Enantioselective synthesis of C_3 fluoro-MEP

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The first enantioselective synthesis of C_3 fluoro-MEP is herein reported. The synthetic pathway developed takes advantage of a selective hydrofluorination of a 2,3-epoxy-1-alcohol to introduce the required tertiary fluoride unit.

Introduction

Many biological functions including electron transport in respiration and photosynthesis, hormone-based signalling, the regulation of transcription and post-translational processes that control lipid biosynthesis, meiosis, apoptosis, protein cleavage and degradation are dependent on isoprenoids.

Nature utilises two distinct biosynthetic routes for the synthesis of isoprenoids. Initially, the mevalonate-dependent pathway was originally considered the sole source of isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). However, recently it was determined that in chloroplasts, algae, cyanobacteria, many species of eubacteria, and apicomplexa, isoprenoids are synthesised by the 2*C*-methyl-D-erythritol 4-phosphate (MEP) pathway, which uses seven enzymes (Fig. 1).[1]

The MEP pathway starts with the condensation of pyruvate and glyceraldehyde 3-phosphate to produce 1-deoxy-D-xylulose 5-phosphate (DOXP) which is then converted to 2*C*-methyl-D-erythritol 4-phosphate (MEP) in reactions catalysed by DOXP synthase and DOXP reductoisomerase respectively. MEP reacts with CTP to produce 4-diphosphocytidyl-2*C*-methyl-D-erythritol (CDP-ME) and pyrophosphate in a reaction catalysed by 2*C*-methyl-D-erythritol 4-phosphate cytidylyltransferase (MEP cytidylyltransferase or IspD).[2]

An ATP-dependent 4-(cytidine 5′-diphospho)-2*C*-methyl-erythritol kinase phosphorylates CDP-ME, producing 4-diphosphocytidyl-2*C*-methyl-D-erythritol 2-phosphate (CDP-ME2P). Next, the CDP-ME2P is converted to 2*C*-methyl-D-erythritol-2,4-cyclodiphosphate (MECP) and CMP by MECP synthase (IspF). The cyclic diphosphate product, MECP, is reduced to 1-hydroxy-2-methyl-2(*E*)-butenyl 4-diphosphate by a reductase encoded by the *ispG* (formally *gcpE*) gene, then the *ispH* (or *lytB*) gene product converts the butenyl diphosphate to both isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) (Fig. 1).

The diseases caused by organisms dependent on the MEP pathway include tuberculosis, infections of the upper respiratory tract, a range of sexually transmitted infections, toxoplasmosis, coccidiosis in poultry, and malaria.[3] Furthermore, since the MEP pathway is not present in animal cells, its selective inhibition could provide the opportunity to develop selective anti-parasitic and herbicidal agents.[4]

Thus, it is not surprising that intermediates of the MEP pathway and their labelled forms have been considered as a starting point for the development of biological chemistry tools and potential therapeutic leads through both synthetic and biological methods.[5,6]

However, despite a significant amount of synthetic interest, the numbers of MEP analogues available are fairly limited. This is perhaps not surprising considering the densely packed functionality within a small carbon framework. This is further

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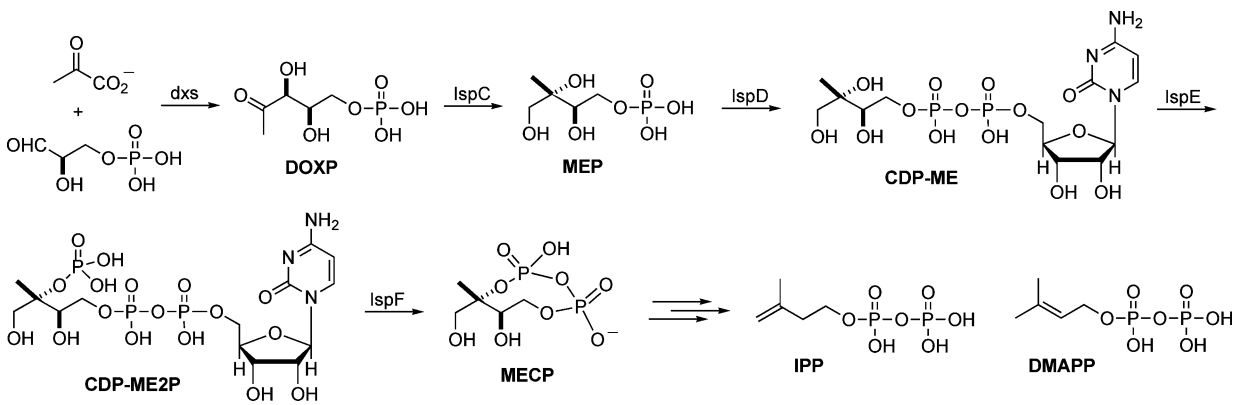
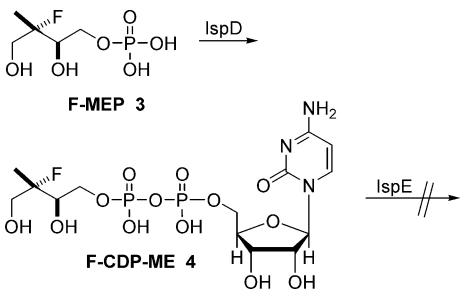


Fig. 1 The non-mevalonate pathway.

complicated by the presence of the tertiary C_3 hydroxyl-bearing stereocentre in MEP **1** (Fig. 2).

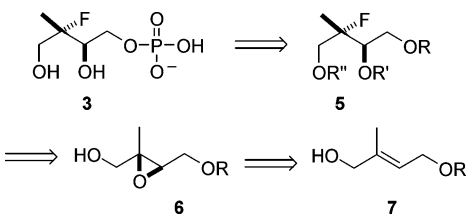
Fig. 2 MEP **1** and putative MEP analogue **2**.

In the first instance, we have decided to focus on the replacement of the MEP C_3 tertiary hydroxyl unit for a fluorine moiety.[7] A readily available fluoro-MEP **3** analogue might be able to inhibit the cytidyltransferase step (IspD) of the pathway through competitive inhibition. However, since the C_3 fluorine is at a non-reactive position at this stage, there is the possibility that it could undergo a conversion with cytidylyltransferase (IspD) and be incorporated into the pathway to generate fluoro-CDP-ME **4**. Fluoro-CDP-ME would then become an inhibitor of the kinase step of the pathway (IspE), as phosphorylation would not be possible, thus preventing the pathway from proceeding any further. This would open the possibility of selectively probing two steps of the MEP pathway with a single chemical probe (Scheme 1).



Scheme 1 Potential fluoro-MEP incorporation.

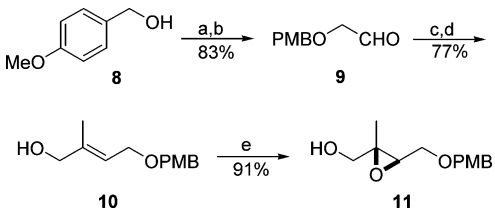
We originally envisioned the highly functionalised fluoro-MEP unit **3** originating from the suitably protected fluoro-erythrol unit **5**. The erythrol unit **5** could then be anticipated from the regio- and stereoselective ring opening of epoxide **6** by fluoride ion (Scheme 2).



Scheme 2 Retrosynthetic analysis.

Results and discussion

Our synthesis began with readily available *p*-methoxybenzyl alcohol **8**, which was allylated and the resulting allyl ether ozonolysed to afford the PMB-protected acetaldehyde **9**. Wittig olefination of acetaldehyde **9** then proceeded cleanly to generate the *E* conjugated ester as a single diastereomer, which upon



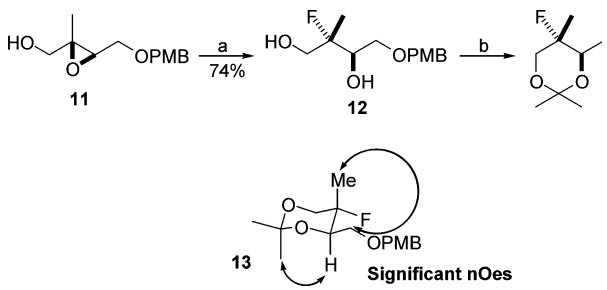
Scheme 3 *Reagents and conditions*: a) allyl bromide, NaH, TBAI, THF, 0 °C; b) O_3, DMS, CH_2Cl_2, −78 °C; c) $Ph_3PC(Me)CO_2Et$, PhH, 80 °C; d) Dibal-H, Et_2O, 0 °C; e) D-(−)-DIPT, $Ti(OiPr)_4$, *t*BuOOH, −20 °C.

reduction provided us with the desired allylic alcohol precursor **10** in excellent overall yield (Scheme 3).

Finally, an asymmetric epoxidation controlled by a Sharpless reagent proceeded in excellent yield and high enantioselectivity to provide us with the key epoxide intermediate **11**.[8]

At this point, we were faced with the most crucial step of the synthesis in which we would attempt to regio- and stereoselectively hydrofluorinate the 2,3-epoxy-alcohol ring at the C_2 position. Whilst there have been some reports for enhanced C_3 epoxide openings with fluorine to generate the 3-fluoro-1,2-diols, the conditions for the generation of the 2-fluoro-1,3-diols have not been developed to the same extent.[9,10] As far as we are aware, the only work in the area of C_2 fluorination was reported by Mikami, in which mixtures of C_2 and C_3 fluorination products were obtained using various mixtures of Lewis acids and fluorine sources. Furthermore, to the best of our knowledge Mikami's study did not extend to the synthesis of tertiary fluorides, which were required as part of our synthesis.[11]

Unfortunately, treatment of epoxy-alcohol **11** under Mikami and Yoneda's conditions failed to generate any of the desired tertiary fluoride adduct, causing instead material decomposition. However, treatment of our epoxy-alcohol intermediate **11** with triethylamine trihydrofluoride cleanly generated the desired fluoro-erythrol compound **12** in high yield and with complete regio- and stereocontrol (Scheme 4).[12] To the best of our knowledge, this is the first time that trisubstituted epoxy-alcohols have been used to generate the corresponding tertiary 2-fluoro-1,3-diols.

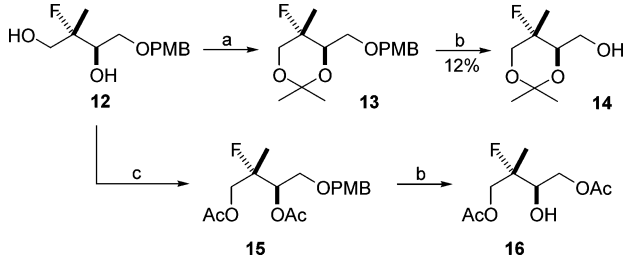


Scheme 4 *Reagents and conditions*: a) TEA–3HF, 100 °C; b) 2-methoxypropene, CSA, CH_2Cl_2, RT.

Protection of the newly generated 1,3-diol afforded the dimethyl ketal **13**, which proved invaluable in corroborating the relative stereochemistry through 2-dimensional NOE studies (Scheme 4).

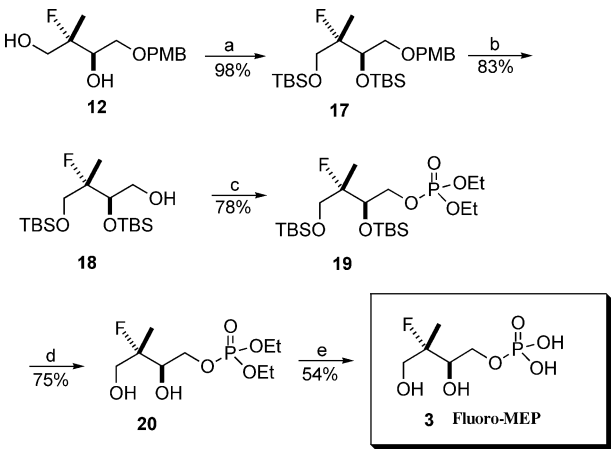
Having obtained the differentially protected fluoro-triol **13**, we switched our attention to the selective removal of the PMB protecting group. Unfortunately, despite a significant amount of experimentation, the highest yielding deprotection conditions

involving DDQ afforded the desired primary alcohol **14** in 12% yield (Scheme 5).



Scheme 5 *Reagents and conditions*: a) 2-methoxypropene, CSA, CH_2Cl_2, RT; b) DDQ, CH_2Cl_2, 0 °C to RT; c) Ac_2O, Py, RT.

Faced with this disheartening low yield for the PMB removal step, a different protecting group strategy had to be devised. Thus, acetylation of the diol intermediate **12** proceeded to generate the expected bis-acetate **15** in excellent yield. Unfortunately, PMB removal under the previously developed conditions cleanly produced the secondary alcohol **16** in good yield, which can be easily explained through a simple 1,2-acetate migration of the primary alcohol intermediate (Scheme 5). However, protection of the diol intermediate **12** as the bis-TBS ether **17** proceeded in good yield despite the amount of steric hindrance being built into the system. Gratifyingly, PMB removal under carefully monitored conditions cleanly provided us with the desired primary alcohol **18** with an improved yield (Scheme 6).[13]



Scheme 6 *Reagents and conditions*: a) TBSOTf, 2,6-lutidine, 0 °C; b) $SnCl_4$, PhSH, 0 °C; c) $(EtO)_2P(O)I$, Py; d) 90% TFA, 0 °C; e) TMSBr, CH_2Cl_2, 0 °C.

The newly obtained primary alcohol **18** was then treated with diethyl iodophosphate to sucessfully generate the desired phosphate unit **19** in high yield.[14] Finally, carefully controlled removal of both TBS groups generated the diol **20**, which upon phosphate hydrolysis then provided us with the desired enantiomerically pure fluoro-MEP analogue **3** in excellent yield.

Conclusions

In conclusion, we have now reported the synthesis of the first C_3 MEP analogue reported to date, taking advantage of a regio- and stereoselective C_2-epoxide hydrofluorination reaction.

Efforts in our group are currently underway to explore the biological effects of the fluoro-MEP unit on the non-mevalonate pathway and on co-crystallisation studies. We are also currently developing the synthesis of other MEP analogues, as well as exploring the scope and limitations of the epoxide hydrofluorination reaction for the generation of tertiary 2-fluoro-1,3-diol units.

Experimental

General methods

All reactions were performed in oven-dried glassware under an inert argon atmosphere. Anhydrous DMF was purchased from Aldrich Chemical Co. Tetrahydrofuran (THF), diethyl ether, and dichloromethane (DCM) were distilled before use. Anhydrous dichloromethane (DCM) was obtained by refluxing over calcium hydride for one hour, followed by distillation under argon. Anhydrous THF and diethyl ether were obtained by refluxing over sodium-benzophenone for one hour, followed by distillation under argon. All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C using a Buchi Rotavapor.

IR spectra were recorded either as thin films on NaCl plates using a Perkin–Elmer Spectrum BX Fourier Transform spectrometer. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}), with the following abbreviations used to describe absorption intensity: w, weak; m, medium; s, strong and br, broad.

^1H NMR spectra were recorded at 500 MHz using a Bruker Avance500 instrument. Chemical shifts (δ_H) are reported in parts per million (ppm), and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad), (3) coupling constant (J) quoted in Hertz to the nearest 0.5 Hz, and (4) assignment. ^{13}C NMR spectra were recorded at 75.1 or 125.7 MHz using Bruker DPX300 or Bruker Avance500 instruments. ^{19}F NMR spectra were recorded at 376 MHz using Bruker DPX400 instruments and are referenced to $CFCl_3$. The ^{19}F NMR data was acquired both in coupled and decoupled mode, with the single decoupled signal being reported. Phosphorus magnetic resonance spectra (^{31}P) were recorded at 121 MHz using a Bruker Avance500 instrument. Chemical shifts (δ_C) are quoted in parts per million (ppm) and are referenced to the appropriate solvent peak. The assignment is quoted in parentheses.

High resolution mass spectra were recorded on a Bruker MicroTOF spectrometer by electrospray ionisation mass spectrometer operating at a resolution of 15 000 full widths at half height.

Flash chromatography was performed using silica gel (Apollo Scientific Silica Gel 60, 40–63 micron) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F_{254}). The plates were visualised by the quenching of UV fluorescence (λ_{max} 254 nm) and/or by staining with either anisaldehyde or potassium permanganate followed by heating.

(4-Methoxybenzyloxy)acetaldehyde, 9. A solution of 4-methoxybenzyl alcohol **8** (33 g, 0.24 mol) in THF (50 mL) was added to a suspension of previously washed sodium hydride (60% oil dispersion, 8.59 g, 0.36 mol) in dry THF (550 mL) at 0 °C, and the mixture was stirred for 30 min. Allyl bromide (60 mL, 0.70 mol) and tetrabutylammonium iodide (4.22 g, 11.42 mmol)

were then added at 0 °C. The reaction was allowed to warm up to room temperature and was then stirred overnight. The reaction mixture was then extracted with dichloromethane (500 mL) and water (300 mL). The organic layer was dried over magnesium sulfate and the filtrate was evaporated to give 1-allyloxymethyl-4-methoxybenzene (41 g, 96%); R_F [light petroleum–ether (7 : 3)] 0.65; ν_{max} (film) 1613 (C=C); δ_H (300 MHz, $CDCl_3$) 7.14 (2 H, d, *J* 8.6, 3,5-H; Ar), 6.74 (2 H, d, *J* 8.6, 2,6-H; Ar), 5.82–5.77 (1 H, m, CH), 5.20–5.13 (1 H, dd, *J* 10.5 and 1.5, CH_AH$_B$), 5.08–5.04 (1 H, dd, *J* 10.5 and 1.4, CH$_A$$H_B$), 4.31 (2 H, s, Ar-$CH_2$), 3.86 (2 H, d, *J* 5.6, OCH_2) and 3.64 (3 H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 159.6, 135.3, 130.9, 129.8, 117.4, 114.3, 72.2, 71.3 and 55.6 (Found MNa^+, 201.0886. $C_{11}H_{14}NaO_2$ requires 201.0994).

A solution of freshly prepared 1-allyloxymethyl-4-methoxybenzene (17.43 g, 0.10 mol) in dichloromethane (800 mL), was treated with ozone at −78 °C until the blue colour of ozone endured. At this point, argon was bubbled through until the blue colour disappeared. Methyl sulfide (120 mL, 1.63 mol) was then added to the solution and the resulting mixture stirred until TLC analysis indicated reaction completion (*ca.* 3 h). The solvents were evaporated under vacuum, and the crude residue purified by flash column chromatography (silica gel, light petroleum–ether (4 : 6)) to generate the desired glycoaldehyde **9** as a clear oil (15.12 g, 86%); R_F [light petroleum–ether (4 : 6)] 0.27; ν_{max} (film) 1732 (C=O); δ_H (500 MHz, $CDCl_3$) 10.2 (1 H, s, CH), 7.23 (2 H, s, 3,5-H; Ar), 6.79 (2 H, s, 2,6-H; Ar), 4.78 (2 H, s, CH_2), 4.23 (2 H, s, CH_2) and 3.65 (3 H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 200.7, 163.1, 129.6, 128.8, 114.0, 75.0, 73.4 and 55.6 (Found MNa^+, 203.0679. $C_{10}H_{12}NaO_3$ requires 203.0786).

4-(4-Methoxybenzyloxy)-2-methylbut-2-en-1-ol, 10. A solution of (4-methoxybenzyloxy)acetaldehyde **9** (20 g, 0.11 mol) in benzene (700 mL) was treated with (carbethoxyethylidene)triphenylphosphorane (58.5 g, 0.16 mol) and was refluxed overnight. The solvent was evaporated under vacuum, and the crude residue triturated with diethyl ether. The mixture was then filtered to remove the solid triphenylphosphine oxide, and the filtrate was then evaporated under vacuum to give the desired (2*E*)-4-(4-methoxybenzyloxy)-2-methylbut-2-enoic acid ethyl ester (23.6 g, 81%); R_F [DCM] 0.33; ν_{max} (film) 1625 (C=C) and 1715 (C=O); δ_H (300 MHz, $CDCl_3$) 7.3 (2 H, d, *J* 8.4, 3,5-H; Ar), 6.93–6.87 (3 H, m, CH and 2,6-H; Ar), 4.50 (2 H, s, Ar-CH_2), 4.26–4.12 (4 H, m, 2 × CH_2), 3.83 (3 H, s, OCH_3), 1.85 (3 H, s, CH_3) and 1.32 (3 H, t, *J* 7.2, CH_3); δ_C (75 MHz, $CDCl_3$) 167.9, 159.7, 138.4, 130.2, 129.9, 129.8, 114.2, 72.8, 66.9, 61.1, 55.7, 14.6 and 13.2 (Found MNa^+, 287.1254. $C_{15}H_{20}NaO_4$ requires 287.1362).

Diisobutylaluminium hydride (155 mL, 1 M in hexane) was added to a solution of 4-(4-methoxybenzyloxy)-2-methylbut-2-enoic acid ethyl ester (15.4 g, 58.3 mmol) in dry ether (300 mL) at 0 °C, and the resulting reaction mixture was stirred at 0 °C for 1 h. Water (3 mL) was added, and the resulting white precipitate stirred for 1 h at room temperature. The crude mixture was then filtered through Celite and the filtrate evaporated under vacuum to afford 4-(4-methoxybenzyloxy)-2-methylbut-2-en-1-ol **10** as a clear oil (12.35 g, 95%); R_F [DCM] 0.21; ν_{max} (film) 1612 (C=C) and 3390 (O–H); δ_H (300 MHz, $CDCl_3$) 7.17 (2 H, d, *J* 8.7, 3,5-H; Ar), 6.78 (2 H, d, *J* 8.7, 2,6-H; Ar), 5.75–5.51 (1 H, m, CH), 4.34 (2 H, s, Ar-CH_2), 3.95 (2 H, d, *J* 7.3, CH_2), 3.88 (2 H, s, CH_2), 3.70 (3 H, s, OCH_3), 2.47 (1 H, s, OH) and 1.55 (3 H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 159.6, 139.7, 130.8, 129.8 (2 × CH), 121.6, 114.5 (2 × CH), 72.4, 68.2, 66.6, 55.7 and 14.3 (Found MNa^+, 245.1148. $C_{13}H_{18}NaO_3$ requires 245.1256).

[3-(4-Methoxybenzyloxymethyl)-2-methyloxiranyl]methanol, 11. Diethyl L-tartrate (3.60 mL, 21.1 mmol) and titanium(IV) isopropoxide (5.14 mL, 17.4 mmol) were added to a flask charged with activated powdered 4 Å molecular sieves (3 g) in dry dichloromethane (180 mL) at −23 °C. The mixture was stirred while *tert*-butyl hydroperoxide (23.6 mL, 5–6 M in decanes) in dry dichloromethane (60 mL) was added dropwise, and the resulting solution was stirred for 30 min at −23 °C. A solution of 4-(4-methoxybenzyloxy)-2-methylbut-2-en-1-ol **10** (10 g, 45.1 mol) in dry dichloromethane (50 mL) was then added slowly, and the resulting reaction mixture was stirred for 6 h at −23 °C. The reaction was then quenched with water (98.1 g; 20 times the weight of the titanium(IV) isopropoxide used) and was stirred for a further 40 min, while allowing the suspension to warm to room temperature. To hydrolyse the tartrate, a 30% aqueous solution of sodium hydroxide saturated with sodium chloride was added and the biphasic mixture was stirred vigorously for 30 min. The mixture was filtered through a pad of silica and Celite to break up the emulsion, and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 100 mL), the combined organic extracts were dried over magnesium sulfate and the filtrate was evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with light petroleum–ether (3 : 7) to give [3-(4-methoxybenzyloxymethyl)-2-methyloxiranyl]methanol **11** (9.72 g, 91%, >90% ee); R_F [DCM] 0.13; $[\alpha]_D$ −4 (*c* = 0.1, DCM); ν_{max} (film) 3390 (O–H); δ_H (300 MHz, $CDCl_3$) 7.20 (2 H, d, *J* 8.6, 3,5-H; Ar), 6.81 (2 H, d, *J* 8.6, 2,6-H; Ar), 4.51 (1 H, d, *J* 11.5, CH_2) 4.40 (1 H, d, *J* 11.5, CH_2), 3.73 (3 H, s, OCH_3), 3.64–3.46 (4 H, m, CH, CH_2 and CH_AH$_B$), 3.23–3.20 (1 H, dd, *J* 6.1 and 4.5, CH$_A$$H_B$)), 2.10 (1 H, bs, OH) and 1.19 (3 H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 159.7, 130.2, 130.0 (2 × CH), 114.2 (2 × CH), 73.3, 68.5, 65.5, 60.6, 58.6, 55.7 and 14.7 (Found MNa^+, 261.1097. $C_{13}H_{18}NaO_4$ requires 261.1205).

2-Fluoro-4-(4-methoxybenzyloxy)-2-methylbutane-1,3-diol, 12. Triethylamine trihydrofluoride (35 mL, 220 mmol) and [3-(4-methoxybenzyloxymethyl)-2-methyloxiranyl]methanol **11** (12.72 g, 53.5 mmol) were refluxed at 100 °C for 20 h. The mixture was then cooled down to room temperature, poured into chloroform (190 mL) and neutralised with sat. sodium hydrogen carbonate. The organic layer was separated, dried over magnesium sulfate and the solvent was evaporated under vacuum. The crude residue was then purified by flash chromatography on silica gel eluting with 100% diethyl ether to afford the desired 2-fluoro-4-(4-methoxybenzyloxy)-2-methylbutane-1,3-diol **12** as a yellow oil (10.15 g, 74%); R_F [DCM] 0.11; $[\alpha]_D$ −14 (*c* = 0.1, DCM); ν_{max} (film) 3408 (O–H); δ_H (300 MHz, $CDCl_3$) 7.28 (2 H, d, *J* 8.4, 3,5-H; Ar), 6.91 (2 H, d, *J* 8.5, 2,6-H; Ar), 4.53 (2 H, s, CH_2), 4.09–4.03 (1 H, m, CH), 3.83 (3 H, s, OCH_3), 3.78–3.55 (4 H, m, 2 × CH_2), 2.69 (2 H, bs, 2 × OH) and 1.32 (3 H, d, J_{HF} 22.6, $CFCH_3$); δ_C (75 MHz, $CDCl_3$) 164.1, 130.0, 129.9 (2 × CH), 114.3 (2 × CH), 97.3 (d, J_{CF} 171.2), 73.7, 71.9 (d, J_{CF} 26.8), 70.1, 66.5 (d, J_{CF} 24.1), 55.7 and 17.7 (d, J_{CF} 22.5); δ_F (376.4 MHz, $CDCl_3$, $CFCl_3$) −162.8 (Found MNa^+, 281.1148. $C_{13}H_{19}FNaO_4$ requires 281.1267).

1-[2,4-Bis(*tert*-butyldimethylsilanyloxy)-3-fluoro-3-methylbutoxymethyl]-4-methoxybenzene, 17. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (2.7 mL, 11.76 mmol) and 2,6-lutidine (1.82 mL, 15.6 mmol) were added to a solution of 2-fluoro-4-(4-methoxybenzyloxy)-2-methylbutane-1,3-diol **12** (1.0 g, 3.87 mmol) in dry dichloromethane (76 mL) at −78 °C. The solution was stirred for 1 h at −78 °C and was then quenched with a (1 : 1) mixture of concentrated pH 7 buffer and water at −78 °C. The mixture was then allowed to warm to room temperature over 30 min, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 40 mL). The combined organic layers were then dried over sodium sulfate, and the solvent removed under vacuum. The crude residue was then purified by flash column chromatography on silica gel eluting with 10% ether in light petroleum ether to give 1-[2,4-bis-(*tert*-butyldimethylsilanyloxy)-3-fluoro-3-methylbutoxymethyl]-4-methoxybenzene **17** as a clear oil (1.85 g, 98%); R_F [light petroleum–ether (9 : 1)] 0.83; $[\alpha]_D$ −4.2 ($c = 1$, DCM); ν_{max} (film) 2954 (Ar–H); δ_H (500 MHz, $CDCl_3$) 7.24 (2 H, d, *J* 8.7, 3,5-H; Ar), 6.85 (2 H, d, *J* 8.7, 2,6-H; Ar), 4.41 (2 H, s, CH_2), 4.07–4.04 (1 H, m, CH), 3.78 (3 H, s, OCH_3), 3.68–3.63 (1 H, m, CH_AH_B), 3.62–3.60 (2 H, m, CH_2), 3.42–3.38 (1 H, m, CH_AH_B), 1.19 (3 H, d, J_{HF} 22.0, $CFCH_3$), 0.88 (9 H, s, 3 × CH_3), 0.85 (9 H, s, 3 × CH_3), 0.07 (3 H, s, CH_3), 0.06 (3 H, s, CH_3), 0.05 (3 H, s, CH_3) and 0.00 (3 H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 159.0, 130.4, 129.2 (2 × CH), 113.7 (2 × CH), 97.3 (d, J_{CF} 172.7), 72.9, 72.7 (d, J_{CF} 27.2), 72.0 (d, J_{CF} 4.5), 65.7 (d, J_{CF} 24.7), 25.7 (3 × CH_3), 25.6 (3 × CH_3), 18.2, 18.1, 17.3 (d, J_{CF} 22.7), −2.9, −4.1, −5.0 and −5.2; δ_F (376.4 MHz, $CDCl_3$, $CFCl_3$) −158.96 (Found MNa^+, 509.2880. $C_{25}H_{47}FNaO_4Si_2$ requires 509.2889).

2,4-Bis(*tert*-butyldimethylsilanyloxy)-3-fluoro-3-methylbutan-1-ol, 18. A −78 °C solution of 1-[2,4-bis(*tert*-butyldimethylsilanyloxy)-3-fluoro-3-methylbutoxymethyl]-4-methoxybenzene **17** (1.37 g, 2.82 mmol) and thiophenol (0.36 mL, 3.51 mmol) in dry dichloromethane (18 mL) was treated with tin(IV) chloride (2.91 mL, 1 M solution in dichloromethane). The reaction mixture was stirred at −78 °C for 20 min and was then quenched with saturated sodium hydrogen carbonate (15 mL). The aqueous layer was extracted with DCM (2 × 30 mL), the combined organic layers were dried over sodium sulfate, and the solvent removed under vacuum. The crude residue was purified by flash column chromatography on silica gel eluting with DCM to give the desired 2,4-bis(*tert*-butyldimethylsilanyloxy)-3-fluoro-3-methylbutan-1-ol **18** as a clear oil (0.86 g, 83%); R_F [light petroleum–ether (9 : 1)]; $[\alpha]_D$ −2.4 ($c = 1$, DCM); ν_{max} (film) 3300 (O–H); δ_H (500 MHz, $CDCl_3$) 3.92–3.88 (1 H, m, CH), 3.67–3.53 (4 H, m, 2 × CH_2), 2.22 (1 H, bs, OH), 1.21 (3 H, d, J_{HF} 22.3, $CFCH_3$), 0.84 (9 H, s, 3 × CH_3), 0.83 (9 H, s, 3 × CH_3), 0.06 (3 H, s, CH_3), 0.05 (3 H, s, CH_3), 0.01 (3 H, s, CH_3) and 0.00 (3 H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 97.8 (d, J_{CF} 171.5), 73.8 (d, J_{CF} 26.2), 65.3 (d, J_{CF} 26.2), 63.1 (d, J_{CF} 5.5), 25.9 (6 × CH_3), 18.3, 18.2, 17.9 (d, J_{CF} 22.9), −4.6, −4.9, −5.4 and −5.6; δ_F (376.4 MHz, $CDCl_3$, $CFCl_3$) −160.0 (Found MH^+, 367.2494. $C_{17}H_{40}FO_3Si_2$ requires 367.2495).

Phosphoric acid 2,4-bis(*tert*-butyldimethylsilanyloxy)-3-fluoro-3-methylbutyl ester diethyl ester, 19. Iodine (0.20 g, 0.79 mmol) was added to a solution of triethyl phosphite (0.15 mL, 0.88 mmol) in dry DCM (2 mL) at 0 °C, and the solution was stirred for 20 min at 0 °C and then for 1 h at room temperature. The freshly made phosphorylation agent was then added slowly to a round-bottomed flask containing 2,4-bis(*tert*-butyldimethylsilanyloxy)-3-fluoro-3-methylbutan-1-ol **18** (0.28 g, 0.77 mmol) and pyridine (0.25 mL, 3.09 mmol) in dry DCM (10 mL) at −40 °C. The reaction was allowed to warm up to room temperature and stirred for 2 h. The mixture was then washed with a solution of 3% $KHSO_4$ (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL). The organic layer was then dried over magnesium sulfate and the solvent was removed under vacuum. The crude residue was then purified by flash chromatography on silica gel eluting with diethyl ether–petroleum ether (40–60) (7 : 3) to give the expected phosphoric acid 2,4-bis(*tert*-butyldimethylsilanyloxy)-3-fluoro-3-methylbutyl ester diethyl ester **19** as a yellow oil (0.3 g, 78%); R_F [DCM] 0.12; $[\alpha]_D$ −7.7 ($c = 1$, DCM); ν_{max} (film) 1265 (P=O); δ_H (500 MHz, $CDCl_3$) 4.19–4.16 (1 H, m, CH), 4.09–4.04 (5 H, m, 2 × CH_2 and CH_AH_B), 3.90–3.84 (1 H, m, CH_AH_B), 3.61–3.54 (2 H, m, CH_2), 1.29–1.26 (6 H, m, 2 × CH_3), 1.17 (3 H, d, J_{HF} 5.7, $CFCH_3$), 0.85 (9 H, s, 3 × CH_3), 0.82 (9 H, s, 3 × CH_3), 0.07 (3 H, s, CH_3), 0.04 (3 H, s, CH_3), 0.01 (3 H, s, CH_3), 0.00 (3 H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 96.7 (d, J_{CF} 173.3), 72.5 (d, J_{CF} 9.0), 68.8 (d, J_{CF} 11), 65.4 (d, J_{CF} 25.2), 63.8, 63.7, 25.8 (6 × CH_3), 18.3, 18.1, 17.3 (d, J_{CF} 22.4), 16.2, 16.1, −4.4, −5.1, −5.3 and −5.5; δ_F (376.4 MHz, $CDCl_3$, $CFCl_3$) −162.3; δ_P (200.2 MHz, $CDCl_3$) −0.96 (Found MH^+, 503.2782. $C_{21}H_{49}FO_6PSi_2$ requires 503.2784).

Phosphoric acid diethyl ester 3-fluoro-2,4-dihydroxy-3-methylbutyl ester, 20. A solution of phosphoric acid 2,4-bis(*tert*-butyldimethylsilanyloxy)-3-fluoro-3-methylbutyl ester diethyl ester **19** (0.27 g, 0.54 mmol) in dichloromethane (4 mL) was treated with 90% TFA (2.5 mL) at room temperature, and the resulting mixture stirred for 30 min. The volatile solvents were then evaporated and the crude residue was co-evaporated with toluene and finally purified by flash chromatography on silica gel eluting with 10% methanol in DCM to give phosphoric acid diethyl ester 3-fluoro-2,4-dihydroxy-3-methylbutyl ester **20** as a clear oil (0.11 g, 75%); R_F [DCM–MeOH (9 : 1)] 0.63; $[\alpha]_D$ −5.4 ($c = 1$, DCM); ν_{max} (film) 3412 (O–H) and 1266 (P=O); δ_H (500 MHz, $CDCl_3$) 4.24–4.19 (1 H, m, CH), 4.13–4.01 (6 H, m, 3 × CH_2), 3.76–3.57 (2 H, m, CH_2), 1.29 (6 H, t, *J* 7.1, 2 × CH_3) and 1.20 (3 H, d, J_{HF} 22.3, $CFCH_3$); δ_C (75 MHz, $CDCl_3$) 96.1 (d, J_{CF} 170.7), 70.9 (d, J_{CF} 29.1), 68.7 (d, J_{CF} 5.9), 66.3 (d, J_{CF} 23.1), 64.4, 64.3, 16.6 (d, J_{CF} 22.6), 16.1 and 16.0; δ_F (376.4 MHz, $CDCl_3$, $CFCl_3$) −163.4; δ_P (200.2 MHz, $CDCl_3$) −0.10 (Found MH^+, 275.1063. $C_9H_{21}FO_6P$ requires 275.1054).

Phosphoric acid 3-fluoro-2,4-dihydroxy-3-methylbutyl ester, 3. Trimethylsilyl bromide (0.69 mL, 5.31 mmol) was added to a solution of phosphoric acid diethyl ester 3-fluoro-2,4-dihydroxy-3-methylbutyl ester **20** (0.22 g, 0.80 mmol) in dichloromethane (3 mL), and the resulting mixture stirred at room temperature for 24 h. The volatile solvents were then evaporated and a 1 : 1 solution of ethanol and water (4 mL) was added to the residue. After 30 min, the solvents were evaporated under vacuum, and this procedure was repeated three times. Finally, the crude residue was purified by flash chromatography on silica gel C_{18}-reversed phase eluting with 10% methanol in DCM to generate the phosphoric acid 3-fluoro-2,4-dihydroxy-3-methylbutyl ester **3** as a clear oil (94 mg, 54%); R_F [DCM–MeOH (3 : 7)] 0.39; $[\alpha]_D$ −7 ($c = 0.1$, DCM); ν_{max} (film) 3300 (O–H); δ_H (300 MHz, DMSO) 7.90–5.77 (4 H, bs, 4 × OH), 4.01–3.91 (1 H, m, CH), 3.92–3.71 (2 H, m, CH_2), 3.52–2.28 (2 H, m, CH_2) and 1.14 (3 H, d, *J* 22.7, CH_3); δ_C (75 MHz, DMSO)

99.6 (d, J_{CF} 171.2), 70.7 (d, J_{CF} 25.8), 66.6, 64.4 (d, J_{CF} 23.1) and 17.2 (d, J_{CF} 23.1); δ_F (376.4 MHz, $CDCl_3$, $CFCl_3$) −160.9; δ_P (200.2 MHz, $CDCl_3$) 0.91 (Found MH^- 217.0272. $C_5H_{11}FO_6P$ requires 217.0277).

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