Synthesis of 3'-Arylsulfonyl-4'-[(diethoxyphosphoryl)difluoromethyl]thymidine Analogs

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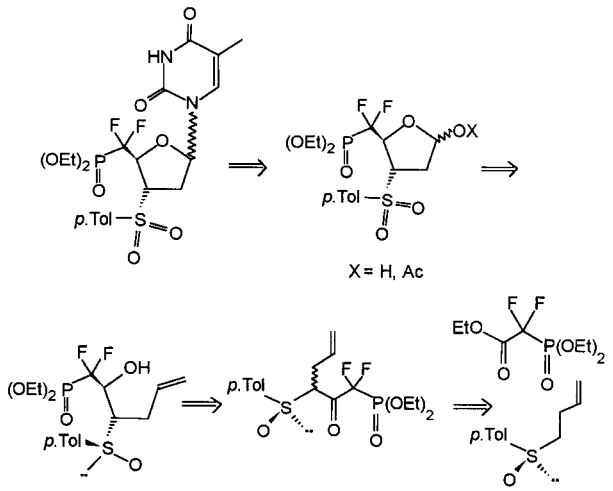
Abstract: D- and L-Diethoxyphosphoryldifluoromethyl nucleoside analogs **8**, bearing a sulfonylic moiety at C-3' were synthesized following the building block approach to chiral fluorinated molecules. The condensation of ethyl 2-(diethoxyphosphoryl)-2,2-difluoroacetate **(2)** and 4-(4-methylphenylsulfinyl)but-1-ene **(3)** followed by reduction of the thus formed ketones **4** to alcohols **5** and oxidative cyclization to the furanose derivatives **6** were the key steps of the synthetic sequence.

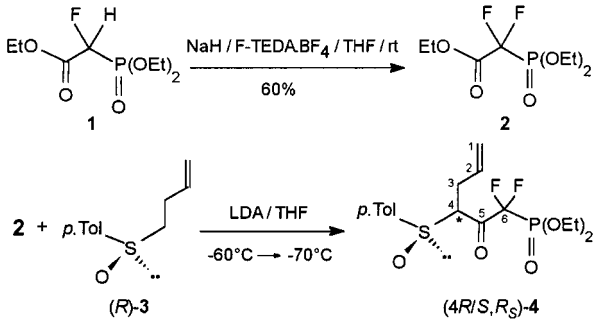
Key words: fluorinated nucleosides, 4'-[(diethoxyphosphoryl)difluoromethyl]thymidines, (difluoromethyl)phosphonates, antiviral agents, lactol formation

The concept of using phosphonate isosters as stable phosphate mimics in biological systems has been employed extensively.[1] Fluoro substitution on the α-carbon of phosphonates enhances their utilization because fluorine may increase the effectiveness of the phosphonate mimicry on geometric and electronic grounds.[2] The replacement of fluorophosphonates for phosphates has provided a number of analogs with significant biological activity.[3] A number of fluoromethylphosphonate isosters of nucleotides has been prepared and tested as antiviral agents.[4]

As a part of our program devoted to explore the utility of the 4-methylphenylsulfinyl chiral auxiliary group for the synthesis of new fluoro-substituted nucleoside analogs, we have recently reported the synthesis of an enantiomerically pure 3'-arylsulfonylthymidine phosphonate analog bearing a fluoromethyl group at C-4'.[5] Further development of this approach focused on the synthesis of α,α-difluoromethylphosphonate derivatives. The key intermediate, 6-(diethoxyphosphoryl)-6,6-difluoro-5-hydroxy-4-(4-methylphenylsulfinyl)hex-1-ene, was obtained by acylation of the α-lithium salt of but-3-enyl 4-methylphenyl sulfoxide by the diethoxyphosphoryldifluoromethyl group of ethyl 2-(diethoxyphosphoryl)-2,2-difluoroacetate.[6] A reaction sequence, already utilized for the construction of fluoro-substituted nucleoside analogs,[7] has been used to transform the thus obtained 5-oxo difluoromethylphosphonate intermediates into the final diethoxyphosphoryldifluoromethyl thymidine analogs, as summarized in the retrosynthesis given in Scheme 1.



Scheme 1



Scheme 2

A small-scale laboratory synthesis of ethyl 2-(diethoxyphosphoryl)-2,2-difluoroacetate **(2)** was set up: fluorination of the lithium derivative of commercially available ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate **(1)** with a moderate excess of F-TEDA•BF_4 gave the corresponding difluoro derivative **2** in good chemical yields.

The acylation of the lithium derivative of 4-(4-methylphenylsulfinyl)but-1-ene **(3)** by ethyl 2-(diethoxyphosphoryl)-2,2-difluoroacetate **(2)** was the crucial step of all the sequence (Scheme 2).

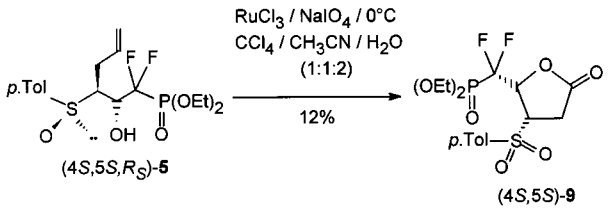
The lithium derivative was obtained in THF at –60 °C by LDA and the acylation was accomplished at –70 °C in the same solvent. The thus obtained mixture of diastereomeric ketones **4** was quite unstable, both in solution and as isolated compounds. Rapid workup afforded a crude mixture which was employed without further purification, by rapid treatment of its solution (THF) with diisobutylaluminum hydride at –60 °C, or with sodium borohydride at –10 °C to obtain the secondary alcohols **5** in 85% and 83% overall yields, respectively. The four diastereomers **5** were obtained in different relative ratios depending on the experimental conditions. They were isolated, after repeated flash chromatographic purification, as enantiomerically and diastereomerically pure compounds (de 95% by ^{19}F NMR analyses).

The terminal C=C bond of (4*S*,5*R*,R_S)-**5** (Scheme 3) then underwent oxidative cleavage by sodium periodate/ruthenium trichloride in a two-phase system (CCl_4/CH_3CN/H_2O 1:1:2). The ring-closure reaction of the intermediate aldehyde on to the secondary hydroxy group and the oxidation side reaction of the sulfinylic into sulfonylic moiety spontaneously followed and the lactol **6** was obtained and detected in chloroform by ^1H and ^{19}F NMR analyses as a 2.5:1.0 mixture of β(1*R*) and α(1*S*) anomers.[8] The corresponding γ-lactone, (4*S*,5*R*)-**9**, which was formed in very low yields (7%) under these conditions, was isolated and converted back to the anomeric lactol mixture **6** by reduction with DIBAH in toluene (Scheme 3).

The acetylation of **6** with acetic anhydride in pyridine gave a 3:1 epimeric mixture of, respectively, β(1*S*)- and α(1*R*)-acetyl derivatives **7**. The reaction with persilylated thymine in dichloromethane at 40 °C for 1 hour, in the presence of trimethylsilyl triflate as catalyst, afforded the corresponding 4'-[(diethoxyphosphoryl)difluoromethyl]-3'-(4-methylphenylsulfonyl)thymidine analogs as a ca. 1:1 epimeric mixture of (1'*R*/*S*,3'*S*,4'*R*)-**8** in 80% overall yield. The same synthetic sequence when applied to (4*R*,5*S*,R_S)-**5** afforded in comparable overall chemical yields the (phosphoryldifluoromethyl)thymidine derivatives (1'*R*/*S*,3'*R*,4'*S*)-**8**, corresponding to the L-series of the nucleoside analogs.

Both the reactive hydroxy sulfinyl intermediates (4*S*,5*R*,R_S)- and (4*R*,5*S*,R_S)-**5** were successfully utilized as described and shown to have a 4,5-*syn* relationship between the propenylic chain and the hydroxy moiety. This relative disposition of the two groups resulted in lactols **6** having the 4-methylphenylsulfonyl and the diethoxyphosphoryldifluoromethyl functionalities 3,4-*trans* disposed.

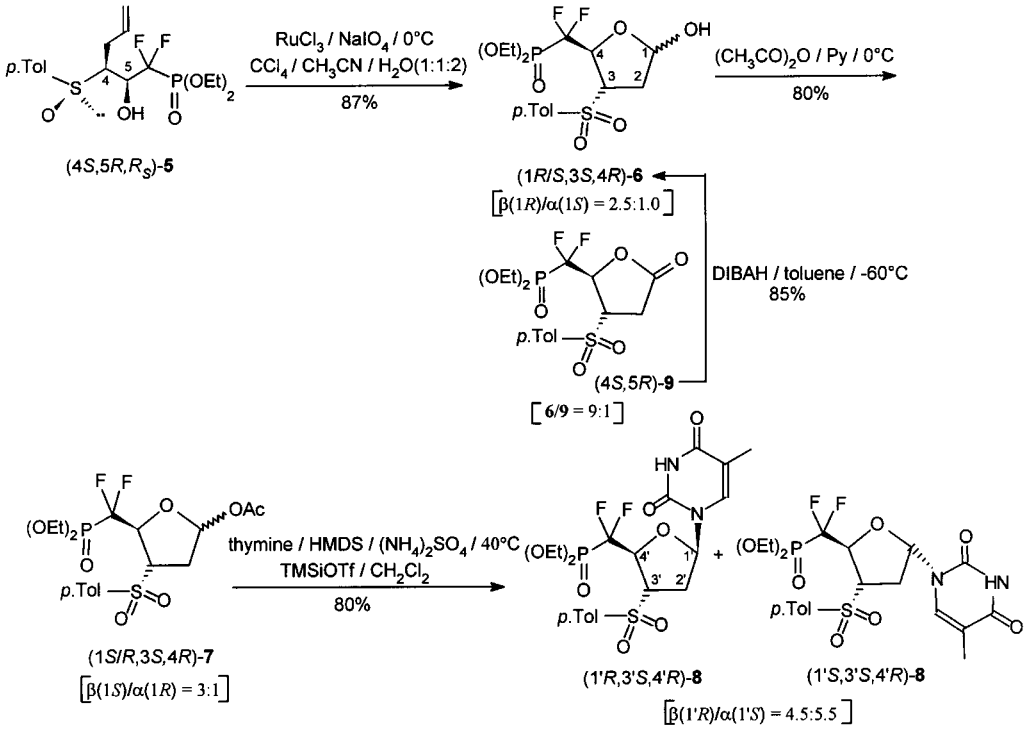
In contrast, the corresponding secondary alcohols **5**, having a 4,5-*anti* relationship between the same groups, were fairly sensitive to the oxidative conditions. In fact, the compound (4*S*,5*S*,R_S)-**5** when submitted to the oxidative cleavage in the same conditions gave only moderate yields (12%) of the γ-lactone (4*S*,5*S*)-**9** which showed the sulfonylic and phosphonylic appendages 4,5-*cis* disposed. The lactol **6** or any other product could not be isolated or detected by NMR analysis of the crude reaction mixture (Scheme 4).



Scheme 4

As a consequence of the sensitivity to oxidation of the 4,5-*anti* diastereomers **5**, enantiomerically pure nucleoside analogs (1'*R*,3'*S*,4'*R*)- and (1'*S*,3'*S*,4'*R*)-**8** could be obtained directly starting from a 4*S*/*R* (*syn*/*anti*) epimeric mixture of the corresponding secondary alcohols **5**. Specifically, when reacting a mixture of (4*S*,5*R*,R_S)- and (4*R*,5*R*,R_S)-**5**, only the (1*R*/*S*,3*S*,4*R*)-**6** lactols derived from the *syn* compound were isolated.

The structures of compounds **4–9** were assigned with the aid of ^1H, ^{13}C, ^{19}F, and ^{31}P NMR studies (Tables 1, 2 and experimental section). The absolute stereochemistry at C-5 of three of the four sulfenylic secondary alcohols **10** was assigned by comparing the chemical shift values of the



Scheme 3

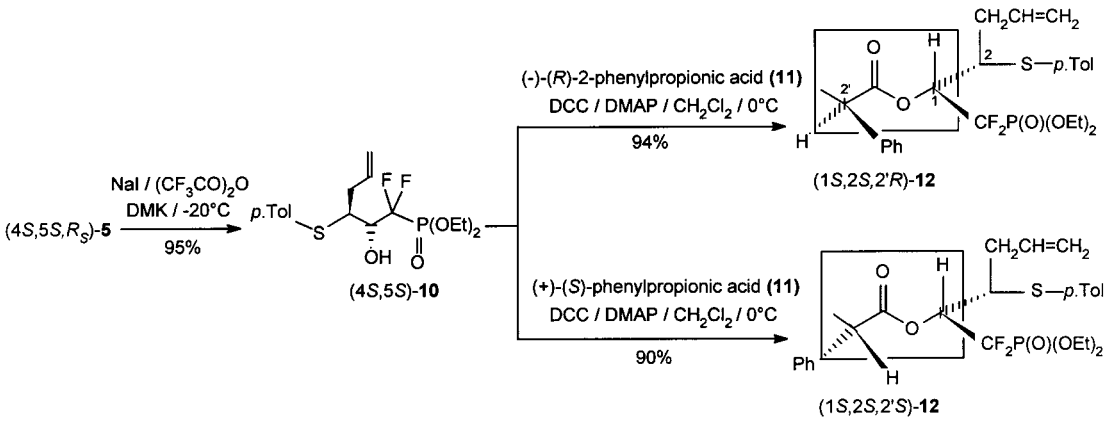
Table 1. NMR Data for Compounds **4**, **5** and **13**

Compound[a]	^{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)
(4*R*/*S*,*R*$_S$)-**4**	1.37 (6H, m, 2 × OCH_2CH_3), 2.42 (3H, brs, ArMe), 2.2–2.6 (2H, m, H_2-3), 4.1–4.4 (5H, m, H-4 and 2 × OCH_2CH_3), 5.0–5.2 (2H, m, H_2-1), 5.5–5.9 (1H, m, H-2), 7.2–7.6 (4H, m, ArH)	–120.98, –118.74, –120.56, –118.91 (2F, dd, J = 318, 95.0, F_2-6)	3.5–4.0 (1P, m, P-6)
(4*S*,5*S*,*R*$_S$)-**5**	1.38 and 1.40 (6H, brt, J = 7.2, 2 × OCH_2CH_3), 2.19 (1H, brddd, J = 15.0, 5.5, 4.5, H-3a), 2.42 (3H, brs, ArMe), 2.58 (1H, brddd, J = 15.0, 9.0, 8.0, H-3b), 3.09 (1H, ddd, J = 9.0, 4.5, 3.5, H-4), 4.33 and 4.34 (4H, m, 2 × OCH_2CH_3), 4.46 (1H, m, H-5), 5.05 and 5.06 (2H, m, H_2-1), 5.29 (1H, d, J = 6.6, OH), 5.52 (1H, m, H-2), 7.35 and 7.52 (4H, m, ArH)	–122.35 (1F, brddd, J = 303.8, 99.5, 21.3 F_a), –116.06 (1F, brddd, J = 303.8, 99.1, 8.8 F_b)	6.56 (1P, brdd, J = 99.5, 99.1, P)
(4*S*,5*R*,*R*$_S$)-**5**	1.38 (6H, brt, J = 7.2, 2 × OCH_2CH_3), 2.3–2.8 (2H, m, H_2-3), 2.43 (3H, brs, ArMe), 3.21 (1H, m, H-4), 4.2–4.4 (4H, m, 2 × OCH_2CH_3), 4.75 (1H, m, H-5), 4.97 and 4.98 (2H, m, H_2-1), 5.68 (1H, m, H-2), 7.33 and 7.54 (4H, m, ArH)	–125.74 (1F, brddd, J = 303.0, 102.6, 23.2, F_a), –115.79 (1F, brddd, J = 303.0, 97.5, 5.7, F_b)	7.31 (1P, brdd, J = 102.6, 97.5, P)
(4*R*,5*S*,*R*$_S$)-**5**	1.35 (6H, brt, J = 7.2, 2 × OCH_2CH_3), 2.43 (3H, brs, ArMe), 2.7–3.1 (3H, m, H_2-3 and H-4), 4.2–4.4 (4H, m, 2 × OCH_2CH_3), 4.60 (1H, m, H-5), 5.22 and 5.27 (2H, m, H_2-1), 5.95 (1H, m, H-2), 7.36 and 7.50 (4H, m, ArH)	–124.67 (1F, brddd, J = 303.9, 101.6, 22.4, F_a), –118.04 (1F, brddd, J = 303.9, 99.3, 7.5, F_b)	6.25 (1P, brdd, J = 101.6, 99.3, P)
(4*R*,5*R*,*R*$_S$)-**5**	1.37 (6H, brt, J = 7.2, 2 × OCH_2CH_3), 2.21 and 2.63 (2H, m, H_2-3), 2.42 (3H, brs, ArMe), 3.37 (1H, dt, J = 7.8, 5.5, H-4), 4.2 and 4.4 (4H, m, 2 × OCH_2CH_3), 4.63 (1H, m, H-5), 5.08 and 5.13 (2H, m, H_2-1), 5.71 (1H, m, H-2), 7.34 and 7.63 (4H, m, ArH)	–125.07 (1F, brddd, J = 304.7, 102.2, 21.8, F_a), –112.41 (1F, brddd, J = 304.7, 97.5, 5.2, F_b)	6.74 (1P, brdd, J = 102.2, 97.5, P)
(*E*,*R*$_S$)-**13**	1.37 and 1.38 (6H, brt, J = 7.1, 2 × Me), 3.62 (1H, br, OH), 4.2–4.4 (4H, m, 2 × OCH_2), 4.56 (1H, m, H-5), 5.19 and 5.31 (2H, brd, J = 9.9, 16.1, H_2-1), 5.78 (1H, brdd, J = 14.6, 6.2, H-4), 6.39 (1H, brddd, J = 16.1, 10.7, 9.9, H-2), 6.47 (1H, brdd, J = 14.6 and 10.7, H-3)	–124.66 (1F, brddd, J = 305.8, 103.0, 16.7, F-6a), –117.04 (1F, brddd, J = 305.8, 102.1, 7.9, F-6b)	7.30 (1P, brdd, J = 103.0, 102.1, P-6)

[a] Satisfactory microanalyses obtained: C, H ± 0.4.

protons of the butenyl fragments of the esters **12** obtained through reaction with (–)-(*R*)- and (+)-(*S*)-2-phenylpropionic acids **(11)**[9] as shown on Scheme 5 for the diastereomeric esters (1*S*,2*S*,2'*R*)- and (1*S*,2*S*,2'*S*)-**12**. For example, the above mentioned protons of (1*S*,2*S*,2'*R*)-**12** resonated at higher fields than the corresponding protons of (1*S*,2*S*,2'*S*)-**12** as a consequence of the shielding effect exerted by the phenyl ring of the 1-phenylacetate group. The absolute stereochemistry at C-5 of the secondary alcohols **5** directly followed from that exhibited by **10** as during deoxygenation at sulfur, with sodium iodide and trifluoroacetic anhydride in acetone[10] the C-5 stereocenter was not affected. The structures of compounds **10** and **12** were assigned with the aid of ^{1}H, ^{19}F, and ^{31}P NMR studies (Tables 2 and 3).

Finally, the absolute configurations of the remaining carbon stereocenters of the cyclic compounds **6–9** (C-1 and



Scheme 5

Table 2. NMR Data for Compounds **6–10**

Compound[a]	^{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)
(1*S*/3*S*,4*R*)-**6**	1.35 and 1.37 (6H, brt, J = 7.1, 2 × OCH_2CH_3), 2.48 (3H, brs, ArMe), 2.48 (1H, ddd, J = 15.3, 2.5, 2.0, H-2α), 2.65 (1H, ddd, J = 15.3, 10.0, 5.5, H-2β), 4.1–4.4 (5H, m, 2 × OCH_2CH_3 and H-3), 4.83 (1H, d, J = 12.5, OH-1), 4.94 (1H, dddd, J = 14.7, 10.2, 5.8, 3.0, H-4), 5.62 (1H, ddd, J = 12.5, 5.5, 2.0, H-1), 7.80 and 7.84 (4H, m, ArH)	–118.54 (1F, brddd, J = 309.0, 97.8, 10.2, F-5a), –124.44 (1F, brddd, J = 309.0, 97.6, 14.7, F-5b)	4.76 (1P, dddt, J = 97.8, 97.6, 6.3 and 5.8, P-5)
(1*R*,3*S*,4*R*)-**6**	1.36 and 1.38 (6H, brt, J = 7.1, 2 × OCH_2CH_3), 2.22 (1H, ddd, J = 14.2, 9.0, 3.5, H-2β), 2.47 (3H, brs, ArMe), 2.67 (1H, m, H-2α), 4.1 and 4.4 (5H, m, 2 × OCH_2CH_3 and H-3), 4.62 (1H, d, J = 11.0, OH-1), 4.80 (1H, dddd, J = 16.0, 10.6, 5.5, 4.0, H-4), 5.62 (1H, ddd, J = 11.0, 10.0, 3.5, H-1), 7.39 and 7.80 (4H, m, ArH)	–114.29 (1F, brddd, J = 306.5, 96.2, 10.6, F-5a), –121.08, – 121.11 (1F, brddd, J = 306.5, 103.3, 16.0, F-5b, 1:2 ratio)	5.97 (1P, dddt, J = 103.3, 96.2, 6.3 and 5.5, P-5)
(1*S*,3*S*,4*R*)-**7**	0.96 and 1.00 (6H, brt, J = 7.1, 2 × OCH_2CH_3), 1.68 (3H, s, $OCOCH_3$), 1.79 (3H, brs, ArMe), 2.05 (1H, ddd, J = 14.2, 9.0, 2.6, H-2β), 2.68 (1H, ddd, J = 14.2, 6.4, 5.8, H-2α), 3.9–4.2 (4H, m, 2 × OCH_2CH_3), 4.39 (1H, ddd, J = 9.0, 6.4, 4.4, H-3), 5.33 (1H, brddd, J = 20.2, 7.2, 4.4, H-4), 6.36 (1H, ddd, J = 5.8, 2.6, 2.1, H-1), 6.69 and 7.67 (4H, m, ArH)[b]	–118.52 (1F, dddd, J = 307.0, 96.0, 7.2, 2.1, F-5a), –124.66 (1F, ddd, J = 307.0, 96.0, 20.2, F-5b)[b]	5.49 (1P, m, P-5)
(1*R*,3*S*,4*R*)-**7**	0.92 and 0.96 (6H, brt, J = 7.1, 2 × OCH_2CH_3), 1.68 (3H, s, $OCOCH_3$), 1.77 (3H, brs, ArMe), 2.44 (1H, ddd, J = 15.1, 11.2, 5.7, H-2β), 2.74 (1H, ddd, J = 15.1, 3.0, 1.3, H-2α), 3.9–4.2 (4H, m, 2 × OCH_2CH_3), 4.34 (1H, ddd J = 11.2, 4.3, 3.0, H-3), 5.47 (1H, dddd, J = 13.5, 9.5, 8.4, 4.3, H-4), 6.38 (1H, dd, J = 5.7, 1.3, H-1), 6.66 and 7.71 (4H, m, ArH)[b]	–116.16 (1F, ddd, J = 309.0, 96.5, 8.4, F-5a), –123.02 (1F, ddd, J = 309.0, 96.5, 13.5, F-5b)[b]	4.53 (1P, m, P-5)
(1′*R*,3′*S*,4′*R*)-**8**	1.36 (6H, t, J = 7.1, 2 × OCH_2CH_3), 1.99 (3H, d, J = 1.3, CH_3-5), 2.21 (1H, ddd, J = 14.8, 9.7, 9.3, H-2′β), 2.49 (3H, brs, ArMe), 2.83 (1H, ddd, J = 14.8, 5.6, 1.0, H-2′α), 4.2–4.4 (4H, m, 2 × OCH_2CH_3), 4.36 (1H, ddd, J = 9.7, 2.8, 1.0, H-3′β), 4.95 (1H, dddd, J = 14.4, 10.2, 4.5, 2.8, H-4'), 6.37 (1H, brdd, J = 9.3, 5.6, H-1'), 7.43 and 7.84 (4H, m, ArH), 7.86 (1H, q, J = 1.3, ArH), 9.70 (1H, br, NH)[b]	–118.20 (1F, ddd, J = 309.5) 97.5, 10.2, F-5'a), –123.27 (1F, ddd, J = 309.5, 97.0, 4.4, F-5'b)	4.44 (1P, brdd, J = 97.5, 97.0, P-5')
(1′*S*,3′*S*,4′*R*)-**8**	1.38 (6H, t, J = 7.1, 2 × OCH_2CH_3), 1.93 (3H, d, J = 1.3, CH_3-5), 2.48 (3H, brs, ArMe), 2.49 (1H, ddd, J = 15.0, 6.3, 5.3, H-2′α), 2.87 (1H, ddd, J = 15.0, 10.5, 7.4, H-2′β), 4.2–4.4 (4H, m, 2 × OCH_2CH_3), 4.35 (1H, ddd, J = 10.5, 5.3, 2.6, H-3'), 5.10 (1H, dddd, J = 19.5, 8.4, 3.7, 2.6, H-4'), 6.56 (1H, brdd, J = 7.4, 6.3, H-1'), 7.43 and 7.82 (4H, m, ArH), 7.68 (1H, q, J = 1.3), 9.76 (1H, br, NH)	–119.00 (1F, brddd, J = 310.5, 97.5, 8.4, F-5'a), –123.85 (1F, brddd, J = 310.5, 95.5, 19.5, F-5'b)	4.44 (1P, brddd, J = 97.5, 95.5, P-5')
(4*S*,5*R*)-**9**	1.34 (6H, brt, J = 7.2, 2 × OCH_2CH_3), 2.50 (3H, brs, ArMe), 2.94 (1H, ddt, J = 19.3, 2.7, 1.2, H-3α), 3.20 (1H, brdd, J = 19.3, 10.1, H-3β), 4.1–4.4 (4H, m, 2 × OCH_2CH_3), 4.61 (1H, ddd, J = 10.1, 2.7, 2.0, H-4), 5.24 (1H, dddd, J = 13.0, 12.0, 3.9, 2.0, H-5), 7.58 and 7.94 (4H, m, ArH)[c]	–120.31 (1F, ddd, J = 313.3, 96.2, 11.3, F_a), –123.80 (1F, ddd, J = 313.3, 92.5, 12.3, F_b)	4.28 (1P, brdd, J = 96.2, 92.5, P-6)
(4*S*,5*S*)-**9**	1.40 and 1.38 (6H, brt, J = 7.2, 2 × OCH_2CH_3), 2.47 (3H, brs, ArMe), 2.53 (1H, ddd, J = 17.4, 8.6, 1.2, H-3β), 3.23 (1H, ddd, J = 17.4, 11.8, 3.4, H-3α), 4.30 (1H, m, H-4), 4.4–4.2 (4H, m, 2 × OCH_2CH_3), 5.25 (1H, dd, J = 26.5, 7.2, H-5), 7.40 and 7.83 (4H, m, ArH)	–115.78 (1F, brdd, J = 313.0, 96.5, F_a), –125.55 (1F, brddd, J = 313.0, 92.5, 26.5, F_b)	4.22 (1P, brdd, J = 96.5, 92.5, P-6)
(4*S*,5*R*)-**10**	1.32 (6H, m, 2 × OCH_2CH_3), 2.32 (3H, brs, ArMe), 2.40 and 2.75 (2H, m, H_2-3), 3.12 (1H, d, J = 6, OH), 3.55 (1H, m, H-4), 4.2–4.4 (5H, m, 2 × OCH_2CH_3 and H-5), 5.12 and 5.20 (2H, m, H_2-1), 6.02 (1H, m, H-2), 7.12 and 7.35 (4H, m, ArH)	–118.10 (1F, brddd, J = 305.5, 99.6, F-6a), –124.05 (1F, brddd, J = 305.5, 105, 23.5, F-6b)	6.75 (1P, brdd, J = 105, 99, P-6)
(4*R*,5*R*)-**10**	1.38 (6H, m, 2 × OCH_2CH_3), 2.33 (3H, brs, ArMe), 2.35 and 2.56 (2H, m, H_2-3), 3.49 (1H, m, H-4), 3.54 (1H, d, J = 5.5, OH), 4.03 (1H, m, H-5), 4.2–4.4 (4H, m, 2 × OCH_2CH_3), 5.13 and 5.15 (2H, m, H_2-1), 5.90 (1H, m, H-2), 7.14 and 7.39 (4H, m, ArH)	–114.52 (1F, brddd, J = 306.5, 100, 5.5, F-6a), –125.70 (1F, brddd, J = 306.5, 104.5, 22.5, F-6b)	6.97 (1P, brdd, J = 104.5, 100, P-6)

[a] Satisfactory microanalyses obtained: C, H ± 0.4.
[b] Recorded in C_6D_6.
[c] Recorded in acetone-d_6.

Table 3. ^{1}H NMR Data of Compounds **12**

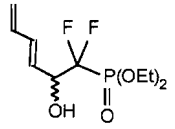
Compound[a]	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)
(4*R*,2*S*,2'*R*)-**12**	1.21 and 1.26 (6H, t, J = 7.0, 2 × OCH_2CH_3), 1.58 (3H, d, J = 7.2, Me-2'), 1.80 and 2.57 (2H, m, H_2-3), 2.31 (3H, brs, ArMe), 3.57 (1H, m, H-2), 3.87 (1H, 9, J = 7.2, H-2'), 3.9–4.3 (4H, m, 2 × OCH_2CH_3), 4.97 and 5.02 (2H, m, H_2-5), 5.48 (1H, m, H-1), 5.83 (1H, m, H-4), and 7.0–7.5 (9H, m, ArH)
(1*R*,2*R*,2'*R*)-**12**	1.36 (6H, brt, J = 7.1, 2 × OCH_2CH_3), 1.56 (3H, d, J = 7.2, Me-2'), 2.11 and 2.21 (2H, m, H_2-3), 2.32 (3H, brs, ArMe), 3.51 (1H, m, H-2), 3.83 (1H, q, J = 7.2, H-2'), 4.2–4.4 (4H, m, 2 × OCH_2CH_3), 4.93 and 5.00 (2H, m, H_2-5), 5.58 (1H, m, H-1), 5.63 (1H, m, H-4), and 7.0–7.5 (9H, m, ArH)
(1*S*,2*S*,2'*R*)-**12**	1.26 and 1.29 (6H, t, J = 7.2, 2 × OCH_2CH_3), 1.56 (3H, d, J = 7.2, Me-2'), 2.32 (3H, brs, ArMe), 2.36 (2H, m, H_2-3), 3.67 (1H, m, H-2), 3.77 (1H, q, J = 7.2, H-2'), 4.0–4.2 (4H, m, 2 × OCH_2CH_3), 5.06 and 5.08 (2H, m, H_2-5), 5.58 (1H, m, H-1), 5.78 (1H, m, H-4), and 7.0–7.5 (9H, m, ArH)
(1*S*,2*S*,2'*S*)-**12**	1.16 and 1.20 (6H, t, J = 7.0, 2 × OCH_2CH_3), 1.63 (3H, d, J = 7.1, Me-2'), 2.17 and 2.75 (2H, m, H_2-3), 2.32 (3H, brs, ArMe), 3.67 (1H, m, H-2), 3.90 (1H, q, J = 7.1, H-2'), 4.0–4.3 (4H, m, 2 × OCH_2CH_3), 5.12 and 5.14 (2H, m, H_2-5), 5.49 (1H, m, H-1), 5.97 (1H, m, H-4), and 7.0–7.5 (9H, m, ArH)

[a] Satisfactory microanalyses obtained: C, H ± 0.4.

C-3 for **6** and **7**; C-4 for **9**; C-3' for **8**) followed from NOE experiments and from the magnitude of ^{1}H–^{1}H coupling constants of the ring protons. Specifically, in the α-anomer (1*S*,3*S*,4*R*)-**6**, the small values observed for the ^3J between H-4, assumed as α in the formula, and H-3β, H-3β and H-2α, and H-2α and H-1β (^3J = 3.0, 2.5 and 1.2 Hz, respectively) indicated a *trans* pseudoequatorial relationships. As a consequence, the hydroxy and the 4-methylphenylsulfonyl groups were both *trans* oriented with respect to the diethoxyphosphoryldifluoromethyl moiety. It must be noted that in the β-anomer (1*R*,3*S*,4*R*)-**6**, in which the hydroxy and the diethoxyphosphoryldifluoromethyl groups were *cis* disposed, the fluorine atom resonating at δ = *ca.* 121 showed in its ^{19}F NMR spectrum two signals in a 1:2 ratio exhibiting the same pattern. This fact might be attributed to the presence of intramolecular hydrogen bonding between the fluorine atom and the hydroxy proton,[11] this latter partially deuterated by the D_2O contained in the solvent, which gave rise to an isotope effect of 28.3 × 10^{-3} ppm. Similar effects have been observed in the ^{1}H NMR spectra of sugar derivatives as a consequence of the formation of intramolecular hydrogen bonding between partially deuterated hydroxy groups under slow-exchange conditions.[12]

The NOE observed between H-1 and H-4 (1%) in the acetate (1*S*,3*S*,4*R*)-**7** implied that these protons were on the same side of the molecule; accordingly, in the epimer (1*R*,3*S*,4*R*)-**7**, which, on the other hand, exhibited ^{1}H–^{1}H coupling constants similar to those observed for the corresponding lactol (1*S*,3*S*,4*R*)-**6**, a sizeable NOE was observed between H-1 and the fluorine at δ = –116.16 (1%). The mutual NOE enhancements observed between H-4' and H-6 (1 and 2%) in (1'*S*,3'*S*,4'*R*)-**8** and between H-4' and H-1' (2 and 2.5%) in (1'*R*,3'*S*,4'*R*)-**8**, in conjunction with the NOEs observed between F_2-5' and H-1' (3.5%) in the former compound and between F_2-5' and H-6 (2.5%) in the latter, established the stereochemistry of the title compounds, while the presence of signals at δ = 171.52 and 170.28 in the ^{13}C NMR spectra of (3*S*,4*R*)- and (3*S*,4*S*)-**9**, attributable to lactone carbonyl carbons, gave conclusive evidence for the assignment of their structures.

The elimination of the sulfonyl substituent from nucleoside analogs **8** to obtain the corresponding sulfur-free compounds could not be achieved. Finally, *syn* elimination of the sulfinyl residue from alcohols **5** occurred under mild conditions and gave selectively the corresponding (*E*)-6-(diethoxyphosphoryl)-6,6-difluoro-2-hydroxyhexa-1,3-diene **(13)**. The structure of compound **13** was assigned with the aid of ^{1}H, ^{19}F, and ^{31}P NMR studies (Table 1).



(*E*)-**13**

In conclusion, difluoromethylphosphonate nor-analogs of thymidine nucleotide were obtained by assembling the diethoxyphosphoryldifluoromethyl framework of the pyranose moiety through condensation of ethyl 2-(diethylphosphoryl)-2,2-difluoroacetate **(2)** and 4-(4-methylphenylsulfinyl)but-1-ene **(3)** followed by quick reduction of the carbonyl of the intermediate labile ketones **4** to secondary alcohols **5**. Their subsequent oxidation and cyclization was feasible only for the *syn* compounds. The nucleoside analogs **8** belonging to the D-series were obtained from the (5*R*)-**5** epimers; the same analogs **8**, belonging to the series, were obtained from the (5*S*)-**5** ketones.

$[\alpha]_D$ Values were obtained on a JASCO DIP-181 and PROPOL polarimeters. TLC was performed on silica gel 60 F_{254} Merck; flash column chromatography was performed with silica gel 60 (60–200 μm, Merck). ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were run at r.t. on a Bruker AC 250L spectrometer operating at 250 MHz in $CDCl_3$ and equipped with a supplementary Broadband Modulator BM1. Chemical shifts

were expressed in ppm (δ), using TMS as internal standard for ^{1}H and ^{13}C nuclei (δ_H and δ_C = 0.00), while C_6F_6 was used as internal standard (δ_F = –162.90) for ^{19}F and H_3PO_4 (δ_P = 0) for ^{31}P nucleus. MS were recorded on a TSQ 70 Finnigan Mat three-stage quadrupole instrument. A DIS (Direct Inlet System) was used for pure compounds. HPLC analyses were performed on Waters 600E System Controller instrument using a Lambda-Max Model 481 LC spectrophotometer operating at 260 nm. Analytical data were elaborated by a Waters 745 Data Module instrument; analyses were performed on Hibar Pre-Packed column RT 250–4 (Li Chrosorb Si 60–5 μm, Merck). Combustion microanalyses were performed by Redox SNC, Cologno Monzese (Milano). THF was freshly distilled from Na, *i*-Pr_2NH was freshly distilled from CaH_2; in all other cases, commercially available reagent-grade solvents were employed without purification. In ^{13}C NMR analyses of spectra, capital letters referred to the pattern resulting from one bond (C,H) coupling constants and small letters referred to (C,F) and (C,P) coupling constants.

Ethyl 2-(Diethoxyphosphoryl)-2,2-difluoroacetate (2):
To a suspension of NaH (240 mg, 8.0 mmol, 80% mineral oil) in THF (12 mL) stirred at 0°C under N_2, commercially available **1** (2.0 g, 8.0 mmol) in THF (12 mL) was added dropwise. Stirring was continued for 15 min and the mixture was allowed to reach r.t. F-TEDA•BF_4 (2.92 mg, 8.0 mmol) was added neat followed by DMF (8.0 mL). The reaction was continued for 3 d, then the mixture was poured into ice/water, extracted with EtOAc (3 × 20 mL), dried (Na_2SO_4), filtered and, after evaporation of the solvent, the residue was flash chromatographed (hexane/EtOAc 1:1) to give **2** (1.3 g, 60%). Physicochemical and analytical data were identical to those already described.[6]

(4*S*,5*R*,*R*$_S$)-, (4*R*,5*S*,*R*$_S$)-, (4*S*,5*S*,*R*$_S$)-, (4*R*,5*R*,*R*$_S$)-6-(Diethoxyphosphoryl)-6,6-difluoro-5-hydroxy-4-(4-methylphenylsulfinyl)hex-1-ene (5):
To a solution of LDA (1.1 mL, 7.7 mmol) in THF (13 mL) stirred at –78°C under N_2, 4-(4-methylphenylsulfinyl)but-1-ene (1.3 g, 6.5 mmol) in THF (25 mL) was added dropwise. After 5 min, **2** (2.1 g, 7.7 mmol) in THF (13 mL) was added. After 2 min, sat. NH_4Cl was added, the organics extracted with Et_2O, dried (Na_2SO_4), filtered and, after evaporating the solvent, the residue was composed by a 1:1 mixture of (4*R*,*R*$_S$)-(4*S*,*R*$_S$)-4. NMR Data are reported in Table 1.
The thus obtained mixture was reduced following two different procedures.

(a) DIBAH: The residue in THF (10 mL) was cooled to –78°C under stirring in N_2. 1.0 M DIBAH in hexane (12.9 mL) was added and, after 5 min, sat. NH_4Cl was added, the pH adjusted to 6 (dil HCl), the organics extracted with Et_2O, processed as usual and the residue was flash chromatographed (hexane/EtOAc 3:7). Four different diastereomers (^{1}H and ^{19}F NMR analyses of the crude) were present in the ratio: (4*S*,5*R*,*R*$_S$)/(4*R*,5*S*,*R*$_S$)/(4*S*,5*S*,*R*$_S$)/(4*R*,5*R*,*R*$_S$) 3.5:1.0:2.0:2.0 (2.17 g, 85%).

(4*S*,5*R*,*R*$_S$)-**5**: yield: 871 mg (34%); R_f 0.35 (hexane/EtOAc 3:7); $[\alpha]_D^{20}$ +84.0 (*c* = 1.8, $CHCl_3$); diastereoisomeric purity of the present material: 90%.
^{1}H, ^{19}F, and ^{31}P NMR Data are reported in Table 1.

(4*R*,5*S*,*R*$_S$)-**5**: yield: 261 mg (10%); R_f 0.35 (hexane/EtOAc 3:7); $[\alpha]_D^{20}$ +30.1 (*c* = 0.7, $CHCl_3$); diastereoisomeric purity of the present material: 93%.
^{1}H, ^{19}F, and ^{31}P NMR Data are reported in Table 1.

(4*S*,5*S*,*R*$_S$)-**5**: yield: 545 mg (21%); R_f 0.30; $[\alpha]_D^{20}$ +56.0 (*c* = 1.0, $CHCl_3$); diastereoisomeric purity of the present material: 95%.
^{1}H, ^{19}F, and ^{31}P NMR Data are reported in Table 1.
^{13}C NMR ($CDCl_3$): δ = 16.35 (Qd, $J_{C,P}$ = 5.5 Hz, 2 × OCH_2CH_3), 21.37 (Q, ArMe), 26.27 (T, C-3), 60.92 (Dbrd, $J_{C,F}$ = 5.0 Hz, C-4), 65.03 (Td, $J_{C,P}$ = 6.5 Hz, 2 × OCH_2CH_3), 70.83 (Dddd, $J_{C,F}$ = 25.5 and 21.5, $J_{C,P}$ = 15.5 Hz, C-5), 118.99 (T, C-1), 124.51 (D), 129.90 (D), 137.58 (S) and 141.40 (S) (ArC) and 133.63 (D, C-2).
MS (EI): *m/z* (%) = 411 ($[M + H]^{+\cdot}$, 70), 392 ($[M + H – F]^{+\cdot}$, 4), 271 ($[C_{10}H_{17}PO_4F_2]^{+\cdot}$, 100), 253 ($[271 – H_2O]^{+\cdot}$, 68), 215 ($[C_6H_{10}PO_4F_2]^{+\cdot}$, 100), 205 ($[C_{12}H_{13}SO]^{+\cdot}$, 30), 177 ($[C_{11}H_{13}S]^{+\cdot}$, 45), 139 ($[C_7H_7SO]^{+\cdot}$, 48), 136($[215 – H_3PO_3]^{\cdot}$, 17), 91 ($[C_7H_8]^{+\cdot}$, 38), 81($[H_2PO_3]^{+\cdot}$, 17).
HPLC: t_R = 12.0 min (cyclohexane/EtOAc 4:96; μ = 1.2 mL/min; λ = 260 nm).

(4*R*,5*R*,*R*$_S$)-**5**: yield: 502 mg (19%); R_f 0.35 (hexane/EtOAc 3:7); $[\alpha]_D^{20}$ +36.1 (*c* = 0.6, $CHCl_3$); diastereoisomeric purity of the present material: 95%.

(b) $NaBH_4$: The crude dissolved in MeOH/30% aq NH_3 (9:1, 30 mL), was cooled to –10°C and $NaBH_4$ (291 mg, 7.7 mmol) in the same solvent mixture (30 mL) was added. After 10 min, the reaction was quenched (dil HCl up to pH 4), the solvents evaporated and the organics extracted with Et_2O (3 × 30 mL), dried (Na_2SO_4) and, after the usual procedure, the residue was analyzed by ^{1}H and ^{19}F NMR showing the diastereoisomeric ratio: (4*S*,5*R*,*R*$_S$)/(4*R*,5*S*,*R*$_S$)/(4*S*,5*S*,*R*$_S$)/(4*R*,5*R*,*R*$_S$) 1:1:1:2 (2.12 g, 83%).

(1*R*/*S*,3*S*,4*R*)-4-*C*-[(Diethoxyphosphoryl)difluoromethyl]-3-(4-methylphenylsulfonyl)-2,3,5-trideoxy-*glycero*-pentofuranose (6); General Procedure:
40% aq $RuCl_3$ (27 mg, 0.05 mmol) was added at 0°C to **5** (871 mg, 2.21 mmol) in $CCl_4/CH_3CN/H_2O$ (1:1:2, 4 mL). After 1 min, $NaIO_4$ (1.92 mg, 8.42 mmol) was added and the mixture was allowed to reach r.t. Water (4 mL) was added and the organics extracted with CH_2Cl_2 (3 × 8 mL). After the usual procedure, the residue was flash chromatographed (hexane/EtOAc 3:7). From (4*S*,5*R*,*R*$_S$)-5, after 2 h, **6** was obtained (823 mg, 87% yield) (2.5:1.0 β/α by NMR analysis), and (3*S*,4*R*)-**9** (66 mg, 7% yield).

(1*R*/*S*,3*S*,4*R*)-**6**: R_f 0.35; $[\alpha]_D^{20}$ –10.0 (*c* = 0.1, $CHCl_3$) at t_0, $[\alpha]_D^{20}$ –12.2 (*c* = 0.1, $CHCl_3$) after 7 h; diastereo- and enantiomeric purity of the present material: 90%.

(1*S*,3*S*,4*R*)-**6** (α-anomer): ^{1}H, ^{19}F, and ^{31}P NMR Data are reported in Table 2.
^{13}C NMR ($CDCl_3$): δ = 16.31 (Qd, $J_{C,P}$ = 6.5 Hz, 2 × OCH_2CH_3), 21.76 (Q, ArMe), 35.11 (T, C-2), 63.88 (Dt, $J_{C,F}$ = 3.5 Hz, C-3), 65.05 and 65.15 (Td, $J_{C,P}$ = 7 Hz, 2 × OCH_2CH_3), 78.00 (Dddd, $J_{C,F}$ = 27 and 24, $J_{C,P}$ = 16.0 Hz, C-4), 100.60 (D, C-1), 117.17 (Sddd, $J_{C,F}$ = 268.5 and 265.5, $J_{C,P}$ = 208.5 Hz, C-5), 146.12 (S), 132.99 (S), 130.39 (D) and 128.9 (D) (ArC).

(1*R*,3*S*,4*R*)-**6** (β-anomer): ^{1}H, ^{19}F, and ^{31}P NMR Data are reported in Table 2.
^{13}C NMR ($CDCl_3$): δ = 16.31 (Qd, $J_{C,P}$ = 6.5 Hz, 2 × OCH_2CH_3), 21.71 (Q, Ar*Me*), 35.72 (T, C-2), 63.34 (Dt, $J_{C,F}$ = 3.5 Hz, C-3), 65.39 and 65.11 (Td, $J_{C,P}$ = 7 Hz, 2 × OCH_2CH_3), 78.40 (Dm, C-4), 100.80 (D, C-1), 117.63 (Sm, C-5), 145.39 (S), 134.29 (S), 130.18 (D) and 128.75 (D) (ArC).
MS(EI): *m/z* (%) = 427 ($[M – H]^{+\cdot}$, 20), 428 ($[M]^{\cdot}$, 6), 411 ($[M – OH]^{+\cdot}$, 16), 400 ($[M – CO]^{+\cdot}$, 7), 362 ($[M – COF_2]^{+\cdot}$, 4), 273 ($[C_9H_{17}PO_5F_2]^{+\cdot}$, 28), 245 ($[273 – CO]^{+\cdot}$, 16), 188 ($[C_5H_{11}PO_3F_2]^{\cdot}$,100), 161 ($[188 – C_2H_3]^{+\cdot}$, 63), 139 ($[C_4H_{12}PO_3]^{+\cdot}$, 38), 132 ($[161 – C_2H_5]^{+\cdot}$, 23), 91 ($[C_7H_8]^{+\cdot}$, 44), 29 ($[C_2H_5]^{+\cdot}$, 8).

(3*S*,4*R*)-**9**: R_f 0.37; $[\alpha]_D^{20}$ +15.53 (*c* = 0.1, $CHCl_3$). ^{1}H, ^{19}F, and ^{31}P NMR Data are reported in Table 2.
^{13}C NMR ($CDCl_3$): δ = 16.31 and 16.25 (Qd, $J_{C,P}$ = 5.5 Hz, 2 × OCH_2CH_3), 21.76 (Q, Ar*Me*), 28.75 (T, C-2), 58.72 (Dt, $J_{C,F}$ = 2.5 Hz, C-3), 65.71 and 65.57 (Td, $J_{C,P}$ = 7.0 Hz, 2 × OCH_2CH_3),

76.74 (Dm, C-4), 146.43 (S), 132.55 (S), 130.52 (D) and 128.97 (D) (ArC) and 171.52 (s, C-1).
NOE experiment (acetone-d_6): irradiation of the two protons at δ = 7.94 enhanced H-2α (1.5%), H-3 (2.5%), H-4 (3%) and 2 × H at δ = 7.58 (7%).

From a 2:1 mixture of (4*S*,5*R*,R_S)- and (4*R*,5*R*,R_S)-**5**, the same products above described were detected in comparable chemical yields.

From (4*S*,5*S*,R_S)-**5** (545 mg, 1.38 mmol), after 5 h, (3*S*,4*S*)-**9** was formed (71 mg, 12%); R_f 0.45; $[\alpha]_D^{20}$ +2.27 (*c* = 0.4, $CHCl_3$). No other isolable product was formed; diastereo- and enantiomeric purity of the present material: 90%.
^{1}H, ^{19}F, and ^{31}P NMR Data are reported in Table 2.
^{13}C NMR (C_6D_6): δ = (selected signal) 170.28 (C-1).
NOE experiments ($CDCl_3$): irradiation of the F atom at δ = –125.55 enhanced H-2α (3%); {H-3} enhanced H-2β (6%) and H-4 (6.5%).

From (4*R*,5*S*,R_S)-**5** (261 mg, 0.66 mmol), after 2 h, an anomeric mixture of β(1*R*)/α(1*S*)-**6** was detected in $CHCl_3$ (230 mg, 81%) (1.0:2.5 β/α by NMR).

(1*R*/*S*,3*R*,4*S*)-**6**: R_f 0.35; $[\alpha]_D^{20}$ +10.8 (*c* = 0.3, $CHCl_3$) at t_0, $[\alpha]_D^{20}$ +13.2 (*c* = 0.3, $CHCl_3$) after 7 h; diastereo- and enantiomeric purity of the present material: 93%; ^{1}H, ^{19}F and ^{31}P NMR data were superimposable on that of the above described enantiomers (1*R*/*S*,3*S*,4*R*)-**6.**

(4*S*,5*R*)-4-(4-Methylphenylsulfonyl)-5-[(diethoxyphosphoryl)difluoromethyl]dihydrofuran-2(3*H*)-one (9); Reduction to Lactol 6:
1.0 M DIBAH in toluene (154 µL) was added to a solution of (4*S*,5*R*)-**9** (66 mg, 0.15 mmol) in toluene (4.0 mL) stirred at –60 °C under N_2. After 30 min, sat. NH_4Cl was added, organics were extracted with EtOAc, dried (Na_2SO_4) and, after the usual procedure, the residue was flash chromatographed (hexane/EtOAc 3:7) to give (1*R*/*S*,3*S*,4*R*)-**6** (55 mg, 85%). Physicochemical and spectroscopic data were identical to those of the already described mixture of epimers.

1-*O*-Acetyl-4-*C*-[(diethoxyphosphoryl)difluoromethyl]-3-(4-methylphenylsulfonyl)-2,3,5-trideoxy-*glycero*-pentofuranoside (7); General Procedure:
To a solution of **6** (α/β mixture) (428 mg, 1.0 mmol) in pyridine (280 µL) stirred at 0 °C, neat Ac_2O (280 µL, 2.0 mmol) was added and the mixture was allowed to reach r.t. After stirring overnight, water was added (430 µL), the organics extracted in EtOAc (3 × 400 µL) and, after the usual procedures, the crude was flash chromatographed (hexane/EtOAc 1:1).

From (1*R*/*S*,3*S*,4*R*)-**6** (823 mg, 1.92 mmol), **7** was obtained as a 3:1 epimeric mixture of β(1*S*)/α(1*R*) (D-series) (722 mg, 80%); R_f 0.35; $[\alpha]_D^{20}$ –7.17 (*c* = 0.3, $CHCl_3$).

From (1*S*/*R*,3*R*,4*S*)-**6** (230 mg, 0.54 mmol), the acetyl derivatives (1*R*/*S*,3*R*,4*S*)-**7** were obtained as a 3:1 epimeric mixture of α(1*R*)/β(1*S*) (L-series) (215 mg, 85%); R_f 0.35; $[\alpha]_D^{20}$ +7.95 (*c* = 1.1, $CHCl_3$).
^{1}H, ^{19}F, and ^{31}P NMR Data are reported in Table 2.

1-{4'-*C*-[(Diethoxyphosphoryl)difluoromethyl]-3'-(4-methylphenylsulfonyl)-2',3',5'-trideoxy-*glycero*-pentofuranosyl}thymine (8); General Procedure:
Thymine (321 mg, 2.6 mmol) and $(NH_4)_2SO_4$ (86 mg, 0.64 mmol) in HMDS (7.6 mL) were heated at reflux for 4 h under N_2. After evaporation of the solvent, the crude mixture was added to a solution of **7** (471 mg, 1.0 mmol) in anhyd dichloroethane (11 mL), stirred for 10 min at 40 °C and then TMSOTf (364 µL, 1.2 mmol) was added and stirring continued for 1 h at the same temperature. Then, CH_2Cl_2 (7 mL) was added, the mixture washed ($NaHCO_3$), treated with brine and, after the usual procedure, the crude was flash chromatographed (hexane/EtOAc 3:7).

From (1*S*/*R*,3*S*,4*R*)-**7** (722 mg, 1.54 mmol), (1'*R*/*S*,3'*S*,4'*R*)-**8** (D-series) was obtained (660 mg, 80%) (β(1'*R*)/α(1'*S*) 4.5:5.5); R_f 0.23; $[\alpha]_D^{20}$ +5.58 (*c* = 1.2, $CHCl_3$).

The crude when treated with benzene/$CHCl_3$ (5:1), gave crystals enriched in (1'*R*,3'*S*,4'*R*)-**8**; mp 98–100 °C; diastereoisomeric purity 75%.
^{1}H, ^{19}F, and ^{31}P NMR Data are reported in Table 2.
^{13}C NMR ($CDCl_3$): δ = 12.33 (Q, Me-5), 16.35 (Qd, $J_{C,P}$ = 5.5 Hz, 2 × OCH_2CH_3), 21.74 (Q, ArMe), 32.62 (T, C-2'), 63.55 (Dt, $J_{C,F}$ = 3 Hz, C-3'), 65.58 and 65.22 (Td, $J_{C,P}$ = 7 Hz, 2 × OCH_2CH_3), 77.21 (Dddd, $J_{C,F}$ = 28.5 and 23.5 Hz, $J_{C,P}$ = 15Hz, C-4'), 86.09 (D, C-1'), 111.50 (S, C-5), 117.14 (Sddd, $J_{C,F}$ = 271 and 267, $J_{C,P}$ = 208 Hz, C-5'), 134.82 (D, C-6), 146.09 (S), 133.28 (S), 130.42 (D) and 129.01 (D) (ArC), 150.25 and 163.93 (S, C-2 and C-4).
MS(EI): *m/z* (%) = 536 ([M]$^{\cdot}$, 18), 255 ([$C_9H_{14}PO_4F_2$]$^{+\cdot}$, 20), 205 ([255 – CH_2F_2]$^{+\cdot}$, 6), 177 ([205 – C_2H_4]$^{+\cdot}$, 100), 164 ([205 – C_3H_5]$^{\cdot}$, 100), 136 ([164 – C_2H_4]$^{\cdot}$, 38), 77 ([C_6H_5]$^{+\cdot}$, 12); 51 ([CHF_2]$^{+\cdot}$, 5).

(1'*S*,3'*S*,4'*R*)-**8** was the major compound in the mother liquor (diastereoisomeric purity 70%).
^{1}H, ^{19}F, and ^{31}P NMR Data are reported in Table 2.
^{13}C NMR ($CDCl_3$): δ = 12.67 (Q, Me-5), 16.35 (Qd, $J_{C,P}$ = 5.5 Hz, 2 × OCH_2CH_3), 21.76 (Q, ArMe), 31.96 (T, C-2'), 62.23 (Dt, $J_{C,F}$ = 3 Hz, C-3'), 65.43 and 65.17 (Td, $J_{C,P}$ = 7 Hz, 2 × OCH_2CH_3), 78.21 (Dddd, $J_{C,F}$ = 29 and 23 Hz, $J_{C,P}$ = 15.5 Hz, C-4'), 85.63 (D, C-1'), 112.30 (S, C-5), 117.45 (Sddd, $J_{C,F}$ = 271 and 267, $J_{C,P}$ = 208 Hz, C-5'), 135.41 (D, C-6), 146.10 (S), 133.72 (S), 130.44 (D) and 128.70 (D) (ArC), and 150.49 and 163.73 (S, C-2 and C-4).

The diastereomeric purity of both the so obtained materials was not enough to allow optical rotation value measurements.

(1*R*/*S*,3*R*,4*S*)-**7** (215 mg, 0.56 mmol) Gave a 1:1 mixture of α(1'*S*) and β(1'*R*) nucleoside derivatives (1'*S*/*R*,3'*R*,4'*S*)-**8** (L-series) was obtained (213 mg, 71%); R_f 0.23; $[\alpha]_D^{20}$ –5.39 (*c* = 1.4, $CHCl_3$).
NMR Spectra were superimposable on those of the enantiomers described above.

(4*S*,5*R*)- and (4*S*,5*S*)-6-(Diethoxyphosphoryl)-6,6-difluoro-5-hydroxy-4-(4-methylphenylthio)hex-1-ene (10); General Procedure:
$(CF_3CO)_2O$ (726 µL, 0.54 mmol) in acetone (5 mL) was added dropwise to a suspension of **5** (70 mg, 0.18 mmol), and NaI (51 mg, 0.36 mmol) in acetone (5 mL) stirred at –40 °C under N_2. After 10 min, sat. Na_2SO_3 and sat. $NaHCO_3$ were added, the organics extracted with Et_2O and, after the usual procedure, the residue was flash chromatographed (hexane/EtOAc 7:3).

(a) From (4*S*,5*R*,R_S)-/(4*R*,5*R*,R_S)-**5** (2:1), a 2:1 mixture of (4*S*,5*R*)- (41 mg, 60%; R_f 0.35) and (4*R*,5*R*)-**10** (20 mg, 30%; R_f 0.35) was obtained.
NMR Data are collected in Table 2.

(b) From (4*S*,5*S*,R_S)-**5**, (4*S*,5*S*)-**10** was obtained (65 mg, 95%), R_f 0.35; $[\alpha]_D^{20}$ –13.1 (*c* = 0.5, $CHCl_3$).
^{1}H, ^{19}F, and ^{31}P NMR Data were superimposable on those of the (4*R*,5*R*)-**10** enantiomer described above.
MS(EI): *m/z* (%) = 394 ([M + H]$^{+\cdot}$, 16), 257 ([$C_{13}H_{15}SOF_2$]$^{+\cdot}$, 7), 240 ([257 – OH]$^{\cdot}$, 100), 199 ([$C_{10}H_9SF_2$]$^{+\cdot}$, 50), 189 ([$C_{12}H_{13}S$]$^{+\cdot}$, 20), 149 ([C_9H_9S]$^{+\cdot}$, 18), 123 ([C_7H_7S]$^{+\cdot}$, 38), 91 ([C_7H_7]$^{+\cdot}$, 14), 77 ([C_6H_5]$^{+\cdot}$, 10), 41 ([C_3H_5]$^{+\cdot}$, 4).

1-[(Diethoxyphosphoryl)difluoromethyl]-2-(4-methylphenylthio)pent-4-enyl 2'-Phenylpropionates 12; General Procedure:
Neat DMAP (30 mg, 0.24 mmol) was added to a solution of **10** (100 mg, 0.26 mmol), chiral **11** (300 μL, 2.7 mmol) and DCC (550 mg, 2.7 mmol) in CH_2Cl_2 (4 mL), stirred at 0 °C. After 10 min, a white precipitate formed, the temperature was allowed to rise to r.t. and stirring continued for 1 h. Then, the dicyclohexylurea was filtered off, the solution evaporated to dryness and the residue flash chromatographed (hexane/EtOAc 7:3).

(a) From (–)-(*R*)-**11**: (4*S*,5*R*)-/(4*R*,5*R*)-**10** (2:1) gave (1*R*,2*S*,2'*R*)-/(1*R*,2*R*,2'*R*)-**12** (2:1) (133 mg, 97%); R_f 0.35.
^{1}H NMR Data of both the diastereomers are reported in Table 3.

From (4*S*,5*S*)-**10**: (1*S*,2*S*,2'*R*)-**12** was obtained (128 mg, 94%); R_f 0.35.
^{1}H NMR Data are reported in Table 3.
MS(EI): *m/z* (%) = 649 ([M + C_7H_7S]$^{+\cdot}$, 5), 526 ([M]$^{\cdot}$, 40), 423 ([M – C_7H_7S]$^{+\cdot}$, 5), 377 ([M – $C_9H_9O_2$]$^{+\cdot}$, 23), 356 ([377 – H_2F^+]$^{\cdot}$, 10), 265 ([356 – $C_7H_8^+$]$^{\cdot}$, 4), 253 ([377 – C_7H_5S]$^{+\cdot}$, 58), 218 ([356 – $C_4H_{11}O_3P$]$^{\cdot}$, 32), 177 ([$C_{11}H_{13}S$]$^{+\cdot}$, 22), 149 ([$C_9H_{10}O_2$]$^{+\cdot}$, 12), 105 ([C_8H_9]$^{+\cdot}$, 100), 77 ([C_6H_5]$^{+\cdot}$, 32), 29 ([C_2H_5]$^{+\cdot}$, 7).

From (+)-(*S*)-**11**: (4*S*,5*R*)-/(4*R*,5*R*)-**10** (2:1) gave (1*R*,2*S*,2'*S*)-/(1*R*,2*R*,2'*S*)-**12** (2:1) (123 mg, 90%); R_f 0.35.
^{1}H NMR Data of (4*S*,5*R*,2'*S*)-**12** are reported in Table 3; (1*R*,2*R*,2'*S*)-**12** showed a ^{1}H NMR spectrum superimposable on that of the (1*S*,2*S*,2'*R*)-**12** enantiomer described.

From (4*S*,5*S*)-**10**, (1*S*,2*S*,2'*S*)-**12** was obtained (123 mg, 90%): R_f 0.35.
^{1}H NMR spectrum was superimposable on that of the (1*R*,2*R*,2'*R*)-**12** enantiomer described.

(*E*)-6-(Diethoxyphosphoryl)-6,6-difluoro-5-hydroxyhex-1,3-diene (13); Pyrolytic *syn*-Elimination of the Sulfinylic Moiety:
Alcohol **5** (unresolved diastereomeric mixture) (394 mg, 1.0 mmol), dissolved in *p*-xylene (10 mL), were stirred under N_2 at reflux for 30 min giving (*E*)-**13** (94 mg, 24%); R_f 0.35 (hexane/EtOAc 2:3).
^{1}H, ^{19}F, and ^{31}P NMR Data are given in Table 1.

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