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From Oxygen to Sulfur and Back: Difluoro-*H*-Phosphinothioates as a Turning Point in the Preparation of Difluorinated Phosphinates. Application to the Synthesis of Modified Dinucleotides.

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Difluoro-H-phosphinothioate, difluorophosphinate, phosphorus radical, Michaelis-Becker, dinucleotide analogue

ABSTRACT: A simple, two-step procedure to convert α,α–difluorinated–*H*-phosphinic acids into the corresponding *H*-phosphinothioates is described. The usefulness of these species is demonstrated by their transformation into difluorinated phosphinothioyl radicals and their addition onto alkenes. Additionally, sequential treatment of *H*-phosphinothioates by a strong base and a primary alkyl iodide constitutes an alternate route to the formation of the C-P bond. Both methods efficiently deliver difluorinated phosphinothioates. Similar reactions carried out with the fully oxygenated counterparts clearly indicate the superiority of the sulfur-based species and emphasize the crucial role played by sulfur in the construction of the second C-P bond. Oxydation easily transforms the thereby obtained phosphinothioates into the corresponding phosphinates. The whole strategy is applied to the stereoselective preparation of dinucleotide analogues featuring either a difluorophosphinothioyl or a difluorophosphinyl unit linking the two furanosyl rings.

INTRODUCTION

The pivotal role of phosphoric acid derivatives in the chemistry of life has long been established. Thus esters and anhydrides of phosphoric acid have been shown to play a major role in such crucial processes as energy transfer or cell signalling, and are an essential constituent of nucleic acids, among others. Enzymes such as kinases, phosphorylases, phosphatases and nucleases are dedicated to the catalysis of O-P bond formation or cleavage, and the controlled balance of their implication secure related biochemical transformations. Disruption of these balances may of course result in severe malfunctions and diseases; for instance, hyperphosphorylation of tau protein has been linked to neuronal apoptosis and may play a key role in the development of both Alzeimer's disease and Parkinson's disease.[1] Hence, for decades, scientists have devoted efforts to design and prepare potent isosters to phosphoric acid esters. While the first phosphonates (encompassing one C-P bond) and phosphinates (featuring two C-P bonds) were reported more than a century ago, it is not before the early 1980s that α,α-difluorophosphonates were independently reported by Blackburn and McKenna.[2] The beneficial effects of fluorine atoms on both structural and electronic properties of this functional group were later demonstrated[3] and, in the past three decades, difluorophosphonic acids **1** have emerged as very close mimics of phosphoric acid monoesters **2** (Figure 1), resulting in the development of numerous methodologies[4] and the preparation of more potent enzymatic inhibitors, when compared to unfluorinated phosphonates.[5]

Reports of difluorophosphinic acids **3**, however, have been scarce, in spite of both their putative usefulness as close mimics of phosphoric acid diesters **4** and their stability *in vivo* resulting from the two hydrolytically stable carbon-phosphorus bonds.[6] Previouswork from this group led us to introduce α,α-difluoro-*H*-phosphi phosphinic acids **5** and demonstrate their usefulness as in-termediates to prepare a variety of phosphorus-centered functional groups.[6g] Thus, for instance, these species were shown to add onto carbon-carbon double bonds in the presence of a radical initiator to generate difluorinated phosphinic acids **3**, isolated in good yields in the form of their methyl esters (Scheme 1).

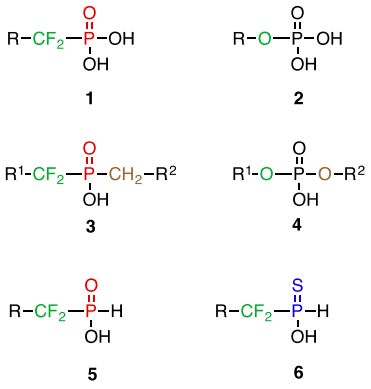
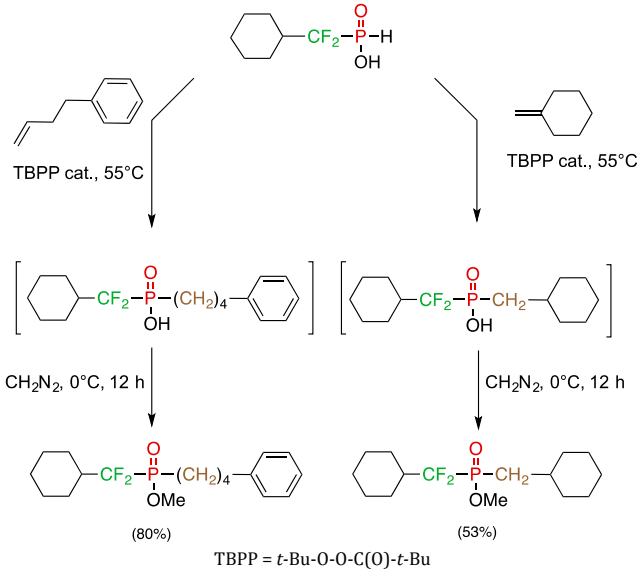


Figure 1. Structures of difluorophosphonic acid **1**, phosphoric acid monoesters **2**, difluorophosphinic acid **3**, phosphoric acid diesters **4**, difluoro-*H*-phosphinic acids **5** and difluoro-*H*-phosphinothioic acids **6**.

Diesterified phosphates in dinucleotides seemed well suited for an application of our hereabove-mentioned methodology.[7] Indeed, the replacement of the phosphoric

acid diester with a difluorinated phosphinyl unit would generate an internucleosidyl link essentially inert towards the action of nucleases. Numerous phosphoryl linkages have been described in literature following the reported possi-ility of interfering with the biosynthesis of proteins at the translational stage and the demonstration of the efficacy of oligonucleotides in the process aiming at the regulation of gene expression.[8] The antisense strategy and, more recently, the approach based on small interference RNAs (*si*RNA) both rely on the use of natural or modified oligonucleotides to force the biochemical machinery to down-regulate gene expression, and have resulted in a number of applications.[9,10,11]

Scheme 1. Previous work: examples of preparation of difluorophosphinic acids 3 from *H*-phosphinic acids 5, and their conversion into methyl esters.[6g]



Applying the above methodology to more sensitive substrates (protected furanoses), however, proved more tedious than anticipated. As shown hereunder, the acidity of *H*-phosphinic acids, the strength of the P–H bond and the emergence of side-reactions led to poor conversions and yields. In this paper, we show that esters of the hitherto unreported α,α-difluorinated *H*-phosphinothioic acids **6** constitute a new class of much more efficient synthetic tools than their fully oxygenated counterparts for the preparation of difluorophosphinates **3**.

RESULTS AND DISCUSSION

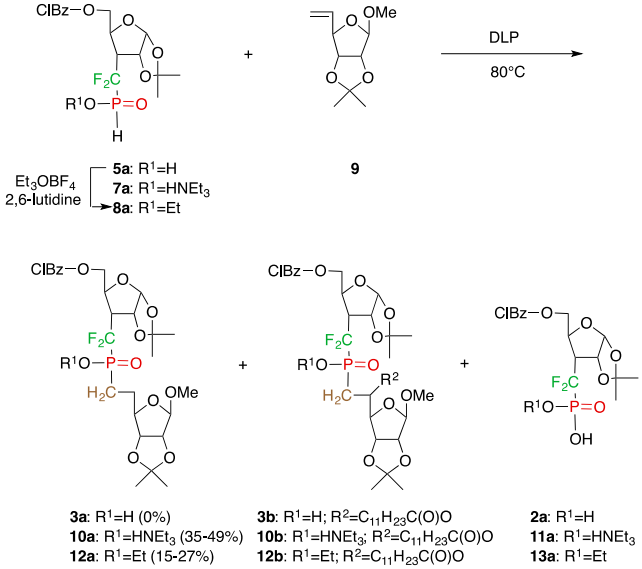
Radical reactions.

Reacting *H*-phosphinic acid **5a**[6g,12] with protected 4-vinylfuranosyl derivative **9**[13] in the presence of a radical initiator (DLP)[14] only yielded intractable mixtures, presumably the result of deleterious interactions between the strongly acidic substrate and the acid sensitive functional groups, and no trace of adduct **3a** could be detected in the crude reaction mixture (Scheme 2A). The use of the less acidic triethylammonium salt **7a** partly solved the problem: the desired adduct **10a** was formed in varying amounts (isolated yields 35-49%), along with side-product **10b** and phosphonate **11a**. The formation of such side-products may be explained by a coupling reaction between the carbon-centered radical adduct and the radical generated by the homolytic cleavage of DLP, and through an oxidative process on either the starting *H*-phosphinyl unit or the phosphorus-centered radical, respectively. A similar and somewhat disappointing result was obtained when furanose **14**[15] was used (Scheme 2B): the crude mixture of triethylammonium salts **10c** and debenzylated side-product **10d** were acidified (aqueous $KHSO_4$ solution) and esterified with a freshly prepared solution of diazomethane in diethyl ether to deliver low isolated yields (14-27%) of the desired phosphinate **15a** and debenzylated methyl ester **15b** in similar amounts (12-21%). This debenzylation process is presumably the result of a sequential intramolecular 1,5 hydrogen abstraction by the initial radical adduct and an oxidative step.

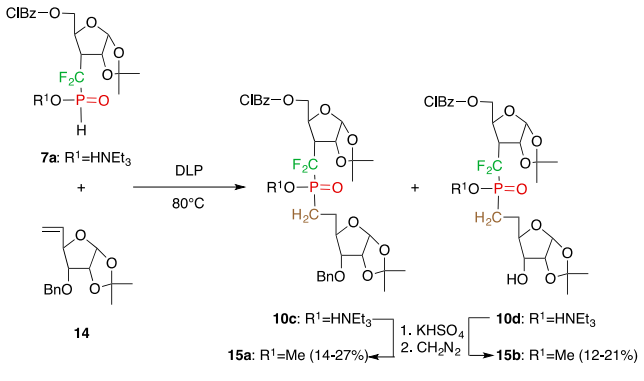
The requirement for a more neutral substrate was met through esterification of *H*-phosphinic acid **5a** with Meerwein's salt: *O*-ethyl-*H*-phosphinate **8a** was obtained in quantitative yield and in a form pure enough to be used in a subsequent reaction (^{1}H, ^{19}F and ^{31}P NMR spectrometries). *O*-Ethyl difluoro-*H*-phosphinates are, however, not very stable on silica: a rapid filtration on a plug of silica using petroleum ether/AcOEt (4/1) as eluent led to a 50% loss of material. They are also of limited stability when kept in the cold and undergo slow but significant oxidation. The reaction of **8a** as radical precursor proved much faster; complete consumption of starting alkene occurred in 10 h with **8a**, and within 24-120 h, depending on the reaction conditions, when using **7a**. This is in line with a more favored SOMO/HOMO interaction between the *O*-ethyl phosphinyl radical derived from **8a** (when compared to the corresponding ammonium salt **7a**) and alkene **9**. However, similar results were obtained: the desired adduct **12a** was produced in low isolated yield (15-27%), partly due to its tedious separation from analogous side-products **12b** and **13a** (Scheme 2A).

Scheme 2. Radical addition reactions between 5a, 7a or 8a and alkenes 9 or 14.

A. Reaction with alkene **9** (DLP = DiLauroylPeroxide).

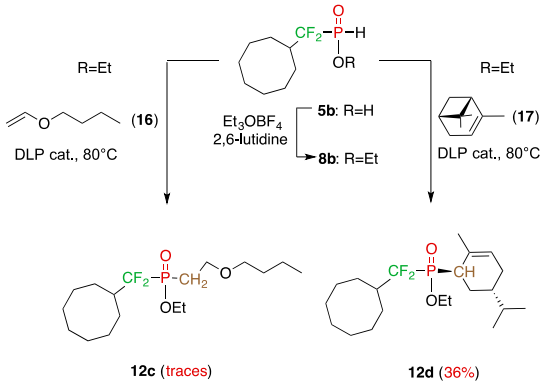


B. Reaction with alkene **14** (DLP = DiLauroylPeroxide).



Results along the same line were obtained when ethyl *H*-phoshinate **8b** (similarly obtained by treatment of the corresponding *H*-phosphinic acid **5b** with Meerwein's salt and 2,6-lutidine) was reacted with model alkenes **16** or **17** (Scheme 3), thus indicating that the low yields, in the case of substrate **8b**, were not only the result of competitive functional group interactions under the reactions conditions. Quite clearly, the more nucleophilic α-alkoxyl radical generated by the addition of the phosphinyl radical onto butyl vinyl ether (**16**) makes the chain reaction even less efficient than with alkene **17**, the result of a slower hydrogen abstraction on *H*-phosphinate **8b** by the radical adduct: interaction between the HOMO of the P-H σ-bond and the SOMO of the radical-adduct derived from **16** will be less favoured than the analogous one involving the lower-energy SOMO of the radical-adduct derived from **17**.

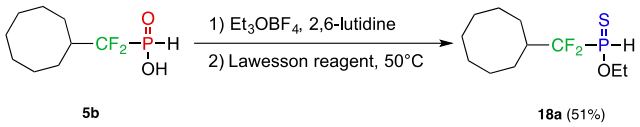
Scheme 3. Radical addition reaction between 8b and model alkenes 16 and 17.



The low yields and the formation of the above side-products are clearly indicative of too strong a P-H bond in the phosphorus-centered radical precursors, inducing coupling reactions or other, competitive hydrogen abstraction. The documented higher lability of the P-H bond in thiophosphites[16], when compared to phosphites, led us to consider the ethyl esters **18** of α,α-difluoro-*H*-phosphinothioic acids **6** as putatively more efficient radical precursors to generate the second C-P bond.[17]

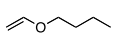
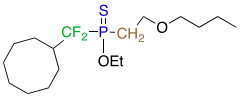
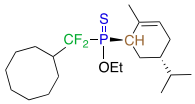
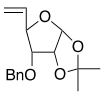
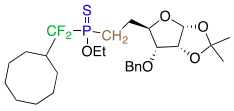
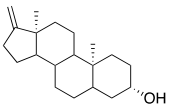
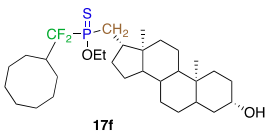
There is no report in literature on either difluorinated *H*-phosphinothioic acids **6** or their esters. Thus treatment of *H*-phosphinic acid **5b** with triethyloxonium tetrafluoroborate and 2,6-lutidine, followed by heating the resultant crude *O*-ethyl-*H*-phosphinate **8b** with Lawesson reagent[18], work-up and purification allowed the isolation of the corresponding *O*-ethyl cyclooctyldifluoromethyl-*H*-phosphinothioate (**18a**) in an unoptimized 51% overall yield (Scheme 4). All the *O*-ethyl difluorinated *H*-phosphinothioates described in this paper were found to be much more stable than the corresponding *O*-ethyl difluoro-*H*-phosphinates, and could be kept for months in the cold and under argon. They displayed a typical chemical shift around 65 ppm in ^{31}P NMR spectra with $^{1}J_{P\text{-}H}$ value around 600 Hz and $^{2}J_{P\text{-}F}$ value around 95 Hz (see Experimental Section).

Scheme 4. Transformation of *H*-phosphinic acid 5b into diethyl *H*-phosphinothioate 18a.



The efficacy of difluorinated *H*-phosphinothioate in the radical based construction of the C-P bond was demonstrated by reacting *H*-phosphinothioate **18a** with model alkenes **14**, **16**, **17** and **19** (Table 1). While *H*-phosphinate **8b** failed to give the desired adducts **12c** and **12d** in practical yields (see Scheme 3), *H*-phosphinothioate **18a** cleanly delivered the expected products **20a**-**20d** in good to excellent yields. Noteworthy is the comparison between the results depicted in Scheme 3 and entries 1 and 2 of Table 1, which illustrates the clear superiority of *H*-phosphinothioate over its fully oxygenated counterpart in the construction of the second carbon phosphorus bond.

Table 1. Radical addition reaction between cylooctyl-CF_2-P(S)(OEt)H (18a) and alkenes 14, 16, 17 and 19.[a]

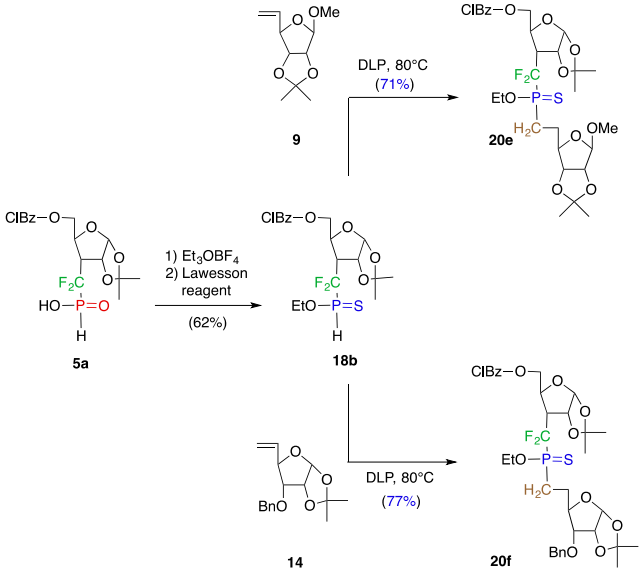
entry	alkene	product	yld[b]
1	 **16**	 **20a**	96
2	 **17**	 **20b**	80[c]
3	 **14**	 **20c**	60
4	 **19**	 **20d**	81

a: Reaction carried out at 80 °C in the presence of 0.2 equivalent of dilauroyl peroxide (DLP) for 5 h. *b*: Isolated yields as 1:1 mixtures of epimers at phosphorus. *c*: Diastereomeric ratio of 1.25/1 at phosphorus (see text).

This strategy was next applied to *H*-phosphinic acid **5a**. Similar treatment with triethyloxonium tetrafluoroborate and 2,6-lutidine, followed by heating the resultant crude *O*-ethyl-*H*-phosphinate **8a** with Lawesson reagent, work-up and purification delivered the analogous *H*-phosphinothioate **18b** in a satisfactory 62% overall yield (Scheme 5).

Interaction of the latter compound in the presence of DLP with either alkenylfuranose **9** or **14** induced a much faster transformation, the reaction being complete in 2 to 4 hours. Chromatography and elution led to the isolation of expected adducts **20e** or **20f** in 71 and 77% yields, respectively. *As important is the fact that analysis indicated this time the crude reaction mixtures to be nearly devoid of any byproducts*. Thus, the more labile P-H bond in *H*-phosphinothioate
18b resulted in a much faster hydrogen abstraction, thereby significantly reducing the formation of byproducts of the type **10b**, **10d**, **11a**, **12b** or **13a** (see Scheme 2).

Scheme 5. Preparation of *H*-phosphinothioate 18b and radical addition reaction of 18b onto alkenes 9 and 14.



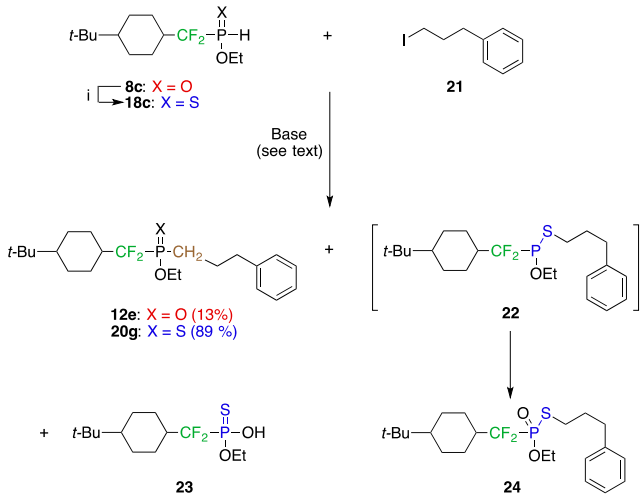
Michaelis-Becker reaction.

The established acidity of the P-H bond in *H*-phosphinates and *H*-phosphinothioates[19] led us to also consider the formation of the second C-P bond by conducting a nucleophilic substitution reaction under basic conditions (Michaelis-Becker reaction).[20] The transformation was found to strongly depend on the reaction conditions. Thus, for instance, interaction of a THF solution of fluorinated *H*-phosphinothioate **18c** (prepared by treatment of **8c** with Lawesson reagent) and 1-iodo-3-phenylpropane **21** in the presence of potassium *tert*-butanolate generated a mixture containing the desired difluorophosphinothioate **20g** (32%), the product resulting from a competing *S*-alkylation process **22** (isolated as its oxidized phosphonothioate **23** in 45% yield) and phosphonothioic acid **24** (23%)[21] (Scheme 6). Screening a number of other basic conditions led to the identification of powdered potassium hydroxide and triethylbenzyl ammonium chloride (TEBAC) in methylene chloride as the best option: in this medium, the desired phosphinothioate **20g** was selectively produced and could be isolated in 89% yield. Similar reactions with either 3-phenylpropyl bromide, triflate or chloride under identical conditions were found to be less efficient and yielded difluorophosphinate **20g** in 23%, 12% and less than 1%, respectively. *Especially noteworthy is the fact that, under identical conditions, interaction between the corresponding H-phosphinate **8c** and iodide **21** delivered the analogous, fully oxygenated counterpart **12e** in only 13 % yield, thus indicative of the reactive superiority of H-phosphinothioates.*

A nearly identical result was obtained from the alkylation of difluoro-*H*-phosphinothioate **18b** with **21** under the same conditions (Scheme 7): phosphinothioate **20h** could be isolated in 84% yield. We were thus delighted that similar selectivity and efficiency were obtained when these conditions were applied to furanosyl-3'-difluoro-*H*-phosphinothioate **18b** and furanosyl iodide **25**[22]: the desired phosphinothioate **20f** was formed and isolated in an excellent 86% yield.

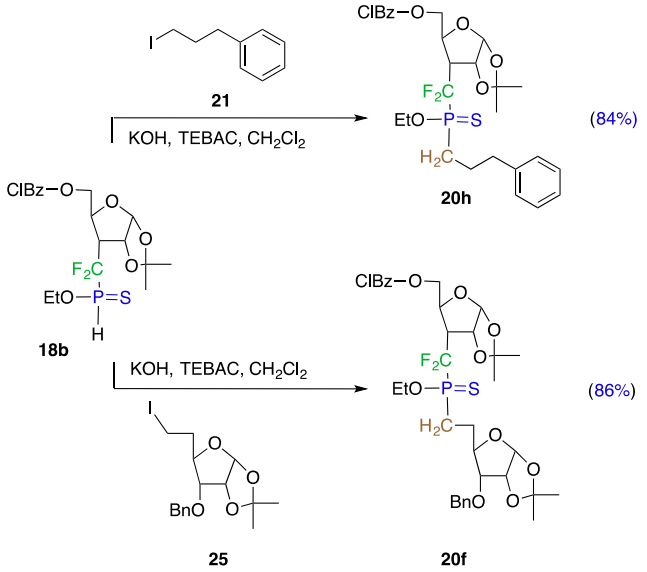
The preparation of dinucleotide analogue **12h** was next undertaken (Scheme 8). Fluorinated phosphinothioate **20f** was sequentially oxidized with *m*-chloroperbenzoic acid into its P=O counterpart **12f** (88%)[23] and treated with acetic anhydride in acetic acid to stereoselectively deliver phosphinate **12g** (77%). The same compound could also be obtained by inverting this sequence of reactions, thus producing first phosphinothioate **20i**, then oxidizing **20i** into **12g**. However, all attempts to introduce the two thymines on the anomeric positions resulted in intractable mixtures.[24]

Scheme 6. Michaelis-Becker reaction between *H*-phosphinate 8c or *H*-phosphinothioate 18c with iodide 21.



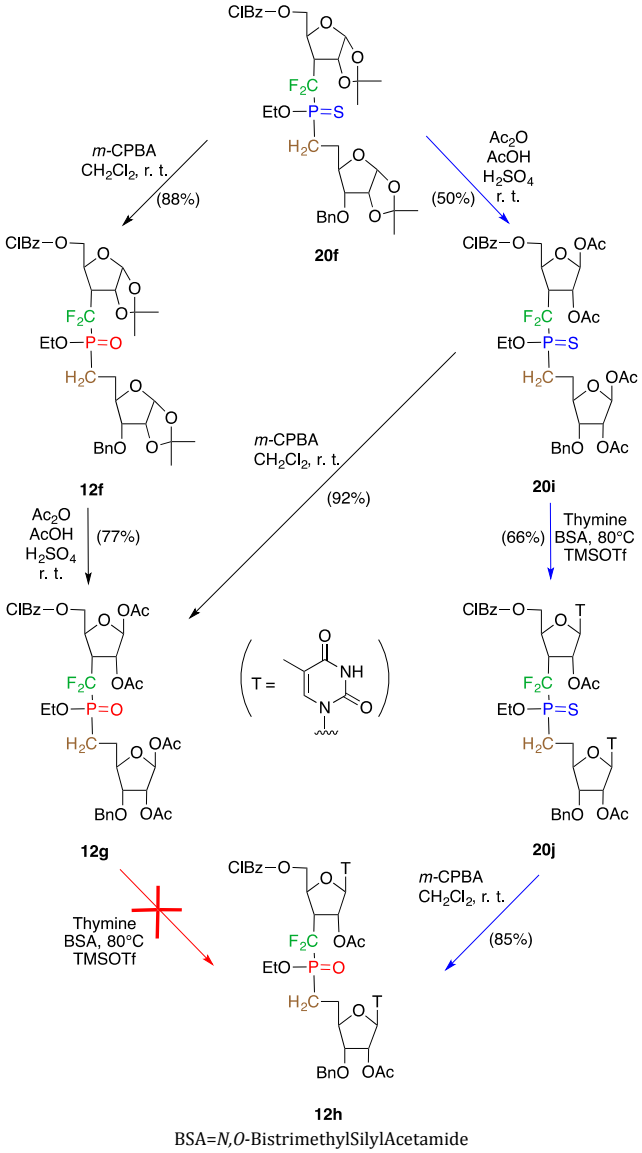
i: Lawesson reagent, toluene, 85°C (85%).

Scheme 7. Alkylation of *H*-phosphinothioate 18b under basic conditions.



Reversal of the whole reaction sequence eventually allowed us to isolate dinucleotide analogue **12h** in good overall yield (Scheme 8). Thus, treatment of phosphinothioate **20f** with acetic anhydride in acetic acid led to the replacement of both acetonide units with acetate groups and stereoselectively delivered phosphinothioate **20i**, albeit in moderate yield (50%). Introduction of both thymines under the Vorbrüggen conditions cleanly gave dinucleotide analogue **20j** (66%) with complete diastereoselectivity. Phosphinothioate **20j** smoothly underwent the oxidative process: the desired difluorinated phosphinate **12h** was isolated in 85% yield.

Scheme 8. Transformation of difluorophosphinothioate 20f into target compound 12h.



Stereochemical issues at phosphorus.

Ethyl *H*-difluorophosphinates **8**, difluorophosphinates **12**, *H*-difluorophosphinothioates **18**, and difluorophosphinothioates **20** are all featuring a chiral phosphorus atom. No diastereoselectivity was of course observed during the esterification reaction of *H*-phosphinic acids **5** – including **5a** featuring remote chiral centers -, and the esters **8** were isolated as 1:1 mixtures of diastereomers. Likewise, treatment with Lawesson reagent yielded *H*-phosphinothioates **18** as 1:1 mixtures of diastereomers. Phosphonyl and phosphinyl radicals, as well as their thio derivatives, have all been shown to possess a pyramidal structure, and to add onto alkenes with complete retention of configuration at phosphorus.[25] The chain reactions involving difluorinated phosphinyl and phosphinothioyl radicals thus and expectedly delivered 1:1 mixtures of diastereomeric adducts **12** and **20**, except in the case of (+)-α-pinene, which yielded a 1.25:1 mixtures of diastereomers (**12d** and **20b**)(based on ^{19}F and ^{31}P NMR spectra of the crude reaction mixtures). At this time, the reason for this slight diastereomeric excess is unclear and will need further

investigation; the nature of the doubly bonded chalcogen does not however seem to influence it, as the diastereoselectivity was identical for **12d** and **20b**. Likewise, Michaelis-Becker reactions carried out from 1:1 diastereomeric mixture of *H*-difluorophosphinothioates **18b** and **18c** delivered 1:1 mixtures of difluorophosphinothioates **20f**, **20g** or **20h**.

With regards to the modified dinucleotides **12h**, incorporation of these analogues into modified oligonucleotides will ultimately be followed by a full deprotection of the fluorinated phosphinyl units; prototropy in the resultant α,α-difluorophosphinic acids will suppress chirality at phosphorus. By comparison, deprotection of the corresponding phosphinothioyl unit **20j** will generate a 1:1 diastereomeric mixture of phosphinothioic acid. The modified antisense oligonucleotides marketed to date all feature phosphorothioyl units in place of the phosphoryl links; these phosphorothioyl units are present as 1:1 epimers at phosphorus. [26]

CONCLUSION

O-Ethyl α,α-difluoro-*H*-phosphinothioates are easily prepared in good overall yield from the corresponding *H*-phosphinic acids *via* a two-step sequence of reactions. This hitherto unreported class of compounds proves to be more stable than the corresponding *H*-phosphinates and can be kept in the cold and under inert atmosphere for an extended period of time. In the presence of a radical initiator, these species generate difluorophosphinothioyl radicals which add onto alkenes to deliver difluorophosphinothioates in good to high yields. The higher lability of the P-H bond in fluorinated *H*-phosphinothioates, when compared to their fully oxygenated counterparts, results in much cleaner reactions nearly devoid of any competitive process. In addition, treatment of difluorinated *H*-phosphinothioates with a strong base is shown to provide a nucleophilic difluorophosphinothioyl species that will generate analogous phosphinothioates in high yields, when reacted with primary iodides. Here again, the difluorophosphinothioyl anion proves to be a much more efficient species than the corresponding phosphinyl anion. Both these radical and ionic approaches are successfully applied to the preparation of an analogue of dinucleotide featuring a phosphinothioyl moiety linking positions C-3' and C-5' of the ribofuranosyl units. Easy oxidation of the P=S into a P=O bond makes of difluorinated *H*-phosphinothioates useful synthetic tools for the preparation of difluorinated phosphinates. Additionnally, the difluorinated phosphinothioyl unit constitutes a potentially novel mimic of diesters of phosphoric acid.[27]

EXPERIMENTAL SECTION

General Information

All reactions were carried out using dried glassware and magnetic stirring under an atmosphere of argon. All reagents were obtained from commercially available sources and used without further purification. DLP and TBPP refer to DiLauroyl Peroxide and Tert-Butyl PeroxyPivalate, respectively, and BSA to *N,O*-BistrimethylSilylAcetamide. Anhydrous reaction solvents were obtained by distillation over either calcium hydride (dichloromethane, 1,2-dichloroethane, acetonitrile, triethylamine, diisopropylethylamine, dimethylsulfoxide, toluene) or sodium/benzophenone (tetrahydrofuran, ether). Unless otherwise indicated, all drying of organic extracts were carried out over magnesium sulfate and all chromatographic separations were performed on silica (40-63 μm or 60-200 μm) from SdS. Thin-layer chromatography (TLC) were carried out on Merck DC Kieselgel 60 F-254 aluminium sheets. Compounds were visualized by one or both of the two following methods: (1) illumination with a short wavelength UV lamp (λ = 254 nm) and/or (2) staining with phosphomolybdic acid or $KMnO_4$ staining solution followed by heating. Unless otherwise stated, ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), ^{19}F NMR (282 MHz) and ^{31}P NMR (121 MHz) spectra were recorded in deuterated chloroform on a Bruker Avance 300 spectrometer relative to $(CH_3)_4Si$, $CDCl_3$, $CFCl_3$ and 85% H_3PO_4, respectively. Chemical Shifts are expressed in parts per million (ppm) and coupling constants in Hertz (Hz). HSQC and COSY experiments were run on the same apparatus to confirm the reported assignments. Spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), m (multiplet), br (broad signal). In the case of dinucleotide analogues, the carbon atoms in the upper furanose are numbered from I-1' to I-5', and those of the lower furanose, from II-1' to II-5', while the atoms of the thymines are numbered from 1 (trisubstituted nitrogen) to 6 (CH). Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR Spectrum 100 spectrometer. Elemental analyses were carried out with a Flash 2000 Organic Elemental Analyzer (Thermo Scientific). Melting points were recorded on a Kofler bench device and are uncorrected. Optical rotations were measured on a Perkin-Elmer polarimeter 341. Low resolution mass spectra using electron impact (EI, 70 eV) and chemical ionization (CI) techniques were recorded on a Shimadzu GCMS-QP2010 apparatus (direct introduction). Low resolution mass spectra using electrospray (ESI) and atmospheric pressure chemical ionization (APCI) techniques were recorded on a Finnigan LCQ Advantage MAX (ion trap) apparatus. High resolution mass spectra were recorded on a LCT premier XE benchtop orthogonal acceleration time-of-flight (oa-TOF) mass spectrometer (Water Micromass); HRMS of chlorine containing compounds are reported for isotope 35.

5-*O*-(4-Chlorobenzoyl)-3-(*H*-hydroxylphosphino)-difluoromethyl-1,2-*O*-isopropylidene-α-D-xylofuranose (5a). To a stirring solution of the requisite difluoroalkene[6g] (437 mg, 1.21 mmol) and $NaOP(O)H_2.H_2O$ (440 mg, 4.11 mmol) in methanol (10 mL) under argon was added lauroyl peroxide (472 mg, 1.15 mmol). The resultant solution was heated at 80°C for 3.5h, after which period of time ^{19}F NMR spectrometry analysis indicated a full conversion. The solution was cooled down and evaporated under reduced pressure. Water was added to the residue, and the mixture was washed thrice with EtOAc (3x20 mL). The organic layers were separated and the aqueous layer was lyophilized to give a crude white solid which was dissolved in 5% $KHSO_4$ aq. solution (30 mL). The solution was extracted with EtOAc (2x80 mL, then 40 mL), and the combined organic extracts were first washed with brine (60 mL), then dried, and finally concentrated to give compound **5a** 428 mg (83%) as white foam. **^{1}H NMR** δ 1.32 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 2.73-2.91 (m, 1H, 3-H), 4.32 (dd, 1H, 5a-H,

$^2J_{5a,5b}$ = 12.6, $^3J_{5a,4}$ = 4.8), 4.73 (d, 1H, 5b-H, $^2J_{5b,5a}$ = 12.6), 4.89 (t, 1H, 4-H, ^3J = 4.2), 4.96 (dd, 1H, 2-H, $^3J_{2,1}$ = 3.3, $^3J_{2,3}$ = 9.9), 5.90 (d, 1H, 1-H, $^3J_{1,2}$ = 3.6), 7.19 (dd, 1H, P-H, $^1J_{H-P}$ = 643.8, $^3J_{H-F}$ = 6.3), 7.37 (d, 2H, Bz, ^3J = 8.4), 7.93 (d, 2H, Bz, ^3J = 8.4). **^{13}C{^{1}H} NMR** δ 26.2, 26.4 (CH_3), 50.5 (m, C_3), 64.5, 74.4, 79.1, 105.0 (C_1), 113.3 ($\underline{C}(CH_3)_2$), 128.0, 128.8 (2C), 131.3 (2C), 139.8 (Bz), 165.6 (C=O), (CF_2 unobserved due to multiplicity). **^{19}F{^{1}H} NMR** δ -114.1 (dd, 1F, $^2J_{F-F}$ = 324.5, $^2J_{F-P}$ = 101.4), -105.8 (dd, 1F, $^2J_{F-F}$ = 324.5, $^2J_{F-P}$ = 110.7). **^{31}P{^{1}H} NMR** δ 21.8 (dd, $^2J_{P-F}$ = 101.4 and 110.7). **^{31}P NMR** δ 21.8 (dm, $^1J_{P-H}$ = 646.9). **HRMS** (ESI-TOF) m/z: Calcd for $C_{16}H_{17}{}^{35}ClF_2O_7P$ $(M-H)^-$: 425.0374; Found: 425.0373.

5-*O*-(4-Chlorobenzoyl)-3-(*H*-hydroxylphosphino)-difluoromethyl-1,2-*O*-*iso*propylidene-α-D-xylofuranose ammonium salt (7a).[6g] The above procedure was followed to give the crude white solid obtained by lyophilization, which was dissolved in a 1.0 M aqueous triethylammonium carbonate solution (40 mL). The solution was extracted thrice with EtOAc (2x80 mL, then 40 mL), and the combined organic extracts were first dried, then concentrated to give compound **7a** (558 mg, 87%) as a white foam. **^{1}H NMR** δ 1.23 (t, 9H, $N(CH_2C\underline{H}_3)_3$, ^3J = 7.2), 1.23 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.63-2.80 (m, 1H, H_3), 2.97 (q, 6H, ^3J = 7.2, $N(C\underline{H}_2CH_3)_3$), 4.15 (dd, 1H, H_{5a}, $^3J_{5a-5b}$ = 12.3, $^3J_{5a-4}$ = 5.4), 4.70 (d, 1H, H_{5b}, $^3J_{5b-5a}$ = 12.3), 4.78 (dd, 1H, H_4, $^3J_{4-3}$ = 10.2, $^3J_{4-5a}$ = 4.8), 5.01 (dd, 1H, H_2, $^3J_{2-1}$ = 3.6, $^3J_{2,3}$ = 4.2), 5.77 (d, 1H, H_1, $^3J_{1-2}$ = 3.6), 7.10 (dd, 1H, P-H, $^1J_{H-P}$ = 555.6, $^3J_{H-F}$ = 6.9), 7.31 (d, 2H, Bz, ^3J = 8.4), 7.90 (d, 2H, Bz, ^3J = 8.4). **^{19}F{^{1}H} NMR** δ -115.0 (ddd, 1F, $^2J_{F-F}$ = 299.9, $^2J_{F-P}$ = 90.7, $^3J_{F-H}$ = 21.9), -111.3 (ddt, 1F, $^2J_{F-F}$ = 299.3, $^2J_{F-P}$ = 84.7, $^3J_{F-H}$ = 8.5). **^{31}P{^{1}H} NMR** δ 9.1 (dt, $^1J_{P-H}$ = 556.5, $^2J_{P-F}$ = 86.3, 89.9).

General procedure for the preparation of ethyl *H*-phosphinates.

An anhydrous methylene chloride (4 mL) solution of the requisite acid **5** (1 mmol) was added to a stirring, anhydrous methylene chloride (16 mL) solution of triethyloxonium tetrafluoroborate (354 mg, 0.95 mmol) at r. t. under argon. The reaction mixture was stirred at r.t. for 2 h and 2,6-lutidine (130 µL, 1.1 mmol) was then added. Stirring was continued for another 30 min, after which period of time the mixture was diluted with CH_2Cl_2 (10 mL) and sequentially washed twice with a 0.5 M solution of citric acid (2x5mL) then brine (5 mL). The organic layer was dried and filtered, and the solvents were removed under reduced pressure to give the crude ester as a 1:1 mixture of diastereomers pure at 95%. These compounds are somewhat unstable intermediates and were usually engaged without further purification in either the addition reaction or the thionylation step. Purification can be achieved by rapid chromatography on silica despite a significant degradation of the *H*-phosphinates into the corresponding phosphonic acid monoester *via* an oxidative process.

5-*O*-(4-Chlorobenzoyl)-3-(*H*-monoethylphosphino)-difluoromethyl-1,2-*O*-isopropylidene-α-D-xylofuranose (8a). The crude ester **8a** was obtained as a 1:1 mixture of diastereomers A:B, used as such. **^{1}H NMR** δ 1.13-1.20 (m, 6H, 2x0.5xCH_3 and $C\underline{H}_3$-CH_2-O), 1.51 and 1.63 (2s, 3H, 2x0.5xCH_3), 2.79-2.86 (m, 1H, H_3), 4.22-4.39 (m, 3H, H_{5a} and CH_3-$C\underline{H}_2$), 4.69-4.33 (m, 2H, H_{5b} and H_4), 5.07 and 5.19 (2m, 1H, H_2), 5.89 and 5.90 (2d, 1H, J_{1-2} = 3.6, H_1), 7.14 and 7.18 (2dm, 1H, $^1J_{P-H}$ = 636 and 624, P-$\underline{H}$), 7.37 (d, 2H, J = 8.1, H_{Bz}), 7.93 (d, 2H, J = 8.1, H_{Bz}). **^{19}F{^{1}H} NMR** δ diastereomer A: -112.9 (dd, 1F, $^2J_{F-F}$ = 304.0, $^2J_{F-P}$ = 114.8, $^3J_{F-H}$ = 21.1), -107.2 (dt, 1F, $^2J_{F-F}$ = 306.1, $^2J_{F-P}$ = 84.3, $^3J_{F-H}$ = 12.0); diastereomer B: -112.4 (dt, 1F, $^2J_{F-F}$ = 324.3, $^2J_{F-P}$ = 81.8, $^3J_{F-H}$ = 14.1), -104.8 (dd, 1F, $^2J_{F-F}$ = 326, $^2J_{F-P}$ = 112.8, $^3J_{F-H}$ = 9.5). **^{31}P{^{1}H} NMR** δ diastereomer A: 19.9 (dd, $^2J_{F-P}$ = 114.7, 84.3); diastereomer B: 21.5 (dd, $^2J_{F,P}$ = 112.7, 82.3).

Ethyl (cyclooctyldifluoromethyl)phosphinate (8b). Following the general procedure, the reaction was carried out starting from 1.45 g (7.63 mmol) of Meerwein's salt in CH_2Cl_2 (50 mL), a solution of (cyclooctyldifluoromethyl)phosphinic acid[6g] (1.15 g, 5.08 mmol) in CH_2Cl_2 (15 mL) and 1.20 mL (10.2 mmol) of 2,6-lutidine. The crude material (1.13 g) obtained after the above workup was used without further purification. **^{1}H NMR** δ 1.39 (t, 3H, J = 7.1), 1.64-1.40 (m, 10H), 1.81-1.65 (m, 2H), 1.97-1.83 (m, 2H), 2.49-2.19 (m, 1H), 4.36-4.18 (m, 2H), 7.08 (dd, 1H, $^1J_{H-P}$ = 579.3 and $^3J_{H-Fa}$ = 6.3). **^{31}P{^{1}H} NMR** δ 21.7 (dd, $^2J_{P-F1}$ = 128.2, $^2J_{P-F2}$ = 108.7). **^{19}F{^{1}H} NMR** δ -116.2 (dddd, 1F, $^2J_{F2-F1}$ = 296.8, $^2J_{F2-P}$ = 108.7, $^3J_{F2-H}$ = 15.2 and $J_{F2-(P)H}$ = 6.2), -118.5 (dddd, apparent ddd, 1F, $^2J_{F1-F2}$ = 296.8, $^2J_{F1-P}$ = 128.2, $^3J_{F1-H}$ = 21.5).

Ethyl (4-*tert*-butylcyclohexyl)-difluoromethyl-*H*-phosphinate (8c). Following the general procedure, ester **8c** was prepared from 79 mg (0.415 mmol) of Meerwein's salt, 70.5 mg (0.277 mmol) of the requisite *H*-phosphinic acid[6g] and 65 µL (0.554 mmol) of 2,6-lutidine. Obtained as a colorless oil and as 4:1 mixture of inseparable diastereomers (67 mg, 85 %). **^{1}H NMR** δ major diastereomer: 0.84 (s, 9H, $(C\underline{H}_3)_3C$), 1.01-1.04 (m, 2H), 1.25-1.37 (m, 3H), 1.42 (t, 3H, $^3J_{H-H}$ = 6, CH_2-$C\underline{H}_3$), 1.87-2.29 (m, 5H), 4.39 (dq, 2H, $^3J_{H-P}$ = 9, $^3J_{H-H}$ = 6, $C\underline{H}_2$-CH_3), 7.09 (dt, 1H, $^1J_{H-P}$ = 579.1, J_{H-H} = 2.9, $\underline{H}$-P).**^{19}F{^{1}H} NMR** δ major diastereoisomer: -120.0 (dd, 1F, $^2J_{F-F}$ = 265, $^2J_{F-P}$ = 118), -119.4 (dd, 1F, $^2J_{F-F}$ = 265, $^2J_{F-P}$ = 118); minor diastereoisomer: -112.6 (dd, 1F, $^2J_{F-F}$ = 299, $^2J_{F-P}$ = 116), -111.5 (dd, 1F, $^2J_{F-F}$ = 299, $^2J_{F-P}$ = 117). **^{31}P{^{1}H} NMR** δ major diastereoisomer: 21.7 (dt, $^1J_{P-H}$ = 578, $^2J_{P-F}$ = 118); minor diastereoisomer: 22.0 (ddd, $^1J_{P-H}$ = 577, $^2J_{P-F}$ = 117, $^2J_{P-F}$ = 116). **^{13}C{^{1}H} NMR** δ (major diastereomer) 16.1 (CH_2-$\underline{C}H_3$), 23.9-24.8 ($\underline{C}H_2$-CH-CF_2), 26.1 (*t*-Bu-CH-$\underline{C}H_2$), 27.3 (3x$\underline{C}H_3$), 32.3 (CH_3-$\underline{C}$), 41.6 (td, $^1J_{C-F}$ = 19, $^2J_{C-P}$= 14, $\underline{C}$H-CF_2), 47.3 ($\underline{C}$H-*t*-Bu), 63.9 (d, $^2J_{C-P}$ = 7, $C\underline{H}_2$-CH_3), 121.4 (td, $^1J_{C-F}$ = 263, $^1J_{C-P}$ = 143, $\underline{C}F_2$). **MS** (ESI^+, CH_3CN/H_2O) m/z (%) found: 253.27 $[M-(CH_2-CH_3)]^-$.

5,6-Dideoxy-3-*O*-Benzyl-1,2-*O*-*iso*propylidene-α-D-xylofuranose (14). To a solution of oxalyl chloride (0.38 mL, 4.49 mmol) in dry CH_2Cl_2 (8 mL) was added a solution of DMSO (0.33 mL, 4.65 mmol) in CH_2Cl_2 (1 mL) at -78 °C under inert atmosphere. After 10 min stirring at -78 °C, a solution of the requisite alcohol[28] (1.04 g, 3.71 mmol) in CH_2Cl_2 (6 mL) was added, and the reaction mixture was kept stirring at -78 °C for 15 min. Then DIPEA (3.0 mL, 18.15 mmol) was added dropwise to the reaction and stirring was continued at -78 °C for an additional 30 min. The mixture was then warmed up to room temperature over 2.5 h and quenched with a saturated $NaHCO_3$ aqueous solution (15 mL). Extraction with EtOAc (3x30 mL). The combined organic layers were dried, filtered, and the filtrate was concentrated to afford the corresponding crude aldehyde.

KO^tBu (20 wt% in THF, 4.2 mL, 6.95 mmol) was added to a slurry of Ph_3PCH_2Br (2.76 g, 7.57 mmol) in anhydrous THF

(15 mL) (the reaction mixture turned yellow immediately). After stirring at room temperature for 2 hours, a solution of the crude aldehyde prepared as above in THF (6 mL) was added dropwise, and the resultant reaction mixture was stirred at room temperature for an additional 5.5 h. Quenching with saturated $NaHCO_3$ aqueous solution, extraction with EtOAc, drying of the combined organic layers, filtration and evaporation of the volatiles gave a crude residue which was purified by chromatography and eluted with cyclohexane/ethyl acetate (30:1 to 20:1 gradient) to afford compound **14** (817 mg, 80%) as a colorless syrup. **^{1}H NMR** δ 1.36 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 3.51 (dd, 1H, $^3J_{3,4}$ = 9.0, $^3J_{2,3}$ = 4.2, H_3), 4.47 (dd, 1H, $^3J_{4,5}$ = 6.9, $^3J_{4,3}$ = 8.7, H_4), 4.56 (t, 1H, ^3J = 3.9, H_2), 4.62 (d, 1H, AB syst, J = 12.3, Bn-C$\underline{H}_2$-), 4.75 (d, 1H, AB syst, J = 12.3, Bn-C$\underline{H}_2$-), 5.27 (ddd, dt apparent, 1H, $^3J_{6a,5}$ = 10.2, $^2J_{6a,6b}$ = 1.2, $^3J_{6a,4}$ = 1.2, H_{6a}), 5.46 (ddd, dt apparent, 1H, $^3J_{6b,5}$ = 17.1, $^2J_{6b,6a}$ = 1.2, $^3J_{6b,4}$ = 1.2, H_{6b}), 5.74 (d, 1H, $^3J_{1,2}$ = 3.6, H_1), 5.78 (ddd, 1H, $^3J_{5,6a}$ = 10.2, $^3J_{5,6b}$ = 17.1, $^3J_{5,4}$ = 3.6, H_5), 7.35 (m, 5H, $\underline{Ph}$-CH_2).**^{13}C{^{1}H} NMR** δ 26.8, 27.0, 72.5, 77.9, 79.4, 82.0, 104.0, 113.2, 119.2, 128.2, 128.3 (2C), 128.7 (2C), 135.1, 137.8. **$[\alpha]_{20}^{D}$** = + 65.6 (C = 0.44, $CHCl_3$). **Anal.** Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.42; H, 7.64. **MS** (CI, NH_3) found $(M+NH_4)^+$: 294.

3-*O*-Benzyl-5'8-dideoxy-8-iodo-1,2-*O-iso*propylidene-α –*D-ribo*hexofuranose (25). The reaction was carried out in the dark. To a solution of $Cp_2Zr(H)Cl$ (575mg, 2.17 mmol) in dry methylene chloride (6 mL) under argon, was added a solution of alkene **14** (500 mg, 1.81 mmol) in anhydrous methylene chloride (6 mL) and the resultant mixture was stirred until complete dissolution.[29] Iodine (551 mg, 2.17 mmol) and DIPEA (291 µL, 2.17 mmol) were then sequentially added and stirring was continued for 2 additional hours. The mixture was quenched with a 0,1 M aqueous solution of HCl (10 mL) and the organic layer was separated and washed three time with water. Drying of the organic layer, filtration of the solid and removal of the volatiles under reduced pressure left a crude residue which was purified by chromatography and eluted with cyclohexane/EtOAc (15:1) to deliver iodocompound **25** as a colorless oil (592 mg, 81 %). **^{1}H NMR** δ 1.25 and 1.50 (2s, 6H, (C$\underline{H}_3$)$_3$C), 1.79-1.92 (m, 1H, C$\underline{H}_2$CH$_2$I), 2.07-2.20 (m, 1H, C$\underline{H}_2$-CH$_2$I), 3.02-3.16 (m, 2H, C$\underline{H}_2$-I), 3.32 (dd, $^3J_{H\text{-}H}$ = 8.9, $^3J_{H\text{-}H}$ = 4.2, 1H, H_3), 3.95 (td, $^3J_{H\text{-}H}$ = 8.7, $^3J_{H\text{-}H}$ = 3.3, 1H, H_4), 4.41-4.48 (m, 2H, H_2 and C$\underline{H}_2$Ph), 4.68 (d, 1H, AB $^3J_{AB}$ = 12.0, C$\underline{H}_2$Ph), 5.59 (d, $^3J_{H\text{-}H}$ = 3.8, 1H, H_1), 7.27 (m, 5H, H_{Ph}). **^{13}C{^{1}H} NMR** δ 0.0 (CH_2-I), 26.0 and 26.2 (2xCH_3), 36.3 (C_5), 71.5 ($\underline{C}H_2$-Ph), 76.5 (C_4), 77.3 (C_2, overlap with solvent signal and deduced from DEPT experiment), 80.4 (C_3), 103.3 (C_1), 112.4 (CH_3-$\underline{C}$), 127.4 (2C), 127.6, 128.0 (2C), 136.8. **Anal**. Calcd. for $C_{16}H_{21}IO_4$: C, 47.54; H, 5.24. Found: C, 47.63; H, 5.26. **IR** ν_{max}/cm^{-1}: 2935-2810 (C-H_{ar}), 758 (C-I).

***O*-Ethyl (cyclooctyldifluoromethyl)phosphinothioate (18a).** To a solution of ethyl (cyclooctyldifluoromethyl)phosphinate **8b** previously obtained (1.13 g, 4.44 mmol) in toluene (45 ml) was added Lawesson reagent (1.11 g, 2.67 mmol) and the reaction was heated at 50 °C. The reaction was monitored by ^{31}P NMR analysis and after 1 h the reaction was allowed to cool down to r. t. before being concentrated under reduced pressure. The crude residue was purified by chromatography and elution with petroleum ether/EtOAc (99:1 to 97:3 gradient) to give **18a** (700 mg, 51% global yield from the corresponding phosphinic acid - 2 steps) as a colorless oil (containing about 7% of regioisomer). Major regioisomer: **^{1}H NMR** δ 1.35 (t, 3H, J = 7.1), 1.79-1.65 (m, 12H), 1.96-1.80 (m, 2H), 2.71-2.39 (m, 1H), 4.34-4.09 (m, 2H), 6.84 (ddd, 1H, $^1J_{H\text{-}P}$ = 579.3, $^3J_{H\text{-}FA}$ = 6.0, $^3J_{H\text{-}FA'}$ = 3.0). **^{13}C{^{1}H} NMR** δ 16.3 (d, CH_3, $^3J_{C\text{-}P}$ = 6.3), 24.9 (m, CH_2), 25.4 (CH_2), 25.7-25.4 (m, 2xCH_2), 26.4 (2xCH_2), 26.8 (CH_2), 40.7 (ddd, apparent td, $CHCF_2$, $^2J_{C\text{-}F}$ = 18.1 and 18.1, $^2J_{C\text{-}P}$ = 15.0), 63.2 (d, OCH_2CH_3, $^2J_{C\text{-}P}$ = 7.5), (CF_2 unobserved due to multiplicity). **^{31}P{^{1}H} NMR** δ 63.6 (dd, $^2J_{P\text{-}F1}$ = 112.4, $^2J_{P\text{-}F2}$ = 105.3). **^{19}F NMR** δ –114.4 (dddd, 1F, $^2J_{F2\text{-}F1}$ = 280.7, $^2J_{F2\text{-}P}$ = 105.3, $^3J_{F2\text{-}H}$ = 16.4, $^3J_{F2\text{-}(P)H}$ = 6.2), –115.6 (dddd, 1F, $^2J_{F1\text{-}F2}$ = 280.7, $^2J_{F1\text{-}P}$ = 112.4, $^3J_{F1\text{-}H}$ = 19.8 and $^3J_{F1\text{-}(P)H}$ = 2.5). **FTIR** ν_{max} (cm^{-1}) 2922 (CH), 1053 (CF), 925, 893, 765 or 662 (P=S). **HRMS** (ESI-TOF) m/z: Calcd for $C_{11}H_{21}F_2OPS$ $[M^{\cdot}]^+$: 270.1019; Found 270.1007. Minor regioisomer: **^{1}H NMR** δ (*diagnostic signals only*) 6.84 (ddd, apparent dt, 1H, $^1J_{H\text{-}P}$ = 500.8, $^3J_{H\text{-}F1,2}$ = 3.0). ^{31}P NMR δ 73.3 (s).

5-*O*-(4-Chlorobenzoyl)-3-(*O*-ethyl-*H*-phosphinothio)difluoromethyl-1,2-*O-iso*propylidene-α-D-xylofuranose (18b). Lawesson reagent (206 mg, 0.49 mmol) was added to a solution of the crude *H*-phosphinate **8a** obtained as above (430 mg, 0.95 mmol) in distilled toluene (5.0 mL), and the resultant mixture was heated at 85 °C for 40 min. Concentration under reduced pressure and purification of the residue by chromatography and elution with cyclohexane/EtOAc (10:1 to 6:1 gradient) delivered *H*-phosphinothioate **18b** (261 mg, 58%) as a colorless oil. For analytical purposes, a pure fraction of diastereoisomer A was isolated by additional chromatography and characterized separately. Diastereoisomer A: **^{1}H NMR** δ 1.32 (s, 3H, CH_3), 1.36 (t, 3H, ^3J = 4.2, C$\underline{H}_3$CH$_2$O-P), 1.53 (s, 3H, CH_3), 2.85-3.01 (m, 1H, H_3), 4.16-4.39 (m, 3H, H_{5a} and $CH_3C\underline{H}_2$O-P), 4.75-4.80 (m, 2H, H_4 and H_{5b}), 5.09 (t, 1H, H_2, $^3J_{2\text{-}1}$ = 4.5), 5.92 (d, 1H, $^3J_{1\text{-}2}$ = 4.2, H_1), 7.41 (d, 2H, ^3J = 8.4, Bz), 7.90 (dd, 1H, $^1J_{H\text{-}P}$ = 588.3, $^3J_{H\text{-}F}$ = 11.7, P-$\underline{H}$), 7.97 (d, 2H, ^3J = 8.4, Bz). **^{13}C{^{1}H} NMR** δ 16.2 (d, $\underline{C}H_3CH_2$O-P, $^3J_{C\text{-}P}$ = 6.8), 26.4, 26.7 (C($\underline{C}H_3$)$_2$), 48.7 (dt, C_3, $^2J_{C\text{-}P}$ = 21.9, $^2J_{C\text{-}F}$ = 17.4), 63.1 (d, $CH_3\underline{C}H_2$O-P, $^2J_{C\text{-}P}$ = 7.6), 64.5 (d, C_5, $^4J_{C\text{-}F}$ = 2.3), 74.6 (t, C_4, $^3J_{C\text{-}F}$ = 6.6), 78.9 (d, C_2, $^3J_{C\text{-}F}$ = 9.4), 105.3 (s, C_1), 113.3 (s, $\underline{C}$(CH_3)$_2$), 121.2 (ddd, CF_2, $^1J_{C\text{-}F}$ = 281.6, $^1J_{C\text{-}F}$ = 265.0, $^1J_{C\text{-}P}$ = 107.2), 128.2, 128.9 (2C, Bz), 131.2 (2C, Bz), 139.7 (Bz), 165.3 (C=O). **^{19}F{^{1}H} NMR** δ -108.9 (ddd, 1F, $^2J_{F\text{-}F}$ = 285.2, $^2J_{F\text{-}P}$ = 90.4, $^3J_{F\text{-}H}$ = 20.9), -106.9 (ddt, 1F, $^2J_{F\text{-}F}$ = 286.1, $^2J_{F\text{-}P}$ = 90.6, $^3J_{F\text{-}H}$ = 11.6). **^{31}P{^{1}H} NMR** δ 61.4 (t, $^2J_{P\text{-}F}$ = 92.3). Diastereoisomer B: **^{19}F{^{1}H} NMR** δ -110.3 (dddd, 1F, $^2J_{F\text{-}F}$ = 305.0, $^2J_{F\text{-}P}$ = 96.0, $^3J_{F\text{-}H}$ = 8.5, 19.8), -98.02 (ddd, 1F, $^2J_{F\text{-}F}$ = 305.0, $^2J_{F\text{-}P}$ = 98.8, $^3J_{F\text{-}H}$ = 11.3). **^{31}P{^{1}H} NMR** δ 63.2 (dd, $^2J_{P\text{-}F}$ = 94.9, 98.4). **HRMS** (ESI-TOF) m/z: Calcd for $C_{18}H_{21}{}^{35}ClF_2O_6PS$ $(M\text{-}H)^-$: 469.0474; Found: 469.0467.

***O*-Ethyl (4-*tert*-butylcyclohexyl)-difluoromethyl-*H*-phosphinothioate (18c).** To an anhydrous, stirring toluene solution (3 mL) of compound **8c** (77 mg, 0.303 mmol) was added Lawesson reagent (61 mg, 0.15 mmol) under argon. The reaction mixture was stirred at 85 °C for 40 min and then concentrated. Purification by chromatography and elution with cyclohexane/EtOAc (100:1 to 40:1 gradient) gave the colorless, oily compound **18c** (88 mg, 97 %) as a 4:1 mixture of *trans* and *cis* inseparable cyclic diastereomers. **^{1}H NMR** δ (major diastereomer) 0.82 (s, 9H, (C$\underline{H}_3$)$_3$C), 0.93-1.30 (m, 5H), 1.34 (t, 3H, CH_2-C$\underline{H}_3$ $^3J_{H\text{-}H}$ = 7.0), 1.44-2.38 (m, 5H), 4.08-4.32 (m,

2H, C$\underline{H}_2$-CH$_3$), 7.72 (ddd, 1H, $^1J_{H\text{-}P}$ = 588.8, $J_{H\text{-}H}$ = 6.3, $J_{H\text{-}H}$ = 2.1, $\underline{H}$-P). **^{19}F{^{1}H} NMR-^{1}H** δ Major diastereomer: -118.0 (dd, 1F, $^2J_{F\text{-}F}$ = 277, $^2J_{F\text{-}P}$ = 96), -116.7 (dd, 1F, $^2J_{F\text{-}F}$ = 277, $^2J_{F\text{-}P}$ = 96). Minor diastereomer: -109.8 (dd, 1F, $^2J_{F\text{-}F}$ = 280, $^2J_{F\text{-}P}$ = 104), -108.7 (dd, 1F, $^2J_{F\text{-}F}$ = 280, $^2J_{F\text{-}P}$ = 116). **^{31}P{^{1}H} NMR** δ Major diastereomer: 60.8 (ddtm, $^1J_{P\text{-}H}$ = 588, $^2J_{P\text{-}F}$ = 98). Minor diastereomer: 62.6 (dddm, $^1J_{P\text{-}H}$ = 599, $^2J_{P\text{-}F}$ = 101, $^2J_{P\text{-}F}$ = 117). **^{13}C{^{1}H} NMR** δ 16.0 (d, $^3J_{C\text{-}P}$ = 7, CH$_2$-$\underline{C}$H$_3$), 25.0 (d, $^4J_{C\text{-}P}$ = 7, *t*-Bu-CH-$\underline{C}$H$_2$), 26.1 ($\underline{C}$H$_2$-CH-CF$_2$), 27.4 (3x$\underline{C}$H$_3$), 32.4 (CH$_3$-$\underline{C}$), 41.1 (td, $^1J_{C\text{-}F}$ = 19, $^2J_{C\text{-}P}$ = 15, $\underline{C}$H-CF$_2$), 47.4 ($\underline{C}$H-*t*-Bu), 62.9 (d, $^2J_{C\text{-}P}$ = 7, $\underline{C}$H$_2$-CH$_3$), 122.6 (td, $^1J_{C\text{-}F}$ = 271, $^2J_{C\text{-}P}$ = 116, CF$_2$). **Anal**. Calcd. for $C_{13}H_{25}F_2OPS$: C, 52.33; H, 8.45; S, 10.74. Found: C, 52.61; H, 9.10; S, 10.22. **IR** ν_{max}/cm^{-1}: 2957 (C-H), 2853 (P-H), 1023 (P-O), 735 (P=S). **MS** (ESI$^+$, CH$_3$CN/H$_2$O) m/z (%) found: 299 [M+H]$^+$.

Preparation of phosphinates 12a, 12d, 15a, 15b, and phosphinothioates 20a-20f. General procedure for the radical addition reaction. Under Ar, the requisite *H*-phosphinate **8** or *H*-phosphinothioate **18** (1.0 equiv) was dissolved in distilled methylene chloride (18 mL/mmol, unless otherwise stated) and the resultant solution was placed in a Schlenk tube and degassed by bubbling Ar for 30 min. The requisite alkene **9**, **14**, **16**, **17** or **19** (1.5 equiv) was then added and the solution was again degassed by bubbling Ar for 15 min. DLP (0.21 equiv) was added and, after degassing again for 15 min (in some cases, the solution was finally degassed using the freeze/pump/thaw cycle technique), the reaction mixture was heated at 80^o C for 3 h (the reaction can be monitored by ^{19}F and ^{31}P NMR analyses of aliquots). The crude mixture was cooled down to r. t. and the volatiles were evaporated under reduced pressure. Unless otherwise stated, purification was achieved by chromatography using PE/EA (30:1 to 15:1 gradient) as eluent.

5-*O*-(4-Chlorobenzoyl)-3-(*O*-ethyl-*H*-phosphino)-difluoromethyl-1,2-*O*-*iso*propylidene-α-D-xylofuranose (12a). Prepared from phosphinate **8a** (272 mg, 0.60 mmol), alkene **9** (290 mg, 1.45 mmol), anhydrous dichloroethane (8.0 mL) and DLP (106 mg, 0.26 mmol, added to the mixture in 5 crops (every 1.5 h)). The reaction mixture was stirred at 84 °C for a total time of 10 h (at this point, ^{19}F and ^{31}P NMR spectra of aliquots showed full conversion of 8a). Chromatographed and eluted with cyclohexane/EtOAc (3:1 to 1:1 gradient) to give compound **12a** (78 mg, 20% from 8a) as a white foam (a 1:1 mixture of two diastereomers). **^{1}H NMR** δ 1.30 (s, 3H, CH$_3$), 1.31-1.36 (m, 6H, C($\underline{C}$H$_3$)$_2$, OCH$_2$$\underline{C}H_3$), 1.46 (s, 3H, CH$_3$), 1.54 (B) and 1.57 (A) (2s, 3H, CH$_3$), 1.83-2.26 (m, 4H, H$_{5'}$, H$_{6'}$), 2.74-2.92 (m, 1H, H$_3$), 3.32 (A) and 3.34 (B) (2s, 3H, 1'-OCH$_3$), 4.08-4.42 (m, 4H, H$_{4'}$, O$\underline{C}$H$_2$CH$_3$, H$_{5a}$), 4.50-4.52 (m, 1H, H$_{3'}$), 4.59 (d, 1H, H$_{2'}$, $^3J_{2'\text{-}3'}$ = 6.0), 4.73-4.90 (m, 2H, 5b-H$_{5b}$, 4-H$_4$), 4.94 (s, 1H, H$_{1'}$), 5.00 (A) and 5.06 (B) (2t, 1H, H$_2$, ^3J = 4.2), 5.87 (A) and 5.88 (B) (2d, 1H, H$_1$, $^3J_{1,2}$ = 3.3, 3.0), 7.40 (d, 2H, Bz, ^3J = 8.1), 7.96 (2d, 2H, Bz, ^3J = 8.7**). ^{13}C{^{1}H} NMR** δ 16.6 (B) and 16.7 (A) (2d, OCH$_2$$\underline{C}H_3$, $^3J_{C\text{-}P}$ = 6.0), 22.4 (A) and 23.2 (B) (2d, C$_{6'}$, $^1J_{C\text{-}P}$ = 96.6, 98.2), 25.0 (C($\underline{C}$H$_3$)$_2$), 26.4 (d, C$_{5'}$, $^2J_{C\text{-}P}$ = 4.5), 26.6 and 26.6, 26.7, 26.8 (C($\underline{C}$H$_3$)$_2$), 48.6-49.3 (m, C$_3$), 55.2 (B) and 55.4 (A) (2s, 1'-OCH$_3$), 63.1 (A) (d, P-O$\underline{C}$H$_2$CH$_3$, $^2J_{C\text{-}P}$ = 7.6) and 63.4 (B) (dd, P-O$\underline{C}$H$_2$CH$_3$, $^2J_{C\text{-}P}$ = 7.6, $^4J_{C\text{-}F}$ = 3.0), 64.4 (A) (d, C$_5$, $^4J_{C\text{-}F}$ = 2.3) and 64.7 (B) (d, C$_5$, $^4J_{C\text{-}F}$ = 3.8), 74.5-74.7 (m, C$_4$), 79.2 (A) (d, C$_2$, $^3J_{C\text{-}F}$ = 7.6) and 79.3 (B) (d, C$_2$, $^3J_{C\text{-}F}$ = 10.6), 83.8 (B) and 83.9 (A) (2s, C$_{3'}$), 85.4 (s, C$_{2'}$), 87.2 (A) and 87.3 (B) (2d, C$_{4'}$, $^3J_{C\text{-}F}$ = 16.6), 105.0 (A) and 105.2 (B) (2s, C$_1$), 109.6 (B) and 109.8 (A) (2s, C$_{1'}$), 112.6, 113.3 (B) and 113.4 (A) ($\underline{C}$(CH$_3$)$_2$), 128.3 (B) and 128.4 (A) (Bz), 128.9 (2C), 131.2 (2C, Bz), 139.68 (A) and 139.74 (B) (Bz), 165.35 (A) and 165.42 (B) (C=O). **^{19}F{^{1}H} NMR** δ diastereoisomer A: -111.1 (ddd, 1F, $^2J_{F\text{-}F}$ = 305.0, $^2J_{F\text{-}P}$ = 98.8, $^3J_{F\text{-}H}$ = 25.4), -101.2 (ddd, 1F, $^2J_{F\text{-}F}$ = 305.0, $^2J_{F\text{-}P}$ = 76.2, $^3J_{F\text{-}H}$ = 11.3); diastereoisomer B: -108.8 (ddd, 1F, $^2J_{F\text{-}F}$ = 310.6, $^2J_{F\text{-}P}$ = 81.9, $^3J_{F\text{-}H}$ = 22.6), -101.2 (ddd, 1F, $^2J_{F\text{-}F}$ = 310.6, $^2J_{F\text{-}P}$ = 107.3, $^3J_{F\text{-}H}$ = 8.5). **^{31}P{^{1}H} NMR** δ diastereoisomer A: 42.0 (dd, $^2J_{F1\text{-}P}$ = 76.5, $^2J_{F2\text{-}P}$ = 98.4); diastereoisomer B: 42.5 (dd, $^2J_{F1\text{-}P}$ = 81.4, $^2J_{F2\text{-}P}$ = 106.9). **Anal**. Calcd. for $C_{28}H_{38}ClF_2O_{11}P$: C, 51.34; H, 5.85. Found: C, 51.29; H, 5.82. **MS** (ESI, CH$_3$CN/H$_2$O) found: (M+H)$^+$, 654.9; (M+ H$_2$O)$^+$, 671.9.

Ethyl (cyclooctyldifluoromethyl)((1*S*,5*S*)-2,4,4,5-tetramethylcyclohex-2-en-1-yl)phosphinate (12d). Prepared from fluorophosphinate **8b** (100 mg, 0.393 mmol), (+)-α-pinene (17) (81 mg, 0.590 mmol) and DLP (31 mg, 0.079 mmol) in CH_2Cl_2 (6.50 mL). The crude residue was chromatographed and eluted with petroleum ether:EtOAc (9:3) to give **12d** (55 mg, 36%) as a colorless oil (a 1.25:1 mixture of diastereoisomers (^{19}F NMR analysis of the crude reaction mixture). For analytical purposes, pure fractions of each *P*-centered diastereoisomers were isolated by additional chromatography and characterized separately. Major diastereomer: **^{1}H NMR** δ 0.89 (d, 3H, J = 10.7), 0.93 (d, 3H, J = 10.7), 1.30 (t, 3H, J = 6.9), 1.90-1.39 (m, 19H), 2.18-1.92 (m, 3H), 2.45-2.19 (m, 2H), 2.83 (br dd, 1H, J = 16.3 and 5.2), 4.15 (2 x qd, 1 x apparent quin, 2H, J = 6.9), 5.70-5.61 (br m, 1H). **^{13}C{^{1}H} NMR** δ 16.6 (d, *C*H$_3$, $^3J_{C\text{-}P}$ = 5.6), 19.3 (*C*H$_3$), 19.9 (*C*H$_3$), 24.0 (*C*H$_3$), 25.3 (br s, *C*H$_2$), 25.5-25.9 (m, 3x*C*H$_2$), 26.3-26.6 (m, 2x*C*H$_2$), 26.8 (br s, *C*H$_2$), 27.4 (br s, *C*H$_2$), 28.8 (d, *C*H$_2$, $^3J_{C\text{-}F}$ = 3.0), 32.8 (*C*H$_3$), 36.3 (*C*H), 39.2 (d, *C*H, $^1J_{C\text{-}P}$ = 82.5), 41.8 (ddd, *C*HCF$_2$, $^2J_{C\text{-}F}$ = 18.4 and 18.4, $^2J_{C\text{-}P}$ = 10.9), 62.0 (d, O*C*H$_2$CH$_3$, $^2J_{C\text{-}P}$ = 7.5), 127.5 (d, *C*H, $^3J_{C\text{-}P}$ = 10.7), 127.9 (d, *C*, $^2J_{C\text{-}P}$ = 9.7), (*C*F$_2$ unobserved due to multiplicity). **^{31}P{^{1}H} NMR** δ 41.9 (dd, $^2J_{P\text{-}F1}$ = 108.7, $^2J_{P\text{-}F2}$ = 94.6). **^{19}F{^{1}H} NMR** δ -112.8 (ddd, 1F, $^2J_{F2\text{-}F1}$ = 295.9, $^2J_{F2\text{-}P}$ = 94.6, $^3J_{F2\text{-}H}$ = 17.5), -115.1 (ddd, 1F, $^2J_{F1\text{-}F2}$ = 295.9, $^2J_{F1\text{-}P}$ = 108.7, $^3J_{F1\text{-}H}$ = 19.2). **FTIR** (ν_{max} cm^{-1}) 2920 (CH), 1239 (P=O), 1025 (CF). **HRMS** calcd for $C_{21}H_{38}F_2O_2P$ [M+ H]$^+$: 391.2578. Found 391.2575. **$[\alpha]_{20}^D$** = + 85.2 (c = 1.0, CHCl$_3$). Minor diastereomer: **^{1}H NMR** δ 0.87 (d, 3H, J = 6.5), 0.89 (d, 3H, J = 6.5), 1.31 (t, 3H, J = 6.9), 1.85-1.34 (m, 16H), 2.49-1.87 (m, 8H), 2.85 (br dd, 1H, J = 18.1 and 5.2), 4.19 (2 x qd, 1 x apparent quin, 2H, J = 7.1), 5.76-5.64 (br m, 1H). **^{13}C{^{1}H} NMR** δ 16.7 (d, OCH$_2$*C*H$_3$, $^3J_{C\text{-}P}$= 5.6), 19.5 (*C*H$_3$), 19.9 (*C*H$_3$), 24.5 (*C*H$_3$), 25.1 (br s, *C*H$_2$), 25.8-25.4 (m, 3x*C*H$_2$), 26.6-26.2 (m, 3x*C*H$_2$), 26.8 (br s, *C*H$_2$), 29.0 (d, *C*H$_2$, $^3J_{C\text{-}F}$ = 2.5), 32.7 (*C*H), 35.1 (*C*H), 40.3 (d, *C*H, $^1J_{C\text{-}P}$ = 83.0), 41.8 (ddd, *C*HCF$_2$, $^2J_{C\text{-}F}$ = 18.2 and 18.2, $^2J_{C\text{-}P}$ = 10.2), 62.6 (d, O*C*H$_2$CH$_3$, $^2J_{C\text{-}P}$ = 7.5), 127.9 (d, *C*H, $^3J_{C\text{-}P}$ = 11.0), 128.1 (d, *C*, $^2J_{C\text{-}P}$ = 9.8), (*C*F$_2$ unobserved due to multiplicity**). ^{31}P{^{1}H} NMR** δ 40.9 (dd, $^2J_{P\text{-}F1}$ = 111.8, $^2J_{P\text{-}F2}$ = 85.3). **^{19}F{^{1}H} NMR** δ -112.3 (ddd, 1F, $^2J_{F1\text{-}F2}$ = 293.7, $^2J_{F1\text{-}P}$ = 111.8, $^3J_{F1\text{-}H}$ = 14.7), -114.4 (ddd, 1F, $^2J_{F2\text{-}F1}$ = 293.6, $^2J_{F2\text{-}P}$ = 85.3, $^3J_{F2\text{-}H}$ = 22.3). **FTIR** (ν_{max} cm^{-1}) 2920 (CH), 1237 (P=O), 1027 (CF). **HRMS** (ESI-TOF) m/z: Calcd for $C_{21}H_{38}F_2O_2P$ [M+H]$^+$: 391.2578; Found 391.2568. $[\alpha]_{20}^D$ = + 97.2 (c = 1.0, CHCl$_3$).

6-[[[5-*O*-(4-Chlorobenzoyl)-3-deoxy-1,2-*O*-(*iso*propylidene)-α-*D*-*ribo*furanos-3-yl]difluoromethyl]ethoxyphosphinyl]-5,8-dideoxy-1,2-

***O*-(*iso*propylidene)-3-*O*-(benzyl)-*α*-*D*-*ribo*-hexofuranose (15a) and 6-[[[5-*O*-(4-chlorobenzoyl)-3-deoxy-1,2-*O*-(*iso*propylidene)-*α*-*D*-*ribo*furanos-3-yl]difluoromethyl]ethoxyphosphinothioyl]-5,8-dideoxy-1,2-*O*-(*iso*propylidene)-3-*hydroxyl*-*α*-*D*-*ribo*-hexofuranose (15b).** Prepared from phosphinate **7a** (200 mg, 0.38 mmol), alkene **14** (257 mg, 0.93 mmol), 1,2-dichloroethane (6.0 mL) and DLP (315 mg, 0.77 mmol – added in 9 crops every 1.5 h) The reaction mixture was stirred at 86 °C for a total of 36 h. The crude residue obtained after evaporation of the volatiles was dissolved in distilled water (10 mL) and the solution was extracted with EtOAc (2x4 mL). The aqueous solution was lyophilized and a 5% aqueous solution of $KHSO_4$ (10 mL) was added to the residue. After 30 min of stirring, the solution was extracted with EtOAc (3x5 mL) and the combined organic extracts were dried. Evaporation of the solvent under reduced pressure left a residue which was dissolved in methylene chloride (6 mL) and a freshly prepared CH_2N_2 ethereal solution (CAUTION) was added at r.t to the stirring solution until a persistent yellowish color developed. Evaporation of the volatiles, chromatography and elution with cyclohexane/EtOAc (3:1 to 1:1 gradient) delivered **15a** (76 mg, 27%) and **15b** (33 mg, 13%) as white foams. **15a** (a 1:1 mixture of two diastereoisomers A:B due to the phosphorus chiral center) **^{1}H NMR** δ 1.30 (A) and 1.33 (B) (2s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.51 and 1.57 (2s, 6H, CH_3), 1.71-1.89 (m, 1H, $H_{5'a}$), 1.92-2.35 (m, 3H, $H_{5'b}$, H_6), 2.74-2.92 (m, 1H, 3-H), 3.39 (A) and 3.40 (B) (2dd, 1H, $H_{2'}$, $^3J_{3'-2'}$ = 4.2, $^3J_{2'-1'}$ = 8.7), 3.84 (d, 3H, $^3J_{H-P}$ = 10.7, CH_3O-P), 3.94-4.04 (m, 1H, $H_{4'}$), 4.37 (A) and 4.38 (B) (2dd, 1H, H_{5a}, $^2J_{5a-5b}$ = 12.3, $^3J_{5a-4}$ = 7.5), 4.52 (A) and 4.53 (B) (2xd, 1H, AB syst, J = 11.7 and 12.0, Ph-C$\underline{H}_2$-), 4.57 (dd, 1H, $H_{2'}$, $^3J_{2'-3'}$ = 4.2, $^3J_{2'-1'}$ = 3.9), 4.74-4.90 (m, 3H, H_{5b}, Ph-C$\underline{H}_2$-, H_4), 4.98 (A) and 5.02 (B) (2dd, 1H, H_2, $^3J_{2-1}$ = 3.9, $^3J_{2-3}$ = 4.2), 5.68 (A) and 5.69 (B) (2d, 1H, $H_{1'}$, $^3J_{1'-2'}$ = 3.9), 5.86 (2d, 1H, H_1, $^3J_{1-2}$ = 3.9), 7.29-7.42 (m, 7H, Bz, $\underline{Ph}$-CH_2-), 7.95-8.00 (m, 2H, Bz). **^{13}C{^{1}H} NMR** δ 21.2 (A) (d, $C_{6'}$, $^1J_{C-P}$ = 95.9) and 22.2 (B) (d, $C_{6'}$, $^1J_{C-P}$ = 96.6), 23.5 (B) and 23.6 (A) (2d, $C_{5'}$, $^2J_{C-P}$ = 17.0, 17.4), 26.6, 26.6, 26.7, 26.8 (C($\underline{C}H_3$)$_2$), 48.4-49.2 (m, C_3), 53.4 (d, CH_3O-P, $^2J_{C-P}$ = 7.6) and 53.7 (dd, CH_3O-P, $^2J_{C-P}$ = 7.6, $^4J_{C-F}$ = 3.8), 64.4 (B) and 64.6 (A) (d, C_5, $^4J_{C-F}$ = 2.3, 3.2), 72.2 (s, -O$\underline{C}H_2$Ph), 74.5-74.6 (m, C_4), 77.27 and 77.31 ($C_{2'}$), 77.4-77.8 ($C_{4'}$), 79.1 (B) and 79.2 (A) (2d, C_2, $^3J_{C-F}$ = 9.8, 10.6), 81.0 (B) and 81.4 (A) ($C_{3'}$), 104.0 ($C_{1'}$), 105.0 (B) and 105.1 (A) (C_1), 112.9 (A) and 113.0 (B) ($\underline{C}(CH_3)_2$), 113.4 ($\underline{C}(CH_3)_2$), 128.2 (2C), 128.3, 128.4 (2C), 128.7 (2C), 128.9 (2C, Ph), 131.3 (2C, Bz), 137.3 (B) and 137.4 (A) (Ph), 139.67 (B) and 139.71 (A) (Ph), 165.38 (B) and 165.44 (A) (C=O). **^{19}F{^{1}H} NMR** δ diastereoisomer A: -111.8 (ddd, 1F, $^2J_{F-F}$ = 307.8, $^2J_{F-P}$ = 98.8, $^3J_{F-H}$ = 22.6), -101.8 (ddd, 1F, $^2J_{F-F}$ = 307.8, $^2J_{F-P}$ = 76.2, $^3J_{F-H}$ = 11.3); diastereoisomer B: -109.2 (ddd, 1F, $^2J_{F-F}$ = 310.6, $^2J_{F-P}$ = 79.1, $^3J_{F-H}$ = 22.6), -101.2 (ddd, 1F $^2J_{F-F}$ = 310.6, $^2J_{F-P}$ = 107.3, $^3J_{F-H}$ = 8.5). **^{31}P{^{1}H} NMR** δ diastereoisomer A: 43.4 (dd, $^2J_{F1-P}$ = 98.4, $^2J_{F2-P}$ = 77.8); diastereoisomer B: 43.6 (dd, $^2J_{F1-P}$ = 106.9, $^2J_{F2-P}$ = 81.4). **HRMS** (ESI-TOF) m/z: Calcd for $C_{33}H_{40}Na^{35}ClF_2O_{11}P$ $(M+Na)^+$: 739.1857; Found: 739.1891; **MS** (ESI, CH_3CN/H_2O) found: $(M+H_2O)^+$,733.8. **15b** (1:1 mixture of two diastereoisomers A:B due to the phosphorus chiral center) **^{1}H NMR** δ 1.34 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.55 and 1.58 (2s, 6H, CH_3), 1.81-1.99 (m, 1H, $H_{5'a}$), 2.04-2.41 (m, 3H, $H_{5'b}$, H_6), 2.49 (B) and 2.52 (A) (2d, 1H, 3'-OH, J = 10.5, 10.8), 2.75-2.93 (m, 1H, H_3), 3.55-3.64 (m, 1H, $H_{3'}$), 3.71 (B) and 3.74 (A) (2dd, 1H, $H_{4'}$, J = 8.2, 8.1, J = 4.0), 3.86 (d, 3H, $^3J_{H-P}$ = 10.5, CH_3O-P), 4.36 (A) and 4.38 (B) (2dd, 1H, H_{5a}, $^2J_{5a-5b}$ = 12.3, $^3J_{5a,4}$ = 7.5), 4.55 (t, 1H, 2'-H, ^3J = 4.5), 4.74-4.90 (m, 2H, H_{5b}, H_4), 5.00 (B) and 5.06 (A) (2dd, 1H, H_2, $^3J_{2-1}$ = 3.9, $^3J_{2-3}$ = 4.2), 5.75-5.77 (2d, 1H, $H_{1'}$, $^3J_{1'-2'}$ = 3.9), 5.87-5.88 (2d, 1H, H_1, $^3J_{1-2}$ = 3.6), 7.40-7.42 (m, 2H, Bz), 7.95-7.99 (m, 2H, Bz). **^{13}C{^{1}H} NMR** δ 21.2 (B) (d, $C_{6'}$, $^1J_{C-P}$ = 96.6) and 21.8 (A) (d, $C_{6'}$, $^1J_{C-P}$ = 94.4), 24.3 (2d, $C_{5'}$, $^2J_{C-P}$ = 4.5 z), 26.5, 26.55, 26.61, 26.7, 26.8 (C($\underline{C}H_3$)$_2$), 48.5-49.2 (m, C_3), 53.5 (dd, CH_3O-P, $^2J_{C-P}$ = 6.8, $^4J_{C-F}$ = 2.3) and 53.8 (dd, CH_3O-P, $^2J_{C-P}$ = 7.6, $^4J_{C-F}$ = 3.8), 64.3 (B) (d, C_5, $^4J_{C-F}$ = 1.5) and 64.6 (A) (d, C_5, $^4J_{C-F}$ = 2.3), 74.4-74.6 (m, C_4), 75.5 ($C_{3'}$), 78.6 ($C_{2'}$), 79.0-79.3 (C_2), 79.5 (A) and 79.6 (B) (2d, $C_{4'}$, $^3J_{C-P}$ = 15.1), 103.8 ($C_{1'}$), 105.0 (B) and 105.1 (A) (C_1), 112.6 (A) and 112.7 (B) ($\underline{C}(CH_3)_2$), 113.38 (A) and 113.43 (B) ($\underline{C}(CH_3)_2$), 128.2 (A) and 128.3 (B) (Bz), 128.9, (2C, Bz), 131.3 (2C, Bz), 139.68 (B) and 139.74 (A) (Ph), 165.4 (B) and 165.5 (A) (C=O). **^{19}F{^{1}H} NMR** δ diastereoisomer A: -111.7 (1F, ddd, $^2J_{F-F}$ = 307.8, $^2J_{F-P}$ = 98.8, $^3J_{F-H}$ = 22.6), -101.6 (1F, ddd, $^2J_{F-F}$ = 307.8, $^2J_{F-P}$ = 76.2, $^3J_{F-H}$ = 11.3); diastereoisomer B: -109.0 (1F, ddd, $^2J_{F-F}$ = 310.6, $^2J_{F-P}$ = 81.9, $^3J_{F-H}$ = 22.6), -101.1 (1F, ddd, $^2J_{F-F}$ = 310.6, $^2J_{F-P}$ = 107.3, $^3J_{F-H}$ = 8.5). **^{31}P{^{1}H} NMR** δ diastereoisomer A: 43.7 (dd, $^2J_{F1-P}$ = 98.4, $^2J_{F2-P}$ = 77.8); diastereoisomer B: 43.8 (dd, $^2J_{F1-P}$ = 106.9, $^2J_{F2-P}$ = 81.4). **HRMS** (ESI-TOF) m/z: Calcd for $C_{26}H_{34}Na^{35}ClF_2O_{11}P$ $(M+Na)^+$: 649.1388; found: 649.1359; **MS** (ESI, CH_3CN/H_2O) found: $(M+H)^+$, 626.7; $(M+H_2O)^+$, 644.1.

***O*-Ethyl (2-butoxyethyl)(cyclooctyldifluoromethyl)phosphinothioate (20a).** Following the general procedure, crude product **20a** was obtained from *H*-fluorophosphinothioate 18a (100 mg, 0.37 mmol), alkene **16** (56 mg, 0.55 mmol) and DLP (30 mg, 0.079 mmol) in CH_2Cl_2 (6.00 mL). The crude residue was chromatographed and eluted with petroleum ether/EtOAc (98:2 to 9:1 gradient) to give **20a** as a colorless oil (130 mg, 96%). **^{1}H NMR** δ 0.91 (t, 3H, J = 7.4), 1.31 (t, 3H, J = 6.7), 1.20-1.80 (m, 16H), 1.84-2.08 (m, 2H), 2.24-2.75 (m, 3H), 3.44 (t, 2H, J = 6.7), 3.68-3.86 (m, 2H), 4.02-4.26 (m, 2H). **^{13}C{^{1}H} NMR** δ 14.0 ($CH_2\mathit{C}H_3$), 16.4 (d, $OCH_2\mathit{C}H_3$, $^3J_{C-P}$ = 5.6), 19.4 (br s, $\mathit{C}H_2$), 25.6-25.1 (m, 3x$\mathit{C}H_2$), 25.7 ($\mathit{C}H_2$), 26.5 ($\mathit{C}H_2$), 26.6 ($\mathit{C}H_2$), 26.8 ($\mathit{C}H_2$), 31.9 ($\mathit{C}H_2$), 32.5 (d, CH_2, $^1J_{C-P}$ = 69.7), 40.0 (ddd, $\mathit{C}HCF_2$, $^2J_{C-F}$ = 18.3, 18.3 and $^2J_{C-P}$ = 12.8), 62.5 (d, $O\mathit{C}H_2CH_3$, $^2J_{C-P}$ = 7.0), 64.1 ($\mathit{C}H_2O$), 71.0 ($O\mathit{C}H_2$), ($\mathit{C}F_2$ unobserved due to multiplicity). **^{19}F{^{1}H} NMR** δ -111.6 (ddd, 1F, $^2J_{F1-F2}$ = 280.1, $^2J_{F1-P}$ = 113.2, $^3J_{F1-H}$ = 15.8), -116.0 (ddd, 1F, $^2J_{F2-F1}$ = 280.1, $^2J_{F2-P}$ = 89.4, $^3J_{F2-H}$ = 20.9). **^{31}P{^{1}H} NMR** δ 90.8 (dd, $^2J_{P-F1}$ = 113.2, $^2J_{P-F2}$ = 89.4). **FTIR** (ν_{max} cm^{-1}) 2924 (CH), 1032 (CF), 798, 762 or 743 (P=S). **HRMS** (ESI-TOF) m/z: Calcd for $C_{17}H_{34}F_2O_2PS$ $[M+H]^+$: 371.1985; Found 371.1998.

***O*-Ethyl (cyclooctyldifluoromethyl)((1*S*,5*S*)-2,4,4,5-tetramethylcyclohex-2-en-1-yl)phosphinothioate (20b).** Prepared from *H*-fluorophosphinothioate **18a** (90 mg, 0.33 mmol), (+)-α-pinene (68 mg, 0.50 mmol) and DLP (30 mg, 0.079 mmol) in CH_2Cl_2 (5.5 mL). Chromatography and elution of the the crude residue with petroleum ether/EtOAc (99:1 to 98:2 gradient) led to the isolation of **20b** (108 mg, 80%) as a colorless oil (a 1.25:1 mixture of two inseparable *P*-centered diastereoisomers by ^{19}F NMR analysis of the crude reaction mixture). Major + minor diastereomers (*refers to the minor isomer when unambiguous assignment is possible): **^{1}H NMR** δ. 0.95-0.72

(m, 6H), 1.17-1.29 (m, 3H), 1.30-1.82 (m, 17H), 1.84-2.18 (m, 5H), 2.24-2.43 (m, 1H), 2.51-2.79 (m, 1H), 2.92-3.09 (br m, 1H), 3.97-4.24 (m, 2H), 5.60-5.72 (br m, 1H). **^{13}C{^{1}H} NMR** δ 16.1-16.5 (m, CH_3), 19.5 (CH_3), 19.9 (CH_3), 20.1* (CH_3), 24.4 (CH_3), 25.2-26.0 (m, CH_2), 26.5-27.0 (m, CH_2), 28.3-29.0 (m, CH_2), 32.9 (CH), 33.0* (CH), 35.2* (CH), 35.3 (CH), 40.2-41.1 (m, $CHCF_2$), 42.4 (d, CH, $^{1}J_{C\text{-}P}$ = 59.0), 45.9* (d, CH, $^{1}J_{C\text{-}P}$ = 59.0), 62.1 (d, CH_2, $^{2}J_{C\text{-}P}$ = 8.0), 62.8* (d, CH_2, $^{2}J_{C\text{-}P}$ = 8.0), 128.0 (d, CH, $^{2}J_{C\text{-}P}$ = 7.5), 128.2 (d, CH, $^{2}J_{C\text{-}P}$ = 10.5), 128.5 (d, C, $^{3}J_{C\text{-}P}$ = 9.6), 129.1* (d, C, $^{3}J_{C\text{-}P}$ = 7.5), (CF_2 unobserved due to multiplicity). **^{31}P{^{1}H} NMR** δ 94.0* (dd, $^{2}J_{P\text{-}F1}$ = 116.0, $^{2}J_{P\text{-}F2}$ = 83.8), 97.7 (dd, $^{2}J_{P\text{-}F1}$ = 109.8, $^{2}J_{P\text{-}F2}$ = 86.0). **^{19}F{^{1}H} NMR** δ -109.2* (ddd, 1F, $^{2}J_{F1\text{-}F2}$ = 280.0, $^{2}J_{F1\text{-}P}$ = 116.0, $^{3}J_{F1\text{-}H}$ = 12.1), -110.0 (ddd, 1F, $^{2}J_{F1\text{-}F2}$ = 280.0, $^{2}J_{F1\text{-}P}$ = 109.8, $^{3}J_{F1\text{-}H}$ = 14.7), -115.2 (ddd, 1F, $^{2}J_{F2\text{-}F1}$ = 280.0, $^{2}J_{F2\text{-}P}$ = 86.0, $^{3}J_{F2\text{-}H}$ = 21.2), -115.5* (ddd, 1F, $^{2}J_{F2\text{-}F1}$ = 280.0, $^{2}J_{F2\text{-}P}$ = 83.8, $^{3}J_{F2\text{-}H}$ = 23.4). **FTIR** (ν_{max} cm^{-1}) 2920 (CH), 1031 (CF), 780 or 726 (P=S). **HRMS** (ESI-TOF) m/z: Calcd for $C_{21}H_{38}F_2OPS$ $[M+H]^+$: 407.2349; Found 407.2346.

***O*-Ethyl (2-((3a*R*,5*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)ethyl)(cyclooctyldifluoromethyl)phosphinothioate (20c).** Application of the general procedure to *H-di*fluorophosphinothioate **18a** (100 mg, 0.370 mmol), alkene **14** (154 mg, 0.550 mmol) and DLP (30 mg, 0.08 mmol) in CH_2Cl_2 (6.00 mL) furnished, after chromatography and elution with petroleum ether/CH_2Cl_2/EtOAc (50:50:0.3), compound **20c** (120 mg, 59%) as a colorless oil (a 1:1 mixture of *P*-centered diastereoisomers as measured by ^{19}F NMR analysis of the crude reaction mixture). When TBPP (14 mg, 0.08 mmol) was used as radical initiator, product **20c** was isolated in 62% (125 mg). **^{1}H NMR** δ 1.26 and 1.27 (2t, 3H, J = 6.9), 1.33 (s, 3H), 1.57 (s, 3H), 1.37-1.79 (m, 12H), 1.85-2.36 (m, 6H), 2.45-2.69 (m, 1H), 3.42 (dd, 1H, J = 8.9 and 4.4), 3.93-4.09 (m, 2H), 4.10-4.26 (m, 1H), 4.53 (d, 1H, AB syst, J_{AB} = 11.7), 4.53-4.58 (m, 1H), 4.77 (d, 1H, AB syst, J_{AB} = 11.7), 5.69 (2d, 1H, J = 4.2), 7.25-7.39 (m, 5H). **^{13}C{^{1}H} NMR** δ 16.6 (d, OCH_2CH_3, $^{3}J_{C\text{-}P}$ = 5.6), 26.7 (CH_3), 26.9 (CH_3), 24.3-27.1 (m, 8xCH_2), 28.2 (d, CH_2, $^{1}J_{C\text{-}P}$ = 72.8), 28.3 (d, CH_2, $^{1}J_{C\text{-}P}$ = 72.8), 41.2-41.3 (m, $CHCF_2$), 62.6 (d, OCH_2CH_3, $^{2}J_{C\text{-}P}$ = 6.5), 72.2 (OCH_2Ph), 77.4 (CH), 77.6 (overlap with solvent signal and deduced from DEPT experiment / d, CH, $J_{C\text{-}P}$ = 4.0), 77.8 (d, CH, $J_{C\text{-}P}$ = 4.3), 81.4 (CH), 81.5 (CH), 104.1 (CH), 113.0 (C), 128.1 (2xCH), 128.2 (CH), 128.7 (2xCH), 137.5 (C), (CF_2 unobserved due to multiplicity). **^{31}P{^{1}H} NMR** δ 93.9 (dd, $^{2}J_{P\text{-}F1}$ = 108.5, $^{2}J_{P\text{-}F2}$ = 88.9), 93.7 (dd, $^{2}J_{P\text{-}F1}$ = 109.9, $^{2}J_{P\text{-}F2}$ = 88.2**). ^{19}F{^{1}H} NMR** δ -111.3 (ddd, 1F,$^{2}J_{F1\text{-}F2}$ = 281.0, $^{2}J_{F1\text{-}P}$ = 109.5, $^{3}J_{F1\text{-}H}$ = 16.4), -112.1 (ddd, 1F, $^{2}J_{F1\text{-}F2}$ = 281.5, $^{2}J_{F1\text{-}P}$ = 108.5, $^{3}J_{F1\text{-}H}$ = 16.7), -114.7 (ddd, apparent td, 1F, $^{2}J_{F2\text{-}F1}$ = 281.0, $^{2}J_{F2\text{-}P}$ = 88.9, $^{3}J_{F2\text{-}H}$ = 19.5), -115.0 (ddd, apparent td, 1F, $^{2}J_{F2\text{-}F1}$ = 281.0, $^{2}J_{F2\text{-}P}$ = 88.2, $^{3}J_{F2\text{-}H}$ = 20.0). **FTIR** (ν_{max} cm^{-1}) 2923 (CH), 1019 (CF), 732 or 698 (P=S). **HRMS** (ESI-TOF) m/z: Calcd for $C_{27}H_{45}F_2NO_5PS$ $[M+NH_4]^+$: 564.2724; Found 564.2741.

***O*-Ethyl(cyclooctyldifluoromethyl)(((3*S*,10*S*,13*S*)-3-hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)methyl)phosphinothioate (20d).** The above general procedure, when applied to *H*-fluorophosphinothioate **18a** (100 mg, 0.370 mmol), alkene **19** (154 mg, 0.550 mmol) and DLP (30 mg, 0.08 mmol) in CH_2Cl_2 (6.00 mL), generated a crude residue (1:1 mixture of diastereomers at phosphorus center as measured by ^{19}F NMR analysis); chromatography and elution with petroleum ether/EtOAc (3:2) allowed the isolation of phosphinothioate **20d** (145 mg, 69%) as a white solid. **^{1}H NMR** δ 4.29-3.95 (m, 2H), 3.64-3.48 (m, 1H), 2.71-2.44 (m, 1H), 2.35-2.05 (m, 1H), 2.00-1.84 (m, 4H), 1,83-0,83 (m, 36H), 0.79 (s, 3H), 0.71-0.68 (m, 1H), 0.56 (s, 0.55x3H), 0.55 (s, 0.45x3H). **^{13}C{^{1}H} NMR** δ (CF_2 unobserved due to multiplicity), 74.5 (CH), 62.6 (d, CH_2, $^{2}J_{C\text{-}P}$ = 7.0), 62.5 (d, OCH_2CH_3, $^{2}J_{C\text{-}P}$ = 7.4), 55.1-54.6 (m, CH), 45.11 (CH), 45.07 (CH), 44.4 (d, CH, $^{2}J_{C\text{-}P}$ = 5.4), 43.7 (C), 43.6-43.3 (m, CH), 43.2 (C), 41.4-39.6 (m, $CHCF_2$), 38.4 (CH_2), 37.2 (CH_2), 37.0 (CH_2), 35.9 (CH), 35.8 (C), 34.0 (CH_2), 33.4 (CH_2), 32,7 (CH_2), 32,3 (CH_2), 31,9 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 25.3 (CH_2), 25.3 (CH_2), 25.1 (CH_2), 21.1 (CH_2), 16.6 (d, CH_3CH_2OP, $^{3}J_{C\text{-}P}$ = 6.8), 16.5 (d, CH_3CH_2OP, $^{3}J_{C\text{-}P}$ = 6.8), 13.1 (CH_3), 12,7 (CH_3), 12.5 (2xCH_3). **^{31}P{^{1}H} NMR** δ 96.4 (dd, $^{2}J_{P\text{-}F1}$ = 98.0 and $^{2}J_{P\text{-}F2}$ = 94.3), 94.2 (dd, $^{2}J_{P\text{-}F1}$ = 107.9, $^{2}J_{P\text{-}F2}$ = 86.0). **^{19}F{^{1}H} NMR** δ -111,8 (ddd, 1F, $^{2}J_{F1\text{-}F2}$ = 280.7, $^{2}J_{F1\text{-}P}$ = 107.9, $^{3}J_{F1\text{-}H}$ = 16.4), from -112.0 to -113.7 (m, 1F, $^{2}J_{F1\text{-}F2}$ = undetermined due to overlapping signals, $^{2}J_{F1\text{-}P}$ = 98.0, $^{3}J_{F2\text{-}H}$ = 18.3), -113.1-(-)114.9 (m, 1F, $^{2}J_{F2\text{-}F1}$ = undetermined due to overlapping signals, $^{2}J_{F2\text{-}P}$ = 94.3, $^{3}J_{F2\text{-}H}$ = 18.1), -115,2 (ddd, 1F, $^{2}J_{F2\text{-}F1}$ = 280.7, $^{2}J_{F2\text{-}P}$ = 86.0, $^{3}J_{F2\text{-}H}$ = 20.3). **FTIR** (ν_{max} cm^{-1}) 3335 (OH), 2922 (CH), 1035 (CF), 732 or 634 (P=S). **HRMS** (ESI-TOF) m/z: Calcd for $C_{31}H_{52}F_2O_2PS$ $[M-H]^-$: 557.3399; Found 557.3393.

6-[[[5-*O*-(4-Chlorobenzoyl)-3-deoxy-1,2-*O*-(*iso*propylidene)-*α*-*D*-*ribo*furanos-3-yl]difluoromethyl]ethoxyphosphinothioyl]-5,8-dideoxy-1-methoxy-2,3-*O*-(*iso*propylidene)-*α*-*D*-*ribo*-hexofuranose (20e). Prepared from phosphinothioate **18b** (139 mg, 0.295 mmol), alkene **9** (93 mg, 0.464 mmol), anhydrous dichloroethane (4.0 mL) and DLP (13.6 mg, 0.033 mmol). The reaction mixture was stirred at 80 °C for 2 h (^{19}F and ^{31}P NMR analyses showed full conversion) and the crude residue was chromatographed and eluted with cyclohexane/EtOAc, (15:1 to 8:1 gradient) to yield phosphinothioate **20e** as a white foam (140 mg, 71%). Diastereoisomer A could be separated and isolated by additional chromatography. Diastereoisomer A: **^{1}H NMR** δ 1.28 (t, 3H, $C\underline{H}_3CH_2$, ^{3}J = 6.9), 1.31 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.76-1.90 (m, 1H, $H_{5'a}$), 1.97-2.16 (m, 1H, $H_{5'a}$), 2.32-2.41 (m, 2H, $H_{6'}$), 3.03-3.19 (m, 1H, H_3), 3.35 (s, 3H, -$OC\underline{H}_3$), 4.02-4.16 (m, 2H, $CH_3C\underline{H}_2$, $H_{4'}$), 4.24-4.35 (m, 2H, $CH_3C\underline{H}_2$, H_{5a}), 4.55 (d, 1H, $H_{3'}$, $^{3}J_{3'\text{-}2'}$ = 6.0), 4.62 (d, 1H, $H_{2'}$, $^{3}J_{2'\text{-}3'}$ = 6.0), 4.71-4.76 (m, 1H, H_4), 4.80 (d, 1H, H_{5b}, $^{2}J_{5b\text{-}5a}$ = 12.3), 4.96 (s, 1H, $H_{1'}$), 5.03 (dd, 1H, H_2, $^{3}J_{2\text{-}1}$ = 3.9, $^{3}J_{2\text{-}3}$ = 4.2), 5.88 (d, 1H, H_1, $^{3}J_{1\text{-}2}$ = 3.9), 7.40-7.43 (m, 2H, Bz), 7.96-8.00 (m, 2H, Bz). **^{13}C{^{1}H} NMR** δ 16.4 (d, $\underline{C}H_3CH_2O$-P, $^{3}J_{C\text{-}P}$ = 6.0), 25.0, 26.6, 26.8 ($C(\underline{C}H_3)_2$), 27.0 (d, $C_{5'}$, $^{2}J_{C\text{-}P}$ = 3.8), 29.2 (d, $C_{6'}$, $^{1}J_{C\text{-}P}$ = 76.2), 48.2 (ddd, C_3, $^{2}J_{C\text{-}P}$ = 23.4, $^{2}J_{C\text{-}F}$ = 17.4), 55.3 (s, 1'-OCH_3), 63.6 (dd, -CH_2O-P, $^{2}J_{C\text{-}P}$ = 7.6, $^{4}J_{C\text{-}F}$ = 3.0), 64.8 (d, C_5, $^{4}J_{C\text{-}F}$ = 2.3), 75.0 (dd, C_4, $^{3}J_{C\text{-}P}$ = 5.3, $^{3}J_{C\text{-}F}$ = 6.8), 79.1 (d, C_2, $^{3}J_{C\text{-}F}$ = 9.8), 83.9 ($C_{3'}$), 85.4 ($C_{2'}$), 87.1 (d, $C_{4'}$, $^{3}J_{C\text{-}P}$ = 17.4), 105.2 (C_1), 109.6 ($C_{1'}$), 112.5, 113.3 ($\underline{C}(CH_3)_2$), 127.2, 128.3, 128.9 (2C, Bz), 131.3 (2C, Bz), 139.7 (Bz), 165.4 (C=O), (CF_2 unobserved due to multiplicity). **^{19}F{^{1}H} NMR** δ -111.9 (ddd, 1F, $^{2}J_{F\text{-}F}$ = 290.9, $^{2}J_{F\text{-}P}$ = 87.5, $^{3}J_{F\text{-}H}$ = 25.4), -100.4 (ddd, 1F, $^{2}J_{F\text{-}F}$ = 288.0, $^{2}J_{F\text{-}P}$ = 81.9, $^{3}J_{F\text{-}H}$ = 8.5**). ^{31}P{^{1}H} NMR** δ 91.2 (dd, $^{2}J_{F1,P}$ = 86.3, $^{2}J_{F2,P}$ = 81.4). **$[\alpha]_{20}^{D}$** = + 21.4 (C = 0.126, $CHCl_3$). Diastereoisomer B: **^{1}H NMR** δ 1.30 (s, 3H,

CH_3), 1.33 (t, 3H, C<u>H</u>$_3$CH$_2$, ^3J = 6.9), 1.33 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.81-2.02 (m, 2H), 2.15-2.21 (m, 1H), 2.32-2.43 (m, 1H), 3.11-3.24 (m, 1H, 3-H), 3.35 (s, 3H, 1'-OCH_3), 4.04-4.18 (m, 2H, CH_3C<u>H</u>$_2$, H$_{4'}$), 4.25-4.37 (m, 2H, -CH_3C<u>H</u>$_2$, H$_{5a}$), 4.55 (d, 1H, H$_{3'}$, $^3J_{3'-2'}$ = 6.0), 4.61 (d, 1H, H$_{2'}$, $^3J_{2'-3'}$ = 5.7), 4.77-4.84 (m, 2H, 4-H, H$_{5b}$), 4.96 (s, 1H, H$_{1'}$), 4.99 (dd, 1H, H$_2$, $^3J_{2-1}$ = 3.6, $^3J_{2-3}$ = 3.9), 5.88 (d, 1H, H$_1$, $^3J_{1-2}$ = 3.6), 7.41 (d, 2H, Bz, J = 8.7), 7.98 (d, 2H, Bz, J = 9.0). **^{13}C{^{1}H} NMR** δ 16.6 (d, <u>C</u>H$_3$CH$_2$O-P, $^3J_{C\text{-}P}$ = 6.0), 25.0, 26.6, 27.0 (C(<u>C</u>H$_3$)$_2$), 27.3 (s, C$_{5'}$), 27.8 (d, C$_{6'}$, $^1J_{C\text{-}P}$ = 74.0), 46.4-47.1 (m, C$_3$), 55.5 (s, 1'-OCH_3), 62.9 (d, -CH_2O-P, $^2J_{C\text{-}P}$ = 6.8), 64.6 (d, C$_5$, $^4J_{C\text{-}F}$ = 3.8), 75.0 (dd, C$_4$, $^3J_{C\text{-}F}$ = 6.8, $^3J_{C\text{-}P}$ = 3.0), 78.7 (d, C$_2$, $^3J_{C\text{-}F}$ = 9.8), 83.9 (C$_{3'}$), 85.4 (C$_{2'}$), 87.1 (d, C$_{4'}$, $^3J_{C\text{-}P}$ = 18.1), 105.1 (C$_1$), 109.8 (C$_{1'}$), 112.6, 113.4 (<u>C</u>(CH$_3$)$_2$), 128.4, 128.9 (2C), 131.3 (2C), 139.7 (Bz), 165.4 (C=O), (CF_2 unobserved due to multiplicity). **^{19}F{^{1}H} NMR** δ -113.7 (ddd, 1F, $^2J_{F\text{-}F}$ = 290.9, $^2J_{F\text{-}P}$ = 79.1, $^3J_{F\text{-}H}$ = 25.4), -99.6 (ddd, 1F, $^2J_{F\text{-}F}$ = 290.0.0, $^2J_{F\text{-}P}$ = 107.3, $^3J_{F\text{-}H}$ = 5.6). **^{31}P{^{1}H} NMR** δ 91.6 (dd, $^2J_{F1\text{-}P}$ = 108.1, $^2J_{F2\text{-}P}$ = 77.8). **Anal**. Calcd. for $C_{28}H_{38}ClF_2O_{10}PS$: C, 50.11; H, 5.71; S, 4.78. Found: C, 50.82; H, 6.10; S, 4.56. **MS** (ESI, CH_3CN/H_2O) found: (M-H+formic acid)$^-$, 715.1. **IR** (NaCl), ν (cm^{-1}): 1720 (C=O), 1271, 1096, 1019, 959, 762 (P=S).

6-[[[5-*O*-(4-Chlorobenzoyl)-3-deoxy-1,2-*O*-(*iso*propylidene)-α-*D*-*ribo*furanos-3-yl]difluoromethyl]ethoxyphosphinothioyl]-5,8-dideoxy-1,2-*O*-(*iso*propylidene)-3-*O*-(benzyl)-α-*D*-*ribo*-hexofuranose (20f). The radical addition was carried out according to the general procedure above, starting from phosphinothioate **18b** (172 mg, 0.36 mmol), alkene **14** (116 mg, 0.42 mmol) methylene chloride (6 mL) and DLP (31.6 mg, 0.076 mmol – added in two crops at t=0 and t=2h). The reaction mixture was heated at 80 °C for a total of 4 hours. Chromatography and elution with cyclohexane/EtOAc (15:1 to 9:1 gradient) yielded difluorophosphinothioate **20f** as a white foam (201 mg, 77% - a 1:1 mixture of diastereomers). For analytical purposes, a pure fraction of diastereoisomer A could be isolated by additional, careful chromatography and characterized separately. Diastereoisomer A. **^{1}H NMR** δ 1.26 (s, 3H, CH_3), 1.28 (t, 3H, C<u>H</u>$_3$CH$_2$, ^3J = 7.2), 1.35 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.83-1.97 (m, 1H, H$_{5'a}$), 2.00-2.14 (m, 1H, H$_{5'b}$), 2.30-2.41 (m, 2H, H$_{6'}$), 3.02-3.18 (m, 1H, H$_3$), 3.42 (dd, 1H, H$_{3'}$, $^3J_{3'-2'}$ = 4.2, $^3J_{3'-4'}$ = 8.7), 4.05-4.12 (m, 2H, CH_3C<u>H</u>$_2$, H$_{4'}$), 4.20-4.35 (m, 2H, CH_3C<u>H</u>$_2$, H$_{5a}$), 4.54 (d, AB syst, 1H, Ph-C<u>H</u>$_2$-, J_{AB} = 11.7), 4.58 (dd, 1H, H$_{2'}$, $^3J_{2'-3'}$ = 4.2, $^3J_{2'-1'}$ = 3.9), 4.71-4.82 (m, 3H, H$_4$, H$_{5b}$, Ph-C<u>H</u>$_2$-), 4.96 (dd, 1H, H$_2$, $^3J_{2-1}$ = 3.6, $^3J_{2-3}$ = 3.9), 5.69 (d, 1H, H$_{1'}$, $^3J_{1'-2'}$ = 3.9), 5.85 (d, 1H, H$_1$, $^3J_{1-2}$ = 3.6), 7.31-7.44 (m, 7H, Bz, <u>Ph</u>-CH$_2$-), 7.96-8.01 (m, 2H, Bz). **^{13}C{^{1}H} NMR** δ 16.4 (d, <u>C</u>H$_3$CH$_2$, $^3J_{C\text{-}P}$ = 6.0), 24.3 (d, C$_{5'}$, $^2J_{C\text{-}P}$ = 3.8), 26.5, 26.6, 26.7, 26.8 (s, C(<u>C</u>H$_3$)$_2$), 28.5 (d, C$_{6'}$, $^1J_{C\text{-}P}$ = 76.2), 47.9 (ddd, C$_3$, $^2J_{C\text{-}F}$ = 33.2, $^2J_{C\text{-}F}$ = 22.6, $^2J_{C\text{-}P}$ = 16.6), 63.5 (dd, CH$_3$<u>C</u>H$_2$, $^2J_{C\text{-}P}$ = 6.8, $^4J_{C\text{-}F}$ = 2.3), 64.7 (d, C$_5$, $^4J_{C\text{-}F}$ = 3.8), 72.1 (s, -O<u>C</u>H$_2$Ph), 74.9 (dd, C$_4$, $^3J_{C\text{-}F}$ = 6.8, $^3J_{C\text{-}F}$ = 5.3), 77.3 (s, C$_{2'}$), 79.0 (d, C$_2$, $^3J_{C\text{-}F}$ = 9.8), 81.3 (s, C$_{3'}$), 104.0 (s, C$_{1'}$), 105.1 (s, C$_1$), 112.9, 113.4 (s, <u>C</u>(CH$_3$)$_2$), 128.1 (2C), 128.3, 128.4, 128.7 (2C), 128.9 (2C), 131.3 (2C), 137.4, 139.7, 165.4 (C=O), (CF_2 unobserved due to multiplicity). **^{19}F{^{1}H} NMR** δ -111.9 (ddd, 1F, $^2J_{F\text{-}F}$ = 290.9, $^2J_{F\text{-}P}$ = 87.5, $^3J_{F\text{-}H}$ = 25.4), -100.9 (ddd, 1F, $^2J_{F\text{-}F}$ = 288.0, $^2J_{F\text{-}P}$ = 81.9, $^3J_{F\text{-}H}$ = 8.5). **^{31}P{^{1}H} NMR** δ 91.4 (dd, $^2J_{F1\text{-}P}$ = 86.3, $^2J_{F2\text{-}P}$ = 81.4). **$[\alpha]_{20}^{D}$** = + 66.0 (C = 0.206, $CHCl_3$). Diastereoisomer B. **^{1}H NMR** δ 1.33 (t, 3H, C<u>H</u>$_3$CH$_2$, ^3J = 6.2), 1.35 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.65-1.80 (m, 1H, H$_{5'a}$), 2.04-2.40 (m, 3H, H$_{5'b}$, H$_6$), 3.13-3.25 (m, 1H, H$_3$), 3.42 (dd, 1H, H$_{3'}$, $^3J_{3'-2'}$ = 4.5, $^3J_{3'-4'}$ = 9.0), 4.01-4.37 (m, 4H, CH$_3$C<u>H</u>$_2$, H$_{4'}$, H$_{5a}$), 4.53 (d, AB syst, 1H, Ph-C<u>H</u>$_2$-, J_{AB} = 12.0), 4.58 (dd, 1H, H$_{2'}$, $^3J_{2'-3'}$ = 4.2, $^3J_{2'-1'}$ = 3.9), 4.76-4.84 (m, 3H, 4-H$_4$, H$_{5b}$, PhC<u>H</u>$_2$-), 4.98 (dd, 1H, H$_2$, $^3J_{2-1}$ = 3.6, $^3J_{2-3}$ = 3.6), 5.70 (d, 1H, H$_{1'}$, $^3J_{1'-2'}$ = 3.6), 5.87 (d, 1H, H$_1$, $^3J_{1-2}$ = 3.6), 7.26-7.36 (m, 5H, <u>Ph</u>CH$_2$-), 7.41 (d, 2H, Bz, ^3J = 8.4), 7.99 (d, 2H, Bz, ^3J = 8.4). **^{13}C{^{1}H} NMR** δ 16.6 (d, <u>C</u>H$_3$CH$_2$O-P, $^3J_{C\text{-}P}$ = 6.0), 24.5 (s, C$_{5'}$), 26.8 (d, C$_{6'}$, $^1J_{C\text{-}P}$ = 73.2), 26.6, 26.8, 26.9, 27.0 (C(<u>C</u>H$_3$)$_2$), 45.3-47.0 (m, C$_3$), 62.9 (d, -CH$_2$O-P, $^2J_{C\text{-}P}$ = 7.6), 64.6 (d, C$_5$, $^4J_{C\text{-}F}$ = 3.8), 72.20 (s, -O<u>C</u>H$_2$Ph), 75.0 (dd, C$_4$, $^3J_{C\text{-}F}$ = 6.8, $^3J_{C\text{-}F}$ = 3.0), 77.3 (C$_{2'}$), 78.8 (d, C$_2$, $^3J_{C\text{-}F}$ = 9.8), 81.3 (C$_{3'}$), 104.0 (C$_{1'}$), 105.1 (C$_1$), 113.0, 113.4 (<u>C</u>(CH$_3$)$_2$), 128.2 (2C), 128.3, 128.4, 128.7 (2C), 128.9 (2C), 131.3 (2C), 137.4, 139.7, 165.4 (C=O), (CF_2 unobserved due to multiplicity). **^{19}F{^{1}H} NMR** δ -113.8 (1F, ddd, $^2J_{F\text{-}F}$ = 290.9, $^2J_{F\text{-}P}$ = 79.1, $^3J_{F\text{-}H}$ = 25.4), -99.8 (1F, ddd, $^2J_{F\text{-}F}$ = 288.0, $^2J_{F\text{-}P}$ = 107.3, $^3J_{F\text{-}H}$ = 5.6). **^{31}P{^{1}H} NMR** δ 91.9 (dd, $^2J_{F1\text{-}P}$ = 108.1, $^2J_{F2\text{-}P}$ = 79.0). **Anal**. Calcd. for $C_{34}H_{42}ClF_2O_{10}PS$: C, 54.65; H, 5.67; S, 4.29. Found: C, 54.80; H, 6.02; S, 4.17. **MS** (ESI, CH_3CN/H_2O) found: $(M+H)^+$, 747.07; $(M+H_2O)^+$,764.07. **IR** (NaCl), ν (cm^{-1}): 1720 (C=O), 1090, 1013, 758 (P=S).

General procedure for the Michaelis-Becker reaction. To a dry methylene chloride (3 mL) slurry of powdered KOH (56 mg, 1 mmol) and benzyl triethyl ammonium chloride (114 mg, 0.5 mmol) under argon was added a dry CH_2Cl_2 (3 mL) solution of the requisite phosphinate **8** or phosphinothioate **18** (1 mmol) dropwise, followed by a dry CH_2Cl_2 (3 mL) solution of the requisite iodide (1 mmol). The stirring reaction mixture was then heated at 40 °C for 2 h. After cooling down to r.t., the solution was quenched with a saturated aqueous solution of ammonium chloride (15 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2x7 mL). The combined organic layers were washed with brine (15 mL), dried, filtered and concentrated under reduced pressure. Chromatography and elution with cyclohexane/EtOAc, (15:1 to 9:1) delivered the pure products.

***O*-Ethyl (4-*tert*-butylcyclohexyl)difluoromethyl (3-phenyl)propyl phosphinate (12e).** Carried out on *H*-phosphinate **8c** (282 mg, 1 mmol) and iodide **21** (246 mg, 1 mmol). Chromatography and elution of the crude material with cyclohexane/EtOAc, (8:2) delivered phosphinate **12e** (52 mg, 13 % yield) as a 4:1 mixture of *trans* and *cis* cyclic diastereomers. **^{1}H NMR** δ (major diastereomer) 0.84 (s, 9H, (C<u>H</u>$_3$)$_3$C), 1.07-1.52 (m, 8H), 1,76-2.07 (m, 9H), 2.56-2.71 (m, 2H), 4.08-4.27 (m, 2H), 7.16-7.31 (m, 5H). **^{19}F{^{1}H} NMR** δ major diasteromer A: -115.73 (d, 1F, $^2J_{F\text{-}P}$ = 87), -115.72 (d, 1F, $J_{F\text{-}P}$ = 99). Minor diasteromer A: -108.35 (d, 1F, $^2J_{F\text{-}P}$ =102), minor diasteromer B: -108.33 (d, 1F, $^2J_{F\text{-}P}$ =107). **^{31}P{^{1}H} NMR** δ Major diasteromer: 43.4 (dd, $^1J_{P\text{-}F}$ = 92, $^2J_{P\text{-}F}$ =100). Minor diasteromer: 43.3 (t, $^1J_{P\text{-}F}$ = 103, 1P). **^{13}C{^{1}H} NMR** δ 16.6 (d, $^3J_{C\text{-}P}$ = 8, CH$_2$<u>C</u>H$_3$), 24.6-25.3 (m, (<u>C</u>H$_2$)$_2$CHCF$_2$), 26.4 (<u>C</u>H$_2$CH$_2$)$_2$CHCF$_2$), 27.5 (<u>C</u>H$_3$)$_3$C), 31.3, 33.9, 36.5 (<u>C</u>H$_2$<u>C</u>H$_2$<u>C</u>H$_2$Ph), 36.9 (CH$_3$)$_3$<u>C</u>), 42.2 (td, $^2J_{C\text{-}F}$ = 15, $^2J_{C\text{-}P}$ = 17, <u>C</u>HCF$_2$), 47.4 (CH$_3$)$_3$C<u>C</u>H), 62.3 (d, $^2J_{C\text{-}P}$ = 11, <u>C</u>H$_2$CH$_3$), 126.2, 128.5, 140.8 (C$_{Ph}$), (CF_2 unobserved due to multiplicity). **IR** $_{max}$/cm^{-1}: 2928 (C-H), 1238 (P=O), 1034 (C-F). **HRMS** (ESI-TOF) m/z: Calcd for $C_{22}H_{36}F_2O_2P$ $(M+H)^+$: 401.2421; Found: 401.2411.

6-[[[5-*O*-(4-Chlorobenzoyl)-3-deoxy-1,2-*O*-(*iso*propylidene)-α-*D*-*ribo*furanos-3-

yl]difluoromethyl]ethoxyphosphinothioyl]-5,8-dideoxy-1,2-*O*-(*iso*propylidene)-3-*O*-(benzyl)-*α*-*D*-*ribo*-hexofuranose (20f). Prepared from 0,607 mmol of *H*-phosphinothioate **18b** and 0,607 mmol of iodide **25**. Chromatography and elution of the crude material with cyclohexane/EtOAc, (15:1 to 9:1 gradient) allowed the partial separation and pure diastereomer A was obtained first as a white foamy material, followed by a [1:4] mixture of diastereomers A and B (389 mg, total yield: 86 %). Data identical to those obtained with the compound obtained by the radical addition reaction (see above).

***O*-Ethyl (4-*tert*-butylcyclohexyl)difluoromethyl (3-phenyl)propyl phosphinothioate (20g).** Carried out from 0,27 mmol of *H*-phosphinothioate **18c** and 0,27 mmol of iodide **21**. Purified by chromatography and elution with cyclohexane/EtOAc (15:1 to 9:1 gradient) to deliver colorless, oily product **20g** as a 4:1 mixture of *trans* and *cis* cyclic diastereomers (96 mg, 89 %). **^{1}H NMR** δ (major diastereomer) 0.75 (s, 9H), 1.03-1.34 (m, 9H), 1.64-2.23 (m, 8H), 2.38-3.00 (m, 2H), 3.97-4.19 (m, 2H), 7.09-7.23 (m, 5H). **^{19}F{^{1}H} NMR** δ Major Diastereoisomer, -116.4 (dd, 1F, $^2J_{F\text{-}F}$ = 282, $^2J_{F\text{-}P}$ = 86), -114.5 (dd, $^2J_{F\text{-}F}$ = 282, $^2J_{F\text{-}P}$ = 105, 1F). Minor diastereoisomer, -108.4 (dd, $^2J_{F\text{-}F}$ = 282, $^2J_{F\text{-}P}$ = 90, 1F), -105.8 (dd, 1F, $^2J_{F\text{-}F}$ = 282, $^2J_{F\text{-}P}$ = 107). **^{31}P{^{1}H} NMR** δ Major diastereoisomer, 93.3 (dd, $^2J_{P\text{-}F}$ = 105, $^2J_{P\text{-}F}$ = 86). Minor diastereoisomer, 94.0 (dd, $^2J_{P\text{-}F}$ = 107, $^2J_{P\text{-}F}$ = 90). **^{13}C{^{1}H} NMR** δ 16.4 (d, $^3J_{C\text{-}P}$ = 9, $CH_2\underline{C}H_3$), 24.8-25.2 (m, $(\underline{C}H_2)_2CHCF_2$), 26.4 ($(\underline{C}H_2CH_2)_2CHCF_2$), 27.4 ($\underline{C}H_3)_3C$), 31.2, 34.9, 35.3 ($\underline{C}H_2\underline{C}H_2CH_2Ph$), 35.5 ($(CH_3)_3\underline{C}$), 42.1 (td, $^2J_{C\text{-}F}$ = 12, $^2J_{C\text{-}P}$ = 18, $\underline{C}HCF_2$), 47.4 ($(CH_3)_3C\underline{C}H$), 62.2 (d, $^2J_{C\text{-}P}$ = 8, $\underline{C}H_2CH_3$), 126.2, 128.5, 140.8 (C_{Ph}), (CF_2 unobserved due to multiplicity). **MS** (ESI$^+$, CH_3CN/H_2O) m/z (%) found: 417.15 $[M+H]^+$. **IR**, ν max/cm^{-1}: 2945 (C-H), 1028 (C-F), 735 (P=S). **HRMS** (APCI-TOF) m/z: Calcd for $C_{22}H_{36}F_2OPS$ $(M+H)^+$: 417.2187; Found: 417.2137.

***O*-Ethyl-*S*-(3-phenylpropyl)(4-*tert*-butylcyclohexyl)difluoromethylphosphonothioate 24.** **^{1}H NMR** δ (major diastereomers) 0.83 (s, 9H), 0.98 (s, 3H), 1.24-1.37 (m, 6H), 1.84 (s, 2H), 1.98-2.12 (m, 4H), 2.66-2.75 (m, 2H), 2.92-3.02 (m, 2H), 4.19-4.31 (m, 2H), 7.12-7.27 (m, 5H). **^{19}F{^{1}H} NMR** δ Major diastereoisomers, -115.7 (dd, $^2J_{F\text{-}F}$ = 293, $^2J_{F\text{-}P}$ = 131, 1F), -113.8 (dd, $^2J_{F\text{-}F}$ = 225, $^2J_{F\text{-}P}$ = 112, 1F). Minor diastereoisomers, -108.3 (dd, $^2J_{F\text{-}F}$ = 293, $^2J_{F\text{-}P}$ = 121, 1F), -105.0 (dd, $^2J_{F\text{-}F}$ = 276, $^2J_{F\text{-}P}$ = 85, 1F). **^{31}P{^{1}H} NMR** δ (major diastereoisomers), 41.8 (dd, $^2J_{P\text{-}F}$ = 131, $^2J_{P\text{-}F}$ = 112, 1P), minor diastereoisomer could not be detected. **MS** (ESI$^+$, CH_3CN/H_2O) m/z (%) found: 433.3 $[M+H]^+$, 450.7 $[M+H_2O]$. **IR** ν (cm^{-1}): 1239 (P=O), 1023 (P-O), 703 (P-S).

3-Deoxy-3-[difluoro(ethoxyphosphino(phenylpropyl)thioyl)methyl]-1,2-*O*-(isopropylidene)-5-*O*-(acetyl)-*α*-*D*-*ribo*furanose (20h). Prepared from an anhydrous, vigourously stirred, CH_2Cl_2 (1 mL) suspension of powdered KOH (7 mg, 0.1 mmol), TEBAC (6 mg, 0.026 mmol), an anhydrous CH_2Cl_2 (1 mL) solution of *H*-phosphinothioate **18b** (23 mg, 0.049 mmol), and 3-phenylpropyl iodide (1 mg, 0.05 mmol), according to the general procedure above. Chromatography and elution (cyclohexane/EtOAc, 10/1 to 4/1, v/v) delivered the colorless, oily product **20h** as a [1:1] mixture of diastereomers (24 mg, 84 %). **^{1}H NMR** δ 1.20 (s, 0.67×3H, CH_3), 1.25-1.33 (m, 3H and 0.33×3H, CH_2CH_3 and CH_3), 1.47 (s, 0.67×3H, CH_3), 1.53 (s, 0.33 ×3H, CH_3), 1.81-2.38 (m ,4H), 2.60-2.85 (m, 2H), 2.96-3.27 (m, 1H, H_3), 3.97-4.40 (m, 3H, $H_{5b\text{ and }12}$), 4.64-4.85 (m, 2H, $H_{4\text{ and }5a}$), 4.92-5.00 (m, 1H, H_2), 5.83 (d, J = 3.8, 0.67×1H, H_1), 5.85 (d, J = 3.8, 0.33×1H, H_1), 7.17-7.29 (m, 5H, H_{Ph}), 7.41 (m, 2H, H_{Bz}), 7.99 (m, 2H, H_{Bz}). **^{19}F NMR** δ Diastereomer A, -111.6 (ddd, $J_{F\text{-}F}$ = 289, $J_{P\text{-}F}$ = 87, $J_{P\text{-}H}$ = 24, 1F), -100.2 (ddd, $J_{F\text{-}F}$ = 289, $J_{P\text{-}F}$ = 80, $J_{P\text{-}H}$ = 9, 1F). Diastereomer B, -113.1 (ddd, $J_{F\text{-}F}$ = 290, $J_{P\text{-}F}$ = 78, $J_{P\text{-}H}$ = 26, 1F), -99.1 (ddd, $J_{F\text{-}F}$ = 290, $J_{P\text{-}F}$ = 108, $J_{P\text{-}H}$ = 7, 1F). **^{31}P{^{1}H} NMR**-^{1}H δ Diastereomer A, 91.8 (dd, $J_{P\text{-}F}$ = 87, $J_{P\text{-}F}$ = 80). Diastereomer B, 92.0 (dd, $J_{P\text{-}F}$ = 108, $J_{P\text{-}F}$ = 78). **^{13}C{^{1}H} NMR** (*refers to the minor diastereomer when unambiguous distinction is possible) δ 16.4 (d, J = 6), 16.6* (d, J = 7), 23.0 (d, J = 4), 23.3* (d, J = 4.5), 26.6, 26.7*, 26.8, 27.0*, 30.0* (d, J = 71), 31.2 (d, J = 74), 36.6 (d, J = 17) ,46.4-47.2* (m), 47.7-48.7 (m), 63.0* (d, J = 6.7), 63.6 (dd, J = 6.7, 2), 64.7* (d, J = 4.5, C_5), 64.9 (d, J = 3, C_5), 74.9-75.2 (m), 78.9* (d, J = 9, C_2), 79.2 (d, J = 10.5, C_2), 105.24* (C_1), 105,29 (C_1), 113.2, 113.4*, 126.5, 128.5, 128.65*, 128.69, 128.73, 131.4, 139.8, 140.8*, 140.9, 165.46*, 165.52. **IR**, γ_{max}/cm^{-1}: 1723 (C=O), 1022 (C-F), 1014 (P-O), 758 (P=S). **HRMS** (ESI-TOF) m/z: Calcd for $C_{27}H_{32}{}^{35}ClF_2NaO_6PS$ $(M+Na)^+$: 611.1211; Found: 611.1209.

6-[[[5-*O*-(4-Chlorobenzoyl)-3-deoxy-1,2-*O*-(*iso*propylidene)-*α*-*D*-*ribo*furanos-3-yl]difluoromethyl]ethoxyphosphinyl]-5,8-dideoxy-1,2-*O*-(*iso*propylidene)-3-*O*-(benzyl)-*α*-*D*-*ribo*-hexofuranose (12f). *m*-CPBA (140 mg, 0.81 mmol) was added to a methylene chloride (5 mL) solution of compound **20f** (121 mg, 0.16 mmol) and, after 2 hours of stirring at room temperature, the mixture was quenched with a saturated sodium thiosulfate solution. The separated aqueous layer was extracted with CH_2Cl_2 (2x5 mL) and the combined organic layers were sequentially washed with a saturated bicarbonate solution, a saturated ammonium chloride solution and brine, then dried, filtered and concentrated under reduced pressure to generate the crude sample. Purification by chromatography and elution with cyclohexane/EtOAc (7:3 to 1:1 gradient) led to the isolation of 104 mg (88 %) of **12f** as a 2:1 mixture of diastereomers A and B (colorless oil)). **^{1}H NMR** δ 1.27-1.35 (m, 9H), 1.50 (br s, 2H), 1.53-1.57 (m, 4H), 1.66-1.84 (m, 1H, $H_{5'a}$), 1.93-2.35 (m, 4H, $PC\underline{H}_2$, $H_{5'b}$, H_3), 3.34-3.41 (m, 1H, $H_{3'}$), 3.91-4.05 (m, 1H, H_4), 4.06-4.30 (m, 2H, $CH_3C\underline{H}_2$), 4.31-4.40 (m, 1H, H_{5a}), 4.47-4.59 (m, 2H, $H_{2'}$ and Ph-C$\underline{H}_2$), 4.70-4.88 (m, 3H, H_4, H_{5b} and Ph-C$\underline{H}_2$), 4.94-5.03 (m, 1H, H_2), 5.67 (m, 1H, $H_{1'}$), 5.84 (d, 1H, $^3J_{H\text{-}H}$ = 3.5, H_1), 7.26-7.36 (m, 5H, Ar^H), 7.39 (d, 2H, $^3J_{H\text{-}H}$ = 8.5, Bz^H), 7.95 (d, 2H, $^3J_{H\text{-}H}$ = 8.4, Bz^H). **^{19}F{^{1}H} NMR** δ diastereomer A: -110.4 (dd, 1F, $^2J_{F\text{-}F}$ = 306, $^2J_{F\text{-}P}$ = 98), -101.7 (dd, 1F, $^2J_{F\text{-}F}$ = 306, $^2J_{F\text{-}P}$ = 78); diastereomer B: -108.9 (dd, 1F, $^2J_{F\text{-}F}$ = 310, $^2J_{F\text{-}P}$ = 82), -101.1 (dd, 1F, $^2J_{F\text{-}F}$ = 310, $^2J_{F\text{-}P}$ = 106). **^{31}P{^{1}H} NMR** δ diastereomer A: 41.7 (dd, $^2J_{F\text{-}P}$ = 98, $^2J_{F\text{-}P}$ = 78); diastereomer B: 41.9 (dd, $^2J_{F\text{-}P}$ = 106, $^2J_{F\text{-}P}$ = 82). **^{13}C{^{1}H} NMR** (*refers to the minor diastereomer when unambiguous distinction is possible) δ 16.6 (d, $^3J_{C\text{-}P}$ = 5), 22.4 (d, $^1J_{C\text{-}P}$ = 99), 23.4-23.8 (m), 26.57, 26.62, 26.7, 26.8, 48.2-49.5 (m), 63.1* (d, $^2J_{C\text{-}P}$ = 7), 63.4 (d, $^2J_{C\text{-}P}$ = 7), 64.5*, 64.9, 72.2, 74.5-74.8 (m), 77,3, 77.5, 77.9, 79.4-79.1 (m), 81.1*, 81.5, 104.0, 105.0*, 105.1, 112.9, 113.0*, 113.4, 128.1 (2C), 128.2, 128.37, 128.40*, 128.6 (2C), 128.9 (2C), 131.2 (2C), 137.4*, 137.5, 139.66*, 139.68, 165.37*, 165.39, (CF_2 unobserved due to multiplicity). **MS**: ESI$^+$ CH_3CN/H_2O): m/z (%) found: 748.00 $[M+H_2O]^+$. **IR** ν max/cm^{-1}: 1724

(C=O),1265 (P=O), 1014 (C-F). **HRMS** (ESI-TOF) m/z: Calcd for $C_{34}H_{42}Na^{35}ClF_2O_{11}P$ $(M+Na)^+$: 753.2019; Found: 753.2016.

6-[[[5-*O*-(4-Chlorobenzoyl)-3-deoxy-1,2-di-*O*-acetyl-*α*-*D*-*ribo*furanos-3-yl]difluoromethyl]ethoxyphosphinothioyl]-5,8-dideoxy-1,2-di-*O*-(acetyl)-3-*O*-(benzyl)-*α*-*D*-*ribo*-hexofuranose (12g). A solution of compound **12f** (102 mg, 0.139 mmol) in a 67/8/1 (v/v/v) mixture of $AcOH/Ac_2O/H_2SO_4$ (3 mL) was stirred for 15 h at room temperature, then poured into ice-water (10 mL), and stirred for another 1 h. The mixture was extracted with EtOAc (2x5 mL) and the combined organic layers were washed with water, saturated bicarbonate aqueous solution, brine, dried, filtered and evaporated. Purification by chromatography and elution with cyclohexane/EtOAc (8:2 to 4:1 gradient) furnished the colorless, oily phosphinate **12g** as a [1.5:1] mixture of diastereoisomers A and B (101 mg, 77 %). The same compound was obtained in 92% yield by oxidation of phosphinothioate **20i** with *m*-CPBA, using the procedure, work up and purification described above for compound **12f**. **^{1}H NMR** δ 1.18-1.33 (m, 3H, $OCH_2C\underline{H}_3$), 1.75-1.95 (2 × br s and m, 5H), 1.95-2.17 (5 × br s and m, 11H), 3.30-3.09 (m, 1H, H_3), 3.84 (d, 0.4H, J = 4.5, $H_{3'}$), 3.87 (d, 0.6H, J = 4.5, $H_{3'}$), 3.92-4.20 (m, 3H, H_4 and $OC\underline{H}_2CH_3$), 4.28-4.43 (m, 1H), 4.36 (d, 1H, AB syst, J = 12.3, Ph-C$\underline{H}_2$), 4.55 (d, 1H, AB syst, J = 12.3, Ph-CH_2), 4.61-4.76 (m, 1H), 4.82-4.94 (m, 1H, H_4), 5.23 (d, 1H, $^3J_{H\text{-}H}$ = 4.2, $H_{2'}$), 5.48 (d, 1H, $^3J_{H\text{-}H}$ = 4.5, H_2), 6.02 (br s, 2H, H_1 and $H_{1'}$), 7.13-7.39 (m, 7H, Ar^H, Bz^H), 7.93-7.98 (m, 2H, Bz^H).**^{19}F{^{1}H} NMR** δ diastereoisomer B: -112.4 (dd, $^2J_{F\text{-}F}$ = 307, $^2J_{F\text{-}P}$ = 104, 1F), -104.3 (dd, $^2J_{F\text{-}F}$ = 304, $^2J_{F\text{-}P}$ = 82, $^3J_{F\text{-}H}$ = 6); diastereoisomer A: -112.1 (dd, $^2J_{F\text{-}F}$ = 309, $^2J_{F\text{-}P}$ = 85, 1F), -105.9 (dd, $^2J_{F\text{-}F}$ = 307, $^2J_{F\text{-}P}$ = 107, $^3J_{F\text{-}H}$ = 11, 1F). **^{31}P{^{1}H} NMR** δ diastereoisomer A: 40.7 (dd, $^2J_{F\text{-}P}$ = 105, $^2J_{F\text{-}P}$ = 84); diastereoisomer B: 42.6 (dd, $^2J_{F\text{-}P}$ = 107, $^2J_{F\text{-}P}$ = 85). **^{13}C{^{1}H} NMR** δ 16.6 (d, $^3J_{C\text{-}P}$ = 6), 16.7 (d, $^3J_{C\text{-}P}$ = 6), 20.2-21.6 (m), 25.5 (d, $^2J_{C\text{-}P}$ = 3), 25.8 (d, $^2J_{C\text{-}P}$ = 3), 43.5-44.5 (m), 63.1-63.5 (m), 65.8, 65.9, 73.4, 73.6, 75.1 75.5 (m), 77.6 (overlap with solvent signal and deduced from DEPT experiment), 79.97, 80.05, 81.1, 81.3, 128.30, 128.33, 128.4, 128.7 (2 × C), 128.9 (2 × C), 131.1 (2 × C), 137.0, 137.1, 139.8, 139.9, 165.1, 168.7, 168.8, 169.0, 169.1, 169.4, 169.6, 169.8, (CF$_2$ unobserved due to multiplicity). **MS** (ESI$^+$ CH_3CN/H_2O): m/z (%) found: 836.00 $[M+H_2O]^+$; 841.13 $[M+ Na]^+$. **IR** ν max/cm^{-1}: 1744 (C=O), 1210 (P=O)1013 (C-F). **HRMS** (ESI-TOF) m/z: Calcd for $C_{36}H_{42}Na^{35}ClF_2O_{15}P$ $(M+Na)^+$: 841.1816; Found: 841.1817.

6-[[[5-*O*-(4-Chlorobenzoyl)-3-deoxy-1,2-di-*O*-(acetyl)-*α*-*D*-*ribo*furanos-3-yl]difluoromethyl]ethoxyphosphinothioyl]-5,8-dideoxy-1,2-di-*O*-(acetyl)-3-*O*-(benzyl)-*α*-*D*-*ribo*-hexofuranose (20i). Acetic anhydride (0.52 mL, 5.5 mmol) and concentrated sulfuric acid (65 µL) were sequentially added dropwise to a stirring solution of compound **20f** (288 mg, 0.38 mmol) in acetic acid (4.2 mL) at 0 °C. The above procedure (12f→12g) and work up were then followed; purification by chromatography and elution with cyclohexane/EtOAc (6:1 to 4:1) gave compound **20i** (161 mg, 50 %) as a white foam (a 1:1 mixture of diastereomers A and B). **^{1}H NMR** δ 1.26 (B) and 1.30 (A) (3t, 3H, $C\underline{H}_3CH_2O$-P, ^3J = 6.9), 1.75-2.27 (8s and m, 16H, $C\underline{H}_3C(O)$), 5'H, 6'H), 3.45-3.80 (m, 1H, 3-H), 3.92-3.96 (m, 1H, 3'-H), 4.04-4.20 (m, 3H, 4'-H, $CH_3C\underline{H}_2O$), 4.34 (B) and 4.36 (A) (2dd, 1H, 5a-H, $^2J_{5a,5b}$ = 12.3, 12.0, $^3J_{5a,4}$ = 5.7, 6.3), 4.45 (B) and 4.46 (A) (d, 1H, AB syst, J = 11.4, PhC$\underline{H}_2$), 4.62 (B) and 4.63 (A) (d, 1H, AB syst, J = 11.4, PhC$\underline{H}_2$), 4.74 (A) and 4.82 (B) (2d, 1H, 5b-H, $^2J_{5b,5a}$ = 12.3, 12.0), 4.89-4.97 (m, 1H, 4-H), 5.30 (d, 1H, 2'-H, $^3J_{2',3'}$ = 4.5), 5.46 (B) and 5.55 (A) (2d, 1H, 2-H, $^3J_{2,3}$ = 4.5), 6.07 (B) and 6.11 (A,B) (d and s, 2H, 1-H, 1'-H, $^3J_{1',2'}$ = 1.5), 7.28-7.44 (m, 7H, Bz, $\underline{Ph}$-CH_2), 8.00-8.04 (m, 2H, Bz). **^{13}C{^{1}H} NMR** δ 16.36 (B) and 16.40 (A) (d, $\underline{C}H_3CH_2$, $^3J_{C\text{-}P}$ = 6.0), 20.8, 20.9, 21.0, 21.1, 21.17, 21.23 ($\underline{CH_3}COO$), 26.5, 27.2, 27.39 and 27.42 ($C_{5'}$, $C_{6'}$), 42.0-43.4 (m, C_3), 63.1 (2d, $CH_3\underline{C}H_2$, $^2J_{C\text{-}P}$ = 6.8, $^4J_{C\text{-}F}$ = 5.3), 65.7-65.9 (m, C_5), 73.4 (-O$\underline{C}H_2$Ph), 73.67 (B) and 73.72 (A) ($C_{2'}$), 74.9 (B) and 75.7 (A) (2d, C_2, $^3J_{C\text{-}F}$ = 8.3, $^3J_{C\text{-}F}$ = 6.8), 77.4 (C_4), 80.2 ($C_{3'}$), 81.2 (B) and 81.3 (A) (2d, $C_{4'}$, J = 17.9, 17.6), 98.46, 98.51, 98.54, 98.56 (C_1, $C_{1'}$), 128.15, 128.2, 128.3, 128.4, 128.7, 128.9 (Ph), 131.2 (A) and 131.3 (B) (Bz), 137.08 (B) and 137.14 (A) (Ph), 139.88 (B) and 139.94 (A) (Ph), 165.2 (C=O), 168.8 (A), 168.9 (B), 169.06 (A), 169.11 (B), 169.6 (B), 169.7 (A), 169.9 (C=O), CF_2 was not detected. **^{19}F{^{1}H} NMR** δ diastereoisomer B: -115.7 (ddd, 1F, $^2J_{F\text{-}F}$ = 291, $^2J_{F\text{-}P}$ = 78, $^3J_{F\text{-}H}$ = 25), -102.2 (ddd, 1F, $^2J_{F\text{-}F}$ = 294, $^2J_{F\text{-}P}$ = 107, $^3J_{F\text{-}H}$ = 6); diastereoisomer A: -111.7 (ddd, $^2J_{F\text{-}F}$ = 291, $^2J_{F\text{-}P}$ = 102, $^3J_{F\text{-}H}$ = 20, 1F), -103.6 (ddd, $^2J_{F\text{-}F}$ = 294, $^2J_{F\text{-}P}$ = 82, $^3J_{F\text{-}H}$ = 11, 1F). **^{31}P{^{1}H} NMR** δ diastereoisomer A: 91.8 (dd, $^2J_{F\text{-}P}$ = 102, $^2J_{F\text{-}P}$ = 80); diastereoisomer B: 92.6 (dd, $^2J_{F\text{-}P}$ = 107, $^2J_{F\text{-}P}$ = 79). **HRMS** (ESI-TOF) m/z: Calcd for $C_{36}H_{42}Na^{35}ClF_2O_{15}PS$ $(M+Na)^+$: 857.1582; Found: 857.1549. **MS** (ESI$^+$, CH_3CN/H_2O) found: 833.1 $[M+H]^+$, 852.1 $[M+H_2O]^+$. **IR** ν max/cm^{-1}: 1745 and 1728 (C=O), 1014 (C-F), 733 (P=S).

6'-[[[5'-*O*-(4-Chlorobenzoyl)-3'-deoxy-1'-*N*-(1-thymidylyl)-2'-*O*-(acetyl)-*α*-*D*-*ribo*furanos-3'-yl]difluoromethyl]ethoxyphosphinothioyl]-5',8'-dideoxy-2'-*O*-(acetyl)-3'-*O*-(benzyl)-1'-*N*-(1-thymidylyl)-*α*-*D*-*ribo*-hexofuranose (20j). To an anhydrous 1,2-dichloroethane (3.0 ml) solution of thymine (154 mg, 1.19 mmol) was added BSA (0.6 ml, 2.33 mmol), and the mixture was heated at 80 °C for 1 h, after which period of time it was cooled down to 0 °C. An anhydrous 1,2-dichloroethane (3.0 ml) solution of compound **20i** (151 mg, 0.18 mmol) and TMSOTf (74 µl, 0.40 mmol) were then added and the resultant stirring reaction mixture was heated to 80 °C for 2 h, cooled down to room temperature and diluted with CH_2Cl_2 (5 mL). The crude solution was sequentially washed with a saturated aqueous solution of sodium bicarbonate (5 mL) and brine (5 mL). The organic layer was dried, filtered and then concentrated under reduced pressure. The residue was purified by chromatography and eluted with CH_2Cl_2/MeOH (80:1 to 60:1) to give **20j** as a white solid (115 mg, 66 % a 1:1 inseparable mixture of diastereomers A and B). **^{1}H NMR** δ 1.27 (B) and 1.28 (A) (2t, 3H, $\underline{CH_3}CH_2O$-P, ^3J = 7.0), 1.76 (A) and 1.77 (B) (2s, 3H, 5-CH_3), 1.91 (s, 3H, 5-CH_3), 2.10, 2.11, 2.12 and 2.14 (4s, 6H, CH_3COO-), 1.82-2.28 (m, 4H, 5'$_{II}$-H, 6'$_{II}$-H), 3.92-4.24 (m, 5H, 3'$_I$-H, 3'$_{II}$-H, 4'$_{II}$-H, $CH_3\underline{CH_2}O$-P), 4.43-4.61 (m, 3H, 5'$_I$-H, -CH_2-Ph), 4.74-4.90 (m, 2H, 5'$_I$-H, 4'$_I$-H), 5.34 (A) and 5.40 (B) (2d, 1H, 1'$_I$-H, $^3J_{1'\text{-}2'}$ = 1.3, 2.4), 5.44 (B) and 5.49 (A) (2dd, 1H, 2'$_{II}$-H, $^3J_{2'\text{-}1'}$ = 3.3, 2.7, $^3J_{2'\text{-}3'}$ = 5.8), 5.58 (A) and 5.60 (B) (2d, 1H, 1'$_{II}$-H, $^3J_{1'\text{-}2'}$ = 2.7, 3.3), 5.70 (A) and 5.82 (B) (d and dd, 1H, 2'$_I$-H, $^3J_{2'\text{-}3'}$ = 6.0, 6.6, $^3J_{2'\text{-}1'}$ = 2.4), 6.95-6.97 (m, 2H, 6-H), 7.27-7.34 (m, 5H, Ph), 7.40-7.44 (m, 2H, Bz), 8.01-8.06 (m, 2H, Bz), 9.42 (B), 9.54 (B), 9.63 (A)

and 9.74 (A) (4s, 2H, 3-NH). **^{19}F{^{1}H} NMR** δ diastereoisomer A: -113.4 (ddd, 1F, $^{2}J_{F-F}$ = 291, $^{2}J_{F-P}$ = 81, $^{3}J_{F-H}$ = 25), -100.8 (ddd,1F, $^{2}J_{F-F}$ = 291, $^{2}J_{F-P}$ = 94, $^{3}J_{F-H}$ = 8,); diastereoisomer B: -111.0 (ddd, 1F, $^{2}J_{F-F}$ = 292, $^{2}J_{F-P}$ = 100, $^{3}J_{F-H}$ = 23, 1F), -103.4 (ddd, 1F, $^{2}J_{F-F}$ = 291, $^{2}J_{F-P}$ = 82, $^{3}J_{F-H}$ = 11). **^{31}P{^{1}H} NMR** δ diastereoisomer A: 91.0 (dd, $^{2}J_{F-P}$ = 94, $^{2}J_{F-P}$ = 81); diastereoisomer B: 91.6 (dd, $^{2}J_{F-P}$ = 100, $^{2}J_{F-P}$ = 82). **^{13}C{^{1}H} NMR** δ 12.3 (B), 12.4 (A), 12.5 (A), 12.6 (B) ($C_{7I \text{ and } 7II}$), 16.4 (d, $^{3}J_{C-P}$ = 6, $\underline{C}H_3CH_2$), 20.8 (B), 20.9 (A), 21.1 (B), 21.2 (A) (C_{Ac}), 24.3 (A) and 24.9 (B) ($C_{5'II}$), 26.2 (A) and 26.7 (B) (2d, $^{1}J_{C-P}$ = 74, 74, $C_{6'II}$), 43.3-44.2 (m, $C_{3'I}$), 63.3 (A) and 63.4 (B) (2d, $^{2}J_{C-P}$ = 6, 7, $CH_3\underline{C}H_2$), 64.9-65.2 (m, $C_{5'I}$), 73.6 (A) and 73.7 (B) $C_{\underline{C}H2Ph}$), 73.9 (B) and 74.1 (A) ($C_{2'II}$), 75.4 (B) and 75.6 (A) (2d, $^{3}J_{C-F}$ = 7, 7, $C_{2'I}$), 77.4 (m, $C_{4'I}$), 79.1 ($C_{3'II}$), 80.9 (A) and 81.0 (B) (2d, $^{3}J_{C-P}$ = 18, 17, $C_{4'II}$), 91.5 (B) and 93.0 (A) ($C_{1'II}$), 94.3 (B) and 95.1 (A) ($C_{1'I}$), 111.4 (A), 111.5 (B), 111.6 (B), 111.7 (A) (C_5), 119.8 (m, CF_2), 128.2, 128.3, 128.4, 128.7, 129.0 (Ph), 131.3 (Bz), 137.18 and 137.22 (Ph, q), 138.0, 138.1, 138.2 (C_6), 139.9 (A) and 140.0 (B) (Ph, q), 150.06, 150.11, 150.5 (C_2), 163.8 (A), 164.01 (B), 164.04 (B), 164.4 (A) (C_4), 165.4 ($C_{6'I}$), 170.3 (B), 170.36 (A), 170.44 (A), 170.5 (B) (C_{Ac}). **HRMS** (ESI-TOF) m/z: Calcd for $C_{42}H_{45}{}^{35}ClF_2N_4O_{14}PS$ $(M-H)^-$: 965.2053; Found: 965.2057. **MS** (ESI, CH_3CN/H_2O) found: 966.9 $[M+H]^+$, 990.3 $[M+Na]^+$. **IR** ν max/cm^{-1}: 1720, 1688 (C=O), 1227 (C-N), 1090 (C-F), 1014 (P-O), 759 (P=S).

6'-[[[5'-*O*-(4-Chlorobenzoyl)-3'-deoxy-1'-*N*-(1-thymidylyl)-2'-*O*-(acetyl)-*α*-*D*-*ribo*furanos-3'-yl]difluoromethyl]ethoxyphosphinyl]-5',8'-dideoxy-2'-*O*-(acetyl)-3'-*O*-(benzyl)-1'-*N*-(1-thymidylyl)-*α*-*D*-*ribo*-hexofuranose (12h). To a stirring solution of compound **20j** (89 mg, 0.09 mmol) in dry CH_2Cl_2 (2 ml) at 0 °C was added *m*-CPBA (59 mg, 0.24 mmol) in one crop. The mixture was stirred for 3 h and quenched with a saturated aqueous solution of sodium thiosulfate (5 mL). The aqueous layer was extracted twice with CH_2Cl_2 (2x5 mL) and the combined organic layers were sequentially washed with a sodium bicarbonate saturated aqueous solution (5 mL), a saturated aqueous solution of ammonium chloride (5 mL) and brine (5 mL). Drying, filtration and concentration under reduced pressure afforded a crude residue which was purified by chromatography and eluted with CH_2Cl_2/MeOH (10:1) to deliver a [1:1] mixture of diastereomers **12h** (61 mg, 81 %, white solid). For analytical purposes, a 4:1 mixture of each *P*-centered diastereoisomers A:B was isolated by additional chromatography and fully characterized. **^{1}H NMR** δ 1.31 (t, 0.8x3H, *J* = 7.0, A), 1.32 (t, 0.2x3H, *J* = 7.0, B), 1.76 (s, 0.8x3H, A), 1.78 (s, 0.3x3H, B), 1.89 (s, 3H), 2.09 (2s, 2x0.8x3H, A), 2.11 (2s, 2x0.2x3H, B), 1.85-2.13 (m, 4H), 3.66-4.00 (m, 2H), 4.04-4.29 (m, 3H), 4.41-4.62 (m, 3H), 4.72-4.92 (m, 2H), 5.38-5.54 (m, 3H), 5,71 (0.2H, dd, min, *J* = 6.9 and 2.5, B), 5,79 (0.8H, dd, maj, *J* = 7.0 and 3.2, A), 6.87-7.00 (m, 2H, C*H* ^{thymine}), 7.21-7.36 (m, 5H, Ar^{H}), 7.37-7.45 (m, 2H, Ar^{H}), 7.96-8.06 (m, 2H, Ar^{H}), 8.81 (0.8H, A, N*H*), 8.84 (0.2H, B, N*H*), 8.92 (0.2H, B, N*H*), 8.96 (0.8H, A, N*H*). **^{13}C{^{1}H} NMR** δ 12.5 (CH_3), 12.6 (CH_3), 16.8 (d, $^{3}J_{C-P}$ = 5.0, CH_3), 20.9-21.1 (m, 2xC), 24.0 (br, CH_2), 29.9 (br, CH_2), 43.2-44.0 (m, *C*H), 63.5 (d, $^{2}J_{C-P}$ = 6.6, CH_2), 65.1 (CH_2), 73.8 (CH_2), 73.9 (*C*H), 75.1 (d, $^{3}J_{C-F}$ = 6.0, *C*H), 76.8 (m, *C*H, overlap with solvent signal and deduced from DEPT experiment), 79.0 (*C*H), 81.2 (d, $^{3}J_{C-P}$ = 16.5, *C*H), 92.4 (*C*H), 94.8 (*C*H), 111.6 (*C*), 111,7 (*C*), 128.2 (*C*), 128.3 (*C*H), 128.5 (*C*H), 128.8 (*C*H), 129.1 (*C*H), 131.4 (*C*H), 137.3 (*C*), 137.8 (*C*H), 138.1 (*C*H), 140.1 (*C*), 150.0 (*C*), 150.1 (*C*), 163.7 (*C*=O), 163.8 (*C*=O), 165.4 (*C*=O), 170.4 (*C*=O), 170.6 (*C*=O), (CF_2 unobserved due to multiplicity). **^{19}F{^{1}H} NMR** δ diastereoisomer B: -112.4 *(*dd, 1F, J_{F-F} = 306.4, J_{P-F} = 101.1, J_{F-H} = 22.9), -105.6 (dd, 1F, J_{F-F} = 306.4, J_{P-F} = 85.9, J_{F-H} = 20.5); diastereoisomer A: -111.8 (dd, 1F, J_{F-F} = 307.0, J_{P-F} = 101.1, J_{F-H} = 20.5), -106.5 (dd, 1F, J_{F-F} = 307.0, J_{P-F} = 84.5, J_{F-H} = 15.5). **^{31}P{^{1}H} NMR** δ diastereoisomer B: 40.2 (dd, 1P, J_{P-F} = 101.1, J_{P-F} = 85.9); diastereoisomer A: 40.9 (dd, 1P, J_{P-F} = 101.1, J_{P-F} = 84.5). **IR** ν max/cm^{-1}: 1695 (C=O), 1265 (P=O), 1229 (C-N), 1092 (C-F), 1015 (P-O). **MS** (ESI^-, CH_3CN/H_2O) found: 921,27 $[M-Et]^-$. **Anal**. Calcd. for $C_{42}H_{46}ClF_2N_4O_{15}P$: C, 53.03; H, 4.87; N, 5.89. Found: C, 53.08; H, 4.89; N, 5.92.

ASSOCIATED CONTENT

Supporting Information

Copy of ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra of the compounds (PDF)

The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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