N-Glycosylation of 2,3-Dideoxyfuranose Derivatives Having Difluoromethylene-phosphonate and -phosphonothioate Functionality at the 3α-Position

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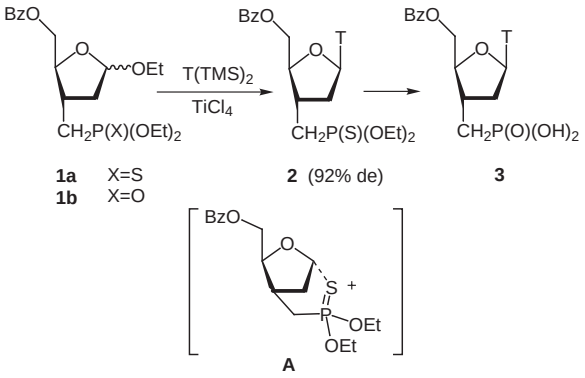
Abstract: $TiCl_4$-Mediated N-glycosylation of 2,3-dideoxyribofunanosides having a difluoromethylene-phosphonate or -phosphonothioate functional group at the 3α-position with silylated pyrimidines was examined. The phosphonate functional was a good directing group to induce α-N-glycosylation for α-N^3-pyrimidine-nucleotide analogue **13** in high diastereoselectivity. The phosphonothioate was an effective functional group to give β-N^1-pyrimidine-nucleotide analogues **18a**–**c** with good diastereoselectivity. The nucleotide analogue **18a** was transformed to the difluoromethylenephosphonate analogue **20** of thymidine-3′-phosphate by oxidation with MCPBA, followed by aqueous work-up.

Key words: nucleotide analogues, N-glycosylations, neighbouring-group effects, phosphorus, fluorine

Since the discovery of certain sugar-modified nucleosides and nucleotides having potential antiviral and antitumor effects, many useful strategies for modification of naturally occurring nucleosides and nucleotides have been devised in the search for novel nucleotide analogues having significant biological activity.[1] Replacement of 3′- or 5′-phosphate moiety of naturally occurring nucleotides with metabolically stable methylenephosphonate functional group has been introduced to synthesize novel nucleotide analogues which act as a pseudoterminator of polymerase-catalyzed RNA-synthesis[2] or as important components of antisense oligonucleotides having increased resistance to nuclease.[3]

In the synthesis of a series of metabolically stable 2′,3′-dideoxynucleotide analogues having a methylenephosphonate functionality at the 3′α-position, previously, we have pursued Lewis acid-mediated N- and C-glycosylation of 2,3-dideoxyfuranose derivatives **1a**,**b** possessing a methylenephosphonate or methylenephosphonothioate functionality.[8] In the N-glycosylation with the phosphonothioate **1a**, the phosphonothioate functional group effectively participates in forming the bicyclic cationic intermediate **A** to give the β-nucleotide analogue **2** stereoselectively (92% de) under the modified Vorbrüggen conditions (Scheme 1).[8a,9] The nucleotide analogue **2** was transformed to the phosphonic acid analogue **3** of thymidin-3′-phosphate through exchanging the phosphonothioate functionality to phosphonic acid.



Scheme 1

With a view to obtaining metabolically stable nucleotide analogues which act as a mimic for the naturally occurring nucleotides, replacement of the phosphate moiety with a difluoromethylenephosphonic acid would be a good tactic.[4] Many α,α-difluoromethylenephosphonate derivatives have been studied as a potential enzyme inhibitor and as a useful probe for elucidation of biochemical processes.[5] Methods for synthesis of 5′-deoxy-5′-difluoromethylenephosphonate nucleotide analogues **4** have been developed.[6] However, to the best of our knowledge, methods for stereoselective synthesis of 2′,3′-dideoxy-3′-difluoromethylenephosphonate nucleotide analogues of general structure **5** have not been developed.[7] In this paper, we report stereoselective synthesis of 2′,3′-dideoxy-3′-difluoromethylenephosphonate nucleotide analogues by the phosphnothioate-assisted N-glycosylation with pyrimidine bases as an extension of our previous work (Figure 1).

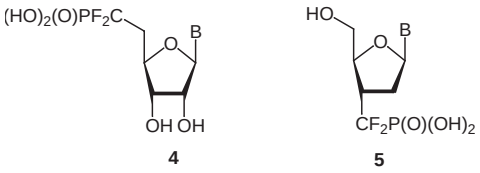


Figure 1

First, we examined N-glycosylation of the glycosyl donor **12** having the difluoromethylenephosphonate functionality (Scheme 3). The glycosyl donor **12** was readily prepared from 1,2-*O*,*O*-isopropylidene-(*R*)-glyceraldehyde **6** as shown in Scheme 2. Horner–Emmons–Wadsworth reaction of **6** with *tert*-butyl diethylphosphonoacetate

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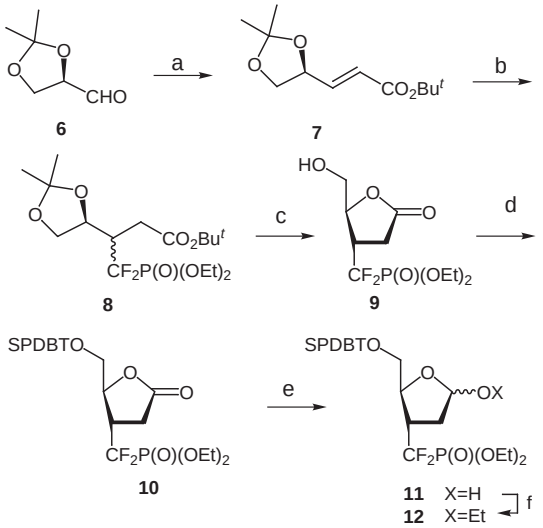
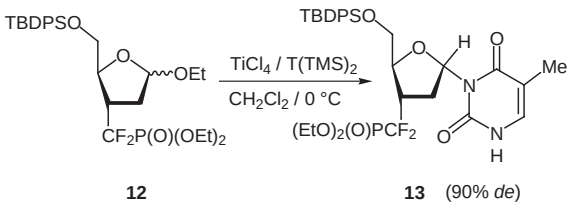
gave the unsaturated ester **7** in 80% yield. Reaction between **7** and diethyl (lithiodifluoromethyl)phosphonate[10] at –78 °C in THF gave the Michael adduct **8** in 81% yield as a 1:1 mixture of diastereoisomers. Treatment of the mixture with concentrated HCl in EtOH at 25 °C reproducibly gave the *trans*-lactone **9**[11] as the sole product in 50% yield. Under the conditions, the (3*R*,4*S*)-diastereoisomer of **8** was rapidly lactonized, but the (3*S*,4*S*)-diastereoisomer decomposed during the reaction.[12] The relative stereochemistry of **9** was deduced by a NOESY-experiment, which showed a strong correlation between H-3 and the methylene protons α to the hydroxyl. Reduction of **10** with BH_3·THF in THF at 0 °C gave the lactol **11** in 80% yield without affecting the phosphonate functional group. The lactol **11** was transformed to an anomeric mixture of 1-ethoxy derivative **12** (α:β = 1:1) in 95% yield on treatment with triethyl orthoformate in EtOH in the presence of a catalytic amount of ammonium nitrate.



Scheme 2 *Reagents and conditions*: (a) $(EtO)_2P(O)CH_2CO_2$-*t*-Bu, NaH, THF, 80%; (b) $LiCF_2P(O)(OEt)_2$, THF, –78 °C, 81%; (c) concd HCl, EtOH, 50%; (d) TBDPSCl, imidazole, DMF, 85%; (e) BH_3·THF, THF, 0 °C, 80%; (f) $CH(OEt)_3$, cat. NH_4NO_2, EtOH, 80 °C, 95%.

N-Glycosylation of **12** with bis-trimethylsilylthymine $T(TMS)_2$ was carried out at 0 °C in CH_2Cl_2 in the presence of $TiCl_4$. The reaction gave the α-N^3-nucleotide analogue **13** of a high diastereomeric excess (90% de) in 42% yield. In this reaction, $T(TMS)_2$ reacted with **12** preferably at the N^3-nitorogen of the pyrimidine from α-face of the glycosyl donor.[9c] The site of glycosylation on the pyrimidine could be assigned by characteristic downfield shift (δ = 6.83, t, *J* = 7.7 Hz) of the anomeric proton as well as a strong correlation between N^1-H and H-6 in the NOESY spectrum (Figure 2). α-Configuration of **13** was assigned on the basis of the observed NOESY-relay correlations among protons in the sugar moiety depicted in Figure 2.

With the results of N-glycosylation of **12** having a difluoromethylenephosphonate functionality in mind, we next



Scheme 3

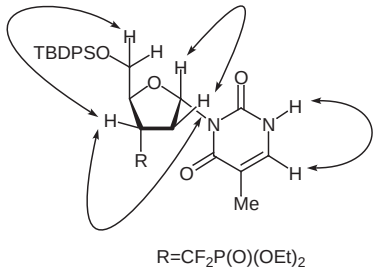
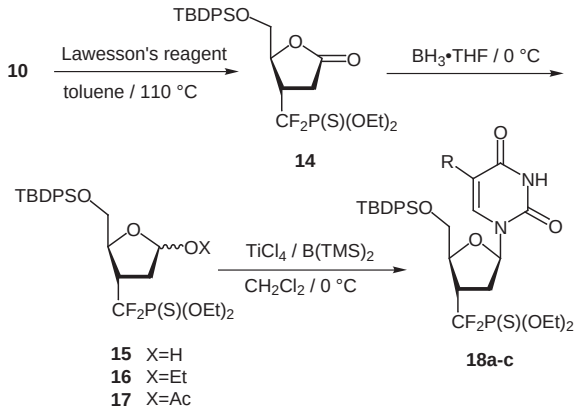


Figure 2 NOESY-correlations of **13**

examined N-glycosylation of the phosphonothioate analogues **16** and **17** with bis-trimethylsilylpyrimidines (Scheme 4 and Table 1). The glycosyl donors **16** and **17** were prepared from the lactone **10**. Thionylation of **10** with Lawesson's reagent in refluxing toluene gave the phosphonothioate **14** in 80% yield, which was transformed to an anomeric mixture of 1-ethoxy derivative **16** (α:β = 1:1) via the lactol **15** in good overall yield (76%) in an analogous manner to that of synthesis of **12**. The lactol **15** was also transformed to an anomeric mixture of 1-acetoxy derivative **17** (α:β = 1:1) by the standard protocol (Ac_2O, pyridine). The previous results of Lewis acid-mediated N-glycosylation of non-fluorinated glycosyl donor **1a** with ($T(TMS)_2$) revealed that $TiCl_4$ was the best Lewis acid to induce the high stereoselectivity and yield.[8a] Then, 1-ethoxy derivative **16** was treated with $T(TMS)_2$ in the presence of $TiCl_4$ in CH_2Cl_2 at 0 °C for 3 hours. In contrast to N-glycosylation of the phosphonate analogue **12**, the desired β-N-glycosylation proceeded with a good diastereoselectivity (β:α = 89:11) to give β-N^1-nucleotide analogue **18a** in 93% yield (entry 1). The relative stereomisty of **18a** and the site of glycosylation on the pyrimidine were confirmed on the basis of the NOESY-experiments. The diagnostic NOESY-correlations are depicted in Figure 3. Under the same conditions, bis-trimethylsilyluracil [$U(TMS)_2$] reacted with **16** to give **18b** in 63% yield with comparable diastereoselectivity (entry 2). However, significant decrease in diastereoselectivity was observed in the reaction with bis-trimethylsilyl-5-fluorouracil [5-FU$(TMS)_2$] (entry 3). The 1-acetoxy derivative **17** seems to be less potent as a glycosyl donor than 1-ethoxy derivative**16**; the reaction of **17** with $T(TMS)_2$ under the same conditions resulted in a significant loss of the diastereoselectivity and yield (entries 1 vs. 4). A similar trend was observed for the reaction with $U(TMS)_2$ (entries 2 vs. 5).



Scheme 4

Table 1 N-Glycosylation of **16** and **17** with Silylated Pyrimidines in the Presence of $TiCl_4$

Entry[a]	Glycosyl donor	Base[b]	**18**	R	Yield	Ratio (β:α)[c]
1	**16**	$T(TMS)_2$	**18a**	Me	93	89:11
2	**16**	$U(TMS)_2$	**18b**	H	64	87:13
3	**16**	5-FU$(TMS)_2$	**18c**	F	84	76:24
4	**17**	$T(TMS)_2$	**18a**	Me	72	70:30
5	**17**	$U(TMS)_2$	**18b**	H	52	84:16

[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-trimethylsilylacetamide (2.0 equiv) and the base (2.0 equiv) in the solvent.
[c] Determined by ^1H NMR (400 MHz, $CDCl_3$).

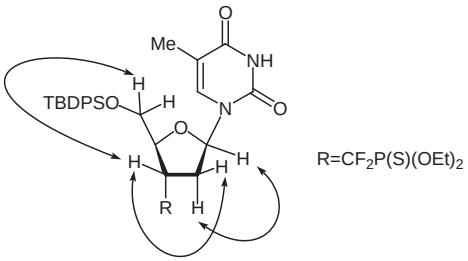
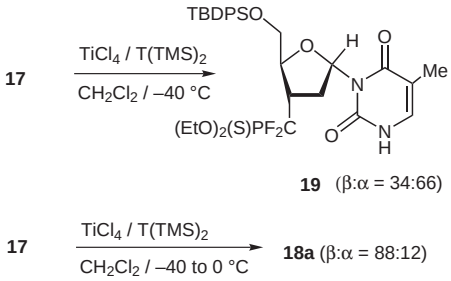


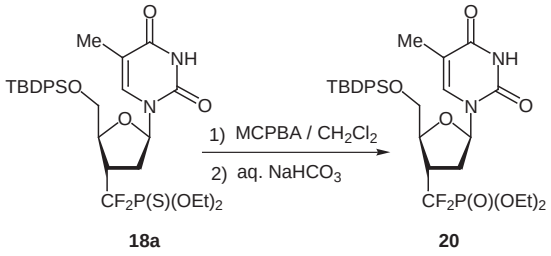
Figure 3 NOESY-correlations of **18a**

The reactivity of the $TiCl_4$-mediated N-glycosylation of 1-acethoxy derivative **17** with $T(TMS)_2$ was significantly affected by the reaction temperature.[13] On reaction of **17** with $T(TMS)_2$ (2 equiv) in CH_2Cl_2 in the presence of $TiCl_4$ (5 equiv) at –40 °C for 3 hours, $T(TMS)_2$ reacted at the N^3-nitrogen to give a 66:34 mixture of α-N^3-nucleotide analogue **19** and the corresponding β-anomer in 72% yield. However, when the reaction was carried out at –40 ºC for 3 hours, and was quenched after being stirred at 0 °C for an additional 3 hours, β-N^1-nucleotide analogue **18a** (β:α = 88:12) was produced in 78% yield (Scheme 5). The results may suggest that the N-glycosylation of **17** with $T(TMS)_2$ in the presence of $TiCl_4$ kinetically produces the α-N^3-nucleotide analogue **19** with poor diastereoselectivity, which isomerizes to the thermodynamically more stable β-N^1-nucleotide analogue **18a** with good diastereoselectivity under the conditions.



Scheme 5

The nucleotide analogue **18a** (β:α = 89:11) thus obtained was converted to the difluoromethylenephosphonate analogue **20** of thymidine-3′-phosphate in 64% yield by oxidation with MCPBA (5.0 equiv), followed by aqueous work-up. Diastereomerically pure **20** could be isolated by preparative HPLC [Inertsil (GL-science), hexane:EtOAc = 1:1, Scheme 6].



Scheme 6

In summary, we have developed an efficient method for the stereoselective synthesis of novel 2′,3′-dideoxyribonucleotide analogues, in which the difluoromethylenephosphonate functionality is incorporated to the 3′α-position as a phosphate isostere.

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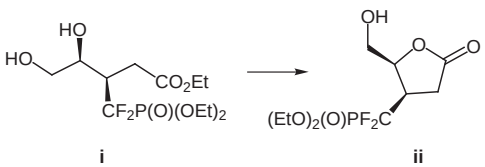
(11) Spectroscopic data for selected new compounds: Compound **9**: $[\alpha]_D^{20}$ +13.8 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.90–4.83 (1 H, m), 4.38–4.23 (4 H, m), 4.00 (1 H, dd, *J* = 2.6, 12.5 Hz), 3.72 (1 H, dd, *J* = 2.9, 12.5 Hz), 3.40–3.22 (1 H, m), 2.85 (2 H, d, *J* = 8.4 Hz), 2.56 (1 H, br s), 1.40 (6 H, 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} = 7.1 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, $CDCl_3$, benzotrifluoride): δ = –54.49 (1 F, dd, J_{HF} = 4.9 Hz, J_{PF} = 105.2 Hz), –54.54 (1 F, 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). MS (EI): *m/z* = 303 [M^+ + 1], 285 [M^+ – OH], 271 [M^+ – CH_2OH]. IR(film): 3247, 2988, 1789, 1645 cm^{-1}. Anal. Calcd for $C_{10}H_{17}O_6F_2P$: C, 39.74; H, 5.67. Found: C, 39.43; H, 5.66. Compound **13**: $[\alpha]_D^{20}$ +60.4 (*c* 1.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.56 (1 H, d, *J* = 5.6 Hz), 7.74–7.62 (4 H, m), 7.48–7.31 (6 H, m), 6.91 (1 H, dd, *J* = 1.1, 5.6 Hz), 6.83 (1 H, t, *J* = 7.7 Hz), 4.90–4.83 (1 H, m), 4.34–4.19 (4 H, m), 4.02–3.94 (1 H, m), 3.82–3.74 (1 H, m), 3.64–3.45 (1 H, m), 3.02 (1 H, ddd, *J* = 8.4, 12.4, 12.4 Hz), 2.59–2.48 (1 H, m), 1.89 (3 H, d, *J* = 1.1 Hz), 1.37 (3 H, t, *J* = 7.1 Hz), 1.36 (3 H, t, *J* = 7.1 Hz), 1.07 (9 H, 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 (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, $CDCl_3$, benzotrifluoride): δ = –47.1 (1 F, dd, J_{FF} = 300.9 Hz, J_{FP} = 105.7 Hz), –58.5 (1 F, ddd, J_{FF} = 300.9 Hz, J_{FP} = 111.5 Hz, J_{FH} = 26.1 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 6.77 (dd, J_{PF} = 105.7, 111.5 Hz). MS (EI): *m/z* = 593 [M^+ – *t*-Bu]. HRMS (EI): *m/z* calcd for $C_{27}H_{32}N_2O7F_2PSi$ [M^+ – *t*-Bu]: 593.1697. Found: 593.1697. Anal. Calcd for $C_{31}H_{41}N_2O_7F_2PSi$: C, 57.22; H, 6.35; N, 4.30. Found: C, 56.61; H, 6.35; N, 4.22.
Compound **18a**: $[\alpha]_D^{20}$ +30.2 (*c* 1.3, $CHCl_3$) for a sample of 78% de. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (1 H, br s), 7.71–7.62 (4 H, m), 7.49–7.34 (7 H, m), 6.19 (1 H, t, *J* = 6.8 Hz), 4.46–4.40 (1 H, m), 4.31–4.17 (4 H, m), 4.16–4.08 (1 H, m), 3.84 (1 H, dd, *J* = 2.4, 11.6 Hz), 3.68–3.50 (1 H, m), 2.82–2.72 (1 H, m), 2.21–2.11 (1 H, m), 1.56–1.53 (3 H, m), 1.36 (32 H, t, *J* = 7.0 Hz), 1.34 (3 H, t, *J* = 7.0 Hz), 1.11 (9 H, 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 (2 carbons), 127.9 (2 carbons), 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, 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, $CDCl_3$, benzotrifluoride): δ = –50.3 (1 F, ddd, J_{HF} = 13.1 Hz, J_{FF} = 289.5 Hz, J_{FP} = 110.6 Hz), –54.7 (1 F, ddd, J_{HF} = 21.9 Hz, J_{FF} = 289.5 Hz, J_{FP} = 107.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 74.9 (dd, J_{PF} = 107.7 Hz, 110.6 Hz). MS (EI): *m/z* = 609 [M^+ – *t*-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.
Compound **20**: $[\alpha]_D^{20}$ +34.0 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (1 H, br s), 7.71–7.61 (4 H, m), 7.48–7.33 (6 H, m), 6.19 (1 H, t, *J* = 6.9 Hz), 4.48–4.42 (1 H, m), 4.35–4.21 (4 H, m), 4.16–4.08 (1 H, m), 3.84 (1 H, dd, *J* = 2.5, 11.6 Hz), 3.46–3.25 (1 H, m), 2.85–2.73 (1 H, m), 2.24–2.12 (1 H, m), 1.54 (3 H, s), 1.38 (6 H, t, *J* = 7.1 Hz), 1.10 (9 H, 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 (2 carbons), 127.9 (2 carbons), 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, $CDCl_3$, benzotrifluoride): δ = –51.1 (1 F, ddd, J_{HF} = 14.5 Hz, J_{FF} = 302.9 Hz, J_{PF} = 106.8 Hz), –54.0 (1 F, 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). MS (EI): *m/z* = 593 [M^+ – *t*-Bu]. HRMS (EI): *m/z* calcd for $C_{27}H_{32}N_2O7F_2PSi$ [M^+ – *t*-Bu]: 593.1697. Found: 593.1672.

(12) Percy et al. reported that the diol **i**, in situ prepared stereoselectively from the corresponding olefin by OsO_4-catalyzed dihydroxylation, was not readily cyclized to the *cis*-lactone **ii** under the conditions.[7b] They were never able to isolate more than 11% of **ii**. The results are consistent with our findings (Scheme 7).



i **ii**

Scheme 7

(13) The 1-ethoxy derivative **16** did not react with $T(TMS)_2$ in the presence of $TiCl_4$ at –40 °C and the lactol **15** was recovered in 80% yield.