Pergamon

Tetrahedron, Vol. 53, No. 44, pp. 15085-15100, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10007-2

Free Radical Chain Reactions for the Preparation of Novel Anomeric Carbohydrate Difluoromethylene -phosphonates and -phosphonothioates.

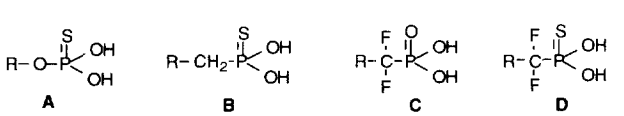
Timothée F. Herpin, William B. Motherwell*, Brian P. Roberts, Sylvain Roland and Jean-Marc Weibel.

Department of Chemistry, Christopher Ingold Laboratories, University College London, 20 Gordon Street, London WC1H 0AJ.

Abstract: The generation of phosphonyl or thiophosphonyl radicals in the presence of carbohydrate gem-difluoroenol ethers provides new routes to anomeric difluoromethylenephosphonates and difluoromethylenephosphonothioates, respectively. © 1997 Elsevier Science Ltd.

The ubiquitous presence of the phosphate group in a vast array of molecules of biological interest has stimulated intense research effort in the search for structural analogues where differing constitution and chemical reactivity allow them to be used either as mechanistic probes or potent inhibitors in enzymatic reactions, with many consequent applications in medecine, pharmacology and agrochemistry. Thus, phosphorothioates (**A**) and phosphonothioates (**B**) have been of considerable interest because of their use as irreversible inhibitors of acetylcholinesterase, as insecticides, and for their role in the elucidation of enzymatic and metabolic pathways.[1] The study of phosphoryl and nucleotidyl transferases using phosphorothioate analogues of nucleosides has also proved to be an important application[2] as has the development of such derivatives in oligonucleotide chemistry both as efficient anti sense inhibitors[3] and for possible therapeutic applications because of their resistance to nuclease promoted degradation.[4]

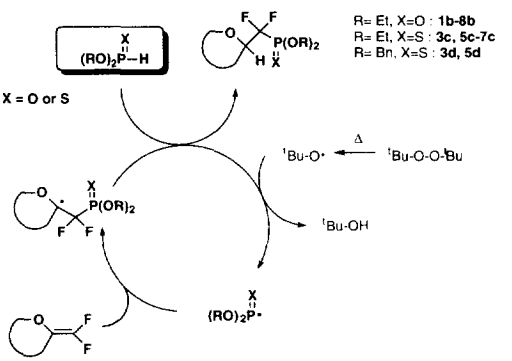
The elegant concept of using the 1,1-difluoromethylenephosphonate grouping (**C**) as an isopolar, isosteric and hydrolytically stable analogue of a phosphate ester has also provided numerous bioactive analogues of such fundamental natural products as phosphoenol pyruvate, glycerol-3-phosphate and nucleotides which have been used to study metabolism in enzymatic pathways.[5] Most recently, the first examples of a new class of analogues, the 1,1-difluoromethylenephosphonothioates (**D**), featuring the ingenious combination of the difluoromethylene group and the doubly bonded sulfur atom, have been reported by Piettre.[6]



A **B** **C** **D**

Within this framework, as part of our programme on the site specific replacement of the exocyclic anomeric oxygen atom in carbohydrates by a difluoromethylene unit,[7] we now report, in full detail,[8] on the preparation of anomeric difluoromethylene phosphonates, together with the first examples of their sulfur counterparts, the difluoromethylenephosphonothioates.

The introduction of a difluoromethylene phosphonate unit has traditionally been achieved by formation of a carbon-carbon bond using (lithiodifluoromethyl)phosphonate,[9,10] or the corresponding cadmium[5e,11], zinc[12] or cerium[13] reagents as nucleophiles in ionic displacement reactions. Reported alternatives have also included the direct transformation of benzylic α-oxophosphonates with diethylaminosulfur trifluoride[14] (DAST) or the transition metal mediated addition of iododifluoromethylphosphonate across alkenes.[15] However, since we had previously shown that the addition of sulfur[7a] and carbon centered radicals[7b] to carbohydrate *gem*-difluoroenol ethers provided a regiospecific route to CF_2-glycoside derivatives, we initially chose to investigate the possibility of phosphorous-carbon bond formation through the classical peroxide initiated free radical chain addition of dialkyl phosphites.[16] (Scheme 1, X=O)



Scheme 1

During the course of our own work, and subsequently in an interactive exchange, a conceptually similar strategy towards the preparation of 1,1-difluoromethylenephosphonates and thionophosphonates of classes (**C**) and (**D**) respectively using simple 1,1-difluoroalkenes was being studied by Piettre.[6, 17, 18]

The results for a series of reactions involving di-*tert*-butyl peroxide initiated addition of diethyl phosphite to carbohydrate *gem*-difluoroenol ethers (**1a-8a**) are shown in Table 1 (Method A) and confirmed that the formation of anomeric difluoromethylene phosphonates was possible. Moreover, in contrast to the behaviour of the parent 2,2-dialkyl-1,1-difluoroalkenes,[18] the only adducts isolated corresponded to regiospecific phosphorus-carbon bond formation at the difluoromethylene terminus of the difluoroenol ether unit. Yields however were low, presumably because of the severity of the reaction conditions and the possibility of competing benzylic hydrogen atom abstraction from certain substrates (entries 7 and 8). In the case of alkenes (**2a**), (**4a**), (**7a**), and (**8a**), this method failed completely and no addition products were isolated.

The inherent problem in the direct free radical chain addition reactions above resides of course in the energetically demanding propagation step which requires hydrogen atom abstraction by the anomeric radical from diethyl phosphite. We therefore considered, as shown in scheme 2, that this problematical step could be effectively circumvented by the incorporation of an additional step into the propagation sequence. Thus, we reasoned that the combination of tri-*n*-butylstannane and diethyl (phenylselenyl)phosphonate (**9**) would lead, *via* bimolecular homolytic substitution of (**9**) with a tri-*n*-butylstannyl radical to the liberation of a

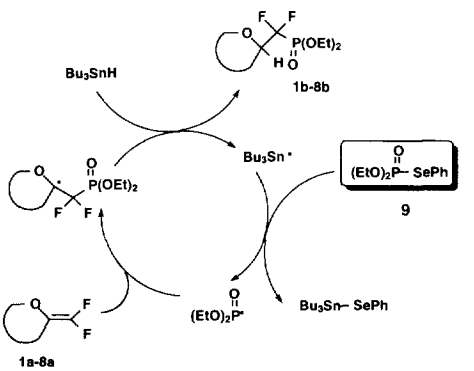
Entry	Substrate	Phosphonates (yield[a], ratio)	
		Method A[b]	Method B[c]
1	1a	**1b** (5%, α:β , 6:4)	**1b** (52%, α:β,45:55)
2	2a	-[e]	**2b** (31%, α:β , 1:1)
3	3a	**3b** (47%, α:β , 0:1)	**3b** (73%, α:β , 1:6)[d]
4	4a	-[e]	**4b** (44%)
5	5a	**5b** (23%)	**5b** (29%, α:β, 0:1)
6	6a	**6b** (8%)	**6b** (36%, α:β, 0:1)
7	7a	-[e]	**7b** (28%)
8	8a	-[e]	**8b** (14%)

[a] Yields of isolated product. In all cases, the diastereomers were separated by column chromatography or HPLC. [b] Reaction of **1a-8a** (1 eq.) and diethyl phosphite (3 eq) in refluxing octane in the presence of di-*tert*-butyl peroxide (0.5 eq.). [c] Reaction of **1a-8a** (1 eq.) and **9** (3 eq.) in refluxing benzene with tributyltin hydride (4 eq.) and AIBN (0.5 eq.). [d] Reaction in refluxing octane and with di-*tert*-butyl peroxide (0.5 eq.) as initiator. [e] No addition products observed.

Table 1

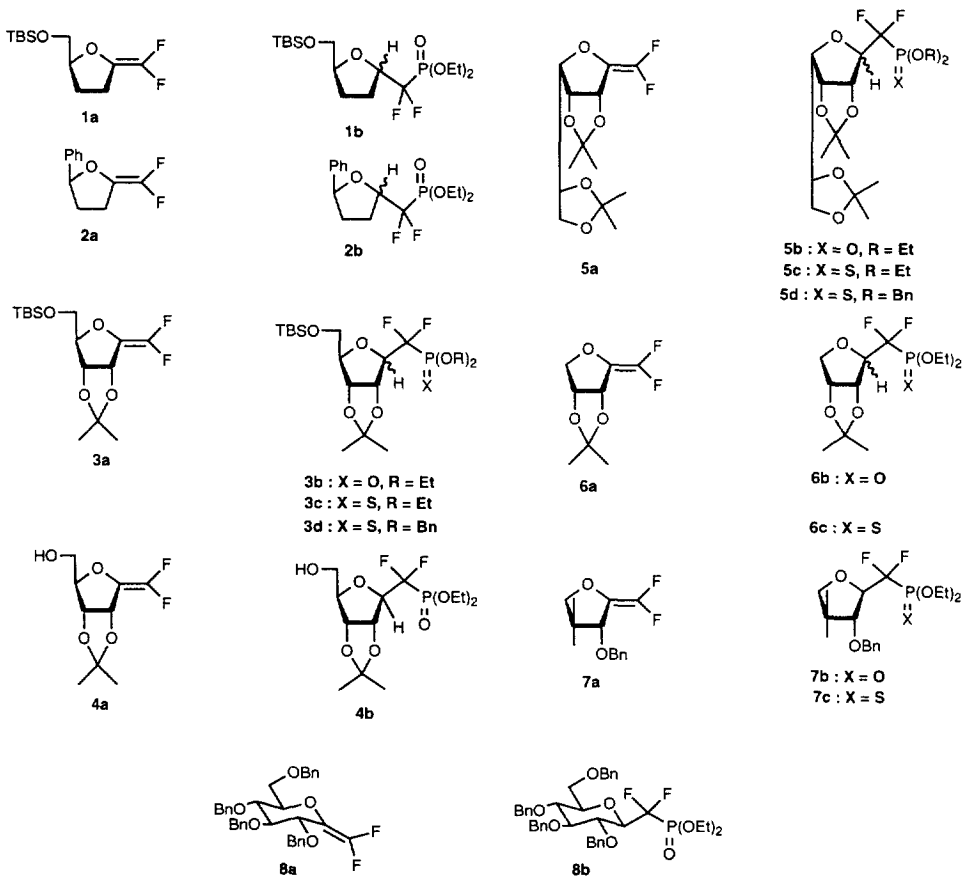
phosphonyl radical with formation of a strong tin-selenium bond as a driving force. Subsequent addition of the phosphonyl radical to the difluoroenol ether could then be followed by a much more facile hydrogen atom capture of the resultant anomeric radical from the stannane and liberation of the chain carrier. Although reagent (**9**) is readily prepared by an Arbuzov reaction between phenylselenyl bromide and triethyl phosphite,[19] its use in free radical chain reactions has not, to the best of our knowledge, been described.

The results obtained are summarised in Table 1 (Method B). Reactions were routinely carried out by slow addition of a solution of tri-*n*-butyltin hydride containing AIBN as initiator in benzene to a refluxing solution of the *gem*-difluoroenol ether substrates and diethyl (phenylselenyl)phosphonate (**9**) in the same solvent. Comparison of the yields obtained in this approach with those obtained by Method A reveals that the three component addition sequence is more efficient, and can even be successful in cases (entries 2, 4, 7 and 8)



Scheme 2

where the reaction with diethyl phosphite failed. In particular, the milder conditions of Method B are tolerant of free hydroxyl functionality (Entries 3 and 4) and also appear to be much more compatible with those substrates which are liable to potentially competing hydrogen atom abstraction reactions (Entries 1, 2, 6, 7 and 8). It is apparent however that in this series (Entry 8), where operation of the 'radical anomeric effect' gave the expected β-isomer,[20] that considerable scope still exists for alternative methodology.



The Stereochemical preference in the furanose series for the formation of the apparently more hindered β-anomer (*vide infra*) is based, not only on 1H NMR spectral comparison with our library of adducts derived from addition of sulphur and carbon centred radicals, but also by careful examination of the coupling constants between the anomeric proton and its vicinal neighbour on the ring. Thus, in the β-adducts (**5b**) and (**6b**) a coupling constant of $J_{H_2 \cdot H_3} = 0$ Hz was determined, consistent with a pseudoaxial position of the difluoromethylene substituent. Furthermore, in the cases of (**1b**), (**3b**), (**5b**) and (**7b**), comparative analyses of NOE spectral effects were performed for each anomer. For example, in the β-anomer of the ribose

derivative (**3b**), enhancements between the anomeric proton and its *cis* proton H-5 were observed, and also between H-4 and H-6 ($J_{2,3}$=4.1Hz and $J_{4,5}$=3.4Hz). These observations are consistent with a structure in which the ring adopts a conformation in which the substituents at C-2 and C-5 are pseudoequatorial in order to minimise 1,3 diaxial interactions. These enhancements are absent in the corresponding α-anomer. The proposed structure for the β-anomer (**4b**) was further confirmed by protection of the free hydroxyl group to give (**3b**). The β conformation of the pyranose (**8b**) was deduced from its diaxial coupling constant $J_{H_2\text{-}H_3}$ = 9.0 Hz between the anomeric hydrogen atom and its vicinal neighbour.

With the obtention of an improved method for the preparation of anomeric 1,1-difluoroalkylphosphonates, our attention was then directed towards the preparation of the corresponding phosphonothioates derivatives of class (**D**). In the first instance, we elected to return to the direct peroxide-initiated free radical chain addition reaction of dialkyl thiophosphites to carbohydrate *gem*-difluoroenol ethers (Scheme 1, X=S). The required thiophosphites were readily prepared from commercially available phosphites by exchange using Lawesson's reagent[17, 18, 21] and addition reactions were typically carried out by slow addition of a solution of di-*tert*-butyl peroxide in octane to a refluxing solution of diethyl or dibenzyl thiophosphite and the appropriate difluoroenol ether in the same solvent.

Entry	Substrate	R	Phosphonothioates (yield[a], ratio[b])
1	**2a**	Et	[c]
2	**3a**	Et	**3c** (94%, α:β , 1:9)[d]
3	**3a**	Bn	**3d** (76%, α:β,1:9)
4	**5a**	Et	**5c** (86%, α:β , 35:65)
5	**5a**	Bn	**5d** (37%, α:β , 35:65)
6	**6a**	Et	**6c** (66%, α:β , 45:55)
7	**7a**	Et	**7c** (6.5%, α:β , 0:1)
8	**8a**	Et	[c]

[a] Yields of isolated product. [b] Ratio measured by ^{19}F-NMR of the crude and confirmed with the mass of isolated compounds except for **5d** where the ratio of isolated compounds is α:β , 45:55. [c] No addition products observed. [d] The *tert*-butyldimethylsilyl group on the β-isomer was partially removed during this reaction.

Table 2

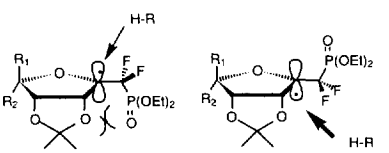
From the results shown in Table 2, it is immediately apparent that the yields of difluoromethylenephosphonothioates are much higher than in the corresponding additions of diethyl phosphite. This is presumably a consequence of greatly increased efficiency in the hydrogen atom abstraction step of the propagation sequence, since the lower electronegativity of the sulfur atom will make a substantial contribution towards weakening the phosphorus-hydrogen bond in the thiophosphite. As in the case of the phosphite additions however, the presence of benzylic sites for competing hydrogen atom abstraction (Entries 1, 7 and 8) leads to much lower yields. It should also be noted that selective partial deprotection of the *tert*-butyldimethylsilyl group occured from the β-isomer during the reaction of substrate (**3a**) (Entry 2).

Within this series, we have also shown that the use of dibenzyl thiophosphite is possible (Entries 3 and 5), although direct comparison with the same substrates using diethyl thiophosphite (Entries 2 and 4) reveals it to be a less efficient reagent. The assignment of the stereochemistry was determinated by comparison with the ^{1}H, ^{13}C and ^{19}F-NMR spectra of the corresponding α or β difluoromethylenephosphonates, the chemical shifts and coupling constants being enough similar in the two series for no ambiguity to appear. Particularly, the more simple ^{19}F-NMR spectra were very useful for an easier attribution and also to measure the ratio of α and β isomer.

At this stage, it is now appropriate to discuss the stereochemical outcome for the furanose substrates in these reactions. Throughout our study, this feature proved to be of especial interest, inasmuch as it ran entirely contrary to our initial expectations. Thus, for example, in the furanoside derivatives (**3a-6a**) containing the 2,3-isopropylidene unit, a distinct preference was always observed for the formation of the β-stereoisomer at the anomeric center, especially in the case of the phosphonates. This behaviour, which is apparently indicative of hydrogen atom capture from the more hindered face of the molecule, is in direct opposition to that which is generally predicted for such classical V-shaped molecules,[20,22] and also contrasts with our own observations on the addition of both sulfur and carbon centered radicals to the same substrates.[7] Moreover, the fact that no less than four reagents (diethyl phosphite, tri-*n*-butylstannane, and the two thiophosphites) all of differing efficiency and size, have been used to deliver the required hydrogen atom to the anomeric radical, would argue that the spatial requirements of the difluoromethylene phosphonate or, to a lesser extent, the phosphonothioate grouping are playing a determining role in these reactions.

Further careful scrutiny of the substrates used reveals that the location of a substituent on the 2α-position of the difluoroenol ether is mandatory for a higher β-stereoselectivity. Thus, the absence of such a functional group, as in substrates (**1a**) and (**2a**) leads to an essentially equimolar mixture of products, whereas introduction of the α-benzyl ether substituent as in (**7a**) leads, once again, to reinstallation of the preference for formation of β-adducts.

A possible explanation for this apparently inherent stereoselective preference is shown in scheme 3 and may arise through hyperconjugative interaction of the unpaired electron with the C-P bonding electrons. Maximisation of such a stabilising interaction requires that an eclipsed conformation, as shown in structures **A** and **B** be adopted, and this has indeed been confirmed in a study of β-phosphorus substituted radicals by EPR spectroscopy.[23,24,25]



A less favored **B** most favored

R = $SnBu_3$, $P(O)(OEt)_2$, $P(S)(OEt)_2$ or $P(S)(OBn)_2$

Scheme 3

Of the two possible conformers **A** or **B** in 2,3-isopropylidene derived substrates, steric factors would tend to favour B whose phosphorus substituent effectively impedes delivery of the hydrogen atom by abstraction from the top (β) face. As evidenced by the case of the difluoroenol ether (**6a**) however, it should be noticed that this argument applies more strongly in the case of the phosphonates than their phosphonothioate counterparts. At first sight, the introduction of a single substituent in the 4-position, as in difluoroenol ethers (**1a**) and (**2a**) appears to play no significant role in influencing the stereochemistry at the anomeric center for the preparation of difluoromethylenephosphonates. In the additional presence of the 2,3-isopropylidene group however, the 4β substituent in substrates (**3a**) and (**4a**) appears to diminish the preference for formation of β-substituted anomeric derivatives while the 4α subsituent in (**5a**) continues to furnish the β-adduct exclusively. By way of contrast, in the preparation of difluoroalkylphosphonothioates, the role played in the ribose side chain in (**3a**) leads to a relative enhancement in the proportion of the β-difluoromethylenephosphonothioate, when compared with the congeneric phosphonate. It is of interest to note that the relative ratio of α and β-phosphonothioates at the anomeric center are unaffected by the nature (Et or Bn) of the thiophosphite reagent used. In the final analysis, it is apparent that no simple predictive generalisations can be made for the effect of substitution in the 4-position and the final stereochemical outcome must hinge on a combination of more subtle steric and electronic factors.

In summary, from a preparative standpoint, of the three free radical chain reactions leading to regiospecific carbon-phosphorus bond formation at the difluoromethylene terminus of carbohydrate *gem*-difluoroenol ethers, the classical addition of thiophosphites is clearly preferable for robust furanoside derivatives. For substrates possessing abstractable benzylic hydrogen atoms however, the lower operating temperatures which can be achieved using the diethyl (phenylselenyl)phosphite-stannane combination can be advantageous.

Acknowledgements: We are grateful to the European Community for the award of a fellowship (JMW) and to the Royal Society European Exchange Programme for a postdoctoral grant (SR). We also wish to thank the Ministère de l'Enseignement Supérieur et de la Recherche for a studentship (TFH). We also wish to acknowledge friendly and helpful discussion with Dr S. Piettre (Marion-Merrel Dow, Strasbourg) throughout this study.

Experimental section

All reactions were carried out under argon or nitrogen with exclusion of moisture. Benzene was distilled from sodium-benzophenone ketyl and octane from calcium hydride. Diethyl phosphite, di-*tert*-butyl peroxide, tri-*n*-butyltin hydride and 2,2'-azobisisobutyronitrile (AIBN) were of commercial origin. Diethyl thiophosphite and dibenzyl thiophosphite were synthetized from the corresponding phosphites using Lawesson's reagent.[17,18,21] The *gem*-difluoroenol ethers (**1a-8a**) were obtained from the corresponding lactones according to our procedure.[26] Diethyl (phenylselenyl)phosphonate (**9**) was prepared from phenylselenyl bromide and triethyl phosphite.[19] 'Petrol' refers to petroleum ether, boiling range 40-60°C and 'ether' implies diethyl ether. ^{1}H, ^{19}F and ^{13}C-NMR spectra were recorded on a Varian VXR-400 spectrometer. Coupling constants were measured in Hertz and chemical shifts in ppm relative to the internal

reference. Infrared spectra were recorded in wavenumbers (cm^{-1}), using NaCl plates or a KBr disc as appropriate, on a Perkin Elmer 1605 FT-IR spectrophotometer. Mass spectra were recorded on VG 12 253 and VG ZAB-e instruments by EI and CI with NH_3 carrier gas, by the EPSRC mass spectrometry service. FAB spectra were run on a VG 7070 instrument at UCL, or on a VG ZAB-SE double focussing spectrometer by the ULIRS. Accurate mass measurements were recorded by the ULIRS on a VG micromass 305 instrument by EI and on a VG ZAB-SE double focussing spectrometer by FAB. Any MALDI-TOF spectra were obtained on a VG TofSpec instrument by the ULIRS. Elemental analyses were performed by the UCL Chemistry Department microanalytical laboratory. Preparative column chromatography was performed at low positive pressure on Merck Kieselgel 60 (230-400 mesh). Chromatographie purification of the difluoromethylene-phosphonates and phophonothioates reported in this work proved to be extremely difficult and the 1H NMR spectra invariably indicated the presence of the anomeric diastereoisomer as a minor contaminent. For this reason, $[\alpha]_D$ values were not determined in this series.

General procedures for the synthesis of 1,1-difluoromethylenephosphonates:

Procedure A: A solution of *gem*-difluoroenol ether (**1a-8a**) (1 mmol) and diethyl phosphite (3 mmol) in octane (7 mL) was degassed at reflux for 1 h. To this refluxing solution (145°C) was added a solution of di-*tert*-butyl peroxide (0.5 mmol) in octane (5 mL) over 10 h *via* syringe pump. The mixture was refluxed 3 h after addition and concentrated.

Procedure B: A solution of *gem*-difluoroenol ether (**1a-8a**) (1 mmol) and diethyl (phenylselenyl)phosphonate (**9**) (3 mmol) in dry benzene (7 mL) was degassed at reflux for 1 h. To this refluxing solution was added a solution of AIBN (0.5 mmol) and tri-*n*-butyltin hydride (4 mmol) in dry degassed benzene (3.5 mL) over 10 h *via* syringe pump. The mixture was refluxed for 4 h after addition and concentrated.

(5S) Diethyl (5-*tert*-butyldimethylsilanyloxymethyl-tetrahydro-fur-2-yl) difluoro-methylenephosphonate (1b).

Procedure A: From 211 mg (0.842 mmol) of (**1a**), after flash chromatography of the crude material (Petrol:Ether, 7:3), were obtained in order of elution: (**1b**β)(10 mg) and (**1b**α)(6 mg) as colourless oils. Yield: 5%.

Procedure B: From 246 mg (0.982 mmol) of (**1a**), after flash chromatography of the crude material (Petrol:Ether, 75:25) were obtained in order of elution (**1b**β)(93 mg) and (**1b**α)(112 mg) as colourless oils. Yield: 52%.

β-isomer: ^{1}H-NMR (400 MHz, $CDCl_3$): 4.50-4.38 (1H, m, H-2), 4.38-4.25 (4H, m, $OC\underline{H}_2CH_3$), 4.19 (1H, m, H-5), 3.63 (2H, d, J = 4.5 Hz, H-6), 2.29-2.02 (3H, m), 1.85-1.75 (1H, m), 1.38 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.37 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 0.89 (9H, s, ^{t}Bu), 0.05 (6H, s, Si-Me); ^{13}C-NMR (100 MHz, $CDCl_3$): 81.4, 78.4 (ddd, J = 26.8, 21.9 and 15.0 Hz, C-2), 65.5, 64.5 (m, $O\underline{C}H_2CH_3$), 27.5, 25.9, 25.4 (m), 18.3, 16.4 (m), -5.5 (Me-Si); ^{19}F-NMR (376 MHz, $CDCl_3$): -118.7 (1F, ddd, J = 305, 101 and 10 Hz), -123.8 (1F, ddd, J = 305, 103 and 18 Hz); IR (cm^{-1}; in CCl_4): 2933, 2861, 1467,

1395, 1267, 1082, 1031, 979; m/z (EI): 387 $[M-Me]^+$, 345, 317, 289, 257, 215, 201, 155, 117, 59; Accurate Mass (FAB): Observed $(M-Me)^+$: 387.1564; $C_{15}H_{30}F_2O_5PSi$ requires: 387.1381.

α-isomer: ^{1}H-NMR (400 MHz, $CDCl_3$): 4.44-4.24 (5H, m, H-2 and $OC\underline{H}_2CH_3$), 4.10 (1H, quint., J = 6.3 Hz, H-5), 3.70 (1H, dd, J = 10.3 and 5.2 Hz, H-6), 3.54 (1H, dd, J = 10.3 and 6.2 Hz, H-6), 2.28-2.16 (1H, m), 2.10-1.94 (2H, m), 1.88-1.76 (1H, m), 1.38 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.37 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 0.89 (9H, s, ^{t}Bu), 0.05 (6H, s, Me-Si); ^{13}C-NMR (100 MHz, $CDCl_3$): 118 (m, C-1), 81.5, 78.1 (ddd, J = 27.5, 21.0 and 15.0 Hz, C-2), 65.2, 64.5 (dd, J = 10.4 and 6.6 Hz, $O\underline{C}H_2CH_3$), 27.9, 25.9, 25.7 (m), 18.3, 16.4 (m), -5.5 (Me-Si); ^{19}F-NMR (376 MHz, $CDCl_3$): -120.1 (1F, ddd, J = 304, 101 and 9 Hz), -125.0 (1F, ddd, J = 304, 103 and 18 Hz); IR (cm^{-1}; in CCl_4): 2953, 2933, 2861, 1467, 1390, 1267, 1087, 1031, 979; m/z (EI): 387 (3%, $[M-Me]^+$), 345 (100%), 317 (33%), 289 (55%), 215 (36%), 155 (26%), 109 (19%), 73 (97%); Accurate Mass (FAB): Observed $(M-Me)^+$: 387.1564: $C_{15}H_{30}F_2O_5PSi$ requires: 387.1381.

(5S) Diethyl (5-phenyl-tetrahydro-fur-2-yl) difluoromethylene phosphonate (2b).

Procedure B: From 227 mg (1.157 mmol) of (**2a**), after flash chromatography of the crude material (Petrol:Ether, 1:1 to 4:6) were obtained 119 mg (31%) as two diastereomers, not characterized.

Isomer A (less polar): 57 mg (15%); colourless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.34-7.26 (5H, m, Ph), 5.11 (1H, dd, J = 8.1 and 5.6 Hz, H-5), 4.75-4.62 (1H, m, H-2), 4.35-4.22 (4H, m, $OC\underline{H}_2CH_3$), 2.48-2.32 (2H, m), 2.28-2.18 (1H, m), 1.92-1.82 (1H, m, H-4), 1.38 (3H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.34 (3H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): 141.8, 128.4, 127.5, 125.6, 119.1 (ddd, J = 267, 263 and 209 Hz, C-1), 82.3, 78.3 (ddd, J = 26.9, 22.1 and 15.2 Hz, C-2), 64.6 (dd, J = 11.1 and 6.5 Hz, $O\underline{C}H_2CH_3$), 34.7, 25.7, 16.4 (OCH_2-$\underline{C}H_3$); ^{19}F-NMR (376 MHz, $CDCl_3$): -119.0 (1F, ddd, J = 306, 101 and 11 Hz), -123.3 (1F, ddd, J = 306, 102 and 17 Hz); IR (cm^{-1}; in CCl_4): 2985, 1451, 1394, 1370, 1270, 1069, 1032; m/z (FAB): 357 (6%, $[M+Na]^+$), 335 (100%, $[M+H]^+$), 179 (26%), 91 (20%); Accurate Mass (FAB): Observed $[M+H]^+$: 335.1228; $C_{15}H_{22}F_2O_4P$ requires: 335.1224.

Isomer B (more polar): 62 mg (16%); colourless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.44-7.25 (5H, m, Ph), 4.96 (1H, dd, J = 9.5 and 5.7 Hz, H-5), 4.62-4.50 (1H, m, H-2), 4.36-4.12 (4H, m, $OC\underline{H}_2CH_3$), 2.45-2.37 (1H, m), 2.34-2.16 (2H, m), 1.97-1.87 (1H, m), 1.37 (3H, t, J = 7.4 Hz, $OCH_2C\underline{H}_3$), 1.29 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): 141.3, 128.1, 126.8, 126.1, 118.3 (ddd, J = 265, 256 and 206 Hz, C-1), 83.3, 78.0 (ddd, J = 28.0, 22.0 and 13.7 Hz, C-2), 64.3 (t, J = 5.8 Hz, $O\underline{C}H_2CH_3$), 35.2, 20.6, 16.4 (t, J = 5.7 Hz, OCH_2-$\underline{C}H_3$); ^{19}F-NMR (376 MHz, $CDCl_3$): -118.4 (1F, ddd, J = 305, 101 and 8 Hz), -126.7 (1F, ddd, J = 305, 102 and 20 Hz); IR (cm^{-1}; in CCl_4): 2984, 1455, 1394, 1370, 1215, 1165, 1032; m/z (EI): 334 (14%, $[M]^+$), 215 (57%), 188 (53%), 161 (51%), 147 (74%), 129 (58%), 105 (57%), 91 (69%), 77 (57%), 65 (47%); Accurate Mass (FAB^+): Observed $[M+Na]^+$: 357.1040; $C_{15}H_{21}F_2NaO_4P$ requires: 357.1043.

Diethyl (2,3-*O*-isopropylidene-5-*O*-*tert*-butyldimethylsilanyl-D-*ribo*-furanos-1-yl) difluoromethylenephosphonate (3b).

Procedure A: From 200 mg (0.59 mmol) of (**3a**), after flash chromatography of the crude material (Petrol:Ether, 1:1) was obtained (**3bβ**)(130 mg, 47%) as a yellow oil.

Procedure B: From 150 mg (0.45 mmol) of (**3a**), after flash chromatography of the crude material (Petrol:Ether, 1:1) was obtained (**3b**)(155 mg, 75%) as a yellow oil, mixture of two diastereomers. HPLC (ethyl acetate:hexane, 25:75) allowed the separation of the two isomers, as two yellow oils.

β-isomer: ^{1}H-NMR (400 MHz, $CDCl_3$): 4.92 (1H, dd, J = 4.1 and 6.4 Hz, H-3), 4.63 (1H, dd, J = 3.4 and 6.4 Hz, H-4), 4.43-4.36 (1H, m, H-2), 4.25 (4H, m, $OC\underline{H}_2CH_3$), 4.17 (1H, q, J = 4.8 Hz, H-5), 3.74 (1H, dd, J = 4.8 and 11.0 Hz, H-6a), 3.66 (1H, dd, J = 5.4 and 11.0 Hz, H-6b), 1.55 (3H, s, $C\underline{Me}_2$), 1.35 (9H, m, $C\underline{Me}_2$ and $OCH_2C\underline{H}_3$), 0.90 (9H, s, *t*-Bu), 0.05 (6H, s, Me-Si); ^{13}C-NMR (100 MHz, $CDCl_3$): 117.5 (ddd, J = 209, 261 and 269 Hz, C-1), 114.3 ($\underline{C}Me_2$), 86.2, 84.0 (ddd, J = 14, 21 and 28 Hz, C-2), 81.6, 79.9, 64.8 (t, J = 7 Hz, $O\underline{C}H_2CH_3$), 63.0, 27.4 ($C\underline{Me}_2$), 25.8 ($C\underline{Me}_3$), 25.5 ($C\underline{Me}_2$), 18.1 ($\underline{C}Me_3$), 16.4 ($OCH_2\underline{C}H_3$), 16.3 ($OCH_2\underline{C}H_3$), -5.6 (Me-Si), -5.8 (Me-Si); ^{19}F-NMR (376 MHz, $CDCl_3$): -118.5 (1F, ddd, J = 9, 100 and 313 Hz), -124.5 (1F, ddd, J = 18, 100 and 313 Hz); IR (neat): ν_{max}= 3056, 2987, 2932, 2859, 1472, 1385, 1266, 1215, 1025, 838, 779, 740, 705 cm^{-1}; m/z (EI): 459 $[M\text{-}Me]^+$, 417, 267, 73; Accurate Mass (FAB): Observed $[M+Na]^+$: 497.1916; $C_{19}H_{37}O_7F_2PSiNa$ requires: 497.1912.

α-isomer: ^{1}H-NMR (400 MHz, $CDCl_3$): 4.98 (1H, dd, J = 4.5 and 5.9 Hz, H-3), 4.84 (1H, d, J = 6.2 Hz, H-4), 4.60 (1H, m, H-2), 4.25 (5H, m, $OC\underline{H}_2CH_3$, H-5), 3.81 (1H, dd, J = 3.1 and 11.0 Hz, H-6a), 3.73 (1H, dd, J = 2.8 and 11.0 Hz, H-6b), 1.53 (3H, s, $C\underline{Me}_2$), 1.37 (9H, m, $C\underline{Me}_2$ $OCH_2C\underline{H}_3$), 0.90 (9H, s, *t*-Bu), 0.05 (6H, s, Me-Si); ^{13}C-NMR (100 MHz, $CDCl_3$): 117.5 (m, C-1), 113.3 ($\underline{C}Me_2$), 85.0, 82.6, 81.4, 80.0 (m, C-2), 65.2, 64.8 (m, $O\underline{C}H_2CH_3$), 26.0 ($C\underline{Me}_2$), 25.8 ($C\underline{Me}_3$), 28.0 ($C\underline{Me}_2$), 18.1 ($\underline{C}Me_3$), 16.4 ($OCH_2\underline{C}H_3$), 16.3 ($OCH_2\underline{C}H_3$), -5.6 (Me-Si), -5.8 (Me-Si); ^{19}F-NMR (376 MHz, $CDCl_3$): -118.7 (1F, ddd, J = 18, 102 and 314 Hz), -121.1 (1F, ddd, J = 8, 101 and 314 Hz); IR (neat): ν_{max}= 3056, 2987, 2932, 2859, 1472, 1385, 1266, 1215, 1025, 838, 779, 740, 705 cm^{-1}; m/z (EI): 459 $[M\text{-}Me]^+$, 417, 267, 73; Accurate Mass (FAB): Observed $[M+H]^+$: 497.1916; $C_{19}H_{37}O_7F_2NaPSi$ requires: 497.1912.

Diethyl (2,3-*O*-isopropylidene-β-D-*ribo*-furanos-1-yl) difluoromethylene phospho-nate (4b).

Procedure B: From 200 mg (0.9 mmol) of (**4a**), after flash chromatography of the crude material (Petrol:Ether, 75:25) were obtained 158 mg (44%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 5.00 (1H, dd, J = 6.2 and 3.4 Hz, H-3), 4.72 (1H, dd, J = 6.2 and 2.8 Hz, H-4), 4.44-4.25 (6H, m, H-2, H-5 and $OC\underline{H}_2CH_3$), 3.75 (1H, dd, J = 12.6 and 2.8 Hz, H-6), 3.61 (1H, dd, J = 12.6 and 5.6 Hz, H-6), 1.55 (3H, s, Me), 1.39 (6H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.36 (3H, s, Me); ^{13}C-NMR (100 MHz, $CDCl_3$): 118 (m, C-1), 113.9, 87.3, 85.0 (ddd, J = 36.3, 16.6 and 12.7 Hz, C-2), 81.2, 80.6 (t, J = 2.6 Hz), 65.0 (dd, J = 20.7 and 6.8 Hz), 62.2, 27.2, 26.4, 25.2, 24.7, 16.3 (d, J = 5.6 Hz); ^{19}F-NMR (376 MHz, $CDCl_3$): -121.2 (1F, ddd, J = 313, 106 and 18 Hz), -112.1 (1F, ddd, J = 313, 94 and 10 Hz); IR (cm^{-1}; in CCl_4): 3424, 2989, 2939, 1380, 1260, 1216, 1028, 980, 865; m/z (FAB^+): 383 (16%, $[M+Na]^+$), 361 (100%, $[M+H]^+$), 303 (14%); Accurate Mass (FAB): Observed $[M\text{-}Me]^+$: 345.0910; $C_{12}H_{20}F_2O_7P$ requires: 345.0915.

Diethyl (2,3;5,6-di-*O*-isopropylidene-β-D-*gulo*-furanos-1-yl) difluoromethylene phosphonate (5b).

Procedure A: From 200 mg (0.68 mmol) of (**5a**), after flash chromatography of the crude material (Petrol:Ether, 4:6) were obtained 68 mg (23%) as a colourless oil.

Procedure B: From 200 mg (0.68 mmol) of (**5a**), after flash chromatography of the crude material (Petrol:Ether, 4:6) were obtained 85 mg (28%) as a colourless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): 5.15 (1H, d, J = 6.0 Hz, H-3), 4.70 (1H, dd, J = 4.2 and 6.1 Hz, H-4), 4.50 (1H, ddd, J = 3.0, 9.2 and 23.2 Hz, H-2), 4.30 (5H, m, $OC\underline{H}_2CH_3$ and H-6), 4.15 (1H, dd, J = 6.7 and 8.4 Hz, H-7a), 4.07 (1H, m, H-5), 3.65 (1H, dd, J = 7.1 and 8.4 Hz, H-7b), 1.45 (3H, s, $C\underline{Me}_2$), 1.38 (3H, s, $C\underline{Me}_2$), 1.37-1.34 (6H, m, $OCH_2C\underline{H}_3$), 1.33 (3H, s, $C\underline{Me}_2$), 1.28 (3H, s, $C\underline{Me}_2$); ^{13}C-NMR (100 MHz, $CDCl_3$): 119.0 (ddd, J = 208, 267 and 270 Hz, C-1), 113.5 ($\underline{C}Me_2$), 109.7 ($\underline{C}Me_2$), 85.5, 84.1 (ddd, J = 13, 21 and 27 Hz, C-2), 81.2, 81.1, 76.1, 66.0, 64.9 (t, J = 6 Hz, $O\underline{C}H_2CH_3$), 26.7 ($C\underline{Me}_2$), 26.2 ($C\underline{Me}_2$), 25.3 ($C\underline{Me}_2$), 24.8 ($C\underline{Me}_2$), 16.5 ($OCH_2\underline{C}H_3$); ^{19}F-NMR (376 MHz, $CDCl_3$): -115.0 (1F, ddd, J = 10, 98 and 317 Hz), -122.2 (1F, ddd, J = 24, 98 and 317 Hz); IR (neat): ν_{max}= 2987, 2938, 1445, 1373, 1265, 1212, 1185, 1164, 1068, 1026, 975, 912, 853, 796, 735 cm^{-1}; m/z (EI): 415 $[M\text{-}Me]^+$, 357, 138, 101; Accurate Mass (FAB): Observed $[M+Na]^+$: 453.1461; $C_{17}H_{29}F_2NaO_8P$ requires: 453.1466.

Diethyl (2,3-*O*-isopropylidene-β-D-*erythro*-furanos-1-yl) difluoromethylene phos-phonate (6b).

Procedure A: From 200 mg (1 mmol) of (**6a**), after flash chromatography of the crude material (Petrol:Ether, 2:8) were obtained 26 mg (7.5%) as a colourless oil.

Procedure B: From 100 mg (0.52 mmol) of (**6a**), after flash chromatography of the crude material (Petrol:Ether, 4:6) were obtained 61 mg (36%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 5.05 (1H, d, J = 6.1 Hz, H-3), 4.85 (1H, t, J = 5.0 Hz, H-4), 4.40 (1H, dd, J = 8.7 and 24.4 Hz, H-2), 4.28 (4H, m, $OC\underline{H}_2CH_3$), 4.08 (1H, m, H-5a), 4.0 (1H, dt, J = 3.9 and 10.4 Hz, H-5b), 1.48 (3H, s, $C\underline{Me}_2$), 1.40-1.31 (9H, m, $OCH_2C\underline{H}_3$ $C\underline{Me}_2$); ^{13}C-NMR (100 MHz, $CDCl_3$): 119.0 (ddd, J = 208, 267 and 269 Hz, C-1), 113.1 ($\underline{C}Me_2$), 84.3 (ddd, J = 13, 20 and 27 Hz, C-2), 81.1, 80.7, 74.8, 64.8 (m, $O\underline{C}H_2CH_3$), 26.5 ($C\underline{Me}_2$), 24.9 ($C\underline{Me}_2$), 16.43 ($OCH_2\underline{C}H_3$), 16.39 ($OCH_2\underline{C}H_3$); ^{19}F-NMR (376 MHz, $CDCl_3$): -114.9 (1F, ddd, J = 8, 98 and 315 Hz), -121.6 (1F, ddd, J = 24, 100 and 315 Hz); IR (DCM): ν_{max}= 2987, 1735, 1382, 1375, 1266, 1211, 1161, 1109, 1028, 738 cm^{-1}; $[\alpha]_D$= -32.3° (c= 0.7, DCM); m/z (FAB): 331 $[M+H]^+$, 315 $[M\text{-}Me]^+$, 273, 217, 43; Accurate Mass (FAB): Observed $[M+H]^+$: 331.1125; $C_{12}H_{22}F_2O_6P$ requires: 331.1122.

(2R,3R) Diethyl (4,4-dimethyl-3-benzyloxy-tetrahydro-fur-2-yl) difluoromethylene phosphonate (7b).

Procedure B: From 243 mg (0.9 mmol) of (**7a**), after flash chromatography of the crude material (Petrol:Ether, 1:1) were obtained 97 mg (28%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.36-7.26 (5H, m, Ph), 4.65 (1H, d, J = 11.5 Hz, H-5), 4.54 (1H, d, J = 11.5 Hz, H-5), 4.36-4.22 (5H, m, $OC\underline{H}_2CH_3$ and H-2), 4.04 (1H, d, J = 5.6 Hz, H-3), 3.65 (2H, s, -$C\underline{H}_2$-Ph), 1.39 (3H, t, J = 7.4 Hz, CH_2-$C\underline{H}_3$), 1.35 (3H, t, J = 7.4 Hz, CH_2-$C\underline{H}_3$), 1.15 (3H, s, Me), 1.08 (3H, s, Me); ^{13}C-NMR (100 MHz, $CDCl_3$): 138.0 (C-4), 128.2 (Ph), 127.6 (Ph), 119.0 (m, C-1), 85.1 (t, J = 3.8 Hz), 83.0 (ddd, J = 34.4, 21.6 and 12.6 Hz, C-2), 80.0, 73.0, 64.5 (d, J = 6.6 Hz, $O\underline{C}H_2CH_3$), 42.4 (Me-4), 23.8 (Me-4), 20.0 (OCH_2-$\underline{C}H_3$), 16.3 (OCH_2-$\underline{C}H_3$); ^{19}F-NMR (376 MHz, $CDCl_3$): -116.0 (1F, ddd, J = 309, 101 and 7 Hz), -123.0 (1F, ddd, J = 309, 103 and 21 Hz); IR (cm^{-1}; in CCl_4): 2976, 2872, 1462, 1368, 1273, 1074, 1028, 981; m/z (EI): 393 (86%, $[M+H]^+$), 301 (25%, $[M-Bn]^+$), 286 (77%, $[M-Bn-Me]^+$), 236 (33%), 217 (61%), 188 (73%), 161 (92%), 153 (25%), 132 (23%), 109 (28%), 99 (100%); Accurate Mass (FAB): Observed $[M+H]^+$: 393.1646; $C_{18}H_{28}F_2O_5P$ requires: 393.1642.

Diethyl (2,3,4,6-tetra-*O*-benzyl-β-D-*gluco*-pyranos-1-yl) difluoromethylene phosphonate (8b).

Procedure B: From 205 mg (0.36 mmol) of (**8a**), after flash chromatography of the crude material (Petrol:Ether, 1:1 to 4:6) were obtained 97 mg (14%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.34-7.16 (20H, m, Ph), 4.95-4.47 (8H, m, -O-$C\underline{H}_2$-Ph), 4.35-4.20 (4H, m, $OC\underline{H}_2CH_3$), 4.01 (1H, t, J = 9.0 Hz, H-3), 3.96-3.84 (1H, m, H-2), 3.78-3.68 (4H, m, 7 pics, H-4, H-5 and H-7), 3.53 (1H, m, J = 9.3 Hz, H-6), 1.32 (6H, J = 7.0 Hz, $OCH_2C\underline{H}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): 138.5, 138.0, 137.9, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 86.7, 79.5, 77.8 (m, C-2), 77.4, 77.2 (t, J = 3.7 Hz), 77.1, 76.8, 75.9, 75.1, 74.9, 73.5, 68.7, 64.6 (dd, J = 19.9 and 9.4 Hz, $O\underline{C}H_2CH_3$), 16.5 (d, J = 5.8 Hz, OCH_2-$\underline{C}H_3$); ^{19}F-NMR (376 MHz, $CDCl_3$): -112.4 (1F, ddd, J = 312, 98 and 6 Hz), -121.9 (1F, ddd, J = 312, 102 and 18 Hz); IR (cm^{-1}; in CCl_4): 2869, 1454, 1360, 1273, 1206, 1104, 1065, 1028; m/z (EI): 708 (4%, $[M+H]^+$), 619 (13%), 513 (12%), 497 (29%), 405 (26%), 220 (39%), 205 (100%), 181 (31%); Accurate Mass (FAB): Observed $[M+H]^+$: 708.2660; $C_{39}H_{43}F_2O_8P$ requires: 708.2664.

General procedure for the synthesis of 1,1-difluoromethylenephosphonothioates.

A solution of *gem*-difluoroenol ether (**1a-8a**) (1 mmol) and thiophosphite (3 mmol) in octane (7 mL) was degassed at reflux for 1 h. To this refluxing solution (145°C) was added a solution of di-*tert*-butyl peroxide (0.5 mmol) in octane (5 mL) over 10 h *via* syringe pump. The mixture was refluxed 3 h after addition and concentrated.

Diethyl (2,3-*O*-isopropylidene-5-*O*-*tert*-butyldimethylsilanyl-D-*ribo*-furanos-1-yl) difluoromethylene phosphonothioate (3c).

From 300 mg (0.893 mmol) of (**3a**), after flash chromatography of the crude material (Petrol:Ether, 95:5, 1% NEt3) were obtained 413 mg (94%) as two diastereomers:

β-isomer: 373 mg (85%); colourless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): 4.95 (dd, 1H, J = 6.5 and 3.7 Hz), 4.65 (dd, 1H, J = 6.5 and 3.4 Hz), 4.54 (m, 1H), 4.36-4.2 (m, 4H), 4.16 (q, 1H, J = 3.9 Hz), 3.72 (dd, 1H, J = 10.9 and 4.7 Hz), 3.65 (dd, 1H, J = 10.9 and 5.9 Hz), 1.55 (s, 3H), 1.45-1.3 (m, 9H), 0.9

(s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 117.2 (m), 113.9, 86.1, 83.2 (m), 81.6, 80.2, 65.0, 62.9, 27.3, 25.8, 25.4, 18.3, 16.2, -5.6, -5.8. ^{19}F-NMR (376 MHz, $CDCl_3$): -118.3 (1F, ddd, J = 297, 104 and 9 Hz), -125.8 (1F, ddd, J = 297, 99 and 18 Hz). IR (cm^{-1}, neat): 2983, 2954, 2931, 2858, 1473, 1383, 1258, 1214, 1159, 1086, 1020, 970, 837, 779, 648. Anal. Calcd for $C_{19}H_{37}F_2O_6PSSi$: C, 46.51; H, 7.60. Found: C, 46.34; H, 7.51.

α-isomer: 40 mg (9%); colourless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): 4.95 (dd, 1H, J = 6 and 4.2 Hz), 4.88 (d, 1H, J = 6.1 Hz), 4.78 (tt, 1H, J = 13.1 and 3.9 Hz), 4.35-4.2 (m, 5H), 3.81 (dd, 1H, J = 11 and 2.7 Hz), 3.73 (dd, 1H, J = 11 and 2.7 Hz), 1.52 (s, 3H), 1.37-1.33 (m, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 128.0 (m), 113.2, 84.9, 83.3, 81.8, 79.2 (m), 65.5, 65.1, 64.9, 26.2, 26.0, 24.6, 18.1, 16.0, -5.5, -5.8. ^{19}F-NMR (376 MHz, $CDCl_3$): -120 (2F, dd, J = 178 and 22 Hz). IR (cm^{-1}, neat): 2931, 2857, 1472, 1382, 1257, 1211, 1163, 1136, 1097, 1020, 971, 837, 816, 778, 645. Anal. Calcd for $C_{19}H_{37}F_2O_6PSSi$: C, 46.51; H, 7.60. Found: C, 46.88; H, 7.75.

Dibenzyl (2,3-*O*-isopropylidene-5-*O*-*tert*-butyldimethylsilanyl-D-*ribo*-furanos-1-yl) difluoromethylene phosphonothiate (3d).

From 300 mg (0.893 mmol) of (**3a**), after flash chromatography of the crude material (Petrol:Ether, 98:2, 1% NEt_3) were obtained 418 mg (76%) as two diastereomers:

β-isomer: 378 mg (69%); colourless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 (s, 10H), 5.17 (d, 4H, J = 10.6 Hz), 4.96 (dd, 1H, J = 6.8 and 3.7 Hz), 4.61 (m, 1H), 4.17 (q, 1H, J = 3.2 Hz), 3.66 (dd, 1H, J = 11 and 4.7 Hz), 3.6 (dd, 1H, J = 11 and 6 Hz), 1.55 (s, 3H), 1.46 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 135.6, 128.6, 128.4, 128.1, 119.0 (m), 114.0, 86.1, 83.4 (m), 81.8, 80.1, 69.7, 62.9, 27.4, 25.9, 25.4, 18.3, -5.6, -5.8. ^{19}F-NMR (376 MHz, $CDCl_3$): -118 (1F, ddd, J = 298, 83 and 8 Hz), -125.2 (1F, ddd, J = 298, 100 and 19 Hz). IR (cm^{-1}, neat): 2953, 2930, 2886, 2857, 1498, 1472, 1456, 1375, 1257, 1214, 1085, 997, 837, 778, 741, 696, 666. Anal. Calcd for $C_{29}H_{41}F_2O_6PSSi$: C, 56.66; H, 6.72. Found: C, 56.92; H, 6.86.

α-isomer: 40 mg (7%); colourless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.4-7.3 (m, 10H), 5.3-5.1 (m, 4H), 4.98 (dd, 1H, J = 5.9 and 4.2 Hz), 4.88 (d, 1H, J = 5.9 Hz), 4.86 (m, 1H), 4.25 (s, 1H), 3.79 (dd, 1H, J = 11 and 2.7 Hz), 3.74 (dd, 1H, J = 11 and 2.7 Hz), 1.52 (s, 3H), 1.33 (s, 3H), 0.88 (s, 9H), 0.06 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): 135.9, 128.5, 128.4, 128.1, 128.0, 113.3, 84.9, 82.6, 81.6, 79.5 (m), 70.0, 69.6, 65.5, 26.1, 25.9, 25.0, 18.1, -5.6, -5.8. ^{19}F-NMR (376 MHz, $CDCl_3$): -119.4 (2F, dd, J = 103 and 13 Hz). IR (cm^{-1}, neat): 3033, 2953, 2896, 2857, 1498, 1456, 1375, 1255, 1213, 1165, 1136, 1086, 995, 936, 836, 778, 749, 696, 669. Anal. Calcd for $C_{29}H_{41}F_2O_6PSSi$: C, 56.66; H, 6.72. Found: C, 56.93; H, 6.81.

Diethyl (2,3;5,6-di-*O*-isopropylidene-D-*gulo*-furanos-1-yl) difluoromethylene phosphonothioate (5c).

From 280 mg (0.962 mmol) of (**5a**), after flash chromatography of the crude material (Petrol:Ether, 9:1) were obtained 368 mg (86%) as two diastereomers:

β-isomer: 239 mg (56%), colourless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): 5.08 (d, 1H, J = 5.8 Hz), 4.71 (dd, 1H, J = 26.6 and 7.8 Hz), 4.70 (dd, 1H, J = 4.55 and 5.85 Hz), 4.4-4.23 (m, 5H), 4.2 (dd, 1H, J = 8.8 and 6.8 Hz), 4.02 (dt, 1H, J = 8.5 and 3.9 Hz), 3.67 (dd, 1H, J = 8.5 and 7.1 Hz), 1.48 (s, 3H), 1.42 (s, 3H), 1.4-1.33 (m, 9H), 1.32 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 113.2, 109.7, 85.3, 83.2, 81.4, 81.1, 76.1, 66.1, 65, 64.6, 26.8, 26.2, 25.3, 24.8, 11.2. ^{19}F-NMR (376 MHz, $CDCl_3$): -114.3 (1F, ddd, J = 300, 105 and 8 Hz), -123.4 (1F, ddd, J = 300, 95 and 27 Hz). IR (cm^{-1}, neat): 2986, 2936, 1449, 1370, 1210, 1162, 1062, 970, 889, 846, 816, 630. Anal. Calcd for $C_{17}H_{29}F_2O_7PS$: C, 45.74; H, 6.55. Found: C, 45.91; H, 6.83.

α-isomer: 129 mg (30%), colourless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): 4.95 (dd, 1H, J = 6 and 3.6 Hz), 4.67 (dd, 1H, J = 6 and 4.4 Hz), 4.43 (q, 1H, J = 7.8 Hz), 4.38-4.1 (m, 6H), 3.72 (dd, 1H, J = 8.4 and 7.2 Hz), 3.58 (dd, 1H, J = 8.6 and 3.6 Hz), 1.5 (s, 3H), 1.42 (s, 3H), 1.42-1.32 (m, 9H), 1.3 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 113.8, 109.8, 84.0, 80.6, 80.5, 78.2 (m), 75.1, 66.0, 65.7, 65.0, 26.8, 25.7, 25.4, 24.9, 16.0. ^{19}F-NMR (376 MHz, $CDCl_3$): -117.9 (1F, ddd, J = 310, 98 and 17 Hz), -123.5 (1F, ddd, J = 310, 106 and 8 Hz). IR (cm^{-1}, neat): 2986, 2936, 2873, 1456, 1372, 1210, 1162, 1062, 974, 889, 846, 816, 750, 664, 648. Anal. Calcd for $C_{17}H_{29}F_2O_7PS$: C, 45.74; H, 6.55. Found: C, 45.95; H, 6.89.

Dibenzyl (2,3;5,6-di-*O*-isopropylidene-D-*gulo*-furanos-1-yl) difluoromethylene phosphonothioate (5d).

From 278 mg (0.955 mmol) of (**5a**), after flash chromatography of the crude material (Petrol:Ether, 9:1) were obtained 197 mg (37%) as two diastereomers:

β-isomer: 106 mg (20%); colourless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.4-7.3 (m, 10H), 5.37 (t, 1H, J = 12 Hz), 5.16 (d, 2H, J = 10.4 Hz), 5.09 (d, 1H, J = 5.6 Hz), 4.82 (dd, 1H, J = 26.6 and 6.7 Hz), 4.71 (dd, 1H, J = 5.9 and 4.2 Hz), 4.38 (q, 1H, J = 7.3 Hz), 4.22 (dd, 1H, J = 8.5 and 6.7 Hz), 4.1 (m, 1H), 3.7 (t, 1H, J = 8.2 Hz), 1.51 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 136.2, 135.5, 128.5, 128.3, 128.1, 113.4, 109.7, 85.4, 83.2, 81.3, 81.2, 76.2, 70.2, 69.4, 66.0, 26.7, 26.1, 25.3, 24.7. ^{19}F-NMR (376 MHz, $CDCl_3$): -114 (1F, ddd, J = 303, 101 and 6 Hz), -123.1 (1F, ddd, J = 303, 94 and 30 Hz). IR (cm^{-1}, neat): 3034, 2987, 2937, 1498, 1456, 1372, 1239, 1213, 1162, 1065, 851, 738, 696, 679, 652. Anal. Calcd for $C_{27}H_{33}F_2O_7PS$: C, 56.83; H, 5.83. Found: C, 57.07; H, 5.87.

α-isomer: 91 mg (17%); white crystalline solid; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.4-7.3 (m, 10H), 5.24 (dd, 4H, J = 15.2 and 9.2 Hz), 4.97 (dd, 1H, J = 6 and 3.8 Hz), 4.68 (dd, 1H, J = 5.4 and 4.2 Hz), 4.7 (q, 1H, J = 7.8 Hz), 4.23 (m, 2H), 3.74 (t, 1H, J = 8.2 Hz), 3.64 (dd, 1H, J = 8 and 4 Hz), 1.49 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.27 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 136.0, 135.7, 128.5, 128.2, 128.1, 119.0 (m), 114.0, 109.8, 84.0, 80.6, 80.5, 78.3 (m), 75.3, 70.6, 69.6, 66.0, 26.9, 25.7, 25.4, 24.8. ^{19}F-NMR (376 MHz, $CDCl_3$): -118.2 (1F, ddd, J = 301, 99 and 16 Hz), -119.3 (1F, ddd, J = 301, 102 and 8 Hz). IR (cm^{-1}, in $CHCl_3$): 3018, 2940, 1498, 1456, 1383, 1374, 1215, 1165, 1113, 1066, 1044, 997, 863. Anal. Calcd for $C_{27}H_{33}F_2O_7PS$: C, 56.83; H, 5.83. Found: C, 56.84; H, 5.65.

Diethyl (2,3-*O*-isopropylidene-D-*erythro*-furanos-1-yl) difluoromethylene phosphonothioate (6c).

From 192 mg (1 mmol) of (**6a**), after flash chromatography of the crude material (Petrol:Ether, 95:5) were obtained 229 mg (66%) as two diastereomers:

β-isomer: 124 mg (36%); colourless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): 5.05 (d, 1H, J = 6 Hz), 4.85 (dd, 1H, J = 6 and 3.5 Hz), 4.57 (dd, 1H, J = 24 and 7.5 Hz), 4.32-4.18 (m, 4H), 4.05 (dt, 1H, J = 10 and 2 Hz), 3.95 (dt, 1H, J = 10 and 3.5 Hz), 1.5 (s, 3H), 1.4-1.3 (m, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): 119.0 (m), 113, 83.8 (m), 81.2, 81.1, 74.4, 64.8, 64.7, .26.5, 25.0, 16.1. ^{19}F-NMR (376 MHz, $CDCl_3$): -113.7 (1F, ddd, J 315, 100 and 8 Hz), -122.8 (1F, ddd, J 315, 100 and 24 Hz) .IR (cm^{-1}, neat): 2984, 1462, 1383, 1275, 1236, 1211, 1161, 1109, 1049, 1024, 968, 859, 818, 662. Anal. Calcd for $C_{12}H_{21}F_2O_5PS$: C, 41.64; H, 6.11. Found: C, 41.81; H, 6.08.

α-isomer: 105 mg (30%); colourless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): 4.93 (dd, 1H, J = 6.2 and 4.2 Hz), 4.83 (dd, 1H, J = 6 and 4.2 Hz), 4.4-4.2 (m, 4H), 4.17 (d, 1H, J = 11 Hz), 4.08 (m, 1H), 1.52 (s, 3H), 1.45-1.3 (m, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): 113.1, 80.5, 80.3, 78.8 (m), 73.2, 65.1, 65.0, 25.9, 25.0, 16.2. ^{19}F-NMR (376 MHz, $CDCl_3$): -118.3 (1F, ddd, J = 310, 100 and 9 Hz), -119.3 (1F, ddd, J = 310, 100 and 16 Hz). IR (cm^{-1}, neat): 2990, 1464, 1385, 1275, 1236, 1211, 1115, 1109, 1050, 1024, 985, 967, 859, 818, 662. Anal. Calcd for $C_{12}H_{21}F_2O_5PS$: C, 41.64; H, 6.11. Found: C, 41.81; H, 5.97.

(2R,3R) Diethyl (4,4-dimethyl-3-benzyloxy-tetrahydro-fur-2-yl) difluoromethylene phosphonothioate (7b).

From 286 mg (1.13 mmol) of (**7a**), after flash chromatography of the crude material (Petrol:Ether, 95:5) were obtained 30 mg (6.5%), as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.4-7.2 (m, 5H), 4.65 (dd, 1H, J = 11.5 and 3.1 Hz), 4.52 (dd, 1H, J = 11.5 and 3.5 Hz), 4.42 (dm, 1H, J = 24.8 Hz), 4.36-4.05 (m, 4H), 4.0 (dd, 1H, J = 4.9 and 3.6 Hz), 3.62 (m, 2H), 1.45-1.25 (m, 6H), 1.15 (s, 3H), 1.1 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 138.1, 128.3, 128.2, 127.7, 85.5, 82.8 (m), 80.0, 73.0, 64.7, 42.5, 23.8, 20.1, 16.2. ^{19}F-NMR (376 MHz, $CDCl_3$): -114 (1F, dd, J = 297 and 105 Hz), -125 (1F, ddd, J = 297, 102 and 24 Hz). IR (cm^{-1}, neat): 2982, 2933, 1467, 1454, 1390, 1370, 1216, 1161, 1075, 1020, 968. Anal. Calcd for $C_{18}H_{26}F_2O_4PS$: C, 53.06; H, 6.43. Found: C, 52.73; H, 6.36.

References and notes

1. a) Eckstein, F. *J. Am. Chem. Soc.* **1970**, *92*, 4718. b) Usher, D. A.; Erenrich, E. S.; Eckstein, F. *Proc. Nat. Acad. Sci. USA* **1972**, *69*, 115. c) Eckstein, F. *Angew. Chem. Int. Ed. Eng.* **1983**, *22*, 423.
2. a) Rothermel, J. D.; Stec, W. J.; Baraniak, J.; Jarstoff, B.; Botelho, L. H. P. *J. Biol. Chem.* **1983**, *258*, 12125. b) De Wit, R. J. W.; Hekstra, D.; Jarstoff, B.; Stec, W. J.; Van Haastert, P. J. M.; Van Driel, R.; Jarstoff, B.; Baraniak, J.; Stec, M. W.; Averill, B. A.; Knowles, J. R. *J. Am; Chem. Soc.* **1993**, *115*, 2974.
3. a) Eckstein, F. *Ann. Rev. Biochem.* **1985**, *54*, 367. b) Matsukura, M.; Sinozuka, K.; Zon, G.; Mitsuya, H.; Reitz, M.; Cohen, J., S.; Broder, S. *Proc. Nat. Acad. Sci. USA* **1987**, *84*, 7706.
4. Matsukura, M.; Zon, G.; Sinozuka, K.; Robert-Guroff, M.; Shimada, T.; Stein, C. A.; Wong-Stall, F.; Mitsuya, Cohen, J., S.; Broder, S. *Proc. Nat. Acad. Sci. USA* **1987**, *86*, 4244.
5. a) Blackburn, G. M.; Kent, D. E.; Kohlman, F. *J. Chem. Soc., Perkin Trans.*, **1984**, 1119. b) Blackburn, G. M.; Eckstein, F.; Kent, D. E.; Perrée, T. D. *Nucleosides and Nucleotides*, **1985**, *4*, 165. c) Hebel, D.; Kirk, K. L.; Kinjo, J.; Kovac's, T.; Lesjak, K.; Balzarini, J.; De Clercq, E.; Torrence, P. F. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 357. d) Chambers, R. D.; Jaouhari, R.; O'Hagan, J. *J. Chem. Soc. Chem. Comm.* **1988**, 1169. e) Chambers, R. D.; Jaouhari, R.; O'Hagan, J. *Tetrahedron*, **1989**, *45*, 5101. f) Phillion, D. P.; Cleary, D. G. *J. Org. Chem.* **1992**, *57*, 2763. g) Thatcher,G. R. J.; Campbell, A. S. *J. Org. Chem.* **1993**, *58*, 2272.
6. Piettre, S.; Raboisson, P. *Tetrahedron Lett.*, **1996**, *37*, 2229.
7. a) Motherwell, W. B.; Tozer, M. J.; Ross, B. C. *Synlett*, **1989**, 68. b) Herpin, T. F.; Motherwell, W. B.; Tozer, M. J. *Tetrahedron : Asymmetry*, **1994**, *5*, 2269.
8. Herpin, T. F.; Houlton, J. S.; Motherwell, W. B.; Roberts, B. P.; Weibel, J.-M. *J. Chem. Soc. Chem. Commun.*, **1996**, 613 and references herein.
9. Martin, S. F.; Dean, D. W.; Wagman, A. S. *Tetrahedron Lett.*, **1992**, *33*, 1839.
10. Berkowitz, D. B.; Eggen, M.; Shen, Q.; Sloss, D. *J. Org. Chem.*, **1993**, *58*, 6174.
11. Burton, D. J.; Shin-Ya, S.; Takei, R. *J. Fluorine Chem.*, **1981**, *18*, 197.
12. a) Blackburn, G. M.; Jakeman, D. L.; Ivory, A. J.; Williamson, M. P. *Bioorg. and Med. Chem. Lett.*, **1994**, *4*, 2573. b) Burton, D. J.; Sprague, L. G. *J. Org. Chem.*, **1988**, *53*, 1523. c) Burton, D. J.; Sprague, L. G. *J. Org. Chem.*, **1989**, *54*, 613.
13. a) Lequeux, T. P.; Percy, J. M. *Synlett*, **1995**, 361. b) Lequeux, T. P.; Percy, J. M. *J. Chem. Soc., Chem. Commun.*, **1995**, 2111.
14. Smyth, M. S.; Burke Jr., T. R. *Tetrahedron Lett.*, **1994**, *35*, 551.
15. a) Yang, Z.-Y.; Burton, D. J. *Tetrahedron Lett.*, **1991**, *32*, 1019. b) Yang, Z.-Y.; Burton, D. J. *J. Org. Chem.*, **1992**, *57*, 4676. c) Hu, C.-M.; Chen, J. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 327.
16. Sosnovsky, G. *Free Radical Reactions in Preparative Organic Chemistry*; M^{c}Millan, New York, 1964.
17. Piettre, R. *Tetrahedron Lett.*, **1996**, *37*, 4707.
18. Piettre, R. *Tetrahedron Lett.*, **1996**, *37*, 2233.
19. Petragnani, N.; Toscano, V. G.; Moura Campos, M. *Chem. Ber.*, **1968**, *101*, 3070.
20. Giese, B. *Angew. Chem., Int. Ed. Engl.*, **1989**, *28*, 969.
21. Diethyl thiophosphite was obtained in 85% yield in refluxing toluene for 5 min. In our modified procedure, dibenzyl thiophosphite was obtained in 60% yield by heating the solution for 2h at 95°C. Our attempts to synthesise di-*tert*-butyl thiophosphite even at a lower temperature only led to decomposition of the starting di-*tert*-butyl phosphite.
22. a) Barton, D. R. H.; Gero, S. D.; Quiclet-Sire, B.; Samaldi, M. *Tetrahedron: Asymmetry*, **1994**, *5*, 2123. b) Giese, B. *Angew. Chem., Int. Ed. Engl.*, **1989**, *28*, 969.
23. Davies, A. G.; Griller, D.; Roberts, B. P. *J. Am. Chem. Soc.*, **1972**, *94*, 1782.
24. Neil, I. G.; Roberts, B. P. *J. Organomet. Chem.*, **1975**, *102*, C17.
25. Roberts, B. P.; Singh, K. *J. Organomet. Chem.*, **1978**, *159*, 31.
26. Houlton, S. J.; Motherwell, W. B.; Ross, B. C.; Tozer, M. J.; Williams, D. J.; Slawin, A. M. Z. *Tetrahedron*, **1993**, *49*, 8087.

(*Received in UK* 20 *May* 1997; *accepted* 4 *September* 1997)