C$ (75 MHz; $CDCl_3$) 26.5 and 27.8 (2×acetonide *C*$H_3$), 67.5 (*C*(4)H), 71.9 (benzyl *C*$H_2$), 75.0 (*C*(3)H), 76.1 (*C*(5)H), 78.5 (*C*(6)H), 101.5 (*C*(1)), 110.1 (acetonide *C*), 128.1, 128.5 and 128.9 (aromatic *C*H), 136.8 (*C*(2)H), 137.5 (aromatic *ipso-C*); *m/z* (CI/$NH_3$) 420 ($MNH_4^+$, 40%), 403 ($MH^+$, 35), 294 (60), 277 (25), 106 (45), 58 (100) (Found 420.0674, $C_{16}H_{23}INO_4$ ($MNH_4^+$) requires 420.0672).

**4.1.3. (3*R*,4*R*,5*S*,6*S*)-1-Iodo-3-*O*-benzyl-4-*O*-acetyl-5-*O*,6-*O*-(propane-2′,2′-diyl)-cyclohex-1-ene-3,4,5,6-tetraol (19).** To a stirred solution of the benzyl ether **18** (0.04 g, 0.1 mmol) and DMAP (a few crystals) in $CH_2Cl_2$ (1 mL), under an atmosphere of nitrogen, was added acetic anhydride (0.5 mL, 5.3 mmol) followed by pyridine (0.5 mL, 6.2 mmol). After stirring at room temperature for 6 h, the reaction mixture was quenched by the addition of a saturated aqueous solution of ammonium chloride (10 mL). Organic material was extracted into $CH_2Cl_2$ (3×10 mL) and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give the product **19** as a viscous oil, which was of sufficient purity for spectroscopic analysis. $\nu_{max}$ (film)/$cm^{-1}$ 2986w, 2932w and 2870w (C–H), 1747s (C=O); $\delta_H$ (300 MHz; $CDCl_3$) 1.37 and 1.40 (2×3H, 2×s, 2×acetonide C$H_3$), 2.09 (3H, s, OC(=O)C$H_3$), 4.14 (1H, td, *J* 3.5, 1.5, C(3)*H*), 4.39 (1H, t, *J* 5.5, C(5)*H*), 4.51 (1H, d, *J* 11.7, OC$H_a$$H_b$Ph), 4.62 (1H, d, *J* 11.7, OC$H_a$$H_b$Ph), 4.64 (1H, d, *J* 5.5, C(6)*H*), 5.53 (1H, dd, *J* 5.5, 3.5, C(4)*H*), 6.48 (1H, br d, *J* 3.5, C(2)*H*), 7.26–7.34 (5H, m, aromatic C*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 21.3 (OC(=O)*C*$H_3$), 26.4 and 27.8 (2×acetonide *C*$H_3$), 69.2 (*C*(4)H), 72.1 (benzyl *C*$H_2$), 73.3 (*C*(3)H), 74.2 (*C*(5)H), 79.0 (*C*(6)H), 100.1 (*C*(1)), 110.4 (acetonide *C*), 128.1, 128.3 and 128.8 (aromatic *C*H), 137.8 (aromatic *ipso-C*), 138.6 (*C*(2)H), 170.6 (*C*=O); *m/z* (CI/$NH_3$) 462 ($MNH_4^+$, 60%), 445 ($MH^+$, 25), 336 (100) (Found 462.0779, $C_{18}H_{25}INO_5$ ($MNH_4^+$) requires 462.0778).

**4.1.4. (2′*S*,3′*S*,4*R*,5*R*,6*S*)-2-Iodo-4-*O*-benzyl-5-*O*,6-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-cyclohex-2-ene-1-one-4,5,6-triol (21).** A solution of alcohol **18** (0.290 g, 0.72 mmol) in a 1:1 mixture of water and TFA (12 mL) was stirred at room temperature for 3 h and the residual solvents were then removed directly in vacuo to give the intermediate triol in quantitative yield. This material was dissolved in dry methanol (7 mL) under an atmosphere of nitrogen and to the stirred solution were added CSA (a few crystals), trimethylorthoformate (1.6 mL, 14.4 mmol) and 2,3-butandione (0.14 mL, 1.56 mmol). The reaction mixture was then heated at reflux for 24 h, during which time it developed a deep red colouration. It was then allowed to cool to room temperature and $Et_3N$ (0.2 mL, 1.4 mmol) was added. Residual solvents were then removed in vacuo and the crude product was partially purified by flash column chromatography ($SiO_2$; EtOAc/petroleum ether (40–60), 1:9), to give a mixture of compounds consisting predominantly of the desired isomer **20** (0.256 g).

A solution of DMSO (0.05 mL, 0.70 mmol) in $CH_2Cl_2$ (2.5 mL) was added dropwise, under an atmosphere of nitrogen, to a solution of oxalyl chloride (0.06 mL, 0.69 mmol) in $CH_2Cl_2$ (2.5 mL), maintaining the reaction temperature below −60 °C. The reaction mixture was stirred for 30 min at <−60 °C, before a pre-cooled solution of the crude bisacetal **20** (0.256 g) in $CH_2Cl_2$ (3.5 mL) was added dropwise. The reaction mixture was stirred below −60 °C for a further 65 min before $Et_3N$ (0.34 mL, 2.43 mmol) was added dropwise and the resulting yellow solution was allowed to warm gradually to room temperature. After stirring for a further 4 h at room temperature, the reaction mixture was quenched by the addition of a saturated aqueous solution of ammonium chloride (150 mL). The organic phase was collected and combined with three further $CH_2Cl_2$ extracts (3×100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography ($SiO_2$; EtOAc/petroleum ether (40–60), 1:12) gave the title compound as a viscous oil (0.125 g, 36% from **18**). $R_f$ 0.16 (EtOAc/petroleum ether (40–60), 1:19); $[\alpha]_D^{27}$ −7.70 (*c* 1.03, $CH_2Cl_2$); $\nu_{max}$ (film)/$cm^{-1}$ 2924m (C–H), 1711s (C=O); $\delta_H$ (300 MHz; $CDCl_3$)

1.43 and 1.46 (2×3H, 2×s, 2×butyl C$H_3$), 3.31 and 3.38 (2×3H, 2×s, 2×acetal OC$H_3$), 4.11 (1H, dd, *J* 10.8, 3.5, C(5)*H*), 4.24 (1H, dd, *J* 6.4, 3.5, C(4)*H*), 4.72 (1H, d, *J* 11.3, OC$H_a$H$_b$Ph), 5.02 (1H, d, *J* 10.8, C(6)*H*), 5.12 (1H, d, *J* 11.3, OCH$_a$$H_b$Ph), 7.35–7.52 (5H, m, aromatic C*H*), 7.59 (1H, d, *J* 6.4, C(3)*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 17.88 and 17.90 (2×butyl *C*H$_3$), 48.4 and 48.7 (2×acetal O*C*H$_3$), 69.2 (*C*(6)H), 69.7 (*C*(5)H), 73.7 (*C*(4)H), 74.4 (benzyl *C*H$_2$), 99.7 and 100.4 (2×acetal *C*), 107.3 (*C*(2)), 128.4, 128.6 and 128.8 (aromatic *C*H), 138.3 (aromatic *ipso-C*), 151.3 (*C*(3)H), 186.4 (*C*=O); *m/z* (CI/NH$_3$) 492 ($MNH_4^+$, 32%), 391 (57), 136 (52), 124 (56), 106 (100), 100 (90), 88 (80) (Found 492.0885, $C_{19}H_{27}INO_6$ ($MNH_4^+$) requires 492.0883).

**4.1.5. (2′*S*,3′*S*,3*R*,4*R*,5*S*,6*R*)-1-Iodo-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-6-*O*-benzoyl-cyclohex-1-ene-3,4,5,6-tetraol (22).** To a solution of the mixture of bis-acetals containing **20** prepared as described above (0.42 g, 0.88 mmol) in THF (8 mL) was added a solution of triphenylphosphine (0.92 g, 3.52 mmol) in THF (10 mL) followed by a solution of benzoic acid (0.22 g, 1.76 mmol) in THF (5 mL) and finally diisopropylazodicarboxylate (0.35 mL, 1.76 mmol). The reaction mixture was stirred for 18 h when the solvent was removed in vacuo to give the crude product as a yellow oil. Purification by flash column chromatography ($SiO_2$; EtOAc/petroleum ether (40–60), 1:19) gave the title compound as colourless crystals (0.440 g, 49% from **18**). $R_f$ 0.15 (EtOAc/petroleum ether (40–60), 1:9); mp 52.9–55.1 °C; $[\alpha]_D^{23}$ +63.71 (*c* 1.78, $CH_2Cl_2$); $\nu_{max}$ (film)/cm$^{-1}$ 2991w, 2945m and 2832w (C–H), 1730s (C=O); $\delta_H$ (300 MHz; $CDCl_3$) 1.28 and 1.39 (2×3H, 2×s, 2×butyl C$H_3$), 3.22 and 3.33 (2×3H, 2×s, 2×acetal OC$H_3$), 3.95 (1H, dd, *J* 11.0, 3.7, C(4)*H*), 4.03 (1H, dd, *J* 6.0, 3.7, C(3)*H*), 4.54 (1H, dd, *J* 11.0, 8.2, C(5)*H*), 4.70 (1H, d, *J* 11.3, OC$H_a$H$_b$Ph), 5.08 (1H, d, *J* 11.3, OCH$_a$$H_b$Ph), 5.94 (1H, d, *J* 8.2, C(6)*H*), 6.65 (1H, d, *J* 6.0, C(2)*H*), 7.30–7.76 (8H, m, aromatic C*H*), 8.16 (2H, d, *J* 8.5, benzoyl *o*-C*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 18.0 (2×butyl *C*H$_3$, coincident), 48.0 and 48.3 (2×acetal O*C*H$_3$), 67.5 (*C*(5)H), 69.1 (*C*(4)H), 73.8 (*C*(3)H), 74.0 (benzyl *C*H$_2$), 75.4 (*C*(6)H), 99.3 and 99.6 (2×acetal *C*), 102.7 (*C*(1)), 128.1, 128.6, 128.66, 128.70, 130.3 and 133.5 (aromatic *C*H), 130.1 & 138.8 (aromatic *ipso-C*), 138.7 (*C*(2)H), 165.6 (*C*=O); *m/z* (+ve ion electrospray) 603 ([M+Na]$^+$, 100%) (Found 603.0855, $C_{26}H_{29}O_7INa$ ([M+Na]$^+$) requires 603.0850).

**4.1.6. (2′*S*,3′*S*,3*R*,4*R*,5*S*)-1-Iodo-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-6,6-difluoro-cyclohex-1-ene-3,4,5-triol (24).** A sample of the enone **21** (0.160 g, 0.34 mmol) was cooled to 0 °C under an atmosphere of nitrogen and [bis-(2-methoxyethyl)]-aminosulfurtrifluoride (DeoxoFluor®) (0.94 mL, 5.1 mmol) was carefully added. The reaction mixture was allowed to warm to room temperature and was stirred for 72 h before being diluted with $CH_2Cl_2$ (100 mL) and quenched by the careful addition of a saturated aqueous solution of sodium bicarbonate (100 mL). The organic phase was collected and combined with three subsequent $CH_2Cl_2$ extracts (3×100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give the crude product as a brown oil. Purification by flash column chromatography ($SiO_2$; EtOAc/petroleum ether (40–60), 1:19) gave the title compound as an oil (0.060 g, 36%) and the allylically rearranged isomer **23** also as an oil (0.050 g, 30%). Data for **24**: $R_f$ 0.67 (EtOAc/petroleum ether (40–60), 1:4); $[\alpha]_D^{19}$ +26.1 (*c* 1.36, $CH_2Cl_2$); $\nu_{max}$ (film)/cm$^{-1}$ 2994m, 2957m, 2925m and 2836m (C–H); $\delta_H$ (300 MHz; $CDCl_3$) 1.42 and 1.46 (2×3H, 2×s, 2×butyl C$H_3$), 3.33 and 3.40 (2×3H, 2×s, 2×acetal OC$H_3$), 4.01 (1H, dd, *J* 11.0, 3.7, C(4)*H*), 4.06 (1H, ddd, *J* 5.5, 3.7, 1.9, C(3)*H*), 4.62 (1H, ddd, *J* 14.7, 11.0, 8.6, C(5)*H*), 4.67 (1H, d, *J* 11.1, OC$H_a$H$_b$Ph), 5.06 (1H, d, *J* 11.1, OCH$_a$$H_b$Ph), 6.75 (1H, dd, *J* 5.5, 2.4, C(2)*H*), 7.35–7.50 (5H, m, aromatic C*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 17.87 and 17.95 (2×butyl *C*H$_3$), 48.47 and 48.48 (2×acetal O*C*H$_3$), 65.9 (dd, *J* 23.0, 17.6, *C*(5)H), 67.3 (d, *J* 8.3, *C*(4)H), 73.4 (*C*(3)H), 74.4 (benzyl *C*H$_2$), 97.8 (dd, *J* 33.3, 27.9, *C*(1)), 99.6 and 99.9 (2×acetal *C*), 115.2 (dd, *J* 246.0, 243.3, *C*(6)F$_2$), 128.2, 128.5 and 128.7 (aromatic *C*H), 138.4 (aromatic *ipso-C*), 142.3 (t, *J* 7.2, *C*(2)H); $\delta_F$ (376.3 MHz; $CDCl_3$) −104.6 (1F, dd, *J* 265.3, 14.7, one of C(6)$F_2$), −91.6 (1F, ddd, *J* 265.3, 8.6, 2.4, one of C(6)$F_2$); *m/z* (CI/NH$_3$) 514 ($MNH_4^+$, 4%), 482 (3), 388 (3), 356 (6), 307 (6), 85 (100) (Found 514.0905, $C_{19}H_{27}F_2INO_5$ ($MNH_4^+$) requires 514.0896). Data for **23**: $R_f$ 0.80 (EtOAc/petroleum ether (40–60), 1:4); $[\alpha]_D^{19}$ +84.8 (*c* 1.0, $CH_2Cl_2$); $\nu_{max}$ (film)/cm$^{-1}$ 2993m, 2949m, 2924m and 2834m (C–H), 1667m (C=C); $\delta_H$ (300 MHz; $CDCl_3$) 1.41 and 1.42 (2×3H, 2×s, 2×butyl C$H_3$), 3.31 and 3.36 (2×3H, 2×s, 2×acetal OC$H_3$), 4.04 (1H, dt, *J* 8.5, 2.3, C(5)*H*), 4.16 (1H, dt, *J* 9.0, 2.1, C(4)*H*), 4.72 (1H, d, *J* 11.6, OC$H_a$H$_b$Ph), 4.88 (1H, ddd, *J* 11.3, 9.0, 3.7, C(3)*H*), 5.00 (1H, d, *J* 11.6, OCH$_a$$H_b$Ph), 5.04 (1H, ddd, 46.7, 6.8, 2.3, C(6)*H*F), 7.35–7.43 (5H, m, aromatic C*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 17.90 and 17.94 (2×butyl *C*H$_3$), 48.4 and 48.5 (2×acetal O*C*H$_3$), 64.1 (dd, *J* 21.6, 2.9, *C*(3)H), 68.2 (d, *J* 4.1, *C*(4)H), 70.8 (dd, *J* 22.4, 21.9, *C*(1)), 74.0 (benzyl *C*H$_2$), 76.3 (dd, *J* 27.3, 1.7, *C*(5)H), 93.0 (dd, *J* 182, 7.5, *C*(6)HF), 100.7 (2×acetal *C*), 128.3 and 128.8 (aromatic *C*H), 137.9 (aromatic *ipso-C*), 161.4 (dd, *J* 279.3, 11.2, *C*(2)F); $\delta_F$ (376.3 MHz; *C*D*C*l$_3$) −163.7 (1F, ddddd, *J* 46.7, 11.3, 8.5, 6.8, 2.0, C(6)H*F*), −85.7 (1F, td, *J* 6.8, 3.7, C(2)*F*); *m/z* (CI/NH$_3$) 514 ($MNH_4^+$, 1%), 482 (2), 356 (1), 307 (1), 85 (100) (Found 514.0902, $C_{19}H_{27}F_2INO_5$ ($MNH_4^+$) requires 514.0896).

**4.1.7. (2′*S*,3′*S*,3*R*,4*R*,5*S*)-1-Methoxycarbonyl-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-6,6-difluoro-cyclohex-1-ene-3,4,5,-triol (30).** Palladium acetate (0.5 mg, 0.002 mmol), tri-2-furylphosphine (1.2 mg, 0.005 mmol) and $CH_3OH$ (0.17 mL) were placed in a three-necked, pear-shaped flask fitted with two Suba Seals® and a balloon filled with CO. Diisopropylethylamine (0.016 mL, 0.094 mmol) and a solution of the vinyl iodide **24** (0.044 g, 0.09 mmol) in DMF (1 mL) were added to the flask. CO was bubbled through the solution for 5 min and the whole system was then flushed several times with CO. The reaction mixture was stirred under a balloon atmosphere of CO at room temperature for 24 h. Diethyl ether (10 mL) and water (5 mL) were then added to the flask. The organic phase was collected and washed with water (3×5 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography ($SiO_2$; EtOAc/petroleum ether (40–60), 1:19) gave the title compound as colourless crystals (0.021 g, 56%). $R_f$ 0.37 (EtOAc/petroleum ether (40–60), 1:4); mp 133 °C; $[\alpha]_D^{19}$ +2.9 (*c* 1.36, $CH_2Cl_2$); $\nu_{max}$

(film)/cm$^{-1}$ 1733s (C═O); $\delta_H$ (400 MHz; $CDCl_3$) 1.39 and 1.43 (2×3H, 2×s, 2×butyl C$H_3$), 3.30 and 3.36 (2×3H, 2×s, 2×acetal OC$H_3$), 3.82 (3H, s, $CO_2CH_3$), 3.96 (1H, dd, *J* 10.8, 3.8, C(4)*H*), 4.25 (1H, dd, *J* 5.8, 3.8, C(3)*H*), 4.50 (1H, dt, *J* 13.6, 10.8, C(5)*H*), 4.68 (1H, d, *J* 11.2, OC$H_a$H$_b$Ph), 5.05 (1H, d, *J* 11.2, OCH$_a$$H_b$Ph), 7.08 (1H, dd, *J* 5.8, 2.4, C(2)*H*), 7.29–7.40 (3H, m, aromatic *m*- and *p*-C*H*), 7.45 (2H, d, *J* 7.6, aromatic *o*-C*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 17.90 and 17.96 (2×butyl *C*H$_3$), 48.4 and 48.5 (2×acetal O*C*H$_3$), 52.8 ($CO_2CH_3$), 66.9 (dd, *J* 21.3, 18.4, *C*(5)H), 67.1 (dd, *J* 6.0, 1.2, *C*(4)H), 70.1 (*C*(3)H), 74.8 (benzyl *C*H$_2$), 99.6 and 99.8 (2×acetal *C*), 115.9 (t, *J* 245.1, *C*(6)F$_2$), 128.3, 128.6 and 128.7 (aromatic *C*H), 129.1 (dd, *J* 26.5, 22.9, *C*(1)), 138.4 (aromatic *ipso*-*C*), 141.3 (t, *J* 6.6, *C*(2)H), 163.2 (t, *J* 1.4, *C*═O); $\delta_F$ (376.3 MHz; $CDCl_3$) −106.5 (1F, ddd, *J* 278.3, 10.8, 2.4, one of C(6)$F_2$), −107.4 (1F, dd, *J* 278.3, 13.6, one of C(6)$F_2$); *m*/*z* (CI/$NH_3$) 446 ($MNH_4^+$, 100%), 414 (25), 340 (52), 188 (25), 102 (67) (Found 446.1987, $C_{21}H_{30}F_2NO_7$ ($MNH_4^+$) requires 446.1990).

**4.1.8. (−)-Shikimic acid (1).** Methyl shikimate (**32**) (0.024 g, 0.13 mmol) was stirred at 60–70 °C in a mixture of water and concentrated HCl (1:1, 1 mL) for 12 h. After this time, the solvent was removed directly in vacuo to give (−)-shikimic acid in essentially pure form as a yellow oil. Analytical material was obtained by purification using reverse phase HPLC [Rainin Dynamax C18 (21.4×250 mm); eluent: $H_2O$/formic acid, 99.9:0.1; UV detection at 255 nm] to give the title compound as colourless crystals (0.019 g, 86%). Mp 182–184 °C (Lit.[27] mp 184–186 °C); $[\alpha]_D^{23}$ −186.1 (*c* 1.07, $H_2O$) (Lit.[27] $[\alpha]_D^{25}$ −170.0 (*c* 0.86, $H_2O$)); $\delta_H$ (300 MHz; $D_2O$) 2.16 (1H, ddt, *J* 18.2, 6.3, 1.8, one of C(6)$H_2$), 2.67 (1H, ddt, *J* 18.2, 5.3, 1.8, one of C(6)$H_2$), 3.71 (1H, dd, *J* 8.2, 4.1, C(4)*H*), 3.97 (1H, ddd, *J* 8.2, 6.3, 5.3, C(5)*H*), 4.38 (1H, ~t, *J* 4.1, C(3)*H*), 6.80 (1H, ~dt, *J* 4.1, 1.8, C(2)*H*); $\delta_C$ (75.4 MHz; $D_2O$) 30.5 (*C*(6)H$_2$), 66.0 (*C*(3)H), 66.8 (*C*(5)H), 71.3 (*C*(4)H), 129.9 (*C*(1)), 137.6 (*C*(2)H), 170.3 (*C*═O); *m*/*z* (−ve ion electrospray) 347 ([M$_2$−H]$^-$, 60%), 173 ([M−H]$^-$, 100).

**4.1.9. 3-*epi*-Shikimic acid (34).** Methyl shikimate (**32**) (0.011 g, 0.06 mmol) was stirred at 100 °C in a mixture of water and concentrated HCl (1:1, 1 mL) for 30 h. After this time, the solvent was removed directly in vacuo to give the crude product mixture as a yellow solid. Purification using reverse phase HPLC [Rainin Dynamax C18 (21.4×250 mm); eluent: $H_2O$/formic acid, 99.9:0.1; UV detection at 255 nm] gave the title compound as a colourless solid (0.0021 g, 21%) as well as *para*-hydroxy benzoic acid (0.0016 g, 21%) and (−)-shikimic acid (0.0008 g, 8%). Data for **34**: mp 164–166 °C (Lit.[28] mp 164–165 °C); $[\alpha]_D^{21}$ −28.0 (*c* 0.1, $H_2O$) (Lit.[28] $[\alpha]_D$ −31.0 (*c* 0.1, $H_2O$)); $\delta_H$ (300 MHz; $D_2O$) 2.11 (1H, dddd, *J* 17.2, 10.0, 3.8, 2.9 one of C(6)$H_2$), 2.68 (1H, ddd, *J* 17.2, 5.9, 1.6, one of C(6)$H_2$), 3.38 (1H, dd, *J* 10.0, 8.1, C(4)*H*), 3.68 (1H, td, *J* 10.0, 5.9, C(5)*H*), 4.17 (1H, dddd, *J* 8.1, 3.8, 2.2, 1.6, C(3)*H*), 6.57 (1H, ~t, *J* 2.5, C(2)*H*); *m*/*z* (−ve ion electrospray) 347 ([M$_2$−H]$^-$, 43%), 173 ([M−H]$^-$, 100).

**4.1.10. (2′*S*,3′*S*,3*R*,4*R*,5*S*)-1-Methoxycarbonyl-3-*O*-benzyl-6,6-difluoro-cyclohex-1-ene-3,4,5-triol (35).** The methyl ester **30** (0.021 g, 0.050 mmol) was stirred at room temperature in a mixture of water and TFA (1:6, 1 mL) for 3 h and the solvent was then removed directly in vacuo. After storage under high vacuum for several hours, the title compound was obtained in a sufficiently pure state (assessed by $^1$H NMR analysis) to be carried on directly to the final step (0.016 g, ~quant.). $\delta_H$ (300 MHz; $CDCl_3$) 3.89 (3H, s, $CO_2CH_3$), 4.09–4.14 (1H, m, C(4)*H*), 4.29 (1H, ~q, *J* 9.0, C(5)*H*), 4.37–4.43 (1H, m, C(3)*H*), 4.79 (2H, s, benzyl C$H_2$), 7.20 (1H, br s, C(2)*H*), 7.37–7.48 (5H, m, aromatic C*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 52.8 ($CO_2CH_3$), 69.1 (d, *J* 5.7, *C*(4)H), 71.5 (dd, *J* 26.2, 20.7, *C*(5)H), 71.9 (*C*(3)H), 73.1 (benzyl *C*H$_2$), 115.9 (dd, *J* 245.4, 241.3, *C*(6)F$_2$), 127.7 (t, *J* 25.6, C(1)), 128.3, 128.76 and 129.0 (aromatic *C*H), 137.1 (aromatic *ipso*-*C*), 142.9 (t, *J* 7.2, *C*(2)H), 163.30 (*C*═O).

**4.1.11. 6,6-Difluoroshikimic acid (11).** The diol **35** (0.016 g) was stirred at 60–70 °C in a mixture of water and concentrated HCl (1:1, 1 mL) for 12 h. After this time, the solvent was removed directly in vacuo to give the title compound in quantitative yield as a viscous, yellow oil. Analytical material could be obtained by further purification using reverse phase HPLC [Rainin Dynamax C18 (21.4×250 mm); eluent: $H_2O$/TFA, 99.9:0.1; UV detection at 254 nm] to give the title compound as a colourless foam (0.010 g, 68% from **30**). $[\alpha]_D^{25}$ −128.0 (*c* 0.10, $H_2O$); $\delta_H$ (400 MHz; $D_2O$) 3.78 (1H, ddd, *J* 9.6, 4.0, 1.6, C(4)*H*), 3.99 (1H, ~dt, *J* 12.0, 9.6, C(5)*H*), 4.38 (1H, br t, *J* 4.0, C(3)*H*), 6.91 (1H, dd, *J* 4.4, 2.0, C(2)*H*); $\delta_C$ (100 MHz; $D_2O$) 67.4 (*C*(3)H), 71.1 (d, *J* 6.8, *C*(4)H), 72.5 (dd, *J* 24.3, 19.9, *C*(5)H), 119.9 (t, *J* 241.2, *C*(6)F$_2$), 145.3 (t, *J* 7.2, *C*(2)H), 159.6 (*C*═O), (*C*(1) not detected); $\delta_F$ (376.3 MHz; $D_2O$) −104.8 (1F, br d, *J* 278.1, one of C(6)$F_2$), −109.3 (1F, dd, *J* 278.1, 12.0, one of C(6)$F_2$); *m*/*z* (−ve ion electrospray) 209 ([M−H]$^-$, 60%), 189 (100) (Found 209.0270, $C_7H_7F_2O_5$ ([M−H]$^-$) requires 209.0267).

**4.1.12. (2′*S*,3′*S*,3*R*,4*R*,5*S*,6*S*)-1-Iodo-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-cyclohex-1-ene-3,4,5,6-tetraol (20).** The vinyl bromide **13** (0.150 g, 0.35 mmol), copper (I) iodide (4 mg, 0.02 mmol) and potassium iodide (0.087 g, 0.52 mmol) were placed in a flask, which was evacuated and backfilled with nitrogen five times. $^n$Butanol (3 mL) and *N*,*N*′-dimethylethylenediamine (3.1 μL, 10 mol %) were added and the flask was evacuated and backfilled with nitrogen a further five times. The stirred mixture was then heated at 120 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (10 mL) and washed with dilute aqueous ammonia solution (20 mL) followed by water (3×10 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a viscous, dark yellow oil. Purification by flash column chromatography ($SiO_2$; EtOAc/petroleum ether (40–60), 1:9) yielded the title compound, contaminated with <10% of **13**, as a pale yellow oil (0.121 g). $R_f$ 0.10 (EtOAc/petroleum ether (40–60), 1:9); $\nu_{max}$ (film)/cm$^{-1}$ 3468br, m (O–H), 3027m, 2991m, 2948m, 2926m and 2832m (C–H), 1626w (C═C); $\delta_H$ (300 MHz; $CDCl_3$) 1.36 (6H, s, 2×butyl C$H_3$), 2.78 (1H, br s, 6-O*H*), 3.28 and 3.32 (2×3H, 2×s, 2×acetal OC$H_3$), 3.98 (1H, dd, *J* 6.0, 3.8, C(3)*H*), 4.10 (1H, dd, *J* 10.4, 3.8, C(4)*H*), 4.34–4.40 (2H, m, C(5)*H* and C(6)*H*), 4.60 (1H, d, *J* 11.1, OC$H_a$H$_b$Ph), 5.01 (1H, d, *J* 11.1, OCH$_a$$H_b$Ph), 6.51 (1H, d, *J* 6.0, C(2)*H*),

7.30–7.47 (5H, m, aromatic C*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 18.0 and 18.1 (2×butyl *C*$H_3$), 48.3 and 48.4 (2×acetal O*C*$H_3$), 65.7 (*C*(4)H), 65.9 (*C*(5)H), 74.1 (benzyl *C*$H_2$), 74.5 (*C*(3)H), 75.4 (*C*(6)H), 99.6 and 100.0 (2×acetal *C*), 101.8 (*C*(1)), 128.0, 128.5 and 128.6 (aromatic *C*H), 138.9 (*C*(2)H), 149.7 (aromatic *ipso-C*); *m/z* (CI/$NH_3$) 494 ($MNH_4^+$, 5%) (Found 494.1053, $C_{19}H_{29}O_6IN$ ($MNH_4^+$) requires 494.1040).

**4.1.13. (2′*S*,3′*S*,3*R*,4*R*,5*S*,6*R*)-1-Iodo-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-6-fluoro-cyclohex-1-ene-3,4,5-triol (40).** DAST (0.06 mL, 0.49 mmol) was added under an atmosphere of nitrogen to a stirred solution of the allylic alcohol **20** (0.107 g, 0.22 mmol) in anhydrous $CH_2Cl_2$ (3 mL) at −78 °C. The stirred reaction mixture was allowed to warm to room temperature, and stirring was continued for a further 2.5 h. The reaction mixture was then cooled to −20 °C and $CH_3OH$ (10 mL) was gradually added followed by calcium carbonate and the mixture was then filtered. Concentration of the filtrate in vacuo gave a dark yellow viscous oil, which was purified by flash column chromatography ($SiO_2$; EtOAc/petroleum ether (40–60), 1:9) to give the title compound as a colourless oil (0.057 g, 38% from **13**). $R_f$ 0.38 (EtOAc/petroleum ether (40–60), 1:9); $[\alpha]_D^{26}$ +52.0 (*c* 1.5, $CH_2Cl_2$); $\nu_{max}$ (film)/$cm^{-1}$ 2992–2883m (C–H), 1624w (C═C); $\delta_H$ (300 MHz; $CDCl_3$) 1.39 and 1.41 (2×3H, 2×s, 2×butyl C*H*$_3$), 3.32 and 3.39 (2×3H, 2×s, 2×acetal OC*H*$_3$), 3.79 (1H, ddd, *J* 11.0, 3.7, 0.7, C(4)*H*), 3.96 (1H, dd, *J* 6.0, 3.7, C(3)*H*), 4.54 (1H, ddd, *J* 18.3, 11.0, 7.3, C(5)*H*), 4.66 (1H, d, *J* 11.4, OC*H*$_a$H$_b$Ph), 4.88 (1H, ddd, *J* 50.1, 7.3, 1.2, C(6)*H*F), 5.02 (1H, d, *J* 11.4, OCH$_a$*H*$_b$Ph), 6.62 (1H, dd, *J* 6.0, 1.2, C(2)*H*), 7.33–7.49 (5H, m, aromatic C*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 17.9 (2×butyl *C*$H_3$, coincident), 48.3 and 48.4 (2×acetal O*C*$H_3$), 67.6 (d, *J* 13.1, *C*(5)H), 68.2 (d, *J* 8.7, *C*(4)H), 73.6 (*C*(3)H), 73.8 (benzyl *C*$H_2$), 93.1 (d, *J* 182.0, *C*(6)H), 99.2 and 99.6 (2×acetal *C*), 100.6 (d, *J* 22.5, *C*(1)), 128.0, 128.5 and 128.6 (aromatic *C*H), 138.7 (aromatic *ipso-C*), 139.2 (d, *J* 4.6, *C*(2)H); $\delta_F$ (376.3 MHz; $CDCl_3$) 172.2 (dd, *J* 50.1, 18.3, *C*(6)HF); *m/z* (+ve ion electrospray) 501 ([M+Na]$^+$, 70%) (Found 501.0549, $C_{19}H_{24}FIO_5Na$ ([M+Na]$^+$) requires 501.0545).

**4.1.14. (2′*S*,3′*S*,3*R*,4*R*,5*S*,6*S*)-1-Methoxycarbonyl-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxy-butane-2′,3′-diyl)-6-fluoro-cyclohex-1-ene-3,4,5,-triol (41).** An identical procedure to that used in Section 4.1.7 was used to transform the vinyl iodide **40** (0.070 g, 0.17 mmol). Purification by flash column chromatography ($SiO_2$; $Et_2O$/petroleum ether (40–60), 1:1) gave the title compound as a colourless solid (0.035 g, 58%). $R_f$ 0.28 ($Et_2O$/petroleum ether (40–60), 1:1); mp 113–115 °C; $[\alpha]_D^{19}$ +34.5 (*c* 1.08, $CHCl_3$); $\nu_{max}$ (film)/$cm^{-1}$ 1730s (C═O); $\delta_H$ (300 MHz; $CDCl_3$) 1.47 and 1.49 (2×3H, 2×s, 2×butyl C*H*$_3$), 3.38 and 3.47 (2×3H, 2×s, 2×acetal OC*H*$_3$), 3.69 (1H, dd, *J* 11.4, 3.4, C(4)*H*), 3.89 (3H, s, $CO_2CH_3$), 4.20 (1H, dd, *J* 6.0, 3.4, C(3)*H*), 4.57 (1H, ddd, *J* 21.3, 11.4, 7.1, C(5)*H*), 4.73 (1H, d, *J* 11.4, OC*H*$_a$H$_b$Ph), 5.05 (1H, d, *J* 11.4, OCH$_a$*H*$_b$Ph), 5.38 (1H, dd, *J* 49.2, 7.1, C(6)*H*F), 6.91 (1H, d, *J* 6.0, C(2)*H*), 7.34–7.51 (5H, m, aromatic C*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 17.9 and 18.0 (2×butyl *C*$H_3$), 48.3 and 48.4 (2×acetal O*C*$H_3$), 52.5 ($CO_2CH_3$), 68.1 (d, *J* 4.6, *C*(4)H), 68.3 (d, *J* 8.1, *C*(5)H) 70.6 (*C*(3)H), 74.1 (benzyl *C*$H_2$), 88.6 (d, *J* 175.7, *C*(6)HF), 99.2 and 99.7 (2×acetal *C*), 128.1, 128.5 and 128.6 (aromatic *C*H), 131.9 (d, *J* 19.2, *C*(1)), 137.3 (d, *J* 5.4, *C*(2)H), 138.7 (aromatic *ipso-C*), 165.3 (*C*═O); $\delta_F$ (376.3 MHz; *C*$DCl_3$) −183.9 (dd, *J* 49.2, 21.3, C(6)H*F*); *m/z* (+ve ion electrospray) 433 (100%, [M+Na]$^+$) (Found 433.1631, $C_{21}H_{27}FO_7Na$ ([M+Na]$^+$) requires 433.1633).

**4.1.15. (2′*S*,3′*S*,3*R*,4*R*,5*S*,6*S*)-1-Methoxycarbonyl-3-*O*-benzyl-6-fluoro-cyclohex-1-ene-3,4,5-triol (42).** The methyl ester **41** (0.035 g, 0.09 mmol) was stirred vigorously at room temperature in a mixture of water and TFA (1:9, 2 mL) for 2 h and the solvent was then removed in vacuo. Purification by flash column chromatography ($SiO_2$; EtOAc/petroleum ether (40–60), 1:2) gave the title compound as an oily half-solid (0.018 g, 72%). $R_f$ 0.17 (EtOAc/petroleum ether (40–60), 1:2); $[\alpha]_D^{24}$ −128.6 (*c* 0.87, $CHCl_3$); $\nu_{max}$ (film)/$cm^{-1}$ 3432br (O–H), 2925m (C–H), 1726s (C═O); $\delta_H$ (300 MHz; $CDCl_3$) 2.46 (2H, br s, 4-O*H* and 5 O–*H*), 3.67 (1H, dd, *J* 9.4, 4.1, C(4)*H*), 3.86 (3H, s, $CO_2CH_3$), 4.17–4.31 (2H, m, C(3)*H* and C(5)*H*), 4.72 (1H, d, *J* 11.6, OC*H*$_a$H$_b$Ph), 4.82 (1H, d, *J* 11.6, OCH$_a$*H*$_b$Ph), 5.26 (1H, dd, *J* 48.5, 6.2, C(6)*H*F), 6.99 (1H, d, *J* 5.0, C(2)*H*) 7.34–7.42 (5H, m, aromatic C*H*); *m/z* (+ve ion electrospray) 319 (100%, [M+Na]$^+$) (Found 319.0950, $C_{15}H_{17}FO_5Na$ ([M+Na]$^+$) requires 319.0952).

**4.1.16. (6*S*)-6-Fluoroshikimic acid (5).** The diol **42** (0.018 g, 0.06 mmol) was stirred at 60–70 °C in a mixture of water and concentrated HCl (1:1, 1.5 mL) for 10 h. After this time, the solvent was removed directly in vacuo to give the title compound as a viscous oil. Purification using reverse phase HPLC [Rainin Dynamax C18 (21.4×250 mm); eluent: $H_2O$/formic acid, 99.98:0.02; UV detection at 254 nm] followed by lyophilisation gave the title compound as a colourless solid (0.071 g, 61%). $[\alpha]_D^{24}$ −28.7 (*c* 0.71, $H_2O$); $\delta_H$ (300 MHz; $D_2O$) 3.64 (1H, dd, *J* 9.6, 3.9, C(4)*H*), 4.01 (1H, ddd, *J* 18.0, 9.6, 5.8, C(5)*H*), 4.39 (1H, ~td, *J* 4.5, 1.5, C(3)*H*), 5.10 (1H, dd, *J* 48.6, 5.8, C(6)*H*F), 6.83 (1H, d, *J* 4.8, C(2)*H*); $\delta_C$ (100 MHz; $D_2O$) 64.9 (d, *J* 2.3, *C*(3)H), 68.2 (d, *J* 7.6, *C*(4)H), 69.6 (d, *J* 20.6, *C*(5)H), 89.6 (d, *J* 169.4, *C*(6)HF), 139.1 (d, *J* 6.0, *C*(2)H), 168.4 (*C*═O), (*C*(1) not detected); $\delta_F$ (376.3 MHz; $D_2O$) −176.5 (dd, *J* 48.6, 18.0, C(6)H*F*); *m/z* (−ve ion electrospray) 191 ([M−H]$^-$, 100%), 171 (82) (Found 191.0357, $C_7H_8FO_5$ ([M−H]$^-$) requires 191.0361).

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10. The diol **16** was generously donated by Professor Derek Boyd at The Queens University of Belfast. It is commercially available from the QUESTOR Centre at the Queens University of Belfast. For further details, contact Professor Derek Boyd, The School of Chemistry, The Queens University of Belfast, David Keir Building, Stranmills Road, Belfast BT9 5AG, Northern Ireland.
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