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N-Glycosylation of 2,3-dideoxyfuranose derivatives having a (diethoxyphosphorothioyl)difluoromethyl group at the 3α-position

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Abstract—Lewis acid-mediated *N*-glycosylation of 2,3-dideoxyribofunanosides having a (diethoxyphosphorothioyl)difluoromethyl group at the 3α-position with silylated nucleobases was examined. The phosphorothioyldifluoromethyl was found to be an effective functional group for the diastereoselective synthesis of β-*N*^{1}-pyrimidine-nucleotide analogues **26** and **28**–**30**. However, the method was not useful for the diastereoselective synthesis of adenine nucleotide analogues. The nucleotide analogue **26** was transformed to the difluoromethylene-phosphonate analogue **31** of thymidine-3′-phosphate by oxidation with *m*-CPBA, followed by aqueous work-up.

1. Introduction

Structural modification of naturally-occurring nucleosides and nucleotides has been studied in the search for novel nucleic acid analogues showing biological activity such as antiviral and antitumor effects.[1] Extensive studies have been devoted to the structural modification of 3′- or 5′-phosphorylated nucleosides to the metabolically stable analogues, since the resulting nucleotide analogues serve as potent and selective pseudoterminator of polymerase-catalyzed RNA-synthesis[2] or as important components of antisense oligonucleotides having increased resistance to nuclease.[3]

Methods for the synthesis of 5′-deoxy-5′-difluoromethyl-enephosphonate nucleotide analogues **1** have been studied,[4] since α,α-difluoromethylenephosphonic acids (R–$CF_2PO_3H_2$, DFMPA) are considered to act as a non-hydrolyzable mimic for phosphates (R–OPO_3H_2) due to the close similarity in their structural and physical properties.[5] Many DFMPA derivatives have been prepared for potential enzyme inhibitors and for a useful probe to elucidate biochemical processes.[6] The synthetic chemistry of 3′-*C*-branched 2′,3′-dideoxyribonucleosides toward difluoromethylene analogues **3** of 3′-phosphorylated nucleosides **2** has also received much attention because of their potential usefulness as building blocks of nuclease-resistant antisense oligonucleotides (Fig. 1).[7]

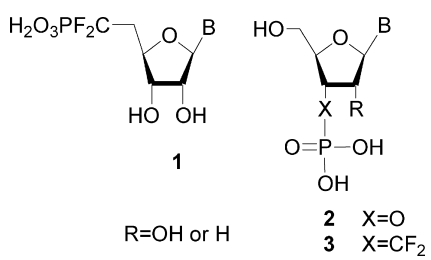

Figure 1.

For the synthesis of a series of nucleotide analogues **3**, especially for a series of the 2′-deoxy derivatives, establishment of methodology for the stereoselective glycosylation of 2,3-dideoxyfuranose derivatives is an important issue to be solved. As a part of our work on a synthesis of 3′-*C*-branched 2′,3′-dideoxynucleotide analogues,[8] we have previously developed a new methodology for highly β-selective *N*-glycosylation of 2,3-dideoxyfuranose derivatives by means of a remote-controlled reaction using glycosyl donor **4** having the diethoxyphosphorothioylmethyl group at the C3-position (Scheme 1).[8c,d] The high diastereoselectivity would result, most possibly, by taking the non-bonding bicyclic cationic intermediate **B** arising from the neighbouring group participation of the phosphorothioylmethyl moiety toward the C1-position, rather than the intermediate **A**.[9] Thus, nucleophilic attack of the activated pyrimidine bases to the less-hindered β-side of **A** yields the β-nucleotide analogue **5** stereoselectively. The sulphur of the phosphorothioyl group might significantly contribute to the neighbouring group participation, since the replacement of the sulphur by oxygen resulted in

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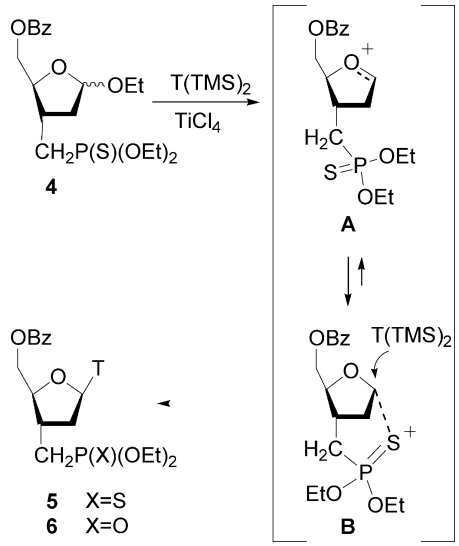


Scheme 1.

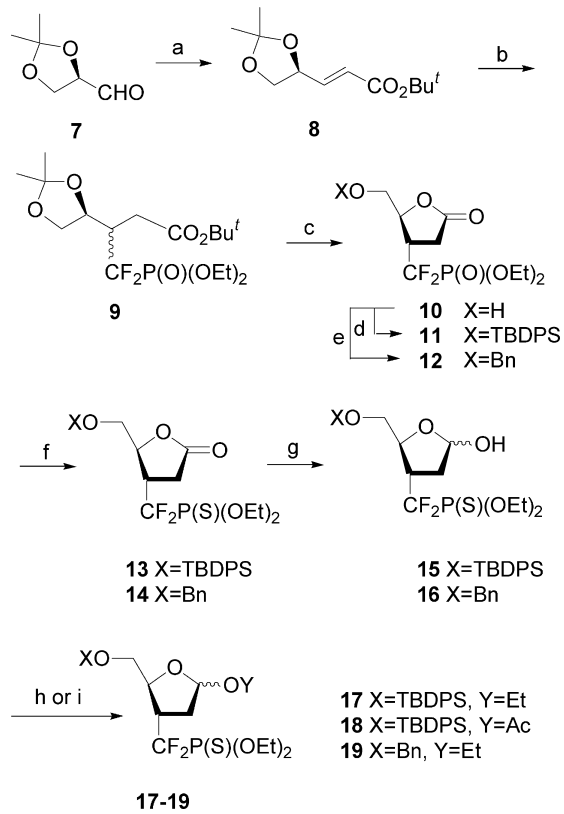
poor-diastereoselective glycosylation. Conversion of **5** to the corresponding phosphonic acid analogue **6** was readily achieved by oxidation with *m*-CPBA followed by aqueous quenching (Scheme 1).

We have successively investigated whether the methodology could be widely applicable to synthesis of the difluoromethylene analogues **3** (R=H). A part of the work has been communicated recently.[10] In this paper, we wish to report experimental details for the synthesis of 2′,3′-dideoxy-3′-difluoromethylenephosphonate nucleotide analogues by the remote-controlled *N*-glycosylation with pyrimidine bases, in addition to the results on *N*-glycosylation reaction with purine bases.

2. Results and discussion

2.1. Preparation of glycosyl donors having a phosphorothioyldifluoromethyl group

2.1.1. 5-*O*-TBDPS- and 5-*O*-Bn-protecting derivatives. The glycosyl donors **17**–**19** having a (diethoxyphosphoroylthioyl)difluoromethyl group at the C3-position, in which the 5-hydroxyl is protected by a *tert*-butyldiphenylsilyl (TBDPS) or benzyl (Bn) group, were prepared as shown in Scheme 2. Horner–Emmons–Wadsworth reaction of 1,2-*O*-isopropylidene-(*R*)-glyceraldehyde **7** with *tert*-butyl diethylphosphonoacetate gave the unsaturated ester **8**. The Michael reaction of **8** with diethyl (lithiodifuruoromethyl)-phosphonate[11] at −78°C in THF afforded **9** in 91% yield as a 1:1 mixture of diastereoisomers. Upon treatment of the mixture with conc. HCl in EtOH at 25°C, the *trans*-lactone **10** was obtained as the sole product in 50% yield through lactonization of (3*R*,4*S*)-diastereoisomer of **9**. In this reaction, the alternative (3*S*,4*S*)-isomer decomposed without any formation of the desired lactone.[12] The relative stereochemistry of **10** was deduced by a strong correlation between H-3 and the methylene protons α to the hydroxyl observed in an NOESY-experiment. Protection of the hydroxyl group of **10** with TBDPS or Bn afforded **11** and **12**. The compounds **11** and **12** were readily converted to the



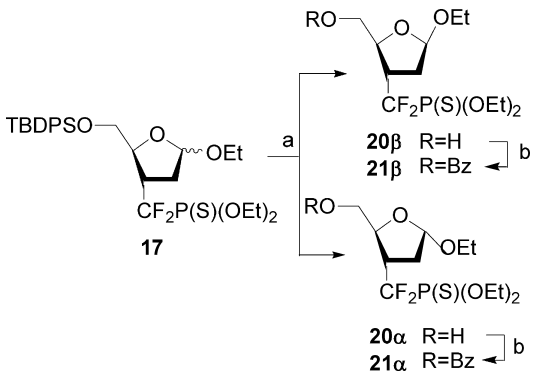
Scheme 2. *Reagent and conditions*: (a) $(EtO)_2P(O)CH_2CO_2Bu^t$, NaH, THF, 93%; (b) $LiCF_2P(O)(OEt)_2$, THF, −78°C, 91%; (c) c. HCl, EtOH, 50%; (d) TBDPSCl, imidazole, DMF, 93%; (e) $CCl_3C(=NH)OBn$, TfOH, CH_2Cl_2–petroleumether, 84%; (f) Lawesson's reagent, toluene, 84% for **13**, 76% for **14**; (g) BH_3·THF, THF, 0°C, 92% for **15**, 62% for **16**; (h) $CH(OEt)_3$, cat. NH_4NO_3, EtOH, 80°C, 90% for **17**; 85% for **19**. (i) Ac_2O, pyridine, 96%.

corresponding phosphonothioate **13** and **14**, respectively, by the conventional method (Lawesson's reagent, refluxing toluene). Reduction of **13** and **14** with BH_3·THF in THF at 0°C gave the corresponding lactols **15** and **16**, respectively, as a mixture of anomeric isomers. Treatment of **15** and **16** with triethyl orthoformate in EtOH in the presence of a catalytic amount of ammonium nitrate afforded the corresponding 1-ethoxy derivative **17** and **19**, respectively, as an anomeric mixture (α/β=1:1) in good yield. The lactol **15** was transformed to an anomeric mixture of 1-acetoxy derivative **18** by the standard protocol.

2.1.2. 5-*O*-Bz-protecting derivatives. The 5-*O*-benzoyl-protecting derivatives **21**α and **21**β were synthesized from **17**. Treatment of **17** with tetrabutylanmonium fluoride (TBAF) in THF gave a mixture of **20**α and **20**β in quantitative yield. The individual diastereomers **20**α and **20**β were isolated in 49 and 48% yield, respectively, by column chromatography on silica gel. Benzoylation of **20**α and **20**β under the standard conditions gave **21**α and **21**β, respectively (Scheme 3). The stereochemistry of **21**α and **21**β was confirmed on the basis of 2D NMR analysis (NOESY and COSY).

2.2. *N*-Glycosylation of 5-*O*-Bz-protecting derivatives with pyrimidine bases

With a variety of glycosyl donors in hand, we first investigated *N*-glycosylation of 5-*O*-Bz-protecting glycosyl



Scheme 3. *Reagent and conditions*: (a) TBAF, THF, followed by separation on SiO_2; (b) BzCl, pyridine.

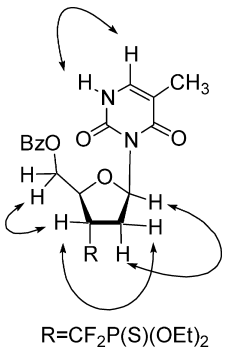


Figure 2. NOESY correlations of **23**.

donors **21**α and **21**β with silylated thymine $T(TMS)_2$ under the conditions ($TiCl_4/CH_2Cl_2$/0°C/3 h) that gave the best results for the non-fluorinated analogue **4** (Scheme 4 and Table 1).[8c] As shown in Table 1, the reaction with the α-anomer **21**α gave the desired N^1-adduct **22** in very low yield along with large amounts of unexpected N^3-adduct **23** (entry 1). Although de of **22** was very poor, **23** was found to possess a high degree of de. The relative stereochemisty of **23** and the site of glycosylation on the pyrimidine were confirmed by characteristic downfield shift (δ 6.75, dd, J=3.8, 9.1 Hz) of the anomeric proton in addition to the observed NOESY correlations among protons in the sugar and pyrimidine moieties depicted in Figure 2. Although the distribution ratio of **22** and **23** was not improved, the reaction of the β-anomer **21**β with $T(TMS)_2$ gave the desired **22** of 70% de in 11% yield (entry 2). The β-anomer seems to be the better glycosyl donor than the α-anomer in respect of the diastereoselectivity. These results are consistent with the fact that the neighbouring group participation of the phosphonothioate works well in *N*-glycosylation of the β-anomer of non-fluorinated analogue **4** rather than the corresponding α-anomer.[8c] When the *N*-glycosylation of **21**β was carried out at 25°C, the reaction preferably occurred at the N^1-nitrogen of the pyrimidine to give **22** (56% de) and **23** (98% de) in 50 and 23% yield, respectively (entry 3). Thus, the reaction temperature was found to affect strongly the distribution ratio of **22** and **23** (entry 2 vs 3).

The predominant formation of **23** in *N*-glycosylation of **21**α and **21**β with $T(TMS)_2$ at 0°C might be accounted for by considering the Lewis acid–base complex (σ-complex) **24** as shown in Figure 3. It is known that $T(TMS)_2$ forms a σ-complex at the electron-rich centre of the N^1-nitrogen with Lewis acids such as $SnCl_4$ and TMSOTf, and these species ($T(TMS)_2$, the σ-complex, and the Lewis acid) exist in an equilibrium.[13a,c] Therefore, the stronger Lewis acid $TiCl_4$ would bind to $T(TMS)_2$ more tightly and set up similar equilibrium between T(TMS) and the σ-complex **24**. Since **24** is blocked at the N^1-nitrogen with the Lewis acid, **24** would react at the N^3-nitrogen rather than at the N^1-nitrogen with the glycosyl donors to give N^3-adduct **23**.

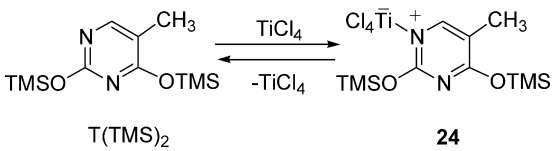
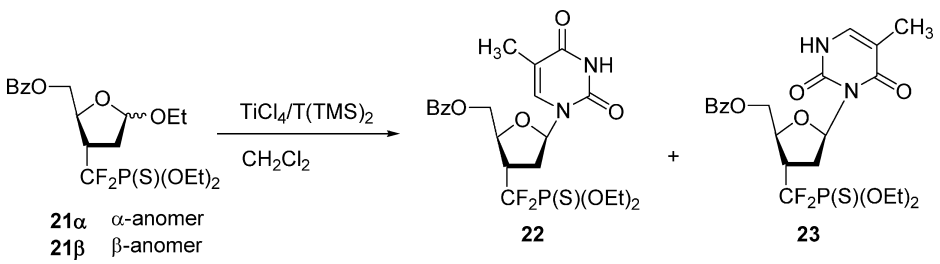


Figure 3.

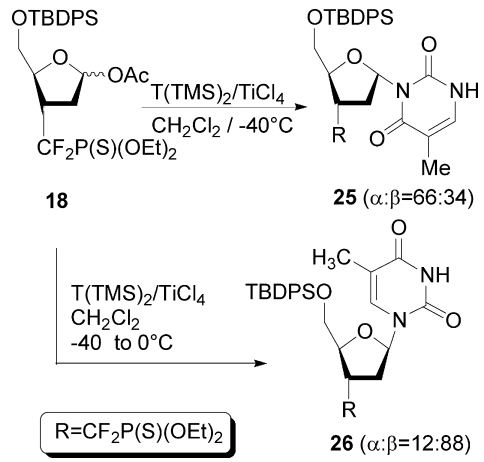


Scheme 4.

Table 1. *N*-Glycosylation of **21**α and **21**β with silylated thymine

Entry[a]	Donor	Temperature (°C)	**22**		**23**	
			Yield (%)	de (%)	Yield (%)	de (%)
1	**21**α	0	6	20	79	90
2	**21**β	0	11	70	69	92
3	**21**β	25	50	56	23	98

[a] All reactions were carried out in CH_2Cl_2 in the presence of $TiCl_4$ (5 equiv.) and silylated thymine (2 equiv.).



Scheme 5.

Predominant formation of **23** over **22** in the reaction at 0°C may suggest that **24** is the major species in the equilibrium under the conditions. The equilibrium ratio for $T(TMS)_2$ and **24** may be highly dependent on the reaction temperature, since the major adduct was reversed from **23** to **22** upon conducting the reaction at 25°C as described above.

2.3. *N*-Glycosylation of 5-*O*-TBDPS-protecting derivative with pyrimidine bases

As discussed in Section 2.2, concentration of $T(TMS)_2$ and σ-complex **24** in the equilibrium would be critical to control the regiochemical outcomes of the reaction site for the pyrimidine in the *N*-glycosylation of **21**α and **21**β. The equilibrium concentrations of $T(TMS)_2$ and **24** were found to be highly dependent on the temperature. The equilibrium concentrations would be also highly dependent upon the polarity of the solvent and subtle change of glycosyl donors in the structure and basicity.[13a,c] Then we next examined *N*-glycosylation of 5-*O*-TBDPS-protecting glycosyl donor **18** with $T(TMS)_2$ in CH_2Cl_2 using $TiCl_4$ as a Lewis acid at varied temperatures. Since **18** possesses an acetoxy function, the better leaving group than ethoxy, at the C1-position, its high reactivity towards the Lewis acid allowed us to survey the reactivity at varied temperatures including below 0°C. These results are summarized in Scheme 5.

When **18** was treated with $T(TMS)_2$ (2 equiv.) in CH_2Cl_2 in the presence of $TiCl_4$ (5 equiv.) at −40°C for 3 h, followed by aqueous quenching, a diastereomeric mixture (α/β=66:34) of N^3-adduct **25** was obtained in 72% yield, without detecting the N^1-adduct. In contrast to the results, when the reaction was carried out at −40°C for 3 h and then at 0°C for

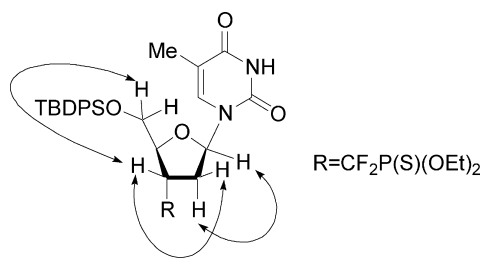


Figure 4. NOESY correlations of **26**.

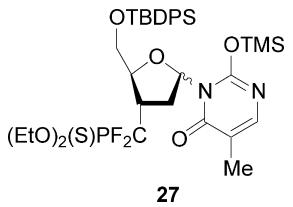


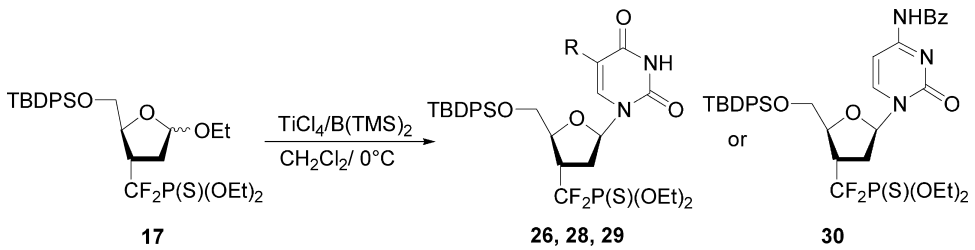
Figure 5.

an additional 3 h, the glycosylation occurred at the N^1-nitrogen to give **26** in 78% yield with the predominant formation of the β-anomer (α/β=12:88). When the reaction was carried out at 0°C for 3 h, N^1-adduct **26** was also produced in 72% yield whereas the α/β ratio (30:70) slightly decreased. The stereochemistry of **25** and **26** was confirmed by careful analyses of their 2D NMR spectrum including COSY and NOESY. The diagnostic NOESY correlations for **26** are shown in Figure 4.

The above results reveal that the presumed N^3-adduct **27**, initially formed by the reaction of the glycosyl donor with σ-complex **24** at −40°C, further reacts with $T(TMS)_2$ to give **26** stereoselectively upon elevating the reaction temperature to 0°C. The reaction would involve processes in which leaving of the nucleobase moiety of **27** occurs prior to *N*-glycosylation and the resulting 1-sugar cation is captured by $T(TMS)_2$ from the β-face in a remote assistance of the phosphonothioate group (Fig. 5). A mechanism for rearrangement of **27** to **26** via the 1-sugar cation would be ruled out by the following two experiments. Regeneration of **27** from **25** with *N*,*O*-bis(trimethylsilyl)acetamide in CH_2Cl_2, followed by treatment with one equivalent of $T(TMS)_2$ in the presence of $TiCl_4$ (5 equiv.) at 0°C for 3 h gave an anomeric mixture (α/β=15:85) of **26** in 97% yield. However, decomposition of **25** was observed when the similar reaction was carried out in the absence of $T(TMS)_2$.

On the basis of the findings with the *N*-glycosylation of **18** and $T(TMS)_2$, we examined similar *N*-glycosylation of the glycosyl donor **17** in CH_2Cl_2 using $TiCl_4$ as an acid promotor. Since **17** possesses a less reactive ethoxy function than acetoxy as a leaving group, the *N*-glycosylation did not occur at below 0°C and was best carried out under ice-cooling conditions (Scheme 6 and Table 2). Treatment of **17** with $T(TMS)_2$ under the conditions for 3 h afforded 93% yield of **26** with the α/β ratio of 11:89 (entry 1). In this reaction, the corresponding N^3-adduct was not detected. The α/β ratio is better than that (30:70) for the product derived from **18** under the same conditions (vide supra). Therefore, *N*-glycosylation of **17** by the use of other TMS-pyrimidines ($U(TMS)_2$, $5FU(TMS)_2$, and $NBz\text{-}C(TMS)_2$) derived from uracil, 5-fluorouracil, and *N*-benzoylcytosine, was further examined (entries 2–4). All reactions gave the desired β-nucleotide analogues **28**–**30** in good yield in comparable diastereoselectivity.

The nucleotide analogue **26** (β/α=89:11) thus obtained could be easily converted to the difluoromethylene-phosphonate analogue **31** of thymidine-3′-phosphate in 64% yield by oxidation with *m*-CPBA, followed by aqueous work-up. Diastereomerically pure **31** was isolated by preparative HPLC (Scheme 7).

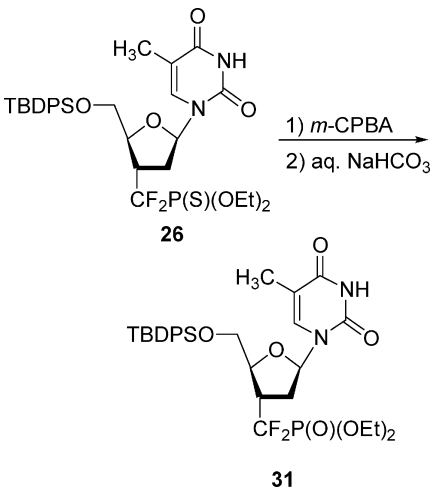


Scheme 6.

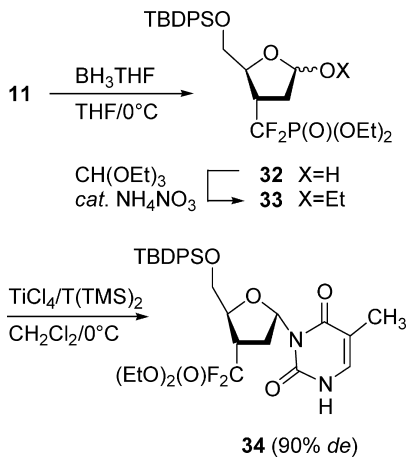
Table 2. *N*-Glycosylation of glycosyl donor **17** with silylated pyrimidines in the presence of $TiCl_4$

Entry[a]	$B(TMS)_2$[b]	Product	R	Yield	Ratio (β/α)[c]
1	$T(TMS)_2$	**26**	Me	93	89:11
2	$U(TMS)_2$	**28**	H	64	87:13
3	5-FU$(TMS)_2$	**29**	F	84	76:24
4	NBz-C$(TMS)_2$	**30**	–	87	83:17

[a] All reactions were carried out at 0°C for 3 h in the presence of 5.0 equiv. of $TiCl_4$ in CH_2Cl_2.
[b] Prepared in situ from bis(trimethylsilyl)acetamide (4.0 equiv.) and the base (2.0 equiv.) in the solvent.
[c] Determined by ^1H NMR (400 MHz, $CDCl_3$).



Scheme 7.



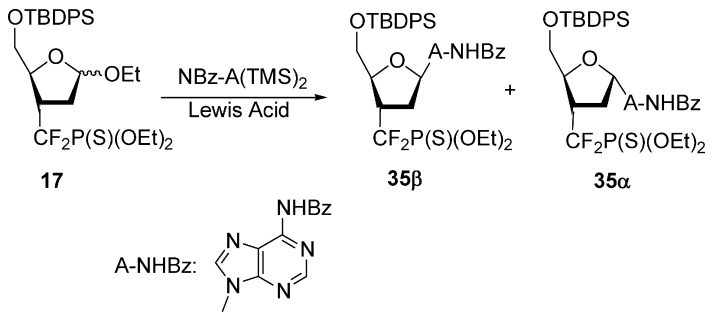
Scheme 8.

2.4. Effect of a phosphonate functional group on the *N*-glycosylation

To clarify the usefulness of the phosphonothioate functionality in β-stereoselective *N*-glycosylation, *N*-glycosylation of the phosphonate analogue **33**, prepared from **11** in an analogous manner for synthesis of the thioate **17**, was examined (Scheme 8). Treatment of **33** with $T(TMS)_2$ in the presence of $TiCl_4$ in CH_2Cl_2 at 0°C in analogy with the synthesis of **26** gave α-*N*^{3}-nucleotide analogue **34** of 90% de in 42% yield. These results strongly suggest that the equilibrium concentration of σ-complex **24** is significantly high under the conditions. This may be due to subtle changes of the glycosyl donor in the basicity by replacing the sulphur atom with the less basic oxygen atom on the C3-functional group.[13a,c] Although it is difficult to give evidence for the reasons why the reaction proceeds with a high α-selectivity, it may be the result from the fact that T(TMS) traps the 1-sugar cation from the α-face to avoid a bulky TBDPS group rather than a bicyclic cationic intermediate hardly arising from neighbouring group participation of the phosphonate to the C1-position.

2.5. *N*-Glycosylation with adenine bases

The results obtained for the synthesis of pyrimidine nucleotide compounds were taken into consideration for the synthetic application to the adenine nucleotide analogues. For this study, we examined *N*-glycosylation of **17** with silylated *N*^{6}-benzoyladenine (NBz-A$(TMS)_2$) under a variety of conditions (Scheme 9). The representative results are summarized in Table 3. Upon treatment of **17** with 2 equiv. of NBz-A$(TMS)_2$ in CH_2Cl_2 in the presence of $TiCl_4$ (5 equiv.) at 0°C for 15 h, a 48:52 mixture of **35**α and **35**β was produced in 23% yield (entry 1). In a similar reaction carried out at 25°C, decomposition of **17** was observed and no desired *N*-glycosylation products were detected (entry 2). When the reaction was carried out in CH_2Cl_2 at 25°C for 24 h by replacement of $TiCl_4$ with the weaker Lewis acid of $SnCl_4$, decomposition of **17** was partially suppressed and an 89:11 mixture of **35**α and **35**β was obtained, though the yield (8%) was very poor (entry 3). Upon conducting the reaction in CH_3CN in the presence of 5 equiv. of $SnCl_4$, a 58:42 mixture of **35**α and **35**β was obtained in 51% yield (entry 4). CH_3CN was found to be a superior solvent to CH_2Cl_2 with respect to yield of the *N*-glycosylation. The yield significantly increased to 77% without changing the α/β ratio upon using 10 equiv. of $SnCl_4$ and 4 equiv. of NBz-A$(TMS)_2$ (entry 5). TMSOTf was found to be also a good Lewis acid as $SnCl_4$ for *N*-glycosylation in CH_3CN (entry 6). Although all reactions showed poor diastereoselectivity, it is worthy of note that



Scheme 9.

Table 3. *N*-Glycosylation of **17** with NBz-A(TMS)$_2$

Entry[a]	Lewis acid (equiv.)[b]	Solvent	Equiv. of NBz-A(TMS)$_2$[b,c]	Temperature (°C)	Yield (%)	**35**α/**35**β[d]
1	$TiCl_4$ (5)	CH_2Cl_2	2	0	23	48:52
2	$TiCl_4$ (5)	CH_2Cl_2	2	25	0	–
3	$SnCl_4$ (5)	CH_2Cl_2	2	25	8	89:11
4	$SnCl_4$ (5)	CH_3CN	2	25	51	58:42
5	$SnCl_4$ (10)	CH_3CN	4	25	77	58:42
6	TMSOTf (5)	CH_3CN	2	40	44	58:42

[a] All reactions were conducted for 15–24 h.
[b] Equivalent to the glycosyl donor **17**.
[c] Generated from N^6-benzoyladenine and *N*,*O*-bis(trimethylsilyl)acetamide in the solvent.
[d] Determined by ^{1}H NMR (300 MHz, $CDCl_3$).

individual isomers **35**α and **35**β were readily separated by column chromatography on silica gel. Thus, the stereochemistry of **35**α and **35**β was easily confirmed by careful analyses of their NOESY correlations.

The poor diastereoselectivity for *N*-glycosylation of **17** with NBz-A(TMS)$_2$ indicates that the desired bicyclic cationic intermediate arising from the neighbouring group participation of the phosphorothioyl group would not be formed under the conditions and the reaction proceeded under the steric influence of both substituents at C3- and C5-positions. The observed low α-selectivity reveals that the reaction rate from the α-face is slightly faster than that from the β-face, most probably due to the steric congestion of the β-face by a bulky TBDPS group. This postulate may be supported by the fact that a mixture of **36**α and **36**β was produced in 42% yield in modest β-selectivity (α/β=39:61), when the reaction of NBz-A(TMS)$_2$ with **19** having the less bulky Bn as a protecting group of 5-hydroxyl was carried out in CH_3CN in the presence of $SnCl_4$ at 25°C (Scheme 10).

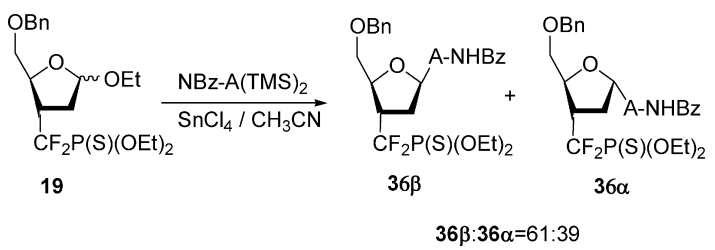
In conclusion, the *N*-glycosylation of 2,3-dideoxyglycosyl donors having a (diethoxyphosphorothioyl)difluoromethyl functionality at the 3α-position by using pyrimidine base, was found to give rise to formation of the β-anomers predominantly. The method was not effective for the diastereoselective synthesis of nucleotide analogues with an adenine base, possibly owing to the low reactivity of the silylated purine base to the glycosyl donors.[13c]

3. Experimental

3.1. General

All melting points are uncorrected. All reactions were carried out under nitrogen atmosphere. NMR data were obtained on a Bruker DPX 400 for a solution in the indicated solvent unless otherwise specified. ^{13}C NMR (100 MHz) and ^{31}P NMR (162 MHz) were taken with broad-band ^{1}H decoupling. The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4. ^{19}F NMR spectra (376 MHz) were measured using benzotrifluoride as an internal reference. Mass spectra were recorded on a VG Auto Spec. or a Micromass LCT using either electron impact ionization (EI) or electrospray ionization (ESI) techniques.

3.1.1. *tert*-Butyl (2*E*)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enoate (8). To a stirred suspension of NaH (3.1 g, 66% dispersion in mineral oil) in THF (75 mL) was added a solution of *tert*-butyl (diethoxyphosphoryl)acetate (21.3 g, 84.5 mmol) in THF (15 mL) at −15°C. After being



Scheme 10.

stirred at the same temperature for 30 min, a solution of **7** (10 g, 76.8 mmol) in THF (15 mL) was added dropwise. The mixture was stirred at −15°C for 1 h and the reaction was quenched by addition of saturated aqueous NH_4Cl. The biphasic mixture was extracted with ether and the extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel. Elution with hexane/AcOEt (15:1) gave **8** (16.3 g, 93%) as an oil: $[\alpha]_D^{25}$=+32.4 (c=1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (1H, dd, J=5.9, 15.6 Hz), 6.01 (1H, dd, J=1.4, 15.6 Hz), 4.68–4.59 (1H, m), 4.17 (1H, dd, J=6.5, 8.2 Hz), 3.67 (1H, dd, J=7.4, 8.2 Hz), 1.48 (9H, s), 1.45 (3H, s), 1.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 143.2, 124.2, 109.9, 80.5, 74.9, 68.7, 27.9, 26.3, 25.6; IR (film) 2983, 1715, 1370, 1309, 1258, 1154, 1064 cm^{-1}; EIMS m/z 213 (M^+−Me). Anal. calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.54; H, 8.64.

3.1.2. *tert*-Butyl 2,3-dideoxy-3-[(diethoxyphosphoryl)(difluoro)methyl]-4,5-*O*-(1-methylethylidene)-D-*glycero*-pentonate (9). To a solution of LDA [prepared from 39.6 mL (282 mmol) of diisopropylamine and 176 mL (282 mmol) of 1.6 M hexane solution of *n*-BuLi at 0°C] in THF (440 mL) was added a solution diethyl difluoromethylphosphonate (48.6 g, 259 mmol) in THF (160 mL) at −78°C. After the stirring was continued for 20 min at the same temperature, to this solution was added a solution of **8** (26.9 g, 118 mmol) in THF (110 mL) at −78°C. After the stirring was continued for 12 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ether. The extracts were washed with brine, dried ($MgSO_4$) and evaporated. The resulting residue was chromatographed on silica gel (hexane/AcOEt=5:1) to give **9** (47.6 g, 91%) as an oil: $[\alpha]_D^{25}$=+15.2 (c=1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (0.5H, dt, J=4.4, 6.8 Hz), 4.45 (0.5H, q, J=6.6 Hz), 4.34–4.22 (4H, m), 4.16–4.10 (0.5H, m), 4.03–3.94 (0.5H, m), 3.69 (1H, t, J=7.9 Hz), 3.48–3.31 (0.5H, m),3.04–2.88 (0.5H, m), 2.76 (0.5H, dd, J=4.6, 17.3 Hz) and 2.63 (0.5H, dd, J=6.0, 16.9 Hz), 2.57 (0.5H, dd, J=6.8, 17.3 Hz) and 2.44 (0.5H, dd, J=5.3, 16.9 Hz), 1.45 (9H, s), 1.43–1.31 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 and 170.6, 120.7 (dt, J_{CP}=212.3 Hz, J_{CF}=263.8 Hz) and 120.4 (dt, J_{CP}=212.8 Hz, J_{CF}=263.7 Hz), 108.8 and 108.3, 80.6 and 80.4, 73.1–72.8 (m) and 72.4–72.2 (m), 68.7 and 65.2, 64.9–64.5 (m), 64.3 (d, J_{CP}=6.3 Hz), 43.5 (dt, J_{CP}=15.0 Hz, J_{CF}=19.1 Hz) and 43.5 (dt, J_{CP}=15.2 Hz, J_{CF}=18.7 Hz), 31.0 and 28.4, 27.9, 26.1 and 26.0, 25.2 and 24.7, 16.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −47.1 (0.5F, ddd, J_{FF}=307.5 Hz, J_{PF}=105.6 Hz, J_{HF}=15.0 Hz) and −48.1 (0.5F, ddd, J_{FF}=306.8 Hz, J_{PF}=105.2 Hz, J_{HF}=13.9 Hz), −49.6 (0.5F, ddd, J_{FF}=306.8 Hz, J_{PF}=108.1 Hz, J_{HF}=20.2 Hz), −52.5 (0.5F, ddd, J_{FF}=307.5 Hz, J_{PF}=105.6 Hz, J_{HF}=23.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 6.39 (0.5P, dd, J_{PF}=105.2, 108.1 Hz) and 6.23 (0.5P, t, J_{PF}=105.6 Hz); IR (film) 2984, 2936, 1733, 1370, 1271, 1160, 1024 cm^{-1}; EIMS m/z 417 (M^++1). Anal. calcd for $C_{17}H_{31}F_2O_7P$: C, 49.03; H, 7.50. Found: C, 48.89; H, 7.31.

3.1.3. (2*S*,3*S*)-[Difluoro(2-hydroxymethyl-5-oxotetrahydrofuran-3-yl)methyl]phosphonic acid diethyl ester (10). A mixture of **9** (16.5 g, 39.6 mmol), EtOH (30 mL) and conc. HCl (11 mL) was stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the resulting residue was chromatographed on silica gel. Elution with hexane/AcOEt (1:1) afforded **10** (6.1 g, 50%) as an oil: $[\alpha]_D^{25}$=+13.8 (c=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90–4.83 (1H, m), 4.38–4.23 (4H, m), 4.00 (1H, dd, J=2.6, 12.5 Hz), 3.72 (1H, dd, J=2.9, 12.5 Hz), 3.40–3.22 (1H, m), 2.85 (2H, d, J=8.4 Hz), 2.56 (1H, br), 1.40 (6H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 119.1 (dt, J_{CP}=215.4 Hz, J_{CF}=263.0 Hz), 78.6 (d, J_{CP}=4.0 Hz), 65.2 (d, J_{CP}=7.0 Hz), 65.0 (d, J_{CP}=7.1 Hz), 63.0, 40.1 (dt, J_{CP}=15.8 Hz, J_{CF}=21.0 Hz), 20.3 16.0 (d, J_{CP}=5.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −54.49 (1F, dd, J_{HF}=4.9 Hz, J_{PF}=105.2 Hz), −54.54 (1F, dd, J_{HF}=5.8 Hz, J_{PF}=105.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 5.76 (t, J_{PF}=105.2 Hz); IR (film) 3427, 2988, 1789, 1645 cm^{-1}; EIMS m/z 303 (M^++1). Anal. calcd for $C_{10}H_{17}F_2O_6P$: C, 39.74; H, 5.67. Found: C, 39.43; H, 5.66.

3.1.4. (2*S*,3*S*)-{[2-(*tert*-Butyldiphenylsilanyloxymethyl)-5-oxotetrahydrofuran-3-yl]difluoromethyl}phosphonic acid diethyl ester (11). To a solution of **10** (27.2 g, 90 mmol) and imidazole (12.3 g, 180 mmol) in DMF (270 mL) was added *tert*-butyldiphenylsilyl chloride (27.7 mL, 108 mmol) at 0°C. The mixture was kept at room temperature for 1.5 h under stirring. The solvent was evaporated in vacuo and water was added. The biphasic mixture was extracted with $CHCl_3$. The extracts were washed with brine, dried ($MgSO_4$), and evaporated. The remaining residue was chromatographed on silica gel. Elution with hexane/AcOEt (5:1) yielded **11** (45.0 g, 93%) as an oil: $[\alpha]_D^{20}$=+16.7 (c=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.60 (4H, m), 7.48–7.34 (6H, m), 4.93–4.87 (1H, m), 4.37–4.20 (4H, m), 3.98 (1H, dd, J=2.1, 11.7 Hz), 3.71 (1H, dd, J=2.2, 11.7 Hz), 3.46–3.28 (1H, m), 2.93–2.87 (2H, m), 1.38 (6H, t, J=7.1 Hz), 1.05 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 133.5, 135.3, 132.5, 131.9, 129.9, 127.8, 119.2 (dt, J_{CP}=214.7 Hz, J_{CF}=263.1 Hz), 78.1 (dt, J_{CP}=4.2 Hz, J_{CF}=4.2 Hz), 65.0 (d, J_{CP}=7.0 Hz), 64.9 (d, J_{CP}=6.0 Hz), 64.9, 40.6 (dt, J_{CP}=15.5 Hz, J_{CF}=21.0 Hz), 29.0, 26.6, 19.1, 16.2 (d, J_{CP}=5.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −53.9 (1F, ddd, J_{HF}=15.3 Hz, J_{PF}=105.2 Hz, J_{FF}=303.3 Hz), −55.2 (1F, ddd, J_{HF}=18.5 Hz, J_{PF}=105.2 Hz, J_{FF}=303.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 5.96 (t, J_{PF}=105.2 Hz); IR (neat) 2933, 2859, 1789, 1274, 1184, 1114, 1022 cm^{-1}; EIMS m/z 541 (M^++1). Anal. calcd for $C_{26}H_{35}F_2O_6PSi$: C, 57.76; H, 6.53. Found: C, 57.59; H, 6.55.

3.1.5. (2*S*,3*S*)-[(2-Benzyloxymethyl-5-oxotetrahydrofuran-3-yl)difluoromethyl]phosphonic acid diethyl ester (12). To a stirred solution of **10** (6.21 g, 20.6 mmol) in CH_2Cl_2 (80 mL) and petroleum ether (40 mL) was successively added $Cl_3CC(=NH)OBn$ (4.6 mL, 24.7 mmol) and CF_3SO_3H (0.38 mL, 4.1 mmol) at 0°C. The mixture was stirred at the same temperature for 1 h and poured onto saturated $NaHCO_3$. The organic phase was separated. The extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (3:1) gave **12** (6.8 g, 84%) as an oil: $[\alpha]_D^{25}$=+15.4 (c=1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.24 (5H, m), 4.99–4.93 (1H, m), 4.60 (1H, d, J=11.9 Hz), 4.53 (1H, d, J=11.9 Hz), 4.37–4.20 (4H, m), 3.80 (1H, dd, J=2.2,

10.9 Hz), 3.63 (1H, dd, J=2.6, 10.9 Hz), 3.35–3.20 (1H, m), 2.86 (1H, dd, J=9.4, 18.4 Hz), 2.81 (1H, dd, J=6.1, 18.4 Hz), 1.39 (3H, t, J=7.1 Hz), 1.38 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 137.3, 128.4, 127.8, 127.5, 119.2 (dt, J_{CP}=214.0 Hz, J_{CF}=263.4 Hz), 77.0, 73.5, 70.7, 65.0 (d, J_{CP}=6.9 Hz), 64.9 (d, J_{CP}=7.0 Hz), 40.9 (dt, J_{CP}=15.7 Hz, J_{CF}=21.1 Hz), 28.7 (d, J_{CP}=1.1 Hz), 16.2 (d, J_{CP}=5.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −54.4 (1F, ddd, J_{HF}=16.9 Hz, J_{FF}=303.4 Hz, J_{PF}=104.5 Hz), −55.3 (1F, ddd, J_{HF}=17.8 Hz, J_{FF}=303.4 Hz, J_{PF}=104.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 5.75 (t, J_{PF}=104.5 Hz); IR (film) 2986, 2870, 1789, 1272, 1184, 1027 cm^{-1}; ESIMS m/z 415 (M^++Na), 393 (M^++H). Anal. calcd for $C_{17}H_{23}O_6F_2P$: C, 52.04; H, 5.91; Found C, 51.82; H, 5.83.

3.1.6. A typical example of thionylation with Lawesson's reagent. (2*S*,3*S*)-{[2-(*tert*-Butyldiphenylsilanyloxymethyl)-5-oxotetrahydrofuran-3-yl]difluoromethyl}phosphonothioic acid *O*,*O*-diethyl ester (13). A solution of **11** (13.5 g, 25 mmol) and Lawesson's reagent (5.6 g, 13.8 mmol) in toluene (26 m) was heated at 120°C for 2 h. The solvent was evaporated in vacuo and the remaining residue was chromatographed on silica gel. Elution with hexane/AcOEt (20:1) gave **13** (11.6 g, 84%) as an oil: $[\alpha]_D^{20}$=+12.5 (c=1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.61 (4H, m), 7.48–7.34 (6H, m), 4.89–4.84 (1H, m), 4.31–4.18 (4H, m), 3.98 (1H, dd, J=2.1, 11.5 Hz), 3.72 (1H, dd, J=2.3, 11.5 Hz), 3.70–3.53 (1H, m), 2.89 (2H, d, J=8.3 Hz), 1.35 (3H, t, J=7.0 Hz), 1.34 (3H, t, J=7.0 Hz), 1.05 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 136.0, 135.9, 133.0, 132.5, 130.4 (2C), 128.3, 120.6 (ddd, J_{CP}= 177.2 Hz, J_{CF}=267.0, 269.9 Hz), 78.9 (dt, J_{CP}=4.2 Hz, J_{CF}=3.6 Hz), 65.3 (d, J_{CP}=6.8 Hz), 65.2, 65.1 (d, J_{CP}= 6.8 Hz), 40.3 (dt, J_{CP}=17.0 Hz, J_{CF}=21.3 Hz), 30.0 (t, J_{CF}=3.6 Hz), 27.1, 19.6, 16.5 (d, J_{CP}=6.2 Hz); ^{19}F NMR (376 MHz,$CDCl_3$) δ −53.0 (1F, ddd, J_{HF}=13.6 Hz, J_{PF}= 110.2 Hz, J_{FF}=290.6 Hz), −55.6 (1F, ddd, J_{HF}=19.8 Hz, J_{PF}=110.2 Hz, J_{FF}=290.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 74.4 (t, J_{PF}=110.2 Hz); IR (film) 2932, 2859, 1789, 1114, 1018 cm^{-1}; EIMS m/z 557 (M^++1). Anal. calcd for $C_{26}H_{35}F_2O_5PSSi$: C, 56.10; H, 6.34. Found: C, 56.15; H, 6.37.

3.1.7. (2*S*,3*S*)-[(2-Benzyloxymethyl-5-oxotetrahydrofuran-3-yl)difluoromethyl]phosphonothioic acid *O*,*O*-diethyl ester (14). This compound was prepared from **12** (16.9 g, 43.1 mmol) in 76% yield in an analogous manner to that for preparation of **13**. Purification by column chromatography on silica gel (hexane/AcOEt=15:1) gave **14** (13.5 g, 76%) as an oil: $[\alpha]_D^{25}$=+16.1 (c=1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (5H, m), 4.98–4.91 (1H, m), 4.61 (1H, d, J=12.0 Hz), 4.54 (1H, d, J=12.0 Hz), 4.32–4.18 (4H, m), 3.81 (1H, dd, J=2.1, 10.9 Hz), 3.62 (1H, dd, J=2.9, 10.9 Hz), 3.52–3.35 (1H, m), 2.87–2.80 (2H, m), 1.35 (6H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 137.3, 128.4, 127.8, 127.5, 119.9 (ddd, J_{CP}=177.1 Hz, J_{CF}=266.7, 270.3 Hz), 77.4, 73.5, 70.7, 64.9 (d, J_{CP}=6.9 Hz), 64.6 (d, J_{CP}=6.8 Hz), 40.3 (dt, J_{CP}= 16.9 Hz, J_{CF}=21.3 Hz), 29.3, 16.0 (d, J_{CP}=6.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −53.0 (1F, ddd, J_{HF}=13.6 Hz, J_{FF}=290.9 Hz, J_{PF}=110.6 Hz), −55.4 (1F, ddd, J_{HF}= 19.4 Hz, J_{FF}=290.9 Hz, J_{PF}=106.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 74.0 (dd, J_{PF}=106.7, 110.6 Hz); IR (film) 2985, 1789, 1016 cm^{-1}; ESIMS m/z 431 (M^++Na), 409 (M^++H). Anal. calcd for $C_{17}H_{23}O_5F_2PS$; C, 50.00; H, 5.68. Found C, 50.20; H, 5.75.

3.1.8. A typical example of preparation of lactols. (2*S*, 3*S*)-{[2-(*tert*-Butyldiphenylsilanyloxymethyl)-5-hydroxytetrahydrofuran-3-yl]-difluo-romethyl}phosphonothioic acid *O*,*O*-diethyl ester (15). To a solution of **13** (2.9 g, 5.3 mmol) in THF (10 mL) was added 17.4 mL (18.4 mmol) of BH_3·THF (1 M solution in THF) in small portions under ice-cooling. After stirring was continued for 12 h, the reaction was quenched with 1 mL of 1 M HCl and saturated NH_4Cl solution. The mixture was extracted with $CHCl_3$. The extracts were washed with brine, dried ($MgSO_4$) and evaporated in vacuo. The remaining residue was chromatographed on silica gel. Elution with hexane/AcOEt (20:1) afforded **15** (2.7 g, 92%) as an oil: $[\alpha]_D^{20}$=−9.80 (c=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.63 (4H, m), 7.49–7.34 (6H, m), 5.63–5.57 (0.1H, m), 5.49–5.41 (0.9H, m), 4.59–4.55 (0.1H, m), 4.51–4.46 (0.9H, m), 4.31–4.13 (4H, m), 3.89 (0.9H, dd, J=1.9, 11.2 Hz), 3.85–3.67 (0.3H, m), 3.62 (0.9H, dd, J=2.7, 11.2 Hz), 3.59–3.43 (0.9H, m), 2.53–2.27 (0.2H, m), 2.26–2.10 (1.8H, m), 1.34 (3H, t, J=7.1 Hz), 1.32 (3H, t, J=7.1 Hz), 1.09 (8.1H, s), 1.02 (0.9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 136.0, 132.7, 132.5, 130.5, 130.4, 128.3 (2C), 121.6 (ddd, J_{CP}= 178.9 Hz, J_{CF}=263.6, 270.2 Hz), 99.0, 79.9, 66.2, 65.1 (d, J_{CP}=6.6 Hz), 64.6 (d, J_{CP}=6.8 Hz), 40.7 (dt, J_{CP}=16.3 Hz, J_{CF}=20.5 Hz), 37.2, 27.2, 19.6, 16.5 (d, J_{CP}=5.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −48.4 (0.9F, ddd, J_{HF}=9.3 Hz, J_{PF}=114.0 Hz, J_{FF}=287.7 Hz), −49.0–50.5 (0.1F, m), −53.7 (0.1F, ddd, J_{HF}=23.4 Hz, J_{PF}=110.8 Hz, J_{FF}= 288.3 Hz), −57.7 (0.9F, ddd, J_{HF}=22.9 Hz, J_{PF}= 109.4 Hz, J_{FF}=287.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 75.5 (0.9P, dd, J_{PF}=109.4, 114.0 Hz), 75.6 (0.1P, dd, J_{PF}= 110.8, 112.6 Hz); IR (film) 2933, 2858, 1113, 1037 cm^{-1}; EIMS m/z 541 (M^+−OH). Anal. calcd for $C_{26}H_{37}F_2O_5PSSi$: C, 55.90; H, 6.68. Found: C, 55.61; H, 6.59.

3.1.9. (2*S*,3*S*)-[(2-Benzyloxymethyl-5-hydroxytetrahydrofuran-3-yl)difluoromethyl]phosphonothioic acid *O*,*O*-diethyl ester (16). This compound was prepared from **14** (2.65 g, 6.49 mmol) in an analogous manner to that for preparation of **15**. Purification by column chromatography on silica gel (hexane/AcOEtc=5:1) gave **16** (1.66 g, 62%) as an oil: $[\alpha]_D^{25}$=+12.7 (c=1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.19 (5H, m), 5.61–5.54 (0.2H, m), 5.47–5.38 (0.8H, m), 4.67 (0.8H, d, J= 11.8 Hz), 4.64–4.36 (2.2H, m), 4.31–4.13 (4H, m), 3.82–3.71 (1H, m), 3.67–3.28 (2H, m), 2.44–2.27 (0.2H, m), 2.22–2.07 (1.6H, m), 2.04–1.89 (0.2H, m), 1.38–1.21 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 128.6, 128.3, 128.0, 127.9, 127.6, 121.0 (ddd, J_{CP}=179.0 Hz, J_{CF}=264.4, 269.5 Hz), 98.8, 77.9 (dt, J_{CP}=3.1 Hz, J_{CF}=4.6 Hz), 73.7, 71.7, 64.6 (d, J_{CP}=6.8 Hz), 64.3 (d, J_{CP}=6.9 Hz), 41.1 (dt, J_{CP}=16.5 Hz, J_{CF}=20.7 Hz), 36.4, 16.1 (d, J_{CP}=6.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.2 (1F, ddd, J_{HF}= 12.0 Hz, J_{FF}=288.0 Hz, J_{PF}=113.8 Hz), −55.9 (1F, ddd, J_{HF}=20.4 Hz, J_{FF}=288.0 Hz, J_{PF}=109.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 75.2 (dd, J_{PF}=109.6, 113.8 Hz); IR (film) 3435, 2982, 2935, 2867, 1454, 1027 cm^{-1}; ESIMS m/z 433 (M^++Na), 393 (M^+−OH); HRMS (ESI) calcd for $C_{17}H_{25}O_5F_2NaPS$ (M^++Na): 433.1026, Found: 433.1039.

3.1.10. (2*S*,3*S*)-{[2-(*tert*-Butyldiphenylsilanyloxymethyl)-5-ethoxytetrahydrofuran-3-yl]difluoromethyl}phosphonothioic acid *O*,*O*-diethyl ester (17). A mixture of **15** (2.37 g, 4.2 mmol), ethyl orthoformate (0.84 mL, 5.0 mmol), ammonium nitrate (10 mg) and EtOH (8.4 mL) was heated at 90°C for 12 h. $NaHCO_3$ solution (5 mL) was added to the reaction mixture and the mixture was extracted with ether. The extract was evaporated and the remaining residue was chromatographed on silica gel. Elutuion with hexane/AcOEt (20:1) afforded **17** (2.24 g, 90%) as an oil: $[\alpha]_D^{20}$=+1.51 (c=1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.65 (4H, m), 7.45–7.32 (6H, m), 5.27–5.20 (0.5H, m) and 5.16–5.11 (0.5H, m), 4.49 (0.5H, dt, J=4.0, 6.5 Hz) and 4.44–4.37 (0.5H, m), 4.31–4.13 (4H, m), 3.96 (0.5H, d, J=2.3 Hz), 3.85–3.62 (2.5H, m), 3.50 (0.5H, dq, J=9.6, 7.1 Hz) and 3.37 (0.5H, dq, J=9.5, 7.1 Hz) 3.36–3.22 (0.5H, m) and 3.19–2.97 (0.5H, m), 2.38 (0.5H, ddd, J=5.4, 10.5, 13.6 Hz), 2.21–2.06 (1.5H, m), 1.37–1.26 (6H, m), 1.22 (1.5H, t, J=7.1 Hz), 1.12–0.98 (10.5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (2C), 133.5, 133.4, 129.5, 127.6 (2C), 121.1 (ddd, J_{CP}=178.4 Hz, J_{CF}=263.3, 271.2 Hz), 120.9 (ddd, J_{CP}=178.9 Hz, J_{CF}=264.5, 273.8 Hz), 103.7 and 103.5, 79.8 and 77.6, 67.4 and 64.9, 64.6 (d, J_{CP}=6.9 Hz) and 64.5 (d, J_{CP}=6.8 Hz), 64.1 (d, J_{CP}=6.8 Hz), 63.3 and 62.4, 42.6 (dt, J_{CP}=15.9 Hz, J_{CF}=20.6 Hz) and 41.0 (dt, J_{CP}=16.1 Hz, J_{CF}=20.2 Hz) 34.3, 26.7, 19.3 and 19.2, 16.1 (d, J_{CP}=6.0 Hz), 15.2 and 14.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −47.3 (0.5F, ddd, J_{HF}=8.5 Hz, J_{PF}=116.5 Hz, J_{FF}=288.1 Hz), −47.9 (0.5F, ddd, J_{HF}=8.4 Hz, J_{PF}=115.6 Hz, J_{FF}=287.4 Hz), −56.3 (0.5F, ddd, J_{HF}=25.2 Hz, J_{PF}=110.2 Hz, J_{FF}=287.4 Hz), −57.2 (0.5F, ddd, J_{HF}=23.9 Hz, J_{PF}=110.8 Hz, J_{FF}=288.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 76.1 (0.5P, dd, J_{PF}=110.2, 115.6 Hz), 75.6 (0.5P, dd, J_{PF}=110.8, 116.5 Hz); IR (film) 3072, 2932, 2858, 1428, 1390, 1113, 1027 cm^{-1}; EIMS m/z 586 (M^+), 529 (M^+-*tert*-Bu). Anal. calcd for $C_{28}H_{41}F_2O_5PSSi$: C, 57.32; H, 7.04. Found: C, 57.20; H, 7.11.

3.1.11. (2*S*,3*S*)-[(2-Benzyloxymethyl-5-ethoxytetrahydrofuran-3-yl)-difluoromethyl]phosphonothioic acid *O*,*O*-diethyl ester (19). This compound was prepared from **16** (1.46 g, 3.5 mmol) in an analogous manner to that for preparation of **17**. Purification by column chromatography on silica gel (hexane/AcOEt=20:1) gave **19** (1.32 g, 85%) as an oil: $[\alpha]_D^{25}$=+8.5 (c=1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.23 (5H, m), 5.25–5.19 (0.5H, m) and 5.18–5.12 (0.5H, m), 4.76–4.49 (2.5H, m), 4.48–4.41 (0.5H, m), 4.32–4.15 (4H, m), 3.82 (0.5H, d, J=11.1 Hz), 3.79–3.66 (1H, m), 3.63 (0.5H, dd, J=3.0, 10.1 Hz), 3.58 (0.5H, dd, J=4.7, 11.1 Hz), 3.54–3.35 (1.5H, m), 3.19–2.91 (1H, m), 2.37 (0.5H, ddd, J=5.6, 10.9, 13.8 Hz), 2.20–2.06 (1.5H, m), 1.33 (6H, t, J=7.1 Hz), 1.20 (1.5H, t, J=7.1 Hz) and 1.11 (1.5H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.7, 128.2, 128.0, 127.9, 121.4 (ddd, J_{CP}=178.0 Hz, J_{CF}=262.9, 272.1 Hz) and 121.3 (ddd, J_{CP}=179.1 Hz, J_{CF}=264.6, 269.1 Hz), 104.2 and 103.6, 78.5 and 76.6, 74.9, 73.8, 73.6, 71.3, 65.0 (d, J_{CP}=7.1 Hz) and 64.9 (d, J_{CP}=6.8 Hz), 64.7 (d, J_{CP}=6.9 Hz) and 64.6 (d, J_{CP}=6.9 Hz), 63.5 and 62.8, 43.6 (dt, J_{CP}=16.0 Hz, J_{CF}=20.8 Hz) and 42.2 (dt, J_{CP}=16.0 Hz, J_{CF}=20.4 Hz), 34.6 (2C), 16.5 (d, J_{CP}=5.5 Hz), 15.6 and 15.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −48.3 (0.5F, dd, J_{FF}=286.5 Hz, J_{PF}=114.7 Hz) and −49.3 (0.5F, ddd, J_{HF}=9.0 Hz, J_{FF}=288.6 Hz, J_{PF}=114.5 Hz), −56.0 (0.5F, ddd, J_{HF}=25.1 Hz, J_{FF}=286.5 Hz, J_{PF}=108.7 Hz) and −56.2 (0.5F, ddd, J_{HF}=20.8 Hz, J_{FF}=288.6 Hz, J_{PF}=111.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 75.6 (0.5P, dd, J_{PF}=108.7, 114.7 Hz) and 75.3 (0.5P, dd, J_{PF}=111.0, 114.5 Hz); IR (neat) 2979, 2906, 1453, 1104, 1028 cm^{-1}; ESIMS m/z 461 (M^++Na). Anal. calcd for $C_{19}H_{29}O_5F_2PS$: C, 52.05; H, 6.67. Found: C, 52.18; H, 6.67.

3.1.12. (4*S*,5*S*)-5-{[*tert*-Butyl(diphenyl)silyl]methyl}-4-[(diethoxyphosphorothioyl)(difluoro)methyl]tetrahydrofuran-2-yl acetate (18). To a solution of **15** (2.37 g, 4.2 mmol) in pyridine (5 mL containing 10 mg of dimethylaminopyridine) was added acetic anhydride (0.48 mL, 5.1 mmol) at 0°C, then the reaction mixture was allowed to stand at room temperature for 24 h under stirring. To the reaction mixture was added 5% $KHSO_4$ and extracted with $CHCl_3$. The solvent was dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/AcOEt (15:1) gave **18** (2.43 g, 96%). $[\alpha]_D^{25}$=+3.6 (c=1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.64 (4H, m), 7.48–7.34 (6H, m), 6.38–6.32 (1H, m), 4.61–4.55 (0.2H, m), 4.54–4.48 (0.8H, m), 4.29–4.16 (4H, m), 3.96 (0.2H, dd, J=1.7, 11.4 Hz), 3.92 (0.8H, dd, J=2.6, 11.2 Hz), 3.78–3.72 (1H, m), 3.57–3.44 (1H, m), 2.53 (0.2H, ddd, J=5.5, 11.3, 14.5 Hz), 2.43–2.25 (1.6H, m), 2.24–2.13 (0.2H, m), 2.06 (0.6H, s), 1.82 (2.4H, s), 1.38–1.30 (6H, m), 1.07 (7.2H, s), 1.05 (1.8H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (minor), 169.9 (major), 135.4, 135.3, 133.2 (major), 133.0 (minor), 132.9 (major), 132.8 (minor), 129.5 (2C), 127.5, 120.5 (ddd, J_{CP}=179.0 Hz, J_{CF}=264.4, 270.0 Hz), 98.5 (minor), 98.0 (major), 81.3 (major), 80.0 (minor), 65.6 (minor), 65.5 (major), 64.5 (d, J_{CP}=6.8 Hz, major), 64.4 (d, J_{CP}=6.8 Hz, minor), 64.2 (d, J_{CP}=6.9 Hz, minor), 64.1 (d, J_{CP}=6.9 Hz, major), 64.0, 40.6 (dt, J_{CP}=16.6 Hz, J_{CF}=20.8 Hz, major), 40.5 (dt, J_{CP}=15.2 Hz, J_{CF}=21.1 Hz, minor), 34.0 (major), 33.8 (minor), 26.6, 21.0 (major), 19.1 (minor), 15.9 (d, J_{CP}=5.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −47.8 (0.8F, ddd, J_{HF}=7.9 Hz, J_{FF}=288.7 Hz, J_{PF}=113.7 Hz), −49.7 (0.2F, ddd, J_{HF}=12.1 Hz, J_{FF}=288.2 Hz, J_{PF}=116.3 Hz), −54.0 (0.2F, ddd, J_{HF}=23.3 Hz, J_{FF}=288.2 Hz, J_{PF}=112.2 Hz), −57.5 (0.8F, ddd, J_{HF}=23.2 Hz, J_{FF}=288.7 Hz, J_{PF}=108.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 75.7 (0.2P, dd, J_{PF}=112.2, 116.3 Hz), 75.0 (0.8P, dd, J_{PF}=108.7, 113.7 Hz); IR (film) 2932, 2858, 1750, 1428, 1235, 1113, 1020 cm^{-1}; EIMS m/z 543 (MH^+-*tert*-Bu). Anal. calcd for $C_{28}H_{38}O_6F_2PSSi$: C, 56.08; H, 6.39. Found: C, 55.91; H, 6.43.

3.1.13. (2*S*,3*S*,5*S*)-[(5-Ethoxy-2-hydroxymethyltetrahydrofuran-3-yl)difluoromethyl]phosphonothioic acid *O*,*O*-diethyl ester (20α) and (2*S*,3*S*,5*R*)-[(5-ethoxy-2-hydroxymethyltetrahydrofuran-3-yl)difluoromethyl]-phosphonothioic acid *O*,*O*-diethyl ester (20β). To a stirred solution of **17** (2.16 g, 3.68 mmol) in THF (15 mL) was added TBAF (1.44 g, 5.52 mmol) under ice-cooling. The mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo and the residue was portioned between water and $CHCl_3$. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel. Elution with hexane/AcOEt (10:1) afforded **20**β (614 mg, 48%) as an oil:

$[\alpha]_D^{20}=-28.2$ (c=1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.16–5.10 (1H, m), 4.60–4.53 (1H, m), 4.32–4.20 (4H, m), 3.81 (1H, dd, J=2.1, 12.0 Hz), 3.77 (1H, dq J=7.1, 9.6 Hz), 3.58 (1H, dd, J=3.9, 12.0 Hz), 3.51 (1H, dq, J=7.1, 9.6 Hz), 3.41–3.23 (1H, m), 2.31–2.15 (2H, m), 1.36 (6H, t, J=7.1 Hz), 1.22 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.9 (dt, J_{CP}=179.1 Hz, J_{CF}=266.9 Hz), 103.9, 80.5 (dt, J_{CP}=3.5 Hz, J_{CF}=4.2 Hz), 65.1, 64.5 (d, J_{CP}=6.8 Hz), 64.4 (d, J_{CP}=6.9 Hz), 63.6, 41.2 (dt, J_{CP}=16.0 Hz, J_{CF}=20.8 Hz), 34.5, 16.1 (d, J_{CP}=6.2 Hz), 15.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.9 (1F, ddd, J_{HF}=13.2 Hz, J_{PF}=112.8 Hz, J_{FF}=288.8 Hz), −54.8 (1F, ddd, J_{HF}=19.6 Hz, J_{PF}=112.8 Hz, J_{FF}=288.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 75.3 (t, J_{PF}=112.8 Hz); IR (film) 3465, 2980, 2933, 1025 cm^{-1}; EIMS m/z 303 (M^+−OEt). Anal. calcd for $C_{12}H_{23}F_2O_5PS$: C, 41.38: H, 6.65. Found: C, 41.86; H, 6.72. Successive elution with hexane/AcOEt (8:1) gave **20**α (628 mg, 49%) as an oil: $[\alpha]_D^{20}=+69.6$ (c=1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.22–5.14 (1H, m), 4.41–4.33 (1H, m), 4.31–4.18 (4H, m), 3.94 (1H, dd, J=2.3, 12.1 Hz), 3.74 (1H, dq, J=7.1, 9.7 Hz), 3.68 (1H, dd, J=3.9, 12.1 Hz), 3.47 (1H, dq, J=7.1, 9.7 Hz), 3.12–2.94 (1H, m), 2.36 (1H, ddd, J=5.6, 10.9, 13.9 Hz), 2.21–2.12 (1H, m), 1.35 (6H, t, J=7.1 Hz), 1.20 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.8 (ddd, J_{CP}=178.3 Hz, J_{CF}=263.6, 271.4 Hz), 103.1, 77.1 (dt, J_{CP}=3.4 Hz, J_{CF}=6.6 Hz), 64.6 (d, J_{CP}=6.8 Hz), 64.3 (d, J_{CP}=6.9 Hz), 63.3, 63.0, 41.4 (dt, J_{CP}=15.9 Hz, J_{CF}=20.5 Hz), 34.4 (d, J_{CP}=3.8 Hz), 16.1 (d, J_{CP}=6.1 Hz), 15.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −48.6 (1F, ddd, J_{HF}=9.1 Hz, J_{PF}=114.7 Hz, J_{FF}=287.8 Hz), −55.0 (1F, ddd, J_{HF}=24.0 Hz, J_{PF}=109.2 Hz, J_{FF}=287.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 75.6 (dd, J_{PF}=109.2, 114.7 Hz); IR (film) 3474, 2980, 2932, 1162 cm^{-1}; EIMS m/z 331 (M^+−OH), 303 (M^+−OEt). Anal. calcd for $C_{12}H_{23}F_2O_5PS$: C, 41.38; H, 6.65. Found: C, 41.22; H, 6.69.

3.1.14. Benzoic acid (2*S*,3*S*,5*R*)-3-[(diethoxythiophosphoryl)difluoromethyl]-5-ethoxytetrahydrofuran-2-ylmethyl ester (21β). To a stirred solution of **20**β (840 mg, 2.4 mmol) in pyridine (0.5 mL) was added a solution of benzoyl chloride (310 mg, 2.6 mmol) in CH_2Cl_2 (5 mL) at 0°C. After being stirred at the same temperature for 12 h, water was added. The mixture was extracted with $CHCl_3$ and the extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt=15:1) to give **21**β (920 mg, 85%) as an oil: $[\alpha]_D^{20}=-23.4$ (c=1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14–8.07 (2H, m), 7.60–7.50 (1H, m), 7.48–7.40 (2H, m), 5.21–5.16 (1H, m), 4.68 (1H, dt, J=3.5, 7.0 Hz), 4.51 (1H, dd, J=3.5, 11.5 Hz), 4.40 (1H, dd, J=7.2, 11.5 Hz), 4.31–4.19 (4H, m), 3.73 (1H, dq, J=7.1, 9.6 Hz), 3.41 (1H, dq, J=7.1, 9.7 Hz), 3.34–3.16 (1H, m), 2.32–2.13 (2H, m), 1.34 (3H, t, J=7.1 Hz), 1.33 (3H, t, J=7.1 Hz), 1.13 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 133.0, 130.0, 129.7, 128.3, 120.6 (ddd, J_{CP}=179.5 Hz, J_{CF}=264.5, 269.7 Hz), 103.9, 67.8, 64.6 (d, J_{CP}=6.6 Hz), 64.4 (d, J_{CP}=6.6 Hz), 62.7, 43.3, 16.1 (d, J_{CP}=6.2 Hz), 14.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −49.1 (1F, ddd, J_{HF}=10.7 Hz, J_{PF}=114.4 Hz, J_{FF}=289.5 Hz), −56.2 (1F, ddd, J_{HF}=20.7 Hz, J_{PF}=111.2 Hz, J_{FF}=289.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 75.2 (dd, J_{PF}=111.2, 114.4 Hz); IR (film) 2979, 1724, 1452, 1276 cm^{-1}; ESIMS m/z 475 (M^++Na); HRMS(ESI) calcd for $C_{19}H_{27}O_6F_2NaPS$ (M^++Na): 475.1132. Found: 475.1142.

3.1.15. Benzoic acid (2*S*,3*S*,5*S*)-3-[(diethoxythiophosphoryl)difluoromethyl]-5-ethoxytetrahydrofuran-2-ylmethyl ester (21α). This compound was prepared from **20**α (760 mg, 2.18 mmol) in an analogous manner to that for preparation of **20**β. Purification by column chromatography on silica gel (hexane/AcOEt=15:1) gave **21**α (970 mg, 98%) as an oil: $[\alpha]_D^{20}=+28.6$ (c=0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.07–8.01 (2H, m), 7.58–7.51 (1H, m), 7.47–7.40 (3H, m), 5.26–5.20 (1H, m), 4.69 (1H, dd, J=2.2, 11.9 Hz), 4.65–4.59 (1H, m), 4.40 (1H, dd, J=4.9, 11.9 Hz), 4.34–4.20 (4H, m), 3.76 (1H, dq, J=7.1, 9.7 Hz), 3.49 (1H, dq, J=7.1, 9.8 Hz), 3.18–2.98 (1H, m), 2.43 (1H, ddd, J=5.6, 10.8, 13.9 Hz), 2.22–2.14 (1H, m), 1.34 (6H, t, J=7.1 Hz), 1.21 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 133.0, 130.0, 129.6, 128.3, 120.6 (ddd, J_{CP}=178.4 Hz, J_{CF}=263.4, 271.9 Hz), 103.1, 74.7, 65.5, 64.7 (d, J_{CP}=6.1 Hz), 64.4 (d, J_{CP}=6.7 Hz), 63.2, 42.7 (dt, J_{CP}=16.3 Hz, J_{CF}=20.5 Hz), 34.2, 16.1 (d, J_{CP}=6.1 Hz), 15.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −48.7 (1F, ddd, J_{HF}=8.8 Hz, J_{PF}=114.6 Hz, J_{FF}=288.4 Hz); −55.6 (1F, ddd, J_{HF}=23.6 Hz, J_{PF}=108.2 Hz, J_{FF}=288.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 75.3 (dd, J_{PF}=108.2, 114.6 Hz); IR (film) 2979, 1724, 1452, 1025 cm^{-1}; ESIMS m/z 475 (M^++Na); HRMS (ESI) calcd for $C_{19}H_{27}O_6F_2NaPS$ (M^++Na): 475.1132. Found: 475.1108.

3.1.16. A typical procedure for *N*-glycosylation of 21β. Benzoic acid (2*S*,3*S*,5*R*)-3-[(diethoxythiophosphoryl)difluoromethyl]-5-(5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)tetrahydrofuran-2-ylmethyl ester (22) and benzoic acid (2*S*,3*S*,5*R*)-3-[(diethoxythiophosphoryl)difluoromethyl]-5-(5-methyl-2,6-dioxo-3,6-dihydro-2*H*-pyrimidin-1-yl)-tetrahydrofurn-2-ylmethyl ester (23). A suspension of thymine (180 mg, 0.88 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (200 mg, 0.44 mmol) in CH_2Cl_2 (9 mL) was heated at 40°C for 4 h. To this mixture was added a solution of **21**β (200 mg, 0.44 mmol) in CH_2Cl_2 (3 mL). The mixture was treated with a solution of $TiCl_4$ (0.24 mL, 2.2 mmol) in CH_2Cl_2 (3 mL) at 0°C. After being stirred at 0°C for 3 h, the reaction was quenched with sat. $NaHCO_3$. The mixture was extracted with $CHCl_3$. The extracts were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=1:1) to give a mixture of **22** and **23** (187 mg, 80%). The mixture was analyzed by ^1H NMR spectroscopy (400 MHz, $CDCl_3$) to determine the diastereoselectivity and the ratio of **22** and **23** (Table 1). The analytical samples for **22** and **23** were obtained by preparative HPLC (Inertsil (GL-science), hexane/AcOEt=1:1). **22** (70% de): an oil $[\alpha]_D^{20}=-8.19$ (c=1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.86 (1H, broad s), 8.07–7.98 (2H, m), 7.63–7.56 (1H, m), 7.49–7.42 (2H, m), 7.27–7.23 (1H, m), 6.10 (1H, t, J=6.4 Hz), 4.79 (1H, dd, J=2.1, 12.2 Hz), 4.74–4.68 (1H, m), 4.53 (1H, dd, J=4.0, 12.2 Hz), 4.36–4.19 (4H, m), 3.47–3.29 (1H, m), 2.81 (1H, ddd, J=6.5, 6.5, 13.9 Hz), 2.24 (1H, ddd, J=6.5, 10.0, 14.3 Hz), 1.63 (3H, d, J=1.0 Hz), 1.36 (6H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 164.0, 150.2, 134.9, 133.5, 129.7, 129.4, 128.6, 120.3 (ddd, J_{CP}=177.2 Hz, J_{CF}=265.9, 270.4 Hz), 111.1, 85.4, 76.9,

65.1, 65.0 (d, J_{CP}=7.4 Hz), 64.7 (d, J_{CP}=6.5 Hz), 42.6 (dt, J_{CP}=16.5 Hz, J_{CF}=20.6 Hz), 33.0, 16.1 (d, J_{CP}=5.9 Hz), 12.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.5 (1F, ddd, J_{HF}=12.0 Hz, J_{PF}= 110.7 Hz, J_{FF}=290.6 Hz), −54.7 (1F, ddd, J_{HF}=20.5 Hz, J_{PF}=105.7 Hz, J_{FF}=290.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 74.2 (dd, J_{PF}=105.7, 110.7 Hz); IR (film) 3191, 2985, 1715, 1693, 1664, 1275, 1025 cm^{-1}; EIMS *m/z* 533 (M^++1), 407 (M^+−thymine). Anal. calcd for $C_{22}H_{27}N_2O_7F_2PS$: C, 49.62; H, 5.11; N, 5.26. Found: C, 49.57; H, 5.27; N, 4.95. **23** (92% de): mp 52–53°C; $[\alpha]_D^{20}$=−25.1 (*c*=1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (1H, d, *J*=5.6 Hz), 8.11–8.01 (2H, m), 7.54–7.47 (1H, m), 7.43–7.34 (3H, m), 7.01 (1H, dd, *J*=1.1, 5.6 Hz), 6.75 (1H, dd, *J*=3.8, 9.1 Hz), 4.74–4.50 (3H, m), 4.33–4.17 (4H, m), 3.84–3.65 (1H, m), 2.75–2.54 (2H, m), 1.87 (3H, d, *J*=1.1 Hz), 1.34 (3H, t, *J*=7.1 Hz), 1.33 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 163.6, 152.5, 135.2, 129.8, 129.6, 128.1, 120.7 (ddd, J_{CP}= 177.9 Hz, J_{CF}=263.8, 271.0 Hz), 110.2, 82.4, 78.0, 66.4, 64.7 (d, J_{CP}=6.6 Hz), 64.3 (d, J_{CP}=6.7 Hz), 44.1 (dt. J_{CP}= 16.9 Hz, J_{CF}=19.8 Hz), 30.7, 16.0 (d, J_{CP}=6.1 Hz), 12.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −48.9 (1F, ddd, J_{HF}= 7.8 Hz, J_{FF}=288.8 Hz, J_{PF}=112.7 Hz), −56.9 (1F, ddd, J_{HF}=23.8 Hz, J_{FF}=288.8 Hz, J_{PF}=107.6 Hz); ^{31}P NMR (376 MHz, $CDCl_3$) δ 74.9 (dd, J_{PF}=107.6, 112.7 Hz); IR (KBr) 3247, 2983, 1720, 1656, 1276, 1025 cm^{-1}; EIMS *m/z* 533 (M^++1), 407 (M^+−thymine). Anal. calcd for $C_{22}H_{27}F_2O_7PS\cdot 1/2H_2O$: C, 48.80; H, 5.21; N, 5.17. Found: C, 48.99; H, 5.22; N, 5.13.

3.1.17. *N*-Glycosylation of 18 with T(TMS)$_2$ at −40°C. A solution of T(TMS)$_2$ in CH_2Cl_2 (8 mL) was prepared from thymine (126 mg, 1.0 mmol) and *N*,*O*-bis(trimethylsilyl)-acetamide (0.49 mL, 2.0 mmol) as described in Section 3.1.16. The solution was cooled to −40°C, and was successively treated with a solution of **18** (300 mg, 0.5 mmol) in CH_2Cl_2 (4.0 mL) and $TiCl_4$ (0.31 mL, 2.5 mmol) in CH_2Cl_2 (4.0 mL). After being stirred at −40°C for 3 h, the mixture was poured onto cold sat. $NaHCO_3$. The biphasic mixture was extracted with $CHCl_3$. The extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt=1:1) to give **25** (240 mg, 72%) as an anomeric mixture (α/β=66:34). Mp 62–63°C; $[\alpha]_D^{20}$= +40.8 (*c*=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23–9.15 (1H, m), 7.77–7.64 (4H, m), 7.45–7.30 (3H, m), 6.90–6.85 (1H, m), 6.82 (0.66H, t, *J*=7.7 Hz), 6.70 (0.34H, dd, *J*=3.8, 9.1 Hz), 4.87–4.80 (0.66H, m), 4.47–4.39 (0.34H, m), 4.31–4.14 (4H, m), 4.01–3.95 (1H, m), 3.92 (0.34H, dd, *J*=6.9, 11.0 Hz), 3.80–3.63 (1.32H, m), 3.60–3.45 (0.34H, m), 2.97 (0.66H, dt, *J*=8.9, 12.1 Hz), 2.68–2.59 (0.34H, m), 2.57–2.45 (1H, m), 1.88 (1.98H, d, *J*=0.9 Hz), 1.84 (1.02H, s), 1.33 (6H, t, *J*=7.1 Hz), 1.07 (5.94H, s), 1.02 (3.06H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (α-isomer), 163.6 (β-isomer), 152.8 (α-isomer), 152.7 (β-isomer), 135.7 (α-isomer), 135.6 (2C), 135.5 (β-isomer), 134.9, 133.7 (β-isomer), 133.4 (2C), 133.1 (α-isomer), 129.5 (2C, α-isomer), 129.4 (two carbons, β-isomer), 127.6 (α-isomer), 127.2 (β-isomer), 121.0 (dt, J_{CP}=178.9 Hz, J_{CF}=271.9 Hz), 110.4, 83.2 (α-isomer), 82.4 (β-isomer), 81.3 (β-isomer), 80.2 (d, J_{CP}=7.5 Hz, α-isomer), 66.2 (β-isomer), 64.7 (d, J_{CP}=6.7 Hz, β-isomer), 64.6 (d, J_{CP}=6.7 Hz, α-isomer), 64.3 (α-isomer), 64.2 (d, J_{CP}=6.8 Hz), 43.5 (dt, J_{CP}=17.0 Hz, J_{CF}=19.4 Hz, β-isomer), 41.7 (dt, J_{CP}=16.2 Hz, J_{CF}=20.1 Hz, α-isomer), 30.7 (β-isomer), 30.3 (α-isomer), 26.8 (α-isomer), 26.7 (β-isomer), 19.3 (α-isomer), 19.1 (β-isomer), 16.2 (d, J_{CP}= 6.3 Hz, α-isomer), 16.1 (d, J_{CP}=6.7 Hz, β-isomer), 12.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −46.3 (0.66F, dd, J_{FF}= 286.9 Hz, J_{PF}=112.2 Hz), −48.5 (0.34F, ddd, J_{HF}=6.9 Hz, J_{FF}=287.8 Hz, J_{PF}=113.9 Hz), −57.3 (0.34F, ddd, J_{HF}= 24.6 Hz, J_{FF}=287.8 Hz, J_{PF}=107.5 Hz), −59.4 (0.66F, ddd, J_{HF}=26.6 Hz, J_{FF}=286.9 Hz, J_{PF}=112.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 75.7 (0.66P, t, J_{PF}=112.2 Hz), 75.4 (0.34P dd, J_{PF}=107.5, 113.9 Hz); IR (KBr) 3237, 3072, 2933, 2858, 1720, 1660, 1429, 1043 cm^{-1}; ESIMS *m/z* 689 (M^++Na). Anal. calcd for $C_{31}H_{41}N_2O_6F_2PSSi\cdot 1/2H_2O$: C, 55.10; H, 6.26; N, 4.15. Found: C, 55.20; H, 6.12; N, 4.09.

3.1.18. *O*,*O*-Diethyl (2*S*,3*S*,5*R*)-[2-{[*tert*-butyl(diphenyl)-siloxy]methyl}-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl](difluoro)methylphosphonothioate (26). *Method A*. A solution of T(TMS)$_2$ in CH_2Cl_2 (5.0 mL) was prepared from thymine (63 mg, 0.5 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (0.25 mL, 1.0 mmol). The solution was cooled to −40°C, and was successively treated with a solution of **18** (150 mg, 0.25 mmol) in CH_2Cl_2 (1.5 mL) and $TiCl_4$ (0.14 mL, 1.25 mmol) in CH_2Cl_2 (1.5 mL). After being stirred at −40°C for 3 h, the mixture was warmed to 0°C during 3 h and poured onto sat. $NaHCO_3$. The biphasic mixture was extracted with $CHCl_3$. The extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt=1:1) to give **26** (130 mg, 78%, α/β=12:88) as colorless crystals: mp 59–60°C; $[\alpha]_D^{25}$=+45.8 (*c*=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, b), 7.71–7.62 (4H, m), 7.49–7.34 (7H, m), 6.19 (1H, t, *J*=6.8 Hz), 4.46–4.40 (1H, m), 4.31–4.17 (4H, m), 4.16–4.08 (1H, m), 3.84 (1H, dd, *J*=2.4, 11.6 Hz), 3.68–3.50 (1H, m), 2.78 (1H, dt, *J*=14.0, 5.6 Hz), 2.16 (1H, ddd, *J*=7.2, 10.3, 14.0 Hz), 1.56–1.53 (3H, m), 1.36 (3H, t, *J*=7.0 Hz), 1.34 (3H, t, *J*=7.0 Hz), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 150.3, 135.5, 135.2, 135.0, 133.1, 132.3, 130.0 (2C), 127.9 (2C), 120.9 (dt, J_{CP}= 176.5 Hz, J_{CF}=268.4 Hz), 111.3, 84.5, 78.9, 64.9 (d, J_{CP}= 6.7 Hz), 64.5 (2C), 41.5 (dt, J_{CP}=16.6 Hz, J_{CF}=20.4 Hz), 33.1, 26.9, 19.4, 16.1 (d, J_{CP}=5.7 Hz), 11.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −50.3 (1F, ddd, J_{HF}=13.1 Hz, J_{FF}= 289.5 Hz, J_{PF}=110.6 Hz), −54.7 (1F, ddd, J_{HF}=21.9 Hz, J_{FF}=289.5 Hz, J_{PF}=107.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 74.9 (dd, J_{PF}=107.7, 110.6 Hz); IR (KBr) 3048, 2933, 2858, 1702, 1471, 1264, 1058, 1024 cm^{-1}; EIMS *m/z* 609 (M^+−*tert*-Bu), 541 (M^+−thymine). Anal. calcd for $C_{31}H_{41}N_2O_6F_2PSSi$: C, 55.84; H, 6.20; N, 4.20. Found: C, 55.65; H, 6.14; N, 4.01. *Method B*. To a solution of T(TMS)$_2$ in CH_2Cl_2 (10 mL), prepared from thymine (126 mg, 1.0 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (0.49 mL, 2.0 mmol) as above, were successively added a solution of **17** (290 mg, 0.5 mmol) in CH_2Cl_2 (3.0 mL) and a solution of $TiCl_4$ (0.31 mL, 2.5 mmol) in CH_2Cl_2 (3 mL) at 0°C. The mixture was stirred at the same temperature for 3 h and worked up as above. Purification of the crude by column chromatography (SiO_2, hexane/AcOEt=1:1) gave **26** (310 mg, 93%, α/β=11:89) as crystals. The spectroscopic data and melting points of **26** were identical to those of the authentic sample prepared by Method A. *Method C*. A

solution of **25** (α/β=66:34, 67 mg, 0.1 mmol), thymine (13 mg, 0.1 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (74 μL, 0.3 mmol) in CH_2Cl_2 (2 mL) was heated at reflux for 4 h. To the solution was added a solution of $TiCl_4$ (0.05 mL, 0.5 mmol) at 0°C. The mixture was stirred at the same temperature for 3 h. Work-up and purification as above gave **26** (65 mg, 97%, α/β=15:89) as crystals. The spectroscopic data and melting points of **26** were identical to those of the authentic sample prepared by Method A.

3.1.19. (2*S*,3*S*,5*R*)-{[2-(*tert*-Butyldiphenylsilanyloxymethyl)-5-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-tetrahydro-furan-3-yl]-difluoromethyl}phosphonothioic acid *O*,*O*-diethyl ester (28). This compound was prepared in 64% yield as an anomeric mixture (α/β=13:87) from urasil (112 mg, 1.0 mmol) and **18** (290 mg, 5.0 mmol) in a similar manner to that described in Method B of Section 3.1.18. Mp 52–53°C; $[\alpha]_D^{25}$=+37.6 (*c*=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (1H, b), 7.86 (1H, d, *J*=8.1 Hz), 7.71–7.60 (4H, m), 7.48–7.33 (6H, m), 6.18 (1H, t, *J*=6.0 Hz), 5.31 (1H, dd, *J*=1.8, 8.1 Hz), 4.46–4.38 (1H, m), 4.33–4.17 (4H, m), 4.13 (1H, d, *J*=11.9 Hz), 3.86 (1H, dd, *J*=1.9, 11.9 Hz), 3.65–3.44 (1H, m), 2.77 (1H, dt, *J*=14.1, 6.9 Hz), 2.20 (1H, ddd, *J*=5.1, 9.3, 14.1 Hz), 1.36 (3H, t, *J*=6.9 Hz), 1.34 (3H, t, *J*=7.2 Hz), 1.10 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 150.3, 139.8, 135.6, 135.2, 132.9, 132.0, 130.0 (2C), 127.9, 120.6 (dt, J_{CP}= 177.5 Hz, J_{CF}=268.1 Hz) 102.3, 84.8, 79.9, 64.9 (d, J_{CP}= 6.7 Hz), 64.3 (d, J_{CP}=6.8 Hz), 64.3, 40.8 (dt, J_{CP}=16.5 Hz, J_{CF}=20.4 Hz), 34.0, 26.9, 19.3, 16.1 (d, J_{CP}=5.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −49.5 (1F, ddd, J_{HF}=10.1 Hz, J_{FF}=289.1 Hz, J_{PF}=111.9 Hz), −56.4 (1F, ddd, J_{HF}= 22.6 Hz, J_{FF}=289.1 Hz, J_{PF}=106.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 74.6 (dd, J_{PF}=106.6, 111.9 Hz); IR (KBr) 2933, 1689, 1463, 1391, 1275, 1113, 1022 cm^{-1}; EIMS *m*/*z* 595 (M^+−*tert*-Bu), 541 (M^+−uracil). Anal. calcd for $C_{30}H_{39}N_2O_6F_2PSSi \cdot 1/2H_2O$; C, 54.45; H, 6.09; N, 4.23. Found C, 54.41; H, 6.01; N, 3.96.

3.1.20. *O*,*O*-Diethyl (2*S*,3*S*,5*R*)-[2-{[*tert*-butyl(diphenyl)-silyl]methyl}-5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl](difluoro)methylphosphonothioate (29). This compound was prepared in 84% yield as an anomeric mixture (α/β=24:76) from 5-fluorourasil (130 mg, 1.0 mmol) and **18** (290 mg, 0.5 mmol) in a similar manner to that described in Method B of Section 3.1.18. Mp 75–76°C; $[\alpha]_D^{25}$=+40.8 (*c*=1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34–8.19 (1H, m), 7.91 (1H, d, *J*=5.9 Hz), 7.71–7.63 (4H, m), 7.49–7.36 (6H, m), 6.12 (1H, t, *J*=6.2 Hz), 4.46–4.42 (1H, m), 4.30–4.18 (4H, m), 4.08 (1H, d, *J*=11.2 Hz), 3.80 (1H, dd, *J*=2.4, 11.2 Hz), 3.59–3.42 (1H, m), 2.81 (1H, dt, *J*=14.0, 6.5 Hz), 2.18 (1H, ddd, *J*=6.1, 9.8, 14.0 Hz), 1.35 (3H, t, *J*=7.0 Hz), 1.33 (3H, t, *J*=7.0 Hz), 1.10 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0 (d, J_{CF}=26.7 Hz), 148.9, 140.5 (d, J_{CF}= 238.8 Hz), 135.7, 135.3, 132.5, 132.1, 130.0, 127.9 (2C), 123.7 (d, J_{CF}=33.7 Hz), 120.6 (dt, J_{CP}=178.2 Hz, J_{CF}= 268.0 Hz), 85.3, 79.8, 64.9 (d, J_{CP}=6.7 Hz), 64.5 (d, J_{CP}= 6.2 Hz), 64.5, 41.3 (dt, J_{CP}=16.9 Hz, J_{CF}=20.4 Hz), 33.7, 26.9, 19.2, 16.1 (d, J_{CP}=5.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −49.9 (1F, ddd, J_{HF}=11.8 Hz, J_{FF}=289.4 Hz, J_{PF}=108.8 Hz), −55.5 (1F, ddd, J_{HF}=21.8 Hz, J_{FF}= 289.4 Hz, J_{PF}=108.8 Hz), −100.7 (1F, d, J_{HF}=5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 74.5 (t, J_{PF}=108.8 Hz); IR (KBr) 3177, 3074, 2933, 2859, 1719, 1471, 1263, 1115, 1016 cm^{-1}; EIMS *m*/*z* 613 (M^+−*tert*-Bu). Anal. calcd for $C_{30}H_{38}N_2O_6F_3PSSi$: C, 53.72; H, 5.71; N, 4.18. Found C, 53.39; H, 5.80; N, 3.95.

3.1.21. (2*S*,3*S*,5*R*)-{[5-(4-Benzoylamino-2-oxo-2*H*-pyrimidin-1-yl)-2-(*tert*-butyldiphenylsilanyloxymethyl)tetrahydrofuran-3-yl]-difluoromethyl}phosphonothioic acid *O*,*O*-diethyl ester (30). This compound was prepared in 87% yield as an anomeric mixture (α/β=17:83) from *N*-benzoylcytosine (220 mg, 1.0 mmol) and **18** (290 mg, 0.5 mmol) in a similar manner to that described in Method B of Section 3.1.18. Mp 58–60°C; $[\alpha]_D^{25}$=+56.4 (*c*=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (1H, broad s), 8.42 (1H, d, *J*=7.0 Hz), 7.92–7.83 (2H, m), 7.72–7.64 (4H, m), 7.63–7.57 (1H, m), 7.54–7.36 (9H, m), 6.19 (1H, dd, *J*=4.2, 7.0 Hz), 4.53–4.47 (1H, m), 4.32–4.14 (5H, m), 3.88 (1H, dd, *J*=2.2, 11.9 Hz), 3.57–3.39 (1H, m), 2.90 (1H, dt, *J*=14.4, 7.0 Hz), 2.31 (1H, ddd, *J*=4.2, 8.9, 14.4 Hz), 1.35 (3H, t, *J*=7.1 Hz), 1.34 (3H, t, *J*=7.1 Hz), 1.13 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 162.2, 154.5, 144.2, 135.6, 135.2, 132.9, 132.6, 132.0, 129.9, 128.8, 127.9, 127.8, 127.5, 120.5 (ddd, J_{CP}=178.2 Hz, J_{CF}= 264.3, 271.3 Hz), 96.4, 86.6, 80.8, 64.9 (d, J_{CP}=6.7 Hz), 64.2 (d, J_{CP}=6.9 Hz), 64.0, 40.1 (dt, J_{CP}=16.4 Hz, J_{CF}= 20.5 Hz), 34.8 (d, J_{CP}=2.7 Hz), 26.9, 19.2, 16.0 (d, J_{CP}= 5.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −48.5 (1F, ddd, J_{HF}=7.7 Hz, J_{FF}=288.9 Hz, J_{PF}=114.0 Hz), −57.2 (1F, ddd, J_{HF}=23.2 Hz, J_{FF}=288.9 Hz, J_{PF}=105.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 74.6 (dd, J_{PF}=105.1, 114.0 Hz); IR (KBr) 2932, 1670, 1485, 1316, 1258, 1113, 1021 cm^{-1}; ESIMS *m*/*z* 756 (M^++H). Anal. calcd for $C_{37}H_{44}N_3O_6F_2PSSi \cdot H_2O$: C, 57.42; H, 5.99; N, 5.43. Found C, 57.67; H, 5.91; N, 5.44.

3.1.22. (2*S*,3*S*,5*R*){[2-(*tert*-Butyldiphenylsilanyloxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-tetrahydrofuran-3-yl]-difluoromethyl}phosphonic acid diethyl ester (31). To a solution of **26** (180 mg, 0.27 mmol) in CH_2Cl_2 (8 mL) was added *m*-chloroperbenzoic acid (230 mg, 1.35 mmol) at 0°C. After being stirred at room temperature for 4 h, the mixture was poured onto 5% $NaHCO_3$ solution and extracted with $CHCl_3$. The extracts were washed with brine and evaporated in vacuo. The remaining residue was choromatographed on silica gel. Elution with hexane/AcOEt (1:1) afforded **34** (110 mg, 64%, α/β=11:89). Diastereomerically pure **34** was obtained by preparative HPLC (Inertsil (GL-science), hexane/AcOEt=1:1). Mp 53–55°C; $[\alpha]_D^{20}$=+40.8 (*c*=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (1H, bs), 7.71–7.61 (4H, m), 7.48–7.33 (6H, m), 6.19 (1H, t, *J*= 6.9 Hz), 4.48–4.42 (1H, m), 4.35–4.21 (4H, m), 4.16–4.08 (1H, m), 3.84 (1H, dd, *J*=2.5, 11.6 Hz), 3.46–3.25 (1H, m), 2.85–2.73 (1H, m), 2.24–2.12 (1H, m), 1.54 (3H, s), 1.38 (6H, t, *J*=7.1 Hz), 1.10 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 150.3, 135.5, 135.4, 135.2, 133.1, 132.3, 130.0 (2C), 127.9 (2C), 119.9 (dt, J_{CP}=214.3 Hz, J_{CF}= 263.3 Hz), 111.3, 84.5, 78.5, 64.9 (d, J_{CP}=6.8 Hz), 64.8 (d, J_{CP}=7.0 Hz), 64.6, 42.3 (dt, J_{CP}=15.0 Hz, J_{CF}=20.2 Hz), 32.7, 26.9, 19.4, 16.3 (d, J_{CP}=5.2 Hz), 11.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −51.1 (1F, ddd, J_{HF}=14.5 Hz, J_{FF}= 302.9 Hz, J_{PF}=106.8 Hz), −54.0 (1F, ddd, J_{HF}=21.5 Hz,

J_{FF}=302.9 Hz, J_{PF}=106.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 6.31 (t, J_{PF}=106.8 Hz); IR (KBr) 2932, 1695, 1472, 1272, 1025 cm^{-1}; EIMS *m/z* 593 (M^+−*tert*-Bu). Anal. calcd for $C_{31}H_{41}N_2O_7F_2PSi{\cdot}H_2O$; C, 55.68; H, 6.48; N, 4.19. Found C, 55.68; H, 6.27; N, 4.01.

3.1.23. (2*S*,3*S*)-Diethyl(2-{[*tert*-butyl(diphenyl)silyl]-methyl}-5-ethoxytetrahydrofuran-3-yl)(difluoro)methylphosphonate (33). To a stirred solution of **11** (1.23 g, 2.28 mmol) in THF (5 mL) was added dropwise a THF-solution of $BH_3{\cdot}$THF (7.9 mmol, 7.7 mL of 1.04 M solution) at 0°C. After stirring had been continued for 18 h at the same temperature, the reaction mixture was quenched with 1 M HCl (2.5 mL) and saturated NH_4Cl aqueous solution. The mixture was extracted with Et_2O and dried (Mg_2SO_4) and evaporated. The residue was chromatographed on silica gel. Elution with hexane/AcOEt (5:1) afforded the lactol **32** (850 mg, 69%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.60 (4H, m), 7.47–7.32 (6H, m), 5.62–5.57 (0.2H, m), 5.48–5.43 (0.8H, m), 4.56–4.53 (0.2H, m), 4.52–4.46 (0.8H, m), 4.34–4.17 (4H, m), 3.90 (0.8H, dd, *J*=2.2, 11.2 Hz), 3.85 (0.2H, dd, *J*=2.8, 11.1 Hz), 3.79–3.68 (0.4H, m), 3.65 (0.8H, dd, *J*=3.1, 11.2 Hz), 3.39–3.21 (0.8H, m), 2.57–2.47 (0.2H, m), 2.27–2.15 (1.8H, m), 1.41–1.28 (6H, m), 1.09 (7.2H, s), 1.05 (1.8H, s); ESIMS *m/z* 525 (M^+−OH). Since **32** is unstable at room temperature, **32** was immediately used for the next reaction. A solution of **32** (850 mg, 1.57 mmol), triethylorthoformate (0.31 mL, 1.88 mmol) and ammonium nitrate (3 mg) in EtOH (3 mL) was heated at 90°C for 18 h. The mixture was quenched with $NaHCO_3$ and extracted with Et_2O. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with hexane/AcOEt (15:1) afforded **33** (950 mg, 67%) as an oil: $[\alpha]_D^{25}$=+3.8 (*c*=1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.65 (4H, m), 7.45–7.31 (6H, m), 5.28–5.21 (0.5H, m), 5.19–5.13 (0.5H, m), 4.55–4.48 (0.5H, m), 4.47–4.41 (0.5H, m), 4.33–4.18 (4H, m), 3.98 (0.5H, d, *J*=11.3 Hz), 3.86–3.64 (2.5H, m), 3.50 (0.5H, dq, *J*=9.7, 7.1 Hz), 3.37 (0.5H, dq, *J*=9.5, 7.1 Hz), 3.24–2.91 (1H, m), 2.40 (0.5H, ddd, *J*=5.4, 10.7, 13.7 Hz), 2.28–2.12 (1.5H, m), 1.41–1.30 (6H, m), 1.21 (1.5H, t, *J*=7.1 Hz), 1.08 (4.5H, s), 1.07 (4.5H, s), 1.06 (1.5H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.5, 133.5, 133.4, 129.5, 127.6, 120.1 (dt, J_{CP}=217.4 Hz, J_{CF}=261.9 Hz), 103.7 and 103.4, 79.3 and 77.3, 67.3 and 64.9, 64.4, 63.2 and 62.5, 43.2 (dt, J_{CP}=14.9 Hz, J_{CF}=20.4 Hz) and 41.7 (dt, J_{CP}=14.9 Hz, J_{CF}=20.2 Hz), 33.9, 26.7, 19.2 (2C), 16.3 (d, J_{CP}=5.4 Hz), 15.2 and 14.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −47.7 (0.5F, ddd, J_{HF}=8.8 Hz, J_{FF}=300.5 Hz, J_{PF}=109.0 Hz), −49.1 (0.5F, ddd, J_{HF}=10.2 Hz, J_{FF}=300.4 Hz, J_{PF}=109.0 Hz), −55.4 (0.5F, ddd, J_{HF}=24.7 Hz J_{FF}=300.4 Hz, J_{PF}=109.0 Hz), −57.2 (0.5F, ddd, J_{HF}=24.6 Hz, J_{FF}=300.5 Hz, J_{PF}=109.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.06 (0.5P, t, J_{PF}=109.0 Hz), 6.91 (0.5P, t, J_{PF}=109.0 Hz); IR (film) 3012, 2932, 2858, 1429, 1270, 1217, 1113, 1031 cm^{-1}; EIMS *m/z* 513 (M^+−*tert*-Bu). Anal. calcd for $C_{28}H_{41}O_6F_2PSi$: C, 58.93; H, 7.24. Found: C, 58.70; H, 7.29.

3.1.24. Diethyl (2*S*,3*S*,5*S*)-[2-{[*tert*-butyl(diphenyl)silyl]-methyl}-5-(5-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl](difluoro)methylphosphonate (34). This compound was prepared in 42% yield as an anomeric mixture (α/β=95:5) from thymine (250 mg, 2.0 mmol) and **33** (570 mg, 1.0 mmol) in a similar manner to that described in Method B of Section 3.1.18. Mp 56–57°C; $[\alpha]_D^{25}$=+60.4 (*c*=1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (1H, d, *J*=5.6 Hz), 7.74–7.62 (4H, m), 7.48–7.31 (6H, m), 6.91 (1H, dd, *J*=1.1, 5.6 Hz), 6.83 (1H, t, *J*=7.7 Hz), 4.90–4.83 (1H, m), 4.34–4.19 (4H, m), 4.02–3.94 (1H, m), 3.82–3.74 (1H, m), 3.64–3.45 (1H, m), 3.02 (1H, ddd, *J*=8.4, 12.4, 12.4 Hz), 2.59–2.48 (1H, m), 1.89 (3H, d, *J*=1.1 Hz), 1.37 (3H, t, *J*=7.1 Hz), 1.36 (3H, t, *J*=7.1 Hz), 1.07 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 152.6, 135.6, 135.5, 135.0, 133.4, 133.1, 129.6, 127.6, 120.1 (dt, J_{CP}=216.2 Hz, J_{CF}=263.7 Hz), 110.3, 83.1, 79.8, 64.7 (d, J_{CP}=6.7 Hz), 64.5 (d, J_{CP}=6.9 Hz), 64.1, 42.3 (dt, J_{CP}=14.4 Hz, J_{CF}=20.7 Hz), 29.9, 26.8, 19.3, 16.4 (d, J_{CP}=5.2 Hz), 12.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −47.1 (1F, dd, J_{FF}=300.9 Hz, J_{PF}=105.7 Hz), −58.5 (1F, ddd, J_{HF}=26.1 Hz, J_{FF}=300.9 Hz, J_{PF}=111.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 6.77 (dd, J_{PF}=105.7, 111.5 Hz); IR (KBr) 3182, 3073, 2932, 2858, 1719, 1658, 1429, 1265, 1114, 1040 cm^{-1}; EIMS *m/z* 593 (M^+−*tert*-Bu). Anal. calcd for $C_{31}H_{41}N_2O_7F_2PSi{\cdot}1/2H_2O$: C, 56.44; H, 6.42; N, 4.25. Found: C, 56.61; H, 6.42; N, 4.22.

3.1.25. A typical procedure for *N*-glycosylation of 17 with NBz-A(TMS)$_2$. (2*S*,3*S*,5*S*)-{[5-(6-Benzylamino-purin-9-yl)-2-(*tert*-butyl-diphenylsilanyloxymethyl)-tetrahydrofuran-3-yl]-difluoromethyl}-phosphonothioic acid *O*,*O*-diethyl ester (35α) and (2*S*,3*S*,5*R*)-{[5-(6-benzylamino-purin-9-yl)-2-(*tert*-butyldiphenylsilanyloxymethyl)tetrahydrofuran-3-yl]-difluoromethyl}phosphonothioic acid *O*,*O*-diethyl ester(35β). A suspension of *N*-benzoyladenine (120 mg, 0.5 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (0.25 mL, 1.0 mmol) in CH_3CN (5 mL) was heated at 40°C for 3 h. To the resulting homogeneous solution was added successively a solution of **17** (150 mg, 0.25 mmol) in CH_3CN (3 mL) and $SnCl_4$ (0.29 mL, 2.5 mmol) at 0°C. The mixture was stirred at 25°C for 24 h, and then poured onto sat. $NaHCO_3$. The biphasic mixture was extracted with $CHCl_3$. The extracts were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (1:2) gave **35**α (76.8 mg, 38%) as colourless crystals: mp 53–54°C; $[\alpha]_D^{25}$=+21.9 (*c*=1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (1H, b), 8.80 (1H, s), 8.21 (1H, s), 8.03 (2H, d, *J*=7.4 Hz), 7.76–7.66 (4H, m), 7.61 (1H, t, *J*=7.4 Hz), 7.53 (2H, t, *J*=7.4 Hz), 7.48–7.34 (6H, m), 6.55 (1H, t, *J*=6.3 Hz), 4.84–4.78 (1H, m), 4.30–4.15 (4H, m), 4.01 (1H, dd, *J*=1.9, 11.4 Hz), 3.79 (1H, dd, *J*=2.7, 11.4 Hz), 3.76–3.58 (1H, m), 2.99 (1H, ddd, *J*=6.3, 9.5, 13.9 Hz), 2.82 (1H, dt, *J*=7.0, 13.9 Hz), 1.31 (3H, t, *J*=7.1 Hz), 1.30 (3H, t, *J*=7.1 Hz), 1.12 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 152.5, 151.4, 149.4, 140.7, 135.5 (2C), 133.7, 132.7, 132.5, 129.8 (2C), 128.6, 127.8, 127.7, 123.4, 120.6 (ddd, J_{CP}=177.6 Hz, J_{CF}=265.5, 270.3 Hz), 85.4, 79.9, 65.4, 64.8 (d, J_{CP}=6.6 Hz), 64.3 (d, J_{CP}=6.8 Hz), 42.2 (dt, J_{CP}=16.7 Hz, J_{CF}=20.8 Hz), 34.2, 26.8, 19.2, 16.0 (d, J_{CP}=6.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −49.3 (1F, ddd, J_{HF}=11.8 Hz, J_{FF}=288.7 Hz, J_{PF}=111.3 Hz), −55.5 (1F, ddd, J_{HF}=22.1 Hz, J_{FF}=288.7 Hz, J_{PF}=107.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 74.6 (dd, J_{PF}=107.5, 111.3 Hz); IR (KBr) 2933, 2858, 1700, 1610, 1582, 1456, 1251, 1113,

1017 cm^{-1}; ESIMS *m/z* 780 (M^++H). HRMS (ESI) calcd for $C_{38}H_{45}N_5O_5F_2PSSi$ (MH^+): 780.2616. Found: 780.2623. Anal. calcd for $C_{38}H_{44}N_5O_5F_2PSSi$; C, 58.52; H, 5.69; N, 8.98. Found C, 58.10; H, 5.78; N, 8.83. Successive elution with hexane/AcOEt (1:2) gave **35**β (43.2 mg, 22%) as colorless crystals: mp 56–57°C; $[\alpha]_D^{25}$=+17.8 (*c*=1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (1H, broad s), 8.77 (1H, s), 8.31 (1H, s), 8.02 (2H, d, *J*=7.5 Hz), 7.65–7.57 (5H, m), 7.53 (2H, t, *J*=7.5 Hz), 7.44–7.37 (2H, m), 7.36–7.28 (4H, m), 6.39 (1H, t, *J*=5.9 Hz), 4.61–4.54 (1H, m), 4.32–4.21 (4H, m), 4.06 (1H, dd, *J*=2.2, 11.6 Hz), 3.82 (1H, dd, *J*=3.7, 11.6 Hz), 3.79–3.64 (1H, m), 2.93 (1H, dt, *J*=14.0, 6.9 Hz), 2.84 (1H, ddd, *J*=5.1, 9.1, 14.0 Hz), 1.35 (3H, t, *J*=7.1 Hz), 1.34 (3H, t, *J*=7.1 Hz), 1.05 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 152.5, 151.2, 149.5, 141.2, 135.5, 135.3, 133.7, 132.7, 132.6, 132.5, 129.7 (2C), 128.7, 127.8, 127.7, 127.6, 123.3, 120.6 (ddd, J_{CP}=177.8 Hz, J_{CF}=265.9, 269.9 Hz), 84.7, 80.4, 64.8 (d, J_{CP}=6.7 Hz), 64.5, 64.4 (d, J_{CP}=6.7 Hz), 41.6 (dt, J_{CP}=16.4 Hz, J_{CF}=20.6 Hz), 33.6, 26.8, 19.1, 16.1 (d, J_{CP}=6.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −49.0 (1F, ddd, J_{HF}=9.7 Hz, J_{FF}=289.4 Hz, J_{PF}=109.7 Hz), −56.0 (1F, ddd, J_{HF}=23.2 Hz, J_{FF}=289.4 Hz, J_{PF}=109.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 74.6 (t, J_{PF}=109.7 Hz); IR (KBr) 2932, 1703, 1610, 1580, 1456, 1252, 1114, 1025 cm^{-1}; ESIMS *m/z* 780 (M^++H). Anal. calcd for $C_{38}H_{44}N_5O_5F_2PSSi$: C, 58.52; H, 5.69; N, 8.98. Found: C, 58.12; H, 5.69; N, 8.86.

3.1.26. *N*-Glycosylation of 19 with NBz-A(TMS)$_2$. (2*S*,3*S*,5*RS*)-{[5-(6-Benzoylamino-purin-9-yl)-2-benzyloxymethyltetrahydrofuran-3-yl]difluoromethyl}phosphonothioic acid *O*,*O*-diethyl ester (36α and 36β). A solution of NBz-A(TMS)$_2$ in CH_3CN (5 mL), prepared from N^6-benzoyladenine (120 mg, 0.5 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (0.25 mL, 1.0 mmol), was treated with a solution of **19** (109 mg, 0.25 mmol) in CH_3CN (3 mL) and $SnCl_4$ (0.15 mL, 1.25 mmol) in an analogous manner for the reaction of **35**. Work-up as described in Section 3.1.25, followed by purification (SiO_2, hexane/AcOEt=1:3) gave a mixture of **36**α and **36**β (66.6 mg, **36**α/**36**β=39:61, 42%) as an oil: $[\alpha]_D^{25}$=−2.8 (c=1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (0.4H, s), 8.76 (0.6H, s), 8.44 (0.6H, s), 8.24 (0.4H, s), 8.06–7.98 (2H, m), 7.65–7.47 (3H, m), 7.40–7.19 (5H, m), 6.52 (0.4H, t, *J*=6.3 Hz), 6.43 (0.6H, t, *J*=5.4 Hz), 4.91–4.84 (0.4H, m), 4.69–4.63 (1H, m), 4.60 (0.4H, d, *J*=12.2 Hz), 4.58 (0.6H, d, *J*=12.1 Hz), 4.32–4.13 (4H, m), 3.85 (0.6H, dd, *J*=1.4, 10.7 Hz), 3.82 (0.4H, dd, *J*=1.9, 10.7 Hz), 3.71–3.53 (1.6H, m), 3.52–3.30 (0.4H, m), 2.94 (0.4H, ddd, *J*=6.5, 9.5, 13.9 Hz), 2.89–2.81 (1.2H, m), 2.77 (0.4H, dt, *J*=13.9, 7.0 Hz), 1.35 (1.8H, t, *J*=7.0 Hz), 1.34 (1.8H, t, *J*=7.1 Hz), 1.32 (1.2H, t, *J*=7.0 Hz), 1.31 (1.2H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 152.5 (α-isomer) and 152.4 (β-isomer), 151.5 (α-isomer) and 151.3 (β-isomer), 149.5 (α-isomer) and 149.4 (β-isomer), 141.8 (β-isomer) and 140.8 (α-isomer), 137.7 (α-isomer) and 137.4 (β-isomer), 133.7 (α-isomer) and 132.7 (β-isomer), 128.8, 128.5 (2 carbons), 127.9, 127.8, 127.7, 123.3 (2C), 124.0–117.0 (m), 85.2 (α-isomer) and 85.1 (β-isomer), 79.7 (β-isomer) and 78.7 (α-isomer), 73.6 (α-isomer) and 73.4 (β-isomer), 71.7 (α-isomer) and 70.7 (β-isomer), 64.9 (d, J_{CP}=6.7 Hz), 64.6 (d, J_{CP}=6.5 Hz, β-isomer) and 64.5 (d, J_{CP}=6.5 Hz, α-isomer), 43.0 (dt, J_{CP}=18.4 Hz, J_{CF}=19.3 Hz, α-isomer) and 42.2 (dt, J_{CP}=16.3 Hz, J_{CF}=20.8 Hz, β-isomer), 34.0, 16.1 (d, J_{CP}=5.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −49.4 (0.6F, ddd, J_{HF}=10.8 Hz, J_{FF}=289.6 Hz, J_{PF}=109.3 Hz) and −49.5 (0.4F, ddd, J_{HF}=12.1 Hz, J_{FF}=288.7 Hz, J_{PF}=112.2 Hz), −55.1 (0.4F, ddd, J_{HF}=21.1 Hz, J_{FF}=288.7 Hz, J_{PF}=105.7 Hz) and −55.6 (0.6F, ddd, J_{HF}=21.5 Hz, J_{FF}=289.6 Hz, J_{PF}=109.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 74.4 (0.6P, t, J_{PF}=109.3 Hz) and 74.3 (0.4P, dd, J_{PF}=105.7, 112.2 Hz); IR (neat) 2983, 1700, 1611, 1582, 1517, 1454, 1253, 1027 cm^{-1}; ESIMS *m/z* 632 (M^++H); HRMS (ESI) calcd for $C_{29}H_{33}N_5O_5F_2PS$: 632.1908 (M^++H). Found: 632.1884.

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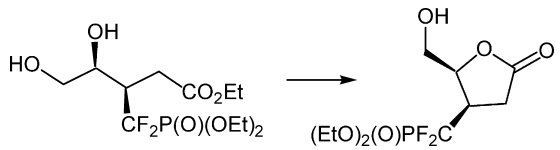

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