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Tetrahedron 60 (2004) 6523–6531
Tetrahedron

Syntheses of ethyl 3-deoxy-3,3-difluoro-D-*arabino*-heptulosonate and analogues

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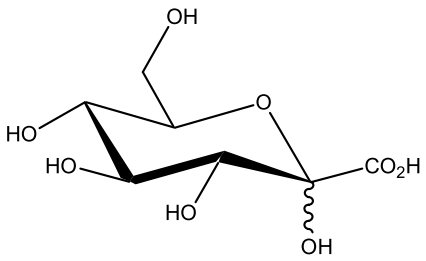
Received 16 March 2004; revised 14 May 2004; accepted 3 June 2004

Available online 24 June 2004

Abstract—The difluorinated analogues of 3-deoxy-D-*arabino*-heptulosonic acid (DAH) **12**, **24** and its enantiomer have been synthesised from D- and L-erythrose via a Reformatsky reaction which gave a mixture of diastereoiosmers in favour of the *anti* isomer.

The enzymatic conversion of carbohydrates to essential aromatics and aromatic amino acids utilised by micro-organisms, fungi and higher plants forms the shikimate pathway.[1] The recent discovery that this pathway is also operative in apicomplexan parasites including the most virulent malarial parasites (Plasmodium falciparum) has led to a resurgence of interest in the inhibitors of this biosynthetic pathway.[2] The shikimate pathway is absent in mammals and they have to obtain the three aromatic amino acids (L-phenylalanine, L-tyrosine, and L-tryptophan) through dietary means. It is therefore expected that inhibitors of the shikimate pathway will be devoid of toxicity and have low environmental impact. The most successful commercial enzyme inhibitor used in agriculture is glyphosate (*N*-phosphonomethylglycine), the active ingredient of the herbicide Roundup. It works by specifically inhibiting the 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase, the sixth enzyme of the shikimate pathway.[3] Numerous analogues of shikimate pathway intermediates have been synthesised,[4,5] among which the fluorinated analogues have provided important insights into the mechanisms of several of the enzymes including dehydroquinate synthase,[5h] type I and II dehydroquinase,[5j,k] EPSP synthase[5d] and chorismate synthase.[5b]



DAH

To date extensive studies have yet to deliver a potent inhibitor of the 'upstream' enzymes of the shikimate pathway. Consideration of these results suggests the need for an alternative avenue for the search of pathway inhibitors, we therefore directed our attention to the study of inhibitors of the early intermediates in the shikimate pathway. Here we examined the synthesis of analogues of 3-deoxy-D-*arabino*-heptulosonic acid (DAH) as potential inhibitors for the enzymes of type II dehydroquinase and shikimate kinase,[6] and report on our synthesis of difluorinated analogues of DAH which are expected to have modified biological activities due to the replacement of hydrogen by fluorine atoms.

We have synthesised both enantiomers of the difluorinated DAH analogues. Treatment of D-ribose **1** in acetone with a small amount of concentrated hydrochloric acid gave the acetonide (90%) which was reduced with sodium borohydride and then oxidised with sodium periodate in one-pot to yield the L-erythrose derivative **2** in 80% yield (Scheme 1). Deprotection of compound **2** with aqueous acetic acid gave

Keywords: Reformatsky reaction; Shikimate pathway; Carbohydrate; Fluorinated ulosonates; Enzyme inhibitors.
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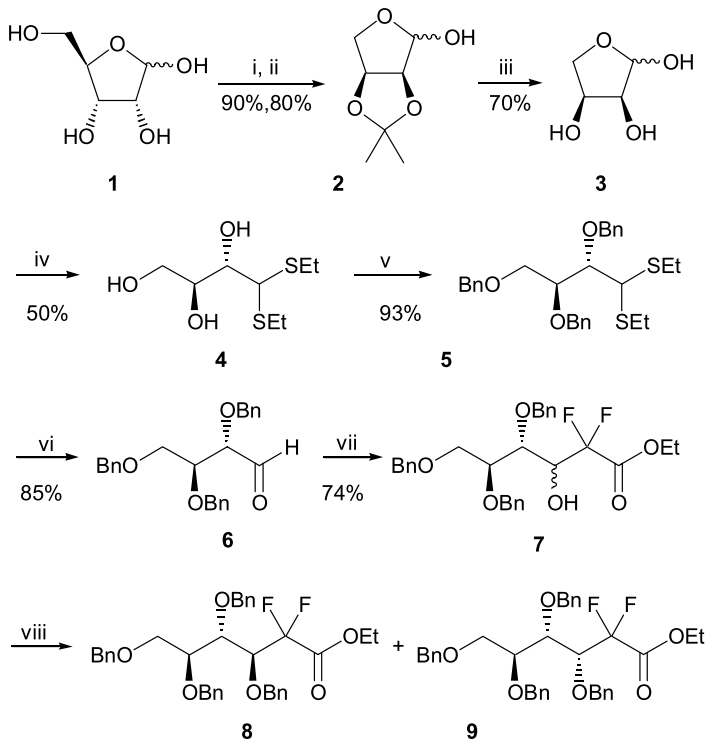
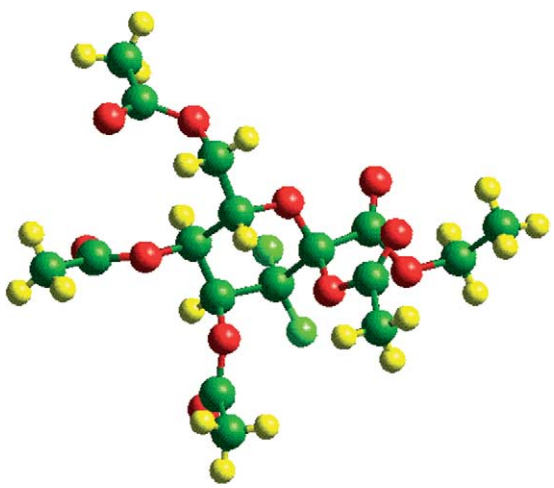
doi:10.1016/j.tet.2004.06.048



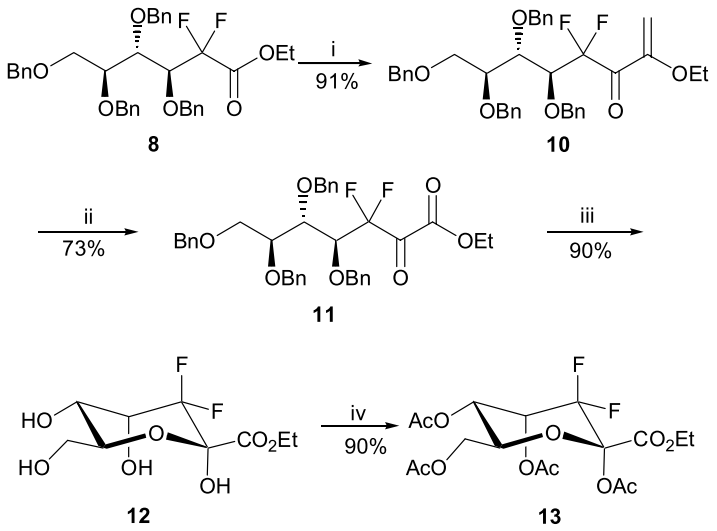
Scheme 1. Reagents and conditions: (i) acetone, conc. HCl (cat.), rt, 4 h; (ii) $NaBH_4$, MeOH–H_2O, 0 °C, 1 h, then $NaIO_4$, rt, 1 h; (iii) aq. HOAc, 4 h; (iv) conc. HCl, EtSH, rt, 2 h; (v) BnBr, NaH, DMF, rt, 8 h; (vi) $HgCl_2$, $CaCO_3$, MeCN–H_2O, rt, 3 h; (vii) Zn, $BrCF_2CO_2Et$, THF, reflux, 2 h; (viii) BnBr, NaH, DMF, rt, 8 h, 68% for **8** and 17% for **9**.

the free L-erythrose **3** (70%). Its diethyl dithioacetal **4** was prepared by treatment of L-erythrose with ethanethiol and concentrated hydrochloric acid. Benzylation of the hydroxyl groups in **4** with excess of benzyl bromide and sodium hydride gave the tri-*O*-benzyl derivative **5** (93%). Dethioacetalisation of compound **5** with mercury (II) chloride and calcium carbonate in aqueous acetonitrile provided the aldehyde **6** in 85% yield. With the aldehyde **6** available we examined its reaction under Reformatsky conditions with ethyl bromodifluoroacetate.[7] The reaction afforded alcohol **7** as a mixture of diastereoisomers in a yield of 74%. Our attempts to separate the diastereoisomers by flash chromatography were unsuccessful. However, further protection of alcohol **7** with benzyl bromide enabled the separation of the subsequent two diastereoisomers **8** and **9** in a ratio of ca. 3:1. At this juncture, we presumed that the major product **8** was the *syn* isomer. This assumption was based on literature precedence that gave support to a α-chelation transition state during the addition of the nucleophile to the carbonyl group, which often results in the *syn* isomer being formed as the major product.[7a,b,8] However, in our case this assumption was proved to be erroneous, as shown by our subsequent structural elaboration and data analysis (Scheme 2).

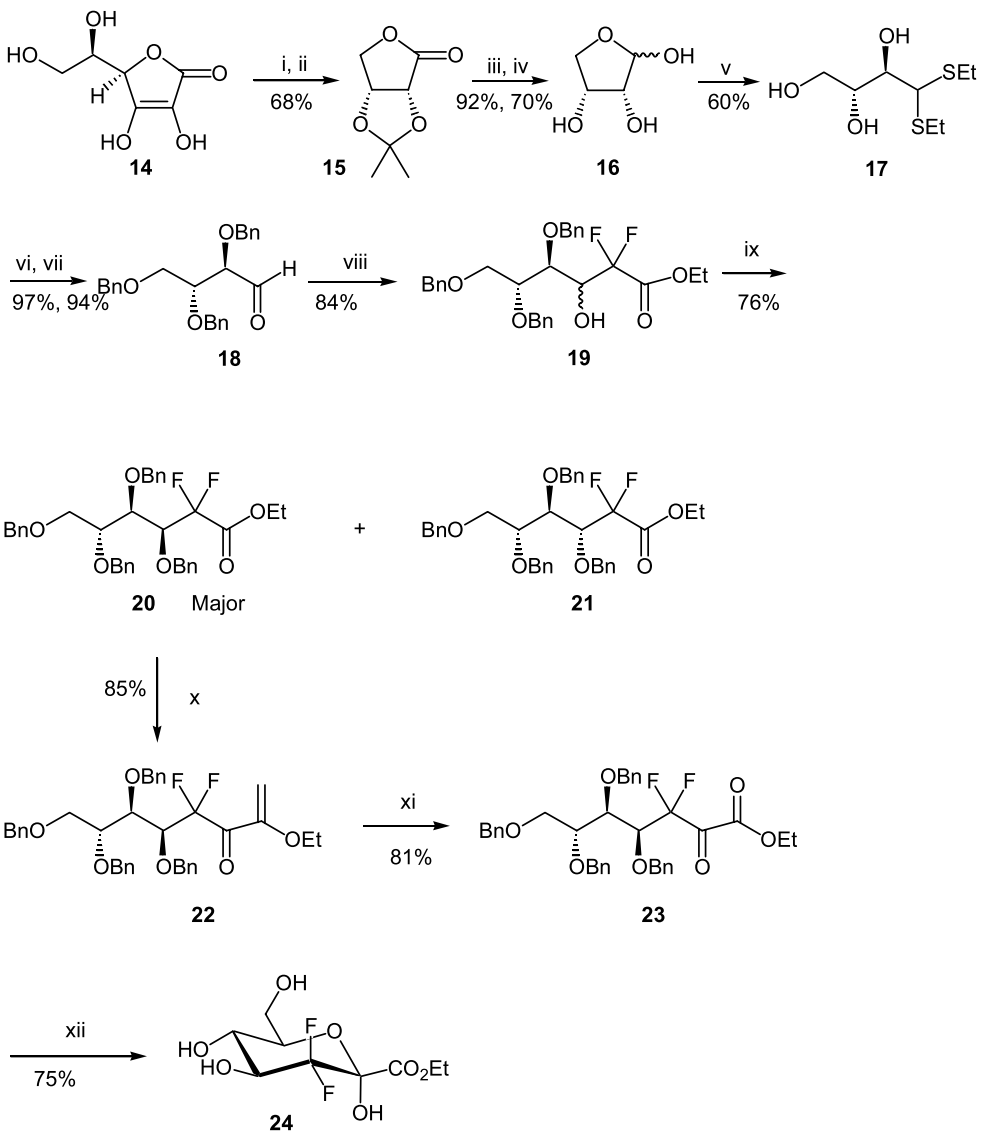


The major isomer **8** was treated with 1-ethoxyvinyllithium that was generated by treating ethyl vinyl ether with *tert*-butyllithium in tetrahydropyran to yield the intermediate ketone **10** in a yield of 91%.[9] Ozonolysis of the double bond in **10** gave the keto ester **11** (73%). Its debenzylation was effected using Pearlman's catalyst under transfer hydrogenation conditions to furnish the ethyl ulosonate **12** (90%) whose complex NMR spectrum made the stereochemical assignment on C-4 very difficult. We therefore converted **12** to tetraacetate **13** by acetylation. The compound **13** was crystalline and that enabled the single crystal X-ray diffraction data to be obtained to establish the stereochemistry at C-4.[10] The result showed that the major isomer **8** was in fact the *anti* isomer and the Reformatsky reaction probably proceeded by the Felkin-Anh transition state rather than an α-chelation one.

Following the above results, we then undertook the same chemistry using D-erythrose **16** as the starting material (Scheme 3). D-Erythrose was obtained from D-isoascorbic acid in four steps using published procedures,[11] and was



Scheme 2. Reagents and conditions: (i) 1-ethoxyvinyllithium, THF, −78 °C, 1 h; (ii) O_3, EtOH–CH_2Cl_2, −78 °C, 1 h, then Me_2S; (iii) $Pd(OH)_2$-C, cyclohexene, EtOH, reflux, 4 h; (iv) Ac_2O, DMAP, pyridine, rt, 2 h.



Scheme 3. Reagents and conditions: (i) Na_2CO_3, H_2O, then H_2O_2, 45 °C, Norit PN5, then aq. HCl; (ii) acetone, $Me_2C(OMe)_2$, *p*-TsOH, $MgSO_4$, rt, 3 h; (iii) DIBAL-H, CH_2Cl_2, −78 °C, 1 h,; (iv) aq. HOAc, 4 h; (v) conc. HCl, EtSH, rt, 2 h; (vi) BnBr, NaH, DMF, rt, 8 h; (vii) $HgCl_2$, $CaCO_3$, MeCN–H_2O, rt, 3 h; (viii) Zn, $BrCF_2CO_2Et$, THF, reflux, 2 h; (ix) BnBr, NaH, DMF, rt, 8 h; (x) 1-ethoxyvinyllithium, THF, −78 °C, 1 h; (xi) O_3, EtOH–CH_2Cl_2, −78 °C, 1 h, then Me_2S; (xii) $Pd(OH)_2$-C, cyclohexene, EtOH, reflux, 4 h.

then converted to the alcohols **19** by a sequence of reactions similar to those described above. The desired tetra-*O*-benzyl isomer **20** was reacted with 1-ethoxyvinyllithium, followed by ozonolysis and debenzylation to give the difluorinated analogue of DAH **24**. In much the same way that its enantiomer was synthesised from compound **3**.

In summary, we have synthesised the difluorinated analogues of 3-deoxy-D-*arabino*-heptulosonic acid (DAH) from both L- and D-erythrose. These compounds are currently undergoing biological testing, and the results will be reported in due course.

1. Experimental

1.1. General

^{1}H NMR spectra were measured at 270 MHz with JEOL GSX 270 FT NMR spectrometer. Chemical shifts were measured relative to internal tetramethyl silane (δ 0). ^{13}C NMR spectra were recorded at 67.8 MHz on same instrument with internal $(CH_3)_4Si$ (δ 0, $CDCl_3$). IR spectra were recorded on a UNICAM series FT- instrument. Mass spectra were recorded on AEI MS 902 or VG ZAB-E instruments. Melting points were determined on Gallen-Kamp capillary melting point apparatus and are uncorrected. Optical rotations were measured in chloroform solution using Bellingham and Stanley ADP 220 polarimeter. Flash chromatography was performed using Fluka silica gel 60 (230–400 mesh) and the solvent petroleum ether (boiling range 40–60 °C) was distilled prior to use. Thin layer chromatography was carried out using pre-coated aluminium plates (Merck Kieselgel 60 F_{254}) which were visualised under UV light and then with either phosphomolybdic acid or basic aqueous potassium permanganate as appropriate. All anhydrous reactions were carried out under argon or nitrogen. Anhydrous transfers were done with standard syringe techniques, all glassware was pre-dried overnight. Dichloromethane was distilled from calcium hydride and stored over 4 Å molecular sieves.

1.1.1. L-Erythro diethyl dithioacetal 4.[12a] L-Erythrose (4 g), was treated with conc. HCl (6 ml) and ethanethiol (6 ml) the resultant mixture was stirred for 3 h at rt. To this mixture water (60 ml) was added and the mixture neutralised by the addition of aq. sodium carbonate. The resultant mixture was extracted with CH_2Cl_2 (3×60 ml). The organic extracts were combined, dried and evaporated to yield L-erythrose diethyl dithioacetal as a syrup (4.6 g). Chromatography on silica gel eluting with light petroleum ether–diethyl ether (1:9) gave L-erythrose diethyl dithioacetal **4** (2.15 g, 31% for two steps) as colourless oil. $[\alpha]_D=-16.0$ (*c* 1.3 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3411. δ_H (270 MHz, $CDCl_3$) 1.19–1.25 (6H, t, *J*=7.4 Hz, 2×CH_2CH_3), 2.54–2.76 (4H, m, 2×CH_2CH_3), 3.77–3.85 (5H, m), 4.09 (1H, s, O*H*), 4.10 (1H, s, O*H*), 4.14 (1H, s, O*H*); δ_C (67.8 MHz, $CDCl_3$) 14.3, 14.5 (2C, 2×CH_3CH_2), 25.2, 25.3 (2C, 2×CH_2CH_3), 54.4 (*C*HSEtSEt), 63.3 (CH_2OH), 71.8 ($CH_2OHCHOHCHOH$), 73.6 ($CH_2OHCHOH$); *m/z* HRMS (CI, NH_3) found: 244.1039 $[M+NH_4]^+$ $C_8H_{22}NO_3S_2$ requires 244.1041.

1.1.2. 2,3,4-Tri-*O*-benzyl-L-erythro diethyl dithioacetal 5. A stirred, cooled (0 °C) solution, of **4** (2.15 g, 9.5 mmol) in 35 ml of dry DMF was treated with 2.27 g of sodium hydride (60% dispersion in mineral oil, 56.8 mmol). The mixture was stirred for 10 min after which time a catalytic amount of tetrabutyl ammonium iodide was added. After further 20 min stirring, benzyl bromide (7.04 g, 41.2 mmol, 4.9 ml) was added dropwise to the mixture. The resultant mixture was stirred at 0 °C for 15 min and then warmed to rt and stirring continued for a further 10 h. The mixture was cooled in an ice bath and ethanol was added, carefully, in order to destroy the excess of sodium hydride. Following this the mixture was evaporated under reduced pressure and the residue partitioned between saturated aqueous sodium chloride (100 ml) and ethyl acetate (100 ml). The aqueous phase was extracted further with EtOAc (2×100 ml) and the organic layers were combined, dried (Na_2SO_4) and evaporated to afford a residue which was purified on silica gel eluting with light petroleum ether–diethyl ether (10:1) to afford to afford **5** (4.65 g, 99%) as a colourless oil. $[\alpha]_D=-26.7$ (*c* 1.5 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3087, 1604, 1585, 1051, 1027, 912. δ_H (270 MHz, $CDCl_3$) 1.21–1.26 (3H, t, *J*=7.4 Hz, CH_2CH_3), 1.26–1.31 (3H, t, *J*=7.4 Hz, CH_2CH_3), 2.63–2.77 (4H, m, 2×CH_2CH_3), 3.68–3.73 (1H, dd, *J*=4.0, 10.6 Hz, C*H*HOBn), 3.81–3.85 (1H, dd, *J*=2.3, 10.6 Hz, CH*H*OBn), 3.99–4.04 (1H, ddd, *J*=2.3, 4.0, 7.9 Hz, C*H*OBnCH_2OBn), 4.06–4.10 (1H, dd, *J*=2.5, 7.9 Hz, C*H*OBnCHOBnCH_2OBn), 4.27–4.28 (1H, d, *J*=2.5 Hz, C*H*SEtSEt), 4.57–4.99 (6H, m, 3×CH_2Ph) and 7.25–7.38 (15H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 14.4, 14.5 (2C, 2×CH_2CH_3), 24.9, 26.0 (2C, 2×CH_2CH_3), 53.7 (*C*HSEtSEt), 68.5 (CH_2OBn), 72.3, 73.3, 75.0 (3C, 3×CH_2Ph), 78.9 (CH_2OBnCHOBn*C*HOBn), 81.8 (CH_2OBn*C*HOBn), 127.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.3 (15C, phenyl *C*H), 138.2, 138.3 and 138.4 (3C, phenyl *C*).

1.1.3. 2,3,4-Tri-*O*-benzyl-L-erythrose 6. A solution of 2,3,4-tri-*O*-benzyl-L-erythrose diethyl dithioacetal **5** (3.7 g, 7.45 mmol) in 80 ml of CH_3CN/H_2O (4:1) was treated with $HgCl_2$ (5.06 g, 18.63 mmol) and $CaCO_3$ (2.12 g, 21.16 mmol), and the mixture stirred for 2 h. The mixture was filtered and the filtrate concentrated. The residue was treated with 180 ml of CH_2Cl_2, washed with 150 ml KI (1% aqueous solution). The aqueous layer was further extracted with CH_2Cl_2 (2×100 ml). The organic layers were combined and washed again with 100 ml of KI (1% aqueous solution) and water (2×100 ml). The organic layer were dried, (Na_2SO_4), and evaporated to give a residue which was purified by column chromatography, silica gel, eluting with light petroleum ether–diethyl either (4:1) to afford **6** (2.47 g, 85%) as a colourless oil. $[\alpha]_D=0$; ν_{max} (film)/cm^{-1} 3087, 1731, 1604, 910. δ_H (270 MHz, $CDCl_3$) 3.68–3.73 (1H, dd, *J*=5.3, 9.9 Hz, C*H*HOBn), 3.80–3.86 (1H, dd, *J*=6.6, 9.9 Hz, CH*H*OBn), 4.04–4.10 (1H, ddd, *J*=3.6, 6.6, 9.9 Hz, C*H*OBnCH_2OBn), 4.15–4.17 (1H, dd, *J*=1.5, 3.6 Hz, C*H*OBnCHOBnCH_2OBn), 4.49–4.85 (6H, m, 3×CH_2Ph), 7.26–7.42 (15H, m, *Ph*) and 9.77–9.78 (1H, d, *J*=0.7 Hz, C*H*O); δ_C (67.8 MHz, $CDCl_3$) 67.9 (CH_2OBn), 72.29, 72.9, 73.2 (3C, 3×CH_2Ph), 78.8 (CH_2OBn*C*HOBn), 82.6 (CH_2OBnCHOBn*C*HOBn), 127.5, 127.7, 127.9, 128.0, 128.1, 128.3, 128.4 (15C, phenyl *C*H), 137.2, 137.6, 137.7 (3C, phenyl *C*) and 201.7 (C-1).

1.1.4. 4,5,6-Tri-*O*-benzyl-L-erythro 2-deoxy-2,2-difluoro ethyl acetates 7. To a refluxing suspension of activated zinc dust (0.505 g, 7.72 mmol) in dry THF (20 ml) was added ethyl bromodifluoroacetate (1.18 g, 0.74 ml, 5.79 mmol). After 1 min, a solution of 2,3,4-tri-*O*-benzyl-L-erythrose (1.51 g, 3.86 mmol) dissolved in 10 ml of THF was added dropwise, over 15 min. After complete addition the reaction was refluxed for a further 2 h. The mixture was cooled to rt and carefully poured into 20 ml 1 M HCl and 20 g of ice. Stirring of the resultant mixture was continued until all of the ice had melted. The mixture was extracted with EtOAc (3×100 ml). The organic layers were combined and washed with saturated $NaHCO_3$ (2×100 ml) and sat. aq. NaCl (2×100 ml), dried (Na_2SO_4) and concentrated in vacuo to give a residue. Chromatography, silica gel, eluting with light petroleum ether–diethyl either (4:1) gave **7** (two diastereoisomers not separable) (1.48 g, 74%) as a colourless oil. $[\alpha]_D$=+10.1 (*c* 1.3 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3450, 3089, 1770, 1606, 1587, 1093, 1027, 912.

Major diastereoisomer. δ_H (270 MHz, $CDCl_3$) 1.11–1.16 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.47–3.49 (1H, d, *J*=5.1 Hz, O*H*), 3.67–3.73 (1H, dd, *J*=5.0, 10.1 Hz, CH*H*OBn), 3.82–3.88 (1H, dd, *J*=4.6, 10.1 Hz, C*H*HOBn), 3.92–4.08 (4H, m), 4.44–4.75 (7H, m, 3×CH_2Ph and C*H*OH) and 7.16–7.40 (15H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.6 (CH_2CH_3), 62.5 (CH_2CH_3), 68.9 (CH_2OB_n), 70.6–71.3 (1C, dd, $J_{(C,F)}$=22.8, 23.6 Hz, *C*HOH), 72.6, 73.4, 73.5 (3C, 3×*C*H_2Ph), 77.9, 78.6 (2C, 2×*C*HOBn), 110.7–118.2 (1C, dd, $J_{(C,F)}$=251.0, 257.1 Hz, CF_2CO_2), 127.6, 127.7, 127.8, 128.0, 128.2, 128.4 and 128. 5 (15C, phenyl *C*H), 137.5 (2C), 137.9 (3C, phenyl *C*) and 162.6–163.6 (1C, t, $J_{(C,F)}$=31.4 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, *J*=257.15 Hz), 123.5–124.61 (1F, dd, *J*=19.1, 263.5 Hz); *m/z* HRMS (CI, NH_3) found: 532.2514 $[M+NH_4]^+$ $C_{29}H_{36}F_2NO_6$ requires 532.2511.

Minor diastereoisomer. δ_H (270 MHz, $CDCl_3$) 1.22–1.27 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.31–3.35 (1H, d, *J*=10.4 Hz, O*H*), 3.70–3.81 (2H, m, CH_2OBn), 3.92–4.09 (2H, m, 2×C*H*OBn), 4.23–4.29 (2H, q, *J*=7.1 Hz, CH_2CH_3), 4.46–4.76 (7H, m) and 7.26–7.35 (15H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.8 (CH_2CH_3), 63.0 (CH_2CH_3), 67.6 (CH_2OBn), 69.5 (1C, t, $J_{(C,F)}$=23.6, *C*HOH), 72.5, 73.4, 73.9 (3C, 3×*C*H_2Ph), 77.9, 78.6 (2C, 2×*C*HOBn), 110.8–118.3 (1C, dd, $J_{(C,F)}$=261.4, 267.8, CF_2CO_2), 127.7–130.9 (15C, phenyl *C*H), 137.3, 137.8, 137.9 (3C, phenyl *C*) and 163.1–163.9 (1C, t, $J_{(C,F)}$=30.4 Hz, CF_2CO_2).

1.1.5. 2-Deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-L-erythro ethyl acetate 8,9. A stirred, cooled (0 °C) solution, of **7** (2.56 g, 5.0 mmol) in 60 ml of dry DMF was treated with 0.46 g of sodium hydride (60% dispersion in mineral oil, 10.15 mmol). The mixture was stirred for 10 min after which time a catalytic amount of tetrabutyl ammonium iodide was added. After further 20 min stirring, benzyl bromide (1.30 g, 7.6 mmol, 0.9 ml) was added dropwise to the mixture. The resultant mixture was stirred at 0 °C for 15 min and then warmed to rt and stirring continued for a further 10 h. The mixture was cooled in an ice bath and ethanol was added, carefully, in order to destroy the excess of sodium hydride. Following this the mixture was evaporated under reduced pressure and the residue partitioned between saturated aqueous sodium chloride (150 ml) and ethyl acetate (150 ml). The aqueous phase was extracted further with EtOAc (2×150 ml) and the organic layers were combined, dried (Na_2SO_4) and evaporated to afford a residue which was purified on silica gel eluting with light petroleum ether–diethyl ether (10:1) to afford two diastereoisomers: 2-deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-L-erythrose ethyl acetate (2.54 g, 85%) (ratio, major/minor, 3.2:1) as colourless oils.

Less polar **8** (*anti product*). $[\alpha]_D$=−3.1 (*c* 0.98 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3089, 1772, 1606, 1587, 1095, 1027, 910. δ_H (270 MHz, $CDCl_3$) 1.01–1.06 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.62–3.81 (3H, m), 3.84–4.00 (3H, m), 4.35–4.83 (8H, m, 4×CH_2Ph), 4.48–4.53 (1H, dd, *J*=3.3, 9.1 Hz, C*H*OBnCF$_2$) and 7.18–7.34 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.6 (CH_2CH_3), 62.3 (CH_2CH_3), 70.1 (CH_2OBn), 72.6, 73.3, 73.4, 75.4–75.4 (1C, d, $J_{(C,F)}$=4.2 Hz) (4C, 4×*C*H_2Ph), 77.2, 77.9, 78.3 (3C, 3×*C*HOBn), 111.8–119.3 (1C, dd, $J_{(C,F)}$=257.9, 259.6 Hz, CF_2CO_2), 127.6, 127.9, 128.2, 128.3, 128.7, 128.8, 128.9 and 129.6 (20C, phenyl *C*H), 137.3, 137.5, 138.1, 138.4 (4C, phenyl *C*) and 162.5–163.4 (1C, dd, $J_{(C,F)}$=32.5, 32.7 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, *J*=257.2 Hz), 123.5–124.6 (1F, dd, *J*=19.1, 263.5 Hz); *m/z* HRMS (CI, NH_3) found: 622.2973 $[M+NH_4]^+$ $C_{36}H_{42}F_2NO_6$ requires 622.2980.

More polar **9** (*syn product*). $[\alpha]_D$=0 (*c* 0.58 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3089, 1764, 1606, 1587, 1027, 910. δ_H (270 MHz, $CDCl_3$) 1.16–1.21 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.63–3.71 (1H, m), 3.78–3.87 (2H, m), 4.07–4.16 (2H, q, *J*=7.1 Hz, CH_2CH_3), 4.26–4.46 (2H, m), 4.48–4.75 (8H, m, 4×CH_2Ph) and 7.10–7.33 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.7 (CH_2CH_3), 62.8 (CH_2CH_3), 68.4 (CH_2OBn), 71.8, 73.3, 74.2, 74.9 (4C, 4×*C*H_2Ph), 76.5, 77.8, 78.1 (3C, 3×*C*HOBn), 111.2–118.7 (1C, dd, $J_{(C,F)}$=254.0, 260.0 Hz, CF_2CO_2), 127.4, 127.6, 127.7, 127.8, 127.8, 128.0, 128.1, 128.2, 128.3, 128.5 and 128.8 (20C, phenyl *C*H), 137.6, 138.1, 138.2, 138.2 (4C, phenyl *C*) and 162.9–163.8 (1C, t, $J_{(C,F)}$=31.0 Hz, CF_2CO_2); δ_F(67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, *J*=257.2 Hz), 123.5–124.6 (1F, dd, *J*=19.1, 263.5 Hz); *m/z* HRMS (CI, NH_3) found: 622.2990 $[M+NH_4]^+$ $C_{36}H_{42}F_2NO_6$ requires 622.2980.

1.1.6. 2-Deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-L-erythro vinyl ether 10. To a stirred, cooled (−78 °C) solution, of ethyl vinyl ether (0.62 g, 8.64 mmol, 0.8 ml) in tetrahydropyran (THP, 3 ml), *t*-BuLi (6.64 mmol, 1.7 M, 3.9 ml) was added dropwise. The mixture was stirred at −78 °C for 10 min, warmed to −3 to −5 °C, and stirred for a further 30 min. Following this the mixture was recooled to −78 °C, diluted with THF (6.0 ml) and treated with **21** (0.80 g, 0.95 mmol) in THF (1 ml). After stirring for 1 h at −78 °C, the reaction mixture was poured into water 20 ml) and evaporated under reduced pressure. The resultant residue was partitioned between water (150 ml) and EtOAc (150 ml). The aqueous phase was extracted with EtOAc (2×150 ml) and the combined organics dried (Na_2SO_4), and evaporated to give a residue which was purified on silica gel eluting with light petroleum ether–diethyl ether (10:1) to afford 2-deoxy-2, 2-difluoro-3, 4, 5, 6-tetra-*O*-benzyl-L-erythro vinyl ether **10** (1.58 g, 90%) as colourless oil.

$[\alpha]_D$=+26.9 (*c* 1.25 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3031, 2927, 1729 (C=O), 1610 (C=C) and 1101. δ_H (270 MHz, $CDCl_3$) 1.20 (3H, t, *J*=6.9 Hz, CH_2CH_3), 3.56–3.72 (4H, m), 3.79 (1H, d, *J*=9.7 Hz), 4.00 (1H, t, *J*=5.7 Hz), 4.26 (1H, d, *J*=10.9 Hz, CHPh), 4.36–4.42 (3H, m, 3×CHPh), 4.53 (1H, d, *J*=11.1 Hz, CHPh), 4.62–4.68 (3H, m, 2×CHPh and C=CH), 4.79 (1H, ddd, *J*=3.1, 9.8, 21.4 Hz), 4.88 (1H, d, *J*=10.7 Hz, CHPh), 5.10 (1H, d, *J*=2.6 Hz, C=CH) and 7.10–7.29 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 14.0 (CH_2CH_3), 63.9 (CH_2CH_3), 70.5 (CH_2OB_n), 72.2 (CH_2Ph), 72.8 (CH_2Ph), 73.2 (CH_2Ph), 75.2 (1C, d, $J_{(C,F)}$=4.4 Hz, CH_2Ph); 77.8 (CHOBn), 78.1 (CHOBn), 78.7 (CHOBn), 94.5 (C=CH_2), 118.1 (1C, dd, $J_{(C,F)}$=251.6, 257.5 Hz, CF_2CO_2), 127.5–128.3 (20C, phenyl CH), 137.2 (phenyl *C*), 137.4 (phenyl *C*), 138.2 (phenyl *C*), 138.6 (phenyl *C*), 155.0 (C=CH_2) and 181.9 (1C, t, $J_{(C,F)}$=26.5 Hz, CF_2CO_2); δ_F (282.4MHz, $CDCl_3$) 113.0 (1F, d, *J*=257.2 Hz), 124.1 (1F, dd, *J*=19.1, 263.5 Hz); *m*/*z* (CI, NH_3) $[M+NH_4]^+$ found: 648.3140 $C_{38}H_{44}F_2NO_6$ requires 648.3137.

1.1.7. 2-Deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-L-erythro-keto ethylacetate 11. The vinyl ether **10** (1.18 g, 1.87 mmol) was dissolved in 16 ml CH_2Cl_2–EtOH (1:1). The solution was ozonolysised at −78 °C. The production of the ozonide was determined by monitoring the presence of an excess of ozone using starch-KI paper. After 1 h of stirring, the reaction was quenched by the addition of 4 ml Me_2S at −78 °C. The reaction mixture was warmed to rt and evaporated under vacuum. The residue was partitioned between water (100 ml) and EtOAc (100 ml), and the aqueous layer extracted further with EtOAc (2×100 ml). The organic layers were combined, dried (Na_2SO_4) and evaporated to afford a residue which was subjected to chromatography, silica gel, eluting with light petroleum ether–diethyl ether (2:1) to afford 2-deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-L-erythro-keto ethylacetate **11** (0.86 g, 73%) as a colourless oil. $[\alpha]_D$=+6.0 (*c* 1.1 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3089, 1758, 1737, 1606, 1587, 975, 912. δ_H (270 MHz, $CDCl_3$) 1.01–1.07 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.60–3.63 (1H, d, *J*=5.8 Hz), 3.67–3.75 (1H, m), 3.76–3.80 (1H, d, *J*=10.1 Hz), 3.85–4.18 (3H, m), 4.42–4.98 (8H, m, 4×CH_2Ph), 4.92–5.05 (1H, ddd, *J*=3.9, 10.6, 21.6 Hz, CHOBnCF_2) and 7.09–7.31 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.4 (CH_2CH_3), 62.6 (CH_2CH_3), 69.8 (CH_2OBn), 72.3, 72.8, 73.3, 75.4 (1C, d, $J_{(C,F)}$=3.9 Hz) (4C, 4×CH_2Ph), 77.8, 78.1, 78.1 (3C, 3×CHOBn), 113.3–120.7 (1C, dd, $J_{(C,F)}$=250.7, 258.4 Hz, CF_2CO_2), 127.5, 127.6, 127.6, 127.7, 127.9, 127.9, 128.0, 128.1, 128.3, 128.3, 128.5, 128.5 and 128.8 (20C, phenyl CH), 136.2, 137.2, 138.0, 138.2 (4C, phenyl *C*), 158.3 ($CF_2COCOOC_2H_5$) and 174.8–175.6 (1C, t, $J_{(C,F)}$=28.1 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, *J*=257.2 Hz), 123.5–124.6 (1F, dd, *J*=19.1, 263.5 Hz);); *m*/*z* (ES+) [M+Na] found: 655.2488.$C_{37}H_{38}F_2O_7Na$ requires 655.2483.

1.1.8. 3-Deoxy-3,3-difluoro-2,4,5,6-tetra-*O*-acetyl-L-*arabino*-hept-2-ethylulosonate 13. The ester **11** (0.37 g, 0.58 mmol) was dissolved in ethanol (8 ml). To the resultant solution $Pd(OH)_2$-C (30 mg) and cyclohexene (2 ml) were added. The mixture was heated at reflux for 48 h, cooled to rt and stirred at this temperature for 24 h. The mixture was filtered through a pad of celite and concentrated in vacuo to afford crude 3-deoxy-3,3-difluoro-L-*arabino*-hept-2-ethylulosonate which was utilised without further purification. The crude product was treated with pyridine (4 ml) and acetic anhydride (2 ml). The whole mixture was shaken into clear solution and maintained at a temperature range of 0–4 °C for 12 h. Water (2 ml) was added into the mixture to destroy the excess acetic anhydride. The mixture was partitioned between H_2SO_4 (2.5 M) (50 ml) and CH_2Cl_2 (50 ml). The aqueous phase was extracted with CH_2Cl_2 (2×50 ml). The organic layers was combined, washed with saturated $NaHCO_3$ (50 ml) and sat. aq. NaCl (50 ml), dried (Na_2SO_4) and concentrated in vacuo to give a residue which was purified by column chromatography, silica gel, eluting with diethyl ether to afford the title compound (0.21 g, 82%). $[\alpha]_D$=−69.1 (*c* 1.03, $CHCl_3$); ν_{max} (film)/cm^{-1} 2983, 1756 1083. δ_H (270 MHz, $CDCl_3$) 1.30 (3H, t, *J*=7.1 Hz, CH_2CH_3), 2.02 (3H, s, OCOCH_3), 2.08 (3H, s, OCOCH_3), 2.22 (6H, s, 2×OCOCH_3), 4.21–4.88 (5H, m), 5.19 (1H, d, *J*=8.7 Hz, CF_2CHOAcCHOAc) and 5.72 (1H, ddd, *J*=3.5, 5.8, 9.2 Hz, CF_2CHOAc); δ_C (67.8 MHz, $CDCl_3$) 13.6 (CH_2CH_3), 20.1 (OCOCH_3), 20.2 (OCOCH_3), 20.3 (OCOCH_3), 20.4 (OCOCH_3), 61.2 (CH_2CH_3), 64.1 (1C, d, *J*=3.9 Hz, CF_2CHOAcCHOAc), 67.0 (AcOCH_2CH), 67.3 (1C, dd, *J*=24.9, 34.5 Hz, CF_2CHOAc), 93.7 (1C, dd, *J*=27.5, 35.0 Hz, OCOAc$CO_2C_2H_5$), 112.2 (1C, dd, $J_{(C,F)}$=251.6, 270.0 Hz, CF_2), 161.7 (1C, d, $J_{(C,F)}$=1.6 Hz, $CO_2C_2H_5$), 167.0 (OCOCH$_3$), 168.6 (OCOCH$_3$), 168.8 (OCOCH$_3$) and 170.6 (OCOCH$_3$); δ_F (282.4 MHz, $CDCl_3$) 116.5 (1F, dd, *J*=2.0, 6.0 Hz), 116.8 (1F, d, *J*=6.0 Hz); *m*/*z* (CI, NH_3) $[M+NH_4]^+$ found: 458.1477 $C_{17}H_{26}F_2NO_{11}$ requires 458.1474.

1.1.9. D-Erythro-diethyl dithioacetal 17.[12a] D-Erythrose **16** (3.78 g), was treated with conc. HCl (6 ml) and ethanethiol (6 ml) were stirred for 3 h at rt. To this mixture water (60 ml) was added and the mixture neutralised by the addition of aq. sodium carbonate. The resultant mixture was extracted with CH_2Cl_2 (3×60 ml). The organic extracts were combined, dried and evaporated to yield D-erythro-diethyl dithioacetal as a syrup (4.6 g). Chromatography, silica, eluting with light petroleum ether–diethyl ether (1:9) gave D-erythro-diethyl dithioacetal **17** (2.63 g, 40% for two steps) as colourless oil. $[\alpha]_D$=+16.8 (*c* 0.97, $CHCl_3$); ν_{max} (film)/cm^{-1} 3411, 2965, 1644. δ_H (270 MHz, $CDCl_3$) 1.19–1.25 (6H, t, *J*=7.4 Hz, 2×CH_2CH_3), 2.54–2.76 (4H, m, 2×CH_2CH_3), 3.77–3.85 (5H, m), 4.09 (1H, s, OH), 4.10 (1H, s, OH), 4.14 (1H, s, OH); δ_C (67.8 MHz, $CDCl_3$) 14.3, 14.5 (2C, 2×CH_3CH_2), 25.2, 25.3 (2C, 2×CH_2CH_3), 54.4 (CHSEtSEt), 63.3 (CH_2OH), 71.8 ($CH_2OHCHOHCHOH$), 73.6 ($CH_2OHCHOH$).

1.1.10. 2,3,4-Tri-*O*-benzyl-D-erythrose 18.[12b] A stirred, cooled, (0 °C), solution, of **17** (2.63 g, 11.6 mmol) in 40 ml of dry DMF was treated with 2.77 g of sodium hydride (60% dispersion in mineral oil, 69.3 mmol). The mixture was stirred for 10 min after which time a catalytic amount of tetrabutyl ammonium iodide was added. After further 20 min stirring, benzyl bromide (8.59 g, 50.2 mmol, 6.0 ml) was added dropwise to the mixture. The resultant mixture was stirred at 0 °C for 15 min and then warmed to rt and stirring continued for a further 10 h. The mixture was cooled in an ice bath and ethanol was added, carefully, in

order to destroy the excess of sodium hydride. Following this, the mixture was evaporated under reduced pressure and the residue partitioned between saturated aqueous sodium chloride (100 ml) and ethyl acetate (100 ml). The aqueous phase was extracted further with EtOAc (2×100 ml) and the organic layers were combined, dried (Na_2SO_4) and evaporated to afford a residue which was purified by chromatography, silica, eluting with light petroleum ether–diethyl ether (10:1) to afford the 2,3,4-tri-*O*-benzyl-D-erythro-diethyl dithioacetal (5.60 g, 97%) as colourless oil. $[\alpha]_D$=+27.1 (*c* 0.94, $CHCl_3$); ν_{max}(film)/cm^{-1} 3087, 3062, 1604. δ_H (270 MHz, $CDCl_3$) 1.16–1.21 (3H, t, *J*=7.4 Hz, CH_2CH_3), 1.21–1.26 (3H, t, *J*=7.4 Hz, CH_2CH_3), 2.58–2.71 (4H, m, 2×CH_2CH_3), 3.63–3.69(1H, dd, *J*=4.0, 10.6 Hz, C*H*HOBn), 3.76–3.81 (1H, dd, *J*=2.3, 10.6 Hz, CH*H*OBn), 3.94–4.05 (1H, ddd, *J*=2.3, 3.9, 7.9 Hz, C*H*OBnCH$_2$OBn), 4.01–4.05 (1H, dd, *J*=2.5, 7.9 Hz, C*H*OBnCHOBnCH$_2$OBn), 4.21–4.22 (1H, d, *J*=2.6 Hz, C*H*SEtSEt), 4.52–4.94 (6H, m, 3×CH_2Ph) and 7.12–7.33 (15H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 14.4, 14.5 (2C, 2×CH_2CH_3), 24.9, 26.1 (2C, 2×CH_2CH_3), 53.7 (*C*HSEtSEt), 68.6 (CH_2OBn), 72.4, 73.3, 75.0 (3C, 3×CH_2Ph), 78.9 (CH$_2$OBnCHOBn*C*HOBn), 81.9 (CH$_2$OBn*C*HOBn), 127.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.3, 128.4 (15C, phenyl *C*H) and 138.3, 138.3 and 138.4 (3C, phenyl *C*).

A solution of 2,3,4-tri-*O*-benzyl-D-erythrose diethyl dithioacetal (5.5 g, 11.1 mmol) in 125 ml of CH_3CN/H_2O (4:1) was treated with $HgCl_2$ (7.51 g, 27.7 mmol) and $CaCO_3$ (3.15 g, 31.5 mmol), and the mixture stirred for 2 h. The mixture was filtered and the filtrate concentrated. The residue was treated with 180 ml of CH_2Cl_2, washed with 150 ml KI (1% aqueous solution). The aqueous layer was further extracted with CH_2Cl_2 (2×100 ml). The organic layers were combined and washed again with 100 ml of KI (1% aqueous solution) and water (2×100 ml). The organic layers were dried, (Na_2SO_4), and evaporated to give a residue (4.3 g, 99.5%) which was directly used to next step.

1.1.11. 2-Deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-D-erythro ethyl acetate 20, 21. To a refluxing suspension of activated zinc dust (1.37 g, 21.0 mmol) in dry THF (35 ml) was added ethyl bromodifluoroacetate (3.20 g, 2.02 ml, 15.75 mmol). After 1 min, a solution of 2,3,4-tri-*O*-benzyl-D-erythrose (4.30 g, 11.0 mmol) dissolved in 15 ml of THF was added dropwise, over 15 min. After complete addition the reaction was refluxed for a further 2 h. The mixture was cooled to rt and carefully poured into 50 ml 1 M HCl and 50 g ice. Stirring of the resultant mixture was continued until all of the ice had melted. The mixture was extracted with EtOAc (3×100 ml). The organic layers were combined and washed with saturated $NaHCO_3$ (2×100 ml) and sat. aq. NaCl (2×100 ml), dried (Na_2SO_4) and concentrated in vacuo to give a residue. Chromatography, silica gel, eluting with light petroleum ether–diethyl either (4:1) gave two diastereoisomers **19**, (not separable) (4.49 g, 79% for two steps) as colourless oils; ν_{max} (film)/cm^{-1} 3450, 3089, 3064, 3031, 2981, 2908, 2871, 1955, 1876, 1770, 1606, 1587, 1496, 1454, 1371, 1311, 1209, 1093, 1027, 912, 852, 746 and 698.

Major diastereoisomer. δ_H (270 MHz, $CDCl_3$) 1.11–1.16 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.47–3.49 (1H, d, *J*=5.1 Hz, O*H*), 3.67–3.73 (1H, dd, *J*=5.0, 10.1 Hz, CH*H*OBn), 3.82–3.88 (1H, dd, *J*=4.6, 10.1 Hz, C*H*HOBn), 3.92–4.08 (4H, m), 4.44–4.75 (7H, m, 3×CH_2Ph and C*H*OH) and 7.16–7.40 (15H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.6 (CH_2CH_3), 62.5 (CH_2CH_3), 68.9 (CH_2OB_n), 70.6–71.3 (1C, dd, $J_{(C,F)}$= 22.8, 23.6 Hz, *C*HOH), 72.6, 73.4, 73.5 (3C, 3×CH_2Ph), 77.9, 78.6 (2C, 2×*C*HOB$_n$), 110.7–118.2 (1C, dd, $J_{(C,F)}$= 251.0, 257.1 Hz, CF_2CO_2), 127.6, 127.7, 127.8, 128.08, 128.2, 128.4 and 128. 5 (15C, phenyl *C*H), 137.5 (2C), 137.9 (3C, phenyl *C*) and 162.6–163.6 (1C, t, $J_{(C,F)}$=31.4 Hz, CF_2CO_2).

Minor diastereoisomer. δ_H (270 MHz, $CDCl_3$) 1.22–1.27 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.31–3.35 (1H, d, *J*=10.4 Hz, O*H*), 3.70–3.81 (2H, m, CH_2OBn), 3.92–4.09 (2H, m, 2×C*H*OBn), 4.23–4.29 (2H, q, *J*=7.1 Hz, CH_2CH_3), 4.46–4.76 (7H, m) and 7.26–7.35 (15H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.8 (CH_2CH_3), 63.0 (CH_2CH_3), 67.6 (CH_2OB_n), 69.5 (1C, t, $J_{(C,F)}$=23.6 Hz, *C*HOH), 72.5, 73.4, 73.9 (3C, 3×CH_2Ph), 77.9, 78.6 (2C, 2×*C*HOB$_n$), 110.8–118.3 (1C, dd, $J_{(C,F)}$=261.4, 267.8 Hz, CF_2CO_2), 127.7–130.9 (15C, phenyl *C*H), 137.3, 137.8, 137.9 (3C, phenyl *C*) and 163.1–163.9 (1C, t, $J_{(C,F)}$=30.4 Hz, CF_2CO_2).

A stirred, cooled (0 °C) solution, of the above mixture of daistereoisomers (3.0 g, 5.83 mmol), in 60 ml of dry DMF, was treated with 0.46 g of sodium hydride (60% dispersion in mineral oil, 10.15 mmol). The mixture was stirred for 10 min after which time a catalytic amount of tetrabutyl ammonium iodide was added. After further 20 min stirring, benzyl bromide (1.50 g, 8.75 mmol, 1.0 ml) was added dropwise to the mixture. The resultant mixture was stirred at 0 °C for 15 min and then warmed to rt and stirring continued for a further 10 h. The mixture was cooled in an ice bath and ethanol was added, carefully, in order to destroy the excess of sodium hydride. Following this the mixture was evaporated under reduced pressure and the residue partitioned between saturated aqueous sodium chloride (150 ml) and ethyl acetate (150 ml). The aqueous phase was extracted further with EtOAc (2×150 ml) and the organic layers were combined, dried (Na_2SO_4) and evaporated to afford a residue which was purified on silica gel eluting with light petroleum ether–diethyl ether (10:1) to afford two diastereoisomers: 2-deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-D-erythrose ethyl acetate **20**, **21** (2.69 g, 76%) (major/minor, 3.6:1) as colourless oils.

Less polar (*anti product*). $[\alpha]_D$=0; ν_{max}(film)/cm^{-1} 3089, 3064, 1760, 1606, 1587, 910. δ_H (270 MHz, $CDCl_3$) 3.34 (3H, s, CH_3), 3.61–3.73 (2H, m, CH_2OBn), 3.87–3.90 (1H, d, *J*=9.2 Hz, CH$_2$OBnCHOBnC*H*OBn), 3.96–4.00 (1H, t, *J*=5.6 Hz, CH$_2$OBnC*H*OBn), 4.48–4.52 (1H, dd, *J*=3.2, 9.1 Hz, C*H*OBnCF$_2$), 4.38–4.83 (8H, m, 4×CH_2Ph) and 7.13–7.35 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 52.6 (CH_3), 70.0 (CH_2OB_n), 72.7, 73.3, 73.5, 75.4–75.5 (1C, d, $J_{(C,F)}$=4.4 Hz) (4C, 4×CH_2Ph), 77.1–77.7 (1c, t, $J_{(C,F)}$= 21.5 Hz), 78.0–78.1 (1C, d, $J_{(C,F)}$=2.9 Hz), 78.3 (3C, 3×*C*HOB$_n$), 111.9–119.3 (1C, dd, $J_{(C,F)}$=258.3, 264.3 Hz, CF_2CO_2), 127.6, 127.6, 127.7, 127. 9, 128.2, 128.2, 128.2, 128.3 and 128.4 (20C, phenyl *C*H), 137.3, 137.5, 138.2, 138.4 (4C, phenyl *C*) and 163.0–163.9 (1C, t, $J_{(C,F)}$= 31.9 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2

(1F, d, J=257.15 Hz), 123.5–124.6 (1F, dd, J=19.1, 263.5 Hz)); m/z HRMS (CI, NH_3) found: 622.2992 $[M+NH_4]^+$ $C_{36}H_{42}F_2NO_6$ requires 622.2980.

More polar (*syn product*). $[\alpha]_D$=+3.4 (c 0.89 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3089, 3064, 1764, 1606, 1587, 910. δ_H (270 MHz, $CDCl_3$) 3.64 (3H, s, CH_3), 3.67–3.71 (1H, m), 3.79–3.91 (2H, m), 4.05–4.09 (1H, t, J=5.4 Hz), 4.24–4.34 (1H, ddd, J=4.3, 9.6, 13.7 Hz, CHOBnCF_2), 4.42–4.72 (8H, m, 4×CH_2Ph) and 7.11–7.33 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 53.2 (CH_3), 68.5 (CH_2OB$_n$), 71.9, 73.3, 74.2, 75.0 (4C, 4×CH_2Ph), 76.5, 77.6–78.3 (1C, t, J=25.5 Hz), 78.0 (3C, 3×CHOB$_n$), 111.3–118.8 (1C, dd, $J_{(C,F)}$=254.5, 260.0 Hz, CF_2CO_2), 127.5, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3, 128.3 and 128.4 (20C, phenyl *C*H), 137.5, 138.1, 138.2 (2C) (4C, phenyl *C*) and 163.8–164.7 (1C, t, $J_{(C,F)}$=33.1 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, J=257.2 Hz), 123.5–124.6 (1F, dd, J=19.1, 263.5 Hz)); m/z HRMS (CI, NH_3) found: 622.2985 $[M+NH_4]^+$ $C_{36}H_{42}F_2NO_6$ requires 622.2980.

1.1.12. 2-Deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-D-erythro vinyl ether 22. To a stirred, cooled (−78 °C) solution, of ethyl vinyl ether (0.74 g, 10.3 mmol, 1.0 ml) in THP (3.5 ml), *t*-BuLi (7.92 mmol, 1.7 M, 4.7 ml) was added dropwise. The mixture was stirred at −78 °C for 10 min, warmed to −3 to −5 °C, and stirred for a further 30 min. Following this the mixture was recooled to −78 °C, diluted with THF (8.0 ml) and treated with **19** (1.95 g, 3.3 mmol) in THF (3.0 ml). After stirring for 1 h at −78 °C, the reaction mixture was poured into water, (20 ml), and evaporated under reduced pressure. The resultant residue was partitioned between water (150 ml) and EtOAc (150 ml). The aqueous phase was extracted with EtOAc (2×150 ml) and the combined organics dried (Na_2SO_4), and evaporated to give a residue which was purified on silica gel eluting with light petroleum ether–diethyl ether (10:1) to afford 2-deoxy-2, 2-difluoro-3,4,5,6-tetra-*O*-benzyl-D-erythrose vinyl ether **22** (1.48 g, 85%) as colourless oil. $[\alpha]_D$=−23.7 (c 0.9 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3089, 3064, 3031, 2979, 2925, 2871, 1953, 1917, 1776, 1731, 1610, 1496, 1454, 1365, 1303, 1216, 1101, 1072, 1027, 973, 854, 738 and 698. δ_H (270 MHz, $CDCl_3$) 1.18–1.23 (3H, t, J=6.9 Hz, CH_2CH_3), 3.55–3.73 (4H, m), 3.77–3.81 (1H, d, J=9.9 Hz), 3.98–4.02 (1H, t, J=5.5 Hz), 4.24–4.28 (1H, d, J=10.9 Hz, CHHPh), 4.33–4.68 (7H, m), 4.72–4.85 (1H, ddd, J=3.3, 9.9, 21.3 Hz), 4.86–4.90 (1H, d, J=10.7 Hz, CHHPh), 5.11–5.12 (1H, d, J=2.6 Hz, C=CHH) and 7.12–7.29 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 14.0 (CH_2CH_3), 63.9 (CH_2CH_3), 70.5 (CH_2OBn), 72.3, 72.9, 73.2, 75.2–75.3 (1C, d, $J_{(C,F)}$=4.2 Hz) (4C, 4×CH_2Ph); 77.8–78.5 (1C, t, $J_{(C,F)}$=20.9 Hz), 77.8–77.9 (1C, d, $J_{(C,F)}$=3.9 Hz), 78.7 (3C, 3×CHOBn), 94.5–94.6 (1C, d, $J_{(C,F)}$=2.3 Hz, C=CH_2), 114.3–121.8 (1C, dd, $J_{(C,F)}$=251.8, 257.6 Hz, CF_2CO_2), 127.5, 127.5, 127.5, 127.7, 127.9, 127.9, 128.2, 128.2, 128.3, 128.3, 128.3, 128.4, 137.2, 137.4, 138.2, 138.6 (4C, phenyl *C*), 155.1 (C=CH_2) and 181.5–182.3 (1C, t, $J_{(C,F)}$=27.0 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, J=257.2 Hz), 123.5–124.6 (1F, dd, J=19.1, 263.5 Hz)); m/z (CI, NH_3) $[M+NH_4]^+$ found: 648.3142 $C_{38}H_{44}F_2NO_6$ requires 648.3137.

1.1.13. 2-Deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-D-erythro-keto-ethylacetate 23. The vinyl ether **22** (1.45 g, 2.3 mmol) was dissolved in 18 ml CH_2Cl_2–EtOH (1:1). The solution was ozonolysized at −78 °C. The production of the ozonide was determined by monitoring the presence of an excess of ozone using starch-KI paper. After 1 h of stirring, the reaction was quenched by the addition of 4 ml Me_2S at −78 °C. The reaction mixture was warmed to rt and evaporated under vacuum. The residue was partitioned between water (100 ml) and EtOAc (100 ml), and the aqueous layer extracted further with EtOAc (2×100 ml). The organic layers were combined, dried (Na_2SO_4) and evaporated to afford a residue which was subjected to chromatography, silica gel, eluting with light petroleum ether–diethyl ether (3:1) to afford 2-deoxy-2,2-difluoro-3,4,5,6-tetra-*O*-benzyl-D-erythrose-keto-ethylacetate **23** (1.06 g, 81%) as a colourless oil. $[\alpha]_D$=−8.9 (c 0.8 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3089, 3064, 3031, 2925, 2871, 1955, 1878, 1809, 1758, 1737, 1606, 1587, 1496, 1454, 1394, 1369, 1311, 1216, 1103, 1025, 975, 912, 740 and 698. δ_H (270 MHz, $CDCl_3$) 1.01–1.07 (3H, t, J=7.1 Hz, CH_2CH_3), 3.60–3.63 (1H, d, J=5.8 Hz), 3.67–3.75 (1H, m), 3.76–3.80 (1H, d, J=10.1 Hz), 3.85–4.18 (3H, m), 4.42–4.98 (8H, m, 4×CH_2Ph), 4.92–5.05 (1H, ddd, J=3.9, 10.6, 21.6 Hz, CHOBnCF_2) and 7.09–7.31 (20H, m, *Ph*); δ_C (67.8 MHz, $CDCl_3$) 13.4 (CH_2CH_3), 62.6 (CH_2CH_3), 69.8 (CH_2OBn), 72.3, 72.8, 73.3, 75.4–75.4 (1C, d, $J_{(C,F)}$=3.9 Hz) (4C, 4×CH_2Ph), 77.8, 78.1, 78.1 (3C, 3×CHOBn), 113.3–120.7 (1C, dd, $J_{(C,F)}$=250.7, 258.4 Hz, CF_2CO_2), 127. 5, 127.6, 127.6, 127.7, 127.9, 127.9, 128.0, 128.1, 128.3, 128.3, 128.5, 128.5, 128.8, 136.2, 137.2, 138.0, 138.2 (4C, phenyl *C*), 158.3 ($CF_2COCOOC_2H_5$) and 174.8–175.6 (1C, t, $J_{(C,F)}$=28.1 Hz, CF_2CO_2); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, J=257.2 Hz), 123.5–124.6 (1F, dd, J=19.1, 263.5 Hz); m/z (ES+) [M+Na] found: 655.2485.$C_{37}H_{38}F_2O_7Na$ requires 655.2483.

1.1.14. Ethyl-3-deoxy-3,3-difluoro-D-*arabino* ulosonate 24. The keto ester **23** (0.98 g, 1.55 mmol) was dissolved in ethanol (15 ml). To the resultant solution $Pd(OH)_2$-C (100 mg) and cyclohexene (3 ml) were added. The mixture was heated at reflux for 48 h, cooled to rt and stirred at this temperature for 24 h. The mixture was filtered through a pad of celite and concentrated in vacuo to afford crude ethyl-3-deoxy-3,3-difluoro-D-*arabino* ulosonate. Chromatography, silica gel, eluting with ethyl acetate, yielded the title compound **20** (0.30 g, 72%). $[\alpha]_D$=+34.1 (c 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3451, 3359, 2987, 2942, 1745, 1643, 1448, 1396, 1374, 1301, 1284, 1224, 1178, 1095, 919 and 898. δ_H (270 MHz, CD_3OD) 1.29–1.34 (3H, t, J=7.1 Hz, CH_2CH_3), 3.60–3.91 (3H, m), 4.05–4.12 (2H, m), 4.21–4.35 (2H, m) and 4.88 (4H, s, 4×OH); δ_C (67.8 MHz, $CDCl_3$) 14.2 (CH_2CH_3), 62.0 (CH_2CH_3), 63.7 (CH_2OH), 66.1 (CHOCH$_2$-OH), 71.2 (CHOHCHOCH$_2$OH), 72.0–72.8 (1C, t, $J_{(C,F)}$=26.1 Hz, CHOHCF_2), 95.2–96.1 (1C, t, $J_{(C,F)}$=29.7 Hz, COHCO$_2$C$_2$H$_5$), 112.3–119.8 (1C, dd, $J_{(C,F)}$=254.0, 260.2 Hz, CF_2CO$_2$C$_2$H$_5$) and 168.3 (CO_2C$_2$H$_5$); δ_F (67.8 MHz, $CDCl_3$) 111.2–112.2 (1F, d, J=257.2 Hz), 123.5–124.6 (1F, dd, J=19.1, 263.5 Hz); m/z (CI, NH_3) $[M+NH_4]^+$ found: 290.1054 $C_9H_{18}F_2NO_7$ requires 290.1051.

1.1.15. Ethyl 3-deoxy-3,3-difluoro-D-*arabino*-ulosonate, [C-4 diastereomer 24], (*syn* diastereoisomer). The C-4

syn diastereoisomer of **23** (0.11 g, 0.18 mmol) was dissolved in ethanol (8 ml). To the resultant solution $Pd(OH)_2$-C (100 mg) and cyclohexene (2 ml) were added. The mixture was heated at reflux for 48 h, cooled to rt and stirred at this temperature for 24 h. The mixture was filtered through a pad of celite and concentrated in vacuo to afford crude ethyl 3-deoxy-3,3-difluoro-D-*arabino*-ulosonate. Chromatography, silica gel, eluting with ethyl acetate gave the title compound [Diastereomeric **24**] (37 mg, 75%). $[\alpha]_D$=+46.7 (*c* 0.9 in CH_3OH). δ_H (270 MHz, CD_3OD) 1.32 (3H, t, *J*=7.1 Hz, CH_2CH_3), 3.74–3.85 (3H, m), 3.98 (1H, ddd, *J*=5.4, 9.4, 21.6 Hz), 4.26–4.33 (3H, m) and 4.94 (4H, s, 4×O*H*); δ_C (67.8 MHz, CD_3OD) 14.3 (CH_2CH_3), 62.0 (CH_2CH_3), 63.7 (CH_2OH), 69.6 (1C, d, $J_{(C,F)}$=7.0 Hz, *C*HOHCHOCH$_2$OH), 72.7 (1C, t, $J_{(C,F)}$=19.2 Hz, *C*HOHCF$_2$), 75.3 (*C*HOCH$_2$OH), 95.3 (1C, t, $J_{(C,F)}$=35.1 Hz, *C*OHCO$_2$C$_2$H$_5$), 118.2 (1C, dd, $J_{(C,F)}$=247.4, 262.5 Hz, *C*F$_2$CO$_2$C$_2$H$_5$) and 168.3 (*C*O$_2$C$_2$H$_5$); δ_F (282.4 MHz, CD_3OD) 122.7 (1F, d, *J*=248.5 Hz), 130.3 (1F, d, *J*=248.5 Hz); *m/z* (CI, NH_3) $[M+NH_4]^+$ found: 290.1052 $C_9H_{18}F_2NO_7$ requires 290.1051.

Acknowledgements

We thank the EPSRC for financial support and for access to the mass spectrometry service at the University of Wales, Swansea (Director, Prof. A. G. Brenton). We also thank the University of Reading for funds for the Image Plate system.

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