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The Synthesis of 1-Fluoro- and 1,1-Difluoro- Analogues of 1-Deoxy-D-xylulose

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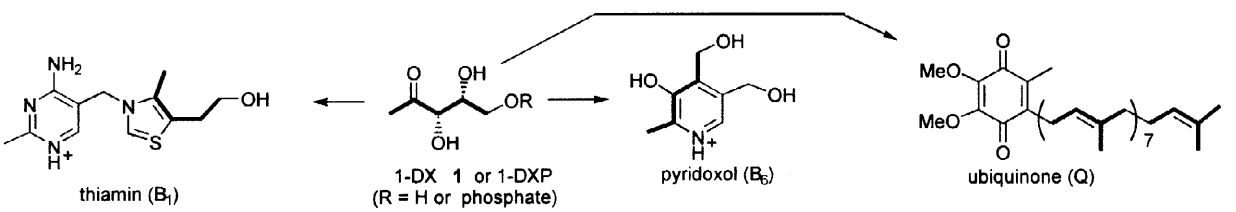
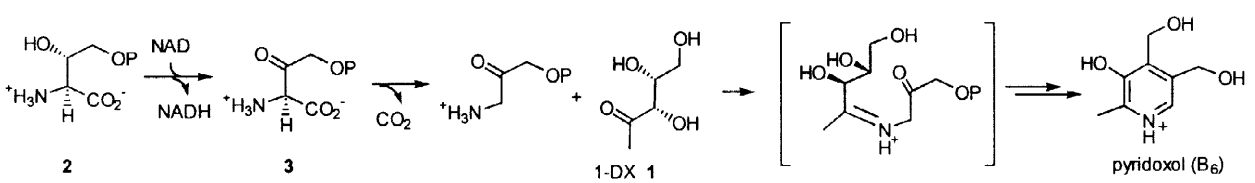
Abstract: 1-Deoxy-D-xylulose is a key intermediate in bacterial co-factor biosynthesis. We report the synthesis of the 1-fluoro- and 1,1-difluoro- analogues of 1-deoxy-D-xylulose as potential antimetabolites of bacterial 1-deoxy-D-xylulose metabolism.

Recent reports on the biosynthesis of three enzyme co-factors in bacteria have raised the profile of 1-deoxy-D-xylulose (1-DX) **1** and its phosphate (1-DXP) as an intermediate metabolite. It emerges that 1-DX /1-DXP are pivotal metabolites in the biosynthesis of the bacterial co-factors pyridoxal phosphate (PLP)[1], thiamine pyrophosphate (TPP)[2] and the phytyl chain of ubiquinone (co-enzyme Q) in *E. coli*.[3]



Scheme 1 1-DX or 1-DXP is involved in the biosynthesis of three bacterial co-factors

These co-factors are involved in many enzymes of primary metabolism or in electron transport processes. The involvement of 1-DX in PLP biosynthesis is summarised in Scheme 1. A NAD dependent dehydrogenase which mediates the oxidation of 4-(phosphohydroxy)-L-threonine **2** to ketone **3** has recently been characterised[4] and the evidence suggests that there is a second gene coding an enzyme which mediates the condensation of the decarboxylated product of **3** with 1-DX **1**. For the other two co-factors, the involvement of 1-DXP is implicated, although it is known in *E.coli* for example, that 1-DX added exogenously is activated by phosphorylation to 1-DXP *in vivo*. So appropriate analogues may be similarly activated. With this background we set about preparing analogues of 1-DX **1** which may act as anti-metabolites in co-factor biosynthesis with potential as new antibiotic leads.



Scheme 2 Current understanding of the biosynthesis of pyridoxol involving 1-DX **1**

Ketones containing α-fluorinated substituents are well known[5] to promote hydration of the carbonyl group and this has been used very successfully[6] as a strategy to inhibit enzymatic processes involving tetrahedral intermediates, such as esterases and acylases. Extending this strategy to the current programme we have identified the mono- and difluoro- analogues **4** and **5** as our target compounds. It was anticipated that these compounds may inhibit enzymes involved in 1-DX/1-DXP metabolism.

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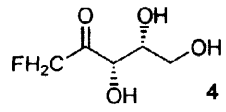
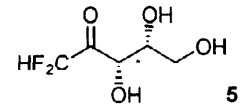
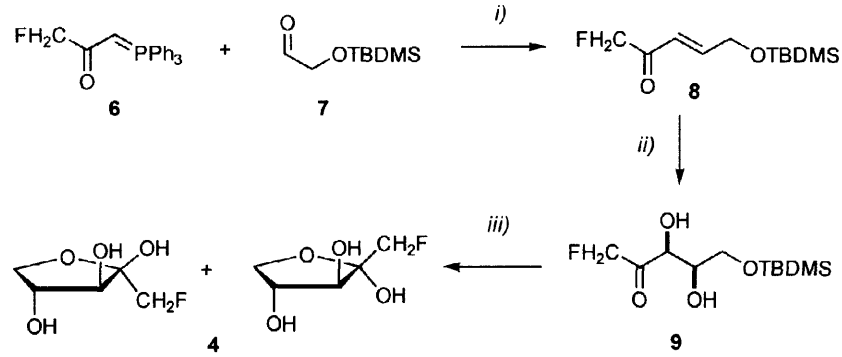


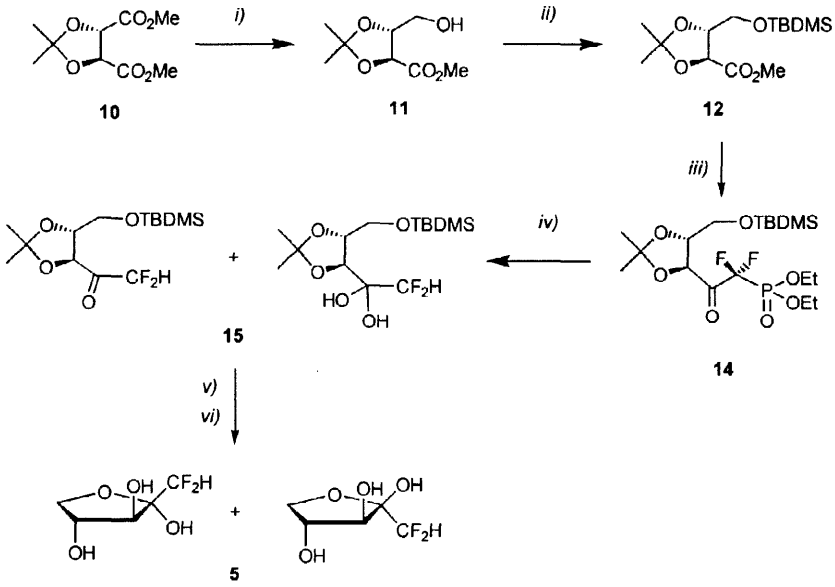


There has been a significant interest in the synthesis of 1-deoxy-D-xylulose especially as there has been a requirement[7-11] for isotopically labelled samples of 1-deoxy-D-xylulose for biosynthesis experiments. In order to prepare the monofluorinated analogue **4** we employed a Wittig strategy followed by a dihydroxylation as illustrated in Scheme 3. The monofluorinated phosphorous ylid **6** was prepared as previously described[12] and



Scheme 3 *i)* CH_2Cl_2, reflux 3 d, 60%. *ii)* OsO_4, acetone, $AcO^- N(Et)_4^+$, *t*BuOOH, 12h RT, 56%. *iii)* TBAF, THF, 60 min, 88%.

was coupled to aldehyde **7**[13] in a sluggish reaction, generating product in moderate yield. Initial attempts at asymmetric dihydroxylation of the resultant enone **8**, using Sharpless methodology[14] failed, as purification of the product from the AD-mix-β ligand proved an insurmountable separation problem. However **8** was successfully dihydroxylated with osmium tetroxide[15] to generate the racemic diol **9** in moderate yield. Removal of the silyl protecting group with fluoride ion gave the target sugar **4**. ^{19}F-NMR analysis of **4** in water indicated a ~ 3:2 ratio of two forms of the sugar. In the ^{13}C-NMR in Figure 1 there are no carbonyl resonances, instead the two peaks at 101.5 ppm and 104.1 ppm indicate both anomers (α and β) of the cyclic sugar, although these could not be assigned unambiguously.



Scheme 4 *i)* 0.5 eq $NaBH_4$, MeOH, 0°C. *ii)* TBDMSCl, DMF, Imidazole, RT. *iii)* $(EtO)_2POCF_2Li$ (**13**), THF, -78°C, 75%. *iv)* MeONa (1M), MeOH, RT, 5h, 49%. *v)* HCl 1 N, RT, 12h. *vi)* TBAF, THF, RT, 60 min, 73% (from **15**).

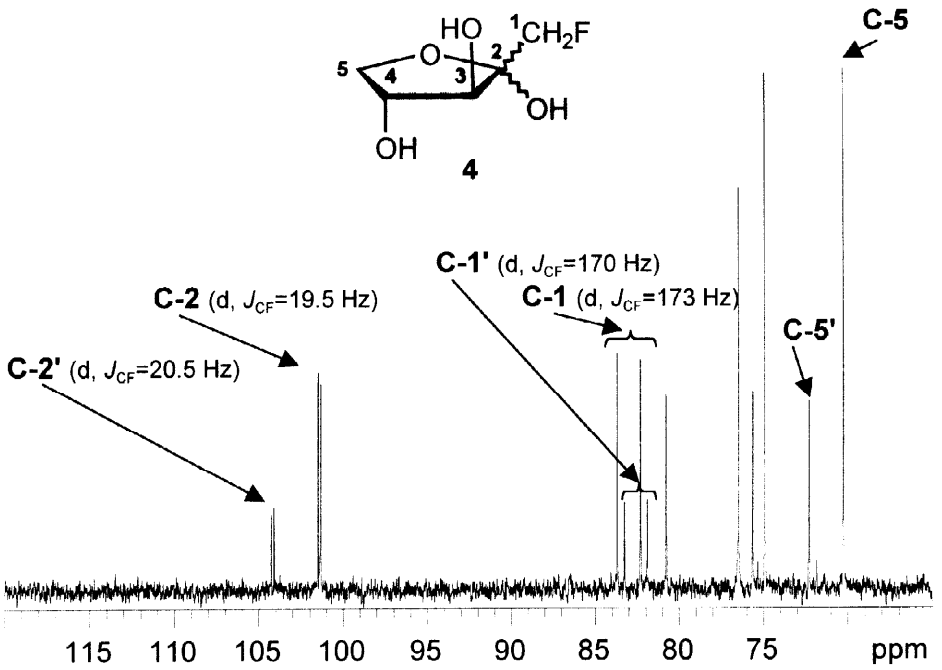


Figure 1 ^{13}C-NMR (500 MHz, D_2O) α/β anomers of 1-Deoxy-1-fluoro-D,L-xylulose **4**

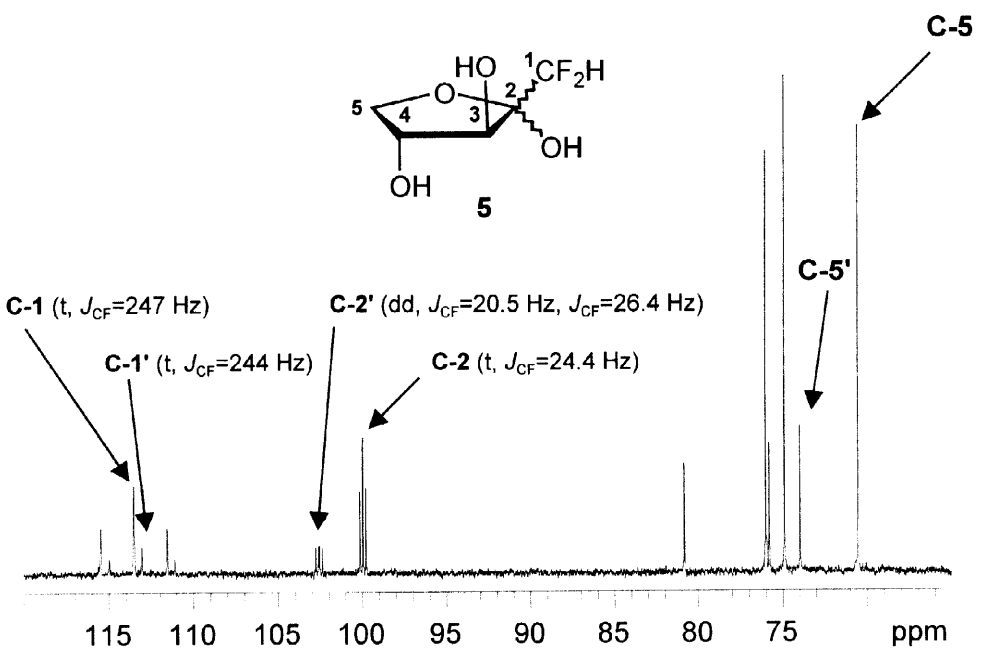


Figure 2 ^{13}C-NMR (500 MHz, D_2O) α/β anomers of 1-Deoxy-1,1-difluoro-D-xylulose **5**

The difluoro- analogue **5** was prepared as illustrated in Scheme 4. The key step involved introduction of the difluoromethylene group following the strategy developed by Piettre *et al.*[16] This involved cleavage of the CF_2-P bond of a α,α-difluoro-β-ketophosphonate in basic MeOH. The synthesis started from the tartrate derivative **10**[8] which was treated with $NaBH_4$ to generate the mono-alcohol **11** followed by TBDMS protection to give **12** as previously described.[17] Preparation of the requisite α,α-difluoro-β-ketophosphonate **14** was carried out by condensation[18] of the lithiated difluoromethylphosphonate **13** with ester **12**. Treatment of **14** with sodium methoxide[16] delivered the protected difluoro- sugar **15** as a mixture of its ketone and hydrate forms. Sequential deprotection delivered the target difluoro analogue **5**. Satisfactory micro-analysis proved very difficult to obtain for both **4** and **5**, due to the hygroscopic nature of these compounds. ^{19}F-NMR analysis of an aqueous solution of **5** again indicated that both the α and β forms of the cyclic sugar were present, this time in a ~3:1 ratio. This is again clearly indicated in the ^{13}C-NMR spectrum of **5** in Figure 2 where signals for each of the cyclic anomers (α and β not assigned) are present and there is no indication of any carbonyl resonances.

With samples of compounds **4** and **5** available they were tested to assess their antibiotic activity against *E. coli* and *S. aureus*, however they did not elicit any antibacterial response. It is noteworthy that 1-deoxy-D-xylulose exists in aqueous solution, predominantly in its ring opened keto form[10] therefore perhaps the predominant cyclic nature of these fluorinated analogues disfavours ring opening for the necessary activation by phosphorylation to generate the corresponding 1-DXP analogues *in vivo*.

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We thank Dr Tony Fawcett, Department of Biological Sciences, University of Durham, for antibiotic testing, the EU for a grant to support DB and Dr Alan Kenwright and Ian McKeag for NMR analysis.

Experimental

General : IR spectra were recorded on a Perkin-Elmer 257 Spectrometer and mass spectra on a VG-7070E instrument. NMR spectra were obtained on Varian 200, 400 and 500 instruments in $CDCl_3$ and D_2O. Chemical shifts are quoted relative to TMS for ^{1}H- and ^{13}C- NMR spectra, ^{19}F chemical shifts are quoted as negative values relative to fluorotrichloromethane and ^{31}P chemical shifts are quoted relative to phosphoric acid. Solvents were dried and distilled prior to use. Reactions requiring anhydrous conditions were conducted under an atmosphere of nitrogen and column chromatography was carried out over silica gel (Merck, Kieselgel 60, 230 - 400 mesh). Petrol refers to petroleum ether (boiling fraction 40-60°C). Optical rotations $[\alpha]_D$ were recorded at 25 °C in 2 ml cells, using an AA-10 Automatic Polarimeter Optical activity Ltd.

(E)-1-Fluoro-5-[(tert-butyldimethylsilyl)oxy]-pent-3-ene-2-one **8**

A solution of [(*tert*-butyldimethylsilyl)oxy]acetoaldehyde **7** (0.9 g, 5.1×10^{-3} mol) in CH_2Cl_2 (5 mL) was added to a stirred solution of (1-fluoroacetyl)-methylenetriphenylphosphorane **6** (1.7 g, 5×10^{-3} mol) in CH_2Cl_2 (30 mL). The reaction was heated under reflux for 3 d. After removal of the solvent the product was purified over silica gel (Et_2O / petrol : 10 / 90), to give **8** (0.52 g, 60%) as a clear oil.

IR, ν_{max} (neat)/cm^{-1} 1698.9, 1631.9. ^{19}F NMR ($CDCl_3$, 200 MHz) : δ -229.2 (t, J_{FH}= 47 Hz). ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.1 (6H, s, $(CH_3)_2Si$), 0.9 (9H, s, $(CH_3)_3CSi$), 4.4 (2H, dd, J= 3 Hz, *J*=2 Hz CH_2OSi), 4.97 (2H, d, J_{HF}=47.5 Hz, CH_2F), 6.6 (1H, ddt, *J*=15 Hz, J_{HF}=5 Hz, *J*=2 Hz CH_2CH=CH), 7.1 (1H, dt, *J*=15 Hz, *J*=3 Hz, $CHCOCH_2F$). ^{13}C NMR ($CDCl_3$, 200 MHz) : δ -5.4 (CH_3Si), 18.3 ($C(CH_3)_3$), 26.2 ($C(CH_3)_3$), 61.8 (CH_2OSi), 83.8 (d, J_{CF}=184 Hz, CH_2F), 121.4 (OCH_2CH), 148.6 (d, J_{CF}=3 Hz, $CHCOCH_2F$), 193.6 (d, J_{CF} =22 Hz, *C*O). HRMS: (CI) Calcd. For (M) $C_{11}H_{21}O_2SiF$: 232.1294, Found: 232.1290

1-Deoxy-1-fluoro-5-O-tert-butyldimethylsilyl-D,L-xylulose **9**

Tetraethylammonium acetate tetrahydrate (135 mg) and *tert*-butylhydroperoxide (70% in water, 0.5 mL) were added to a solution of (*E*)-1-fluoro-5-[(*tert*-butyldimethylsil)oxy] pent-3-ene-2-one **8**, (0.5 g, 2.1×10^{-3} mol) in acetone (5 mL). The mixture was stirred until the ammonium salt was completely dissolved and the reaction was cooled to 0°C. A catalytic amount of osmium tetroxide (0.5% mol, 0.39 M solution in toluene) was

introduced and the reaction stirred for 1h at 0°C and then allowed to warm to ambient temperature. When the starting material was consumed (^{19}F NMR), the reaction was quenched with $NaSO_3H$ solution. Sat. NH_4Cl solution was added and the mixture extracted into dichloromethane and then also EtOAc. The combined organic layers were dried and evaporated. Distillation under reduced pressure (100°C, 0.2 mmHg) gave **9**, (56%, 0.315 g) as pale green oil: IR, ν_{max} (neat)/cm^{-1} 3438, 1732. ^{19}F NMR ($CDCl_3$, 200 MHz) : δ -234.4 (t, J_{FH}= 47 Hz). ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.1 (6H, s, (CH_3)$_2$Si), 0.9 (9H, s, (CH_3)$_3$CSi), 3.7 (2H, d, J=6.4 Hz, CH_2OSi), 4.0 (1H, m, CHCH$_2$O), 4.4 (1H, m, FCH$_2$COC*H*), 5.1 (2H, d, J_{HF}=47 Hz, CH_2F). ^{13}C NMR ($CDCl_3$, 400 MHz) : δ -5.6 (CH_3Si), 18.2 (C(CH$_3$)$_3$), 25.7 (C(CH$_3$)$_3$), 64.2 (CH_2O), 71.2 (d, J_{CF}=1.4 Hz, FCH$_2$$CO$CHOH), 76.7 ($CHCH_2$O), 84.5 (d, J_{CF}=181 Hz, CH_2F), 206 (d, J_{CF} =17.5 Hz, CO). MS (CI) *m/z* (rel. intensity) 284 (M$^+$ +NH$_4$, 100), 266 (M$^+$, 20.2).

1-Deoxy-1-fluoro-D,L- xylulose **4**

A 1M solution tetrabutylammonium fluoride, TBAF (0.37 mL) was added to a solution of 1-deoxy-1-fluoro-5-*O-tert*-butyldimethylsilyl-D,L-xylulose **9** (0.1 g, 3.7x10^{-4} mol) in THF. After 1 h stirring at room temperature, the mixture was filtered through a plug of silica gel. The solvent was then removed under reduced pressure and the residue purified over silica gel (THF/Et_2O : 50/50). Residual TBAF was removed by washing the product with CH_2Cl_2 (3 mL). Solvent removal gave sugar **4** (50 mg, 88%) as a clear oil. ^{19}F NMR (D_2O, 200 MHz) : δ -228.8 / -231.3 (t, J_{FH}= 45.7 Hz)(major/minor : 57/43). ^{1}H NMR (D_2O, 200 MHz) : δ 3.6 (0.8H, dd, J=9.5 Hz, J=4.6 Hz), 3.9-4.48 (3.2 H, m), 4.29 and 4.31 (2H, d, J_{HF}=45 Hz, CH_2F). ^{13}C NMR (D_2O, 500 MHz) : δ 70.2 (major), 72.2 (minor), 75.0 (major), 75.6 (minor), 73.0 (major), 81.9 (minor), 82.5 (d, J_{CF}=170 Hz, CH_2F, minor) and 83.0 (d, J_{CF}=173 Hz, CH_2F, major), 101.5 (d, J_{CF}=19.5 Hz, C(OH)CH$_2$F, major) and 104.1 (d, J_{CF}=20.5 Hz, C(OH)CH$_2$F, minor). MS (EI) *m/z* (rel. intensity) 135 (M$^+$ - OH, 100), 117 (M$^+$ - 2 x OH, 15.0). Vmax/cm (neat) 3360.63 cm^{-1}; HRMS (EI); Found (M$^+$ -OH) 135.046124. $C_5H_9O_4F$ requires 135.045747.

Diethyl [(3S,4S)-1,1-difluoro-3,4-dihydroxy-3,4-(O-isopropylidene)-5-O-tert-butyldimethylsilyl-2-ketopentyl]phosphonate **14**

n-BuLi (2.5 mL, 1 M in hexanes) was added dropwise to diisopropylamine (0.55 mL, 3.9x10^{-3} mol) in THF (15 mL) at -78°C. The resultant solution was allowed to warm to 0°C for 30 min and was then cooled to -78°C and difluoromethylphosphonate (660 mg, 3.5.10^{-3} mol) was added dropwise *via* syringe. After 30 min at -78°C, methyl [2,3-(*O*-isopropylidene)-4-*O-tert*-butyldimethylsilyl] butanoate **12** (1g, 3.3x10^{-3} mol) was added slowly over 15 min. After 1 h, the reaction was quenched by the addition of glacial HOAc (1 mL), followed by sat NH_4Cl (30mL). The reaction was allowed to warm to room temperature and was then extracted into CH_2Cl_2 (3x20mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Unreacted difluoromethylphosphonate (50°C, 167 mg, 0.2 mmHg) and **12** (90°C, 270 mg, 0.2 mmHg) were removed by distillation and the difluoroketophosphonate **14** (75%, 1.2 g) was recovered as a pale yellow oil. $[\alpha]_D^{25}$ +29.8 (c 4.63, methanol). IR, ν_{max} (neat)/cm^{-1} 1752; ^{19}F NMR ($CDCl_3$, 200 MHz) : δ -117.2 and -117.3 (d, J_{FP}= 94 Hz).

^{31}P NMR ($CDCl_3$, 200 MHz) : δ 3.7 (t, J_{PF}=94 Hz); ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.0 (6H, s, (CH_3)$_2$Si), 0.8 (9H, s, (CH_3)$_3$CSi), 1.3 (6H, t, J=8 Hz, (CH_3CH$_2$)$_2$OP), 1.34 (3H, s, CH_3C), 1.4 (3H, s, CH_3C), 3.76 (2H, AB system J_{AB}=11.4 Hz, d, J=3.8 Hz, CH_2OSi), 4.25 (5H, m, (CH$_3$$CH_2$)$_2$OP and CF$_2$CHOC*H*O), 4.9 (1H, d, J= 8 Hz, CF$_2$COC*H*O). ^{13}C NMR ($CDCl_3$, 400 MHz) : δ -4.8 ((CH_3)$_2$Si), 17.0 (CH_3CH$_2$OP), 18.9 (C(CH$_3$)$_3$), 26.5 (C(CH$_3$)$_3$), 26.8 and 27.7 (C(CH_3)$_2$), 63.1, 66.1 (t, J_{CF}=6.6 Hz, CF$_2$$CO$CHO), 78.8, 79.6, 112.8 (C(CH$_3$)$_2$), 114.0 (t, J_{CF}=271 Hz, CF_2), 197.0 (t, J_{CF} =10.6 Hz, CO). HRMS: (CI) Calcd. For (M-15) $C_{17}H_{32}O_7F_2SiP$: 445.1623, Found: 445.162439

1-Deoxy-1,1-difluoro-3,4-(O-isopropylidene)-5-O-tert-butyldimethylsilyl-D-xylulose **15**

Ketophosphonate **14** (0.2 g, 4.3x10^{-4}, 0.25 M in MeOH) was treated with a solution of NaOMe (0.5 eq, 1 M) in MeOH and the reaction was monitored by TLC until the starting material was consumed. Water (5ml) was added and the mixture extracted into CH_2Cl_2 (3 x 15 mL). The organic layers were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified over silica gel eluting with EtOAc/ petrol (20/80) to afford **15** (68 mg, 49%) as a pale yellow oil. $[\alpha]_D^{25}$ +15.7 (c 1.65, methanol). IR, ν_{max} (neat)/cm^{-1} 3363, 1754. ^{19}F NMR ($CDCl_3$, 200 MHz) : δ [-130.1 (d, J_{FH}= 53 Hz) / -137.8 (AB system

J_{FF}=283.7 Hz, d, J_{FH}=55 Hz)](23/77). ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.0 and 0.1 (6H, s, $(CH_3)_2Si$), 0.8 and 0.85 (9H, s, $(CH_3)_3CSi$), 1.3 and 1.31 (3H, s, CH_3C), 1.4 and 1.41 (3H, s, CH_3C), 3.25 (bs, OH), 3.55 (0.8H, t, J= 9.4 Hz), 3.82 (0.6H, m), 4.0 (1.5H, m), 4.25 (0.25H, m), 4.35 (0.7H, m), 4.7 (0.15H, d, J= 6.7 Hz), 5.5 (bs, OH), 5.7 (0.2H, t, J_{HF}=55 Hz), 6.05 (0.8H, t, J_{HF}=53 Hz). ^{13}C NMR ($CDCl_3$, 400 MHz) : δ -5.7 ($(CH_3)_2Si$), 18.3 ($C(CH_3)_3$), 26.0 ($C(CH_3)_3$), 26.2 and 26.9 ($C(CH_3)_2$), 62.3, 64.2, 74.7, 78.4, 80.8, 90.9 ($CF_2C(OH)_2$, t, J_{CF}=21 Hz), 108 (t, J_{CF}=260 Hz, CF_2, minor), 113.7 (t, J_{CF}=248 Hz, CF_2, major), (*C*O, non observed). HRMS: (CI) Calcd. For (M-15) $C_{13}H_{23}O_4F_2Si$: 309.1333, Found: 309.1335 and (CI) Calcd. For hydrate (M-15) $C_{13}H_{25}O_5F_2Si$: 327.1439, Found: 327.1434

1-Deoxy-1,1-difluoro-D-xylulose **5**

1-Deoxy-1,1-difluoro-3,4-(*O*-isopropylidene)-5-(*O*-*tert*-butyldimethylsilyl)-D-xylulose **15** (0.2 g, $6.1x10^{-4}$ mol) was stirred for 12 h in aq HCl (1 M) solution. After neutralisation with sat. $NaHCO_3$ solution, the mixture was extracted into CH_2Cl_2 (2x 15 mL) and then ethyl acetate (2x 15 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. A 1 M solution of TBAF (0.61 mL) in THF was added to the resultant oil and the reaction stirred for 1h. The mixture was filtered through a plug of silica gel and the solvent was removed under reduced pressure. The residue was chromatographed over silica gel (eluent THF/Et_2O : 50/50) and residual TBAF was removed by washing the product with CH_2Cl_2 (4 mL). Solvent removal gave **5** (75 mg, 73%) as a clear oil. $[\alpha]_D^{25}$ -18.9 (c 0.95, acetone). ^{19}F NMR (D_2O, 200 MHz) : δ -134.6 [(AB system, J_{FF}=275 Hz, d, J_{FH}=53 Hz)/ -136.1 (AB system, J_{FF}=292 Hz, d, J_{FH}=53 Hz)](75/25). ^{1}H NMR (D_2O, 200 MHz) : δ 3.6 (0.8H, dd, J=5.4 Hz, J=9.9 Hz), 3.82 (0.26H, m), 4.05 (0.95H, m), 4.07 (0.95H, m), 4.2 (1.3H, m), [5.7 (t, J_{HF}=53 Hz)/ 5.8 (t, J_{HF}=53 Hz)](75/25). ^{13}C NMR (D_2O, 500 MHz) : δ 70.5 (major), 73.9 (minor), 74.8 (major), 75.8 (minor), 75.9 (major), 80.8 (minor), 99.6 (t, J_{CF}=24.4 Hz, $HOCCF_2H$, major), 102.2 (dd, J_{CF}=20.5 Hz, J_{CF}=26.4 Hz, $HOCCF_2H$, minor), 113.0 (t, J_{CF}=244 Hz, minor), 113.5 (t, J_{CF}=247 Hz, major). MS (CI) *m/z* (rel. intensity) 153 (M+1 $-OH_2$, 100), 135 (M+1- 2 x OH_2, 10.4).

Antibiotic testing; Compounds **4** and **5** were tested as antibiotics against *Escherichia coli* DH5α and *Staphylococcus aureus* NCTC 6571 (National Collection Type Culture Number 6571) however they did not inhibit growth up to 1mg/ml of **4** and **5**.

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