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Difluorinated analogues of shikimic acid

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Abstract—Investigations into the quinate to shikimate transformation have been carried out, the results of which have been exploited in the synthesis of a novel difluoromethylene homologue of shikimic acid from (−)-quinic acid. Martin's sulfurane $\{Ph_2S[OC(CF_3)_2Ph]_2\}$ was the reagent of choice for the key dehydration step of this synthesis. The results of investigations into the synthesis of the important natural product analogue, 6,6-difluoroshikimic acid are also reported. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Over the last decade, there has been much interest from chemists and biochemists alike, in fluorinated analogues of shikimic acid (**1**).[1a–g] Many of these compounds, by virtue of their structural similarity to (**1**), have been targeted as likely inhibitors of enzymes on the shikimic acid pathway and are of biological interest as potential antifungal and antibacterial agents. The recent discovery of the shikimic acid pathway in the apicomplexan parasites *Toxoplasma gondii*, *Plasmodium falciparum* and *Cryptosporidium parvum* has provided a new impetus for the design and synthesis of inhibitors of the pathway as potential antiparasitic agents.[2a–c]

During the course of an ongoing research programme concerned with the biochemical fate of *gem*-difluorinated analogues of polyoxygenated enzyme substrates, we became interested in two analogues of shikimic acid (**2** and **3**) (Fig. 1). The difluoromethylene homologue of shikimic acid (**2**) and 6,6-difluoroshikimic acid (**3**) were both of interest as possible prodrugs for the intracellular generation of the corresponding difluorinated analogues (**4**) and (**5**) of 5-enolpyruvylshikimicacid-3-phosphate. In turn, compounds (**4**) and (**5**) were targeted as likely competitive inhibitors of chorismate synthase, the enzyme which catalyses the seventh step of the shikimic acid pathway.[3] In this paper, we provide details of the completed synthesis of compound (**2**) as well as the results of investigations into the preparation of compound (**3**).

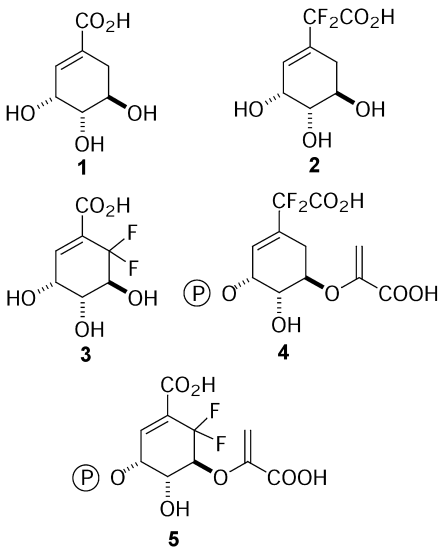

Figure 1.

2. Results and discussion

2.1. Synthesis of the difluoromethylene homologue of shikimic acid[4]

The 'chiral pool' material (−)-quinic acid (**6**) was selected as the starting material for our synthesis of the difluoromethylene homologue of shikimic acid (Scheme 1). The cyclohexane diacetal (CDA) and butane diacetal (BDA) derivatives (**7** and **8**) of methyl quinate were prepared from (**6**) in 73 and 85% yields, respectively.[5,6] Selective silylation of the remaining secondary hydroxyl of both compounds was accomplished most efficiently using the reactive

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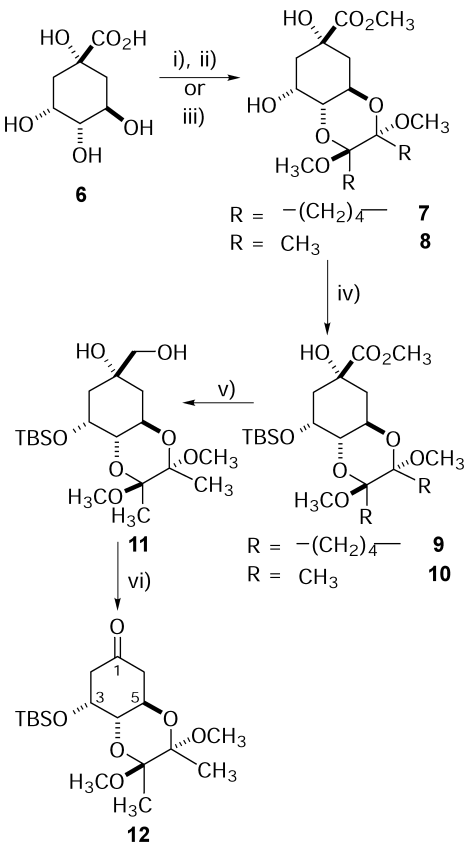


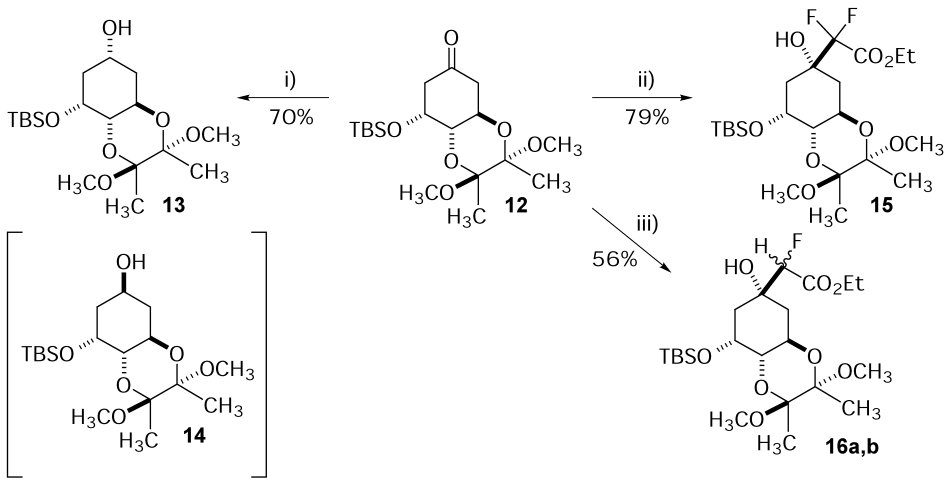
Scheme 1. *Reagents*. (i) CH_3OH, Amberlite® IR 120 (H), △, (ii) 1,1,2,2-tetramethoxycyclohexane, $(CH_3O)_3CH$, camphorsulfonic acid, CH_3OH, △, 73% yield of **7** over 2 steps, (iii) butan-2,3-dione, $(CH_3O)_3CH$, camphorsulfonic acid, CH_3OH, △, 85% yield of **8** over one step, (iv) *tert*-butyldimethylsilyl trifluoromethanesulfonate, Et_3N, CH_2Cl_2, 0°C, 79% for **9**, 97% for **10**, (v) $NaBH_4$, CH_3OH, 0°C to rt, 96%, (vi) $NaIO_4$, H_2O, CH_3OH, pH 6.9, 86%.

silylating reagent, *tert*-butyldimethylsilyltrifluoromethanesulfonate. Accordingly, the crystalline *tert*-butyldimethylsilyl ethers (**9** and **10**) were prepared in 79 and 97% yields, respectively.[7] Although much of our chemistry has been carried out on both series of bis-acetal protected compounds, the higher overall yield of preparation of (**10**) has made the BDA our protecting group of preference. The majority of the work reported herein will therefore focus on the BDA series of compounds.

Reduction of the ester function of (**10**) was initially accomplished in 70% yield using an excess of DIBAL-H in toluene, however, a much more efficient procedure was subsequently adopted which involved the use of an excess of sodium borohydride in methanol. This protocol furnished the corresponding diol (**11**) in 96% yield. Oxidative cleavage of the diol with $NaIO_4$ proceeded smoothly over a period of several days to give the crystalline ketone (**12**) in 86% yield. This highly efficient four-step sequence has allowed the preparation of multi-gram quantities of ketone (**12**). The reactivity of this compound towards a number of nucleophilic reagents has therefore been investigated.

It was our expectation that the constrained *trans*-decalin like structure of (**12**), coupled with the steric influence of the axially located *tert*-butyldimethylsilyloxy substituent at C3, would ensure preferential 'equatorial' approach of nucleophiles to give products possessing quinate-stereochemistry at C1. This, indeed, proved to be the case (Scheme 2). Thus, reduction of (**12**) with $NaBH_4$ in methanol gave a 5:2 mixture of axial alcohol (**13**) and equatorial alcohol (**14**) whereas, the use of K-Selectride® proved more discriminating and furnished (**13**) exclusively in 70% yield after purification by chromatography. Treatment of (**12**) with the zinc reagent derived from ethyl bromodifluoroacetate[8] in THF under reflux, gave a single adduct (**15**), the structure of which was confirmed by extensive NMR analysis of a sample in C_6D_6, which included the use of heteronuclear nOe measurements ($^{19}F-^{1}H$). Similarly, addition of the zinc reagent derived from ethyl bromofluoroacetate in THF under reflux, gave an inseparable mixture (~1:1) of two diastereoisomeric adducts (**16a**,**b**), both of which were shown to possess 'quinate' stereochemistry at C1. A full discussion of the NMR techniques used for the structural determination of several fluorinated intermediates prepared during this programme is given in a later section.

At the outset of our investigations into the synthesis of the difluoromethylene homologue of shikimic acid, we envisaged that the key transformation of the sequence would be dehydration of compound (**15**) to give a product

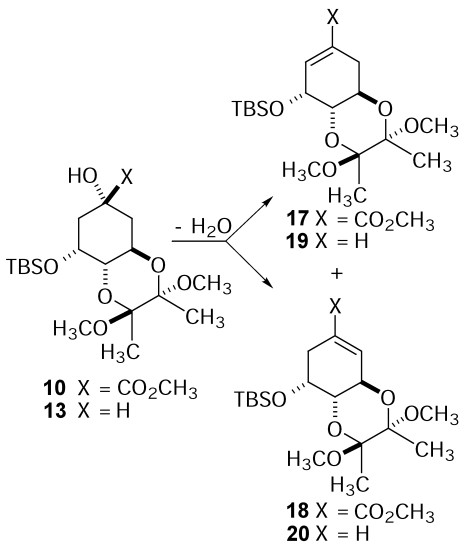


Scheme 2. *Reagents*. (i) K-Selectride®, THF, −78°C, 8 h, (ii) CF_2BrCO_2Et, Zn, THF, △, (iii) $CFBrHCO_2Et$, Zn, THF, △.

possessing a shikimate regiochemistry. Previous literature reports indicated that dehydration of quinic acid derivatives proceeded with varying levels of regioselectivity, although the majority of such reactions were found to proceed via preferential loss of a hydrogen at C2 to give the shikimate isomer as major product.[9] In anticipation of possible problems with the dehydration of (**15**), we carried out further investigations into the quinate to shikimate transformation using alcohols (**10**) and (**13**) as substrates (Scheme 3 and Table 1).

A variety of dehydration conditions was investigated and the ratios of isomeric alkenes arising from these reactions were assessed by examination of the ^{1}H NMR spectra of the crude reaction products and comparison of the integrals for the vinyl hydrogens of the isomeric products. For dehydration of protected methyl quinate (**10**), Martin's sulfurane $\{Ph_2S[OC(CF_3)_2Ph]_2\}$[10a,b] proved to be the reagent of choice, giving a crude product mixture comprising almost exclusively of (**17**). Accordingly, on preparative scale, treatment of (**10**) with an excess of Martin's sulfurane in dichloromethane followed by purification by flash chromatography and recrystallisation gave (**17**) in 84% yield. In agreement with results of dehydration studies reported recently on a substrate similar to (**10**), the use of $POCl_3$ in pyridine at slightly elevated temperature also gave (**17**) as the major product isomer.[11] In our hands, however, it proved impossible to purify (**17**) completely free of the regioisomer (**18**) when using these conditions.

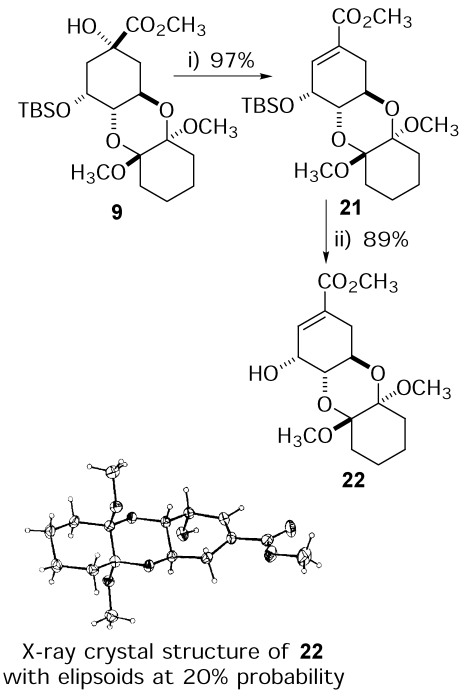
The regiochemical outcome of these dehydrations was



Scheme 3.

Table 1.

Conditions	Isomer ratio	
	17–18	**19–20**
Martin's sulfurane, CH_2Cl_2, rt[10a,b]	~30:1	3:1
$POCl_3$, py, △	15:1	10:1
Burgess reagent, CH_3CN, △[13]	8:1	10:1
DAST, CH_2Cl_2, 0°C to rt[12a,b]	4:1	–



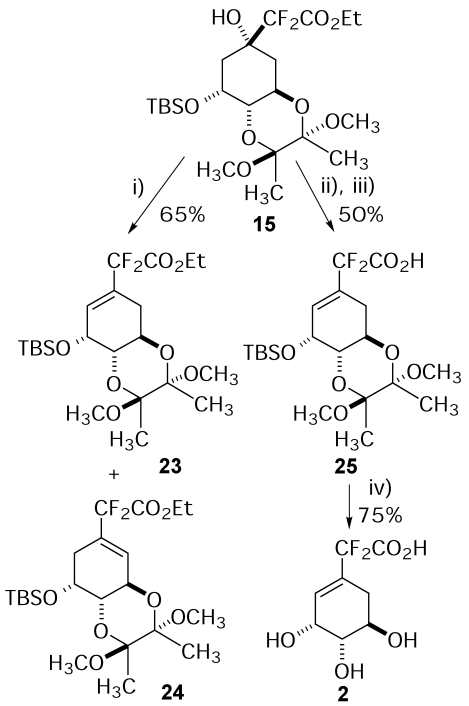
X-ray crystal structure of **22** with elipsoids at 20% probability

Scheme 4. *Reagents.* (i) $Ph_2S[OC(CF_3)_2Ph]_2$, DCM, rt, (ii) TBAF, THF, 0°C to rt.

confirmed as follows: dehydration of CDA protected methyl quinate (**9**) with Martin's sulfurane in dichloromethane gave a single product (**21**) in 97% yield. Selective deprotection of this material with tetrabutylammonium fluoride in THF gave the crystalline allylic alcohol (**22**), the structure of which was confirmed by X-ray crystallographic analysis (Scheme 4).

Dehydration of the secondary alcohol (**13**) with $POCl_3$ in pyridine proceeded with good regioselectively to give (**19**) as the major component of an inseparable mixture of isomers. We were surprised, however, to find that Martin's sulfurane was a much inferior reagent with this substrate, giving a 3:1 mixture of isomers (**19**) and (**20**). Treatment of both (**10**) and (**13**) with the Burgess reagent $[H_3CO_2CN^-SO_2N^+(C_2H_5)_3]$[13] in acetonitrile at elevated temperature also gave the shikimate isomers (**17**) and (**19**) as the major products. An unambiguous explanation for the regioselectivities of these dehydrations is not apparent, however, if product stability is reflected in the transition states for the reactions, then preferential formation of the *trans*-decalin ring-system in (**17**) and (**19**) would be expected.

The structural similarities between (**15**) and (**10**/**13**) led us to believe that the Reformatsky adduct (**15**) would exhibit similar dehydration behaviour under the conditions described above. We were thus disappointed to find that treatment of (**15**) with either $POCl_3$ in pyridine or Burgess reagent in CH_3CN at elevated temperature, induced no detectable reaction. However, treatment of (**15**) with an excess of diethylaminosulfurtrifluoride (DAST) in dichloromethane followed by careful chromatographic purification gave (**23**) contaminated with ~7% of the undesired regioisomer (**24**). Pleasingly, treatment of (**15**) with an excess of Martin's sulfurane in dichloromethane cleanly gave (**23**) which was assigned a 'shikimate' regiochemistry



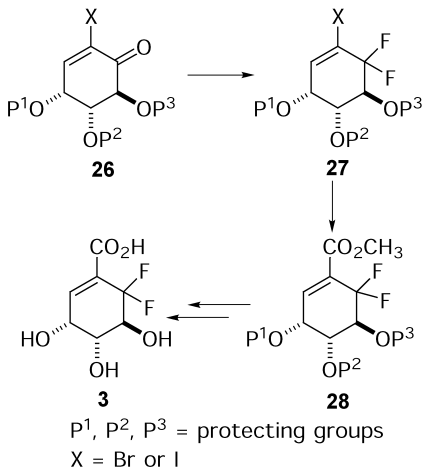
Scheme 5. *Reagents*. (i) DAST, DCM, 0°C for 1 h, then rt for 24 h, (ii) Martin's sulfurane, CH_2Cl_2, rt, (iii) LiOH, H_2O, CH_3OH, (iv) TFA–H_2O (7:1), 0°C.

by comparison of its ^1H NMR data with those of compound (**17**). It proved impossible to separate (**23**) from minor amounts of aromatic contaminants arising from decomposition of the sulfurane, however, subsequent ester hydrolysis under basic conditions followed by chromatographic purification gave the carboxylic acid (**25**) in 50% yield over two steps from (**15**). This compound, not surprisingly, underwent rapid desilylation on storage in a concentrated state and it was therefore exposed immediately to the acidic conditions necessary for concomitant removal of the silyl and bis-acetal protecting groups. Purification of the product of this sequence by reverse phase HPLC gave the target compound (**2**) in pure form (Scheme 5).

2.2. Approaches towards 6,6-difluoroshikimic acid (3)

A suitably protected α-halo enone (**26**) (X=Br or I) was selected as a key intermediate in our synthetic approach to (**3**) (Scheme 6). It was envisaged that fluorodeoxygenation of (**26**) would provide a *gem*-difluoride (**27**) and subsequent palladium catalyzed carbonylation (or alternative transmetallation protocol) would lead to ester (**28**) which, following complete deprotection, would provide the target compound. It should be noted that previous work by our group in this area had indicated that compounds of type (**26**), wherein X is an alkoxycarbonyl moiety, were quite unstable and prone to facile aromatisation thus precluding their consideration as fluorination substrates.

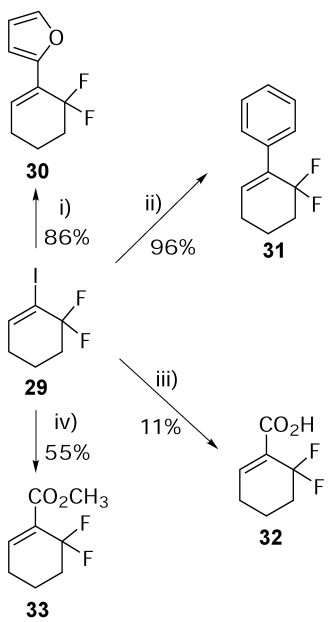
Prior to embarking on a synthetic approach to compounds of type **26** we investigated procedures suitable for the conversion of (**27**) to (**28**) using the vinyl iodide (**29**)[14] as a test substrate (Scheme 7). To our knowledge, palladium catalyzed coupling reactions of substrates of this type had



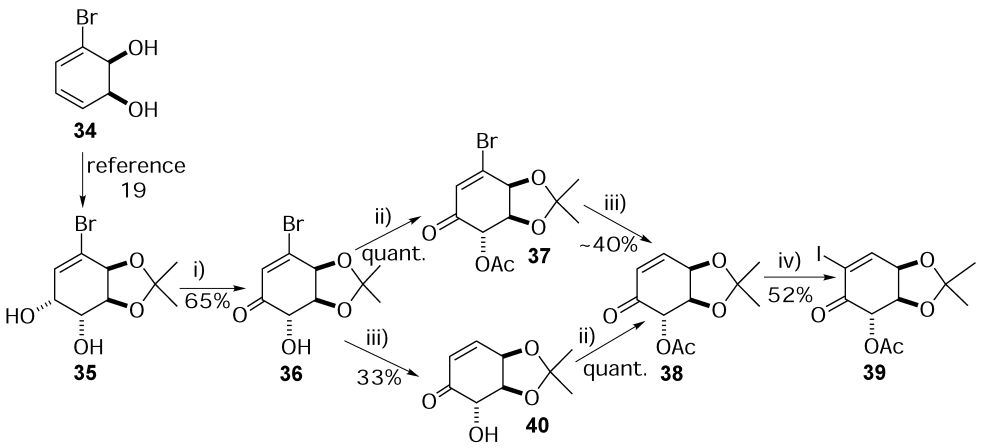
Scheme 6.

not been studied previously and the outcome of these investigations was therefore of general interest.

The vinyl iodide (**29**) proved to be an excellent substrate in both Stille[15] and Suzuki[16] cross-coupling reactions and accordingly, the 2-furyl and phenyl substituted compounds (**30**) and (**31**) were prepared in excellent yields (Scheme 7). Oxidation of furan (**30**) using the Sharpless[17] modification of the Djerassi/Engle[18] conditions gave the conjugated acid (**32**) in just 7% yield. Direct preparation of (**32**) by palladium-catalyzed carbonylation of (**29**) also proceeded in a disappointing 11% yield. It was very pleasing, however, to find that palladium catalyzed carbonylation of (**29**) in the presence of methanol gave the conjugated ester (**33**) in a yield of 55% (89% based on recovered starting material). The success of this transformation provided encouragement that we could proceed with the approach outlined in Scheme 6 with a reasonable level of confidence that the



Scheme 7. *Reagents*. (i) 2-tributylstannyl furan, NMP, $(C_6H_5CN)_2PdCl_2$, tri-2-furylphosphine, CuI, (ii) $C_6H_5B(OH)_2$, $Pd(Ph_3P)_4$, LiCl, Na_2CO_3 (aq.), DME, (iii) CO, KOAc, $Pd(OAc)_2$, DMF, Ph_3P, (iv) CO, $Pd(OAc)_2$, DMF, CH_3OH, tri-2-fuylphosphine, *N*,*N*-diisopropylethylamine.



Scheme 8. *Reagents*. (i) PDC, DMF, 0°C, (ii) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0°C, (iii) Bu_3SnH, AIBN, C_6H_6, △, (iv) I_2, PDC, CH_2Cl_2.

conversion of (**27**) to (**28**) could be accomplished successfully.

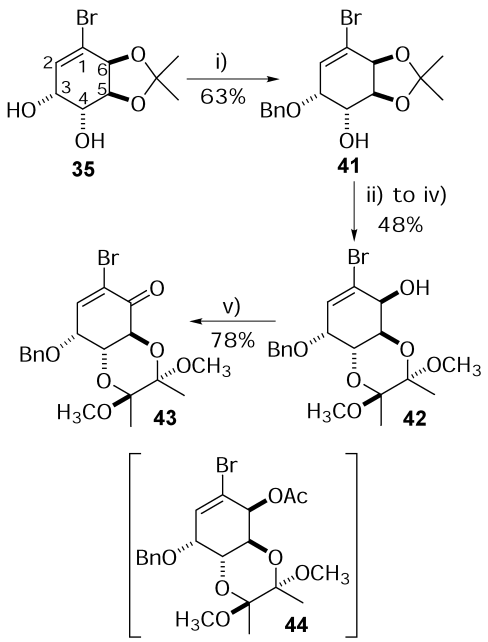
Our first approach towards an α-haloenone of type **26**, utilized the diol (**35**), which was prepared in a straightforward manner from the commercially available compound (**34**) in two steps (Scheme 8).[19] Selective oxidation of the allylic hydroxyl of (**35**) to give enone (**36**) proved to be a capricious transformation, however, it could be accomplished in a maximum 65% yield using 1.5 equiv. of PDC in DMF at 0°C.[20] Acetylation of the remaining free hydroxyl group of (**36**) proceeded smoothly to give α-acetoxyketone (**37**) in excellent yield, however, it was found subsequently that this compound underwent partial epimerisation at the center adjacent to the carbonyl during the course of chromatography on silica gel as well as when stored in a concentrated state.

Radical debromination of (**37**) proved to be a problematic transformation and furnished enone (**38**) in ~40% yield as an inseparable mixture (7:1) with an unidentified side-product. This unstable enone was treated rapidly with iodine and PDC in dichloromethane[21] to give the α-iodoenone (**39**) in ~52% yield. Altering the order of the hydroxyl protection and dehalogenation steps in this sequence had no beneficial effect on the efficiency of the synthesis since radical debromination of (**36**) proceeded in just 33% yield. The problems of inconsistent yields and product instability, which were associated with the synthesis of α-iodoenone (**39**) precluded preparation of sufficient pure material to allow an investigation into the key difluorination step on this compound.

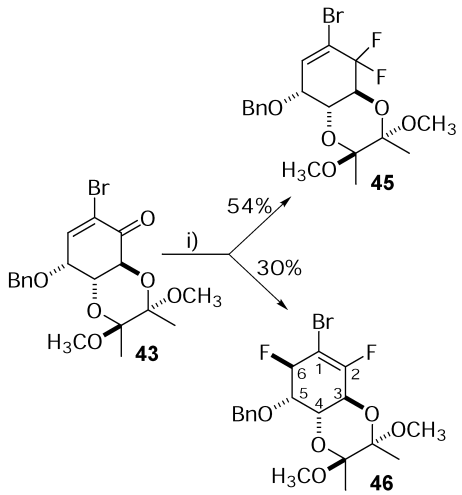
The problems encountered during the synthetic sequence described above, prompted us to consider an alternative approach which did not involve a cumbersome dehalogenation–rehalogenation sequence and which proceeded via robust intermediates which were less susceptible to the problems of epimerisation and elimination (Scheme 9). A key feature of our new approach was the selection of a BDA to block the *trans* disposed oxygens at C4/C5 of (**35**): the stability and conformational rigidity of the *trans*-decalin ring system present in the BDA protected compounds was expected to disfavor epimerisation and elimination during the synthesis.[5]

Selective benzylation of the allylic hydroxyl of (**35**) was accomplished in reasonable yield via an intermediate stannylene acetal.[22a,b] Subsequent exposure of (**41**) to the standard conditions for introduction of the BDA protecting group resulted in the generation of an inseparable mixture of compounds, the major component of which was the desired bis-acetal (**42**). Acetylation of this mixture under standard conditions followed by purification and methanolysis of the resulting acetate (**44**) provided pure allylic alcohol (**42**) in 48% yield from (**41**). Oxidation of the free allylic hydroxyl of (**42**) using Swern conditions[23] lead cleanly to enone (**43**) in 78% yield. This synthesis furnished the *gem*-difluorination precursor (**43**) in five steps from (**35**) and was not plagued with any of the instability problems associated with the previous approach.

Recent investigations by our group into the fluorodeoxygenation of a number of simple enones have shown that



Scheme 9. *Reagents*. (i) Bu_2SnO, C_6H_6, △ then CsF, BnBr, DMF, rt, (ii) butan-2,3-dione, $(CH_3O)_3CH$, CSA, CH_3OH, △, (iii) Ac_2O, pyridine, DMAP, CH_2Cl_2, (iv) K_2CO_3, CH_3OH, (v) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C to rt.



Scheme 10. *Reagents*. $[CH_3O(CH_2)_2]_2NSF_3$, rt.

reasonable levels of substrate conversion can be achieved either in solution, by the application of ultra high pressure,[14] or under solvent free conditions by using the fluorinating agent, (bis-(2-methoxyethyl)amino]sulfurtrifluoride (Deoxo-Fluor®).[24] In the first instance, we decided to investigate the latter of these procedures and a solution of enone (**43**) in the fluorinating agent was stirred for 72 h at rt. Analysis of the crude product mixture indicated complete consumption of starting material and clean formation of two fluorinated compounds (**45**) and (**46**) in an approximately 3:2 ratio. The crystalline *gem*-difluoro compound (**45**) was isolated in 54% yield after careful column chromatography (Scheme 10).

Heteronuclear nOe measurements ($^{19}F-^{1}H$) confirmed the pseudo-axial location of the fluorine atom at the 6-position of (**46**) (see Section 2.3). Mechanistically, this compound may be derived via S_N2' attack by fluoride anion on an activated α-fluorohydrin derived from (**43**) or, alternatively, S_N1' attack on an allylic carbocation derived from the same intermediate.

Previous investigations by our group had demonstrated that a structurally simplified analogue (**47**) of the vinyl fluoride (**46**) underwent facile isomerisation to the corresponding *gem*-difluorinated isomer (**29**) when stored as a solution in CH_2Cl_2 over 4 Å molecular sieves.[14] The mechanism of this

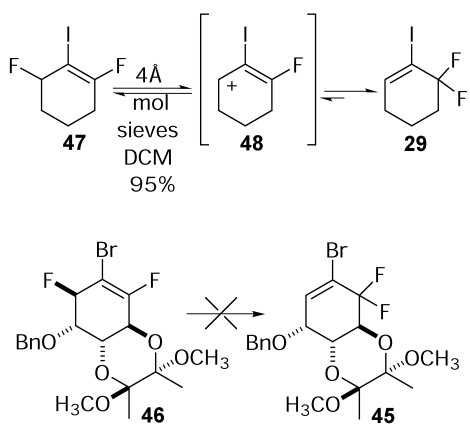


Figure 2.

unusual rearrangement has not been investigated in detail, however, we believe that the reaction almost certainly proceeds via reversible formation of an intermediate allylic carbocation (**48**) (Fig. 2). Unfortunately, all attempts to induce an analogous isomerisation of compound (**46**) were unsuccessful. This finding was particularly disappointing, given the perceived greater thermodynamic stability of the *trans*-decalin ring-system in (**45**) compared with that in (**46**), and is believed to be due to the influence of the highly oxygenated cyclohexene ring in (**46**) which disfavors formation of the necessary cationic intermediate.

With the key difluoride (**45**) in hand, palladium catalyzed carbonylation of this material was investigated using a variety of reaction conditions, however, all of these attempts met with failure. We believe that the contrasting behaviour of compounds (**29**) and (**45**) under similar carbonylation conditions reflects the documented finding that vinyl iodides are superior substrates in palladium catalyzed coupling reactions than the corresponding vinyl bromides. Several attempts have also been made to carry out *trans*-metallation of (**45**) with ^{t}BuLi and to quench the resulting vinyl lithium species with CO_2, however, these also proved to be unsuccessful.

Although the synthetic approach to 6,6-difluoroshikimic acid described above was thwarted at a late stage, the results arising from our endeavours have stimulated renewed investigations into an alternative route to this important natural product analogue, the results of which will be reported in due course.

2.3. Structure determination using $^{1}H-^{19}F$ nuclear Overhauser effect measurements

^{19}F often makes a significant contribution to the spin-lattice relaxation of neighbouring protons, allowing nuclear Overhauser effect measurements to provide information on local geometry. Figure 3 shows a 2D heteronuclear Overhauser effect spectroscopy (HOESY) spectrum of compound (**15**) measured using a simple $90°_F-1/2t_1-180°_H-1/2t_1-90°_F-t_m-90°_H$—acquire pulse sequence.[25–27] For particularly concentrated samples it can be advantageous to add a further $90°_F$ pulse to the end of this sequence to suppress ^{19}F dipolar demagnetizing field effects,[28,29] but this was not necessary with the dilute samples used here. Numerous nOe cross-peaks between ^{19}F and ^{1}H are visible in Figure 3, with those to protons 2_β, 6_β, 2_α and 6_α (in descending order of size) particularly prominent. The partial second-order character of the ^{19}F AB quartet leads to slight perturbations of the relative intensity ratios in the F_1 (^{19}F) multiplet structure; such effects are analogous to those seen in nOe difference spectra of strongly coupled spin systems.[30] In addition to the strong responses seen for protons 2 and 6, a number of smaller nOe's to other protons were seen. A series of five experiments with mixing times t_m of 100, 200, 300, 400 and 500 ms were carried out and cross-peak volumes plotted against t_m to confirm that all the responses were dominated by direct Overhauser effects and not complicated by spin diffusion. The relative buildup rates for the nOe cross-peak volumes are listed in Table 2. All the cross-peak intensities showed linear initial growth, confirming that the magnetization exchange is direct and not mediated by spin diffusion.

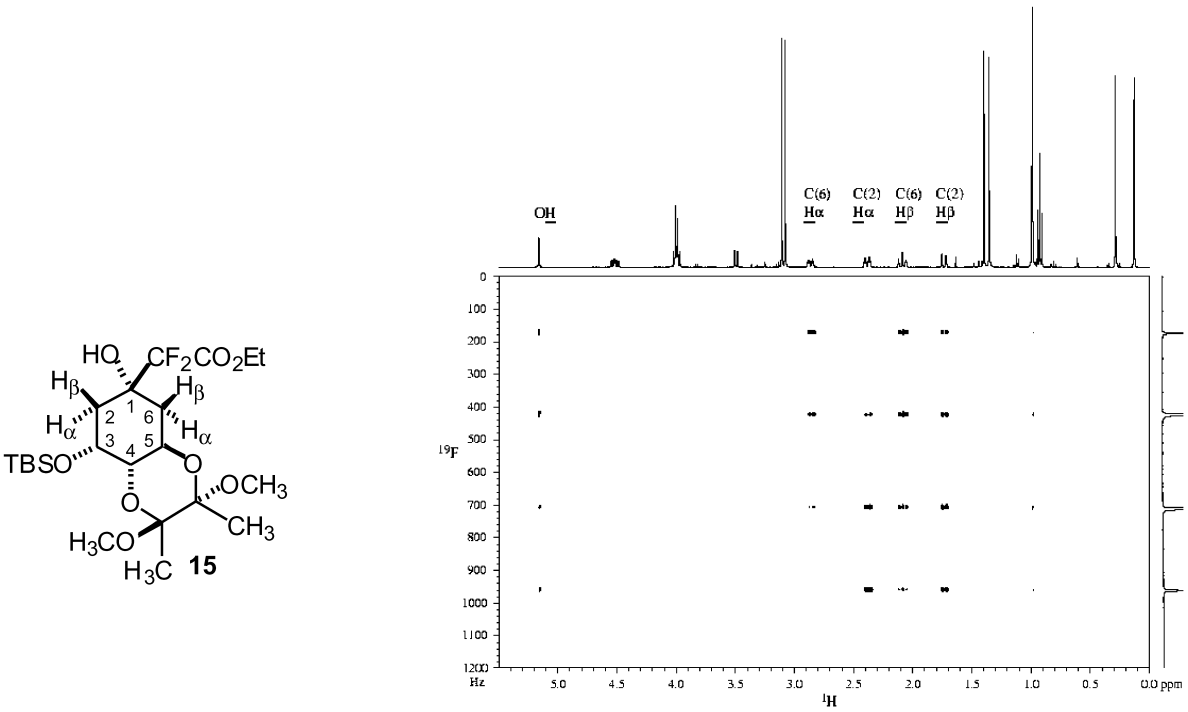


Figure 3.

Table 2. Relative $^{19}F-^{1}H$ nOe cross-peak buildup rates

Proton	Buildup rate (arbitrary units)
2_β	100
6_β	89
2_α	76
6_α	56
OH	13
^{t}Bu	3

The buildup rates reflect the time average of the inverse sixth power of the proton–fluorine separation; the substantial enhancement of the 2/6β buildup rates over those for 2/6α indicates that the β protons in each case are closer to the fluorine than the α, providing clear support for the stereochemistry shown in Figure 3.

Figure 4 shows a cross-section, at the chemical shift of C(6)*F*, through a 2D phase sensitive gradient-enhanced heteronuclear Overhauser effect (gHOESY) spectrum[31] of compound (**46**), with the full proton spectrum for comparison purposes. Clear nOe contacts are seen between C(6)*F* and C(4)*H*, C(5)*H* and C(6)*H*, with a very small nOe to one of the methoxy groups.

3. Conclusions

In conclusion, extensive investigations into the quinate to shikimate transformation have been carried out using two different substrates and a number of different dehydration conditions. In all cases, a preference for the formation of a shikimate regiochemistry was observed although the extent

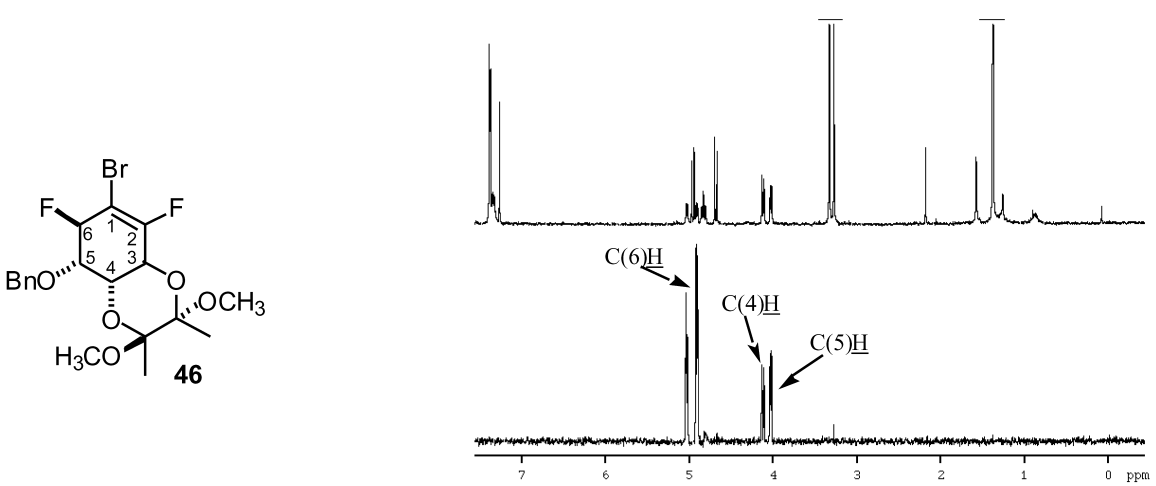


Figure 4.

of the selectivity was dependent on the nature of both the reagent and the substrate. The results of these investigations have been exploited in the synthesis of a novel difluoromethylene homologue of shikimic acid from (−)-quinic acid. Problems with the key dehydration step of this synthesis were solved by the use of Martin's sulfurane $\{Ph_2S[OC(CF_3)_2Ph]_2\}$.

An approach to the synthesis of the important natural product analogue, 6,6-difluoroshikimic acid has also been investigated using the enantiopure diol derived from microbial dihydroxylation of bromobenzene as starting material. The fluorodeoxygenation step of this synthesis was successfully accomplished, however, in spite of the success of model studies using a simpler substrate, the approach was abandoned due to the failure of a key palladium catalyzed carbonylation step.

4. Experimental

4.1. General

Solvents were dried and distilled before use. Chromatography was performed over Merck silica gel 60 (40–63 μm).

Zinc metal was obtained from Fisher Scientific and was freshly activated by successive washes with 20% aq. HCl, water, acetone and anhydrous diethyl ether before being dried in vacuo.

Martin's sulfurane and the Burgess reagent were both obtained from Aldrich and were used without further purification.

IR spectra were recorded on a Perkin–Elmer 881 spectrometer or an AT1-Mattson Genesis Series FTIR spectrometer.

^1H, ^{13}C NMR spectra were recorded on a JEOL EX400 FT-NMR, a Varian Inova 400 MHz spectrometer, a Varian Inova 300 MHz spectrometer or a Bruker DMX250 pulse FT-NMR spectrometer. Chemical shifts are referenced to the residual solvent peak. A ~ sign is used to describe the apparent splitting pattern of a particular resonance when a different pattern is expected but cannot be resolved. Heteronuclear $^1H-^{19}F$ NMR experiments were carried out using a Varian INOVA 400 spectrometer equipped with a 5 mm pulsed field gradient indirect detection probe. The only instrument modification used was the exchange of the synthesizer inputs to the two radiofrequency transmitters, with concomitant exchange of the relevant parameters in the software, to allow the transmitter normally used for proton decoupling to provide ^{19}F pulses. No special filters were used, and the probe was tuned solely to the proton Larmor frequency. In this configuration the instrument can produce both proton and ^{19}F pulses, with both being fed to the observe coil of the probe. This gives full sensitivity and a normal 90° pulse width of 5 μs for protons; because the probe is far from electrical resonance at the ^{19}F Larmor frequency the ^{19}F 90° pulse lengthens to 100 μs, but this is perfectly adequate for most purposes. This instrument configuration also allows time-shared decoupling of protons from ^{19}F.

Mass spectra were recorded on Fisons VG Autospec (EI/CI, low and high resolution), Fisons VG Trio 2000 quadrupole (EI/CI, low resolution), Kratos Concept 1S (EI/CI, high resolution) and Micromass Platform (electrospray) spectrometers.

4.1.1. (2′*S*,3′*S*)-Methyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-quinate (8). To a solution of (−)-quinic acid (11.01 g, 57.3 mmol) and CSA (1.50 g, 6.5 mmol) in CH_3OH (250 mL) was added trimethylorthoformate (49 mL, 448 mmol) and butan-2,3-dione (11.8 mL, 134 mmol). The yellow solution was heated under reflux for 6 h, stirred at rt overnight and then heated under reflux for a further 6 h. After cooling to rt, Et_3N (15 mL, 108 mmol) was added and the solution was concentrated in vacuo to give the crude product as a brown solid. Decolorization of a solution of the crude product in EtOAc with activated charcoal followed by concentration in vacuo and recrystallisation from hot EtOAc and petrol ether (40:60) provided the title compound as colorless crystals (15.67 g, 85%). Mp 134–135°C (lit.[6] Mp 139.8–140.2°C); $[\alpha]_D^{22}=+137.7$ (*c* 0.83, CH_2Cl_2) (lit.[6] $[\alpha]_D^{20}=+116.3$ (*c* 1.06, CH_2Cl_2)); (Found: C, 52.8; H, 7.7. $C_{14}H_{24}O_8$ requires C, 52.5; H, 7.6%); other spectroscopic data in agreement with those reported in the literature.[6]

4.1.2. (2′*S*,3′*S*)-Methyl-3-*O*-^{t}butyldimethylsilyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-quinate (10). A solution of (**8**) (3.57 g, 11.1 mmol) in CH_2Cl_2 (30 mL) was stirred at 0°C under an atmosphere of nitrogen. Triethylamine (5.1 mL, 36.6 mmol) was added dropwise by syringe followed by a solution of TBDMSOTf (2.6 mL, 11.3 mmol) in CH_2Cl_2 (16 mL) and the resulting pale yellow solution was stirred at 0°C for 2 h. The reaction mixture was then poured into H_2O (60 mL), the organic phase was collected and combined with two subsequent CH_2Cl_2 extracts (2×60 mL). The combined organic extracts were washed with water (60 mL), dried ($MgSO_4$) and concentrated in vacuo to give the crude product as a pale yellow solid. Purification by recrystallisation from hot CH_3OH and H_2O gave the target compound as a colorless solid (4.70 g, 97%). Mp 114–115°C; $[\alpha]_D^{24}=+100.5$ (*c* 1.10, CH_2Cl_2); (Found: C, 55.15; H, 8.8. $C_{20}H_{38}O_8Si$ requires C, 55.3; H 8.8%); ν_{max} (Nujol)/cm^{-1} 3456 (OH), 1736 (C=O); δ_H (300 MHz; $CDCl_3$), 0.11 and 0.17 (2×3H, 2×s, $(CH_3)_2Si$), 0.90 (9H, s, $(CH_3)_3C$), 1.26 and 1.28 (2×3H, 2×s, 2×butyl CH_3), 1.86 (1H, ~t, *J*=12.5 Hz, C(6)H_β), 2.05–2.09 (2H, m, C(2)H_2), 2.18 (1H, ~dd, *J*=12.8, 4.6 Hz, C(6)H_α), 3.21 and 3.23 (2×3H, 2×s, 2×acetal OCH_3), 3.48 (1H, dd, *J*=10.1, 2.5 Hz, C(4)*H*), 3.76 (3H, s, CO_2CH_3), 4.20–4.31 (2H, m, C(3)*H* and C(5)*H*); δ_C (75.4 MHz; $CDCl_3$), −5.41 and −4.92 ($(CH_3)_2Si$), 17.47 and 17.69 (2×butyl CH_3), 17.97 ($(CH_3)_3CSi$), 25.56 ($CH_3)_3C$), 38.33 and 39.30 (C(2)H_2 and C(6)H_2), 47.47 and 47.66 (2×acetal OCH_3), 52.45 (CO_2CH_3), 62.33, 70.85 and 72.67 (C(3)H, C(4)H and C(5)H), 76.54 (C(1)), 99.29 and 99.80 (2×acetal *C*), 173.53 (CO_2CH_3); *m*/*z* (CI–NH_3) 452 (MNH_4^+, 10%), 435 (MH^+, 12), 420 (80), 403 (100), 388 (20), 371 (20), 85 (50); (Found: 435.2415. $C_{20}H_{39}O_8Si$ (MH^+) requires 435.2414).

4.1.3. (1*R*,2′*S*,3′*S*,3*R*,4*S*,5*R*)-1-Hydroxymethyl-3-*O*-^{t}butyldimethylsilyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-cyclohexane-1,3,4,5-tetraol (11). Sodium borohydride (4.26 g, 113 mmol) was carefully added portionwise to a stirred solution of (**10**) (7.0 g, 16.1 mmol) in CH_3OH (70 mL) at 0°C. Once effervescence had ceased, the reaction mixture was stirred for 24 h at rt when it was quenched by the addition of a saturated aqueous solution of ammonium chloride (100 mL). Organic material was extracted into EtOAc (3×100 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give the crude product as a pale, yellow oil. Purification by flash column chromatography (SiO_2; EtOAc–cyclohexane, 1:1) furnished the diol (**11**) as a colorless, viscous oil (6.31 g, 96%); $[\alpha]_D^{24}$=+93.0 (*c* 2.62, CH_2Cl_2); (Found: C, 56.1; H, 9.7. $C_{19}H_{38}O_7Si$ requires C, 56.1; H, 9.4%); ν_{max} (film)/cm^{-1} 3498 (bs, O–H), 2951 and 2857 (s, C–H); δ_H (400 MHz; $CDCl_3$), 0.13 and 0.18 (2×3H, 2×s, $(CH_3)_2Si$), 0.91 (9H, s, $(CH_3)_3CSi$), 1.27 and 1.29 (2×3H, 2×s, 2×butyl CH_3), 1.40 (1H, ~t, *J*=12.5 Hz, C(6)H_β), 1.49 (1H, dd, *J*=14.5, 2.3 Hz, one of C(2)H_2), 1.93 (1H, ddd, *J*=12.7, 4.6, 2.8 Hz, C(6)H_α), 2.07 (1H, ~dt, *J*=14.5, 3.3 Hz, one of C(2)H_2), 2.22 (1H, dd, *J*=8.6, 4.0 Hz, CH_2OH), 3.22 and 3.23 (2×3H, 2×s, 2×acetal OCH_3), 3.31 (1H, dd, *J*=11.0, 8.6 Hz, one of CH_2OH), 3.41 (1H, dd, *J*=10.1, 2.5 Hz, C(4)*H*), 3.43 (1H, dd, *J*=11.0, 4.0 Hz, one of CH_2OH), 4.21–4.25 (1H, m, C(3)*H*), 4.26 (1H, ddd, *J*=12.1, 10.1 Hz, 4.6. C(5)*H*), 4.79 (1H, s, O*H*); δ_C (100 MHz; $CDCl_3$), −5.52 and −4.83 ($(CH_3)_2Si$), 17.51 and 17.76 (2×butyl CH_3), 18.04 ($(CH_3)_3CSi$), 25.58 ($(CH_3)_3CSi$), 37.48 ($C(2)H_2$), 38.09 ($C(6)H_2$), 47.54 and 47.65 (2×acetal OCH_3), 62.75 (*C*(5)H), 70.42 (CH_2OH), 70.98 (*C*(3)H), 73.35 (*C*(4)H), 74.12 (*C*(1)), 99.16 and 99.73 (2×acetal *C*); *m*/*z* (CI–NH_3) 407 (MH^+, 4%), 375 (100), 85 (52); (Found: 407.2456. $C_{19}H_{39}O_7Si$ (MH^+) requires 407.2465).

4.1.4. (2′*S*,3′*S*,3*R*,4*S*,5*R*)-1-Oxa-3-*O*-^{t}butyldimethylsilyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-cyclohexane-3,4,5-triol (12). Sodium periodate (4.97 g, 23.0 mmol) was added portionwise to a mixture of the diol (**11**) (6.30 g, 15.5 mmol), CH_3OH (40 mL) and aqueous phosphate buffer (pH 6.9, 40 mL) and the reaction mixture was then stirred at rt for 3 days. The reaction mixture was diluted with H_2O (200 mL) and the organic material was extracted into EtOAc (3×180 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a colorless solid. Purification by flash column chromatography (SiO_2; EtOAc–petroleum ether (40:60), 3:7) furnished the title compound as a colorless crystalline solid (5.00 g, 86%). Mp 100–101°C; $[\alpha]_D^{23}$=+93.5 (*c* 0.86, CH_2Cl_2); (Found: C, 57.8; H, 9.2. $C_{18}H_{34}O_6Si$ requires C, 57.7; H, 9.15%); ν_{max} (Nujol)/cm^{-1} 1713 (s, C=O); δ_H (400 MHz; C_6D_6), 0.07 and 0.19 (2×3H, 2×s, $(CH_3)_2Si$), 0.96 (9H, s, $(CH_3)_3CSi$), 1.27 and 1.28 (2×3H, 2×s, 2×butyl CH_3), 1.82 (1H, dd, *J*=15.2, 2.8 Hz, C(2)H_β), 2.25 (1H, dd, *J*=14.0, 12.4 Hz, C(6)H_β), 2.31 (1H, ~dt, *J*=15.2, 2.8 Hz, C(2)H_α), 2.71 (1H, ddd, *J*=14.0, 5.4, 2.8 Hz, C(6)H_α), 2.94 and 3.07 (2×3H, 2×s, 2×acetal OCH_3), 3.57 (1H, dd, *J*=10.0, 2.4 Hz, C(4)*H*), 3.84 (1H, ~q, *J*=2.8 Hz, C(3)*H*), 4.30 (1H, ddd, *J*=12.4, 10.0, 5.4 Hz, C(5)*H*); δ_C (100 MHz; C_6D_6), −4.96 and −4.38 ($(CH_3)_2Si$), 17.97 and 18.04 (2×butyl CH_3), 18.59 ($(CH_3)_3CSi$), 26.01 ($(CH_3)_3CSi$), 45.17 ($C(6)H_2$), 47.50 and 47.66 (2×acetal OCH_3), 48.65 ($C(2)H_2$), 63.95 (*C*(5)H), 69.37 (*C*(3)H), 72.89 (*C*(4)H), 99.15 and 100.05 (2×acetal *C*), 203.53 (*C*=O); *m*/*z* (CI–NH_3) 392 (MNH_4^+, 10%), 360 (45), 343 (60), 311 (20), 85 (100); (Found: 392.2471. $C_{18}H_{38}O_6NSi$ (MNH_4^+), requires 392.2468).

4.1.5. Treatment of (12) with K-Selectride®. To a stirred solution of the ketone (**12**) (0.085 g, 0.23 mmol) in freshly distilled THF (3 mL) at −78°C under an atmosphere of nitrogen was added a 1 M solution of K-Selectride® in THF (0.27 mL, 0.27 mmol) and the reaction mixture was stirred at −78°C for 8 h before being quenched by the addition of a saturated aqueous solution of NH_4Cl (3 mL). The mixture was allowed to warm to rt when the organic material was extracted into EtOAc (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give an oily white solid. Purification by flash column chromatography (SiO_2; EtOAc–petroleum ether (40:60), 7:20) gave the axial alcohol (**13**) as white crystals (0.060 g, 70%). Mp 79–80°C; $[\alpha]_D^{22}$=+109.3 (*c* 0.91, CH_2Cl_2); (Found: C, 57.5; H, 9.7. $C_{18}H_{36}O_6Si$ requires C, 57.4; H, 9.6%); ν_{max} (Nujol)/cm^{-1} 3528 (m, OH); δ_H (300 MHz; $CDCl_3$) 0.12 and 0.17 (2×3H, 2×s, $(CH_3)_2Si$), 0.91 (9H, s, $(CH_3)_3CSi$), 1.28 (6H, s, 2×butyl CH_3), 1.54 (1H, ~td, *J*=12.6, 2.6 Hz, one of C(2)H_β or C(6)H_β), 1.62 (1H, ~dt, *J*=14.6, 2.7 Hz, one of C(2)H_β or C(6)H_β), 1.70 (1H, bs, O*H*), 2.07–2.19 (2H, m, C(2)H_α and C(6)H_α), 3.23 (6H, s, 2×acetal OCH_3), 3.41 (1H, dd, *J*=10.0, 2.4 Hz, C(4)*H*), 4.12–4.18 (1H, m, C(1)*H*), 4.20 (1H, bdd, *J*=4.9, 2.4 Hz, C(3)*H*), 4.29 (1H, ddd, *J*=12.3, 10.0, 4.6 Hz, C(5)*H*); δ_C (75 MHz; $CDCl_3$), −5.54 and −4.83 ($(CH_3)_2Si$), 17.55 and 17.81 (2×butyl CH_3), 18.07 ($(CH_3)_3CSi$), 25.61 ($(CH_3)_3CSi$), 36.77 and 37.26 ($C(2)H_2$ and $C(6)H_2$), 47.54 and 47.64 (2×acetal OCH_3), 62.21 (*C*(5)H), 68.11 (*C*(3)H), 71.72 (*C*(1)H), 73.31 (*C*(4)H), 99.20 and 99.74 (2×acetal *C*); *m*/*z* (CI–NH_3) 394 (MNH_4^+, 3%), 377 (MH^+, 7), 362 (90), 345 (100), 330 (20), 313 (20), 85 (100); (Found: 377.2359. $C_{18}H_{37}O_6Si$ (MH^+) requires 377.2359).

When the reduction was carried out using $NaBH_4$ in methanol, the isomeric compound (**14**) was also isolated as a colorless crystalline solid. Mp 76–78°C; $[\alpha]_D^{27}$=+110.6 (*c* 1.74, CH_2Cl_2); ν_{max} (Nujol)/cm^{-1} 3319–3260 (b, OH); δ_H (300 MHz; $CDCl_3$), 0.06 and 0.10 (2×3H, 2×s, $(CH_3)_2Si$), 0.89 (9H, s, $(CH_3)_3CSi$), 1.26 and 1.27 (2×3H, 2×s, 2×butyl CH_3), 1.37–1.47 (2H, m, two of C(2)H_2 and C(6)H_2), 1.68 (1H, bs, O*H*, confirmed by D_2O shake), 2.03–2.17 (2H, m, two of C(2)H_2 and C(6)H_2), 3.21 and 3.23 (2×3H, 2×s, 2×acetal OCH_3), 3.36 (1H, dd, *J*=10.0, 2.5 Hz, C(4)*H*), 3.97 (1H, ddd, *J*=12.1, 10.0, 4.3 Hz, C(5)*H*), 4.02–4.05 (1H, m, C(3)*H*), 4.12–4.16 (1H, m, C(1)*H*); δ_C (75 MHz; $CDCl_3$), −5.37 and −4.87 ($(CH_3)_2Si$), 17.52 and 17.74 (2×butyl CH_3), 18.09 ($(CH_3)_3CSi$), 25.62 ($(CH_3)_3CSi$), 38.83 and 41.63 ($C(2)H_2$ and $C(6)H_2$), 47.37 and 47.57 (2×acetal OCH_3), 63.34 (*C*(5)H), 65.39 (*C*(3)H), 68.60 (*C*(1)H), 73.17 (*C*(4)H), 98.82 and 99.50 (acetal *C*); *m*/*z* (CI–NH_3) 362 (MNH_4^+−MeOH 40%), 345 (100), 330 (5), 313 (5), 287 (20), 227 (20), 187 (15), 171 (20), 85 (100).

4.1.6. Treatment of (12) with the zinc reagent derived from ethyl bromodifluoroacetate. A solution of the ketone (**12**) (0.98 g, 2.62 mmol) in freshly distilled THF (11 mL) was added, under an atmosphere of nitrogen, to a stirred

dispersion of freshly activated zinc (0.30 g, 4.6 mmol) in THF (5 mL). Ethyl bromodifluoroacetate (0.47 mL, 3.67 mmol) was added to the stirred mixture, which was then heated directly to reflux and maintained at that temperature for 1.5 h. The reaction mixture was allowed to cool to rt when it was poured into an aqueous solution containing $NaHCO_3$ and $NaHSO_4$. The organic material was extracted into EtOAc (3×50 mL) and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give the crude product as a solid. Purification by flash column chromatography (SiO_2; EtOAc–petroleum ether (40:60), 1:9) furnished the adduct (**15**) as a colorless, crystalline solid (1.03 g, 79%). Mp 94–95°C; (Found: C, 53.3; H, 8.5; F, 7.4. $C_{22}H_{40}F_2O_8Si$ requires C, 53.0; H, 8.1; F, 7.6%); $[\alpha]_D^{25}$=+110.2 (*c* 0.25, CH_2Cl_2); ν_{max} (Nujol)/cm^{-1} 3451 (OH), 1754 (C=O); δ_H (400 MHz; C_6D_6), 0.04 and 0.19 (2×3H, 2×s, $(CH_3)_2Si$), 0.84 (3H, t, *J*=7.2 Hz, CH_3CH_2), 0.90 (9H, s, $(CH_3)_3CSi$), 1.26 and 1.31 (2×3H, 2×s, 2×butyl CH_3), 1.65 (1H, dd, *J*=14.7, 2.5 Hz, C(2)H_β), 2.00 (1H, ddd, *J*=12.8, 12.1, 1.9 Hz, C(6)H_β), 2.30 (1H, dddd, *J*=14.7, 3.9, 3.1, 0.9 Hz, C(2)H_α), 2.78 (1H, dddd, *J*=12.8, 4.7, 3.1, 0.9 Hz, C(6)H_α), 2.99 and 3.02 (2×3H, 2×s, 2×acetal OCH_3), 3.41 (1H, dd, *J*=10.0, 2.5 Hz, C(4)*H*), 3.91 (2H, q, *J*=7.2 Hz, CH_3CH_2), 3.91 (1H, ~dt, *J*=3.9, 2.5 Hz, C(3)*H*), 4.44 (1H, ddd, *J*=12.1, 10.0, 4.7 Hz, C(5)*H*); δ_C (100 MHz; C_6D_6), −5.21 and −4.41 ($(CH_3)_2Si$), 13.87 (CH_3CH_2), 18.15 and 18.41 (2×butyl CH_3), 18.44 ($(CH_3)_3CSi$), 25.93 ($(CH_3)_3CSi$), 35.10 (C(2)H_2), 35.90 (C(6)H_2), 47.48 and 47.59 (2×acetal OCH_3), 62.61 (CH_3CH_2), 62.79 (C(5)H), 71.33 (C(3)H), 73.23 (C(4)H), 76.90 (t, J_{CF}=25 Hz, C(1)), 99.69 and 100.19 (2×acetal C), 115.71 (t, J_{CF}=256.4 Hz, CF_2), 163.41 (t, J_{CF}=31.8 Hz, C=O); δ_F (376 MHz; C_6D_6), −113.42 (1F, d, J_{FF}=251 Hz), −114.85 (1F, d, J_{FF}=251 Hz); *m*/*z* (CI–NH_3) 516 (MNH_4^+, 10%), 499 (MH^+, 10), 484 (50), 467 (100), 452 (20), 435 (20), 85 (95); (Found: 499.2538. $C_{22}H_{41}F_2O_8Si$ (MH^+) requires 499.2538).

4.1.7. Treatment of (12) with the zinc reagent derived from ethyl bromofluoroacetate. A solution of the ketone (**12**) (2.29 g, 6.11 mmol) in freshly distilled THF (24 mL) was added, under an atmosphere of nitrogen, to a stirred dispersion of freshly activated zinc (0.68 g, 10.4 mmol) in THF (12 mL). Ethyl bromofluoroacetate (0.9 mL, 7.6 mmol) was added to the stirred mixture, which was then heated directly to reflux and maintained at that temperature for 1 h. The reaction mixture was allowed to cool to rt when it was poured into an aqueous solution containing $NaHCO_3$ and $KHSO_4$. The organic material was extracted into EtOAc (3×100 mL) and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give the crude product as a solid. Purification by flash column chromatography (SiO_2; EtOAc–petroleum ether (40:60), 1:4) furnished an inseparable mixture of the adducts (**16a**,**b**) as a colorless, crystalline solid (1.65 g, 56%); ν_{max} (KBr)/cm^{-1} 3469 (OH), 1752 (C=O); δ_H (400 MHz; C_6D_6) 0.05, 0.07, 0.21 and 0.22 (4×3H, 4×s, $(CH_3)_2Si$ for **16a** and **16b**), 0.87 (3H, t, *J*=6.8 Hz, CH_3CH_2 for **16a** or **16b**), 0.92 (9H, s, $(CH_3)_3CSi$ for **16a** or **16b**), 0.92 (3H, t, *J*=6.8 Hz, CH_3CH_2 for **16a** or **16b**), 0.93 (9H, s, $(CH_3)_3CSi$ for **16a** or **16b**), 1.27, 1.27, 1.31 and 1.32 (4×3H, 4×s, 4×butyl CH_3 for **16a** and **16b**), 1.47 (1H, dd, *J*=14.4, 2.4 Hz, C(2)H_β for **16a**), 1.57 (1H, br, dd, *J*=14.4, 2.4 Hz, C(2)H_β for **16b**), 1.71 (1H, ddd, *J*=13.0, 12.4, 1.6 Hz, C(6)H_β for **16a**), 1.81 (1H, ddd, *J*=13.0, 12.0, 1.2 Hz, C(6)H_β for **16b**), 2.04 (1H, ~dt, *J*=14.8, 3.2 Hz, C(2)H_α for **16b**), 2.15 (1H, ~dtd, *J*=14.4, 2.8, 1.1 Hz, C(2)H_α for **16a**), 2.53 (1H, ~dt, *J*=13.0, 4.4 Hz, C(6)H_α for **16a**), 2.54 (1H, ~dt, *J*=13.0, 4.4 Hz, C(6)H_α for **16b**), 3.01, 3.01, 3.02 and 3.03 (4×3H, 4×s, 4×acetal OCH_3 for **16a** and **16b**), 3.37 (1H, dd, *J*=10.0, 2.4 Hz, C(4)*H* for **16a** or **16b**), 3.39 (1H, dd, *J*=10.4, 2.4 Hz, C(4)*H* for **16a** or **16b**), 3.85–4.06 (6H, m, CH_3CH_2 and C(3)*H* for **16a** and **16b**), 4.39–4.48 (2H, m, C(5)*H* for **16a** and **16b**) 4.47 (1H, dd, *J*=48.4, 0.8 Hz, C*H*FCO_2Et for **16a**), 4.60 (1H, d, *J*=48.4 Hz, C*H*FCO_2Et for **16b**), 4.80 (1H, br, O*H* for **16a**), 4.90 (1H, d, *J*=1.2 Hz, O*H* for **16b**); δ_F (376 MHz; C_6D_6), −192.6 (1F, d, *J*=48.4 Hz), −193.70 (1F, d, *J*=48.4 Hz); *m*/*z* (CI–NH_3) 498 (MNH_4^+, 2%), 481 (MH^+, 2), 466 (20), 449 (100); (Found: 481.2647. $C_{22}H_{42}FO_8Si$ (MH^+) requires 481.2633).

4.2. Representative dehydration procedures

4.2.1. (2′*S*,3′*S*)-Methyl-3-*O*-^{t}butyldimethylsilyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-shikimate (17). *Using Martin's sulfurane*. A solution of Martin's sulfurane (0.949 g, 1.41 mmol) in CH_2Cl_2 (5 mL) was slowly added under an atmosphere of nitrogen to a stirred solution of (**10**) (0.41 g, 0.94 mmol) in CH_2Cl_2 (10 mL) at rt. The resulting pale yellow solution was stirred for 24 h when the residual solvent was removed in vacuo to yield the crude product as a pale yellow oil. Purification by flash column chromatography (SiO_2; EtOAc–petroleum ether (40:60), 1:9) followed by recrystallisation (CH_3OH–H_2O) furnished the title compound (**17**) as a colorless solid (0.33 g, 84%). Mp 74–75°C; (Found: C, 57.7; H, 8.7. $C_{20}H_{36}O_7Si$ requires C, 57.7; H 8.7%); $[\alpha]_D^{22}$=−16.4 (*c* 1.0, CH_2Cl_2); ν_{max} (film)/cm^{-1} 1724 (s, C=O), 1649 (w, C=C); δ_H (400 MHz; $CDCl_3$), 0.10 and 0.12 (2×3H, 2×s, $(CH_3)_2Si$), 0.89 (9H, s, $(CH_3)_3C$), 1.28 and 1.29 (2×3H, 2×s, 2×butyl CH_3), 2.21 (1H, ddd, *J*=17.6, 10.4, 2.6 Hz, C(6)H_β), 2.80 (1H, dd, *J*=17.6, 6.0 Hz, C(6)H_α), 3.23 and 3.24 (2×3H, 2×s, 2×acetal OCH_3), 3.48 (1H, dd, *J*=10.9, 3.9 Hz, C(4)*H*), 3.75 (3H, s, CO_2CH_3), 4.11 (1H, ddd, *J*=10.9, 10.4, 6.0 Hz, C(5)*H*), 4.31 (1H, dd, *J*=5.5, 3.9 Hz, C(3)*H*), 6.77 (1H, dd, *J*=5.5, 2.6 Hz, C(2)*H*); δ_C (75.4 MHz; $CDCl_3$), −4.89 and −4.76 ($(CH_3)_2Si$), 17.60 and 17.76 (2×butyl CH_3), 18.27 ($(CH_3)_3CSi$), 25.68 ($(CH_3)_3CSi$), 30.34 (C(6)H_2), 47.53 and 47.68 (2×acetal OCH_3), 51.87 (CO_2CH_3), 62.29 (C(5)H), 65.89 (C(3)H), 70.75 (C(4)H), 98.64 and 99.41 (2×acetal C), 129.67 (C(1)), 136.64 (C(2)H), 166.97 (CO_2CH_3); *m*/*z* (CI–NH_3) 434 (MNH_4^+, 25%), 402 (95), 385 (80), 285 (45), 270 (85), 85 (100); (Found: 434.2584. $C_{20}H_{40}NO_7Si$ (MNH_4^+) requires 434.2574).

Using $POCl_3$. $POCl_3$ (1.4 mL, 15 mmol) was added, under an atmosphere of nitrogen, to a solution of (**10**) (3.50 g, 8.05 mmol) in freshly distilled pyridine (12 mL), at 0°C. The reaction mixture was warmed at 40°C for 3 days when it was cooled to 0°C and quenched by the careful addition of a saturated aqueous solution of ammonium chloride (40 mL). The organic material was extracted into EtOAc (3×50 mL). The combined extracts were dried ($MgSO_4$), concentrated in vacuo and the remaining pyridine was removed by azeotropic distillation with toluene to provide yellow crystals of the crude product. Recrystallisation from

CH_3OH-H_2O afforded the title compound (**17**) (contaminated with ~6% of regioisomer (**18**)) as colorless crystals (2.72 g, 81%).

4.2.2. (2′*S*,3′*S*,3*R*,4*R*,5*S*)-3-*O*-[*t*]Butyldimethylsilyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-cyclohex-1-ene-3,4,5-triol (19). *Using the Burgess reagent*. A solution of the Burgess reagent (0.380 g, 1.60 mmol) in dry acetonitrile (5 mL) was added, under an atmosphere of nitrogen, to a solution of (**13**) (0.500 g, 1.33 mmol) in acetonitrile (5 mL). The reaction mixture was heated at reflux for 12 h, then cooled to rt and washed successively with water (30 mL) and brine (40 mL). The aqueous washes were extracted with EtOAc (3×40 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to provide the crude product as an oil. Purification by flash column chromatography (SiO_2; EtOAc–petroleum ether (40:60), 1:4) gave the title compound (**19**) (contaminated with ~5% of regioisomer (**20**)) as a viscous oil (0.272 g, 57%). ν_{max} (film)/cm^{-1} 3058, 2990, 2950, 2929, 2855, 2831 (CH), 1647 (w, C=C); δ_H (300 MHz; $CDCl_3$), 0.09 and 0.11 (2×3H, 2×s, $(CH_3)_2Si$), 0.89 (9H, s, $(CH_3)_3C$), 1.27 and 1.29 (2×3H, 2×s, 2×butyl CH_3), 2.10 (1H, br, dd, J=17.6, 10.1 Hz, C(6)H_β), 2.39 (1H, ddd, J=17.6, 6.1, 4.0 Hz, C(6)H_α), 3.23 and 3.25 (2×3H, 2×s, 2×acetal OCH_3), 3.51 (1H, dd, J=10.8, 3.7 Hz, C(4)*H*), 4.14 (1H, ddd, J=10.8, 10.1, 4.0 Hz, C(5)*H*), 4.19 (1H, ~t, J=3.7 Hz, C(3)*H*), 5.67–5.69 (2H, m, C(1)*H* and C(2)*H*); δ_C (75 MHz; $CDCl_3$), −4.85 and −4.68 ($(CH_3)_2Si$), 17.66 and 17.84 (2×butyl CH_3), 18.32 ($(CH_3)_3CSi$), 25.78 ($(CH_3)_3CSi$), 31.28 (C(6)H_2), 47.52 and 47.63 (2×acetal OCH_3), 62.76 (C(5)H), 66.74 (C(3)H), 71.29 (C(4)H), 98.57 and 99.33 (2×acetal *C*), 126.88 and 128.00 (*C*(1)H and *C*(2)H); *m*/*z* (CI–NH_3) 376 (MNH_4^+, 8%), 344 (10), 327 (100), 312 (10), 295 (5), 269 (30), 209 (40), 169 (45), 74 (50); (Found: 376.2509. $C_{18}H_{38}NO_5Si$ (MNH_4^+) requires 376.2518).

4.2.3. (2″*S*,3″*S*,3′*R*,4′*S*,5′*R*)-Ethyl-2,2-difluoro-2-[3′-*O*-[*t*]butyldimethylsilyl′-4′-*O*,5′-*O*-(2″,3″-dimethoxybutane-2″,3″-diyl)-3′,4′,5′-trihydroxycyclohex-1′-ene-1′-yl]-acetate (23). *Using DAST*. A pre-dried sample of the Reformatsky adduct (**15**) (0.570 g, 1.14 mmol) was dissolved, under an atmosphere of nitrogen, in freshly distilled CH_2Cl_2 (15 mL) and the solution was cooled to 0°C. DAST (0.42 mL, 3.18 mmol) was added carefully by syringe. After stirring at 0°C for 1 h, the reaction mixture was allowed to warm to rt and it was then stirred for a further 24 h. The reaction mixture was cooled in ice and quenched by the careful addition of a saturated aqueous solution of $NaHCO_3$. The organic material was extracted into EtOAc (3×25 mL) and the combined 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), 1:49) gave the title compound (**23**), contaminated with ~7% of the double bond regioisomer (**24**), as a colorless oil (0.357 g, 65%). ν_{max} (film)/cm^{-1} 2952, 2857 (CH), 1768 (C=O); δ_H (300 MHz; $CDCl_3$), 0.11 and 0.14 (2×3H, 2×s, $(CH_3)_2Si$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.31 and 1.32 (2×3H, 2×s, 2×butyl CH_3), 1.36 (3H, t, J=7.2 Hz, CH_3CH_2O), 2.20 (1H, br dd, J=17.2 Hz, 10.6, C(6)H_β), 2.57 (1H, dd, J=17.2, 6.1 Hz, C(6)H_α), 3.26 and 3.27 (2×3H, 2×s, 2×acetal OCH_3), 3.52 (1H, dd, J=10.6, 3.8 Hz, C(4)*H*), 4.17 (1H, ~td, J=10.6, 6.1 Hz, C(5)*H*), 4.29–4.34 (1H, m, C(3)*H*), 4.34 (2H, q, J=7.2 Hz, CH_3CH_2O), 6.19 (1H, br, s, C(2)*H*); δ_C (75 MHz; $CDCl_3$), −5.00 and −4.78 ($Si(CH_3)_2$), 13.83 (CH_3CH_2O), 17.58 and 17.73 (2×butyl CH_3), 18.23 ($SiC(CH_3)_3$), 25.62 ($SiC(CH_3)_3$), 28.68 (C(6)H_2), 47.72 (br, 2×acetal OCH_3, overlapping), 62.01, 65.46 and 70.56 (*C*(3)H, *C*(4)H and *C*(5)H), 63.01 (CH_3CH_2O), 98.73 and 99.46 (2×acetal *C*), 112.80 (t, J=251.5 Hz, $CF_2CO_2C_2H_5$), 129.15 (t, J=8.3 Hz, *C*(2)H), 130.51 (t, J=23.8 Hz, *C*(1)), 163.35 (t, J=33.9 Hz, C=O); *m*/*z* (CI–NH_3) 498 (MNH_4^+, 5%), 466 (45), 449 (100), 417 (35), 331 (30), 85 (50); (Found: 449.2179. $C_{21}H_{35}F_2O_6Si$ [$(M-OCH_3)^+$] requires 449.2171).

4.2.4. (2″*S*,3″*S*,3′*R*,4′*S*,5′*R*)-2,2-Difluoro-2-[3′-*O*-[*t*]butyldimethylsilyl-4′-*O*,5′-*O*-(2″,3″-dimethoxybutane-2″,3″-diyl)-3′,4′,5′-trihydroxycyclohex-1′-ene-1′-yl]-acetic acid (25). A solution of Martin's sulfurane (1.08 g, 1.61 mmol) in CH_2Cl_2 (5 mL) was slowly added under an atmosphere of nitrogen to a stirred solution of (**15**) (0.401 g, 0.80 mmol) in CH_2Cl_2 (10 mL) at rt. The resulting pale yellow solution was stirred for 4 h when a second portion of the sulfurane (1.08 g, 1.61 mmol) was added. The reaction mixture was stirred for a further 16 h when the residual solvent was removed in vacuo to yield the crude product as an orange oil. Purification by flash column chromatography (SiO_2; EtOAc–cyclohexane,1:19) gave the desired compound (**23**), contaminated with small amounts of impurities arising from decomposition of the sulfurane, as a colorless oil. This material was stirred as a dispersion in a mixture of CH_3OH (4 mL) and H_2O (2 mL) and $LiOH.H_2O$ (0.037 g, 0.89 mmol) was added in one portion. The reaction mixture was stirred at rt for 3 h when it was acidified to pH=2 by the addition of 10% HCl. The organic material was extracted into EtOAc (3×10 mL) and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give the crude product. Purification by flash column chromatography (SiO_2; EtOAc–acetic acid, 99:1) gave the title compound (**25**) as a viscous oil (0.182 g, 50%). (This compound underwent rapid desilylation when stored in a concentrated state). δ_H (400 MHz; $CDCl_3$), 0.10 and 0.12 (2×3H, 2×s, $(CH_3)_2Si$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.29 and 1.32 (2×3H, 2×s, 2×butyl CH_3), 2.10–2.20 (1H, m, C(6)H_β), 2.56 (1H, dd, J=17.0, 6.0 Hz, C(6)H_α), 3.25 and 3.26 (2×3H, 2×s, 2×acetal OCH_3), 3.54 (1H, dd, J=10.8, 4.0 Hz, C(4)*H*), 4.19 (1H, ~td, J=10.8, 6.0 Hz, C(5)*H*), 4.31 (1H, ~t, J=4.2 Hz, C(3)*H*), 6.19 (1H, br, s, C(2)*H*); δ_C (100 MHz; $CDCl_3$), −4.70 and −4.56 ($Si(CH_3)_2$), 17.80 (2×butyl CH_3, overlapping), 18.47 ($SiC(CH_3)_3$), 25.84 ($SiC(CH_3)_3$), 28.71 (C(6)H_2), 47.91 and 47.95 (2×acetal OCH_3), 62.47, 65.58 and 70.61 (*C*(3)H, *C*(4)H and *C*(5)H), 99.00 and 99.81 (2×acetal *C*), 128.79 (br, *C*(2)H), 130.39 (t, J=22.8 Hz, *C*(1)), 165.76 (br, C=O) [CF_2 not observed]; δ_F (376 MHz; $CDCl_3$), −103.04 (1F, d, J_{FF}=254 Hz), −106.35 (1F, d, J_{FF}=254 Hz); *m*/*z* (negative ion electrospray) 451 (100%, $[M-H]^-$).

4.2.5. (3′*R*,4′*S*,5′*R*)-2,2-Difluoro-2-[3′,4′,5′-trihydroxycyclohex-1′-ene-1′-yl]-acetic acid (2). A solution of the carboxylic acid (**25**) (0.182 g, 0.40 mmol) in a mixture of TFA (2.75 mL) and H_2O (0.25 mL) was stirred at rt for 2 h when the residual solvents were removed directly in vacuo to give a yellow oil. Trituration with Et_2O (2×5 mL) followed by storage of the insoluble material under high

vacuum gave the title compound in essentially pure form as a colorless oil (0.068 g, 75%). Analytical material could be obtained by purification by reverse phase HPLC [Rainin Dynamax C18 (21.4×250 mm); eluent: H_2O; refractive index detection]; δ_H (300 MHz; D_2O), 1.96 (1H, dd, J=17.7, 7.0 Hz, one of C(6)H_2), 2.46 (1H, dd, J=17.7, 5.4 Hz, one of C(6)H_2), 3.56 (1H, dd, J=8.9, 4.5 Hz, C(4)H), 3.85 (1H, ddd, J=8.9, 7.0, 5.4 Hz, C(5)H), 4.19–4.25 (1H, m, C(3)H), 6.01 (1H, br, s, C(2)H); δ_C (75.4 MHz; D_2O), 28.99 (C(6)H_2), 65.26, 65.97 and 71.16 (C(3)H, C(4)H and C(5)H), 113.90 (t, J=251 Hz, CF_2CO_2H), 127.38 (t, J=8 Hz, C(2)H), 131.25 (t, J=24.1 Hz, C(1)), 167.73 (br, C=O); δ_F (282.4 MHz; D_2O), −105.26 (1F, d, J=245 Hz), −105.59 (1F, d, J=245 Hz); m/z (negative ion electrospray), 223 ($(M-H)^-$); (Found: 223.0416, $C_8H_{10}F_2O_5$ [$(M-H)^-$] requires 223.0418).

4.2.6. 6,6-Difluoro-1-(2-furyl)-cyclohex-1-ene (30). 6,6-Difluoro-1-iodocyclohex-1-ene (**29**)(0.300 g, 1.23 mmol) was dissolved in *N*-methyl-pyrrolidinone (4 mL) under an inert atmosphere. To the stirred solution was added bis-(benzonitrile)dichloropalladium(II) (0.024 g, 0.063 mmol), copper(I) iodide (0.027 g, 0.14 mmol), and tri-2-furylphosphine (0.029 g, 0.12 mmol). 2-(tributylstannyl)furan (0.483 g, 1.35 mmol) was added dropwise and the reaction mixture was stirred at rt. On completion of the reaction (as judged by tlc analysis) the solution was diluted with EtOAc (15 mL). The organic phase was washed with a 10% aqueous solution of potassium fluoride (8 mL) followed by 1 M aqueous ammonium hydroxide solution (4×8 mL). The combined aqueous washes were extracted with EtOAc (3×8 mL) and the combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the product was purified by flash column chromatography (SiO_2; $CHCl_3$–petroleum ether (30:40), 3:97) to yield the title compound (**30**) as a colorless solid (0.195 g, 86%). Mp 45–47°C; ν_{max} (KBr)/cm^{-1} 2965, 1645 (C=C); δ_H (400 MHz; $CDCl_3$), 1.82–1.89 (2H, m), 2.14–2.24 (2H, m), 2.27–2.34 (2H, m), 6.41 (1H, dd, J=3.3, 1.8 Hz), 6.50 (1H, d, J=2.5 Hz), 6.62–6.64 (1H, m), 7.38 (1H, d, J=1.5 Hz); δ_C (100 MHz; $CDCl_3$), 19.34 (t, J=4.5 Hz), 24.99 (t, J=2.0 Hz), 33.76 (t, J=24.5 Hz, C(5)H_2), 107.92 and 111.36 (furan C(3)H and C(4)H), 119.56 (t, J=237 Hz, C(6)F_2), 125.96 (t, J=24.5 Hz, C(1)), 130.87 (t, J=7 Hz, C(2)H), 141.63 and 148.64 (furan C(2), and C(5)H); δ_F (235 MHz; $CDCl_3$), −99.65 to −100.87 (m); m/z (EI) 184 (M^+, 100%) 169 (20), 120 (42), 91 (76), 77 (36); (Found: 184.0699. $C_{10}H_{10}F_2O$ (M^+) requires 184.0700).

4.2.7. 6,6-Difluoro-1-phenylcyclohex-1-ene (31). 6,6-Difluoro-1-iodocyclohex-1-ene (**29**)(0.122 g, 0.50 mmol) was dissolved in dry dimethoxyethane (7.5 mL) and the solution was degassed by bubbling nitrogen through for 15 min. Phenylboronic acid (0.085 g, 0.70 mmol), lithium chloride (0.045 g, 1.06 mmol), an aqueous solution of sodium carbonate (2 M, 2.5 mL) and tetrakis(triphenylphosphine)palladium(0) (0.022 g, 0.019 mmol) were added. The reaction vessel was evacuated and flushed with nitrogen six times and the reaction mixture was then heated at reflux for 15 h. After cooling to rt, CH_2Cl_2 (20 mL) was added and the organic phase was washed with a 2 M sodium carbonate solution (10 mL) containing concentrated aqueous ammonia (0.3 mL). The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic extracts were washed with water (3×50 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2; $CHCl_3$:petroleum ether (30:40), 1:49) gave the title compound (**31**) as a colorless oil (0.093 g, 96%); δ_H (400 MHz; $CDCl_3$), 1.88–1.94 (2H, m), 2.13–2.32 (4H, m), 6.26 (1H, tt, J=4.0, 2.0 Hz, C(2)H), 7.26–7.35 (3H, m, aromatic CH), 7.41–7.47 (2H, m, aromatic CH); δ_F (235 MHz; $CDCl_3$), −90.12 to −90.30 (m); m/z (CI) 194 (M^+, 54%) 175 (100), 130 (30), 115 (9); (Found: 194.0912. $C_{12}H_{12}F_2$ requires 194.0907).

4.2.8. 6,6-Difluoro-1-methoxycarbonyl-cyclohex-1-ene (33). 6,6-Difluoro-1-iodocyclohex-1-ene (**29**) (0.122 g, 0.50 mmol) was dissolved in dry dimethylformamide (2 mL). *N*,*N*-diisopropylethylamine (0.09 mL, 0.52 mmol), palladium acetate (0.003 g, 0.013 mmol), tri-2-furylphosphine (0.007 g, 0.03 mmol) and methanol (0.9 mL, 23 mmol) were added to the solution. The mixture was degassed, flushed three times with carbon monoxide and then stirred under an atmosphere of carbon monoxide at rt for 24 h. Diethyl ether (20 mL) and water (10 mL) were added and the phases were separated. The organic phase was washed with water (3×10 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The product was purified by flash column chromatography (SiO_2; Et_2O–pentane, 1:9) to yield the title compound (**33**) as a colorless oil (0.048 g, 55%). Starting material was also recovered (0.046 g, 38%). ν_{max} (thin film)/cm^{-1} 2965, 1725 (C=O), 1645 (C=C); δ_H (400 MHz; $CDCl_3$), 1.81–1.88 (2H, m), 2.08–2.18 (2H, m), 2.27–2.35 (2H, m), 3.82 (3H, s, CO_2CH_3), 7.34 (1H, tt, J=4.0, 1.8 Hz, C(2)H); δ_C (100 MHz; $CDCl_3$) 18.93 (t, J=4.8 Hz), 25.73 (t, J=1.8 Hz), 33.74 (t, J=24.6 Hz, C(5)H_2), 52.03 (CO_2CH_3), 118.05 (t, J=238.1 Hz, C(6)F_2), 127.74 (t, J=25.9 Hz, C(1)), 148.92 (t, J=7.0 Hz, C(2)H), 164.08 (t, J=1.7 Hz, CO_2CH_3); m/z (EI) 176 (M^+, 6%) 156 (15), 145 (100), 117 (22), 97 (53); (Found: 176.0656, $C_8H_{10}F_2O_2$ (M^+) requires 176.0649).

4.2.9. (3*R*,4*R*,5*S*,6*S*)-1-Bromo-3-benzyloxy-4-hydroxy-5,6-*iso*propylidenedioxy-cyclohex-1-ene (41). The diol (**35**) (0.481 g, 1.81 mmol) and dibutyltinoxide (0.472 g, 1.9 mmol) were placed in a round bottom flask which was evacuated and then purged with nitrogen several times. Dry toluene (10 mL) was added, and the reaction mixture was heated at reflux for 5.5 h in apparatus fitted with a Dean–Stark trap before being allowed to cool to rt. Residual solvents were removed in vacuo to give a crude sample of the stannylene acetal. CsF (pre-dried by storage in vacuo, 0.289 g, 1.90 mmol) was added to the crude stannylene acetal and the flask was kept under vacuum for 1 h. At the end of this time, the mixture was suspended in dry DMF, and benzyl bromide (0.23 mL, 1.93 mmol) was added to the stirred mixture. After stirring for 18 h at rt, the reaction mixture was diluted with water (150 mL) and extracted with Et_2O (3×150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The resulting crude oil was purified by flash column chromatography (SiO_2; EtOAc–petroleum ether (40:60), 3:17) with a pad of KF placed at the top of the column to remove tin residues. The title compound (**41**) was isolated as a colorless oil (0.403 g, 63%); $[\alpha]_D^{20}$=−37.7 (c0.80, CH_2Cl_2); ν_{max} (film)/

cm^{-1} 3580–3399 (bw, O–H), 2986, 2944 and 2891 (w, C–H), 1646 (w, C=C); δ_H (300 MHz; $CDCl_3$), 1.41 and 1.42 (2×3H, 2×s, 2×acetonide CH_3), 2.48 (1H, bs, O*H*), 4.12–4.17 (1H, m, C(3)*H*), 4.34 (1H, ~t, *J*=3.8 Hz, C(4)*H*), 4.49 (1H, ~t, *J*=5.1 Hz, C(5)*H*), 4.65–4.70 (3H, m, C(6)*H* and benzyl CH_2), 7.34–7.42 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$), 26.07 and 27.52 (2×acetonide *C*H_3), 71.60 (benzyl *C*H_2), 67.46, 74.22, 75.97 and 76.07 (*C*(3)H, *C*(4)H, *C*(5)H and *C*(6)H), 110.01 (acetal *C*), 124.18 (*C*(1)), 127.72, 128.13, 128.46 and 128.57 (aromatic *C*H and *C*(2)H), 137.18 (aromatic *ipso-C*); *m/z* (CI–NH_3) 374 (MNH_4^+, ^{81}Br, 100%), 372 (MNH_4^+, ^{79}Br, 100), 281 (15), 279 (25), 108 (30), 101 (55), 91 (30); (Found: 372.0807, $C_{16}H_{23}^{79}BrNO_4$ (MNH_4^+) requires 372.0810).

4.2.10. (2′*S*,3′*S*,3*R*,4*R*,5*S*,6*S*)-1-Bromo-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-6-*O*-acetyl-cyclohex-1-ene-3,4,5,6-tetraol (44). CSA (0.05 g, 0.22 mmol), trimethylorthoformate (1.9 mL, 17.4 mmol) and 2,3-butandione (0.38 mL, 4.33 mmol) were added to a solution of the alcohol (**41**) (0.615 g, 1.73 mmol) in CH_3OH (15 mL) under an atmosphere of nitrogen. The reaction mixture was heated at reflux for 24 h during which time the yellow color disappeared and then became dark red. After cooling to rt, Et_3N (0.7 mL, 5.0 mmol) was added and the reaction mixture was concentrated in vacuo. Purification by flash column chromatography (SiO_2; EtOAc–petroleum ether (40:60), 1:9) yielded a colorless foam which consisted predominantly of compound (**42**) together with starting material and an unidentified isomer of (**42**). The foam (~1.16 g) was dissolved in CH_2Cl_2 (15 mL) and to the resulting solution was added Ac_2O (1 mL), pyridine (1 mL) and DMAP (a few crystals). The reaction mixture was stirred at rt for 6 h, then washed with a saturated aqueous solution of ammonium chloride (40 mL) and extracted with CH_2Cl_2 (3×40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a crude oil. Purification by flash column chromatography (SiO_2; EtOAc–petroleum ether (40:60), 1:9) provided compound (**44**) as colorless crystals (0.404 g, 49.5%). Mp 133–135°C; $[\alpha]_D^{20}$=−46.4 (*c* 0.61, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2992, 2950, 2915, 2832 (m, C–H), 1751 (s, C=O), 1638 (w, C=C); δ_H (300 MHz; $CDCl_3$), 1.16 and 1.26 (2×3H, 2×s, 2×butyl CH_3), 2.06 (3H, s, OC(O)CH_3), 3.19 and 3.21 (2×3H, 2×s, 2×acetal OCH_3), 3.95–4.02 (2H, m, C(3)*H* and C(4)*H*), 4.31 (1H, dd, *J*=10.6, 4.6 Hz, C(5)*H*), 4.51–4.96 (2H, ABq, J_{AB}=11.1 Hz, benzyl CH_2), 5.68 (1H, d, *J*=4.6 Hz, C(6)*H*), 6.23 (1H, d, *J*=5.6 Hz, C(2)*H*), 7.19–7.30 (3H, m, aromatic C*H*), 7.37–7.39 (2H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$), 17.50 and 17.69 (2×butyl *C*H_3), 20.64 (OC(O)*C*H_3), 47.88 and 48.04 (2×acetal O*C*H_3), 64.31, 66.10, 72.09 and 72.63 (*C*(3)H, *C*(4)H, *C*(5)H and *C*(6)H), 73.86 (benzyl *C*H_2), 99.12 and 99.21 (2×acetal *C*), 122.93 (*C*(1)), 127.69, 128.19 and 128.27 (aromatic *C*H), 132.57 (*C*(2)H), 138.43 (aromatic *ipso-C*), 170.11 (*C*=O); *m/z* (CI–NH_3) 490 (MNH_4^+, ^{81}Br, 100%), 488 (MNH_4^+, ^{79}Br, 100), 458 (80), 456 (70), 441 (20), 439 (15), 108 (65), 85 (90); (Found: 488.1274, $C_{21}H_{31}^{79}BrNO_7$ (MNH_4^+) requires 488.1284).

4.2.11. (2′*S*,3′*S*,3*R*,4*R*,5*S*)-1-Bromo-3-*O*-benzyl-4-*O*,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-cyclohex-1-ene-3,4,5,6-tetraol (42). The allylic acetate (**44**) (0.404 g, 0.86 mmol) was stirred with K_2CO_3 (0.071 g, 0.52 mmol) in CH_3OH (15 mL) for 5.5 h at rt. The reaction mixture was then diluted with a saturated aqueous solution of ammonium chloride (80 mL) and extracted with CH_2Cl_2 (4×40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford the title compound (**42**) in essentially pure form (0.357 g, 97%). Mp 69–71°C; $[\alpha]_D^{22}$=−6.2 (*c* 0.94, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3506–3451 (bm, O–H), 3061, 3021 (w, C–H), 2992, 2945, 2927, 2832 (m, C–H), 1640 (m, C=C); δ_H (300 MHz; $CDCl_3$), 1.28 (6H, s, 2×butyl CH_3, overlapping), 2.85 (1H, bs, O*H*), 3.19 and 3.24 (2×3H, 2×s, 2×acetal OCH_3), 3.96–4.04 (2H, m, C(3)*H* and one of C(5)*H* or C(6)*H*), 4.23–4.28 (2H, m, C(4)*H* and one of C(5)*H* or C(6)*H*), 4.51–4.95 (2H, ABq, J_{AB}=11.2 Hz, benzyl CH_2), 6.16 (1H, d, *J*=5.6 Hz, C(2)*H*), 7.19–7.29 (3H, m, aromatic C*H*), 7.36–7.39 (2H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$), 17.66 and 17.75 (2×butyl *C*H_3), 47.92 and 48.08 (2×acetal O*C*H_3), 65.52, 65.55, 72.37 and 72.94 (*C*(3)H, *C*(4)H, *C*(5)H and *C*(6)H), 73.72 (benzyl *C*H_2), 99.33 and 99.63 (2×acetal *C*), 126.01 (*C*(1)), 127.64, 128.15 and 128.26 (aromatic *C*H), 130.48 (*C*(2)H), 138.51 (aromatic *ipso-C*); *m/z* (CI–NH_3) 448 (MNH_4^+, ^{81}Br, 20%), 446 (MNH_4^+, ^{79}Br, 20), 416 (45), 414 (45), 399 (15), 397 (15), 384 (8), 382 (8), 367 (10), 365 (10), 108 (50), 85 (100); (Found: 446.1175, $C_{19}H_{29}^{79}BrNO_6$ (MNH_4^+) requires 446.1179).

4.2.12. (2′*S*,3′*S*,4*R*,5*R*,6*S*)-2-Bromo-4-*O*-benzyl-5-*O*,6-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-cyclohex-2-ene-1-one-3,4,5,-triol (43). To a solution of oxalyl chloride (0.09 mL, 1.03 mmol) in freshly distilled CH_2Cl_2 (3 mL) at −78°C, was added a pre-cooled solution of DMSO (0.08 mL, 1.13 mmol) in CH_2Cl_2 (3 mL), dropwise so as to maintain the temperature below −60°C. The resulting solution was stirred for 30 min at −78°C and then a pre-cooled solution of the allylic alcohol (**42**) (0.359 g, 0.84 mmol) in CH_2Cl_2 was added dropwise. The reaction mixture was stirred at −78°C for a further 65 min, then Et_3N (0.53 mL, 3.80 mmol) was added dropwise and the reaction mixture was allowed to warm to rt. The yellow colored solution was stirred at rt for 4 h, then washed with a saturated aqueous solution of ammonium chloride (200 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude orange product which still contained triethylammonium salts was washed with water (2×100 mL) and extracted with DCM (2×100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to furnish the title compound (**43**), in essentially pure form, as a pale orange oil (0.279 g, 78%). ν_{max} (film)/cm^{-1} 3027 (w, C–H), 2994, 2948, 2883, 2834 (m, C–H), 1718 (s, C=O), 1600 (w, C=C); δ_H (300 MHz; $CDCl_3$) 1.42 and 1.46 (2×3H, 2×s, 2×butyl CH_3), 3.31 and 3.38 (2×3H, 2×s, 2×acetal OCH_3), 4.12 (1H, dd, *J*=10.9, 3.4 Hz, C(5)*H*), 4.33 (1H, dd, *J*=6.6, 3.4 Hz, C(4)*H*), 4.71–5.14 (2H, ABq, J_{AB}=11.2 Hz, benzyl CH_2), 5.02 (1H, d, *J*=10.9 Hz, C(6)*H*), 7.26 (1H, d, *J*=6.6 Hz, C(3)*H*), 7.36–7.44 (3H, m, aromatic C*H*), 7.48–7.51 (2H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$), 17.50 and 17.55 (2×butyl *C*H_3), 48.07 and 48.39 (2×acetal O*C*H_3), 69.23, 69.88 and 72.10 (*C*(4)H, *C*(5)H and *C*(6)H), 74.02 (benzyl *C*H_2), 99.36 and 99.97 (2×acetal *C*), 126.60 (*C*(2)), 128.02, 128.26 and 128.43 (aromatic *C*H), 137.90 (aromatic *ipso-C*), 143.02 (*C*(3)H), 186.85 (*C*=O); *m/z*

(CI–NH_3) 446 (MNH_4^+, ^{81}Br, 35%), 444 (MNH_4^+, ^{79}Br, 35), 414 (45), 412 (45), 397 (8), 395 (8), 382 (8), 380 (8), 365 (8), 363 (8), 260 (30), 228 (30), 108 (100), 85 (100); (Found: 444.1019. $C_{19}H_{27}^{79}BrNO_6$ (MNH_4^+) requires 444.1022).

4.2.13. Reaction of (43) with Deoxo-Fluor® in the absence of solvent. The enone (**43**) (0.221 g, 0.52 mmol) was cooled to 0°C and bis-(2-methoxyethyl)aminosulphur trifluoride (1.5 mL) was added dropwise. The reaction mixture was stirred at rt, under a nitrogen atmosphere, for 72 h, then diluted with $CHCl_3$ (10 mL) and quenched by the careful addition of a saturated aqueous solution of sodium bicarbonate (250 mL). The organic components were extracted into $CHCl_3$ (3×100 mL), dried ($MgSO_4$) and concentrated in vacuo to give a brown oil. Purification by flash column chromatography (SiO_2; EtOAc–petroleum ether (40:60), 1:19) furnished the vinyl fluoride (**46**) as a colorless viscous oil, R_f 0.59 (EtOAc–petroleum ether (40:60), 1:4), (0.070 g, 30%) and the *gem*-difluoride (**45**) as colorless crystals, R_f 0.47 (EtOAc–petroleum ether (40:60), 1:4), (0.126 g, 54%). *Data for (**45**)*; $[\alpha]_D^{23}$=+30.1 (*c* 0.63, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3062, 3028, 2994, 2949, 2835 (m, C–H), 1638 (w, C=C); δ_H (300 MHz; $CDCl_3$), 1.29 and 1.34 (2×3H, 2×s, 2×butyl CH_3), 3.22 and 3.28 (2×3H, 2×s, 2×acetal OCH_3), 3.89 (1H, dd, *J*=11.0, 3.6 Hz, C(4)*H*), 4.02–4.06 (1H, dd, *J*=6.2, 3.6 Hz, C(3)*H*), 4.50 (1H, ddd, *J*=14.6, 11.0, 9.2 Hz, C(5)*H*), 4.52–4.96 (2H, ABq, J_{AB}=11.2 Hz, benzyl CH_2), 6.36 (1H, dd, *J*=6.2, 3.1 Hz, C(2)*H*), 7.18–7.37 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$), 17.50 and 17.59 (2×butyl *C*H_3), 48.14 (2×acetal O*C*H_3, overlapping), 66.38 (dd, *J*=22.3, 17.4 Hz, *C*(5)H), 66.90 (d, *J*=8.5 Hz, *C*(4)H), 71.71 (*C*(3)H), 74.01 (benzyl *C*H_2), 99.25 and 99.49 (2×acetal *C*), 114.27 (t, *J*=245.3 Hz, *C*(6)F_2), 121.07 (~d, *J*=31.1 Hz, C(1)), 127.88, 128.17 and 128.35 (aromatic *C*H), 133.92 (dd, *J*=6.7, 5.5 Hz, *C*(2)H), 138.05 (aromatic *ipso*-C); δ_F (376 MHz; $CDCl_3$), −107.84 (1F, dd, *J*=267.7, 14.6 Hz, one of C(6)F_2), −99.95 (1F, ddd, *J*=267.7, 9.2, 3.1 Hz, one of C(6)F_2); *m/z* (CI–NH_3) 466 (MNH_4^+, ^{79}Br, 7%), 436 (15), 434 (15), 419 (7), 417 (7), 404 (10), 402 (10), 387 (15), 385 (15), 108 (30), 85 (100); (Found: 466.1059. $C_{19}H_{27}^{79}BrF_2NO_5$ requires 466.1041). *Data for (**46**)*: $[\alpha]_D^{23}$=+108.9 (*c* 1.33, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3029, 2994, 2950, 2911, 2835 (m, C–H), 1680 (m, C=C); δ_H (400 MHz; $CDCl_3$) 1.38 and 1.39 (2×3H, 2×s, 2×butyl CH_3), 3.28 and 3.33 (2×3H, 2×s, 2×acetal OCH_3), 4.03 (1H, ddd, *J*=8.5, 2.7 Hz, 2.0 C(5)*H*), 4.12 (1H, ~dt, *J*=8.9, 2.0 Hz, C(4)*H*), 4.67–4.98 (2H, ABq, J_{AB}=11.6 Hz, benzyl CH_2), 4.83 (1H, ddd, *J*=11.9, 8.9, 3.2 Hz, C(3)*H*), 4.97 (1H, ddd, *J*=47.2, 7.6, 2.7 Hz, C(6)*H*F), 7.31–7.40 (5H, aromatic C*H*); δ_F (376 MHz; $CDCl_3$) −167.01 −167.23 (1F, m, C(6)H*F*), −100.88 (1F, ddd, *J*=7.6, 5.2, 3.2 Hz, C(2)*F*); *m/z* (CI–NH_3) 468 (MNH_4^+, ^{81}Br, 10%), 466 (MNH_4^+, ^{79}Br, 10), 436 (30), 434 (30), 419 (20), 417 (10), 404 (15), 402 (15), 387 (23), 385 (26), 108 (60), 85 (100); (Found: 466.1051. $C_{19}H_{27}^{79}BrF_2NO_5$ (MNH_4^+) requires 466.1041).

4.3. X-Ray crystallographic analysis of (22)

Crystal data. $C_{16}H_{28}O_9$, monoclinic, $P2_1$, Z=2, a=6.800(10) Å, b=12.093(16) Å, c=11.789(17) Å, β=105.63(1)°, U=934 Å^3, d_{calc}=1.296 g cm^{-3}, 1701 independent reflections were measured on a MARresearch Image Plate System using Mo Kα radiation. The crystals were positioned at 70 mm from the Image Plate. 100 frames were measured at 2° intervals with a counting time of 2 min. The structure was solved with the Shelx86 program.[32] All non-hydrogen atoms were refined anisotropically. Two solvent water molecules were located in the asymmetric unit. Hydrogen atoms bonded to carbon were positioned in geometric positions, those bonded to oxygen were located in a difference Fourier map. All were refined isotropically with thermal parameters equivalent to 1.2 times that of the atom to which they were bonded. The structure was refined on F^2 using Shelxl[33] to $R1$ 0.0668, $wR2$ 0.1590 for 1198 reflections with $I>2\sigma(I)$. Crystallographic details have been deposited with the Cambridge Crystallographic Data Centre: reference CCDC 168251. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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