Synthesis of Enantiomerically Pure 2′,3′,5′-Trideoxy-4′-[(diethoxyphosphoryl)difluoromethyl]thymidine Analogues

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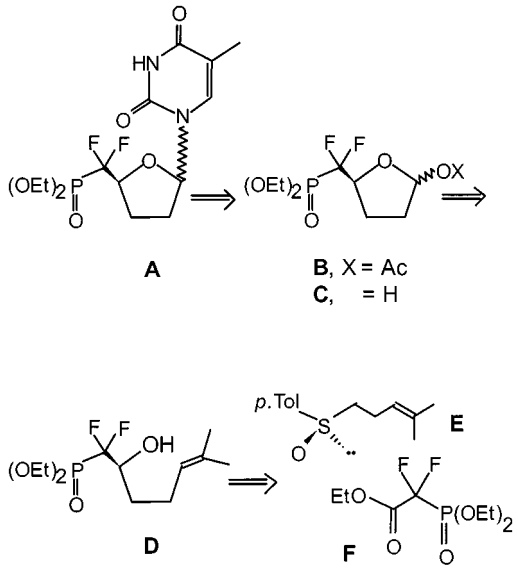
D- and L-(diethoxyphosphoryl)difluoromethyl nucleoside analogues **10** have been synthesized using the building block approach, starting from chiral fluorinated molecules. The key steps of the synthetic sequence were condensation of 2-methyl-5-(4-methylphenylsulfinyl)pent-2-ene (**1**) and ethyl 2-(diethoxyphosphoryl)-2,2-difluoroacetate (**2**), reduction of the thus formed ketones **3** to alcohols **4**, reductive removal of the sulfur moiety to give hydroxy phosphonates **6**, and oxidative cyclization to give furanose derivatives **8**.

Phosphonates[1] and structurally novel phosphonate isosters[2] or non-isosters[3] can mimic phosphates in biological systems. The resistance of the phosphorus−carbon phosphonate linkage to hydrolysis by chemical agents or esterases is one of the features responsible for their increasing popularity. Fluoro-substitution at the α-carbon of phosphonates may increase the effectiveness of these phosphate mimetics as a result of both geometric and electronic factors.[4] The replacement of phosphates by fluorophosphonates has provided a number of analogues showing significant activity.[5] A number of fluoromethylene phosphonates,[6] as well as some anomeric[7] and conformationally constrained[8] isosters of nucleotides have recently been prepared and evaluated with regard to their enzymatic inhibitory activity.

As part of our program devoted to exploring the utility of the 4-methylphenylsulfinyl chiral auxiliary group in the synthesis of new fluoro-substituted nucleoside analogues, we have reported the synthesis of enantiomerically pure 3′-arylsulfonyl thymidine phosphonate analogues bearing a fluoromethyl group at the 4′-position of the sugar ring,[9] and of chiral and enantiomerically pure 4′-difluoromethylphosphonate thymidine analogues bearing a sulfonyl moiety at the 3′-carbon of the glycosidic fragment of the molecule.[10]

Since the removal of the 3′-(4-methylphenylsulfonyl) moiety[11] from 4′-difluoromethylphosphoryl-3′-sulfonyl thymidine analogues[10] did not afford 2′,3′-dideoxy-dihydro-4′-difluoromethylphosphonate thymidine analogues **10**, but rather led to decomposition of the substrates,[12] we focused on a different approach for obtaining enantiomerically pure compounds **10** in a targeted manner.

As depicted in Scheme 1, starting from 2-methyl-5-(4-methylphenylsulfinyl)pent-2-ene (**E**) and ethyl 2-(diethoxyphosphoryl)-2,2-difluoroacetate (**F**)[14] and following a seven-step synthetic sequence, the final derivatives **A** were obtained. As a masked anomeric carbon on sulfoxide **E**, a trisubstituted double bond was chosen in order to avoid total or partial hydrogenation of the olefin during the hydrogenolytic step of the desulfinylation. Ethyl 2-(diethoxyphosphoryl)-2,2-difluoroacetate (**F**) was prepared following the methodology described previously.[10]



Scheme 1. Retrosynthesis

Results and Discussion

Synthesis of α-[(Diethoxyphosphoryl)difluoromethyl]-α′-sulfinyl Alcohols (4)

The lithium derivative of 2-methyl-5-(4-methylphenylsulfinyl)pent-2-ene (**1**) (obtained by treatment with LDA in THF at −60°C) was acylated with ethyl 2-(diethoxyphosphoryl)-2,2-difluoroacetate (**2**) in the same solvent at −70°C (Scheme 2). A mixture of labile diastereomeric ke-

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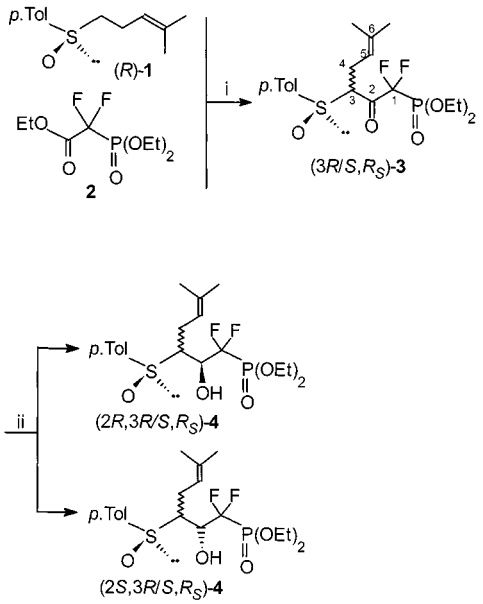
tones **3** was obtained, which, after rapid workup, was treated with sodium borohydride at 0°C to afford the secondary alcohols **4** in 85% overall yield. After repeated flash chromatographic purification, the four diastereomers **4** were isolated as C-3 epimeric pairs of compounds.



Scheme 2. Reagents and conditions: (i) LDA, THF, −70°C; (ii) $NaBH_4$, CH_3OH/NH_3, 0°C

Synthesis of 4′-[(Diethoxyphosphoryl)difluoromethyl]-pentofuranose (8)

The synthetic sequence starting from the aforementioned 3-epimeric mixture of alcohols (2*R*,3*R*/*S*,R_S)-**4** is depicted in Scheme 3. The desulfinylated product **6** was obtained following a two-step sequence: deoxygenation of the sulfinyl group with sodium iodide and trifluoroacetic anhydride[15] followed by hydrogenolytic cleavage of the sulfinylic carbon−sulfur bond with Raney-Ni. The latter step was carried out under carefully controlled reaction conditions designed to minimize (< 5%) the simultaneous hydrogenation of the double bond.[16] The enantiomeric purity of (*S*)-**6** at this stage was checked with the aid of a lanthanide shift reagent (vide infra). In contrast to a literature report on analogous substrates,[17] no evidence of epimerization at the carbon stereocentre of the secondary alcohol was detected in the course the hydrogenolytic desulfinylation step.

The C=C bond of (*S*)-**6** was then subjected to oxidative cleavage with sodium periodate/ruthenium trichloride in a two-phase system ($CCl_4/CH_3CN/H_2O$, 1:1:2). The intermediate aldehyde thus formed underwent spontaneous ring-closure at the secondary hydroxyl group to give the lactol **8** in 88% yield. ^{1}H- and ^{19}F-NMR analyses of the product showed that it consisted of a 1:1 mixture of the β(1*R*) and α(1*S*) anomers. The corresponding γ-lactone, (*S*)-**7**, arising from excessive oxidation of the aldehyde, was formed in low yields (6%). This could be converted back to the lactol **8** by reduction with DIBAH in toluene.

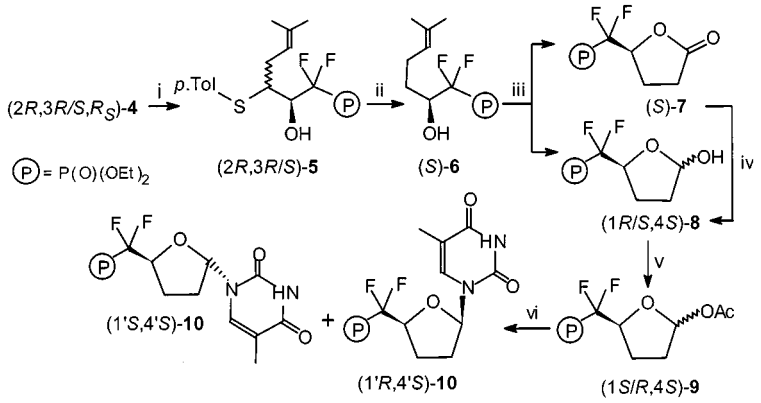
Synthesis of 4′-[(Diethoxyphosphoryl)difluoromethyl] Nucleoside Analogues (10)

Activation of the lactol **8** for the subsequent condensation with the nucleobase was performed by acetylation with acetic anhydride in pyridine and gave a 10:1 *anti*/*syn* epimeric mixture of the α(1*R*) and β(1*S*) acetyl derivatives **9**. Coupling of the activated persilylated thymine with **9** was performed in dichloroethane at 45°C and required 20 min in the presence of trimethylsilyl triflate as catalyst. In this way, the corresponding 4′-[(diethylphosphoryl)difluoromethyl]thymidine analogues were obtained as a 2:1 epimeric mixture of (1′*R*,4′*S*)- [β epimer] and (1′*S*,4′*S*)-**10** [α epimer] in 95% overall yield.

Application of the same synthetic sequence to (2*S*,3*R*/*S*,R_S)-**4** afforded, in comparable overall chemical yield, the nucleoside analogues of the L series: (1′*S*,4′*R*)- [α epimer] and (1′*R*,4′*R*)-**10** [β epimer].

Structural and Configurational Assignments − Enantiomeric Purity

The ^{1}H-, ^{13}C-, ^{19}F-, and ^{31}P-NMR spectra of compounds **4**−**14** were in good agreement with the proposed structures. The stereochemistry at the 2-position of the chain was assigned by esterification of the desulfurized alcohols **6** with chiral phenylpropionic acids and then subjecting the products to ^{1}H-NMR-spectral analyses according to the Helmchen method.[18] ^{19}F-NMR spectra of the alcohols **4** having a 3-methylbut-2-enyl residue at the 3-position of the chain showed close similarity with the corresponding compounds used as substrates in the preceding work,[10] where a ω-propenyl chain was attached to the carbon atom in the position α to the sulfinyl sulfur. This evidence allowed unequivocal assignment of the absolute stereochemistries at C-2 and C-3. The stereochemistries of the 1-acetyl derivatives **9** and of the nucleoside analogues **10** followed from ^{1}H{^{1}H} and ^{1}H{^{19}F} NOE experiments. Thus, upon irradiation of both the OCH_2 protons and the fluorine atoms, 1-H showed sizeable NOE enhancements (0.5%) in (1*S*,4*S*)-**9**, but not in the C-1 epimer. Considering the nucleoside analogues **10**, saturation of the fluorine nuclei at δ = −119.99 and δ = −125.26 in the major isomer (1′*R*,4′*S*)-**10** enhanced the 6-H signal (1.5 and 2.0%, respectively), whereas no NOE enhancements were observed between the corresponding nuclei in the minor epimer (1′*S*,4′*S*)-**10**. It is also interesting to note that in this series of compounds, the ^{13}C-NMR spectra of **10** show long-range, through-space coupling of C-6 of the nucleobase with both diastereotopic F nuclei on the remote R_f moiety. This coupling was detectable only for the β anomer. In the broad-band decoupled ^{13}C{^{1}H}-NMR spectrum of (1′*R*,4′*S*)-**10** [β anomer] in $CDCl_3$ (see Scheme 3), the signal assigned to C-6 appeared as a dd, with two J_{CF} = 2.5 Hz.[19] The corresponding signal of (1′*S*,4′*S*)-**10** [α anomer] appeared as a singlet. Interestingly, the through-space transmitted coupling was no longer seen when the spectrum was recorded in DMSO, even though ^{1}H{^{19}F} NOE experiments in the latter solvent

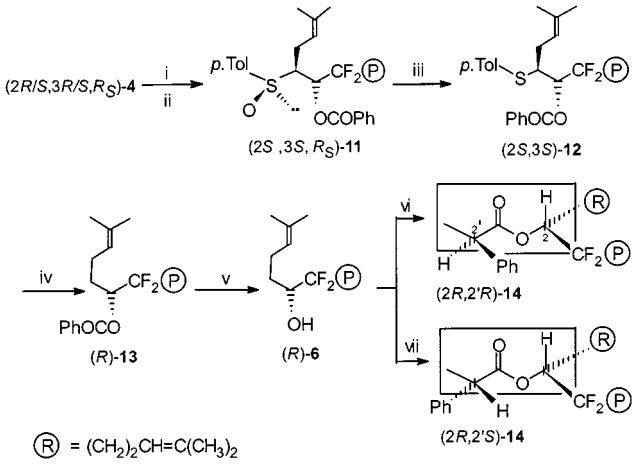


Scheme 3. Reagents and conditions: (i) NaI, $(CF_3CO)_2O$, acetone, −20°C; (ii) Raney-Ni, C_2H_5OH, 80°C; (iii) $RuCl_3$, $CCl_4/CH_3CN/H_2O$ (1:1:2), $NaIO_4$, 0°C; (iv) DIBAH, toluene, −60°C; (v) $(CH_3CO)_2O$, Py, 0°C; (vi) thymine, HMDS, $(NH_4)_2SO_4$, reflux, TMSiOTf, $(CH_2Cl)_2$, 45°C

revealed that both diastereotopic F atoms are in spatial proximity to 6-H of the nucleobase, indicating that the hydrogen-bond properties of the solvent play a role in the transmission of spin-spin coupling. This finding is in good agreement with what has previously been reported in the case of 2′,3′-dideoxy-4′-fluoroalkyl nucleosides.[20] It was demonstrated that this kind of through-space coupling is mediated by intramolecular C−F···H−C hydrogen bonds. The data for the phosphonates **10** confirm that through-space coupling constants may be used as an easy and straightforward stereochemical tool in the structural characterization of compounds of this class.

The enantiomeric purity of (*S*)-**6** was carefully checked by both the lanthanide shift reagent method and by esterification with chiral acids (see Experimental Section). Moreover, Scheme 4 depicts a synthetic sequence starting from a diastereomerically pure benzoyl derivative **11** of the aforementioned alcohols **4**. The epimerization that might affect the C-2 stereocentre during the desulfinylation step can, in fact, be avoided in the presence of the *O*-benzoyl protection.[21] The mixture of diastereomeric alcohols **4** was esterified and the benzoyl derivative, (2*S*,3*S*,R_S)-**11**, was isolated as a pure compound. This was then further reacted to afford the heptenol (*R*)-**6**, which was submitted to esterification with (*R*)- and (*S*)-2-phenylpropionic acids. The ^{1}H- and ^{19}F-NMR spectra of the derivatives **14** were superimposable on those of the analogues derived from the enantiomer (*S*)-**6** without the benzoylation step (Scheme 3). This finding further confirmed that the desulfinylation step was not accompanied by any racemization, even in the absence of the *O*-benzoyl protecting group.

The absolute stereochemistry at C-3 of the benzoyl derivatives **12** was assigned through chemical correlations.[22]



Scheme 4. Reagents and conditions: (i) PhCOOH, DCC, DMAP, CH_2Cl_2, 0°C; (ii) flash column-chromatographic separation; (iii) NaI, $(CF_3CO)_2O$, acetone, −20°C; (iv) Raney-Ni, C_2H_5OH, 80°C; (v) NaOH, CH_3OH, room temp.; (vi) (−)-(*R*)-2-phenylpropionic acid, DCC, DMAP, CH_2Cl_2, 0°C; (vii) (+)-(*S*)-2-phenylpropionic acid, DCC, DMAP, CH_2Cl_2, 0°C

Concluding Remarks

Both D- and L-2′,3′-dideoxy-difluoromethylphosphonate nor-analogues of thymidine nucleotide have been obtained by a total synthesis starting from (R_S)-2-methyl-5-(4-methylphenylsulfinyl)pent-2-ene (**1**) and ethyl 2-(diethoxyphosphoryl)-2,2-difluoroacetate (**2**). Seven steps were required and the products were obtained in 45% overall chemical yield.

Experimental Section

General Details: $[\alpha]_D$ values were obtained on JASCO DIP-181 and PROPOL polarimeters. − TLC was performed on Merck silica gel 60 F_{254}. − Flash column-chromatographic purifications were performed on silica gel 60 (60−200 μm, Merck). − ^{1}H-, ^{13}C-, ^{19}F-, and ^{31}P-NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC 250L spectrometer operating at 250 MHz and equipped with a supplementary broadband modulator BM1. Chemical shifts are expressed in ppm (δ), referenced to internal tetramethylsilane (TMS) for ^{1}H and ^{13}C nuclei (δ_H and δ_C = 0.00); C_6F_6 was used as an internal standard (δ_F = −162.90) for ^{19}F, and external H_3PO_4 (δ_P = 0) for ^{31}P. In descriptions of the ^{13}C-NMR spectra, upper case letters denote the patterns resulting from one bond (C,H) coupling constants, while lower case letters denote (C,F) and (C,P) coupling constants. − Mass spectra were recorded on a TSQ 70 Finnigan MAT three-stage quadrupole instrument. − Infrared

spectra were obtained using a Perkin−Elmer System 2000 FT-IR spectrometer (scan range: 15600 cm^{-1}; combined scan direction). − Combustion microanalyses were performed by Redox SNC, Cologno Monzese (Milano). − THF was freshly distilled from Na; diisopropylamine was freshly distilled from CaH_2; in all other cases, commercially available reagent-grade solvents were employed without purification. − All reactions involving organic solvents were performed under nitrogen atmosphere in flame-dried glassware.

Synthesis of (2*R*,3*R*,R_S)-, (2*R*,3*S*,R_S)-, (2*S*,3*S*,R_S)- and (2*S*,3*R*,R_S)-Diethyl 1,1-Difluoro-2-hydroxy-6-methyl-3-(4-methylphenylsulfinyl)hept-5-enylphosphonates (4): A solution of 2-methyl-5-(4-methylphenylsulfinyl)pent-2-ene (**1**, 6.5 mmol, 1.4 g) in THF (25 mL) was added dropwise to a solution of LDA (7.7 mmol, 1.1 mL) in THF (13 mL) stirred at −70°C under nitrogen atmosphere. After 5 min at this temperature, a solution of diethyl (ethoxycarbonyl)(difluoromethyl)phosphonate (**2**, 7.7 mmol, 2.0 g) in THF (13 mL) was similarly added to the yellow solution. After 2 min, the reaction was quenched by the addition of a saturated solution of NH_4Cl and the organics were extracted with Et_2O. The combined extracts were dried with anhydrous sodium sulfate, filtered, and concentrated to dryness under reduced pressure. The residue thus obtained, consisting of a 1:1 mixture of (3*R*,R_S)-/(3*S*,R_S)-diethyl 1,1-difluoro-6-methyl-3-(4-methylphenylsulfinyl)-2-oxo-hept-5-enylphosphonates (**3**), was reduced directly without further purification.

The crude residue was taken up in a 9:1 mixture of methanol and ammonia (30% aqueous solution, 30 mL), the resulting solution was cooled to 0°C, and a suspension of $NaBH_4$ (7.7 mmol, 291 mg) in the same solvent mixture (30 mL) was added dropwise. After 10 min, the reaction was quenched by adding dilute aq. HCl until pH 4 was attained. The solvents were then evaporated under reduced pressure and to the remaining aqueous phase was added Et_2O (3 × 30 mL). After separation of the layers, the organic phase was dried with anhydrous sodium sulfate and a residue was isolated following standard workup. ^1H- and ^{19}F-NMR spectra of the crude material revealed the following diastereoisomeric ratio: (2*R*,3*R*,R_S)/(2*R*,3*S*,R_S)/(2*S*,3*S*,R_S)/(2*S*,3*R*,R_S)-**4** = 1.8:1.3:1.0:2.4 in 85% overall yield. Repeated flash column chromatography eluting with *n*-hexane/AcOEt, 1:1, allowed the separation of the diastereomeric pairs of alcohols **4**: (2*R*,3*R*,R_S)- together with (2*R*,3*S*,R_S)-**4**: 1.17 g (41%). − R_f = 0.35. − ^1H NMR ($CDCl_3$): δ = 1.2−1.4 (m, 2 × 6 H, 4 × OCH_2CH_3), 1.5−1.8 (br. s, 2 × 6 H, 4 × 6-Me), 2.3−3.1 (m, 2 × 6 H, 2 × 3-H, 2 × 4-H_2 and 2 × ArMe), 4.0−4.7 (m, 2 × 5 H, 2 × 2-H and 4 × OCH_2CH_3), 5.05 and 5.10 (m, 2 × 1 H, 2 × 5-H), and 7.2−7.7 (m, 2 × 4 H, ArH). − ^{19}F NMR ($CDCl_3$): (2*R*,3*R*,R_S)-**4**: δ = −125.65 (br. ddd, *J* = 304.0, 101.3 and 21.9 Hz, 1 F, F-1a) and −111.88 (br. ddd, *J* = 304.0, 98.0 and 5.5 Hz, 1 F, F-1b); (2*R*,3*S*,R_S)-**4**: δ = −126.02 (br. ddd, *J* = 302.5, 101.3 and 23.5 Hz, 1 F, F-1a) and −115.67 (br. ddd, *J* = 302.5, 99.0 and 5.0 Hz, 1 F, F-1b). − ^{31}P NMR ($CDCl_3$): δ = 6.5−7.5 (m, 2 × 1 P, 2 × P-1). − $C_{19}H_{29}F_2O_5PS$ (438): calcd. C 52.05, H 6.67; found C 52.02, H 6.65.

(2*S*,3*R*,R_S)-**4** together with (2*S*,3*S*,R_S)-**4**: 1.28 g (45%). − R_f = 0.32. − ^1H NMR ($CDCl_3$): δ = 1.2−1.4 (m, 2 × 6 H, 4 × OCH_2CH_3), 1.5−1.8 (br. s, 2 × 6 H, 4 × 6-Me), 2.3−3.1 (m, 2 × 6 H, 2 × 3-H, 2 × 4-H_2 and 2 × ArMe), 4.0−4.7 (m, 2 × 5 H, 2 × 2-H and 4 × OCH_2CH_3), 4.90 and 5.29 (m, 2 × 1 H, 2 × 5-H), 7.2 and 7.7 (m, 2 × 4 H, ArH). − ^{19}F NMR ($CDCl_3$): (2*S*,3*R*,R_S)-**4**: δ = −124.84 (br. ddd, *J* = 302.4, 101.1 and 22.6 Hz, 1 F, F-1a), −118.02 (br. ddd, *J* = 302.4, 100.0 and 6.8 Hz, 1 F, F-1b); (2*S*,3*S*,R_S)-**4**: δ = −121.82 (br. ddd, *J* = 303.7, 100.1 and 20.3 Hz, 1 F, F-1a) and −116.43 (br. ddd, *J* = 303.7, 100.3 and 9.0 Hz, 1 F, F-1b). − ^{31}P NMR ($CDCl_3$): δ = 6.1−6.7 (m, 2 × 1 P, 2 × P-1). − $C_{19}H_{29}F_2O_5PS$ (438): calcd. C 52.05, H 6.67; found C 52.07, H 6.68.

As a by-product, (*E*)-diethyl 1,1-difluoro-2-hydroxy-6-methylhepta-3,5-dienylphosphonate was isolated: 116 mg (6%). − R_f = 0.42. − ^1H NMR ($CDCl_3$): δ = 1.36 and 1.38 (t, *J* = 7.0 Hz, 6 H, 2 × OCH_2CH_3), 1.79 (br. s, 6 H, 2 × 6-Me), 3.30 (d, *J* = 6.1 Hz, 1 H, 2-OH), 4.27 (m, 4 H, 2 × OCH_2CH_3), 4.55 (br. ddddd, *J* = 16.5, 8.4, 7.2, 6.5 and 6.1 Hz, 1 H, 2-H), 5.62 (br. dd, *J* = 15.1 and 6.5 Hz, 1 H, 3-H), 5.88 (br. d, *J* = 11.2 Hz, 1 H, 5-H), 6.65 (br. dd, *J* = 15.1 and 11.2 Hz, 1 H, 4-H). − ^{19}F NMR ($CDCl_3$): δ = −124.79 (br. ddd, *J* = 303.0, 100.3 and 16.5 Hz, 1 F, F-1a), −117.01 (br. ddd, *J* = 303.0, 100.2 and 8.4 Hz, 1 F, F-1b). − ^{31}P NMR ($CDCl_3$): δ = 7.59 (br. dd, *J* = 100.3 and 100.2 Hz, 1 P, P-1). − $C_{12}H_{21}O_4F_2P$ (298): calcd. C 48.32, H 7.09; found C 48.37, H 7.10.

Synthesis of (2*R*,3*R*)-, (2*R*,3*S*)-, (2*S*,3*S*)-, and (2*S*,3*R*)-Diethyl 1,1-Difluoro-2-hydroxy-6-methyl-3-(4-methylphenylsulfenyl)hept-5-enylphosphonate (5). − General Procedure: A solution of trifluoroacetic anhydride (5.1 mmol, 724 μL) in acetone (5 mL) was added dropwise to a stirred suspension of the (diethoxyphosphoryl)difluoromethyl sulfinyl **4** (1.7 mmol, 744 mg) and NaI (3.4 mmol, 517 mg) in the same solvent (15 mL) at −20°C under N_2. After 10 min, the reaction was quenched by adding a satd. aq. solution of Na_2SO_3 and $NaHCO_3$, the organics were extracted with Et_2O and, after standard workup, a residue was obtained, which was purified by flash chromatography eluting with *n*-hexane/AcOEt, 8:2.

(a) Reaction of (2*R*,3*R/S*,R_S)-**4** afforded (2*R*,3*R/S*)-**5**: 610 mg (85%). − R_f = 0.35. − $C_{19}H_{29}O_4F_2PS$ (422): calcd. C 54.02, H 6.92; found C 54.00, H 6.97. − ^1H-, ^{19}F-, and ^{31}P-NMR data of compounds (2*R*,3*R*)- and (2*R*,3*S*)-**5** are reported in Table 1.

(b) Reaction of (2*S*,3*S/R*,R_S)-**4** afforded (2*S*,3*S/R*)-**5**: 624 mg (87%). − R_f = 0.35. − ^1H-, ^{19}F-, and ^{31}P-NMR data were superimposable on those of the aforementioned enantiomers (Table 1). − MS (DIS EI); *m/z* (%): 422 [(M + H)$^{+\cdot}$] (25), 285 [$C_{15}H_{19}SOF_2^{+\cdot}$] (14), 267 [(285 − H_2O)$^{+\cdot}$] (100), 199 [$C_{10}H_9SF_2^{+\cdot}$] (30), 149 [$C_9H_9S^{+\cdot}$] (12), 123 [$C_7H_7S^{+\cdot}$] (41), 91 [$C_7H_7^{+\cdot}$] (24), 77 [$C_6H_5^{+\cdot}$] (12), 69 [$C_5H_9^{+\cdot}$] (6), 43 [$C_3H_7^{+\cdot}$] (5). − $C_{19}H_{29}O_4F_2PS$ (422): calcd. C 54.02, H 6.92; found C 54.05, H 6.90.

Synthesis of (*S*)- and (*R*)-Diethyl 1,1-Difluoro-2-hydroxy-6-methylhept-5-enylphosphonate (6). − General Procedure: N_2 was bubbled through a suspension of Raney-Ni (500 mg) in ethanol (5 mL) at room temp. for 2 h. Then, a solution of the thioalcohol **5** (1.18 mmol, 500 mg) in ethanol (15 mL), which had been pretreated by bubbling N_2 for 4 h, and cyclohexene (500 μL) were added. The resulting mixture was refluxed under N_2 for 1 h, and then the Raney-Ni was filtered off, carefully washed with EtOAc (5 × 3 mL), and the combined clear extracts were concentrated to dryness in vacuo. The residue was purified by flash column chromatography eluting with *n*-hexane/EtOAc, 7:3.

(a) Reaction of (2*R*,3*R/S*)-**5** afforded (*S*)-**6**: 284 mg (80%). − R_f = 0.35. − $[\alpha]_D^{20}$ = −9.50 (*c* = 0.5, $CHCl_3$). − $C_{12}H_{23}O_4F_2P$ (300): calcd. C 48.00, H 7.72; found C 48.07, H 7.70. − ^1H-, ^{19}F-, and ^{31}P-NMR data are reported in Table 1.

As a by-product, (*S*)-diethyl 1,1-difluoro-2-hydroxy-6-methylheptylphosphonate was obtained: 18 mg (5%). − R_f = 0.40 (*n*-hexane/AcOEt, 2:3). − $[\alpha]_D^{20}$ = −11.2 (*c* = 0.7, $CHCl_3$). − ^1H NMR ($CDCl_3$): δ = 0.88 (d, *J* = 6.5 Hz, 6 H, 2 × 6-Me), 1.1−1.8 (m, 7 H, 6-H, 3-, 4- and 5-H_2), 1.39 (br. t, *J* = 7.2 Hz, 6 H, 2 × OCH_2CH_3), 2.20 (br. s, 1 H, 2-OH), 3.96 (m, 1 H, 2-H), 4.30 (m, 4 H, 2 × OCH_2Me). − ^{19}F NMR ($CDCl_3$): δ = −126.87 (br. ddd,

Table 1. NMR data for compounds **5**, **6** and **9**

Compound	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{19}F NMR ($CDCl_3$/C_6F_6) δ, *J* (Hz)	^{31}P NMR ($CDCl_3$/H_3PO_4) δ, *J* (Hz)
(2*R*,3*R*)-**5**	1.34 and 1.36 (t, *J* = 7.1 Hz, 6 H, 2 × OCH_2CH_3), 1.56 and 1.71 (br. s, 6 H, 2 × 6-Me), 2.20 and 2.53 (m, 2 H, 4-H_2), 2.31 (br. s, 3 H, ArMe), 2.98 (br. signal, 1 H, 2-OH), 3.43 (m, 1 H, 3-H), 3.99 (dddd, *J* = 21.7, 6.0, 5.3 and 3.2 Hz, 1 H, 2-H), 4.2−4.4 (m, 4 H, 2 × OCH_2Me), 5.23 (m, 1 H, 5-H), 7.10 and 7.36 (m, 4 H, ArH)	−125.81 (br. ddd, *J* = 305.1, 103.0 and 21.7 Hz, 1 F, 1a-F), −114.80 (br. ddd, *J* = 305.1, 101.5 and 6.0 Hz, 1 F, 1b-F)	7.01 (br. dd, *J* = 103.0 and 101.5 Hz, 1 P, P-1)
(2*R*,3*S*)-**5**	1.32 and 1.34 (t, *J* = 7.1 Hz, 6 H, 2 × OCH_2CH_3), 1.64 and 1.73 (br. s, 6 H, 2 × 6-Me), 2.38 and 2.63 (m, 2 H, 4-H_2), 2.33 (br. s, 3 H, ArMe), 2.60 (br. signal, 1 H, 2-OH), 3.53 (m, 1 H, 3-H), 4.1−4.4 (m, 4 H, 2 × OCH_2Me), 4.16 (m, 1 H, 2-H), 5.35 (m, 1 H, 5-H), 7.10 and 7.32 (m, 4 H, ArH)	−124.33 (br. ddd, *J* = 305.5, 105.3, and 23.9 Hz, 1 F, 1a-F), −117.82 (br. ddd, *J* = 305.5, 100.3 and 6.3 Hz, 1 F, 1b-F)	6.85 (br. dd, *J* = 105.3 and 100.3 Hz, 1 P, P-1)
(*S*)-**6**	1.39 (t, *J* = 7.1 Hz, 6 H, 2 × OCH_2CH_3), 1.5−1.8 (m, 2 H, 3-H_2), 1.63 and 1.68 (br. s, 6 H, 2 × 6-Me), 1.9−2.4 (m, 2 H, 4-H_2), 2.86 (d, 1 H, *J* = 6.4 Hz, 2-OH), 3.98 (m, 1 H, 2-H), 4.30 (m, 4 H, 2 × OCH_2Me), 5.12 (m, 1 H, 5-H)	−126.64 (br. ddd, *J* = 304.5, 105.2 and 18.4 Hz, 1 F, 1a-F), −118.28 (br. ddd, *J* = 304.5, 102.3 and 7.5 Hz, 1 F, 1b-F)	7.72 (br. dd, *J* = 105.2 and 102.3 Hz, 1 P, P-1)
(1*R*,4*S*)-**9**	1.38 (br. t, *J* = 7 Hz, 6 H, 2 × OCH_2CH_3), 2.04 (s, 3 H, $OCOCH_3$), 2.1−2.4 (m, 4 H, 2-H_2, 3-H), 4.2−4.4 (m, 4 H, 2 × OCH_2CH_3), 4.65 (ddddd, *J* = 17.8, 9.5, 7.8, 4.2 and 3.2 Hz, 1 H, 4-H), 6.41 (br. d, 1 H, *J* = 4 Hz, 1-H)	−127.13 (br. ddd, *J* = 307.1, 101.1 and 17.8 Hz, 1 F, 5a-F), −120.27 (br. ddd, *J* = 307.1, 99.2 and 9.5 Hz, 1 F, 5b-F)	6.31 (br. dd, *J* = 101.1 and 99.2 Hz, 1 P, P-5)
(1*S*,4*S*)-**9**	1.40 (br. t, *J* = 7 Hz, 6 H, 2 × OCH_2CH_3), 2.04 (s, 3 H, $OCOCH_3$), 2.1−2.6 (m, 4 H, 2-H_2 and 3-H), 4.2−4.4 (m, 4 H, 2 × OCH_2CH_3), 4.55 (m, 1 H, 4-H), 6.32 (br. s, 1 H, 1-H)	−125.50 (br. ddd, *J* = 305.2, 101.8, and 17.5 Hz, 1 F, 5a-F), and −122.90 (br. ddd, *J* = 305.2, 100.7 and 9.2 Hz, 1 F, 5b-F)	6.67 (br. dd, *J* = 101.8 and 100.7 Hz, 1 P, P-5)

J = 303.8, 105.8 and 18.2 Hz, 1 F, F-1a), −118.24 (br. ddd, *J* = 303.8, 101.9 and 7.6 Hz, 1 F, F-1b). − ^{31}P NMR ($CDCl_3$): δ = 7.70 (br. dd, *J* = 105.8 and 101.9 Hz, 1 P, P-1). − $C_{12}H_{25}O_4F_2P$ (302): calcd. C 47.68, H 8.33; found C 47.67, H 8.30.

(b) Reaction of (2*S*,3*S*/*R*)-**5** afforded (*R*)-**6**: 297 mg (84%). − R_f = 0.35. − $[\alpha]_D^{20}$ = +9.29 (*c* = 0.8, $CHCl_3$). − ^{1}H-, ^{19}F-, and ^{31}P-NMR spectra were superimposable on those of the enantiomer (*S*)-**6**. − $C_{12}H_{23}O_4F_2P$ (300): calcd. C 48.00, H 7.72; found C 48.05, H 7.76. The enantiomeric purity of compound (*R*)-**6** was checked by esterification with chiral acids (vide infra).

Synthesis of (1*R*/*S*,4*S*)- and (1*R*/*S*,4*R*)-4-*C*-Diethoxyphosphoryldifluoromethyl-2,3,5-trideoxy-*glycero*-pentofuranose (8). − General Procedure: At 0°C, $RuCl_3$ (40% solution in water, 0.011 mmol, 6 mg) was added to a solution of alcohol **6** (0.5 mmol, 150 mg) in a 1:1:2 mixture of CCl_4/CH_3CN/H_2O (1 mL). After 1 min, $NaIO_4$ (2.0 mmol, 432 mg) was added and the mixture was allowed to warm to room temp. The reaction was quenched by adding water (1 mL) and the organics were extracted with CH_2Cl_2 (3 × 2 mL). After standard workup, the residue was purified by flash chromatography eluting with *n*-hexane/AcOEt, 2:3.

(a) Reaction of (*S*)-**6** for 5 min afforded a 1:1 anomeric mixture of β(1*R*)/α(1*S*)-**8**: 120 mg (88%), together with (*S*)-5-[(diethoxyphosphoryl)difluoromethyl]-γ-lactone **7**: 8 mg (6%). − (1*R*/*S*,4*S*)-**8**: R_f = 0.35. − $[\alpha]_D^{20}$ = +16.9 (*c* = 0.7, $CHCl_3$) at t_0, $[\alpha]_D^{20}$ = −3.88 (*c* = 0.7, $CHCl_3$) after 8 h. − $C_9H_{17}O_5F_2P$ (274): calcd. C 39.42, H 6.25; found C 39.40, H 6.22. − MS (DIS EI, 70 eV); *m/z* (%): 275 [(M + H)$^{+\cdot}$] (40), 274 [M$^{\cdot}$] (10), 257 [(M − OH)$^{+\cdot}$] (13), 246 [(M − CO)$^{+\cdot}$] (26), 188 [$C_5H_{11}PO_3F_2$] (100), 138 [$C_4H_{11}PO_3$] (38), 29 [$C_2H_5^{+\cdot}$] (10).

(*S*)-**7**: R_f = 0.38. − $[\alpha]_D^{20}$ = +13.2 (*c* = 0.2, $CHCl_3$). − $C_9H_{15}O_5F_2P$ (272): calcd. C 39.72, H 5.56; found C 39.76, H 5.58. − ^{1}H-, ^{19}F-, and ^{31}P-NMR data of compounds (1*R*/*S*,4*S*)-**8** and (*S*)-**7** are reported in Table 2.

(b) Reaction of (*R*)-**6** afforded the lactol (1*R*/*S*,4*R*)-**8** and the lactone (*R*)-**7** in a ratio similar to that of the aforementioned enantiomeric products, and in comparable chemical yields. (1*R*/*S*,4*R*)-**8**: R_f = 0.35. − $[\alpha]_D^{20}$ = −16.2 (*c* = 1.2, $CHCl_3$) at t_0, $[\alpha]_D^{20}$ = +3.76 (*c* = 1.2, $CHCl_3$) after 8 h. − $C_9H_{17}O_5F_2P$ (274): calcd. C 39.42, H 6.25; found C 39.40, H 6.22. − ^{1}H-, ^{19}F-, ^{31}P-, and ^{13}C-NMR spectra of (1*S*,4*R*)-**8** and (1*R*,4*S*)-**8** were superimposable on those of (1*R*,4*S*)- and (1*S*,4*R*)-**8**. − MS (DIS EI, 70 eV); *m/z* (%): 275 [(M + H)$^{+\cdot}$] (20), 274 [M$^{\cdot}$] (16), 257 [(M − OH)$^{+\cdot}$] (8), 246 [(M − CO)$^{+\cdot}$] (35), 188 [$C_5H_{11}PO_3F_2$] (100), 138 [$C_4H_{11}PO_3$] (22), 29 [$C_2H_5^{+\cdot}$] (17).

(*R*)-**7**: R_f = 0.38. − $[\alpha]_D^{20}$ = −13.0 (*c* = 0.8, $CHCl_3$). − $C_9H_{15}O_5F_2P$ (274): calcd. C 39.72, H 5.56; found C 39.76, H 5.58.

(*S*)-5-[(Diethoxyphosphoryl)difluoromethyl]dihydrofuran-2(3*H*)-one (7). − Reduction to Lactol 8: A 1.0 M solution of DIBAH in toluene (30 μL) was added to a stirred solution of (*S*)-**7** (8 mg, 0.029 mmol) in toluene (0.8 mL) at −60°C under N_2. After 30 min, satd. aq. NH_4Cl solution was added, the organics were extracted with AcOEt, and the combined extracts were dried over anhydrous Na_2SO_4. Standard workup gave a residue, which was purified by flash chromatography (*n*-hexane/AcOEt, 2:3) to give (1*R*/*S*,4*S*)-**8**: 7 mg (87%). Physicochemical and spectroscopic data were identical to those of the (*R*)-**7** enantiomer described above.

Synthesis of (1*R*/*S*,4*S*)- and (1*S*/*R*,4*R*)-1-*O*-Acetyl-4-*C*-(diethoxyphosphoryldifluoromethyl)-2,3,5-trideoxy-*glycero*-pentofuranoside (9). − General Procedure: To a stirred solution of the α/β anomeric mixture of lactols **8** (1.17 mmol, 320 mg) in pyridine (330 μL) at 0°C, neat acetic anhydride (2.3 mmol, 330 μL) was added dropwise and the mixture was allowed to warm to room temp. After stirring overnight, the reaction was quenched by adding H_2O (500 μL), the organics were extracted with AcOEt (3 × 5 mL) and, after standard workup, the crude product was purified by flash chromatography eluting with *n*-hexane/AcOEt, 3:7.

Table 2. NMR data for compounds **7**, **8** and **10**

Compound	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{19}F NMR ($CDCl_3/C_6F_6$) δ, *J* (Hz)	^{31}P NMR ($CDCl_3/H_3PO_4$), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ, *J* (Hz)
(*S*)-**7**	1.40 (br. t, J = 7.1 Hz, 6 H, 2 × OCH_2CH_3), 2.3−2.8 (m, 4 H, 3-H, 4-H), 4.2−4.4 (m, 4 H, 2 × OCH_2Me), 4.90 (ddddd, J = 16.0, 9.3, 4.4, 3.8 and 3.6 Hz, 1 H, 5-H)	−126.60 (br. ddd, J = 311.8, 97.3 and 16.0 Hz, 1 F, 6a-F), −122.13 (br. ddd, J = 311.8, 98.2 and 9.3 Hz, 1 F, 6b-F)	4.99 (br. dd, J = 98.2 and 97.3 Hz, 1 P, P-6)	16.34 (Qd, $J_{C,P}$ = 6 Hz, 2 × OCH_2CH_3), 20.80 (Tm, C-4), 26.79 (T, C-3), 65.26 and 65.16 (Td, $J_{C,P}$ = 7 Hz, 2 × OCH_2CH_3), 77.00 (Dm, C-5), 117.29 (Sddd, $J_{C,F}$ = 269.5 and 263.5 Hz, $J_{C,P}$ = 208.5 Hz, C-6), 174.47 (s, C-2)
(1*R*/*S*,4*S*)-**8**	1.3 and 1.5 (m, 6 H, 2 × OCH_2CH_3), 1.8−2.6 (m, 4 H, 2-H_2 and 3-H), 4.2−4.7 (m, 6 H, 2 × OCH_2Me and 4-H_2), 5.53 and 5.67 (m, 1 H, 1-H)	−127.20 and −119.90; −118.30 and −112.70 (br. ddd, J = 306.1, 104.0, and 19.5, 306.1, 100.1, and 9.5, 309.0, 102.5, and 9.5, and 309.0, 101.0, and 15.3 Hz, 2 F, 5-F_2)	6.76 and 7.49 (br. dd, J = 104.0 and 100.1, and 102.5 and 101.0 Hz, 1 P, P-5).	16.33 (Qd, $J_{C,P}$ = 6.0 Hz, 2 × OCH_2CH_3), 22.97 and 23.53 (Tt, $J_{C,F}$ = 4.0 and 4.5 Hz, C-3), 32.39 and 33.82 (T, C-2), 64.61, 64.67, 64.92 and 65.14 (Td, $J_{C,P}$ = 7 Hz, 2 × OCH_2Me), 77.32 and 79.82 (Dddd and Ddt, $J_{C,P}$ = 15 and $J_{C,F}$ = 26.5 and 22, and $J_{C,P}$ = 15 and $J_{C,F}$ = 26.5 Hz, C-4), 99.76 and 100.49 (D, C-1), 118.43 and 119.08 (Sdt, $J_{C,P}$ = 209 and $J_{C,F}$ = 262.5, $J_{C,P}$ = 206 and $J_{C,F}$ = 265.5 Hz, C-5)
(1′*R*,4′*S*)-**10**	1.38 (t, J = 7 Hz, 6 H, 2 × OCH_2CH_3), 1.9−2.6 (m, 4 H, 2′-H_2, 3′-H), 1.92 (d, 3 H, J = 1.4 Hz, 5-Me), 4.2−4.4 (m, 4 H, 2 × OCH_2CH_3), 4.49 (ddddd, 1 H, J = 17.4, 9.8, 7.9, 5.2 and 2.2 Hz, 4′-H), 6.21 (t, J = 7.1 Hz, 1 H, 1′-H), 7.48 (q, 1 H, J = 1.4 Hz, 6-H), and 9.32 (br. signal, 1 H, NH)	−125.26 (br. ddd, J = 307.6, 101.2 and 17.4 Hz, 1 F, 5′a-F), −119.99 (br. ddd, J = 307.6, 98.3 and 9.8 Hz, 1 F, 5′b-F)	5.94 (br. dd, J = 101.2 and 98.3 Hz, 1 P, P-5′)	12.57 (Q, 5-Me), 16.34 (Qd, $J_{C,P}$ = 5.5 Hz, 2 × OCH_2CH_3), 24.11 (Tm, C-3′), 30.85 (T, C-2′), 64.94 (Td, $J_{C,P}$ = 6 Hz, 2 × OCH_2CH_3), 78.73 (Dddd, $J_{C,F}$ = 29.0 and 22.5 Hz, $J_{C,P}$ = 15.5 Hz, C-1′), 86.32 (D, C-4′), 111.02 (S, C-5), 118.05 (Sddd, $J_{C,F}$ = 267 and 263, $J_{C,P}$ = 209 Hz, C-5′), 135.17 (Ddd, $J_{C,F}$ = 2.5 and 2.5 Hz, C-6), 150.46 and 163.96 (S, C-2 and C-4)
(1′*S*,4′*S*)-**10**	1.36 (t, J = 7 Hz, 6 H, 2 × OCH_2CH_3), 1.9−2.6 (m, 4 H, 2′-H_2 and 3′-H), 1.92 (d, 3 H, J = 1.4 Hz, 5-Me), 4.2−4.4 (m, 4 H, 2 × OCH_2CH_3), 4.80 (ddddd, J = 17.5, 9.7, 8.0, 5.0 and 2.5 Hz, 1 H, 4′-H), 6.19 (dd, 1 H, J = 6.7 and 5.1 Hz, 1′-H), 7.08 (q, 1 H, J = 1.4 Hz, 6-H), 9.32 (br. signal, 1 H, NH)	−125.59 (br. ddd, J = 307.5, 100.5 and 17.5 Hz, 1 F, 5′a-F), and −120.93 (br. ddd, J = 307.5, 98.9 and 9.7 Hz, 1 F, 5′b-F)	5.94 (br. dd, J = 100.5 and 98.9 Hz, 1 P, P-5′)	12.57 (Q, 5-Me), 16.34 (Qd, $J_{C,P}$ = 5.5 Hz, 2 × OCH_2CH_3), 23.94 (Tm, C-3′), 31.38 (T, C-2′), 64.84 (Td, $J_{C,P}$ = 6 Hz, 2 × OCH_2CH_3), 79.16 (Dddd, $J_{C,F}$ = 29.0 and 22.5 Hz, $J_{C,P}$ = 15.5 Hz, C-4′), 87.76 (D, C-1′), 111.15 (S, C-5), 118.10 (Sddd, $J_{C,F}$ = 267 and 263, $J_{C,P}$ = 209 Hz, C-5′), 135.29 (D, C-6), 150.19 and 163.96 (S, C-2 and −4)

(a) Reaction of (1*R*/*S*,4*S*)-**8** afforded the acetyl derivatives **9** as a resolvable 10:1 epimeric (*anti/syn*) mixture of α(1*R*)/β(1*S*): 344 mg (93%). − (1*R*,4*S*)-**9**: 312 mg (84%). − R_f = 0.35. − $[\alpha]^{20}_D$ = +50.3 (c = 0.5, $CHCl_3$). − $C_{11}H_{19}O_6F_2P$ (316): calcd. C 41.78, H 6.05; found C 41.73, H 6.08. − (1*S*,4*S*)-**9**: 32 mg (9%). − R_f = 0.33. − $[\alpha]_D^{20}$ = −19.9 (c = 0.1, $CHCl_3$). − $C_{11}H_{19}O_6F_2P$ (316): calcd. C 41.78, H 6.05; found C 41.81, H 6.03. − ^{1}H-, ^{19}F-, and ^{31}P-NMR data of compounds (1*R*,4*S*)- and (1*S*,4*S*)-**9** are reported in Table 1.

(b) Reaction of (1*S*/*R*,4*R*)-**8** afforded the resolvable acetyl derivatives (1*S*,4*R*)- and (1*R*,4*R*)-**9** as a 10:1 (*anti/syn*) epimeric mixture of β(1*S*)/α(1*R*): 351 mg (95%). − (1*S*,4*R*)-**9**: 316 mg (86%). − R_f = 0.35. − $[\alpha]_D^{20}$ = −50.8 (c = 0.9, $CHCl_3$). − $C_{11}H_{19}O_6F_2P$ (316): calcd. C 41.78, H 6.05; found C 41.80, H 6.04. − (1*R*,4*R*)-**9**: 35 mg (9%). − R_f = 0.33. − $[\alpha]_D^{20}$ = +19.4 (c = 0.9, $CHCl_3$). − $C_{11}H_{19}O_6F_2P$ (316): calcd. C 41.78, H 6.05; found C 41.80, H 6.04. − ^{1}H-, ^{19}F-, and ^{31}P-NMR spectra were superimposable on those of the enantiomers described above.

Synthesis of 1-{4′-*C*-Diethoxyphosphoryldifluoromethyl-2′,3′,5′-trideoxy-*glycero*-pentofuranosyl}thymine (10). − **General Procedure:** Thymine (2.8 mmol, 352 mg) and $(NH_4)_2SO_4$ (0.7 mmol, 92 mg) were suspended in HMDS (10 mL) and the mixture was refluxed for 4 h under N_2. The solvent was then evaporated under reduced pressure and the crude residue was treated with a solution of the acetyl derivative **9** (1.1 mmol, 350 mg) in anhydrous dichloroethane (15 mL). After stirring for 10 min at room temp., trimethylsilyl trifluoromethanesulfonate (1.7 mmol, 300 μL) was added and stirring was continued for 20 min at 45°C. Then, the reaction mixture was diluted with $(CH_2Cl)_2$ (10 mL), CH_3OH (2 mL) was added, and

stirring was maintained for a further 5 min. The solvents were then evaporated in vacuo and the crude residue was purified by flash chromatography eluting with *n*-hexane/AcOEt, 1:9.

(a) Reaction of (1*R*,4*S*)-**9** afforded an unresolvable 2:1 mixture of β(1′*R*) and α(1′*S*) nucleoside derivatives (1′*R*/*S*,4′*S*)-**10** (D series): 400 mg (95%). − R_f = 0.35. − $[\alpha]_D^{20}$ = +21.6 (*c* = 0.3, $CHCl_3$). − $[\alpha]_{365}^{20}$ = +60.2 (*c* = 0.3, $CHCl_3$). − $C_{14}H_{21}O_6F_2N_2P$ (382): calcd. C 43.98, H 5.49, N 7.33; found C 43.95, H 5.46, N 7.30. − MS (DIS EI, 70 eV); *m/z* (%): 382 [$M^{\cdot}$] (27), 256 [$C_9H_{15}PO_4F_2^{+\cdot}$] (23), 77 [$C_6H_5^{+\cdot}$] (17), 51 [$CHF_2^{+\cdot}$] (15). − ^{1}H-, ^{19}F-, and ^{31}P-NMR data of compounds (1′*R*,4′*S*)- and (1′*S*,4′*S*)-**10** are reported in Table 2.

(b) Reaction of (1*S*,4*R*)-**9** afforded an unresolvable 2:1 mixture of α(1′*S*) and β(1′*R*) nucleoside derivatives (1′*R*/*S*,4′*R*)-**10** (L series): 400 mg (95%). − R_f = 0.35. − $[\alpha]_D^{20}$ = −20.2 (*c* = 0.8, $CHCl_3$). − $[\alpha]_{365}^{20}$ = −59.7 (*c* = 0.8, $CHCl_3$). − $C_{14}H_{21}O_6F_2N_2P$ (382): calcd. C 43.98, H 5.49, N 7.33; found C 43.95, H 5.47, N 7.30. − ^{1}H-, ^{19}F-, and ^{31}P-NMR spectra were superimposable on those of the enantiomers (1′*S*/*R*,4′*S*)-**10** described above.

Synthesis of (2*R*/*S*,3*R*/*S*,R_S)-Diethyl 2-Benzoyloxy-1,1-difluoro-6-methyl-(4-methylphenylsulfinyl)hept-6-enylphosphonate (11): Neat DMAP (0.1 mmol, 12 mg) was added to a stirred 1.8:1.3:1.0:2.4 mixture of (2*R*,3*R*,R_S)-, (2*R*,3*S*,R_S)-, (2*S*,3*S*,R_S)-, and (2*S*,3*R*,R_S)-**4** (1.0 mmol, 440 mg) and DCC (1.1 mmol, 230 mg) in CH_2Cl_2 (10 mL) at room temp. After stirring for 12 h, the white precipitate formed was filtered off, and the clear filtrate was concentrated in vacuo. The residue was purified by flash column-chromatography eluting with *n*-hexane/AcOEt, 7:3, to afford diastereomerically pure (2*S*,3*S*,R_S)-**11**: 76 mg (14%; 91.5% reaction yield). − R_f = 0.25. − $[\alpha]_D^{20}$ = +157.8 (*c* = 0.5, $CHCl_3$). − $C_{26}H_{33}O_6F_2PS$ (542): calcd. C 57.56, H 6.13; found C 57.55, H 6.16. − (2*R*,3*S*,R_S)- and (2*S*,3*R*,R_S)-**11** were isolated as an unresolvable 1:2 diastereomeric mixture: 300 mg (57%; 97% reaction yield). − R_f = 0.20. − $C_{26}H_{33}O_6F_2PS$ (542): calcd. C 57.56, H 6.13; found C 57.59, H 6.11. − ^{1}H-, ^{19}F-, and ^{31}P-NMR data of compounds (2*S*,3*S*,R_S)-, (2*R*,3*S*,R_S)-, and (2*S*,3*R*,R_S)-**11** are reported in Table 3. − (*E*)-Diethyl 1,1-difluoro-2-benzoyloxy-6-methylhepta-3,5-dienylphosphonate, arising from *syn*-elimination of the sulfinyl moiety, was also isolated: 27 mg (7%). − R_f = 0.30. − ^{1}H NMR ($CDCl_3$): δ = 1.31 and 1.32 (t, *J* = 7.1 Hz, 6 H, 2 × CH_2CH_3), 1.80 (br. s, 6 H, 2 × 6-Me), 4.23 (m, 4 H, 2 × CH_2CH_3), 5.64 (br. dd, *J* = 15.3 and 8.5 Hz, 1 H, 3-H), 5.88 (br. d, *J* = 11.3 Hz, 1 H, 5-H), 5.98 (dddd, *J* = 15.0, 10.7, 8.5 and 4.3 Hz, 1 H, 2-H), 6.77 (br. dd, *J* = 15.3 and 11.3 Hz, 1 H, 4-H), 7.45, 7.57, 8.11 (m, 5 H, ArH). − ^{19}F NMR ($CDCl_3$): δ = −121.46 (br. ddd, *J* = 307.5, 103.2 and 15.0 Hz, 1 F, F-1a), −117.35 (br. ddd, *J* = 307.4, 100.0 and 10.7 Hz, 1 F, F-1b). − ^{31}P NMR ($CDCl_3$): δ = 6.19 (br. dd, *J* = 103.2 and 100.0 Hz, 1 P, P-1). − $C_{19}H_{25}O_5F_2P$ (542): calcd. C 56.72, H 6.26; found C 56.79, H 6.21.

(2*S*,3*S*)-Diethyl 2-Benzoyloxy-1,1-difluoro-6-methyl-(4-methylphenylsulfenyl)hept-6-enylphosphonate (12). − Deoxygenation Reaction at Sulfur: Starting from (2*S*,3*S*,R_S)-**11** (0.11 mmol, 60 mg) and following the same procedure as that described for the preparation of **5** from **4**, (2*S*,3*S*)-**12** was obtained after flash column chromatography eluting with *n*-hexane/AcOEt, 7:3. Yield: 50 mg (86%). − $[\alpha]_D^{20}$ = +73.4 (*c* = 0.3, $CHCl_3$). − ^{1}H-, ^{19}F-, and ^{31}P-NMR data are reported in Table 3. − $C_{26}H_{33}O_5F_2PS$ (526): calcd. C 59.30, H 6.32; found C 59.33, H 6.34.

Synthesis of (2*S*,3*S*/*R*)-12. − Benzoylation of (2*S*,3*S*/*R*)-5: Starting from an unresolvable (2*S*,3*R*/*S*)-**5** [(3*S*)/(3*R*) = 2:1] mixture (0.47 mmol, 200 mg), and following the same procedure as that described for the preparation of **11** from the sulfinyl alcohols **4**, an unresolvable mixture of (2*S*,3*S*)- and (2*S*,3*R*)-**12** was obtained after flash column-chromatography eluting with *n*-hexane/AcOEt, 7:3. Yield: 230 mg (93%). − R_f = 0.35. − $C_{26}H_{33}O_5F_2PS$ (402): calcd. C 59.30, H 6.32; found C 59.35, H 6.36. − ^{1}H-, ^{19}F-, and ^{31}P-NMR spectra of the major diastereomer were superimposable on those of the same compound obtained by deoxygenation at the sulfur of (2*S*,3*S*,R_S)-**11** (vide infra). − ^{1}H-, ^{19}F-, and ^{31}P-NMR data of (2*R*,3*R*)-**12** (minor diastereomer) are reported in Table 3.

Hydrogenolytic Desulfinylation: Following the same experimental procedure as that described for the preparation of (*S*)-**6**, reaction of (2*S*,3*S*)-**12** (0.094 mmol, 50 mg) gave after 3 h (*R*)-**13**: 34 mg (89%). − R_f = 0.35 ($CHCl_3$/AcOEt, 95:5). − $[\alpha]_D^{20}$ = +16.8 (*c* = 0.6, $CHCl_3$). − ^{1}H-, ^{19}F-, and ^{31}P-NMR data are reported in Table 3. − MS (DIS EI, 70 eV); *m/z* (%): 405 [$(M + H)^{+\cdot}$] (10), 138 [$C_4H_{11}PO_3^{\cdot}$] (65), 105 [$C_7H_5O^{+\cdot}$] (100), 77 [$C_6H_5^{+\cdot}$] (48), 51 [$CHF_2^{+\cdot}$] (20), 41 [$(CO_2 + H)^{+\cdot}$] (57), 29 [$C_2H_5^{+\cdot}$] (47). − IR (film): $\tilde{\nu}$ = 2932.7 cm^{-1} (CH_3), 1734.9 (COO), 1452.5, 1268.2 (P=O), 1160.3 (P−OC_2H_5), 1109.3 (C−F), 1025.9 (C−OP), 711.3. − $C_{19}H_{27}O_5F_2P$ (404): calcd. C 56.43, H 6.73; found C 56.45, H 6.76.

Hydrolytic Removal of the *O*-Benzoyl Protecting Group: (*R*)-**13** (0.081 mmol, 34 mg) was dissolved in methanol (3 mL) at room temp. and NaOH (0.081 mmol, 3.3 mg) was added. After 8 h, 1 N aq. HCl was added to adjust the pH from 8 to 6, the solution was concentrated in vacuo, diluted with H_2O (2 mL), and the organics were extracted with Et_2O (3 × 2 mL). After treatment with anhydrous Na_2SO_4 and removal of the solvent in vacuo, the residue was purified by flash column-chromatography eluting with *n*-hexane/AcOEt, 7:3, to give (*R*)-**6**: 16 mg (65%). − R_f = 0.35. − $[\alpha]_D^{20}$ = +8.98 (*c* = 0.8, $CHCl_3$). − ^{1}H-, ^{19}F-, and ^{31}P-NMR spectra were superimposable on those of the same compound obtained by hydrogenolytic desulfurization of the (2*S*,3*S*)- and (2*S*,3*R*)-**5** mixture. − $C_{12}H_{23}O_4F_2P$ (300): calcd. C 48.00, H 7.72; found C 48.05, H 7.76. − The enantiomeric purity of the compound (*R*)-**6** obtained from **13** was checked by the method of esterification with chiral acids (vide infra).

Diethyl (1-difluoromethyl-5-methyl-4-hexenyl)phosphate[23] was the main reaction product when the methanolic solution of (*R*)-**13** was heated (ca. 45°C) and then concentrated in vacuo at pH 8. Yield: 10 mg (43%). − R_f = 0.40. − ^{1}H NMR ($CDCl_3$): δ = 1.35 (br. t, *J* = 7.2 Hz, 6 H, 2 × OCH_2CH_3), 1.62 and 1.70 (br. s, 6 H, 2 × 5-Me), 1.76 (m, 2 H, 2-H_2), 2.12 and 2.21 (m, 2 H, 3-H_2), 4.05−4.25 (m, 4 H, 2 × OCH_2CH_3), 4.45 (m, 1 H, 1-H), 5.11 (m, 1 H, 4-H), 5.83 (ddt, *J* = 3.1, 2.8 and 55.5 Hz, 1 H, 1-CF_2H). − ^{19}F NMR ($CDCl_3$): δ = −132.72 (br. ddd, *J* = 287.0, 55.5, and 12.1 Hz, 1 F, 1-CF_a), −129.12 (br. ddd, *J* = 287.0, 55.5 and 9.9 Hz, 1 F, 1-CF_b).

Determination of the Enantiomeric Purities of the Obtained Compounds. − (a) Lanthanide Shift Reagents Method: Two sets of experiments were performed with the lanthanide shift reagent {tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate], europium(III) derivative}, [Eu(tfc)$_3$]: first, on the artificial racemic mixture of (*S*/*R*)-**6** and, second, on the presumed enantiomerically pure compound (*S*)-**6**. Progressive addition of Eu(tfc)$_3$ to the racemic compound gave rise to mixtures of diastereomeric complexes, as evidenced by a doubling of the NMR signals. With the homochiral compound, the addition of Eu(tfc)$_3$ at the same concentrations led only to comparable downfield shifts, but no splitting was observed.

(b) Esterification with Chiral Acids Method: The following procedure was applied in the case of presumed enantiomerically pure compounds, employing both chiral (+)-(*S*)- and (−)-(*R*)-phenylpropionic acids. Neat chiral acid (1.0 mmol) was added to a solu-

Table 3. NMR data for compounds **11**, **12** and **13**

Compound	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{19}F NMR ($CDCl_3/C_6F_6$) δ, *J* (Hz)	^{31}P NMR ($CDCl_3$/H_3PO_4) δ, *J* (Hz)
(2*S*,3*S*,R_S)-**11**	1.37 (br. t, *J* = 7.1 Hz, 6 H, 2 × OCH_2CH_3), 1.38 and 1.62 (br. s, 6 H, 2 × 6-CH_3), 2.17 and 2.40 (m, 2 H, 4-H_2), 2.41 (br. s, 3 H, ArCH_3), 3.29 (br. dd, *J* = 11.3 and 3.8 Hz, 1 H, 3-H), 4.2−4.4 (m, 4 H, 2 × OCH_2CH_3), 4.95 (m, 1 H, 5-H), 5.95 (br. dd, *J* = 16.6 and 13.7 Hz, 1 H, 2-H), 7.33 and 7.58 (m, 4 H, *p*-Tol*H*), 7.49, 7.59 and 8.25 (m, 5 H, Ar*H*)	−118.82 (br. ddd, *J* = 308.7, 101.0 and 16.6 Hz, 1 F, 1a-F), −117.32 (br. ddd, *J* = 308.7, 99.4 and 13.7 Hz, 1 F, 1b-F)	5.00 (br. dd, *J* = 101.0 and 99.4 Hz, 1 P, P-1)
(2*R*,3*S*,R_S)-**11**	1.29 and 1.38 (br. t, *J* = 7.2 Hz, 6 H, 2 × OCH_2CH_3), 1.62 and 1.65 (br. s, 6 H, 2 × 6-CH_3), 2.10 (br. s, 3 H, ArCH_3), 2.58 and 2.88 (m, 2 H, 4-H_2), 3.75 (br. ddd, *J* = 7.8, 5.4 and 2.0 Hz, 1 H, 3-H), 4.1−4.4 (m, 2 H, 2 × OCH_2CH_3), 5.29 (m, 1 H, 5-H), 6.06 (br. dd, *J* = 14.9 and 14.1 Hz, 1 H, 2-H), and 7.1−7.9 (m, 9 H, ArH)	−118.13 (br. ddd, *J* = 308.4, 100.8 and 14.9 Hz, 1 F, 1a-F), −117.52 (br. ddd, *J* = 308.4, 100.4 and 14.1 Hz, 1 F, 1b-F)	4.81 (br. dd, *J* = 100.8 and 100.4 Hz, 1 P, P-1)
(2*S*,3*R*,R_S)-**11**	1.22 and 1.25 (br. t, *J* = 7.1 Hz, 6 H, 2 × OCH_2CH_3), 1.62 and 1.67 (br. s, 6 H, 2 × 6-CH_3), 2.40 (br. s, 3 H, ArCH_3), 2.80 (m, 2 H, 4-H_2), 3.34 (br. dd, *J* = 7.3 and 6.0 Hz, 1 H, 3-H), 4.0−4.3 (m, 2 H, 2 × OCH_2CH_3), 5.22 (m, 1 H, 5-H), 6.05 (br. dd, *J* = 15.9 and 14.4 Hz, 1 H, 2-H), 7.3−8.2 (m, 9 H, ArH)	−119.82 (br. ddd, *J* = 308.4, 100.8 and 15.9 Hz, 1 F, 1a-F), −117.82 (br. ddd, *J* = 308.4, 102.4 and 14.4 Hz, 1 F, 1b-F)	4.65 (br. dd, *J* = 102.4 and 100.8 Hz, 1 P, P-1)
(2*S*,3*S*)-**12**	1.28 and 1.31 (br. t, *J* = 7.2 Hz, 6 H, 2 × OCH_2CH_3), 1.52 and 1.68 (br. s, 6 H, 2 × 6-CH_3), 2.29 (br. s, 3 H, ArCH_3), 2.40 and 2.50 (m, 2 H, 4-H_2), 3.75 (dt, *J* = 4.0 and 6.8 Hz, 1 H, 3-H), 4.1−4.3 (m, 4 H, 2 × OCH_2CH_3), 5.24 (m, 1 H, 5-H), 5.83 (dddd, *J* = 15.8, 11.7, 4.0, 3.2 Hz, 1 H, 2-H), 7.05 and 7.36 (m, 4 H, *p*-Tol*H*), 7.42, 7.58, and 8.08 (m, 5 H, Ar*H*)	−118.62 (br. ddd, *J* = 311.5, 103.8 and 15.8 Hz, 1 F, 1a-F), −115.48 (br. ddd, *J* = 311.5, 102.6 and 11.7 Hz, 1 F, 1b-F)	5.69 (br. dd, *J* = 103.8 and 102.6 Hz, 1 P, P-1)
(2*S*,3*R*)-**12**	1.18 and 1.20 (br. t, *J* = 7.1 Hz, 6 H, 2 × OCH_2CH_3), 1.67 and 1.75 (br. s, 6 H, 2 × 6-CH_3), 2.31 (br. s, 3 H, ArCH_3), 2.38 and 2.85 (m, 2 H, 4-H_2), 3.73 (br. d, *J* = 10.5 Hz, 1 H, 3-H), 3.9−4.3 (m, 4 H, 2 × OCH_2CH_3), 5.41 (m, 1 H, 5-H), 5.77 (dddd, *J* = 15.6, 14.4, 1.9, 1.7 Hz, 1 H, 2-H), 7.13 and 7.44 (m, 4 H, *p*-Tol*H*), 7.47, 7.60, and 8.11 (m, 5 H, ArH)	−118.78 (br. ddd, *J* = 310.6, 102.3 and 14.4 Hz, 1 F, 1a-F), −117.23 (br. ddd, *J* = 310.6, 102.3 and 15.6 Hz, 1 F, 1b-F)	5.30 (br. t, *J* = 102.3 Hz, 1 P, P-1)
(*R*)-**13**	1.29 and 1.34 (t, *J* = 7.2 Hz, 6 H, 2 × OCH_2CH_3), 1.53 and 1.62 (br. s, 6 H, 2 × 6-CH_3), 1.6−2.2 (m, 4 H, 3-H_2 and 4-H), 4.2−4.4 (m, 4 H, 2 × OCH_2CH_3), 5.10 (m, 1 H, 5-H), 5.64 (m, 1 H, 2-H), 7.46, 7.59 and 8.11 (m, 5 H, ArH)	−121.30 (br. ddd, *J* = 310.0, 104.7 and 13.2 Hz, 1 F, 1a-F), −118.66 (br. ddd, *J* = 310.0, 103.4 and 12.3 Hz, 1 F, 1b-F)	6.10 (br. dd, *J* = 104.7 and 103.4 Hz, 1 P, P-1)

tion of the appropriate compound (1.1 mmol) and DCC (1.0 mmol) in CH_2Cl_2 (8 mL). After 5 min, DMAP (0.1 mmol) was added, and after 30 min the white precipitate was filtered off. The clear filtrate was concentrated in vacuo and the residue was directly subjected, without further chemical manipulation, to ^{1}H-NMR analysis. Comparison of the spectra of the two diastereomeric esters allowed assessment of the enantiopurity. In all examined cases, the phenylpropionic esters were obtained as the sole reaction products and in yields ≥ 95%.

(a) Starting from (*R*)-**6** (0.053 mmol, 16 mg) and (−)-(*R*)-phenylpropionic acid (0.053 mmol, 6.0 μL), (2*R*,2′*R*)-**14** was obtained. Yield: 22 mg (95%). − ^{1}H NMR ($CDCl_3$): δ = 1.30 and 1.33 (t, *J* = 7.0 Hz, 6 H, 2 × OCH_2CH_3), 1.50 and 1.66 (br. s, 6 H, 2 × 6-Me), 1.56 (d, *J* = 7.3 Hz, 3 H, 2′-CH_3), 1.7−2.1 (m, 4 H, 3- and 4-H_2), 3.82 (br. q, *J* = 7.3 Hz, 1 H, 2′-H), 4.19 (m, 4 H, 2 × OCH_2CH_3), 5.04 (m, 1 H, 5-H), 5.37 (m, 1 H, 2-H), 7.2−7.4 (m, 5 H, ArH). − ^{19}F NMR ($CDCl_3$): δ = −120.72 (br. ddd, *J* = 307.5, 103.3 and 14.0 Hz, 1 F, F-1a), −119.41 (br. ddd, *J* = 307.5, 103.5 and 10.6 Hz, 1 F, F-1b). − From (+)-(*S*)-phenylpropionic acid, (2*R*,2′*S*)-**14** was obtained. Yield: 23 mg (97%). − ^{1}H NMR ($CDCl_3$): δ = 1.34 and 1.60 (br. s, 6 H, 2 × 6-Me), 1.39 (br. t, *J* = 7.0 Hz, 6 H, 2 × OCH_2CH_3), 1.54 (d, *J* = 7.3 Hz, 3 H, 2′-Me), 1.6−1.9 (m, 4 H, 3- and 4-H_2), 3.81 (br. q, *J* = 7.3 Hz, 1 H, 2′-H), 4.28 (m, 4 H, 2 × OCH_2CH_3), 4.93 (m, 1 H, 5-H), 5.37 (m, 1 H, 2-H), 7.2−7.4 (m, 5 H, ArH). − ^{19}F NMR ($CDCl_3$): δ = −121.51 (br. ddd, *J* = 307.0, 103.3 and 14.5 Hz, 1 F, F-1a), −119.63 (br. ddd, *J* = 307.0, 101.0 and 10.8 Hz, 1 F, F-1b).

(b) Starting from (*S*)-**6** (0.067 mmol, 20 mg) and (−)-(*R*)-phenylpropionic acid (0.072 mmol, 8.2 μL), (2*S*,2′*R*)-**14** was obtained. Yield: 28 mg (97%). − Using (+)-(*S*)-phenylpropionic acid, (2*S*,2′*S*)-**14** was obtained. Yield: 28 mg (97%). − The ^{1}H-NMR spectra of (2*S*,2′*R*)-**14** and (2*S*,2′*S*)-**14** were superimposable on those of (2*R*,2′*S*)-**14** and (2*R*,2′*R*)-**14**, respectively, described above.

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